

VOLUME TWO

Second Edition

Handbook of
**Pharmaceutical
Manufacturing
Formulations**

Uncompressed Solid Products



SARFARAZ K. NIAZI



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V O L U M E T W O

Second Edition

Handbook of
**Pharmaceutical
Manufacturing
Formulations**
Uncompressed Solid Products

S A R F A R A Z K. N I A Z I

*Pharmaceutical Scientist, Inc.
Deerfield, Illinois, USA*

informa

healthcare

New York London

Handbook of Pharmaceutical Manufacturing Formulations Second Edition

Volume Series

Sarfaraz K. Niazi

Volume 1

*Handbook of Pharmaceutical Manufacturing Formulations:
Compressed Solid Products*

Volume 2

*Handbook of Pharmaceutical Manufacturing Formulations:
Uncompressed Solid Products*

Volume 3

*Handbook of Pharmaceutical Manufacturing Formulations:
Liquid Products*

Volume 4

*Handbook of Pharmaceutical Manufacturing Formulations:
Semisolid Products*

Volume 5

*Handbook of Pharmaceutical Manufacturing Formulations:
Over-the-Counter Products*

Volume 6

*Handbook of Pharmaceutical Manufacturing Formulations:
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Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

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No claim to original U.S. Government works
Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-8116-0 (Volume 1; Hardcover)
International Standard Book Number-13: 978-1-4200-8116-9 (Volume 1; Hardcover)
International Standard Book Number-10: 1-4200-8118-7 (Volume 2; Hardcover)
International Standard Book Number-13: 978-1-4200-8118-3 (Volume 2; Hardcover)
International Standard Book Number-10: 1-4200-8123-3 (Volume 3; Hardcover)
International Standard Book Number-13: 978-1-4200-8123-7 (Volume 3; Hardcover)
International Standard Book Number-10: 1-4200-8126-8 (Volume 4; Hardcover)
International Standard Book Number-13: 978-1-4200-8126-8 (Volume 4; Hardcover)
International Standard Book Number-10: 1-4200-8128-4 (Volume 5; Hardcover)
International Standard Book Number-13: 978-1-4200-8128-2 (Volume 5; Hardcover)
International Standard Book Number-10: 1-4200-8130-6 (Volume 6; Hardcover)
International Standard Book Number-13: 978-1-4200-8130-5 (Volume 6; Hardcover)

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Library of Congress Cataloging-in-Publication Data

Niazi, Sarfaraz, 1949–
Handbook of pharmaceutical manufacturing formulations /
Sarfaraz K. Niazi. – 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-4200-8106-0 (set) (hardcover : alk. paper)
ISBN-10: 1-4200-8106-3 (set) (hardcover : alk. paper)
ISBN-13: 978-1-4200-8116-9 (v. 1) (hardcover : alk. paper)
ISBN-10: 1-4200-8116-0 (v. 1) (hardcover : alk. paper)
[etc.]
1. Drugs–Dosage forms–Handbooks, manuals, etc. I. Title.
[DNLM: 1. Drug Compounding–Handbooks. 2. Dosage Forms–Handbooks.
3. Formularies as Topic–Handbooks. 4. Technology, Pharmaceutical–Handbooks.
QV 735 N577h 2009]
RS200.N53 2009
615'.19–dc22

2009009979

For Corporate Sales and Reprint Permission call 212-520-2700 or write to: Sales Department,
52 Vanderbilt Avenue, 16th floor, New York, NY 10017.

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to the memory of Takeru Higuchi



کانال اطلاع رسانی مستندات در صنعت داروسازی

برای پیوستن به کانال اینجا کلیک کنید

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 choose 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 formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 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.

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

Preface to the Series—First Edition

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

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

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

erations have led to the classification of products into these six categories.

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

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

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

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

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

Uncompressed solid products formulations comprise aggregates of powders, such as powders for topical application, for use as insufflations, and for extemporaneous suspensions, as well as hard gelatin capsules or any other form wherein the final form is not compressed. The rationale for this clear demarcation of formulations based on their state of aggregation is important to understand. Whereas compressed solid products require formulation components to render them compressible while allowing free flow into compression cavities, such considerations are of lesser importance for uncompressed solid products. (The flow requirement, nevertheless, stays because the powders must be forced into capsule shells or poured into bottles or other packaging forms.) Uncompressed solid products, on the other hand, offer their own set of formulation problems related to segregation of powders due to static charges, environmental contamination during the filling process, and inevitable problems in wetting and dissolution, thus leading to possible bioavailability problems *in vivo*. In the series of steps that determine the ultimate dissolution of the product, however, uncompressed solid products are one critical step ahead of compressed solid products—disintegration. The formulator is advised to read chapter 4 of this volume, which discusses guidelines on the waiver of bioavailability requirements. Substantial development costs can be reduced when a drug undergoes fast dissolution, and these considerations must therefore be part of any new formulation effort. The reader is also referred to Volume 1 of this series where current and proposed bioavailability guidelines are provided.

Chapter 1 addresses the fundamental issues of good manufacturing practices (GMPs). The chapter provides access addresses to all major guidelines around the world and also highlights the U.S. Food and Drug Administration (FDA) guidelines. A discussion of the most recent changes in the philosophy of establishing the GMP guidelines based on risk assessment is addressed in this chapter as well.

Chapter 2 presents a more recent discussion of how the U.S. FDA inspectors are supposed to conduct inspections; this topic is of continuous importance to all drug manufacturers. Although it is included in this volume, the guidelines apply to all dosage forms.

Chapter 3 discusses the topic of bioequivalence and bioavailability of solid products. Although this is discussed more thoroughly in Volume 1, the emphasis in chapter 3 is placed on the guidelines to request a waiver of bioavailability/bioequivalence testing; this is something of great importance to both the innovator and the generic drug manufacturer.

Chapter 4 highlights the manufacturing aspects of uncompressed drugs as well as various topics of general and specific interest.

Part II provides formulations for more than 400 pharmaceutical products. Included in part are not only the currently approved products but also several innovative products such

as small proteins, instantly liquefiable powders, and nanoparticles. Formulators are strongly urged to review the methodologies described here to serve as a reference point for their own formulations. Some combination products or dosage forms are described that are not currently approved by the FDA (i.e., not included in the *Orange Book*), and they may be in the development phase or in experimental phases. As is always the case, it is the responsibility of the manufacturer to ensure that the formulations used in the production do not violate any intellectual property or proprietary practice laws. The most effective means of establishing this is through a study of the *Orange Book*, which lists the exclusivities and unexpired patents. The patent numbers provided in the *Orange Book* should then be searched for collateral patents, the FDA freedom of information (FOI) database, and other literature to ensure that the intellectual or proprietary property rights are not violated.

Whereas coating solutions are not as important as in the case of compressed solids, nevertheless, some capsules are coated and the granules that are filled in capsules for sustained or timed release are coated, utilizing nonpareil sugar beads most often. The coating solutions are described here, but the reader is further referred to Volume 1 for a detailed description of coating solutions that can be easily adapted to the product intended for formulation into a sustained release profile. Whereas some forms of powders are meant to be sterile, the sterility considerations are discussed in Volume 6.

The subject of powder technology is vast, with applications in many fields. The serious reader is referred to the journal *Advanced Powder Technology* (<http://www.vspub.com/journals/jn-AdvPowTec.html>). Such advances as inhalation insulin in a powder form and the new science of nanoparticles open a new phase of pharmaceutical research and development. Nanotechnology describes the ability to create new materials from building blocks the size of an atom cluster. Nanomaterials are powders and materials optimized at the nanoscale (10⁻⁹ m or a billionth of a meter in size). Nanopowders consist of particles with dimensions that can be measured by X-ray crystallography to be a few hundred atoms in diameter.

The formulations are presented in this volume with a scale for each unit: per capsule or per unit dose of powder. Quantities are expressed for 1000 units. Sometimes, however, a different presentation is chosen for simplicity and clarity. It is often customary for manufacturers to scale formulae for a specific weight, such as 100 or 1000 kg to match the mixing vessel requirements. This can be done roughly by multiplying the weight of each capsule or unit powder by the quantity desired to calculate the size of the batch. The reader should be aware that the actual yield may be different because of differences in the scale and quantity due to differences in the chemical form of drugs used, excesses added, and loss of moisture during manufacturing. Further, adjustment of

quantity based on potency of raw material, where pertinent, changes the quantity requirements. Most of these products are identified in this volume by a brief description before the listing of the Bill of Materials, which may not necessarily represent the commercially available dosage form; the description includes details of the commercial product.

A distinctive feature of this volume is the identification and inclusion of the most often approved capsules and powders in the United States. It is noteworthy that in the preparation of an abbreviated new drug application (ANDA), it is important for both regulatory and scientific reasons to keep the selection of excipients as close as possible to the innovator's product. The listing provided here includes every excipient used in the innovator listing and quantitative formulae in several instances. Whereas, in most instances, sufficient details are provided to assist in the formulation of a generic equivalent with exact quantities of excipients and conditions appropriate for processing, the examples provided for other drugs of a similar type should be sufficient for an astute formulator to develop quickly these formulations. Should there be a need for assistance in finalizing the formulations, however, the reader is invited, without any obligation, to write to the author at niazi@pharmsci.com. It should be emphasized that manufacturers frequently use colored capsule shells to identify their products and often imprint them with logos or other identification marks. It is important to understand that the coloring dyes are not universally approved and, in some instances, may form the basis for a trademark. The formulator is advised to investigate this aspect carefully; nevertheless, in most formulations, the dyes used are disclosed.

Whereas the science and the art of formulations remain within the domain of experienced hands, the wide dissemination of information about drug formulation compositions and problems related to them makes it easier for one to design excellent benchmarked formulations. The Web site of the U.S. FDA (<http://www.fda.gov>) remains one of the best sources of information. At times, however, commercial sources of databases, particularly the details that come under the Freedom of Information Act, can be more useful (e.g., <http://www.foiser-vices.com/>). No endorsement is intended here for any company or resource.

I am grateful to CRC Press I LLC for taking the 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 Stephen Zollo, senior editor at CRC Press, for years. Stephen has done more than any editor I have known to encourage me to complete this work on a timely basis. The editorial assistance provided by the CRC Press staff was indeed exemplary, particularly the assistance of Erika Dery, Samar Haddad, and others at CRC Press. Although much care has gone into correcting errors, any remaining errors are altogether mine. The reader is encouraged to bring any errors to my attention so that I may make corrections in future editions of this volume (niazi@pharmsci.com).

This book is dedicated to Takeru Higuchi. Higuchi was a university regents distinguished professor of pharmaceutical chemistry and chemistry at Kansas University, and the founding chair of the department of pharmaceutical chemistry. He was known for the first systematic application of chemical principles to drug design, delivery, and analysis. His scientific accomplishments earned him the informal title of "father of physical pharmacy." Higuchi died in 1987. A famous quote of Tak Higuchi is that "It is merely a matter of orderly thinking . . . and a little organization." One of his admirers notes, "His uniqueness is that he can look into the future and see things and imagine things that most of us cannot. Higuchi has the ability to identify what will be important in the future—that is his genius." I met Tak several times during my teaching career and heard a lot more about him from my colleagues and teachers who worked with him directly. (It was rumored that he wrote the entire logarithmic table when flying to Japan because he needed to solve an equation.) I learned much of my science by reading Tak's papers, which are full of insight and fresh approaches to old problems. He was also a good businessman and a wonderful role model for industry-academia partnership. His aura is inspiring and his presence overwhelming even though he is not among us anymore. People like Tak Higuchi are rare in any profession; we were just lucky to have him.

Sarfaraz K. Niazi, Ph.D.
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About the Author



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

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Part I

Regulatory and Manufacturing Guidelines

U.S. FDA Good Manufacturing Practices

I. INTRODUCTION

Good Manufacturing Practices (GMPs) is a universal concept with a dual purpose: to make pharmaceutical products both safe and consistent in their effectiveness. Remarkable changes are taking place in the basic approach to achieve these goals. The key regulations and guidelines for the manufacturing of finished pharmaceuticals (as opposed to raw material or active ingredient manufacturing) in this respect are

1. 21 Code of Federal Regulations, Parts 210 and 211 (Part 210—Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals) <http://www.fda.gov/cder/dmpq/cgmpregs.htm>
2. The World Health Organization (WHO): Quality Assurance of Pharmaceuticals: A compendium of guidelines and related materials, Volume 2, Good Manufacturing Practices and Inspection http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html
3. The Rules Governing Medicinal Products in the European Union: Volume 4, Good Manufacturing Practices <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4.en.htm>
4. The European Agency for the Evaluation of Medicinal Products—International Conference on Harmonization (ICH) Guidelines <http://www.emea.europa.eu/Inspections/GMPHome.html>
5. Health Products and Food Branch Inspectorate of Canada. Good Manufacturing Practices Guidelines—<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/guide-ld-2002/index-eng.php>
6. Therapeutic Goods Administration, Government of Australia—Australian Code for Good Manufacturing Practice <http://www.tga.gov.au/docs/html/gmpcodau.htm>

Though there are many common elements among the approach to GMP taken by the worldwide drug regulatory guidelines, there remains a major difference between the approvals awarded in the United States vis-a-vis Europe and the rest of the world. The U.S. Food and Drug Administration (FDA) inspection is triggered only when an application for marketing authorization has been submitted to the FDA. If the FDA chooses to inspect a facility—the so-called preapproval inspection (PAI)—the company is so advised and the approval of the pending New Drug Application (NDA) or abbreviated New Drug Application (aNDA) is delayed until the inspection is completed. The main focus of PAI is to establish if the applicant firm is capable of manufacturing a safe product, the issues relating to efficacy, dosing, and label copy being reviewed by the agency office in Washington, D.C. It is important to realize that all documents labeled

as guidelines remain guidelines and the FDA inspectors are not bound by any specifications, requirements, or designs suggested in the current Good Manufacturing Practices (cGMP) documents. In almost all instances, the FDA inspector visiting a facility for the first time would take time to explain this to the technical team that receives the inspection team. “We are not bound by the CGMP guidelines because these meant to guide you and not bind us.” This comes as a surprise to many who may have otherwise worked out each and every recommendation made in the guideline. In several places, the reader will find the instructions given to the inspection team on what to inspect and how to inspect it and these should be studied carefully. Since PAI is related to a specific product and not to the entire facility, the focus of inspection remains the submitted aNDA or NDA and the facility involved in the manufacturing of that specific product. Except for those systems that directly impinge on the quality of the submitted product, the FDA inspectors would generally keep out of other areas. For example, if the submitted application is a sterile product, the FDA inspection will be limited to the facility filling sterile products. Common elements of warehousing, QC, QA are however always part of any inspection.

The focus of PAI is to establish the robustness of the firm’s QA systems that will allow consistent production of a safe product, meaning the product is free from contamination, complies with the listed specifications, and is packed such as to allow it to reach the consumer with sufficient shelf-life remaining. It is not unusual for the PAI team to perform a more in-depth audit of the document trail and a more superficial inspection of the physical facility. (The EDQM/EMEA and WHO inspections are mostly facility intensive.) Generally, the PAI team will ensure that the standard operating procedures (SOPs) as written by the firm are followed faithfully and that those involved in assuring the safety guarantee of the product are properly trained.

Whereas the FDA’s PAI results in approval of the marketing authorization application, the facility is not declared compliant except for the product for which the inspection was made; thus it is a misnomer to call a firm, “FDA-approved.” The U.S. FDA does not approve facilities, it approves products. The WHO audits can result in awarding a facility preapproval to submit for bids on WHO contracts as a GMP-certified facility.

II. U.S. FDA cGMP GUIDELINES

The U.S. FDA oversees the quality of drug products using a two-pronged approach including a review of information submitted in applications as well as an inspection of manufacturing facilities for conformance to requirements for cGMPs. These two programs have served the United States well by helping to ensure the quality of drug products available. Now, as we approach the twenty-fifth anniversary of the last major

revision to the drug cGMP regulations, the U.S. FDA has undertaken a program to overhaul the entire process of cGMP compliance so that

- the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality,
- the latest scientific advances in pharmaceutical manufacturing and technology are encouraged,
- the submission review program and the inspection program operate in a coordinated and synergistic manner,
- regulation and manufacturing standards are applied consistently,
- management of the program encourages innovation in the pharmaceutical manufacturing sector,
- FDA resources are used most effectively and efficiently to address the most significant health risks.

Over the last two decades, significant changes in the environment of pharmaceutical regulation have occurred and have resulted in incremental adjustments in the FDA's regulatory approach to product quality. These changes include:

- Increased number of pharmaceutical products and a greater role of medicines in health care
- Decreased frequency of FDA manufacturing inspections as a result of fewer resources available for pharmaceutical manufacturing inspections
- The FDA's accumulation of experience with, and lessons learned from, various approaches to the regulation of product quality
- Advances in the pharmaceutical sciences and manufacturing technologies
- Application of biotechnology in drug discovery and manufacturing
- Advances in the science and management of quality
- Globalization of the pharmaceutical industry

The cumulative impact of these changes has been greater than the sum of the parts and warrants a systematic reappraisal of the FDA's approaches to product quality regulation. The following principles will guide implementation of the reappraisal:

Risk-based orientation—To provide the most effective public health protection, the FDA must match its level of effort against the magnitude of risk. Resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production. Although the agency has been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed.

Science-based policies and standards—Significant advances in pharmaceutical sciences and in manufacturing technologies have occurred over the last two decades. Although this knowledge has been incorporated in an ongoing manner into the FDA's approach to product quality regulation, the fundamental nature of the changes dictates a thorough evaluation of the science base to ensure that product quality regulation not only incorporates up-to-date science, but also encourages further advances in technology. Recent science can also contribute significantly to assessment of risk.

Integrated quality systems orientation—Principles from various innovative approaches to manufacturing quality that have been developed in the past decade will be evaluated for applicability, and cGMP requirements and related preapproval requirements will be evaluated according to applicable principles. In addition, interaction of the premarket chemistry, manufacturing and control (CMC) review pro-

cess and the application of cGMP requirements will be evaluated as an integrated system.

International cooperation—The globalization of pharmaceutical manufacturing requires a global approach to regulation. The FDA will collaborate with other regulatory authorities via International Conference on Harmonization and other venues.

Strong public health protection—The initiative will strengthen the public health protection achieved by the FDA's regulation of drug product manufacturing and will not interfere with strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.

To accomplish the reappraisal, the FDA will carry out the following broad actions.

- Perform an external review of the existing cGMP program and product review practices, including an evaluation of potential inconsistencies in implementation.
- Reassess and reevaluate our current scientific approach to both the product review process and the cGMP program to achieve a consistent, integrated systems approach to product quality regulation.
- Enhance the scientific approach of cGMPs to emphasize risk-based control point analysis and to facilitate the latest innovations in pharmaceutical engineering.

The following immediate steps are planned.

- Holding scientific workshops with key stakeholders
- Enhancing expertise in pharmaceutical technologies (e.g., pharmaceutical engineering and industrial pharmacy) by additional training and hiring, and by leveraging external expertise
- Encouraging innovation within the existing framework of statutory provisions and regulations by allowing certain changes in the manufacturing process without prior review/approval (e.g., comparability protocols)
- Evaluating the optimal mechanisms to effectively and efficiently communicate deficiencies to industry, including content, consistency, disclosure, and education
- Shifting the agency lead on the implementation of Part 11 to Center for Drug Evaluation and Research (CDER), with continued involvement from the other centers of the FDA and the Office of Regulatory Affairs
- Including product specialists, as needed, as a part of inspection teams
- Having centers provide a scientific and technical review of all drug cGMP warning letters
- Developing a technical dispute resolution process that integrates technical experts from the centers and addresses perceived inconsistencies between centers
- Emphasizing a risk-based approach in the work planning process
- Improving the operations of team biologics of the Center for Biological Evaluation and Research

Intermediate steps are

- using emerging science and data analysis to enhance compliance programs to target the highest risk areas,
- evaluating the feasibility of establishing dedicated cadres of pharmaceutical inspectors.

Long-term steps are

- enhancing training of agency staff on new scientific approaches and innovative pharmaceutical manufacturing technology,

- developing and publishing policies and procedures reflecting a science-based risk management approach,
- educating industry on new regulatory approaches that encourage innovation.

In conclusion, the industry must keep a close watch on these developments as new cGMP guidelines are drafted by the U.S. FDA. This is particularly important for the new start-ups wherein much of what the FDA would like to see in the future can be readily provided. Whereas it is anticipated that the FDA will loosen its noose on some of the less risky aspects of cGMP, greater emphasis will be placed on protecting patients when high-risk drugs are involved. The basic guidelines, however, are here to stay and an overview of these fundamental concepts is presented next.

A. General Provisions

Title 21 of CFR Parts 210 and 211 describes the current GMP practices; this chapter contains the guidelines current as of 2007 and their amendments current as of 2008. Section 211.1, "Scope," states:

"The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals. Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this part shall not be enforced for over-the-counter (OTC) drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use."

Periodically, the FDA issues amendments, specific product instructions, and other labeling or manufacturing requirements for a variety of drugs. The reader is advised to consult these guidelines routinely. In light of substantial changes made to these guidelines, it is further advised that instead of comparing these guidelines with the older version, the companies discard the old guidelines and adopt the following document in their standard operating procedures.

Manufacturers who have experience in routine FDA inspections as well as special inspections know well that all of these documents are labeled as guidelines, which literally means that the FDA inspectors are not bound by these—these are merely guidelines. In every instance the purpose of inspection is to ensure that the manufacturer is capable of producing a safe product, the efficacy being already established through the filing of the NDA or aNDA.

Part 210—cGMP in Manufacturing, Processing, Packaging, or Holding of Drugs; General

210.1 Status of cGMP regulations

210.2 Applicability of cGMP regulations

210.3 Definitions

210.1 Status of cGMP regulations

- The regulations set forth in this part and in parts 211 through 226 in the FDA guidelines contain the minimum cGMP for methods to be used in and the facilities or controls to be used for the manufacture, processing, packing, or holding of a drug to ensure that such drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.
- The failure to comply with any regulation set forth in this part and in parts 211 through 226 in the FDA guide-

lines in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

- Owners and operators of establishments engaged in the recovery; donor screening; testing (including donor testing); processing; storage; labeling; packaging; or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in 1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 in the FDA guidelines. Failure to comply with any applicable regulation set forth in this part, in parts 211 through 226 in the FDA guidelines, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.

210.2 Applicability of cGMP regulations

- The regulations in this part and in parts 211 through 226 in the FDA guidelines as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a HCT/P that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.
- If a person engages in only some operations subject to the regulations in this part, in parts 211 through 226 in the FDA guidelines, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

210.3 Definitions

- The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in parts 211 through 226 in the FDA guidelines.
- The following definitions of terms apply to this part and to parts 211 through 226 in the FDA guidelines.
 - Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 USC 301 et seq).
 - Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.
 - Component means any ingredient intended for use in the manufacture of a drug product,

- including those that may not appear in such drug product.
4. Drug product means a finished dosage form, for example, tablet, capsule, solution that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.
 5. Fiber means any particulate contaminant with a length at least three times greater than its width.
 6. Non-fiber-releasing filter means any filter, which after any appropriate pretreatment, such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos are deemed to be fiber-releasing filters.
 7. Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect.
 8. Inactive ingredient means any component other than an active ingredient.
 9. In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.
 10. Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.
 11. Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.
 12. Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products.
 13. The term medicated feed means any Type B or Type C medicated feed as defined in 558.3 in the FDA guidelines. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of part 225 in the FDA guidelines.
 14. The term medicated premix means a Type A medicated article as defined in 558.3 in the FDA guidelines. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of part 226 in the FDA guidelines.
 15. Quality control unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
 16. Strength means
 - i. the concentration of the drug substance (e.g., weight/weight, weight/volume, or unit dose/volume basis) and/or
 - ii. the potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, e.g., in terms of units by reference to a standard).
 17. Theoretical yield means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.
 18. Actual yield means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.
 19. Percentage of theoretical yield means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.
 20. Acceptance criteria means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).
 21. Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to ensure that the sample accurately portrays the material being sampled.
 22. Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

Part 211—cGMP for Finished Pharmaceuticals

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- Subpart A—General Provisions
- 211.1 Scope
 - a. The regulations in this part contain the minimum cGMP for preparation of drug products for administration to humans or animals.
 - b. The cGMP regulations in this chapter as they pertain to drug products; in parts 600 through 680 in the FDA guidelines, as they pertain to drugs that are also biological products for human use; and in part

2171 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts in the FDA guidelines, or in parts 600 through 680 in the FDA guidelines, or in part 1271 in the FDA guidelines, the regulation specifically applicable to the drug product in question shall supersede the more general.

- c. Pending consideration of a proposed exemption, published in the federal register of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 in the FDA guidelines, and where applicable, parts 113 to 129 in the FDA guidelines, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under cGMP.
- 211.3 Definitions: The definitions set forth in 210.3 of this chapter apply in this part.
- Subpart B—Organization and Personnel
- 211.22 Responsibilities of quality control unit
- a. There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to ensure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
 - b. Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.
 - c. The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.
 - d. The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.
- 211.25 Personnel qualifications
- a. Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in cGMP (including the cGMP regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions.

- b. Training in cGMP shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with cGMP requirements applicable to them.
- c. Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.
- d. There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

211.28 Personnel responsibilities

- a. Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.
- b. Personnel shall practice good sanitation and health habits.
- c. Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.
- d. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

211.34 Consultants: Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

211.42 Design and construction features

- a. Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations.
- b. Any such building shall have 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, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

- c. Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures.

1. Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;
2. holding rejected components, drug product containers, closures, and labeling before disposition;
3. storage of released components, drug product containers, closures, and labeling;
4. storage of in-process materials;
5. manufacturing and processing operations;
6. packaging and labeling operations;
7. quarantine storage before release of drug products;
8. storage of drug products after release;
9. control and laboratory operations;
10. aseptic processing, which includes as appropriate:
 - i. floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
 - ii. temperature and humidity controls;
 - iii. an air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or non-laminar;
 - iv. a system for monitoring environmental conditions;
 - v. a system for cleaning and disinfecting the room and equipment to produce aseptic conditions;
 - vi. a system for maintaining any equipment used to control the aseptic conditions.

- d. Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

211.44 Lighting: Adequate lighting shall be provided in all areas.

211.46 Ventilation, air filtration, air heating and cooling

- a. Adequate ventilation shall be provided.
- b. Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
- c. Air filtration systems, including prefilters and particulate matter air filters, shall be used, when appropriate, on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.
- d. Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

211.48 Plumbing

- a. Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards shall not be permitted in the potable water system.
- b. Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

211.50 Sewage and refuse: Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

211.52 Washing and toilet facilities: Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

211.56 Sanitation

- a. Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition. Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.
- b. There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.
- c. There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 USC 135).
- d. Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

211.58 Maintenance: Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Subpart D—Equipment

211.63 Equipment design, size, and location: Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitable location to facilitate operations for its intended use and for its cleaning and maintenance.

211.65 Equipment construction

- a. Equipment shall be constructed such that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
- b. Any substances required for operation, such as lubricants or coolants, shall not come into contact with

components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

211.67 Equipment cleaning and maintenance

- a. Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
- b. Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:
 1. Assignment of responsibility for cleaning and maintaining equipment
 2. Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules
 3. A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to ensure proper cleaning and maintenance
 4. Removal or obliteration of previous batch identification
 5. Protection of clean equipment from contamination prior to use
 6. Inspection of equipment for cleanliness immediately before use
- c. Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in 211.180 and 211.182.

211.68 Automatic, mechanical, and electronic equipment

- a. Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance. Written records of those calibration checks and inspections shall be maintained.
- b. Appropriate controls shall be exercised over computer or related systems to ensure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to ensure

that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

211.72 Filters: Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22-micron maximum mean porosity (0.45 microns if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. Use of an asbestos-containing filter, with or without subsequent use of a specific non-fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the FDA that use of a non-fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the injectable drug product.

Subpart E—Control of Components and Drug Product Containers and Closures

211.80 General requirements

- a. There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.
- b. Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.
- c. Bagged or boxed components of drug product containers, or closures, shall be stored off the floor and suitably spaced to permit cleaning and inspection.
- d. Each container or grouping of containers for components or drug product containers, or closures, shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

211.82 Receipt and storage of untested components, drug product containers, and closures

- a. Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.
- b. Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of 211.80.

211.84 Testing and approval or rejection of components, drug product containers, and closures

- a. Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.
- b. Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be

based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by 211.170.

- c. Samples shall be collected in accordance with the following procedures:
 1. The containers of components selected shall be cleaned where necessary, by appropriate means.
 2. The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.
 3. Sterile equipment and aseptic sampling techniques shall be used when necessary.
 4. If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.
 5. Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.
 6. Containers from which samples have been taken shall be marked to show that samples have been removed from them.
- d. Samples shall be examined and tested as follows:
 1. At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.
 2. Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.
 3. Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.
 4. When appropriate, components shall be microscopically examined.
 5. Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.
 6. Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

- e. Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

211.86 Use of approved components, drug product containers, and closures: Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

211.87 Retesting of approved components, drug product containers, and closures: Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with 211.84 as necessary, for example, after storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the component, drug product container, or closure.

211.89 Rejected components, drug product containers, and closures: Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.94 Drug product containers and closures

- a. Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- b. Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
- c. Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to ensure that they are suitable for their intended use.
- d. Standards or specifications; methods of testing; and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

Subpart F—Production and Process Controls

211.100 Written procedures; deviations

- a. There shall be written procedures for production and process control designed to ensure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.
- b. Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

211.101 Charge-in of components

Written production and control procedures shall include the following, which are designed to ensure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess.

a. The batch shall be formulated with the intent to provide not less than 100% of the labeled or established amount of active ingredient.

b. Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information.

1. Component name or item code
2. Receiving or control number
3. Weight or measure in new container
4. Batch for which component was dispensed, including its product name, strength, and lot number

c. Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to ensure that

1. the component was released by the quality control unit;
2. the weight or measure is correct as stated in the batch production records;
3. the containers are properly identified.

d. Each component shall be added to the batch by one person and verified by a second person.

211.103 Calculation of yield: Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

211.105 Equipment identification

a. All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

b. Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

211.110 Sampling and testing of in-process materials and drug products

a. To ensure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate.

1. Tablet or capsule weight variation
2. Disintegration time

3. Adequacy of mixing to ensure uniformity and homogeneity
 4. Dissolution time and rate
 5. Clarity, completeness, or pH of solutions
- b. Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall ensure that the drug product and in-process material conform to specifications.
 - c. In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, for example, at commencement or completion of significant phases or after storage for long periods.
 - d. Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.111 Time limitations on production: When appropriate, time limits for the completion of each phase of production shall be established to ensure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

211.113 Control of microbiological contamination

- a. Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.
- b. Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

211.115 Reprocessing

- a. Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to ensure that the reprocessed batches will conform with all established standards, specifications, and characteristics.
- b. Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G—Packaging and Labeling Control

211.122 Materials examination and usage criteria

- a. There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.
- b. Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

- c. Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.
- d. Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.
- e. Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.
- f. Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.
- g. If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:
 1. dedication of labeling and packaging lines to each different strength of each different drug product;
 2. use of appropriate electronic or electromechanical equipment to conduct 100% examination for correct labeling during or after completion of finishing operations; or
 3. use of visual inspection to conduct 100% examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

h. Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to ensure that all imprinting conforms to the print specified in the batch production record.

211.125 Labeling issuance

- a. Strict control shall be exercised over labeling issued for use in drug product labeling operations.
- b. Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.
- c. Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with 211.192. Labeling reconciliation is waived for cut or roll labeling if 100% examination for correct labeling is performed in accordance with 211.122(g)(2).
- d. All excess labeling bearing lot or control numbers shall be destroyed.
- e. Returned labeling shall be maintained and stored in a manner to prevent mix-ups and provide proper identification.
- f. Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

211.130 Packaging and labeling operations

There shall be written procedures designed to ensure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be fol-

lowed. These procedures shall incorporate the following features:

- a. Prevention of mix-ups and cross-contamination by physical or spatial separation from operations on other drug products.
 - b. Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.
 - c. Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.
 - d. Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.
 - e. Inspection of the packaging and labeling facilities immediately before use to ensure that all drug products have been removed from previous operations. Inspection shall also be made to ensure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.
- 211.132 TEP requirements for OTC human drug products
- a. General. The FDA has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for TEP of OTC drug products that will improve the security of OTC drug packaging and help ensure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.
 - b. Requirements for tamper-evident package:
 1. Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale shall package the product in a tamper-evident package, if this product is accessible to the public while held for sale. A tamper-evident package is one having one or more indicators or barriers to entry, which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-evident package may involve an immediate container and closure system or secondary container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.
 2. In addition to the TEP feature described in paragraph (b)(1) of this section, any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.
 - c. Labeling.
 1. To alert consumers to the specific tamper-evident feature(s) used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampules, containers of compressed medical oxygen, or aerosol products that depend upon the power of a liquefied or compressed gas to expel the contents from the container) is required to bear a statement that
 - i. identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section;
 - ii. is prominently placed on the package; and
 - iii. is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.
 2. If the tamper-evident feature chosen to meet the requirements in paragraph (b) of this section uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say "for your protection, this bottle has an imprinted seal around the neck."
 - d. Request for exemptions from packaging and labeling requirements. A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under 10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from the Tamper-Evident Packaging Rule." The petition is required to contain the following:
 1. The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class
 2. The reasons that the drug product's compliance with the TEP or labeling requirements of this section is unnecessary or cannot be achieved
 3. A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration
 4. Other information justifying an exemption
 - e. OTC drug products subject to approved new drug applications. Holders of approved new drug applications for OTC drug products are required under 314.70 in the FDA guidelines to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under 314.70(c) in the FDA guidelines. Manufacturing changes by which capsules are to be sealed require prior FDA approval under 314.70(b) in the FDA guidelines.

- f. Poison Prevention Packaging Act of 1970. This section does not affect any requirements for “special packaging” as defined under 310.3(l) in the FDA guidelines and required under the Poison Prevention Packaging Act of 1970.

211.134 Drug product inspection

- a. Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.
- b. A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.
- c. Results of these examinations shall be recorded in the batch production or control records.

211.137 Expiration dating

- a. To ensure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166.
- b. Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in 211.166.
- c. If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and un-reconstituted drug products.
- d. Expiration dates shall appear on labeling in accordance with the requirements of 201.17 in the FDA guidelines.
- e. Homeopathic drug products shall be exempt from the requirements of this section.
- f. Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt from the requirements of this section.
- g. New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.
- h. Pending consideration of a proposed exemption, published in the federal register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

Subpart H—Holding and Distribution

211.142 Warehousing procedures

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

- a. Quarantine of drug products before release by the quality control unit
- b. Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected

211.150 Distribution procedures

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

- a. A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this

requirement is permitted if such deviation is temporary and appropriate.

- b. A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart I—Laboratory Controls

211.160 General requirements

- a. The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.
- b. Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:
 1. Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
 2. Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.
 3. Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
 4. The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

211.165 Testing and release for distribution

- a. For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or

pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

- b. There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.
- c. Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.
- d. Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to ensure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.
- e. The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).
- f. Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

211.166 Stability testing

- a. There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:
 1. Sample size and test intervals based on statistical criteria for each attribute examined to ensure valid estimates of stability
 2. Storage conditions for samples retained for testing
 3. Reliable, meaningful, and specific test methods
 4. Testing of the drug product in the same container-closure system as that in which the drug product is marketed
 5. Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted
- b. An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

- c. For homeopathic drug products, the requirements of this section are as follows:
 1. There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.
 2. Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

- d. Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

211.167 Special testing requirements

- a. For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.
- b. For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.
- c. For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

211.170 Reserve samples

- a. An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:
 1. For an active ingredient in a drug product other than those described in paragraph (a)(2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.
 2. For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for
 - i. three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less, or
 - ii. six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.
 3. For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.
- b. An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall

be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

1. For a drug product other than those described in paragraphs (b)(2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.
2. For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for
 - i. three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less, or
 - ii. six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.
3. For an OTC drug product that is exempt for bearing an expiration date under 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

211.173 Laboratory animals: Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that ensures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

211.176 Penicillin contamination: If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in *Procedures for Detecting and Measuring Penicillin Contamination in Drugs*, which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD-470), Center for Drug Evaluation and Research, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740 (www.fda.gov/cder/dmpq/penicillin.pdf).

Subpart J—Records and Reports

211.180 General requirements

- a. Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating

because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch.

- b. Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.
- c. All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.
- d. Records required under this part may be retained either as original records or as copies, such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.
- e. Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for
 1. a review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch;
 2. a review of complaints, recalls, returned or salvaged drug products, and investigations conducted under 211.192 for each drug product.
- f. Procedures shall be established to ensure 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 any investigations conducted under 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the FDA, or any regulatory actions relating to GMP brought by the FDA.

211.182 Equipment cleaning and use log: A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

211.184 Component, drug product container, closure, and labeling records

These records shall include the following:

- a. The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.
- b. The results of any test or examination performed [including those performed as required by 211.82(a), 211.84(d), or 211.122(a)] and the conclusions derived therefrom.
- c. An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.
- d. Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with 211.122(c) and 211.130(c).
- e. The disposition of rejected components, drug product containers, closure, and labeling.

211.186 Master production and control records

- a. To ensure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.
- b. Master production and control records shall include:
 1. The name and strength of the product and a description of the dosage form
 2. The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product and a statement of the total weight or measure of any dosage unit
 3. A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic
 4. An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records
 5. A statement concerning any calculated excess of component
 6. A statement of theoretical weight or measure at appropriate phases of processing
 7. A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 211.192 is required
 8. A description of the drug product containers, closures, and packaging materials, including a

specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling

9. Complete CMC instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed

211.188 Batch production and control records

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

- a. An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed
- b. Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:
 1. Dates
 2. Identity of individual major equipment and lines used
 3. Specific identification of each batch of component or in-process material used
 4. Weights and measures of components used in the course of processing
 5. In-process and laboratory control results
 6. Inspection of the packaging and labeling area before and after use
 7. A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing
 8. Complete labeling control records, including specimens or copies of all labeling used
 9. Description of drug product containers and closures
 10. Any sampling performed
 11. Identification of the persons performing and directly supervising or checking each significant step in the operation
 12. Any investigation made according to 211.192
 13. Results of examinations made in accordance with 211.134

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

211.194 Laboratory records

- a. Laboratory records shall include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays as follows.
 1. A description of the sample received for testing with identification of source (that is,

location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

2. A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establishes that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. [If the method employed is in the current revision of the *U. S. Pharmacopeia*, National Formulary, AOAC INTERNATIONAL, Book of Methods, (copies may be obtained from AOAC INTERNATIONAL, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877) or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice.] The suitability of all testing methods used shall be verified under actual conditions of use.
 3. A statement of the weight or measure of sample used for each test, where appropriate.
 4. A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.
 5. A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
 6. A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.
 7. The initials or signature of the person who performs each test and the date(s) the tests were performed.
 8. The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.
- b. Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and 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.
 - c. Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.
 - d. Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by 211.160(b)(4).
 - e. Complete records shall be maintained of all stability testing performed in accordance with 211.166.

211.196 Distribution records: Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical

gas products, distribution records are not required to contain lot or control numbers.

211.198 Complaint files

- a. Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall 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 and, for such drug products, a determination as to the need for an investigation in accordance with 211.192. Such procedures shall 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 FDA in accordance with 310.305 and 514.80 of this chapter.
- b. A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, such written records shall be maintained for 3 years after distribution of the drug product.
 1. The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.
 2. Where an investigation under 211.192 is conducted, the written record shall include the findings of the investigation and follow-up. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with 211.180(c).
 3. Where an investigation under 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

Subpart K—Returned and Salvaged Drug Products

211.204 Returned drug products: Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality, or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards,

specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

211.208 Drug product salvaging: Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

III. AMENDMENTS TO PART 211

- 3. The authority citation for 21 CFR part 211 continues to read as follows:
Authority: 21 USC 321, 351, 352, 355, 360b, 371, 374; 42 USC 216, 262, 263a, 264
- 4. Section 211.48 is amended by revising paragraph (a) to read as follows:
211.48 Plumbing
 - a. Water supplied by the plumbing system of the facility must be safe for human consumption. This water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.
- 5. Section 211.67 is amended by revising paragraph (a) to read as follows:
211.67 Equipment cleaning and maintenance
 - b. Equipment and utensils shall be cleaned, maintained, and sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
- 6. Section 211.68 is amended by adding paragraph (c) to read as follows:
211.68 Automatic, mechanical, and electronic equipment
 - c. Such automated equipment used for performance of operations addressed by 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections for the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section and one person verifies that the operations addressed in those sections are performed accurately by such equipment.
- 7. Section 211.72 is revised to read as follows:
211.72 Filters: Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22-micron maximum mean porosity (0.45 microns if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product.
- 8. Section 211.82 is amended by revising paragraph (b) to read as follows:
211.82 Receipt and storage of untested components, drug product containers, and closures.
 - b. Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, whichever is appropriate, and released. Storage within the area shall conform to the requirements of 211.80.
- 9. Section 211.84 is amended by revising paragraphs (c)(1), (d)(3), and (d)(6) to read as follows:
211.84 Testing and approval or rejection of components, drug product containers, and closures
 - c. ***
 - 1. The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component.
 - d. ***
 - 3. Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.
 - 6. Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.
- 10. Section 211.94 is amended by revising paragraph (c) to read as follows:
211.94 Drug product containers and closures
 - c. Drug product containers and closures shall be clean and, where indicated by the nature of the drug sterilized and processed to remove pyrogenic properties to ensure that they are suitable for their intended use. Such depyrogenation processes shall be validated.
- 11. Section 211.101 is amended by revising paragraphs (c) and (d) to read as follows:
211.101 Charge-in of components.

- c. Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to ensure that
1. the component was released by the quality control unit;
 2. the weight or measure is correct as stated in the batch production records;
 3. the containers are properly identified. If the weighing, measuring, or subdividing operations are performed by automated equipment under 211.68, only one person is needed to ensure conditions of paragraphs (c)(1), (c)(2), and (c)(3) of this section have been met.
- d. Each component shall either be added to the batch by one person and verified by a second person or, if the components are added by automated equipment under 211.68, only verified by one person.
- 12. Section 211.103 is revised to read as follows:
211.103 Calculation of yield: Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person, or, if the yield is calculated by automated equipment under 211.68, be independently verified by one person.
 - 13. Section 211.110 is amended by revising paragraph (a) introductory text and by adding paragraph (a)(6) to read as follows:
211.110 Sampling and testing of in-process materials and drug products
 - a. To ensure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:
 6. Bioburden testing
 - 14. Section 211.113 is amended by revising paragraph (b) to read as follows:
211.113 Control of microbiological contamination.
 - b. Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.
 - 15. Section 211.160 is amended by revising paragraph (b)(1) to read as follows:
211.160 General requirements
 - b. ***
 1. Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
 - 16. Section 211.182 is revised to read as follows:
211.182 Equipment cleaning and use log: A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under 211.68, only the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.
 - 17. Section 211.188 is amended by revising paragraph (b)(11) to read as follows:
211.188 Batch production and control records
 - b. ***
 - ii. Identification of the persons performing and directly supervising or checking each significant step in the operation, or if a significant step in the operation is performed by automated equipment under 211.68, the identification of the person checking the significant step performed by the automated equipment.

IV. U.S. FDA cGMP OVERVIEW CHECKLIST

1. "C" = current dynamic and evolve over time; "GMP" = Good Manufacturing Practices minimal standards
 - a. Not "best" practices unless "best" is, in fact, current minimal
 - b. cGMP not NDA or firm specific
2. Compliance terms and phrases related to cGMP issues
 - a. Adulteration
 - b. Quality controls, quality assurance, quality systems
 - c. Contamination (e.g., lack of assurance of sterility)
 - d. Cross-contamination (e.g., dirty manufacturing facilities)
 - e. Out-of-specification (OoS) findings
 - f. Equipment-related issues, calibration/maintenance
 - g. Standard operating procedures (SOPs)
 - h. Code of Federal Regulations (CFR), Parts 210 and 211
 - i. Form FDA-483 (Inspectional Observations)
 - j. Establishment Inspection Report (EIR)
 - k. Collection Report (CR)
 - l. Regulatory actions: warning Letters, recall, seizure, injunctions, application approvals, suspensions, revocations, and import detention Good Manufacturing Practice, or GMP
 - m. Good Management Practice, or GMP
 - n. Good Engineering Practice, or GEP
 - o. Good Laboratory Practice, or GLP

- p. Good Safety Practice, or GSP
 - q. Good Clinical Practice, or GCP
 - r. Good Distribution Practice, or GDP
 - s. Good Research Practice, or GRP
 - t. Good Review Management Practice, or GRMP
 - u. Good Recruitment Practice, or GxP
3. Best practice
 - a. A concept of management that asserts that proper processes, checks, and testing can deliver or put out a desired outcome with fewer problems and unforeseen complications
 - b. Definition of processes or methods to do something
 - c. Results in achievement of assurance of quality results and consistency by following the process (the practice) if the process is followed
 - d. In the modern world, the production of goods and services has become complex, dependent on integration of many different specialty activities, which include sophisticated equipment, requiring design, construction, maintenance, and operation
 - e. The central axiom is best practice results in best outcome or good practice results in good outcome (product)
 - f. Applied in sales, manufacturing, teaching, programming software, road construction, health care, insurance, and accounting
 4. Good operating practice
 - a. A strategy for management of activities to produce a desirable outcome/product
 - b. Five hundred and more organizations, institutes, consultants, Web sites offering assistance
 5. cGMP for pharmaceuticals
 - a. Established by government
 - b. Requirement of law
 - c. Definition, or development
 6. U.S. cGMP legal principles
 - a. "Adulterated" drug due to lack of cGMPs
 - b. Defined in 501(a)(2)(B) of FD&C Act: "A drug shall be deemed adulterated: . . . if 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 the Act as to safety and has that identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."
 - c. Quality built into product
 - i. By "taking care" in making medicine
 - ii. Can't "test" into product the quality
 - iii. Controls provided by the practice
 - d. Without/Inadequate cGMP
 - i. Product(s) adulterated (defects need not be shown)
 - ii. Firm and its management are responsible
 - e. Potential problems from
 - i. Noncompliance with cGMP
 - ii. Superpotency or subpotency
 - iii. Contamination
 - iv. Safety and efficacy effects
 - v. Misbranding
 7. cGMP requirements apply to
 - a. Finished pharmaceuticals
 - b. Drug substances/APIs
 - c. OTC and Rx products
 - d. NDA and aNDA drug products
 - e. Approved and unapproved drug products
 - f. Investigational New Drug Application (IND) products administered in clinical studies (human or animal)
 8. U.S. cGMP legal principles excluded from the cGMP requirement
 - a. Positron emission tomography, as per FDAMA (own cGMP to be developed)
 - b. Drug products compounded as per Section 503 Pharmacy Compounding (FDAMA)
 9. U.S. cGMP legal principles
 - a. Feasible and valuable
 - b. No threshold for "percentage" in practice
 - c. Doesn't have to be "predominant"
 - d. Enforceable even if nobody is doing it
 - e. Stronger case if someone is doing it
 10. cGMP regulation scope
 - a. Dosage forms for human/vet/biologics
 - b. OTC, Rx, IND, NDA, medical gases
 - c. Not: pharmacies, ingredients, nonclinical research
 11. cGMP regulation
 - a. cGMP for Finished Pharmaceuticals 21 CFR 210, 211
 - b. Substantive
 - c. Force and effect of law
 - d. Constitute major part of (not entire) cGMP
 - e. Establish "what to" do, not "how to" do
 - f. Minimal standards
 - g. Maximum flexibility
 - h. Specific enough to address problems, for example, penicillin contamination control
 - i. Technology neutral
 - j. Scalable
 12. cGMP guidance documents
 - a. Principles
 - i. Not requirements
 - ii. Agency "current thinking"
 - iii. Detailed, technical
 - iv. Expression of "how to" meet "what to" do (requirements)
 - v. Shape industry behavior
 - vi. Offers routes to efficiency in meeting cGMP requirement, evaluation of compliance
 - b. cGMP guidance documents (examples)
 - i. General principles of process validation
 - ii. Compressed medical gases
 - iii. Sterile drug products produced by aseptic processing
 - iv. Guideline on the preparation of investigational new drug products
 - v. Investigating out-of-specification test results for pharmaceutical production
 - vi. Manufacturing, processing, or holding of active pharmaceutical ingredients
 13. cGMP Requirements: 21 CFR Parts 210 and 211 contain the minimum cGMP regulations for the preparation of finished pharmaceuticals for administration to humans and animals and encompass
 - a. Organization and personnel (e.g., quality control unit)
 - b. Buildings and facilities
 - c. Equipment
 - d. Components and drug product containers
 - e. Production and process controls
 - f. Packaging and labeling controls
 - g. Laboratory controls

- h. Holding and distribution
- i. Records and reports
- 14. cGMP regulations
 - a. 21 CFR 210
 - i. Status of the regulations
 - ii. Applicability of the regulations
 - iii. Definitions
 - iv. Batch
 - v. Lot
 - vi. In-process material
 - vii. Quality control unit
 - viii. Representative sample
 - 15. 21 CFR 211
 - a. Subpart A—General Provisions: this is minimum cGMP
 - i. Overview of cGMP requirements in the regulation
 - ii. cGMP regulations
 - b. Subpart B—Organization and Personnel
 - i. There shall be a quality control unit
 - ii. Quality control unit's responsibility to approve/reject
 - c. Subpart C—Buildings and Facilities
 - i. buildings shall be . . . suitable
 - ii. operations to be in specifically defined areas . . . separate . . . Or such other control systems for . . . operations as are necessary to prevent contamination or mix-ups . . . (see list, includes aseptic processing)
 - iii. "separate" facilities for penicillin
 - iv. building . . . shall be . . . clean and sanitary
 - d. Subpart D—Equipment
 - i. surfaces . . . shall not be reactive, additive, or absorptive
 - ii. Equipment . . . shall be cleaned, maintained and sanitized . . .
 - e. Subpart E—Control of Components, Containers, and Closures
 - i. containers and closures . . . handled in a manner to prevent contamination.
 - ii. Testing or examination of c/c/c's
 - iii. Test to identify each component
 - iv. Tests on components for conformance with specs
 - v. Test c/c/c's microscopically, for adulterants, microscopically
 - f. Subpart F—Production and Process Controls
 - i. Written procedures for production and process control
 - ii. Formulated not less than 100%
 - iii. Portions of components identified, examined by a second person before dispensed for use in manufacture
 - iv. Sampling and testing of in-process materials and products, some specified
 - v. Time limits
 - vi. Reprocessing allowed, but controlled
 - g. Subpart G—Packaging and Labeling Controls
 - i. Examination, approval of labels, labeling
 - ii. Strict control over labeling issue, and return to stock
 - iii. Written procedures, physical separation of labeling operations
 - iv. Examination of materials before use
 - v. Inspection of facilities immediately before
 - vi. Tamper-resistant packaging (for OTC products)
 - vii. Expiration dating
 - h. Subpart H—Holding and Distribution
 - i. Quarantine before release
 - ii. Store under appropriate conditions
 - i. Subpart I—Laboratory Controls
 - i. Establish specs, standards, sampling plans, test procedures.
 - ii. Calibration, of laboratory equipment.
 - iii. Test each batch of drug product.
 - iv. Adequate acceptance criteria.
 - v. Validate test methods.
 - vi. Conduct stability program.
 - j. Subpart I—Laboratory Controls
 - i. Special tests
 - ii. Sterility and pyrogenicity
 - iii. Ophthalmic ointments for foreign/abrasive particles
 - iv. Controlled-release products for rate of release
 - v. Keep reserve samples
 - vi. Test non-penicillin products for penicillin when reasonable possibility of exposure to presence of penicillin
 - k. Subpart J—Records and Reports
 - i. Keep records, make available for inspection.
 - ii. Conduct annual review of each drug product for changes to specs, control procedures.
 - iii. Keep equipment clean and use log.
 - iv. Keep component, container, closure, and labeling records.
 - v. Have SOP for master production and control record, maintain record.
 - vi. Use batch production and control records for manufacture, keep records.
 - vii. Records to be reviewed/approved by quality control unit.
 - viii. Complete data derived from all tests necessary to ensure compliance.
 - ix. Distribution records, with lot numbers (except medical gases) complaint files.
 - l. Subpart K—Returned and Salvaged Drug Products
 - i. If conditions cast doubt, returned product shall be destroyed unless proved okay by test, examination, investigation.
 - ii. Salvage only if evidence from tests and inspection show all standards met.
 - 16. cGMP changes
 - a. Change/Update is continuous.
 - b. Establishment inspections.
 - c. Industry changes/problems.
 - d. Defect reports/complaints/recalls.
 - 17. Litigation
 - a. Agency application reviews
 - b. Trade/Scientific literature
 - c. Citizen petitions
 - 18. Input for cGMP changes
 - a. Establishment inspections
 - b. Industry changes/problems
 - c. Defect reports/complaints/recalls
 - 19. cGMP initiative
 - a. Opportunities
 - b. Major advances in manufacturing science/technology
 - c. Advances in the science of quality management (e.g., quality systems approaches)
 - d. Systems-based drug inspection program
 - e. Advances in application of risk analysis/management

- f. Risk management approaches gaining wider acceptance in other regulatory agencies (e.g., EPA, OSHA, IRS)
- 20. cGMP Compliance Programs—Instructions to FDA inspectors
 - a. Drug manufacturing inspections program
 - b. Systems-based assessment of site
 - c. PAI program
 - d. Points to inspect
 - e. Laboratory support
 - f. Regulatory approaches
- 21. Systems-based approach to GMP described in CPGM 7356.002, drug process inspections
 - a. Quality system
 - i. Quality control unit
 - ii. Responsibility and authority to review and approve all
 - iii. Procedures adequate for their intended use
 - iv. Batch production records
 - v. Training/Qualification of personnel
 - vi. Record-keeping systems
 - vii. Quality control unit evaluates
 - viii. Data collected to identify quality problems
 - ix. Annual product reviews, complaints, OoS findings
 - x. Problems to determine what corrective and preventative actions are needed
 - b. Facilities system
 - i. Adequate design to prevent cross-contamination or mix-up
 - ii. Readily cleanable and sanitizing agents effectively used
 - iii. Properly maintained
 - iv. Adequate storage conditions for components
 - v. Air-handling systems functioning and separate if necessary (e.g. penicillin, beta-lactams, steroids, hormones, cytotoxics)
 - vi. Control system in place for implementing changes
 - vii. Adequate lighting, temperature, humidity controls
 - c. Equipment system
 - i. Installation and operational qualification where appropriate
 - ii. Adequate design, size, and location
 - iii. Equipment surfaces should not be reactive, additive, or absorptive
 - iv. Controls to prevent contamination
 - v. Cleaning procedures and cleaning validation
 - vi. Calibration and maintenance
 - vii. Equipment use logs
 - viii. Control system for implementing changes in the equipment
 - d. Materials system
 - i. Components, drug product containers, and closures.
 - ii. Quarantined until tested or examined and released (or rejected).
 - iii. Representative samples collected, tested, or examined (e.g., containers and closures should not be additive, reactive, or absorptive to the drug product).
 - iv. At least one specific identity test is conducted on each lot of each component.
 - v. A visual identification is conducted on each lot of containers and closures.
 - e. Production system
 - i. Components—"charge in"
 - ii. Formulation/Manufacturing at not less than 100%
 - iii. Equipment properly identified—contents
 - iv. Actual yields and percentage of theoretical yields
 - v. Containers and closures—cleaning/sterilization/depyrogenation
 - vi. Batch production documentation—contemporaneous and complete
 - vii. Time limits for completion of phases of production
 - viii. In-process controls, tests, and examinations (e.g., pH, adequacy of mix, weight variation, clarity)
 - ix. Environmental controls—prevent objectionable microorganisms
 - x. Process validation
 - xi. Computerized or automated processes—validation and security
 - xii. Change control
 - f. Packaging and labeling system
 - i. Adequate storage controls for labels and labeling—both approved and returned after issued
 - ii. Control of labels which are similar in size, shape, and color for different products
 - iii. Cut labels require 100% verification
 - iv. Packaging records include specimens of all labels used
 - v. Control of issuance/reconciliation of labels and labeling
 - vi. Examination of the labeled finished product
 - vii. Physical/Spatial separation between different labeling and packaging lines
 - viii. Line clearance, inspection, and documentation
 - ix. Conformance to TEP packaging requirements—OTC
 - g. Laboratory control system
 - i. Staffing
 - ii. Equipment and facilities
 - iii. Calibration and maintenance of analytical instruments and equipment (e.g., system suitability checks on chromatographic systems)
 - iv. Reference standards
 - v. Specifications, standards, and representative sampling plans
 - vi. Validation/Verification of analytical methods
 - vii. Complete analytical records—includes retention of raw data
 - viii. Documented investigation into any unexpected discrepancy/OoS
 - ix. Reserve samples
 - x. Stability testing program
 - h. cGMP implementation tools
 - i. Compliance policy guides.
 - ii. Specific actions we do related to cGMP.
 - iii. Examples: Subchapter 410—Bulk Drugs.
 - iv. The regulations for finished pharmaceuticals will be applied as guidelines for bulk drugs.

- v. Subchapter 420—Compendial (USP)/Test Requirements. Example: USP not required for release test.
- vi. Other subchapters.
- vii. Labeling and repackaging
- viii. Stability/Expiration
- ix. Process Validation
- x. Other product-specific validation protocols

V. DRUG MASTER FILES AND CERTIFICATIONS

A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an IND, an NDA, an abbreviated New Drug Application (aNDA), another DMF, an export application, or amendments and supplements to any of these.

A DMF is *not* a substitute for an IND, NDA, aNDA, or export application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, aNDA, or an export application.

This guideline does not impose mandatory requirements [21 CFR 10.90(b)]. It does, however, offer guidance on acceptable approaches to meeting regulatory requirements. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable.

DMFs are provided for in 21 CFR 314.420.

DMFs are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or aNDA directly rather than establishing a new DMF.

A. Types of DMFs

a. *Type I*: Manufacturing Site, Facilities, Operating Procedures, and Personnel. A Type I DMF is recommended for a person outside of the United States to assist FDA in conducting on-site inspections of their manufacturing facilities. The DMF should describe the manufacturing site, equipment capabilities, and operational layout. A Type I DMF is normally not needed to describe domestic facilities, except in special cases, such as when a person is not registered and not routinely inspected. The description of the site should include acreage, actual site address, and a map showing its location with respect to the nearest city. An aerial photograph and a diagram of the site may be helpful. A diagram of major production and processing areas is helpful for understanding the operational layout. Major equipment should be described in terms of capabilities, application, and location. Make and model would not normally be needed unless the equipment is new or unique. A diagram of major corporate organizational elements, with key manufacturing, quality control, and quality assurance positions highlighted, at both the manufacturing site and corporate headquarters, is also helpful.

- b. *Type II*: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product. A Type II DMF should, in general, be limited to a single drug intermediate, drug substance, drug product, or type of material used in their preparation. Summarize all significant steps in the CMCs of the drug intermediate or substance. Manufacturing procedures and controls for finished dosage forms should ordinarily be submitted in an IND, NDA, aNDA, or export application. If this information cannot be submitted in an IND, NDA, aNDA, or export application, it should be submitted in a DMF.
- c. *Type III*: Packaging Material. Each packaging material should be identified by the intended use, components, composition, and controls for its release. The names of the suppliers or fabricators of the components used in preparing the packaging material and the acceptance specifications should also be given. Data supporting the acceptability of the packaging material for its intended use should also be submitted as outlined in the *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics*. Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross-reference to another document.
- d. *Type IV*: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation. Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods. Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross-reference to another document. Usually, the official compendia and FDA regulations for color additives (21 CFR Parts 70 through 82), direct food additives (21 CFR Parts 170 through 173), indirect food additives (21 CFR Parts 174 through 178), and food substances (21 CFR Parts 181 through 186) may be used as sources for release tests, specifications, and safety. Guidelines suggested for a Type II DMF may be helpful for preparing a Type IV DMF. The DMF should include any other supporting information and data that are not available by cross-reference to another document.
- e. *Type V*: FDA-Accepted Reference Information. FDA discourages the use of Type V DMFs for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMFs.

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.

Airlock—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 airlock is designed for use either by people or for goods and/or equipment.

- API Starting Material**—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.
- Authorized Person**—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.
- Batch (or Lot)**—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes such 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.
- 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 of 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, storage or transport.
- Contract Manufacturer**—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.
- Critical**—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.
- Critical Operation**—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.
- Cross-Contamination**—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.
- Deviation**—Departure from an approved instruction or established standard.
- Drug (Medicinal) Product**—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)
- Drug Substance**—See Active Pharmaceutical Ingredient.
- Expiry Date (or Expiration Date)**—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.
- Finished Product**—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.
- Impurity**—Any component present in the intermediate or API that is not the desired entity.
- Impurity Profile**—A description of the identified and unidentified impurities present in an API.
- In-Process Control**—Checks performed during production to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.
- Intermediate**—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

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

Lot—See Batch.

Lot Number—See Batch Number.

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

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

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

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

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

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

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

Packaging—All operations, including filling and labeling, that a bulk product has to undergo 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, etc).

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. This standard can be

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 pre-approved as part of the marketing authorization.

Retest Date—The date when a material should be re-examined 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 pre-approved 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 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.

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

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

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

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

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

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

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

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

		Compliance 1 2 3 ^a	Remarks	EU Guide
	Water			
6.58	Loop system for purified water?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. 4
6.59	Antimicrobial treatment of purified water?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. 4
6.60	Loop system for water for injection?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid dead legs?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. 4
6.62	Regular microbiological monitoring?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. 4
6.63	Regular endotoxin control?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. 4
	Special requirements for sterile and aseptic products			Suppl.
	Rooms and equipment			
6.64	Access of staff and materials to clean areas <i>only</i> through airlocks?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		1
6.66	Rooms classified according to the EC Guide?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
	Classification for products to be sterilized:			
6.67	<ul style="list-style-type: none"> Solution preparation (EC: class C, with special precautions class D) 	Class:		5
6.68	<ul style="list-style-type: none"> Filling (EC: under LF in class C) 	Class:		5
	Classification for aseptic products			
6.69	<ul style="list-style-type: none"> Handling of starting materials that can be sterile filtered (EC: class C) 	Class:		6
6.70	<ul style="list-style-type: none"> Handling of starting materials that cannot be sterile filtered (EC: class A in class B) 	Class:		6
6.71	Handling and filling of bulk (EC: class A in Class B)	Class:		6
6.72	All rooms easy to clean/disinfect?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		17
6.73	Doors, windows, frames, lighting, etc. without edges?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		18
6.74	Suspended ceilings (if yes: sealed)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		19
6.75	Traps constructed to avoid microb. contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		21
6.76	Appropriate constructed changing rooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		22
6.77	Measures against opening of both doors of airlocks?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		23
6.78	Overpressure gradient from cleanest areas to others?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		24
6.79	AHU validated and regularly revalidated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		25
6.80	Control instruments for pressure gradient?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		26
6.81	Warning system for errors in air supply?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		26
6.82	Recording of pressure gradients?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		26
6.83	Do conveyor belts leave sterile areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		28
6.84	Maintenance works outside from clean areas possible?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		28
6.85	Cleaning and disinfection procedure after maintenance works?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		29
6.86	Regular revalidation of all equipment and systems?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		32
	<ul style="list-style-type: none"> Disinfection methods? 			
6.89	Microb. monitoring of cleaning and disinfection agents?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		33

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

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

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

		Compliance 1 2 3 ^a	Remarks	EU Guide
	Do records receipt include:			
8.10	• Product name on labels and delivery note?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.11	• Internal name and code?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.12	• Receiving date?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.13	• Name of supplier and/or manufacturer?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.14	• Batch number of supplier?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.15	• Total quantity and number of containers?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.16	• Allocated internal batch number?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.17	SOPs for labeling, quarantine and storage conditions of all incoming goods available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.21
	Sampling procedures (SOPs) include:			
8.18	• Authorized sampling personnel?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.22
8.19	• Methods, equipment and quantities?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.22
8.20	• Safety measures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.3
8.22	Is the master formula approved and signed by the authorized persons?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.3
	The master formula includes:			
8.23	• Product name and code?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14a
8.24	• Description of galenical form, dosage, and batch size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14b
8.25	• All active ingredients with name, code, and weight?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14c
8.26	• All excipients used during manufacture with name, code, and weight?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14c
8.27	• Yields with limits?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14d
	Does the working procedure include:			
8.28	• The production line?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15a
8.29	• Equipment to be used?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15a
8.30	• Reference to methods for cleaning, assembling, and calibration of machines?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15b
8.31	• Detailed stepwise manufacturing prescription?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15c
8.32	• IPCs to be performed with limits?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15d
8.33	• Precautions to be followed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15e
8.34	Are batch records kept for each batch processed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17
	Do batch records include:			
8.35	• Protocol of line clearance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17
8.36	• Name of the product and batch no.?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17a
8.37	• Date and time of start and end of production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17b
8.38	• Name and initials of responsible workers for each step?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17c, d
8.39	• Batch and analytical no. and actual weight of all starting materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17e
8.40	• Equipment used?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17f
8.41	• Results of IPCs with initials of person who carries them out?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17g
8.42	• Yields of the relevant manufacturing steps?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17h
8.43	• Detailed notes on problems and process deviations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17i

		Compliance 1 2 3 ^a	Remarks	EU Guide
8.44	Records on reprocessing of batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	Packaging instructions			
8.45	Packaging instructions for each product, package size, and presentation?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.16
	Do they include:			
8.46	• Product name?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.16a
8.47	• Description of galenical form and strength?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.16b
8.48	• Package size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17c
8.49	• List of all packaging materials with code for a standard batch size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17d
8.50	• Samples of printed packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17e
8.51	• Special precautions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17f
8.52	• Description of the process and equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17g
8.53	• IPCs to be performed with sampling instruction?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18
	Do the packaging batch records include:			
8.55	• Protocol of line clearance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18
8.56	• Name of the product?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18a
8.57	• Date and time when operations have been performed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18b
8.58	• Name of the responsible person?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18c
8.59	• Initials of workers carrying out operations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18d
8.60	• Notes on identity checks and conformity with packaging instructions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18e
8.61	• Results of IPCs	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18e
8.62	• Details of operations and equipment used?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18f
8.63	• Samples of printed packaging materials with codes (MFD, EXP, Batch no., etc.)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18g
8.64	• Record of problems and process deviations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18h
8.65	• Quantities of packaging materials delivered, used, destroyed, or returned?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18i
8.66	• No. of packs consumed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18j
	Testing			
	Do the written testing procedures include:			
8.67	• Test methods?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.23
8.68	• Equipment for testing?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.23
8.69	Tests documented?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.24
8.71	Final release by authorized person?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.24
8.72	Records about distribution of each batch?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.25
	Procedures and protocols about			
8.73	• validation?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.74	• setup and calibration of equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.75	• maintenance, cleaning, and disinfection?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26

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

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

		Compliance 1 2 3 ^a	Remarks	EU Guide
9.42	Reference samples retained for validity plus 1 year?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14
9.43	Storage of reference samples under the recommended storage conditions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14
9.44	Finished products stored in the final packaging?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14
9.46	Sample room secure?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.47	Sample room neatly organized and not overcrowded?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	Testing			
9.48	Are the applied analytical methods validated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.15
9.49	Analytical methods in compliance with the registration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.16
9.50	Are all results recorded and checked for correctness?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.16
9.51	Are all calculations checked?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.16
9.52	Do the testing protocols contain 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?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.17
9.53	Are all IPC methods in production approved by QC?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.2
9.56	Are reagents for prolonged use labeled with date of the preparation? sign of the preparator?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.20
9.57	Are unstable reagents labeled with expiry date? storage conditions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.20
9.58	Are volumetric solutions labeled with the last date of standardization? last current factor?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.20
9.59	Are reference standards labeled with name and potency suppliers' reference date of receipt date of expiry	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.21
9.60	Are reference standards stored properly and under the control of a designated person?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
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?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		

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

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

		Compliance 1 2 3 ^a	Remarks	EU Guide
13	AUDIT OF SUPPLIERS			2.7
13.1	Supplier audits performed for excipients? active substances? packaging material?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		

^a1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

Guideline on the Common Technical Document for the Registration of Pharmaceuticals for Human Use

The International Conference on Harmonization (www.ich.org) has developed a universal format for the registration of pharmaceutical products in the member country states. It took decades to agree on the nature, structure, and substance of this document—it is called Common Technical Document (CTD). This chapter provides an overview of the technical details and data required to complete this filing and to appreciate the great complexity involved in organizing this document. A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between Regulatory Authorities will be simplified. Whether a firm plans to file this document or not, preparing this for every product manufactured helps in cGMP compliance. Provided in this chapter are details regarding the agreed upon common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities.

BACKGROUND

Through the ICH process, considerable harmonization has been achieved among the three regions in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonization of the organization of the registration documents. Each region has its own requirements for the organization of the technical reports in the submission and for the preparation of the summaries and tables. In Japan, the applicants must prepare the GAIYO, which organizes and presents a summary of the technical information. In Europe, expert reports and tabulated summaries are required, and written summaries are recommended. The U.S. FDA has guidance regarding the format and content of the New Drug Application. To avoid the need to generate and compile different registration dossiers, this guideline describes a format for the CTD that will be acceptable in all three regions.

SCOPE OF THE GUIDELINE

This guideline primarily addresses the organization of the information to be presented in registration applications for new pharmaceuticals (including biotechnology-derived products). No reference is provided here to suggest what studies are required, it merely indicates an appropriate format for the data that have been acquired. Applicants should not modify the overall organization of the CTD as outlined in

the guideline. However, in the nonclinical and clinical summaries, applicants can modify individual formats if needed to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results.

GENERAL PRINCIPLES

Throughout the CTD, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (EU and Japan) and 8.5 × 11" paper (United States). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font, is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module. References should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE).

ORGANIZATION OF THE COMMON TECHNICAL DOCUMENT

The CTD is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

Module 1. Administrative Information and Prescribing Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module 2. Common Technical Document Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacological class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page.

Module 2 should contain seven sections in the following order:

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary

- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary

The organization of these summaries is described in Guidelines for M4Q, M4S, and M4E.

Module 3. Quality

Information on Quality should be presented in the structured format described in Guideline M4Q.

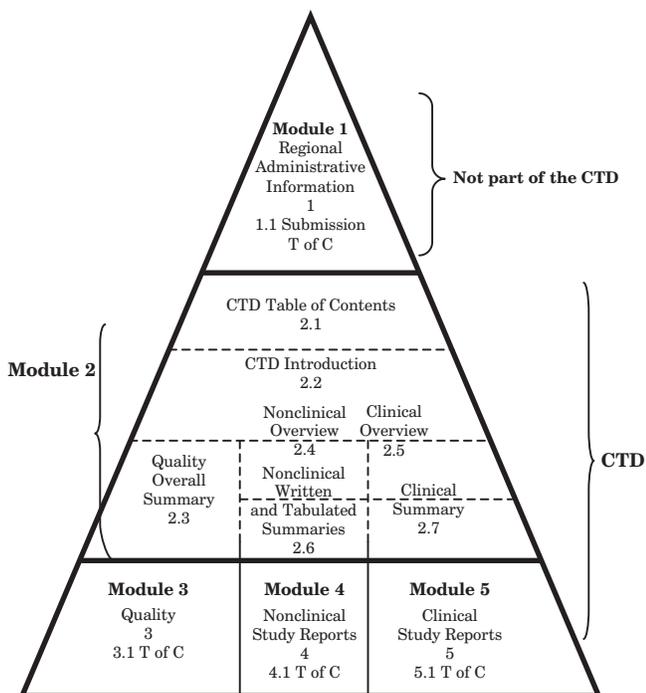
Module 4. Nonclinical Study Reports

The nonclinical study reports should be presented in the order described in Guideline M4S.

Module 5. Clinical Study Reports

The human study reports and related information should be presented in the order described in Guideline M4E.

The overall organization of the CTD is presented on the following pages.



Diagrammatic Representation of the Organization of the ICH CTD Common Technical Document

ORGANIZATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Module 1: Administrative Information and Prescribing Information

- 1.1 Table of Contents of the Submission Including Module 1
- 1.2 Documents Specific to Each Region (e. g., Application Forms, Prescribing Information)

Module 2: Common Technical Document Summaries

- 2.1 Common Technical Document Table of Contents (Modules 2–5)
- 2.2 CTD Introduction
- 2.3 Quality Overall Summary
- 2.4 Nonclinical Overview

- 2.5 Clinical Overview
- 2.6 Nonclinical Written and Tabulated Summaries
 - Pharmacology
 - Pharmacokinetics
 - Toxicology
- 2.7 Clinical Summary
 - Biopharmaceutical Studies and Associated Analytical Methods
 - Clinical Pharmacology Studies
 - Clinical Efficacy
 - Clinical Safety
 - Literature References
 - Synopses of Individual Studies

Module 3: Quality

- 3.1 Table of Contents of Module 3
- 3.2 Body of Data
- 3.3 Literature References

Module 4: Nonclinical Study Reports

- 4.1 Table of Contents of Module 4
- 4.2 Study Reports
- 4.3 Literature References

Module 5: Clinical Study Reports

- 5.1 Table of Contents of Module 5
- 5.2 Tabular Listing of All Clinical Studies
- 5.3 Clinical Study Reports
- 5.4 Literature References

Granularity of Document

The CTD specifies many section headings and numbers. This section provides answer to the following questions:

Could guidance be provided for all modules on headings in relation to document location and the section headings within those documents?

Could guidance also be provided on where in the CTD and eCTD multiple documents can be located in the hierarchy?

As a consequence of this definition, could guidance be given on how documents should be paginated and on what the module Table of Contents should therefore include?

Definition of a Document

A document is defined for a paper submission as a set of pages, numbered sequentially and divided from other documents by a tab (see Document Pagination and Segregation section of this Annex). A document can be equated to a file for an electronic submission. The granularity of the paper and electronic submissions should be equivalent, although if a paper submission is updated to be an electronic submission, some changes in granularity could be introduced to facilitate on-going lifecycle management. In an electronic submission, a new file starts at the same point at which in a paper submission, a tab divides the documents.

In deciding whether one or more documents or files are appropriate, it should be considered that once a particular approach has been adopted, the same approach should be used throughout the life of the dossier since it is the intention that replacement documents/files be provided when information is changed.

The following tables describe the levels in the CTD/eCTD hierarchy at which documents/files should be placed and whether single or multiple documents are appropriate at each point. This describes all sections of a CTD/eCTD but for individual submissions all sections might not be applicable.

Module 2

Module 2	2.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	2.2			
		Introduction		
	2.3 <i>Note 1</i>	2.3.S <i>Note 2</i>	2.3.S.1	
			2.3.S.2	
			2.3.S.3	
			2.3.S.4	
			2.3.S.5	
			2.3.S.6	
			2.3.S.7	
		2.3.P <i>Note 3</i>	2.3.P.1	
			2.3.P.2	
			2.3.P.3	
			2.3.P.4	
			2.3.P.5	
			2.3.P.6	
		2.3.A	2.3.A.1	
			2.3.A.2	
			2.3.A.3	
		2.3.R		
		2.4		
	2.5			
	2.6	2.6.1		
		2.6.2		
		2.6.3		
		2.6.4		
		2.6.5		
		2.6.6		
		2.6.7		
	2.7	2.7.1		
2.7.2				
2.7.3 <i>Note 4</i>				
2.7.4				
2.7.5				
2.7.6				
Key				
Documents rolled up to this level are not considered appropriate				
One document may be submitted at this level				

Note 1: Optionality of granularity for the Quality Overall Summary is provided in order to accommodate different levels of complexity of products. The applicant can choose the level at which the QOS is managed.

Note 2: One document should be submitted for each drug substance.

Note 3: For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P" document.

Note 4: One document for each indication should be submitted, although closely related indications can be within a single document.

Module 3

Module 3 ^{Note 1}	3.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	3.2	3.2.S ^{Note 2}	3.2.S.1	3.2.S.1.1
				3.2.S.1.2
				3.2.S.1.3
			3.2.S.2	3.2.S.2.1
				3.2.S.2.2
				3.2.S.2.3
				3.2.S.2.4
				3.2.S.2.5
				3.2.S.2.6
			3.2.S.3	3.2.S.3.1
				3.2.S.3.2
			3.2.S.4	3.2.S.4.1
				3.2.S.4.2
				3.2.S.4.3
				3.2.S.4.4
				3.2.S.4.5
			3.2.S.5	
			3.2.S.6	
			3.2.S.7	3.2.S.7.1
				3.2.S.7.2
				3.2.S.7.3
			3.2.P.1	
		3.2.P ^{Note 3}	3.2.P.2	3.2.P.2.1 ^{Note 4}
				3.2.P.2.2 ^{Note 4}
				3.2.P.2.3
				3.2.P.2.4
				3.2.P.2.5
				3.2.P.2.6
			3.2.P.3	3.2.P.3.1
				3.2.P.3.2
				3.2.P.3.3

				3.2.P.3.4
				3.2.P.3.5
			3.2.P.4	3.2.P.4.1
				3.2.P.4.2
				3.2.P.4.3
				3.2.P.4.4
				3.2.P.4.5
				3.2.P.4.6
			3.2.P.5	3.2.P.5.1
				3.2.P.5.2
				3.2.P.5.3
				3.2.P.5.4
				3.2.P.5.5
				3.2.P.5.6
			3.2.P.6	
			3.2.P.7	
			3.2.P.8	3.2.P.8.1
				3.2.P.8.2
				3.2.P.8.3
		3.2.A	3.2.A.1	
			3.2.A.2	
			3.2.A.3	
		3.2.R	Note 5	
	3.3	One file		
		per reference ^{Note 6}		
Key				
Documents rolled up to this level are not considered appropriate				
One or multiple documents can be submitted at this level				

Note 1: In choosing the level of granularity for this module, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided in the CTD and eCTD.

Note 2: For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance.

Note 3: For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P," as appropriate.

Note 4: The lower level of headings included in CTD-Q at this point are unlikely to be individual documents or files.

Note 5: Refer to regional guidances.

Note 6: Literature references should be listed in the tables of contents.

Module 4

Module 4	4.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD				
	4.2	4.2.1	4.2.1.1	Studies ^{Note 1}		
			4.2.1.2	Studies ^{Note 1}		
			4.2.1.3	Studies ^{Note 1}		
			4.2.1.4	Studies ^{Note 1}		
		4.2.2	4.2.2.1	Studies ^{Note 1}		
			4.2.2.2	Studies ^{Note 1}		
			4.2.2.3	Studies ^{Note 1}		
			4.2.2.4	Studies ^{Note 1}		
			4.2.2.5	Studies ^{Note 1}		
			4.2.2.6	Studies ^{Note 1}		
			4.2.2.7	Studies ^{Note 1}		
		4.2.3	4.2.3.1	Studies ^{Note 1}		
			4.2.3.2	Studies ^{Note 1}		
			4.2.3.	4.2.3.3.1	Studies ^{Note 1}	
				4.2.3.3.2	Studies ^{Note 1}	
			4.2.3.4	4.2.3.4.1	Studies ^{Note 1}	
				4.2.3.4.2	Studies ^{Note 1}	
				4.2.3.4.3	Studies ^{Note 1}	
				4.2.3.5	4.2.3.5.1	Studies ^{Note 1}
				4.2.3.5.2	Studies ^{Note 1}	
				4.2.3.5.3	Studies ^{Note 1}	
				4.2.3.5.4	Studies ^{Note 1}	
				4.2.3.6	Studies ^{Note 1}	
			4.2.3.7	4.2.3.7.1	Studies ^{Note 1}	
				4.2.3.7.2	Studies ^{Note 1}	
			4.2.3.7.3	Studies ^{Note 1}		
			4.2.3.7.4	Studies ^{Note 1}		
			4.2.3.7.5	Studies ^{Note 1}		
4.2.3.7.6	Studies ^{Note 1}					
	4.2.3.7.7	Studies ^{Note 1}				
	4.3	One file per				
		reference ^{Note 2}				
Key						
Documents rolled up to this level are not considered appropriate						
One or multiple documents can be submitted at this level						

Note 1: Typically, a single document should be provided for each study report included in Module 4. However, where the study report is large (e.g., a carcinogenicity study), the applicant can choose to submit the report as more than one document. In this case, the text portion of the report should be one document and the appendices can be one or more documents. In choosing the level of granularity for these reports, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

Note 2: Literature references should be listed in the tables of contents.

Module 5

Module 5	5.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	5.2			
	5.3	5.3.1	5.3.1.1	Studies ^{Note 1}
			5.3.1.2	Studies ^{Note 1}
			5.3.1.3	Studies ^{Note 1}
			5.3.1.4	Studies ^{Note 1}
		5.3.2	5.3.2.1	Studies ^{Note 1}
			5.3.2.2	Studies ^{Note 1}
			5.3.2.3	Studies ^{Note 1}
		5.3.3	5.3.3.1	Studies ^{Note 1}
			5.3.3.2	Studies ^{Note 1}
			5.3.3.3	Studies ^{Note 1}
			5.3.3.4	Studies ^{Note 1}
			5.3.3.5	Studies ^{Note 1}
		5.3.4	5.3.4.1	Studies ^{Note 1}
			5.3.4.2	Studies ^{Note 1}
		5.3.5 ^{Note 2}	5.3.5.1	Studies ^{Note 1}
			5.3.5.2	Studies ^{Note 1}
			5.3.5.3	Studies ^{Note 1}
	5.3.5.4		Studies ^{Note 1}	
	5.3.6			
	5.3.7	Studies ^{Note 1}		
	5.4	One file per reference ^{Note 3}		
Key				
Documents rolled up to this level are not considered appropriate				
One document can be submitted at this level				
One or multiple documents can be submitted at this level				

Note 1: The applicants should ordinarily provide the study reports as multiple documents (a synopsis, a main body of the study report and appropriate appendices). Appendices should be organized in accordance with the ICH E3 guideline, which describes the content and format of the clinical study report. In choosing the level of granularity for reports the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

Note 2: For applications in support of more than one indication, this section should be repeated for each indication.

Note 3: Literature references should be listed in the tables of content.

Document Pagnation and Segregation

Every document should be numbered starting at page one, except for individual literature references, where the existing journal page numbering is considered sufficient. Applicants need not display the number as “1 of *n*,” where *n* is the total number of pages in the document. Additionally, all pages of a document should include a unique header or footer that briefly identifies its subject matter. In a paper-based drug submission, a similar identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier. An abbreviation of the full section number and title can be used.

If a section contains more than one document, a specific Table of Contents for that section can be included to identify the chronology and titles of the documents contained therein, for example,

- Tab with “3.2.S.4.2 Analytical Procedures”
 - Table of Contents, listing the title of Procedure A, Procedure B, Procedure C
- Tab with “3.2.S.4.2 “Procedure A””;
 - Procedure A (i.e., document, page 1–*n*)
- Tab with “3.2.S.4.2 “Procedure B””;
 - Procedure B (i.e., document, page 1–*n*)
- Tab with “3.2.S.4.2 “Procedure C””;
 - Procedure C (i.e., document, page 1–*n*)

If a section contains only a single document (e.g., 3.2.S.1.1 Nomenclature), only a tab identified by “3.2.S.1.1 Nomenclature” should precede the document.

Section Numbering Within Documents

In order to avoid fifth-, sixth-level subheading numbering (e.g., 2.6.6.3.2.1) within a document, the applicant can use a shortened numbering string. In this case, the document number and the name (e.g., 2.6.6 Toxicology Written Summary) should appear in page headers or footers and then section numbering within the document can be used, for example, 1, 1.1, 2, 3, 3.1, 3.2 etc. Use of the full numbering string (e.g., 2.6.6.3.2.1) is also considered acceptable.

Table of Contents Formatting

Module 2

The 2.1 CTD Table of Contents should go down to the third (e.g., 2.3.S) or fourth (e.g., 2.3.S.1) level, depending on how a document is defined for the Quality Overall Summary. (See Definition of a Document for Module 2.)

Module 3

The Table of Contents provided under section 3.1 should cover the high-level section numbering, the associated section heading, and the volume number in the order that they appear in the drug submission. This Table of Contents would be used to identify the contents of Module 3 as defined in the M4Q guideline. It should go down to the fifth level only (e.g., 3.2.P.2.1). Note that additional subsections and subheadings are defined in the M4Q guideline beyond this level (e.g., under 3.2.P.2) and this formatting should be used within the dossier, despite not being included in the 3.1 Table of Contents. The lower level Table of Contents described under Document Pagnation and Segregation should be excluded from the 3.1 Table of Contents.

At the applicant’s discretion, a Table of Contents can also be included for a particular section that contains multi-

ple documents, in order to identify the chronology and the document subject matter. If there is a desire to introduce additional headers or subsection numbering beyond those which are defined in the M4Q guideline, these should only be included within a document and should be created neither as a separate document nor as a new subsection. In this case, a specific Table of Contents for that document can be included to identify the chronology and titles of the subsections contained therein. These documents and subsections should not appear in the 3.1 Table of Contents.

Furthermore, additional attachments or appendices should not be incorporated into this formatting, except as a document under a section where multiple documents might be provided. In this case, a cross-reference should be made within the relevant section to the attached or appended document. If there is a desire to append or attach additional information to a section that is comprised of only one document, this information should be incorporated within that document.

All Table of Contents title entries should either correspond to heading names and section numbering as defined in the M4Q guideline or to identifiers appearing on tabs (for a paper-based drug submission only), preferably by their full title, which should easily identify any abbreviated title that might be used on the corresponding tab. The Table of Contents should not specify any page numbers.

Literature References should be listed in a Table of Contents specific for this section.

Module 4

The Table of Contents for Module 4 should include all of the numerical items listed in the CTD guideline in order to identify all of the important components of the application (e.g., 4.2.3.5.1 Fertility and Early Embryonic Development) and should continue down to at least the level of the study report. Thus, each study report should be identified in the table of contents. The sections of a study report could be identified in the Module 4 Table of Contents of the dossier or only in the Table of Contents of the individual study report.

Illustration of part of the Module 4 Table of Contents

4.2.3.2	Repeat-Dose Toxicity
Study aa-aaa:	30 day repeat dose toxicity study with drug C in rat
Study bb-bbb:	6 month repeat dose toxicity study with drug C in rat
Study cc-ccc:	30 day repeat dose toxicity study with drug C in dog
Study dd-ddd:	6 month repeat dose toxicity study with drug C in dog
4.2.3.3	Genotoxicity
4.2.3.3.1	In vitro
Study ee-eee:	Ames test with drug C etc.

Module 5

The Table of Contents for Module 5 should include all of the numerical items listed in the CTD guideline in order to identify all of the important components of the application (e.g., 5.3.5.1.1 Placebo-Controlled Trials) and should continue down to at least the level of the clinical study report. Thus, each clinical study report should be identified in the table of contents. The sections of a clinical study report (E3) could be identified in the Module 5 Table of Contents of the dossier or

only in the Table of Contents of the individual clinical study report.

Illustration of part of the Module 5 Table of Contents

5.3.5	Indication Z—Reports of Efficacy and Safety Studies
5.3.5.1	Indication Z—Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication
5.3.5.1.1	Indication Z—Placebo-Controlled Trials
Study xx-xxx:	A double-blind, placebo-controlled trial of drug A in indication Z
Study yy-yyy:	A double blind. . .
5.3.5.1.2	Indication Z—Active Controlled Trials
Study zz-zzz:	A double blind, active controlled trial of drug A versus drug C in indication Z
5.3.5	Indication Q—Reports of Efficacy and Safety Studies
5.3.5.1	Indication Q—Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication etc.

Organization of Module 3

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

2.3: QUALITY OVERALL SUMMARY

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

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

This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).

The *italicized* text below indicates where tables, figures, or other items can be imported directly from Module 3.

INTRODUCTION

The introduction should include proprietary name, nonproprietary name, or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (Name, Manufacturer)

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (Name, Manufacturer)

Information from 3.2.S.2 should include

- information on the manufacturer;
- a brief description of the manufacturing process (including, e.g., reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- a flow diagram, as provided in section 3.2.S.2.2;
- a description of the source and starting material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;
- a discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;
- a description of process validation and/or evaluation, as described in 3.2.S.2.5; and
- a brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

2.3.S.3 Characterization (Name, Manufacturer)

For NCE:

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

For Biotech:

A description of the desired product and product-related substances and a summary of general properties, characteristic features, and characterization data (e.g., primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

For NCE and Biotech:

The QOS should summarize the data on potential and actual impurities arising from the synthesis, manufacture, and/or degradation, and should summarize the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarize the impurity levels in batches of the drug substance used in the nonclinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3.S.4 Control of Drug Substance (Name, Manufacturer)

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials (Name, Manufacturer)

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System (Name, Manufacturer)

A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability (Name, Manufacturer)

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date, or shelf life, where relevant, as described in 3.2.S.7.1.

The postapproval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)**2.3.P.1 Description and Composition of the Drug Product (Name, Dosage Form)**

Information from 3.2.P.1 should be provided.

Composition from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (Name, Dosage Form)

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (Name, Dosage Form)

Information from 3.2.P.3 should include

information on the manufacturer;

a brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality;

a flow diagram, as provided under 3.2.P.3.3; and

a brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients (Name, Dosage Form)

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of Drug Product (Name, Dosage Form)

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterization of impurities should be provided.

Specification(s) from 3.2.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (Name, Dosage Form)

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (Name, Dosage Form)

A brief description and discussion of the information in 3.2.P.7 should be included.

2.3.P.8 Stability (Name, Dosage Form)

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf life and, if applicable, in-use storage conditions and shelf life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The postapproval stability protocol, as described in 3.2.P.8.2, should be provided.

2.3.A APPENDICES**2.3.A.1 Facilities and Equipment (Name, Manufacturer)**

Biotech:

A summary of facility information described under 3.2.A.1 should be included.

2.3.A.2 Adventitious Agents Safety Evaluation (Name, Dosage Form, Manufacturer)

A discussion on measures implemented to control endogenous and adventitious agents in production should be included.

A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.

2.3.A.3 Excipients**2.3.R REGIONAL INFORMATION**

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

Module 3: Quality**SCOPE OF THE GUIDELINE**

This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products as defined in the scope of the ICH Guidelines Q 6A ("NCE") and ICH Guideline Q 6B ("Biotech"). This format may also be appropriate for certain other categories of products. To determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities.

The text following the section titles is intended to be explanatory and illustrative only. The content of these sections should include relevant information described in existing ICH guidelines, but harmonized content is not available for all sections. The "Body of Data" in this guideline merely indicates where the information should be located. Neither the type nor the extent of specific supporting data has been addressed in this guideline, and both may depend upon regional guidance.

The section titles of part 3.2.R (Regional Information) represent examples of typical topics of information that are not common to all ICH regions. Hence, the information to be provided in these sections should be based on the relevant regional guidelines.

3.1 TABLE OF CONTENTS OF MODULE 3

A Table of Contents for the filed application should be provided.

3.2 BODY OF DATA

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.1 General Information (Name, Manufacturer)

3.2.S.1.1 Nomenclature (Name, Manufacturer)

Information on the nomenclature of the drug substance should be provided. For example,

- recommended International Nonproprietary Name (INN);
- compendial name, if relevant;
- chemical name(s);
- company or laboratory code;
- other nonproprietary name(s), for example, national name, United States adopted name (USAN), Japanese accepted name (JAN), British approved name (BAN); and
- chemical abstracts service (CAS) registry number.

3.2.S.1.2 Structure (Name, Manufacturer)

NCE:

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

Biotech:

The schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications and relative molecular mass should be provided, as appropriate.

3.2.S.1.3 General Properties (Name, Manufacturer)

A list should provide physicochemical and other relevant properties of the drug substance, including biological activity for biotech.

Reference ICH Guidelines: Q6A and Q6B.

3.2.S.2 Manufacture (Name, Manufacturer)

3.2.S.2.1 Manufacturer(s) (Name, Manufacturer)

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

3.2.S.2.2 Description of Manufacturing Process and Process Controls (Name, Manufacturer)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example,

NCE:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

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

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

Biotech:

Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage, and shipping conditions.

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g., cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment, and intermediates with acceptance criteria (details provided in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.S.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3, major equipment (details provided in 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment, and intermediates. (Details in 3.2.S.2.4.)

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.S.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.S.2.4).

Filling, storage, and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) The container closure system(s) used for storage of the drug substance (details in 3.2.S.6) and storage and shipping conditions for the drug substance should be described.

Reference ICH Guidelines: Q5A, Q5B, and Q6B.

3.2.S.2.3 Control of Materials (Name, Manufacturer)

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically sourced materials, for example, media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically sourced materials, this can include information regarding the source, manufacture, and characterization. (Details in 3.2.A.2 for both NCE and Biotech.)

Reference ICH Guidelines: Q6A and Q6B.

Biotech:

Control of source and starting materials of biological origin
Summaries of viral safety information for biologically sourced materials should be provided. (Details in 3.2.A.2.)

Source, history, and generation of the cell substrate

Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D.

Cell banking system, characterization, and testing

Information on the cell banking system, quality control activities, and cell line stability during production and storage [including procedures used to generate the Master and Working Cell Bank(s)] should be provided as described in Q5B and Q5D.

Reference ICH Guidelines: Q5A, Q5B, Q5C, and Q5D.

3.2.S.2.4 Controls of Critical Steps and Intermediates (Name, Manufacturer)

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

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

Reference ICH Guidelines: Q6A and Q6B.

Additionally for Biotech: Stability data supporting storage conditions should be provided.

Reference ICH Guideline: Q5C.

3.2.S.2.5 Process Validation and/or Evaluation (Name, Manufacturer)

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

Biotech:

Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The plan for conducting the study should be described and the results, analysis, and conclusions from the executed study or studies should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

3.2.S.2.6 Manufacturing Process Development (Name, Manufacturer)

NCE:

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q3A.

Biotech:

The developmental history of the manufacturing process, as described in 3.2.S.2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance (see Q6B for additional guidance). A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q6B.

3.2.S.3 Characterization (Name, Manufacturer)

3.2.S.3.1 Elucidation of Structure and Other Characteristics (Name, Manufacturer)

NCE:

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

Reference ICH Guideline: Q6A.

Biotech:

For desired product and product-related substances, details should be provided on primary, secondary, and higher-order structure, posttranslational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant.

Reference ICH Guideline: Q6B.

3.2.S.3.2 Impurities (Name, Manufacturer)

Information on impurities should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q5C, Q6A, and Q6B.

3.2.S.4 Control of Drug Substance (Name, Manufacturer)

3.2.S.4.1 Specification (Name, Manufacturer)

The specification for the drug substance should be provided.

Reference ICH Guidelines: Q6A and Q6B.

3.2.S.4.2 Analytical Procedures (Name, Manufacturer)

The analytical procedures used for testing the drug substance should be provided.

Reference ICH Guidelines: Q2A and Q6B.

3.2.S.4.3 Validation of Analytical Procedures (Name, Manufacturer)

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B.

3.2.S.4.4 Batch Analyses (Name, Manufacturer)

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

Reference ICH Guidelines: Q3A, Q3C, Q6A, and Q6B.

3.2.S.4.5 Justification of Specification (Name, Manufacturer)

Justification for the drug substance specification should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q6A, and Q6B.

3.2.S.5 Reference Standards or Materials (Name, Manufacturer)

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

Reference ICH Guidelines: Q6A and Q6B.

3.2.S.6 Container Closure System (Name, Manufacturer)

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

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

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

3.2.S.7 Stability (Name, Manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (Name, Manufacturer)

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

Reference ICH Guidelines: Q1A, Q1B, and Q5C.

3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment (Name, Manufacturer)

The postapproval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A and Q5C.

3.2.S.7.3 Stability Data (Name, Manufacturer)

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

Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B, and Q5C.

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

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

- description of the dosage form;
- composition, that is list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications);
- description of accompanying reconstitution diluent(s); and
- type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Reference ICH Guidelines: Q6A and Q6B.

3.2.P.2 Pharmaceutical Development (Name, Dosage Form)

The pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and

describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance, and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

Reference ICH Guidelines: Q6A and Q6B.

3.2.P.2.1 Components of the Drug Product (Name, Dosage Form)

3.2.P.2.1.1 Drug substance (name, dosage form)

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

For combination products, the compatibility of drug substances with each other should be discussed.

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

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

3.2.P.2.2 Drug Product (Name, Dosage Form)

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

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

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

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

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

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

3.2.P.2.3 Manufacturing Process Development (Name, Dosage Form)

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

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

3.2.P.2.4 Container Closure System (Name, Dosage form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping), and use of the drug product should be discussed. This discussion should consider, for example, choice of materials, protection

from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

3.2.P.2.5 Microbiological Attributes (Name, Dosage Form)

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

3.2.P.2.6 Compatibility (Name, Dosage Form)

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

3.2.P.3 Manufacture (Name, Dosage Form)

3.2.P.3.1 Manufacturer(s) (Name, Dosage Form)

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

3.2.P.3.2 Batch Formula (Name, Dosage Form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (Name, Dosage Form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in section 3.2.P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

Additionally for Biotech, see 3.2.A.1 for facilities, if appropriate.

Reference ICH Guideline: Q6B.

3.2.P3.4 Controls of Critical Steps and Intermediates (Name, Dosage Form)

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P3.3 of the manufacturing process, to ensure that the process is controlled.

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

Reference ICH Guidelines: Q2A, Q2B, Q6A, and Q6B.

3.2.P3.5 Process Validation and/or Evaluation (Name, Dosage Form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

Reference ICH Guideline: Q6B.

3.2.P.4 Control of Excipients (Name, Dosage Form)**3.2.P4.1 Specifications (Name, Dosage Form)**

The specifications for excipients should be provided.

Reference ICH Guideline: Q6A and Q6B.

3.2.P4.2 Analytical Procedures (Name, Dosage Form)

The analytical procedures used for testing the excipients should be provided, where appropriate.

Reference ICH Guidelines: Q2A and Q6B.

3.2.P4.3 Validation of Analytical Procedures (Name, Dosage Form)

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B.

3.2.P4.4 Justification of Specifications (Name, Dosage Form)

Justification for the proposed excipient specifications should be provided, where appropriate.

Reference ICH Guidelines: Q3C and Q6B.

3.2.P4.5 Excipients of Human or Animal Origin (Name, Dosage Form)

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources; specifications; description of the testing performed; viral safety data.) (Details in 3.2.A.2.)

Reference ICH Guidelines: Q5A, Q5D, and Q6B.

3.2.P4.6 Novel Excipients (Name, Dosage Form)

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross-references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3.)

3.2.P.5 Control of Drug Product (Name, Dosage Form)**3.2.P5.1 Specification(s) (Name, Dosage Form)**

The specification(s) for the drug product should be provided.

Reference ICH Guidelines: Q3B, Q6A, and Q6B.

3.2.P5.2 Analytical Procedures (Name, Dosage Form)

The analytical procedures used for testing the drug product should be provided.

Reference ICH Guidelines: Q2A and Q6B.

3.2.P5.3 Validation of Analytical Procedures (Name, Dosage Form)

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B.

3.2.P5.4 Batch Analyses (Name, Dosage Form)

A description of batches and results of batch analyses should be provided.

Reference ICH Guidelines: Q3B, Q3C, Q6A, and Q6B.

3.2.P5.5 Characterization of Impurities (Name, Dosage Form)

Information on the characterization of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

Reference ICH Guidelines: Q3B, Q5C, Q6A, and Q6B.

3.2.P5.6 Justification of Specification(s) (Name, Dosage Form)

Justification for the proposed drug product specification(s) should be provided.

Reference ICH Guidelines: Q3B, Q6A, and Q6B.

3.2.P.6 Reference Standards or Materials (Name, Dosage Form)

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".

Reference ICH Guidelines: Q6A and Q6B.

3.2.P.7 Container Closure System (Name, Dosage Form)

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Noncompendial methods (with validation) should be included where appropriate.

For nonfunctional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

3.2.P.8 Stability (Name, Dosage Form)**3.2.P8.1 Stability Summary and Conclusion (Name, Dosage Form)**

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

Reference ICH Guidelines: Q1A, Q1B, Q3B and Q5C, Q6A.

3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment (name, dosage form)

The postapproval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A and Q5C.

3.2.P.8.3 Stability Data (Name, Dosage Form)

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

Information on characterization of impurities is located in 3.2.P.5.5.

Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B, and Q5C.

3.2.A APPENDICES**3.2.A.1 Facilities and Equipment (Name, Manufacturer)****Biotech:**

A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multiuse) should be provided. Information on preparation, cleaning, sterilization, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

3.2.A.2 Adventitious Agents Safety Evaluation (Name, Dosage Form, Manufacturer)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For nonviral adventitious agents:

Detailed information should be provided on the avoidance and control of nonviral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process, and agent.

Reference ICH Guidelines: Q5A, Q5D, and Q6B.

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are

considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D, and Q6B for further guidance.

Materials of biological origin

Information essential to evaluate the virologic safety of materials of animal or human origin (e.g., biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.S.2.3, and 3.2.P.4.5.) For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.S.2.3.)

Testing at appropriate stages of production

The selection of virologic tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk, or postviral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in 3.2.S.2.4 and 3.2.P.3.4.)

Viral testing of unprocessed bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral clearance studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5.)

Reference ICH Guidelines: Q5A, Q5D, and Q6B.

3.2.A.3 Excipients**3.2.R REGIONAL INFORMATION**

Any additional drug substance and/or drug product information specific to each region should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance.

Some examples are as follows:

- Executed batch records (USA only)
- Method validation package (USA only)
- Comparability protocols (USA only)
- Process validation scheme for the drug product (EU only)

Where validation is still to be completed, a summary of the studies intended to be conducted should be provided.

- Medical device (EU only)

3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

Organization of Module 4

Nonclinical Overview and Nonclinical Summaries of Module 2

Module 2: Common Technical Document Summaries

General Principles of Nonclinical Overview and Summaries

This guideline provides recommendations for the harmonization of the Nonclinical Overview, Nonclinical Written Summary, and Nonclinical Tabulated Summaries.

The primary purpose of the Nonclinical Written and Tabulated Summaries should be to provide a comprehensive factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e., as applicable to labeling) should be addressed in the overview.

2.4 NONCLINICAL OVERVIEW

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages.

General Aspects

The Nonclinical Overview should present an integrated and critical assessment of the pharmacological, PK, and toxicological evaluation of the pharmaceutical. Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidelines should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacological and toxicological effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding its safety should be provided.

Relevant scientific literature and the properties of related products should be taken into account. If detailed refer-

ences to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidelines. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries, in the following format: (Table X.X, Study/Report Number).

Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

Overview of the Nonclinical Testing Strategy
Pharmacology
Pharmacokinetics
Toxicology
Integrated Overview and Conclusions
List of Literature References

Studies conducted to establish the pharmacodynamic (PD) effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the PK, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the PK models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g., impact of the disease states, changes in physiology, antiproduct antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, C_{max}, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to the following:

- pharmacodynamics;
- toxic signs;
- causes of death;
- pathologic findings;
- genotoxic activity—the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds;
- carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data;
- the carcinogenic risk to humans—if epidemiologic data are available, they should be taken into account;
- fertility, embryofetal development, pre- and postnatal toxicity;
- studies in juvenile animals;
- the consequences of use before and during pregnancy, during lactation, and during pediatric development;
- local tolerance; and
- other toxicity studies/studies to clarify special problems.

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a

certain effect/phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to the following:

- Animal species used.
- Numbers of animals used.
- Routes of administration employed.
- Dosages used.
- Duration of treatment or of the study.
- Systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarizing this information are recommended.
- The effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans.

If alternatives to whole animal experiments are employed, their scientific validity should be discussed.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, PKs, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

2.6 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Nonclinical Written Summaries

Introduction

This guideline is intended to assist authors in the preparation of nonclinical pharmacology, PKs, and toxicology written summaries in an acceptable format. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Nonclinical Written Summary sections are described below. It should be emphasized that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the summaries will facilitate their review. A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

General Presentation Issues

Order of presentation of information within sections

When available, *in vitro* studies should precede *in vivo* studies.

Where multiple studies of the same type need to be summarized within the PKs and toxicology sections, studies

should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Nonhuman primate
- Other nonrodent mammal
- Nonmammals.

Routes of administration should be ordered as follows:

- The intended route for human use
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Others

Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures. Examples of formats that might be included in the Written Summaries are shown in Appendix A.

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

Length of Nonclinical Written Summaries

Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100 to 150 pages.

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Content of Nonclinical Written and Tabulated Summaries

2.6.1 Introduction

The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

- Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacological properties.

- Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.

2.6.2 Pharmacology Written Summary

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

- Brief Summary
- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamic Drug Interactions
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.2.1 Brief Summary

The principal findings from the pharmacology studies should be briefly summarized in approximately two to three pages. This section should begin with a brief description of the content of the pharmacological data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

2.6.2.2 Primary Pharmacodynamics

Studies on primary pharmacodynamics should be summarized and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

2.6.2.3 Secondary Pharmacodynamics

Studies on secondary pharmacodynamics should be summarized by organ system, where appropriate, and evaluated in this section.

2.6.2.4 Safety Pharmacology

Safety pharmacology studies should be summarized and evaluated in this section. In some cases, secondary PD studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in humans. In such cases, these secondary PD studies should be considered along with safety pharmacology studies.

2.6.2.5 Pharmacodynamic Drug Interactions

If they have been performed, PD drug interaction studies should be briefly summarized in this section.

2.6.2.6 Discussion and Conclusions

This section provides an opportunity to discuss the pharmacological evaluation and to consider the significance of any issues that arise.

2.6.2.7 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.6.3 Pharmacology Tabulated Summary (See Appendix B)

2.6.4 Pharmacokinetics Written Summary

The sequence of the Pharmacokinetics Written Summary should be as follows:

- Brief Summary
- Methods of Analysis
- Absorption
- Distribution
- Metabolism

- Excretion
- Pharmacokinetic Drug Interactions
- Other Pharmacokinetic Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.4.1 Brief Summary

The principal findings from the PKs studies should be briefly summarized in approximately two to three pages. This section should begin with a description of the scope of the PK evaluation, emphasizing, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

2.6.4.2 Methods of Analysis

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

2.6.4.3 Absorption

The following data should be summarized in this section:

- Absorption (extent and rate of absorption, in vivo and in situ studies)
- Kinetic parameters, bioequivalence, and/or bioavailability (serum/plasma/blood PK studies)

2.6.4.4 Distribution

The following data should be summarized in this section:

- Tissue distribution studies
- Protein binding and distribution in blood cells
- Placental transfer studies

2.6.4.5 Metabolism (Interspecies Comparison)

The following data should be summarized in this section:

- Chemical structures and quantities of metabolites in biological samples
- Possible metabolic pathways
- Presystemic metabolism (GI/hepatic first-pass effects)
- In vitro metabolism including P450 studies
- Enzyme induction and inhibition

2.6.4.6 Excretion

The following data should be summarized in this section:

- Routes and extent of excretion
- Excretion in milk

2.6.4.7 Pharmacokinetic Drug Interactions

If they have been performed, nonclinical pharmacokinetic drug-interaction studies (in vitro and/or in vivo) should be briefly summarized in this section.

2.6.4.8 Other Pharmacokinetic Studies

If studies have been performed in nonclinical models of disease (e.g., renally impaired animals), they should be summarized in this section.

2.6.4.9 Discussion and Conclusions

This section provides an opportunity to discuss the PK evaluation and to consider the significance of any issues that arise.

2.6.4.10 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

2.6.5 Pharmacokinetics Tabulated Summary (See Appendix B)

2.6.6 Toxicology Written Summary

The sequence of the Toxicology Written Summary should be as follows:

- Brief Summary
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Studies in Juvenile Animals
- Local Tolerance
- Other Toxicity Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.6.1 Brief Summary

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than six). In this section, the extent of the toxicological evaluation can be indicated by the use of a table listing the principal toxicological studies (results should not be presented in this table), for example:

TOXICOLOGY PROGRAM

Study Type and Duration	Route of Administration	Species	Compound Administered ^a
Single-dose toxicity	po and IV	Rat and mouse	Parent drug
Single-dose toxicity	po and IV	Rat and mouse	Metabolite X
Repeat-dose toxicity			
1 mo	po	Rat and dog	Parent drug
6 mo	po	Rat	Parent drug
9 mo	po	Dog	Parent drug

^aThis column required only if metabolite(s) are investigated.

The scope of the toxicological evaluation should be described in relation to the proposed clinical use. A comment on the GLP status of the studies should be included.

2.6.6.2 Single-Dose Toxicity

The single-dose data should be very briefly summarized, in order by species, by route. In some instances, it may be helpful to provide the data in the form of a table.

2.6.6.3 Repeat-Dose Toxicity (Including Supportive Toxicokinetics Evaluation)

Studies should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g., nature and severity of target organ toxicity, dose (exposure)/response relationships,

no observed adverse effect levels, etc.). Nonpivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH Guideline M3).

2.6.6.4 Genotoxicity

Studies should be briefly summarized in the following order:

- in vitro nonmammalian cell system;
- in vitro mammalian cell system;
- in vivo mammalian system (including supportive toxicokinetics evaluation); and
- other systems.

2.6.6.5 Carcinogenicity (Including Supportive Toxicokinetics Evaluations)

A brief rationale should explain why the studies were chosen and the basis for high-dose selection. Individual studies should be summarized in the following order:

- Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Other studies

2.6.6.6 Reproductive and Developmental Toxicity (Including Range-Finding Studies and Supportive Toxicokinetics Evaluations)

Studies should be summarized in the following order, giving brief details of the methodology and highlighting important findings:

- Fertility and early embryonic development
- Embryo–fetal development
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted

If modified study designs are used, the subheadings should be modified accordingly.

2.6.6.7 Local Tolerance

If local tolerance studies have been performed, they should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings.

2.6.6.8 Other Toxicity Studies (If Available)

If other studies have been performed, they should be summarized. When appropriate, the rationale for conducting the studies should be provided.

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not reported elsewhere)
- Dependence
- Studies on metabolites
- Studies on impurities
- Other studies

2.6.6.9 Discussion and Conclusions

This section should provide an opportunity to discuss the toxicological evaluation and the significance of any issues that arise. Tables or figures summarizing this information are recommended.

2.6.6.10 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.6.7 Toxicology Tabulated Summary (See Appendix B)

Nonclinical Tabulated Summaries

It is recommended that summary tables for the nonclinical information in the CTD be provided in the format outlined in this guideline. Applicants can modify the format if needed to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

This guideline is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed. Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

The recommended formats for the tables in the Nonclinical Tabulated Summaries are provided in Appendices B and C, which follow. Appendix B contains templates for use in preparation of the tables. The templates are annotated (in italics) to provide guidance on their preparation. (The italicized information should be deleted when the tables are prepared.) Appendix C provides examples of the summary tables. The purpose of the examples is to provide additional guidance on the suggested content and format of the Tabulated Summaries. However, it is the responsibility of the applicant to decide on the best possible presentation of the data for each product. Authors should keep in mind that, in some regions, a review of the Tabulated Summaries (in conjunction with the Written Summaries) represents the primary review of the nonclinical information. Presentation of the data in the formats provided as templates and examples should ensure that a sufficient level of detail is available to the reviewer and should provide concise overviews of related information.

When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study.

The order of presentation given for the Nonclinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries.

Module 4: Nonclinical Study Reports

This guideline presents an agreed format for the organization of the nonclinical reports in the CTD for applications that will be submitted to Regulatory Authorities. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual–animal data is in the study report or as an appendix to the study report.

4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the CTD.

4.2 Study Reports

The study reports should be presented in the following order:

- 4.2.1 Pharmacology
 - 4.2.1.1 Primary pharmacodynamics
 - 4.2.1.2 Secondary pharmacodynamics
 - 4.2.1.3 Safety pharmacology
 - 4.2.1.4 Pharmacodynamic drug interactions
- 4.2.2 Pharmacokinetics
 - 4.2.2.1 Analytical methods and validation reports (if separate reports are available)
 - 4.2.2.2 Absorption
 - 4.2.2.3 Distribution
 - 4.2.2.4 Metabolism
 - 4.2.2.5 Excretion
 - 4.2.2.6 Pharmacokinetic drug interactions (nonclinical)
 - 4.2.2.7 Other pharmacokinetic studies
- 4.2.3 Toxicology
 - 4.2.3.1 Single-dose toxicity (in order by species, by route)
 - 4.2.3.2 Repeat-dose toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
 - 4.2.3.3 Genotoxicity
 - 4.2.3.3.1 In vitro
 - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
 - 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
 - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
 - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
 - 4.2.3.4.3 Other studies
 - 4.2.3.5 Reproductive and developmental toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following subheadings should be modified accordingly)
 - 4.2.3.5.1 Fertility and early embryonic development
 - 4.2.3.5.2 Embryo–fetal development
 - 4.2.3.5.3 Prenatal and postnatal development (including maternal function)
 - 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
 - 4.2.3.6 Local tolerance
 - 4.2.3.7 Other toxicity studies (if available)
 - 4.2.3.7.1 Antigenicity
 - 4.2.3.7.2 Immunotoxicity
 - 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
 - 4.2.3.7.4 Dependence
 - 4.2.3.7.5 Metabolites
 - 4.2.3.7.6 Impurities
 - 4.2.3.7.7 Other

4.3 Literature References

- 2.6.7.16 Local Tolerance
- 2.6.7.17 Other Toxicity Studies

Appendix A

Tables and Figures for Written Summaries

Appendix B

The Nonclinical Tabulated Summaries—Templates

The Nonclinical Tabulated Summaries—Templates

- 2.6.3 Pharmacology
 - 2.6.3.1 Pharmacology: Overview
 - 2.6.3.2 Primary Pharmacodynamics^a
 - 2.6.3.3 Secondary Pharmacodynamics^a
 - 2.6.3.4 Safety Pharmacology
 - 2.6.3.5 Pharmacodynamic Drug Interactions^a
- 2.6.5 Pharmacokinetics
 - 2.6.5.1 Pharmacokinetics: Overview
 - 2.6.5.2 Analytical Methods and Validation Reports^a
 - 2.6.5.3 Pharmacokinetics: Absorption After a Single Dose
 - 2.6.5.4 Pharmacokinetics: Absorption After Repeated Doses
 - 2.6.5.5 Pharmacokinetics: Organ Distribution
 - 2.6.5.6 Pharmacokinetics: Plasma Protein Binding
 - 2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals
 - 2.6.5.8 Pharmacokinetics: Other Distribution Study
 - 2.6.5.9 Pharmacokinetics: Metabolism In Vivo
 - 2.6.5.10 Pharmacokinetics: Metabolism In Vitro
 - 2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways
 - 2.6.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes
 - 2.6.5.13 Pharmacokinetics: Excretion
 - 2.6.5.14 Pharmacokinetics: Excretion into Bile
 - 2.6.5.15 Pharmacokinetics: Drug–Drug Interactions
 - 2.6.5.16 Pharmacokinetics: Other
- 2.6.7 Toxicology
 - 2.6.7.1 Toxicology: Overview
 - 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies
 - 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data
 - 2.6.7.4 Toxicology: Drug Substance
 - 2.6.7.5 Single-Dose Toxicity
 - 2.6.7.6 Repeat-Dose Toxicity: Nonpivotal Studies
 - 2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies
 - 2.6.7.8 Genotoxicity: In Vitro
 - 2.6.7.9 Genotoxicity: In Vivo
 - 2.6.7.10 Carcinogenicity
 - 2.6.7.11 Reproductive and Developmental Toxicity: Nonpivotal Studies
 - 2.6.7.12 Reproductive and Developmental Toxicity—Fertility and Early Embryonic Development to Implantation (Pivotal)
 - 2.6.7.13 Reproductive and Developmental Toxicity—Effects on Embryo–Fetal Development (Pivotal)
 - 2.6.7.14 Reproductive and Developmental Toxicity—Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)
 - 2.6.7.15 Studies in Juvenile Animals^b

^a: Tabulated Summary is optional. It is preferable to include text tables and figures with the Nonclinical Written Summary.

^b: When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study and located in Section 2.6.7.15.

Module 5: Clinical Study Reports

Clinical Overview and Clinical Summary of Module 2

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

2.5: CLINICAL OVERVIEW

Preamble

The Clinical Overview is intended to provide a critical analysis of the clinical data in the CTD. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyze the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives the Clinical Overview should

- describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions;
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance;
- provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent end points, or on use in combination therapy);
- provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimize benefits and manage risks;
- address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved;

- explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them; and
- explain the basis for important or unusual aspects of the prescribing information.

The Clinical Overview should generally be a relatively short document (approximately 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged.

Table of Contents

2.5.1.....	Product Development Rationale
2.5.2.....	Overview of Biopharmaceuticals
2.5.3.....	Overview of Clinical Pharmacology
2.5.4.....	Overview of Efficacy
2.5.5.....	Overview of Safety
2.5.6.....	Benefits and Risks Conclusions
2.5.7.....	Literature References

Detailed Discussion of Content of the Clinical Overview Sections

2.5.1 Product Development Rationale

The discussion of the rationale for the development of the medicinal product should

- identify the pharmacological class of the medicinal product;
- describe the particular clinical/pathophysiologic condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication);
- briefly summarize the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied;
- briefly describe the clinical development program of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the program. Briefly describe plans for the use of foreign clinical data (ICH E5);
- note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct, and analysis of the studies. Pertinent published literature should be referenced. Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, letters from regulatory authorities) should be referenced, with copies included in the references section of Module 5.

2.5.2 Overview of Biopharmaceuticals

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

2.5.3 Overview of Clinical Pharmacology

The purpose of this section is to present a critical analysis of the PK, PD, and related in vitro data in the CTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. It should emphasize unusual results and known or potential problems, or note the lack thereof. This section should address:

- PKs, for example, comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal, and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in PKs; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances.
- Pharmacodynamics, for example, information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable PD effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response.
- Interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies summarized in section 2.7.2.4 of the Clinical Summary.

2.5.4 Overview of Efficacy

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered.

The following issues should generally be considered:

- Relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing should be discussed.
- Implications of the study design(s), including selection of patients, duration of studies, and choice of end points and control group(s). Particular attention should be given to end points for which there is limited experience. Use of surrogate end points should be justified. Validation of any scales used should be discussed.
- For noninferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of noninferiority margin (ICH E10).
- Statistical methods and any issues that could affect the interpretation of the study results (e.g., important

modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol; support for any unplanned analyses; procedures for handling missing data; and corrections for multiple end points).

- Similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.
- Observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).
- Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).
- For products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.
- Data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.
- The clinical relevance of the magnitude of the observed effects.
- If surrogate end points are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.
- Efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

2.5.5 Overview of Safety

The purpose of this section is to provide a concise critical analysis of the safety data, noting how results support and justify proposed prescribing information. A critical analysis of safety should consider:

- Adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.
- Special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).
- Relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.
- The nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database, for example, related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.
- Common and nonserious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.
- Serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of seri-

ous adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.

- Similarities and differences in results among studies, and their effect upon the interpretation of the safety data.
- Any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.
- Relation of adverse events to dose, dose regimen, and treatment duration.
- Long-term safety (E1a).
- Methods to prevent, mitigate, or manage adverse events.
- Reactions due to overdose, the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.
- Worldwide marketing experience. The following should be briefly discussed:
 - the extent of the worldwide experience,
 - any new or different safety issues identified, and
 - any regulatory actions related to safety.
- Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

2.5.6 Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceuticals, clinical pharmacology, efficacy, and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the medicinal product as they compare to available alternative treatments or to no treatment in illnesses, where no treatment may be a medically acceptable option; and should clarify the expected place of the medicinal product in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

- The efficacy of the medicinal product for each proposed indication.
- Significant safety findings and any measures that may enhance safety.
- Dose–response and dose–toxicity relationships, optimal dose ranges, and dosage regimens.
- Efficacy and safety in subpopulations, for example, those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.

- Data in children in different age groups, if applicable, and any plans for a development program in children.
- Any risks to the patient of known and potential interactions, including food–drug interactions and drug–drug interactions, and recommendations for product use.
- Any potential effect of the medicinal product that might affect ability to drive or operate heavy machinery.

Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include the following:

- The drug is for treatment of a nonfatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, proarrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.
- The proposed use is based on a surrogate end point and there is a well-documented important toxicity.
- Safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.

2.5.7 Literature References

A list of references used, stated in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE), or the system used in “Chemical Abstracts” should be provided. Copies of all references cited in the Clinical Overview should be provided in section 5.4 of Module 5.

2.7: CLINICAL SUMMARY

Preamble

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the CTD. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses, or other cross-study analyses for which full reports have been included in Module 5; and postmarketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the CTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

Table of Contents

2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods

2.7.1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the in vitro and in vivo dosage form performance, and the general approach and rationale used in developing the BA, comparative BA, BE, and in vitro dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical

methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

2.7.1.2 Summary of Results of Individual Studies

A tabular listing of all biopharmaceutical studies should generally be provided (see 2.7.1.4 Appendix), together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important in vitro or in vivo data and information relevant to BA and BE. The narrative descriptions should be brief, for example, similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

2.7.1.3 Comparison and Analyses of Results across Studies

This section should provide a factual summary of all in vitro dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies. This overview should typically summarize the findings in text and tables (see 2.7.1.4 Appendix) and should consider the following:

- Evidence of the effects of formulation and manufacturing changes on in vitro dissolution and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), PK studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations, PD studies or clinical trials may be necessary. Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.
- Evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate).
- Evidence of correlations between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.
- Comparative BA, including BE conclusions, for different dosage form strengths.
- Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.
- The source and magnitude of observed inter- and intrasubject variability for each formulation in a comparative BA study.

2.7.1.4 Appendix

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the

document. Lengthy tables can be provided in the appendix at the end of the section.

Tables 2.7.1.1 and 2.7.1.2 are provided as examples of tabular formats for reporting information and results related to bioavailability and in vitro dissolution studies respectively. These examples give results as well as identifying the type and design of the study. Tables prepared for reporting the results of BE studies could also include the mean ratios (test/reference) for C_{max} and AUC and their 90% confidence interval, or the currently recommended metrics for BE assessments.

These tables are not intended to be templates, but only to illustrate the type of information that should be considered by an applicant in designing the tables for biopharmaceutical studies. Applicants should also decide whether information and results from these studies are best presented in tables, text, or figures in order to aid clarity. If, for example, results are best presented in text and figures, tables might be used simply to list the studies.

2.7.2 Summary of Clinical Pharmacology Studies

2.7.2.1 Background and Overview

This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human PK, and PD, and in vitro studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Where appropriate, relevant data that are summarized in sections 2.7.1, 2.7.3, and 2.7.4 can also be referenced to provide a comprehensive view of the approach and rationale for the development of the PK, PK/PD, and human biomaterial database. This section should not include detailed information about individual studies.

This section should begin with a brief overview of the human biomaterial studies that were conducted and that were intended to help in the interpretation of PK or PD data. Studies of permeability (e.g., intestinal absorption, blood-brain barrier passage), protein binding, hepatic metabolism, and metabolic-based drug–drug interactions are particularly relevant. This should be followed by a brief overview of the clinical studies that were carried out to characterize PK and PD of the medicinal product, including studies of PK/PD relationships in healthy subjects and patients, and relevant effects of intrinsic and extrinsic factors on PK and PK/PD relationships (In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively). Critical aspects of study design and data analysis should be noted, for example, the choice of the single or multiple doses used, the study population, choice of the intrinsic or extrinsic factors that were studied, the choice of PD end points, and whether a traditional approach or a population approach was used to collect and analyze data to assess PK or PD.

2.7.2.2 Summary of Results of Individual Studies

A tabular listing of all clinical pharmacology studies should generally be provided (see 2.7.2.5 Appendix), together with

a narrative description of the relevant features and outcomes of each of the critical individual studies that provided in vitro or in vivo data and information relevant to PK, PD and PK/PD relationships. The narrative descriptions should be brief, for example, similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. References or electronic links to the full report of each study should be included in the narratives.

Summaries of dose–response or concentration–response (PK/PD) studies with PD end points should generally be included in this section. In some cases, however, when well-controlled dose–response PD or PK/PD studies provide important evidence of efficacy or safety, they should be placed in 2.7.3 or 2.7.4 as appropriate and referenced, but not summarized, here.

2.7.2.3 Comparison and Analyses of Results across Studies

This section should use the results of all in vitro human biomaterial studies and PK, PD, and PK/PD studies to characterize the PK, PD, and PK/PD relationships of the drug. Results related to the inter- and intraindividual variability in these data and the intrinsic and extrinsic factors affecting these PK relationships should be discussed.

This section (typically with the use of text and tables) should provide a factual presentation of all data across studies pertinent to the following:

- In vitro drug metabolism and in vitro drug–drug interaction studies and their clinical implications.
- Human PK studies, including the best estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualization in the target patient population and in special populations, for example, paediatric or geriatric patients, or patients with renal or hepatic impairment.
- Comparison between single and repeated-dose PK.
- Population PK analyses, such as results based on sparse sampling across studies that address interindividual variations in the PK or PD of the active drug substances that may be due to extrinsic or intrinsic factors.
- Dose–response or concentration–response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the important clinical trials. In addition, information that supports the dosage instructions in the proposed labeling should be discussed in section 2.7.3.4.
- Major inconsistencies in the human biomaterial, PK, or PD database.
- PK studies that were performed to determine whether foreign clinical data could be extrapolated to the new region (see ICH E5). The result of the studies and analysis of the similarity of the PK data between regions or races should be summarized in this section. Such studies that use PD biomarkers (but do not evaluate clinical efficacy) may similarly be summarized here. An independent subsection can be created to summarize these kinds of data.

2.7.2.4 Special Studies

This section should include studies that provide special types of data relevant to specific types of medicinal products. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarized here. Any

observed or potential effects on PK, PD, safety, and/or efficacy should be considered in other appropriate sections of the Clinical Summary as well, with cross-referencing to this section. Human studies that address a specific safety issue should not be reported here, but instead should be reported in the Summary of Clinical Safety (section 2.7.4).

Example 1: Immunogenicity

For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarized in this section. For vaccines or other products intended to induce specific immune reactions, immunogenicity data should be described in the efficacy section 2.7.3. Assays used should be briefly described and information about their performance (e.g., sensitivity, specificity, reliability, validity) should be summarized; the location in the application of detailed information should be cross-referenced.

Data regarding the incidence, titre, timing of onset, and duration of antibody responses should be summarized for each type of antibody assay used (e.g., IgG by ELISA, neutralization). Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarized. For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analyzed and summarized.

It is particularly important to summarize analyses of potential clinically relevant correlates of immunogenicity, for example, to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of PK, changes in PD, loss of efficacy, loss of adverse event profile, or development of adverse events. Particular attention should be paid to events that might be immunologically mediated (e.g., serum sickness) and events that might result from binding of cross-reactive endogenous substances by antibodies to the administered drug.

Example 2: Clinical microbiology

For antimicrobial or antiviral medicinal products, *in vitro* studies to characterize the spectrum of activity are an important part of the program of studies relevant to clinical efficacy. Clinical efficacy studies that include characterization of the susceptibility of the clinical isolates as a part of the efficacy determination should be included in section 2.7.3, Summary of Clinical Efficacy. However, studies that evaluate such findings as the pattern of *in vitro* susceptibility of strains of bacteria from different parts of the world (not in the context of clinical efficacy study) would be included here.

2.7.2.5 Appendix

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

Table 2.7.2.1 is provided as an example of a tabular format for reporting information and results related to PK drug–drug interaction studies. Similar tables could be prepared for PK/PD studies, dose–response studies, studies of effects on human biomaterials, and population PK studies. This table is not intended to be a template, but only to illustrate the type of information that should be considered by sponsors in designing their own tables. Applicants should also decide whether information and results from clinical pharmacology studies are best presented in tables, text, or figures in order

to aid clarity. If, for example, results are best presented in text and figures, the tables might simply list the studies.

In designing tables, if any, for various types of other clinical pharmacology studies such as those listed below, applicants should consider including the following types of information. These examples are for illustrative purposes only and the sponsor should decide which information needs to be presented.

- Metabolism studies using human biomaterials: biomaterials used (e.g., microsomes, hepatocytes), probe drugs, enzymatic pathways and % contribution, and relevant kinetic parameters (e.g., V_{max} , K_m).
- *In vitro* studies of drug–drug interactions using human biomaterials: for studies of other drugs inhibiting the new drug, the metabolite(s) inhibited, enzymatic pathways affected, range of inhibitor concentrations used, IC_{50} and K_i values and proposed mechanism of inhibition should be included. For studies of the new drug inhibiting other drugs, the drugs and metabolites inhibited should be included, along with the information mentioned above.
- Population PK studies: covariates studied, number and type of subjects or patients studied, summary statistical parameters and final estimates of mean (\pm standard deviation) PK parameters.

2.7.3 Summary of Clinical Efficacy

A separate section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one section 2.7.3 is submitted, the sections should be labeled 2.7.3 pneumonia, 2.7.3 URI, etc.

2.7.3.1 Background and Overview of Clinical Efficacy

This section should describe the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought. Any results of these studies that are pertinent to evaluation of safety should be discussed in section 2.7.4, Summary of Clinical Safety.

The section should begin with a brief overview of the design of the controlled studies that were conducted to evaluate efficacy. These studies include dose–response, comparative efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of study design should be discussed, for example, randomization, blinding, choices of control treatment, choice of patient population, unusual design features such as crossover or randomized withdrawal designs, use of run-in periods, other methods of “enrichment,” study end points, study duration, and prespecified plans for analysis of the study results. Although this section is intended to focus on clinical investigations, nonclinical data, and clinical pharmacology data may also be referenced as appropriate to provide a comprehensive summary of human experience related to efficacy. This section should not include detailed information about individual studies.

2.7.3.2 Summary of Results of Individual Studies

A tabular listing of all studies that provided (or were designed to provide) information relevant to product efficacy should generally be provided (see the section 2.7.3.6 Appendix), together with narrative descriptions for important studies. The narrative descriptions should be brief, for example, similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any

important differences among the studies. For studies that also contributed significantly to the safety analysis, study narratives should include information about the extent of exposure of study subjects to the test drug or control agent, and how safety data were collected. These narratives can be abstracted from the synopses of the clinical study reports (ICH E3). References or electronic links to the full report of each study should be included in the narratives.

Narratives of any bridging studies using clinical end points, that is, certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be included in this section. An analysis of the results of such studies, together with other information (e.g., PK and PD data) that addresses the ability to extrapolate the efficacy and safety results of foreign studies, should be performed if necessary. The conclusions of such an analysis should be noted at the start of section 2.7.3.3.2, Comparison of Efficacy Results of All Studies, and the full report of the analysis should be provided in Module 5.

2.7.3.3 Comparison and Analyses of Results across Studies

Using text, figures, and tables as appropriate (see the section 2.7.3.6 Appendix), the subsections of 2.7.3.3 should summarize all available data that characterize the efficacy of the drug. This summary should include analyses of all data, irrespective of their support for the overall conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The section will generally utilize two kinds of analysis: comparison of results of individual studies, and analysis of data combined from various studies. Details of analysis that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Module 5, section 5.3.5.3.

This section should also cross-reference important evidence from section 2.7.2, such as data that support the dosage and administration section of the labeling. These data include dosage and dose interval recommended, evidence pertinent to individualization of dosage and need for modifications of dosage for specific subgroups (e.g., paediatric or geriatric subjects, or subjects with hepatic or renal impairment), and data relevant to dose–response or concentration–response (PK/PD) relationships.

2.7.3.3.1 Study Populations

The demographic and other baseline characteristics of patients across all efficacy studies should be described. The following should be included:

- The characteristics of the disease (e.g., severity, duration) and prior treatment in the study subjects, and study inclusion/exclusion criteria.
- Differences in baseline characteristics of the study populations in different studies or groups of studies.
- Any differences between populations included in critical efficacy analyses and the overall patient population that would be expected to receive the drug when it is marketed should be noted.
- Assessment of the number of patients who dropped out of the studies, time of withdrawal (a defined study day or visit during treatment or follow up period), and reasons for discontinuation.

Tabular presentations that combine and compare study populations across studies may be useful.

2.7.3.3.2 Comparison of Efficacy Results of all Studies

The results of any bridging studies using clinical end points, that is, certain studies used to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be summarized in this section. An analysis of the similarity of efficacy in subjects between regions, as well as any other information that may support extrapolation of the efficacy data to the new region, should be summarized here. An independent subsection can be created to summarize these kinds of data.

The results from all studies designed to evaluate the drug's efficacy should be summarized and compared, including studies with inconclusive or negative results. Important differences in study design such as end points, control group, study duration, statistical methods, patient population, and dose should be identified.

Comparisons of results across studies should focus on prespecified primary end points. However, when the primary end points involved different variables or time points in different efficacy studies, it may be useful to provide cross-study comparisons of important data elements that were obtained in all studies. If results over time are important, results of studies may be displayed in a figure that illustrates the change over time in each study.

Confidence intervals for treatment effects should be given to aid in the interpretation of point estimates. If differences are shown between placebo and test drugs in the change from baseline, the baseline values and the magnitude of effect in all treatment groups, including placebo and active controls (if used), should generally be presented in the table or in text accompanying a figure. If the objective of an active control trial was to show equivalence or non-inferiority, the difference or the ratio of outcomes between treatments should be given with the confidence interval. The results should be evaluated by using the predefined criteria for defining equivalence or noninferiority and the rationale for the criteria and support for the determination that the study (studies) had assay sensitivity should be provided (see ICH E10).

Important differences in outcomes between studies with a similar design should be delineated and discussed. Cross-study comparisons of factors that may have contributed to differences in outcomes should be described.

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or is a post hoc exercise. Any differences in trial designs or populations, or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions (see ICH E9). A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report (section 5.3.5.3 of Module 5).

2.7.3.3.3 Comparison of Results in Subpopulations

The results of individual studies or overview analyses of efficacy in specific populations should be summarized in this section. The purpose of these comparisons should be to show whether the claimed treatment effects are observed consistently across all relevant subpopulations, especially those where there are special reasons for concern. The comparisons may highlight apparent variations in efficacy that require further investigation and discussion. The limitations of such analyses, however, should be recognized (ICH E9), and it is important to note that their purpose is neither to provide

the basis for specific claims, nor to attempt to improve the evidence of efficacy in situations where the overall results are disappointing.

Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) and of other predefined or relevant intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant illness, concomitant drugs, alcohol, tobacco, and body weight) on efficacy. Factors of special interest may arise from general concerns (e.g., the elderly) or from specific issues that are related to the pharmacology of the drug or that have arisen during earlier drug development. Efficacy in the paediatric population should be routinely analyzed in applications for a proposed indication that occurs in children. Depending on the data set, if extensive, detailed efficacy analyses are performed, they can be placed in Module 5, with the results of those analyses reported here.

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data that pertain to the dose–response or blood level–response relationships of effectiveness (including dose–blood level relationships), and thus have contributed to dose selection and choice of dose interval. Relevant data from non-clinical studies may be referenced, and relevant data from PK studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies should be summarized to illustrate these dose–response or blood level–response relationships. For PK and PD studies from which data have been summarized in section 2.7.2.2, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in section 2.7.2.2, without repeating those summaries.

While the interpretation of how these data support specific dosing recommendations should be supplied in the Clinical Overview document, the individual study results and any cross-study analyses that will be used to support the dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualization of dosage) should be summarized here. Any identified deviations from relatively simple dose–response or blood-level response relationships due to nonlinearity of PKs, delayed effects, tolerance, enzyme induction, etc. should be described.

Any evidence of differences in dose–response relationships that result from a patient’s age, sex, race, disease, or other factors should be described. Any evidence of different PK or PD responses should also be discussed, or discussions in section 2.7.2 can be cross-referenced. The ways in which such differences were looked for, even if no differences were found, should be described (e.g., specific studies in subpopulations, analysis of efficacy results by subgroup, or blood level determinations of the test drug).

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

Available information on persistence of efficacy over time should be summarized. The number of patients for whom long-term efficacy data are available, and the length of exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over time) should be noted. Examination of any apparent relationships between dose changes over time and long-term efficacy may be useful.

The primary focus should be on controlled studies specifically designed to collect long-term efficacy data, and

such studies should be clearly differentiated from other, less rigorous, studies such as open extension studies. This distinction also applies to specific studies designed for evaluation of tolerance and withdrawal effects. Data concerning withdrawal or rebound effects pertinent to product safety should be presented in the safety section (see section 2.7.4).

In long-term efficacy trials, the effect of premature discontinuation of therapy or switching to other therapies upon the assessment of the results should be considered. These issues might also be important for short-term trials and should be addressed when discussing the results of these trials, if appropriate.

2.7.3.6 Appendix

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

Tables should identify all studies pertinent to the evaluation of efficacy (including studies that were terminated or are not yet completed, studies that failed to show effectiveness for any reason, studies available only as publications, studies reported in full technical reports (ICH E3), and studies described in abbreviated reports); and should provide the most important results of those studies. Note, however, that unplanned interim analyses on ongoing studies are generally not needed or encouraged. When more than one section 2.7.3 is provided for an application with more than one indication, usually each section should have its own appendix with tables.

Illustrative tables for an antihypertensive drug are provided, but these examples will not be relevant to every application. In general, applications will require tables and/or figures that are developed specifically for the particular drug class and the studies that were carried out.

Table 2.7.3.1 Description of Clinical Efficacy and Safety Studies

Table 2.7.3.2 Results of Efficacy Studies

2.7.4 Summary of Clinical Safety

This section should be a summary of data relevant to safety in the intended patient population, integrating the results of individual clinical study reports as well as other relevant reports, for example, the integrated analyses of safety that are routinely submitted in some regions.

The display of safety-related data can be considered at three levels (ICH E3):

- The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to which safety can be assessed from the database.
- The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarized.
- Serious adverse events (defined in ICH E2A) and other significant adverse events (defined in ICH E3) should be identified and their occurrence should be summarized. These events should be examined for frequency over time, particularly for drugs that may be used chronically.

The safety profile of the drug, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with use of tables and figures.

2.7.4.1 Exposure to the Drug**2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies**

The overall safety evaluation plan should be described briefly, including special considerations and observations concerning the nonclinical data, any relevant pharmacological class effects, and the sources of the safety data (controlled trials, open studies, etc.). A tabular listing of all clinical studies that provided safety data, grouped appropriately, should generally be provided (see the section 2.7.4.7 Appendix). In addition to studies that evaluated efficacy and safety, and uncontrolled studies that generate safety information, this section includes studies that consider special safety issues. Examples would include studies to compare particular adverse event rates for two therapies, to assess safety in particular demographic subsets, to evaluate withdrawal or rebound phenomena, or to evaluate particular adverse events (e.g., sedation, sexual function, effects on driving, absence of a class adverse effect). Studies in indications for which approval is not being sought in the current application and ongoing studies would also be included here if they contribute to the safety analysis.

Narrative descriptions of these studies should be provided here, except that narrative descriptions for studies that contributed both efficacy and safety data should be included in section 2.7.3.2 and cross-referenced here. The narratives should provide enough detail to allow the reviewer to understand the exposure of study subjects to the test drug or control agent, and how safety data were collected (including the methods used and the extent of safety monitoring of the subjects enrolled in the individual studies). If some studies are not analyzed separately but are grouped for safety analysis, that should be noted, and a single narrative description can be provided.

2.7.4.1.2 Overall Extent of Exposure

A table (see example provided in the section 2.7.4.7 Appendix) and appropriate text should be generated to summarize the overall extent of drug exposure from all phases of the clinical study development program. The table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes, and durations. If a large number of different doses and/or durations of exposure were used, these can be grouped in a manner appropriate for the drug. Thus, for any dose or range of doses, duration of exposure can be summarized by the number of subjects exposed for specific periods of time, such as 1 day or less, 2 days to 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more than 1 year (ICH E3). In some applications, it may be important to identify diagnostic subgroups and/or groups receiving specific concomitant therapies deemed particularly relevant to safety assessment in the intended use.

The dose levels used for each subject in this presentation could be the maximum dose received by that subject, the dose with longest exposure, and/or the mean daily dose, as appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m² basis, as appropriate. If available, drug concentration data (e.g., concentration at the time of an adverse event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events or changes in laboratory variables.

It is assumed that all subjects, who were enrolled and received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

2.7.4.1.3 Demographic and Other Characteristics of Study Population

A summary table should provide the reader with an overview of the demographic characteristics (Table 2.7.4.2) of the population that was exposed to the therapeutic agent during its development. Choice of age ranges used should take into account considerations discussed in ICH E7 (Studies in Support of Special Populations: Geriatrics) and ICH E11 (Clinical Investigation of Medicinal Products in the Paediatric Population). If the relative exposure of demographic groups in the controlled trials differed from overall exposure, it may be useful to provide separate tables.

In addition, one or more tables should show the relevant characteristics of the study population, and the numbers of subjects with special characteristics. Such characteristics could include

- Severity of disease
- Hospitalization
- Impaired renal function
- Concomitant illnesses
- Concomitant use of particular medications
- Geographical location

If these characteristics are distributed differently in controlled trials versus the overall database, it will generally be useful to present tables on both groupings.

The text accompanying the table(s) should mention any imbalance(s) between the drug and placebo and/or comparator regarding any of the above demographic characteristics, particularly if they could lead to differences in safety outcomes.

If certain subjects were excluded from studies (concomitant illness, severity of illness, concomitant medications), this fact should be noted.

Separate demographic tables should be provided for every indication, although closely related indications can be considered together, if study subject characteristics are such that risks are believed to be the same.

2.7.4.2 Adverse Events**2.7.4.2.1 Analysis of Adverse Events**

Data on the frequency of adverse events should be described in text and tables. Text should appear in the appropriate subsections of section 2.7.4.2.1 and the tables that are not embedded in the text should be placed in the section 2.7.4.7 Appendix.

All adverse events occurring or worsening after treatment have begun (“treatment emergent signs and symptoms,” those adverse events not seen at baseline and those that worsened even if present at baseline) should be summarized in tables listing each event, the number of subjects in whom the event occurred and the frequency of occurrence in subjects treated with the drug under investigation, with comparator drugs, and with placebo. Such tables could also present results for each dose and could be modified to show, for example, adverse event rates by severity, by time from onset of therapy, or by assessment of causality.

When most of the relevant safety data are derived from a small number of studies (e.g., one or two studies), or when very different study subject populations were enrolled in the studies that were performed, presentation of data by study will often be appropriate. When the relevant exposure data is not concentrated in a small number of studies, however, grouping the studies and pooling the results to improve precision of estimates and sensitivity to differences should generally be considered.

While often useful, pooling of safety data across studies should be approached with caution because in some cases interpretation can be difficult, and it can obscure real differences. In cases where differences are apparent, it is more appropriate to present the data by study. The following issues should be considered:

- It is most appropriate to combine data from studies that are of similar design, for example, similar in dose, duration, methods of determining adverse events, and population.
- If the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
- Any study with an unusual adverse event pattern should be presented separately.
- The appropriate extent of analysis depends on the seriousness of the adverse event and the strength of evidence of drug causation. Differences in rates of drug-related, serious events or events leading to discontinuation or dosage change deserve more investigation, whereas rates of other adverse events do not merit elaborate analysis.
- Examination of which subjects experience extreme laboratory value abnormalities (“outliers”) may be useful in identifying subgroups of individuals who are at particular risk for certain adverse events.

Groups of studies that could be used in pooled safety analyses include

- All controlled studies or subsets of controlled studies, such as all placebo-controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.
- All studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating rarer events.
- All studies using a particular dose route or regimen, or a particular concomitant therapy.
- Studies in which adverse event reports are elicited by checklist or direct questioning, or studies in which events are volunteered.
- Pools of studies by region.

It is almost always useful to carry out the first two groupings; the others chosen would vary from drug to drug and should be influenced by inspection of individual study results. Whatever methods are used, it should be recognized that, as for results of single studies, any numerical rate is often only a rough approximation of reality.

When a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. It is common to combine the numerator events and the denominators for the selected studies. Other methods for pooling results across studies are available, for example, weighting data from studies on the basis of study size or inversely to their variance.

If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g., relevant differences in study populations, in dose administration, or in methods of collecting adverse event data).

Adverse events should be described as shown in the individual study report (ICH E3). In combining data from

many studies, it is important to use standardized terms to describe events and collect synonymous terms under a single preferred term. This can be done with a standard dictionary, and the MedDRA terminology (ICH M1 guideline) should be used. Until MedDRA can be fully implemented, other dictionaries can be used, but should be specified. Frequencies should be presented for preferred terms and for appropriately defined groupings. Examination of which adverse events led to change in therapy (discontinuation of drug use, change in dose, need for added therapy) can help in assessing the clinical importance of adverse events. These rates can be added to the adverse event rate tables, or can be presented in separate tables. Overall discontinuation rates by study may be useful, but it is also important to specify the particular adverse events leading to discontinuation in a separate table. The preferred terms should be grouped by body system and arranged by decreasing frequency.

2.7.4.2.1.1 Common Adverse Events

Tabular displays of adverse event rates (see the section 2.7.4.7 Appendix) should be used to compare rates in treatment and control groups. For this analysis, it may be helpful to combine the event severity categories and the causality categories, if they are used, leading to a simpler side-by-side comparison of treatment groups. It should be noted that while causality categories may be reported, if used, the presentation of the data should include total adverse events (whether deemed related or unrelated to treatment); evaluations of causality are inherently subjective and may exclude unexpected adverse events that are in fact treatment related. Additionally, comparisons of rates of adverse events between treatment and control groups in individual trials should be summarized here. It is often useful to tabulate rates in selected trials (see example table 2.7.4.4, in the section 2.7.4.7 Appendix).

It is usually useful to examine more closely the more common adverse events that seem to be drug related (e.g., those that show that a dose response and/or a clear difference between drug and placebo rates) for relationship to relevant factors, including

- dosage;
- mg/kg or mg/m² dose;
- dose regimen;
- duration of treatment;
- total dose;
- demographic characteristics such as age, sex, race;
- concomitant medication use;
- other baseline features such as renal status;
- efficacy outcomes; and
- drug concentration, where available.

It may also be useful to summarize the results of examination of time of onset and duration for these drug-related events.

Rigorous statistical evaluations of the possible relationship of specific adverse events to each of the above factors are often unnecessary. It may be apparent from initial display and inspection of the data that there is no evidence of a significant relationship to demographic or other baseline features. In that case, no further analysis of these particular factors is needed. Further, it is not necessary that all such analyses be presented in this report. When the safety analyses are too extensive to be presented in detail in this report, they may be presented in a separate report in Module 5, section 5.3.5.3, and summarized here.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates.

2.7.4.2.1.2 Deaths

A table in the section 2.7.4.7 Appendix should list all deaths occurring while on study (including deaths that occurred shortly following treatment termination, for example, within 30 days or as specified in the study protocol, as well as all other deaths that occurred later but may have resulted from a process that began during studies). Only deaths that are clearly disease-related per protocol definitions and not related to the investigational product, either in studies of conditions with high mortality such as advanced cancer or in studies where mortality from disease is a primary study end point, should be excepted from this listing (it is assumed, however, that these deaths would still be reported in the individual ICH E3 study reports). Even these deaths should be examined for any unexpected patterns between study arms, and further analyzed if unexplained differences are observed. Deaths should be examined individually and analyzed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause-specific deaths. Potential relationships to the factors listed in section 2.7.4.2.1.1 should also be considered. Although cause-specific mortality can be difficult to determine, some deaths are relatively easy to interpret. Thus, deaths due to causes expected in the patient population (heart attacks and sudden death in an angina population) are individually not considered to be informative, but even one death due to a QT interval prolongation-associated arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is appropriate before an unusual death is attributed to concomitant illness.

2.7.4.2.1.3 Other Serious Adverse Events

Summaries of all serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be displayed. Serious adverse events that occurred after the drug use was discontinued should be included in this section. The display should include major laboratory abnormalities, abnormal vital signs, and abnormal physical observations that are considered serious adverse events using the ICH E2A definitions. Results of analyses or assessments of serious adverse events across studies should be presented. Serious events should be examined for frequency over time, particularly for drugs that may be used chronically. Potential relationships to the factors listed in section 2.7.4.2.1.1 should also be considered.

2.7.4.2.1.4 Other Significant Adverse Events

Marked hematologic and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a substantial intervention (premature discontinuation of study drug, dose reduction, or substantial additional concomitant therapy), other than those reported as serious adverse events, should be displayed.

Events that led to premature discontinuation of study drug represent an important safety concern and deserve particular attention in the analysis of drug safety for two reasons. First, even for expected events (based on pharmacological activity), the need to discontinue (or otherwise alter) treatment reflects the severity and perceived importance of the event to patient and physician. Second, discontinuation may represent a drug-related event not yet recognized as drug related. Adverse events leading to treatment discontinuation should be

considered possibly drug-related even if this was not recognized initially and even if the event was thought to represent intercurrent illness. Reasons for premature treatment discontinuations should be discussed and rates of discontinuations should be compared across studies and compared with those for placebo and/or active control treatment. In addition, the study data should be examined for any potential relationships to the factors listed in section 2.7.4.2.1.1.

2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome

Assessment of the causality of, and risk factors for, deaths, other serious events, and other significant events is often complicated by the fact that they are uncommon. As a result, consideration of related events as a group, including less important events of potentially related pathophysiology, may be of critical value in understanding the safety profile. For example, the relationship to treatment of an isolated sudden death may become much clearer when considered in the context of cases of syncope, palpitations, and asymptomatic arrhythmias.

It is thus generally useful to summarize adverse events by organ system so that they may be considered in the context of potentially related events including laboratory abnormalities. Such presentations of adverse events by organ system should be placed in subsections of section 2.7.4.2.1.5, labelled as 2.7.4.2.1.5.1, 2.7.4.2.1.5.2, etc., and titled by the organ system under consideration. The list of organ systems to be addressed and the approach to grouping certain events should be selected as appropriate to best present the adverse event data for the medicinal product. If some adverse events tend to occur in syndromes (e.g., influenza-like syndrome, cytokine release syndrome), the sponsor may choose to create some subsections of 2.7.4.2.1.5 for syndromes rather than organ systems.

The same data and summarizations should generally not be repeated in more than one subsection of section 2.7.4.2.1. Instead, a summary presentation may be placed in one subsection and cross-referenced as needed in the other.

2.7.4.2.2 Narratives

The locations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special interest because of clinical importance (as described in ICH E3 individual study reports) should be referenced here for the convenience of the reviewer. The narratives themselves should be a part of the individual study reports, if there is such a report. In cases where there is no individual study report (e.g., if many open studies are pooled as part of a safety analysis and are not individually described), narratives can be placed in Module 5, section 5.3.5.3. Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the drug.

2.7.4.3 Clinical Laboratory Evaluations

This section should describe changes in patterns of laboratory tests with drug use. Marked laboratory abnormalities and those that led to a substantial intervention should be reported in section 2.7.4.2.1.3 or 2.7.4.2.1.4. If these data are also presented in this section, this duplicate reporting should be made clear for the reviewer. The appropriate evaluations of laboratory values will in part be determined by the results seen, but, in general, the analyses described below should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as

compatible with study sizes. In addition, normal laboratory ranges should be given for each analysis (ICH E3). Where possible, laboratory values should be provided in standard international units.

A brief overview of the major changes in laboratory values across the clinical studies should be provided. Laboratory data should include hematology, clinical chemistry, urinalysis, and other data as appropriate. Each parameter at each time over the course of the study (e.g., at each visit) should be described at the following three levels:

- the central tendency, that is, the group mean and median values;
- the range of values, and the number of subjects with abnormal values or with abnormal values of a certain size (e.g., twice the upper limit of normal, 5 times the upper limit; choices should be explained). When data are pooled from centers with differences in normal laboratory ranges, the methodology used in pooling should be described. The analysis of individual subject changes by treatment group can be shown with a variety of approaches (e.g., shift tables, see ICH E3 for examples); and
- individual clinically important abnormalities, including those leading to discontinuations. The significance of the laboratory changes and the likely relation to the treatment should be assessed (e.g., by analysis of such features as relationship to dose, relation to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy). Potential relationships to other factors listed in section 2.7.4.2.1.1 should also be considered.

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

The manner of presenting cross-study observations and comparisons of vital signs (e.g., heart rate, blood pressure, temperature, respiratory rate), weight, and other data (e.g., electrocardiograms, x-rays) related to safety should be similar to that for laboratory variables. If there is evidence of a drug effect, any dose–response or drug concentration–response relationship or relationship to individual variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events. Particular attention should be given to studies that were designed to evaluate specific safety issues, for example, studies of QT interval prolongation.

2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Intrinsic Factors

This section should summarize safety data pertinent to individualizing therapy or patient management on the basis of demographic and other factors defined as “intrinsic ethnic factors” in ICH E5. These factors include age, sex, height, weight, lean body mass, genetic polymorphism, body composition, other illness, and organ dysfunction. Safety in the paediatric population should be routinely analyzed in applications for a proposed indication that occurs in children. Analysis of the impact of such factors on safety outcomes should have been presented in other sections but should be summarized here, together with pertinent PK or other information, for example, in patients with renal or hepatic disease. If a sufficiently large number of subjects with a given comorbid condition such as hypertension, heart disease, or diabetes, was enrolled, analyses should be carried out to as-

sess whether the comorbid condition affected the safety of the drug under study. Cross-reference should be made to the tables or description of adverse events when analyses of such subgroups has been carried out.

2.7.4.5.2 Extrinsic Factors

This section should summarize safety data pertinent to individualizing therapy or patient management on the basis of factors defined as “extrinsic ethnic factors” in ICH E5. These are factors associated with the patient environment. Examples are the medical environment, use of other drugs (see 2.7.4.5.3, Drug Interactions), use of tobacco, use of alcohol, and food habits.

For example, if a potential interaction with alcohol is suggested by the metabolic profile, by the results of studies, by postmarketing experience, or by information on similar drugs, information should be provided here.

2.7.4.5.3 Drug Interactions

Studies on potential drug–drug or drug–food interactions should be summarized in the Summary of Clinical Pharmacology Studies section of the CTD (section 2.7.2). The potential impact on safety of such interactions should be summarized here, based on PK, PD, or clinical observations. Any observed changes in the adverse event profile, changes in blood levels thought to be associated with risk, or changes in drug effects associated with other therapy should be presented here.

2.7.4.5.4 Use in Pregnancy and Lactation

Any information on safety of use during pregnancy or breastfeeding that becomes available during clinical development or from other sources should be summarized here.

2.7.4.5.5 Overdose

All available clinical information relevant to overdose, including signs/symptoms, laboratory findings, and therapeutic measures/treatments and antidotes (if available) should be summarized and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.

2.7.4.5.6 Drug Abuse

Any relevant studies/information regarding the investigation of the dependence potential of a new therapeutic agent in animals and in humans should be summarized and cross-referenced to the nonclinical summary. Particularly susceptible patient populations should be identified.

2.7.4.5.7 Withdrawal and Rebound

Any information or study results pertinent to rebound effects should be summarized. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study medication. Particular emphasis should be given to studies designed to evaluate withdrawal and/or rebound.

Data concerning tolerance should be summarized under section 2.7.3.5 in the Summary of Clinical Efficacy.

2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Safety data related to any impairment in the senses, coordination, or other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability should be summarized. This includes relevant adverse effects reported in safety monitoring

(e.g., drowsiness) and specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability.

2.7.4.6 Postmarketing Data

If the drug has already been marketed, all relevant postmarketing data available to the applicant (published and unpublished, including periodic safety update reports if available) should be summarized. The periodic safety update reports can be included in Module 5. Details of the number of subjects estimated to have been exposed should be provided and categorized, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subjects exposed should be described. If estimates of the demographic details are available from any source, these should be provided.

A tabulation of serious events reported after the drug is marketed should be provided, including any potentially serious drug interactions.

Any postmarketing findings in subgroups should be described.

2.7.4.7 Appendix

Tabular presentations should be provided that summarize the important results from all studies pertinent to the evaluation of safety and particularly to support product labeling.

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

A few illustrative tables are provided, but a clinical summary will routinely need tables and figures that have been developed for the particular drug, drug class, and clinical indication(s).

See sections 2.7.4.2.1, 2.7.4.2.2.3, and 2.7.4.3 of this guidance for additional discussion regarding the content of section 2.7.4 tables.

Table 2.7.4.1	Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure
Table 2.7.4.2	Demographic Profile of Patients in Controlled Trials
Table 2.7.4.3	Incidence of Adverse Events in Pooled Placebo- and Active Controlled Trials
Table 2.7.4.4	Incidence of Adverse Events in the Largest Trials
Table 2.7.4.5	Patient Withdrawals by Study: Controlled Trials
Table 2.7.4.6	Listing of Deaths

2.7.5 Literature References

A list of references cited in the Clinical Summary should be provided. Copies of all important references should be provided in Module 5, section 5.4. The reference list should indicate which references are available in Module 5, section 5.4. All references that have not been provided should be available upon request.

2.7.6 Synopses of Individual Studies

The ICH E3 guideline (Structure and Content of Clinical Study Reports) suggests inclusion of a study synopsis with each clinical study report, and provides one example of a format for such synopses.

This section should include the table entitled Listing of Clinical Studies, described in guidance for Module 5, followed by all individual study synopses organized in the same sequence as the study reports in Module 5.

It is expected that one synopsis will be prepared per study for use in all regions, and that the same synopsis will be included in this section and as part of the clinical study report in Module 5. The length of a synopsis will usually be up to three pages, but a synopsis for a more complex and important study may be longer, for example, 10 pages. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

Table 2.7.1.1

Summary of Bioavailability Studies

Table 2.7.1.2

Summary of In vitro Dissolution Studies

Table 2.7.2.1

Summary of Drug–Drug Interaction PK Studies

MODULE 5: CLINICAL STUDY REPORTS

Preamble

Through the ICH process, a guideline has been published on the structure and content of clinical study reports (E3). This document provides guidance on the organization of these study reports, other clinical data, and references within a CTD for registration of a pharmaceutical product for human use. These elements should facilitate the preparation and review of a marketing application.

This guideline is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that are in the application.

Detailed Organization of Clinical Study Reports and Related Information in Module 5.

This guideline recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as “not applicable” or “no study conducted” should be provided when no report or information is available for a section or subsection.

5.1 Table of Contents of Module 5

A Table of Contents for study reports should be provided.

5.1	Table of Contents of Module 5
5.2	Tabular Listing of All Clinical Studies
5.3	Clinical Study Reports
5.3.1	Reports of Biopharmaceutical Studies
5.3.1.1	Bioavailability (BA) Study Reports
5.3.1.2	Comparative BA and BE Study Reports
5.3.1.3	In vitro–In vivo Correlation Study Reports
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies

- 5.3.2. **Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials**
 - 5.3.2.1 Plasma Protein Binding Study Reports
 - 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
 - 5.3.2.3 Reports of Studies Using Other Human Biomaterials
- 5.3.3. **Reports of Human Pharmacokinetic (PK) Studies**
 - 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports
 - 5.3.3.2 Patient PK and Initial Tolerability Study Reports
 - 5.3.3.3 Intrinsic Factor PK Study Reports
 - 5.3.3.4 Extrinsic Factor PK Study Reports
 - 5.3.3.5 Population PK Study Reports
- 5.3.4. **Reports of Human Pharmacodynamic (PD) Studies**
 - 5.3.4.1 Healthy Subject PD and PK/PD Study Reports
 - 5.3.4.2 Patient PD and PK/PD Study Reports
- 5.3.5. **Reports of Efficacy and Safety Studies**
 - 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
 - 5.3.5.2 Study Reports of Uncontrolled Clinical Studies
 - 5.3.5.3 Reports of Analyses of Data from More Than One Study
 - 5.3.5.4 Other Clinical Study Reports
- 5.3.6. **Reports of Postmarketing Experience**
- 5.3.7. **Case Report Forms and Individual Patient Listings**
- 5.4 **Literature References**

5.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 5.1 of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in section 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutical Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution end points, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in section 5.3.1, and referenced in sections 5.3.1.1 and/or 5.3.1.2.

5.3.1.1 Bioavailability (BA) Study Reports

BA studies in this section should include

- studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form;
- dosage form proportionality studies; and
- food-effect studies.

5.3.1.2 Comparative BA and BE Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

- the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product,
- the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and
- similar drug products from different manufacturers.

5.3.1.3 In Vitro –In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate in vitro data with in vivo correlations, should be placed in section 5.3.1.3. Reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutical studies or in vitro dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in section 5.3.1.4 and referenced in the appropriate individual study reports.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues, and related materials derived from human sources that are used in vitro or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug–drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).

5.3.2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided here. Protein-binding data from PK blood and/or plasma studies should be provided in Section 5.3.3.

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

5.3.2.3 Reports of Studies Using Other Human Biomaterials

Reports of studies with other biomaterials should be placed in this section.

5.3.3 Reports of Human PK Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant

drug use, and to interpreting observed PD differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular those that have pharmacological activity.

The PK studies whose reports should be included in sections 5.3.3.1 and 5.3.3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or feces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells.

On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in section 5.3.3.1 to 5.3.3.2, as appropriate. These studies should characterize the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in sections 5.3.3.1 and/or 5.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug–drug interactions, diet, smoking, and alcohol use) factors. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organized in sections 5.3.3.3 and 5.3.3.4, respectively.

In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose–PK–response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in section 5.3.3.5.

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

5.3.3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in patients should be placed in this section.

5.3.3.3 Intrinsic Factor PK Study Reports

Reports of PK studies to assess effects of intrinsic factors should be placed in this section.

5.3.3.4 Extrinsic Factor PK Study Reports

Reports of PK studies to assess effects of extrinsic factors should be placed in this section.

5.3.3.5 Population PK Study Reports

Reports of population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials should be placed in this section.

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in section 5.3.5.

This section should include reports of (1) studies of pharmacological properties known or thought to be related to the desired clinical effects (biomarkers), (2) short-term studies of the main clinical effect, and (3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose–response studies or together with drug concentration information in PK studies (concentration–response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose–response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

Dose-finding, PD, and/or PK–PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD, and/or PK/PD studies conducted in healthy subjects should be placed in section 5.3.4.1, and the reports for those studies conducted in patients should be placed in section 5.3.4.2.

In some cases, the short-term PD, dose-finding, and/or PK–PD information found in PD studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit end point (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in section 5.3.5, not in section 5.3.4.

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having nontherapeutic objectives in healthy subjects should be placed in this section.

5.3.4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in this section.

5.3.5 Reports of Efficacy and Safety Studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and nonproposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see ICH E3 and individual guidance by region).

Within section 5.3.5, studies should be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be

categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate section 5.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate section 5.3.5 and referenced as necessary in other sections 5.3.5, for example, section 5.3.5A, section 5.3.5B.

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control
- Dose response (without placebo)
- Active control (without placebo)
- External (historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in section 5.3.5.1.

Where a PD study contributes to evidence of efficacy, it should be included in section 5.3.5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in section 5.3.5.1.

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in section 5.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.3.5.3 Reports of Analyses of Data from More than One Study

Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in section 5.3.5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics,

and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.3.5.4 Other Study Reports

This section can include

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports of clinical experiences with the medicinal product that are not included in section 5.3.5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in section 5.3.5.1
- Reports of ongoing studies

5.3.6 Reports of PostMarketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in section 5.3.6.

5.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings that are described as Appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

5.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

1. General Questions

Format or Content?

Will a dossier using the CTD format (Modules 2–5) be identical for all regions? Not necessarily. The CTD provides a common format for the submission of information to regulatory authorities in the three ICH regions. However, the CTD does not address the content of submissions. There are many regional requirements, as well as applicants' preferences, that could affect the contents of dossiers submitted in each region.

Expert Reports: Are expert reports still required for submissions under the CTD format? No. Expert reports are replaced by Module 2. (N.B. For specific European requirements regarding experts' signatures, please refer to the European Commission Web site.)

Tables of Contents and Pagination: For a paper CTD submission, the guideline states that, for the comprehensive Table of Contents in Module 1, no page numbers should be used. Does this apply only to the TOC in Module 1, or for all TOCs in every module? Also, besides the volume numbers and tab identifiers, should the module numbers also be

included? For Modules 3, 4, and 5, should the volume number be part of the Table of Contents? There are no specific guidelines for the page numbers of the TOC. Module numbers, volume numbers, and tab dividers should be part of all TOCs.

How to Paginate Literature References: When provided, how should Literature References be paginated in a paper CTD? Should each reference start with page 1, or should the page number from the source (journal, abstract, etc.) be the only page number included? Literature References should be paginated according to the page numbering of the source (journal, abstract, etc.).

Subheading Numbering, or Numbering Within Sections: How should subnumbering within a document be organized? Some documents can be up to 50 pages in length with no defined CTD guideline heading, and potentially therefore no TOC entries or bookmarks (in the electronic version). Some guidance would be welcome to avoid regional interpretations on what is considered acceptable. Within the document, the applicant can use section numbers at a lower level than those specified in the CTD guideline. However, there should be no other headings appearing in the overall TOC going below the numbering given in the CTD guideline. *For example, for section 3.2.P.3.3 it would be possible to use subsequent numbers (3.2.P.3.3.1, 3.2.P.3.3.2, etc.) to provide further navigation within the document. These should not appear in the overall TOC but can be included as bookmarks within the PDF files.*

Titles of Documents Within Sections (e.g., reports etc.): In the header or footer of each document in a dossier, the appropriate TOC title entry should be included. In case of, for example, a clinical report, the TOC entry is the title of the report and this can be really long. Would the use of the report number (alone) be considered sufficient? In other words, can the layout of the pages throughout the dossier be different: One page layout for reports and another one for Quality sections? It is recommended that a distinct identifier be put in headers/footers on every page. However, it does not need to be the full title. An abbreviation would suffice.

Cross-References/Cross-Strings (in Paper Submissions): It is stated in the CTD that the section should be indicated in cross-strings. What is meant here: The section number, or the section number and section name? (The section name is in many cases too long to indicate in a cross-string.) Providing the section header in addition to the section number improves the clarity of the reference, particularly for the uninitiated reader. To reduce the length of the cross-string while maintaining the ease of use, it is recommended to include only the section number in the cross-string and write the text so the reader will also know the section content. For example, "...as seen in the population PK study 101 (5.3.3.5)" helps the reader to find the referenced study report under the Population PK Study Reports section. The text "...no safety problems were noted in the uncontrolled pneumonia study 101A (5.3.5.2)" helps the reader find the referenced study report under the section Study Reports of Uncontrolled Clinical Studies for the Pneumonia indication.

General Glossary of Terms: Will there be a general glossary of recommended terminology for use in the CTD?

No glossary of terms is planned at this time.

Location of the Information on Biological Comparability: A combined comparability section might be beneficial to the review process. Is it possible to consider a modification to the CTD to provide for such a section for Biological products? *N.B. Currently, comparability data should be included under 2.3.S.2/3; preclinically as proposed; and clinically under 2.5.2 and 2.5.6. Each part should summarize briefly the conclusions from the*

other sections (in the clinical summary, antigenicity should go under either 2.7.4.3 or 2.7.4.4 and in the clinical summary, "AEs of special interest" and "Mortality and Hospital Readmission" should go under 2.7.4.2.1.4 (Other significant AEs). No, for the moment, the CTD does not foresee any separate section combining all the comparability data.

Information for Generic Drug Applications: Should the preclinical and clinical summary sections of the CTD be included in applications for generic drug approvals? More specifically, are Module 4 and 5 of the CTD applicable to Abbreviated New Drug Applications (ANDA) in the US and Abridged Marketing Authorization applications in the EU? Both categories of applications apply to generic drug applications, which ordinarily provide preclinical and clinical data based on available literature. The CTD provides a format for the submission of information to regulatory authorities. It does not define content. Please refer to region-specific requirements to determine content requirements for the specific submission type.

Font Style: On the basis of corporate identity, we use the font style "Arial" for all of our documents. Can we use the font style "Arial" for CTDs, or do we have to use "Times New Roman" style to match the recommendation for narrative texts according to the Guidance for Industry "Organization of the CTD"? "Times New Roman 12 point" is recommended for use in the CTD. This corresponds to MS Mincho, 10.5 point for the text written in Japanese.

Language: Can the CTD be in any language (e.g., Japanese, German, French, English)? Is it limited to a single language? The CTD does not address this issue. Please refer to regional guidance.

Changes of Numbering and Section Headers: With regard to the changes regarding numbering and section headers (September 11–12, 2002), are the details in brackets (e.g., name, manufacturer or name, dosage form) only for use in eCTD format or for paper files also? **Headers and page numbering:** What is your guidance for externally produced documents, for example chromatograms, CTD format DMF, regarding page numbering and appropriate headers? Are there allowances regarding these documents with regard to pagination and headers, that is, are we allowed to submit them in the relevant document without a header or page number? **Tab:** Do Tabs have to be printed? Do we have to use the full title with the number string on the tab? This is very difficult if the title is long. These changes in recommendation apply to all CTD/eCTD submissions. Please refer to the CTD General Q & As No. 5 on the ICH Web site. Tabs should be printed for a paper submission. Tab abbreviations are acceptable.

Is there a difference in the level of analysis in the non-clinical overview and the clinical overview in Module 2? Is there a difference between "critical analysis" (nonclinical overview) and "critical assessment" (clinical overview). Please refer to the general guidance for both the nonclinical and clinical overviews. The level of analysis does not differ between these two overviews. The guidance describes the information that should be included in the "critical and integral" assessment/analysis in both overviews.

Is the term "section," defined in the CTD? Is there a different use of the term in Module 2 and 3? Do the ICH regions define sections differently? Each section in the CTD is identified by a number and a heading. Please refer to the Granularity Document Annex for a description documents to be provided in each section. The annex delineates when multiple documents per heading may be provided. Also, refer to regional guidance as to when one or multiple documents should be provided per heading.

Does the deadline for mandatory submission of the CTD in Japan, the EU, and the US (highly recommended in the US) also refer to eCTD? Has ICH considered planning a seminar to help with CTD and eCTD submissions? The deadline does not refer to the eCTD although the regulatory authorities are accepting eCTD submissions. Please refer to regional guidance for specific guidance on eCTD submissions. Currently the ICH is not planning to conduct a CTD seminar. However, the ICH6 Conference, November 2003 in Osaka Japan, will focus on the CTD and eCTD.

Has the DTD reached its final stage of approval in the ICH process? The eCTD DTD has reached step 5 in the ICH process, which is the implementation step.

Is there a definition of which attachments should be included in the CTD? It is not suggested that additional attachments be included in the CTD.

CTD training

Does ICH recommend any particular comprehensive training course on the implementation of the CTD? No, there are no general ICH recommendations for training on CTD implementation.

Applicant's Logo: is it allowed to add the applicant's logo either on top of the CTD, or in the titles of CTD sections. The applicant is free to put his logo on top of the CTD. However, logos are not acceptable in CTD sections' titles. (The latter have been harmonized internationally; therefore, applicants are not allowed to modify them.)

Herbal CTD: Will a Herbal Products version of the CTD be published and how much will it vary from the pharmaceutical CTD. ICH does not plan to issue any specific version of the CTD for Herbal Products.

Granularity: Section headings and numbers, documents location/hierarchy, documents pagination: The CTD specifies many section headings and numbers. Could guidance be provided for all modules on headings in relation to document location and the section headings within those documents? Could guidance also be provided on where in the CTD and eCTD multiple documents can be located in the hierarchy? As a consequence of this definition, could guidance be given on how documents should be paginated and on what the module Table of Contents should therefore include? Please refer to the Annex of the Organization of the Common Technical Document: "Granularity Document".

Amendments and Variations in CTD Format: Is there a separate format for amendments/variations submitted in CTD format or should applicants use the CTD format as it is now? If used as it is now, is it enough to simply indicate whatever modules are not used? The CTD structure is suitable for amendments and variations (refer to regional guidance for applicabilities). The applicant should not submit the modules that are not used, that is, it is unnecessary to include "not applicable" pages against unused CTD headings.

2. Questions Regarding Location Issues

Introduction: This document is intended to provide additional guidance for the preparation of an application file in the CTD-Q format (see section 2: General Issues). It should be read in conjunction with the CTD-Q guideline (Modules 2 and 3). The document also addresses the relationship be-

tween linked CTD-Q sections for certain parameters, such as polymorphism, impurities, or particle size (see section 3: Associated Information Located in Different Sections). This document also clarifies location issues; that is, it indicates in which CTD-Q section(s), requested information should be placed (see section 4: Location Issues in Drug Substance, section 5: Location Issues in Drug Product, and section 6: Location Issues in Appendices). This document does not address the content of an application file. For content questions, refer to regional guidance.

General Issues

Separate or Repeated Sections. There can be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the CTD-Q heading, for example, 2.3.S Drug Substance (Name, Manufacturer A).

Drug Substance. When more than one drug substance is used in a drug product, information should be presented separately as one complete Drug Substance section followed by other complete Drug Substance sections. In some cases, for a single drug substance, it could be considered appropriate and logical to have information presented in multiple Drug Substance sections. For example, separate sections can be warranted when a single drug substance is made at two different manufacturing sites with differences in the manufacturing processes. However, despite these differences, it is likely that these different processes will be described within the same relevant subsection of 3.2.S. If, on the other hand, the differences result in, for example, different specifications, then adding an additional Drug Substance section is recommended (see also Regional Guidance).

Drug Product. Depending upon regional requirements, different drug product presentations (e.g., strengths, container closure types and configurations, formulations) and/or manufacturing schemes (e.g., aseptic and terminal sterilization) can be submitted in the same dossier. In general, when a single dossier can be submitted, information for each of the product presentations and manufacturing schemes should be combined and presented together in one Drug Product section, with information for each of the product presentations and manufacturing schemes provided in the Appendices and Regional Information sections, as warranted. For example, if 100-mg tablets will be marketed in a bottle and a unit-dose blister package, the information should be presented in one Drug Product section. Where most of the quality information would be identical for the two drug products, the data common to both presentations should appear only once. The information that differs between the two should be presented as separate documents under the appropriate subsections (e.g., 3.2.P.7 Container Closure System, 3.2.P.8 Stability). In some cases, however, for product presentations or manufacturing schemes that can be included in a single dossier, it is considered more appropriate and logical to have information presented separately. Information presented separately means one complete Drug Product section followed by other complete Drug Product sections. One such example is that information on a drug product supplied with a reconstitution diluent should be presented in separate Drug Product sections for the drug product and the reconstitution diluent. These could be titled 3.2.P (Drug Product) and 3.2.P (Diluent).

Excipients. If appropriate, where a novel or noncompendial nonnovel excipient is proposed and a significant amount of data is provided for the excipient, this information should be provided in 3.2.A.3 Excipients, which follows the same format and level of subsections as the Drug Substance section. There should be a complete section of 3.2.A.3 Excipients for each novel excipient, or noncompendial nonnovel excipient.

Appendices. There can be occasions where it is appropriate to repeat an Appendix. For example, where a sponsor registers more than one manufacturing facility for the manufacture of a “Biotech” drug, the Appendix 3.2.A.1 should then be repeated.

Regional Information. The content of the Regional Information section (3.2.R) is not harmonized. In this section the documents, their titling and their order should be consistent with the requirements of the relevant region.

Multiple Containers. When there are two containers (e.g., PVC blister and PE bottle) for one drug product, the documents for the drug product part in Module 3 should generally be common. In this case, one set of documentation, 3.2.P.1 through 3.2.P.8, should be provided. The information for the blister and the bottle should be presented in the corresponding sections of the single drug product part in Module 3 (e.g., 3.2.P.7, 3.2.P.8), divided by subsections for each type of container and identified by the type of container.

Bioanalytical Methods. In the CTD, under what section should bioanalytical methods and their associated validation reports be included? In this context, bioanalytical methods are understood to mean analytical procedures used in clinical studies (human clinical pharmacology/bioavailability/bioequivalence) and/or nonclinical studies (nonhuman pharm/tox. studies). The description of analytical procedures and associated validation reports should be submitted in those modules where the corresponding studies are described (i.e., in Module 4, section 4.2.2.1 for analytical procedures and associated validation reports for nonclinical studies and in Module 5, section 5.3.1.4 for analytical procedures and associated validation reports used in clinical studies).

Drug Master Files (DMFs). Can the Drug Master File use the CTD format? Since the DMF systems differ in the three regions, ICH does not address this issue. Consequently, the applicant should check with the relevant competent authority in the region(s).

Drug Substance Containing Additives. If a drug substance is used in the form of a preparation (e.g., a [commercially available] vitamin trituration) in which module/section should the excipient(s) included in the preparation be described? Should the relevant information be given for example in section 3.2.S Drug Substance or in section 3.2.P.4 Drug Product—Control of Excipients? If the drug substance is defined as two or more materials, the manufacturing information would be described in 3.2.S.2.2 and the control of the additional material(s) [e.g., excipient(s)] would be described in 3.2.S.2.3.

3. Associated Information Located in Different Sections

Below, examples of multiple references in CTD-Q are proposed for polymorphism, particle size, and impurities. They indicate for some parameters that the information should not necessarily be located in one section, but should be split into different sections.

3.1 Polymorphism

- 3.2.S.1.3 If called for, list the polymorphic form(s) present in the proposed active as a characteristic of the drug substance.
- 3.2.S.2.2 Description of manufacturing process and process controls should indicate which polymorphic form is synthesized.
- 3.2.S.3.1 Studies performed to identify the potential polymorphic forms of the drug substance, including study results. Total number of polymorphs should be listed here and those intended to form the active should be summarized in 3.2.S.1.3.
- 3.2.S.4.1 Specification. If a polymorph is to be defined or limited, it should be discussed here.
- 3.2.S.4.2 Analytical procedures.
- 3.2.S.4.3 Validation of analytical procedures.
- 3.2.S.4.4 Results of batch analyses.
- 3.2.S.4.5 Justification of specification (if appropriate).
Reasons as to why a particular limit on form is appropriate (should also probably refer to 3.2.P.2).
- 3.2.P.2. 1.1 and 3.2.P.2.2.3 Identifies the influence of polymorphism on the drug substance and dosage form.
- 3.2.P.5.1 Specification. If polymorphs are to be controlled in the drug product, they should appear here.
- 3.2.P.5.6 Justification of specification (if called for).

3.2 Particle Size

- 3.2.S.2.2 Description of manufacturing process and process controls.
- 3.2.S.3.1 Studies performed to identify the particle size distribution of the drug substance.
- 3.2.S.4.1 Specification.
- 3.2.S.4.2 Analytical procedures.
- 3.2.S.4.3 Validation of analytical procedures.
- 3.2.S.4.4 Results of batch analyses.
- 3.2.S.4.5 Justification of specification.
- 3.2.P.2.1.1 and 3.2.P.2.2.1 Identification of the influence of particle size on, for instance, dissolution performance (consult the ICH Q6A Decision Tree).

3.3 Impurities

- 3.2.S.3.2 Here, the discussion on impurities and information on their qualification should take place (reference to preclinical and clinical studies): For example, absolute amount at which the impurities can be considered as qualified.
- 3.2.S.4.1 Specification.
- 3.2.S.4.2 Analytical procedures.
- 3.2.S.4.3 Validation of analytical procedures.
- 3.2.S.4.4 Results of batch analyses (all batches including development, clinical, stability).
- 3.2.S.4.5 Justification of specification.
- 3.2.P.5.1 Specification.
- 3.2.P.5.2 Analytical procedures.
- 3.2.P.5.3 Validation of analytical procedures.
- 3.2.P.5.4 Results of batch analyses (all batches including development, clinical, stability).

- 3.2.P.5.5 Characterization of impurities (for those impurities not already discussed under section 3.2.S).
- 3.2.P.5.6 Justification of specification.

batches can also be linked to the impurity levels of batches described in 3.2.S.3.2 and 3.2.P.5.5. Appropriate references to Modules 4 and 5 for the nonclinical and clinical studies can also be made.

3.4 New Location of Quality Information for Investigational Formulations

How does the CTD link information on drug substance batch numbers, drug product batch numbers, nonclinical and clinical study numbers, the levels of impurities, history of formulation development, and any other relevant information? Please clarify the assignment of this information to the nonclinical and clinical sections. The history of development for the drug substance should be included in 3.2.S.2.6.A description of batches and the result of batch analyses should be included in 3.2.S.4.4. The history of formulation development should be included in 3.2.P.2.2.1.A description (including a summary table) of batches and the results of batch analyses for the drug product should be included in 3.2.P.5.4. This information on the history of development and description of

3.5 Where Would the Information Related to Nonviral Adventitious Agents be Placed Within Module 3.2?

The following guidance supersedes the first sentence under 3.2.A.2 for nonviral adventitious agents: The detailed information regarding the routine manufacturing control of adventitious agents, such as bacteria, mycoplasma, and fungi, typically using well-established (e.g., pharmacopoeial) analytical procedures, should be provided in the appropriate sections within Module 3.2.S and 3.2.P. If well-established (e.g., pharmacopoeial) analytical procedures are not used, more detailed information regarding the analytical procedure(s) used should also be included in 3.2.S and 3.2.P. With respect to other nonviral adventitious agents, such as transmissible spongiform encephalopathy agents and prions, the detailed information, should be placed in 3.2.A.2.

3. Location Issues Questions in Drug Substance: 3.2.S

CTD-Q Section 3.2.	Issues/Questions	Answers
S.1 General Information		
S.1.1 Nomenclature		
S.1.2 Structure	Should drawings to show secondary and tertiary structures and, if applicable, quaternary structures of proteins be provided in 3.2.S.1.2?	Drawings to show secondary and tertiary structures and, if applicable, quaternary structures should be provided in 3.2.S.3.1.
S.1.3 General Properties	How much detailed information on the general properties of the drug substance should be included in 3.2.S.1.3?	As stated in CTD-Q, a list of physicochemical and other relevant properties of the drug substance, including biological activity, should be included in 3.2.S.1.3. The information on general properties should be provided only for the form of the drug substance used in the drug product, not possible alternative forms (e.g., polymorphs). More detailed information on the properties of the drug substance, including possible alternative forms, should be included in 3.2.S.3.1.
S.2 Manufacture		
S.2.1 Manufacturers		
S.2.2 Description of the Manufacturing Process and Process Controls	Should information on process controls be provided in section 3.2.S.2.2 or 3.2.S.2.4?	All process controls should be identified in 3.2.S.2.2. For critical controls, additional information should be provided in 3.2.S.2.4.
S.2.3 Control of Materials	Should the discussion and justification of starting materials be included in 3.2.S.2.3?	The discussion and justification of starting materials should be included in 3.2.S.2.3.
	Where should analytical procedures for materials described in 3.2.S.2.3 be included? Since the addition of new headings is not an option, where in the CTD should one locate (Quality Section) information regarding a reagent used in the production of the drug substance when the reagent is manufactured via recombinant DNA technology?	The analytical procedures for the control of materials (e.g., starting materials, reagents, raw materials, solvents) should be presented in section 3.2.S.2.3. For materials of biological origin, analytical procedures related to adventitious agent safety evaluation, if applicable, should be presented in 3.2.A.2. The information should be located in 3.2.S.2.3: "Control of Materials."
S.2.4 Control of Critical Steps and Intermediates	Should batch data for intermediates or critical steps be included in 3.2.S.2.4?	Batch data, together with analytical procedures and acceptance criteria for intermediates or critical steps, would be presented in 3.2.S.2.4.
	If release tests are performed on intermediates and at critical steps instead of on drug substance, where would the information on the analytical procedures and acceptance criteria be presented in 3.2.S.4?	Acceptance criteria should be referred to in 3.2.S.4.1 and analytical procedures should be referred to in 3.2.S.4.2.

CTD-Q Section 3.2.	Issues/Questions	Answers
S.2.5 Process Validation and/or Evaluation	Where should justification for reprocessing be included?	If justification for reprocessing is warranted by a regional authority, the information would be included as part of the description of the manufacturing process in 3.2.S.2.2. If there are critical controls associated with the reprocessing operation, the critical controls should be included in 3.2.S.2.4. If validation information is warranted, the validation information should be included in 3.2.S.2.5.
S.2.6 Manufacturing Process Development	Should bioavailability/bioequivalence study results that demonstrate product comparability following process changes be described in 3.2.S.2.6?	Reports of Bioavailability/Bioequivalence studies that demonstrate comparability/equivalence after formulation or process changes should be presented in Module 5. Cross-references to these reports should be placed in section 3.2.S.2.6 (for drug substance process changes), 3.2.P.2.2.1 (for drug product formulation changes), or 3.2.P.2.3 (for drug product process changes). A brief summary of the reports can be placed in these sections when considered appropriate.
S.3 Characterization		
S.3.1 Elucidation of Structure and Other Characteristics	Where should studies conducted to determine the physicochemical characteristics of the drug substance be included?	Information on the studies conducted to determine the physicochemical characteristics of the drug substance should be included in 3.2.S.3.1. Only a list of the general properties of the drug substance should be included in 3.2.S.1.3.
S.3.2 Impurities	Should structural characterization data and a summary of the method of preparation of impurities be included in 3.2.S.3.2? Where should chromatograms be provided for impurities? Where should nonclinical and clinical data supporting impurity levels be summarized? Should data on impurities reported in batch analyses be included in 3.2.S.3.2 or 3.2.S.4.4?	This information should be included in 3.2.S.3.2. Characterization of impurity reference standards should be provided in 3.2.S.5. See also Q&A under 3.3. ICH Q3A identifies the chromatograms as part of the analytical validation studies. Therefore, relevant chromatograms should be included in 3.2.S.4.3. The qualified level of each impurity with cross-reference to the supporting nonclinical/clinical studies should be included in 3.2.S.3.2. Data on observed impurities for relevant batches (e.g., clinical, nonclinical, stability) should be provided in 3.2.S.3.2. The data should be provided whether or not the impurity is included in the specification. This information can be cross-referenced to support other sections of the dossier as appropriate.
S.4 Control of Drug Substance		
S.4.1 Specification	If there are different specifications for a drug substance manufacturer and/ or applicant, should they all be provided in 3.2.S.4.1? If alternative analytical procedures are used to control the drug substance, should they also be listed in the specification (3.2.S.4.1)?	When appropriate, more than one specification should be included in 3.2.S.4.1. Any analytical procedure used to control the drug substance, and the associated acceptance criteria, should be listed in the specification.
S.4.2 Analytical Procedures	Often an analytical procedure changes during the development of the drug substance. If this analytical procedure is submitted to support the dossier, in which section should these analytical procedures be placed? Should an analytical procedure that is only used for stability studies be included in 3.2.S.4.2? If the analytical methods for a drug substance and drug product are identical, can these methods and corresponding validation, if applicable, be described in either 3.2.S or 3.2.P, with a corresponding reference (e.g., a reference from 3.2.S to 3.2.P)?	Information on historical analytical procedures used to generate data included in the batch analyses should be included in 3.2.S.4.4. Information on analytical procedures that are used only for stability studies should be included in 3.2.S.7.3. The analytical methods should be placed in both the relevant sections of 3.2.S and 3.2.P, because the sample preparation, at least, will differ.
S.4.3 Validation of Analytical Procedures	Where should chromatograms be included?	Relevant chromatograms should be included in 3.2.S.4.3.
S.4.4 Batch Analyses	Where should results from all relevant batches be provided? If there are results from tests that are not listed in the specifications, where should they be provided? Where should collated data for a test from multiple batch analyses be presented?	Results from all relevant batches (e.g., clinical, nonclinical, stability), including those batches used to justify acceptance criteria should be provided in 3.2.S.4.4. If results are submitted from tests that are not listed in the specification, they should be provided in 3.2.S.4. If collated data from batch analyses is warranted, the data should be presented in 3.2.S.4.4.

CTD-Q Section 3.2.	Issues/Questions	Answers
S.4.5 Justification of Specification	Should justification for skip testing be included in 3.2.S.4.5? Rather than repeating information, can a summary of data from other sections with a cross-reference to the detailed information be provided to support the justification of specification section of the dossier?	If skip testing is considered appropriate, the justification should be included in 3.2.S.4.5. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.
S.5 Reference Standards or Materials	Reference standards might be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.S.5? Where should characterization data for a reference standard be placed in the CTD-Q?	If information is warranted for a reference standard, the information should be included in 3.2.S.5. Characterization data for the reference standard should be included in 3.2.S.5. Cross-reference to information in other sections (e.g., 3.2.S.3.2) can be included as considered appropriate.
S.6 Container Closure System		
S.7 Stability		
S.7.1 Stability Summary and Conclusions		
S.7.2 Postapproval Stability Protocol and Stability Commitment		
S.7.3 Stability Data	Should stress studies be located in 3.2.S.7.3? Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.S.7.3? Can data from supporting studies be included in 3.2.S.7.3? Should information on analytical procedures unique to the stability program be presented in 3.2.S.7.3?	Stress studies should be located in 3.2.S.7.3. These data can be referenced for validation of analytical procedures as considered appropriate. Information on historical analytical procedures used to generate the stability data should be included in 3.2.S.7.3. Data from supporting studies can be included in 3.2.S.7.3, if considered appropriate. Information on analytical procedures unique to the stability program should be included in 3.2.S.7.3.

4. Location Issues in Drug Product: 3.2.P

CTD-Q Section 3.2.	Issues/Questions	Answers
P.1 Description and Composition of the Drug Product	Where should information related to the composition of inks used on the drug product be placed? Where should information on reconstitution diluents be included? Should an overfill be indicated in 3.2.P.1? Can information on the composition of a drug product, other than what is listed in the CTD-Q guideline, be included in 3.2.P.1?	<ol style="list-style-type: none"> <i>All drug product components should be listed in 3.2.P.1. The composition (e.g., components of the capsule shell, components of inks) should also be included in 3.2.P.1. In some regions, the qualitative composition of proprietary components can be replaced with reference to appropriate DMFs.</i> <i>If the diluent is copackaged with the drug product, the information on the diluent should be placed in a separate Drug Product section. The compatibility of the drug product with reconstitution diluents should be discussed in 3.2.P.2.6.</i> <i>The use of an overfill should be indicated in 3.2.P.1. The rationale for an overfill should be included in 3.2.P.2.2.1.</i> <i>When called for, additional information can be included to adequately describe the composition of the drug product, for example, (1) total weight, volume, etc., of unit, (2) tracers or markers, (3) composition statement for (purchased) mixtures, and (4) capsule shells.</i>

CTD-Q Section 3.2.	Issues/Questions	Answers
P.2 Pharmaceutical Development		
P.2.1 Components of the Drug Product	Where should information on the development of copackaged diluents be placed?	There should be a separate Drug Product (Diluent) section for copackaged diluents. Choice and development of copackaged diluents should be included in 3.2.P.2.2.1 and 3.2.P.2.6.
P.2.1.1 Drug Substance	Where should a discussion of the drug substance stability or key physicochemical characteristics that might influence the manufacturing process of the drug product be provided? Where should a discussion of the effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics be provided? Where should data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics be provided?	Drug substance stability data should be included in 3.2.S.7 and cross-referenced as needed in 3.2.P.2 as appropriate. Discussion of key drug substance physicochemical characteristics that can influence manufacturability of the drug product should be included in 3.2.P.2.1.1. Discussion of effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics should be included in 3.2.P.2.1.1. Data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics should be provided in 3.2.P.2.1.1 [see ICH Q6A Decision Trees 3 and 4 (Part 2)].
P.2.1.2 Excipients	Should justification for using an excipient if there is evidence of incompatibility be included in 3.2.P.2.1.1 or 3.2.P.2.1.2? Where should a discussion of an excipient's influence on the manufacturability of the drug product be included? Where should a discussion of the ability of a functional excipient to perform through shelf-life be included?	Justification for using an excipient, if there is evidence of incompatibility should be included in 3.2.P.2.1.1 Discussion of excipients that can influence the manufacturability of the drug product should be included in 3.2.P.2.1.2. Discussion of the ability of functional excipients (e.g., antioxidants, penetration enhancers) to perform through shelf life should be included in 3.2.P.2.1.2. The effectiveness of antimicrobial preservatives should be discussed in 3.2.P.2.5.
P.2.2 Drug Product	Where should tables that describe the composition of formulations used in development studies be included?	Tables describing different development formulations should be included in 3.2.P.2.2.1.
P.2.2.1 Formulation Development	Where should information on IV-IV correlation be included in CTD-Q? Can cross-reference be made to bioequivalence information in other modules? Where should information to justify a scoring of tablets be included? Should the release mechanism of the dosage form for controlled release drug products be described in 3.2.P.2.2.1?	Summarized information on the in vivo-in vitro (IV-IV) correlation should be included in 3.2.P.2.2.1 with a cross-reference to the studies in Module 5. Cross-referencing to both Modules 2 and 5 can be included to facilitate the review process. The rationale/justification for scoring of tablets should be provided in 3.2.P.2.2.1. Description of the release mechanism in the dosage form for controlled release drug products should be included in 3.2.P.2.2.1.
P.2.2.2 Overages	Where should overages be justified?	Justification for overages should be included in 3.2.P.2.2.2.
P.2.2.3 Physicochemical and Biological Properties	Where should any discussion on dissolution development be included? Where should a discussion of the key drug product physicochemical or biological characteristics that might influence the manufacturing process of the drug product be provided? Where should data from studies on the potential effects of key drug substance physicochemical characteristics on the performance of the drug product be provided?	1. A summary of dissolution development should be included in 3.2.P.2.2.3, with cross-reference to studies in Module 5, as considered appropriate. The justification for the dissolution test should be included in 3.2.P.5.6. 2. A discussion of key drug product physicochemical or biological characteristics that can influence manufacturability of the drug product should be included in 3.2.P.2.2.3. 3. Data from studies on drug product to evaluate the appropriateness of the drug product acceptance criteria for physicochemical/ biological properties should be included in 3.2.P.2.2.3 [see ICH Q6A Decision Trees 4 (Part 3) and 7 (Part 1)].
P.2.3 Manufacturing Process Development	Where should justification of sterilization be provided? What information on clinical trial formulations should be included in 3.2.P.2.3?	1. When called for, justification of sterilization should be included in 3.2.P.2.3. 2. Information on clinical trial formulations should be included in 3.2.P.2.2.1. Information on the differences in the manufacturing process among supporting batches (e.g., clinical, stability) and the proposed production process should be included in 3.2.P.2.3.

CTD-Q Section 3.2.	Issues/Questions	Answers
P.2.4 Container Closure System	<ol style="list-style-type: none"> 1. Should information on container closure system leachables and extractables be included in 3.2.P.2.4? 2. Where should performance characteristics of a container closure be provided? 3. Where should information on studies relating to cleaning of metered dose inhalers be included? 4. Where should information on the light protection characteristics of the container closure be provided? 	<ol style="list-style-type: none"> 1. Information on both should be included in 3.2.P.2.4. When warranted, information on leachables should also be included in 3.2.P.5.1 and 3.2.P.5.5. Also, if leachables are confirmed through shelf life as part of the formal stability studies, the results would be reported in 3.2.P.8.3. 2. Information on performance of the container closure system should be included in 3.2.P.2.4 (e.g., priming and repriming studies for metered dose inhalers). 3. Information on cleaning of metered dose inhalers should be included in 3.2.P.2.4. 4. Suitability of the container closure system to protect from light (e.g., light transmission data) should be discussed in 3.2.P.2.4. Photostability data should be provided in 3.2.P.8.3 (defined as a stress study in Q1A/ Q1B).
P.2.5 Microbiological Attributes	Should discussion of Decision Tree 6 from ICH Q6A be included in 3.2.P.2.5?	Discussions relating to ICH Q6A Decision Tree #6 (nonsterile drug substance and excipients) and Decision Tree #8 (nonsterile solid) should be provided in 3.2.P.2.5.
P.2.6 Compatibility	<ol style="list-style-type: none"> 1. Where should data from constitution or dilution studies performed as part of the formal stability studies to confirm product quality through shelf life be provided? 2. Should compatibility of coadministered drugs be provided in 3.2.P.2.6? 3. Should information on incompatible diluents be provided in 3.2.P.2.6? 	<ol style="list-style-type: none"> 1. Information on the compatibility of reconstitution diluents to support claims on the label should be included in 3.2.P.2.6. Data from constitution or dilution studies that are performed as part of the formal stability studies to confirm product quality through shelf life should be reported in 3.2.P.8.3. 2. Compatibility with coadministered drugs should be included in 3.2.P.2.6. 3. Information on incompatible diluents should be provided in 3.2.P.2.6.
P.3 Manufacture		
P.3.1 Manufacturer(s)		
P.3.2 Batch Formula	Should overages be included in 3.2.P.3.2?	Overages should be included in the batch formula in 3.2.P.3.2.
P.3.3 Description of Manufacturing Process and Process Controls	<ol style="list-style-type: none"> 1. Where should reprocessing be described? 2. Should critical steps and intermediates be identified in P.3.3? 3. Should an overfill be identified in 3.2.P.3.3? 4. Should a statement regarding manipulation of ruminant-derived materials in the drug product manufacturing facility be included in 3.2.P.3.3? 	<ol style="list-style-type: none"> 1. Reprocessing should be included as part of the description of the manufacturing process in 3.2.P.3.3. If there are critical controls associated with the reprocessing operation, the critical controls should be included in 3.2.P.3.4. If validation information is warranted, the validation information should be included in 3.2.P.3.5. 2. All process controls should be identified in 3.2.P.3.3. For critical controls, additional information should be provided in 3.2.P.3.4. 3. An overfill should be identified in 3.2.P.3.3. 4. A statement regarding manipulation of ruminant-derived materials in the drug product manufacturing facility should be included here (3.2.P.3.3). If a potential for cross-contamination with adventitious agents exists, additional information should be provided in 3.2.A.1 and 3.2.A.2.
P.3.4 Controls of Critical Steps and Intermediates	<p>Should the detailed information on critical steps and intermediates that have been identified in 3.2.P.3.3 be included in 3.2.P.3.4?</p> <p>Should critical process control values from relevant batches be included in 3.2.P.3.4 to support numeric ranges, limits, etc., for the critical process controls?</p> <p>Where should information on the analytical procedures for an in-process material test performed in lieu of a finished product test be included?</p> <p>If a process test were to replace an end-product test, where would it be mentioned in the specification?</p>	<p>Detailed information should be provided in 3.2.P.3.4 for critical steps and all intermediates that are controlled. Critical process control values from relevant batches to support numeric ranges, limits, etc., for critical process controls should be included in 3.2.P.3.4.</p> <p>In 3.2.P.3.4, the same information should be provided for an in-process material test performed in lieu of a finished product test as that submitted for a finished product test (analytical procedure, methods validation information).</p> <p>If a process test takes the place of an end-product test, it should be listed in the specification (3.2.P.5.1) and specified as a process test (see ICH Q6A).</p>

CTD-Q Section 3.2.	Issues/Questions	Answers
P.3.5 Process Validation and/or Evaluation		
P.4 Control of Excipients	If a significant amount of data for an excipient (e.g., a novel excipient or a noncompendial nonnovel excipient) needs to be provided, where would it be placed?	This information should be included in 3.2.A.3 excipients, if required. If only a minimal amount of information was necessary for these excipients (e.g., pharmacopoeial), this information should be provided in 3.2.P.4.1 and/or 3.2.P.2.1.2.
P.4.1 Specifications		
P.4.2 Analytical Procedures		
P.4.3 Validation of Analytical Procedures		
P.4.4 Justification of Specifications	Where should certificates of analysis or batch data for excipients be included? Can a summary of data from other sections with a cross-reference to the detailed information be provided, rather than repeating this information to support the Justification of Specifications section of the dossier?	Certificates of analysis or batch data for excipients should be included in 3.2.P.4.4. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.
P.4.5 Excipients of Human or Animal Origin	Where should information on excipients of human or animal origin be located?	Information on excipients of human or animal origin should be included in 3.2.P.4.5. Information on adventitious agent safety evaluation should be included in 3.2.A.2. For the location of certifications relating to TSE/BSE, see region specific guidance.
P.4.6 Novel Excipients		
P.5 Control of Drug Product		
P.5.1 Specification(s)	Where should release and shelf life specifications be located? If alternative analytical procedures are used to control the drug product, should they be listed in the specification (3.2.P.5.1) also?	Both specifications should be included in 3.2.P.5.1 (See also question for 3.2.P.8.1). Any analytical procedure used to control the drug product, and the associated acceptance criteria, should be listed in the specification.
P.5.2 Analytical Procedures	Often an analytical procedure changes during the development of the drug product. If this analytical procedure is submitted to support the dossier, in which section should it be placed? Should an analytical procedure that is only used for stability studies be included in 3.2.P.5.2? If the analytical methods for a drug substance and drug product are identical, can these methods and corresponding validation, if applicable, be described in either 3.2.S or 3.2.P, with a corresponding reference (e.g., a reference from 3.2.S to 3.2.P)?	Information on historical analytical procedures used to generate data included in the Batch Analyses section should be included in 3.2.P.5.4. Information on analytical procedures that are used only for stability studies should be included in 3.2.P.8.3. The analytical methods should be placed in both the relevant sections of 3.2.S and 3.2.P because the sample preparation, at least, will usually differ.
P.5.3 Validation of Analytical Procedures		
P.5.4 Batch Analyses	Should results from all batches be provided in 3.2.P.5.4? Should the description of the batches (e.g., batch number, manufacturing site, use) be included in 3.2.P.5.4? If there are results from tests that are not listed in the specifications, where should they be provided? Where should collated data for a test from multiple batch analyses be presented?	Results from all relevant batches (e.g., clinical, nonclinical, stability), including those batches used to justify acceptance criteria, should be provided in 3.2.P.5.4. Information describing the batches should also be included in 3.2.P.5.4. If results are submitted from tests that are not listed in the specification, they should be provided in 3.2.P.5.4. If collated data from batch analyses is warranted, the data should be presented in 3.2.P.5.4.
P.5.5 Characterization of Impurities	Should all observed impurities be listed in 3.2.P.5.5 even if they are not included in the drug product specification?	All observed impurities should be listed. Justification for not including an observed impurity in the specification should be included in 3.2.P.5.6.

CTD-Q Section 3.2.	Issues/Questions	Answers
P.5.6 Justification of Specification(s)	Should justification for skip testing be included in 3.2.P.5.6? Can a summary of data from other sections with a cross-reference to the detailed information be provided to support the justification of the specification rather than repeating information?	If skip testing is considered appropriate, the justification should be included in 3.2.P.5.6. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.
P.6 Reference Standards or Materials	Reference standards might be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.P.6?	Where considered appropriate, a reference standard cited in 3.2.S.5 can be cross-referenced in 3.2.P.6. Information on all other reference standards should be included in 3.2.P.6.
P.7 Container Closure System		
P.8 Stability		
P.8.1 Stability Summary and Conclusion	Should the shelf life specification be repeated under this section? Where should the design and justification for a reduced stability design (e.g., bracketing or matrixing) be discussed?	The shelf life specification should be indicated in 3.2.P.8.1. The design and justification for a reduced stability design should be included in 3.2.P.8.3.
P.8.2 Postapproval Stability Protocol and Stability Commitment		
P.8.3 Stability Data	Should stress studies be located in 3.2.P.8.3? Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.P.8.3? Can data from supporting studies be included in 3.2.P.8.3? Should information on analytical procedures unique to the stability program be presented in 3.2.P.8.3? Where should the statistical analysis of the stability data be included?	Stress studies should be located in 3.2.P.8.3. These data can be referenced for validation of analytical procedures as considered appropriate. Information on historical analytical procedures used to generate the stability data should also be included in 3.2.P.8.3. Data from supporting studies can be included in 3.2.P.8.3, if considered appropriate. Information on analytical procedures unique to the stability program should be included in 3.2.P.8.3. The detailed statistical analysis report, if included, should go in 3.2.P.8.3, and a summary or conclusions of the statistical analysis should go in 3.2.P.8.1.

5. Location Issues in Appendices: 3.2.A

CTD-Q Section 3.2.	Issues/ Questions	Answers
A Appendices	If information for both the drug substance and the drug product should be included in an appendix (e.g., 3.2.A.1), how should it be presented? Should 3.2.A.3 be retitled from Novel Excipients to Excipients to include noncompendial nonnovel excipients?	If drug substance and drug product information is included in the appendices, then the preferred presentation is drug substance first and then drug product within each section, for example, 3.2.A.1 (Drug Substance, then Drug Product), then 3.2.A.2 (Drug Substance, then Drug Product), then 3.2.A.3 (Drug Substance, if applicable, then Drug Product). At ICH, the title of 3.2.A.3 was changed to Excipients (see 3.2.P.4) to include noncompendial nonnovel excipients.

6. Safety

Kinetics in Pregnant Animals and Neonates: Kinetics in pregnant animals and neonates are included in the PK section. Is it expected that these data will come from PK studies, or can they be from kinetics in the Segment 2 studies? The CTD-S guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

Conduct/Nonconduct of Specific Studies: If a particular category of toxicology studies (e.g., carcinogenicity) is not conducted for a drug because of the nature of the drug (e.g., oncology agent), should the section heading be maintained in the CTD document with an explanation provided as to why these studies were not conducted, or should the heading section be deleted and subsequent sections renumbered? Section headings should be maintained in the CTD document and a brief explanation provided as to why these studies were not conducted.

Pivotal Studies: Would a 3-month toxicity study that was needed to support clinical studies of 3-month duration, that was later replaced with a 9-month toxicity study, be considered “pivotal” and tabulated as in Table 2.6.7.7? Yes. There should be one table for each of the repeat-dose toxicity studies specified by ICH Guideline M3, as well as any other repeat-dose toxicity studies that could be considered pivotal.

Tabulated Summary: Are only toxicologically significant changes, as considered by applicants, to be tabulated in CTD? Only noteworthy findings should be tabulated in CTD. These might include statistically significant differences from controls, as well as noteworthy findings that are not statistically significant.

Impurity Data Table in CTD-Safety—(1) Generally speaking, it is unlikely to have the finalized specification for related substances and their analytical method throughout drug development. Therefore, direct comparison of related-substance data between different stages of development would be very difficult, because of analytical method changes. One purpose of the “Drug Substance” table is to facilitate a review of the qualification of the specified impurities. If the analytical methods have changed, information on early batches may not be applicable for qualification of impurities. In this case, it is recommended to use footnotes in the “Drug Substance” table to identify the batches that are relevant to qualification of impurities.

Impurity Data Table in CTD Safety—(2) Should impurity-specification test results of test articles used in early stage toxicology studies be included in CTD tables? Do test articles of non-GLP studies in the CTD need to have specification test data? There is no requirement to analyze the drug substance used in non-GLP studies. However, if such analyses have been conducted, the results should be included in the “Drug Substance” table.

List of References: A section for list of references of the nonclinical summary (2.6.8 or 2.6.2.8 plus 2.6.4.11 plus 2.6.6.11) is not covered in the guidance, unlike for the clinical summary and both nonclinical and clinical overview. Could you please provide clarity where in these summaries lists of references should be included? Applicants can place the list of references in the most appropriate location and create new subsection numbers as far as it facilitates the best possible understanding by the regulatory reviewers.

Nonclinical PKs: A number of studies in nonclinical PKs could appear more than one place in this section. Should we add nonclinical PK studies to all PKs sections? In such a case, the sponsor could either put that study re-

port in the first place in the CTD module (i.e., Absorption section) and then cross reference to this study report in the remaining sections, or place the full study report in each adequate section. If submitting an eCTD, a sponsor needs not submit multiple files are not required. References to the one file should be provided.

Microbiology data: The microbiology data will include both in vitro and in vivo studies. Where should the microbiology summary, overview, and study reports be included? The Microbiology data from both in vitro and in vivo studies should be included with the Efficacy information. The summary information should be provided in the appropriate section 2.7 Clinical Summary and the reports should be filed in section 5.3.5.4 Other Study Reports. In addition, the microbiology information can be described in the Nonclinical sections as appropriate.

The template for local tolerances (2.6.7.16) in M4S does not provide an example of a tabulated summary of a local tolerance. Is there one available? The template for 2.6.7.16 is the same as the template for 2.6.7.17. Therefore for an example of 2.6.7.16, please refer to the example of 2.6.7.17.

In the development of human monoclonal antibodies, part of the nonclinical development is to perform two cross-reactivity studies (1) animal species cross reactivity study and (2) human tissue cross reactivity study. The animal species cross reactivity test is not really a toxicity study, and the human tissue cross reactivity study is not a study generally performed. We are in doubt where to place these in Module 4. Where should these studies be placed in Module 4? Under 4.2.3.7 Other toxicity studies? Applicants can place such studies in the most appropriate location in Module 4 in order to facilitate the best possible understanding by the regulatory reviewers. (*This can be the similar answer to the Question 8.*)

7. Efficacy

Clinical study reports contained in Module 5 are cited in the Clinical Overview and/or the Clinical Summary in Module 2. Each clinical study report may be given a unique short name when cited. Does the method of citing and naming have to be uniform throughout all modules? We recommend that each study have a unique short identifier that is used consistently throughout the application. The applicant can select the identifier. The full title of the study is provided in the Tabular Listing of All Clinical Studies (section 5.2).

Definitions/Terminology: What is the definition of “Common Adverse Events” as used in the CTD? Guidance is provided by ICH E3 Guideline.

Section Numbering/Title (in Module 5): In the module 5 of the CTD, is it necessary to have a section number for each clinical study report in a certain section, or is it enough just to mention the title:

How many pages should a Clinical Summary be for an application that contains multiple indications? (section 2.7): The estimated size of this document is 50 to 400 pages, assuming one indication. Applications that include multiple indications will be larger, reflecting the submission of multiple efficacy sections.

Section “2.7.3.3” Comparisons and Analyses of Results across Studies: The Guideline provides “This section should also cross-reference important evidence from section 2, such as data that supports the dosage and administration section of the labeling.” However, this

Guideline also provides “section 2.7.3.4. Analysis of Clinical Information Relevant to Recommended Dose.” Please specify how to differentiate the two sections “2.7.3.3” and “2.7.3.4.” Section 2.7.3.3 summarizes the data across all studies that characterize efficacy of the drug; section 2.7.3.4 provides an integrated summary of the dose–response or blood concentration–response relationships of effectiveness. In both cases, supportive data from section 2.7.2 can also be incorporated.

Overall Extent of Exposure (section 2.7): In the Guideline, a table is required to be generated to present the overall extent of drug exposure in all phases of the clinical development. Should the table include “patients alone” or “patients and healthy subjects”? The table should refer to all subjects exposed to at least one dose of the drug product. Appropriate subsets of subjects relevant to the proposed indications should also be identified and considered.

Summary of Clinical Safety (section 2.7): Where should information be described concerning the validity of extrapolation of foreign clinical safety data to a new region? Summaries of any bridging studies using clinical end points [i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5)] should be included in section 2.7.3.2. Where appropriate, such information should also be described in the summarization of safety data as related to intrinsic and extrinsic ethnic factors (ICH E5), in sections 2.7.4.5.1 and 2.7.4.5.2. Finally, some applications might include in section 5.3.5.3a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information. Such information should be included in that detailed analysis of bridging.

Bioavailability/Bioequivalence Study Data (Module 5): Where should the information on bioequivalence studies for a generic application be included? Bioavailability study reports should be included in Module 5 (Clinical documentation), under section 5.3.1 “Reports of Biopharmaceutical Studies.” More specifically, reports of comparative Bioavailability/Bioequivalence studies should go under section 5.3.1.2.

Tabular Listing of Clinical Studies in Paper CTD: In module 5, 5.2 is denoted as the “Tabular Listing of all Clinical Studies.” Is this section for a summary listing of all clinical studies in the submission, or is it for the listings of the individual study reports? In other words, should the listings from the appendices of the individual study reports be included here, rather than as an appendix to the CSR, or are these only listings that summarize all studies?

The tabular listing described in section 5.2 is a listing of all clinical studies in the submission.

ISS/ISE

Does the CTD section on safety in Module 2 replace the section under 21 CFR 314.50(d)(5)(v, vi) calling for integrated summary of safety and effectiveness (ISS/ISE)? The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. FDAs Guideline for the Format and Content of Clinical and Statistical Sections of Application gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyses of all relevant data, not summaries. The Clinical Safety sections of the CTD follow approximately the outline of the sections of

the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (Structure and Content of Clinical Study Reports). The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis. If, the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, then the CTD Module 2 section would fulfill the need for an ISS/ISE. In some cases it will be convenient to write much of what is needed in the CTD Module 2 with appropriate appendices in Module 5. In other cases, the ISS/ISE would be summarized in Module 2, with detailed reports in Module 5. Any questions about these matters can be raised with the reviewing division.

Microbiology Data: The microbiology data will include both in vitro and in vivo studies. Where should the microbiology summary, overview and study reports be included? The Microbiology data from both in vitro and in vivo studies should be included with the Efficacy information. The summary information should be provided in the appropriate section 2.7 Clinical Summary and the reports should be filed in section 5.3.5.4 Other Study Reports. In addition, the microbiology information can be described in the nonclinical sections as appropriate.

Clinical Variation: For a clinical variation application, is it mandatory to submit a clinical overview and a clinical summary, or is it acceptable to submit either only an overview or only a summary? What are the parameters/conditions to be taken into account for choosing one or the other approach? Since variation is a term from the EU regulations, the answer should be provided by the EMEA.

Integrated analysis of efficacy (ISE) – Section 2.7 Clinical Summary—Statistical Listings: What approach should applicants take for the formatting and presentation of their integrated analyzes when they have large amounts of statistical output to present (several thousands of pages)?

As stated in section Reports of Analyzes From More Than One Study 5.3.5.3, where the details of the analysis are too extensive to be reported in a summary document, for example, section Clinical Summary 2.7, they should be presented in a separate report. Such report should be placed in section 5.3.5.3.

Cross references/Cross-strings (in Paper Submissions): It is stated in the CTD that the section should be indicated in cross-strings. What is meant here: The section number, or the section number and section name? (The section name is in many cases too long to indicate in a cross-string.) Providing the section header in addition to the section number improves the clarity of the reference, particularly for the uninitiated reader. To reduce the length of the cross-string while maintaining the ease of use, it is recommended to include only the section number in the cross-string and write the text so the reader will also know the section content. For example, “. . .as seen in the population PK study 101 (5.3.3.5)” helps the reader to find the referenced study report under the Population PK Study Reports section. The text “. . .no safety problems were noted in the uncontrolled pneumonia study 101A (5.3.5.2)” helps the reader find the referenced study report under the section Study Reports of Uncontrolled Clinical Studies for the Pneumonia indication.

Limitations of the Safety Database and Potential Implications: Section 2.5 Clinical Overview and section 2.5.5 Overview of Safety both refer to an assessment of the limitations of the safety database but give few details on

how to describe them. How should these limitations be described? In addition, there is no specific reference to any postmarketing steps the applicant can take to remedy those limitations. Where should a discussion of any postmarketing pharmacovigilance and other postmarketing study plans go? A fuller discussion of how to describe in the CTD the limitations of the safety database and the potential implications for the safety of the drug when marketed is as follows:

- Nonclinical toxicology and safety pharmacology concerns, such as those arising from reproductive/developmental toxicity, carcinogenicity, hepatic injury, central nervous system injury, or effects on cardiac repolarization that are not fully resolved by available human data, or that arise from incomplete testing.
- Limitations of human safety database, such as:
 - Patient selection criteria that excluded people who are likely to be candidates for treatment in medical practice.
 - Evaluations that were deficient for certain purposes (e.g., many drugs with sedative properties are not evaluated for effects on cognitive function in the elderly).
 - Limited exposure of demographic or other subgroups, such as children, women, the elderly, or patients with abnormal hepatic or renal function.
- Identified adverse events and potential adverse events that require further characterization or evaluation with respect to frequency and/or seriousness in the general population or in specific subgroups.
- Important potential risks (e.g., known risks of pharmacologically related drugs) that require further evaluation.
- Drug–drug interactions that have not been assessed adequately.

Such information should be described and discussed in section 2.5.5 Overview of Safety, with appropriate cross references to section 2.7.4 Summary of Clinical Safety and any other relevant sections.

A discussion of any planned postmarketing activity or study to address the limitations of the premarketing safety database, should also be included in section 2.5.5 Overview of Safety, with any protocols for specific studies provided in section 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study).

An ICH guideline (E2E Pharmacovigilance Planning) is being developed to further address the question of how to describe the safety data and its limitations and how to describe planned postmarketing activities and studies.

Multiple Indications: When submitting one dossier for multiple indications, how should the applicant present them in the clinical part of the registration dossier, for example sections 2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy and 5.3.5 Reports of Efficacy and Safety Studies? One section 2.5 Clinical Overview is recommended for multiple indications to be registered along with development rationale and cross-referencing to the corresponding 2.7.3 and 5.3.5 sections; the “benefit/risk” conclusions should support corresponding claimed indications. For section 2.7.3 Summary of Clinical Efficacy, in the case of more than one indication, the following organization is recommended as applicable. The current CTD number-

ing should be retained with identification of the indication, for example:

2.7.3.UTI	Summary of Clinical Efficacy
2.7.3.1.	UTI Background
2.7.3.2.	UTI Summary of Results of Individual Studies
2.7.3.3.	UTI Comparison and Analysis
2.7.3.3.1	UTI Study Population
2.7.3.3.2.	UTI Comparison of Efficacy Results
2.7.3.	Pneumonia Summary of Clinical Efficacy
2.7.3.1.	Pneumonia Background

Other sections follow the same organization where applicable.

For section 5.3.5 Reports of Efficacy and Safety Studies, in case of more than one indication, the following organization is recommended as applicable. The current CTD numbering should be retained with identification of the indications, for example:

5.3.5.	UTI
5.3.5.1.	UTI Controlled Studies
5.3.5.2.	UTI Uncontrolled Studies
5.3.5.	Pneumonia
5.3.5.1.	Pneumonia Controlled Studies
5.3.5.2.	Pneumonia Uncontrolled Studies

Other sections follow the same organization, where applicable.

Narrative descriptions: The CTD guidance for Section Overall Safety Evaluation Plan and Narratives of Safety Studies 2.7.4.1.1 states that narrative descriptions for studies that contributed both efficacy and safety should be included in Section Summary of Results of Individual Studies 2.7.3.2 and only referenced in the safety section. Please clarify whether the narrative to be included in 2.7.3.2 should include the safety results as well as “enough detail to allow the reviewer to understand the exposure. . . and how safety data were collected” or whether the results should be included in section 2.7.4.1.1. In general, safety results should be described in section 2.7.4.1.1, because section Summary of Clinical Efficacy 2.7.3 is devoted to efficacy. To avoid the need to describe the same study twice, section 2.7.3.2 asks for a reasonably complete description of studies pertinent to both safety and efficacy, including, in study narratives, information about the extent of exposure of study subjects to the test drug and how safety data were collected. This approach is confirmed in section 2.7.4.1.1, which notes that narratives for studies contributing both safety and efficacy data should be included in section 2.7.3.2. As noted in section Background and Overview of Clinical Efficacy 2.7.3.1, however, any results of these studies that are pertinent to evaluation of safety should be discussed in section Summary of Clinical Safety 2.7.4.

According to ICH E3 Structure and Content of Clinical Study Reports, the case report forms should be located in Appendix 16.3, the individual patient data listings in Appendix 16.4 and the publications and literature references in Appendices 16.1.11 and 16.1.12 respectively. The CTD organization provides locations for case report forms and individual patient data listings in Module 5.3.7 and for literature references in Module 5.4. Can clarity be provided as

to where these items should actually be placed in CTD and the eCTD submissions? For paper submissions, case report forms and individual patient data listings should be located in Module 5.3.7, identified by study. For eCTD, PDF files for case report forms and individual patient data listings should be organized by study in the folder for Module 5.3.7. However, in the *index.xml* file the leaf elements for the case report forms and individual patient data listings should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element can be placed under the heading 5.3.7 Case Report Forms and In-

dividual Patient Data Listings. Datasets, if required by the region, should be organized according to regional guidance. For paper submissions publications and literature references should be located in Module 5.4. For eCTD, the files for publications and literature references should be located in the folder for Module 5.4. However, in the *index.xml* file the leaf elements for the publications and literature references should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element should be placed under the heading for 5.4 Literature References.

Process Validation: General Principles and Practices

I. INTRODUCTION

This guidance outlines the general principles and approaches that FDA considers to be appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (API or drug substance), collectively referred to in this guidance as drugs or products. This guidance incorporates principles and approaches that manufacturers can use in validating a manufacturing process based on guidance principles listed in the references at the end of this chapter.

This guidance aligns process validation activities with the product lifecycle concept and with existing FDA guidance. The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. This guidance promotes modern manufacturing principles, process improvement, innovation, and sound science and applies to all drugs, human, veterinary, biological, finished products, pharmaceutical and biological API but is not relevant for dietary supplements, medical devices, type A medicated articles and human transplant tissues.

This guidance also does not specifically discuss the validation of automated process control systems (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug manufacturing equipment. This aspect is discussed elsewhere in another chapter. This guidance is relevant, however, to the validation of processes that include automated equipment in processing.

II. BACKGROUND

In the Federal Register of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled “Guideline on General Principles of Process Validation” (the 1987 guidance). This guidance includes many changes to the original concepts of validation and includes FDA’s current thinking on process validation in concordance with the goals of FDA’s initiative entitled “Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach,” particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts.

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The current good manufacturing practice (CGMP) regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess [21 CFR 211.100(a) and 211.110(a)]. Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use; this principle in-

corporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

For purposes of this chapter, process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes the process validation activities in three stages.

- Stage 1—Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2—Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
- Stage 3—Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

This chapter describes activities typical in each stage, but in practice, some activities in different stages might overlap.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions, including those conditions that pose a high risk of process failure.

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process. Manufacturers should

- understand the sources of variation,
- detect the presence and degree of variation,
- understand the impact of variation on the process and ultimately on product attributes, and
- control the variation in a manner commensurate with the risk it represents to the process and product.

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product. Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.

III. STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act, which states the following:

A drug . . . shall be deemed to be adulterated . . . if . . . 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 this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

FDA regulations describing CGMP are provided in 21 CFR parts 210 and 211.

Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that “[t]here shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess” (emphasis added). This regulation requires that manufacturers design a process including operations and controls that will result in a product meeting these attributes. Product quality in the context of process validation means that product performance is consistent from batch-to-batch and unit-to-unit. Many products are single-source or involve complicated processes to manufacture. Validation also offers assurance that a process is reasonably safeguarded from sources of variability affecting production output, the loss of which can cause supply problems, thereby negatively affecting public health.

Other CGMP regulations define the various aspects of validation. Section 211.110(a), Sampling and testing of in-process materials and drug products, requires that control procedures “. . . be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product” (emphasis added). This regulation establishes the requirement that even well-designed processes must include in-process control procedures to assure final product quality.

CGMP regulations require that batch samples represent the batch under analysis [see, e.g., § 211.160(b)(3)] and that the sampling plan result in statistical confidence [§ 211.165(c) and (d)] that the batch meets its predetermined specifications [§ 211.165(a)]. Section 211.110(b) provides two principles to follow when establishing in-process specifications. The first principle is that “. . . in-process specifications for such characteristics (of in-process material and the drug product) shall

be consistent with drug product final specifications. . . .” Accordingly, in-process material should be controlled to assure that the final drug product will meet its quality requirements. The second principle in this regulation further requires that in-process specifications “. . . shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.” This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability.

The CGMP regulations also describe and define activities connected with process design, development, and maintenance. Section 211.180(e) requires that information and data about product performance and manufacturing experience be periodically reviewed to determine whether any changes to the established process are warranted. Ongoing feedback about product performance is an essential feature of process maintenance.

In addition, the CGMP regulations require that facilities in which drugs are manufactured be of suitable size, construction, and location to facilitate proper operations (21 CFR 211.42). Equipment must be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use (21 CFR 211.63). Automated, mechanical, and electronic equipment must be calibrated, inspected, or checked according to a written program designed to assure proper performance (21 CFR 211.68).

In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.

IV. RECOMMENDATIONS

A. General Considerations for Process Validation

In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient. These practices should ensure uniform collection and assessment of information about the process, reduce the chance for redundant information gathering and analysis, and enhance the accessibility of such information later in the product lifecycle.

An integrated team approach is recommended to process validation that includes expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. Project plans, along with the full support of senior management, are essential elements for success.

Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. All studies should be planned and conducted according to sound scientific principles, appropriately documented, and should be approved in accordance with the established procedure appropriate for the stage of the lifecycle.

B. Specific Stages and Activities of Process Validation in the Product Lifecycle

The following subsections describe the recommended stages and specific activities.

1. Stage 1—Process Design

a. Building and Capturing Process Knowledge and Understanding

Process design is the activity of defining the commercial manufacturing process that will be reflected in the master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its critical quality attributes.

Generally, early process design experiments do not need to be performed under CGMP conditions. They should, however, be conducted in accordance with sound scientific methods and principles, including good documentation practices. This recommendation is consistent with ICH guidance for industry, Q10 Pharmaceutical Quality System. Decisions and justification of the controls should be sufficiently documented and internally reviewed to verify and preserve their value for use later in the lifecycle of the process and product.

There are exceptions, however. For example, viral and impurity clearance studies have a direct impact on drug safety and should be performed under CGMP conditions, even when performed at small scale. The quality unit should be involved with these studies as is typical during commercial production.

Product-development activities provide key inputs to the design stage, such as the intended dosage form, the quality attributes, and a general manufacturing pathway. Process information available from the product-development stage can be leveraged in the process-design stage. However, the full spectrum of input variability typical of commercial production is not generally known at this stage. The functionality and limitations of commercial manufacturing equipment should be considered, as well as the contributions of variability by different component lots, production operators, environmental conditions, and measurement systems in the production setting. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability. However, it is not a regulatory expectation that the process be developed and tested until it fails, but rather that a process be controlled within commercial manufacturing conditions, including those combinations of conditions posing a high risk of process failure.

Designing an efficient process with an effective process control approach is dependent on the process knowledge and understanding obtained. Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multifactorial interactions, between the variable inputs (e.g., component characteristics or processing parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product). Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes.

Other activities, such as experiments or demonstrations at laboratory or pilot scale, allow evaluation of certain conditions and prediction of performance of the commercial process. These activities also provide information that can be used to model or simulate the commercial process. Computer-based or virtual simulations of certain unit operations or dynamics can provide process understanding and avoid problems at commercial scale. It is important to understand the degree to which models represent the commercial

process, including any differences that might exist, as this may have an impact on the relevance of information derived from the studies.

It is essential that activities and studies resulting in product understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as significant. This information is useful during the process qualification and continued process verification stages, including when the design is revised or the strategy for control is refined or changed.

b. Establishing a Strategy for Process Control

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.

Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points designed to assure that the operation remains on target and in control with respect to output quality. Special attention to control of the process through operational limits and in-process monitoring is essential (1) where the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination), or (2) when intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified. These controls are included in the master production and control records [see 21 CFR 211.186(a) and (b)(9)].

More advanced strategies, such as process analytical technology (PAT), use timely analysis and control loops to adjust the processing conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of process control. In the case of PAT strategy, the approach to process qualification will be different from that for other process designs. Further information on PAT processes can be found in FDA's guidance for industry on PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>).

The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation.

2. Stage 2—Process Qualification

During the process qualification stage of process validation, the process design is confirmed as being capable of reproducible commercial manufacture. This stage has two elements: (1) design of the facility and qualification of the equipment and utilities, and (2) performance qualification (PQ). During this stage, CGMP-compliant procedures must be followed and successful completion of this stage is necessary before commercial distribution. Products manufactured during this stage, if acceptable, can be released.

a. Design of a Facility and Qualification of Utilities and Equipment

Proper design of a manufacturing facility is required under 21 CFR part 211, subpart C, of the CGMP regulations on Buildings and Facilities. It is essential that activities performed to

assure proper facility design and commissioning precede PQ. Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to in this guidance as qualification. These activities necessarily precede manufacturing products at the commercial scale.

Qualification of utilities and equipment generally includes the following activities:

- Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific use.
- Verifying that utility systems and equipment are built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).
- Verifying that the utility system and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production.

Qualification of utilities and equipment can be covered under individual plans or as part of an overall project plan. The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify (1) the studies or tests to use, (2) the criteria appropriate to assess outcomes, (3) the timing of qualification activities, (4) responsibilities, and (5) the procedures for documenting and approving the qualification. It should also include the firm's requirements for the evaluation of changes. Qualification activities should be documented and summarized in a report with conclusions that address criteria in the plan. The quality control unit must review and approve the qualification plan and report (21 CFR 211.22).

b. Performance Qualification Approach

The PQ is the second element of stage 2, process qualification. The PQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Success at this stage signals an important milestone in the product lifecycle and needs to be completed before a manufacturer commences commercial distribution of the drug product. The decision to begin commercial distribution should be supported by data from commercial batches. Data from laboratory and pilot studies can provide additional assurance.

The approach to PQ should be based on sound science and the manufacturer's overall level of product and process understanding. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PQ. For example, to have sufficient understanding of the commercial process, the manufacturer will need to consider the effects of scale; however, it is not

typically necessary to explore the entire operating range at commercial scale if assurance can be provided by other data. Previous credible experience with sufficiently similar products and processes can also be considered. In addition, it is strongly recommended that firms employ objective measures (e.g., statistical metrics), wherever feasible and meaningful to achieve adequate assurance.

In most cases, PQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch during processing. This greater scrutiny accompanied by a higher level of sampling should continue through the process verification stage, as appropriate.

The extent to which some materials, such as column resins or molecular filtration media, can be reused without adversely affecting product quality can be assessed in relevant laboratory studies, and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture.

A manufacturing process that uses PAT may warrant a different PQ approach. Such a process is one that is designed to measure in real time the attributes of an in-process material and then adjust the process in a timely control loop so the process maintains the desired quality of the output material. The process design stage and the process qualification stage should have as a focus the measurement system and control loop. Regardless, the goal remains the same: establishing scientific evidence that the process is reproducible and will consistently deliver quality products.

c. Performance Qualification Protocol

A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation. It is recommended that the protocol discuss

- The manufacturing conditions including operating parameters, processing limits, and component (raw material) inputs.
- The data to be collected and when and how it will be evaluated.
- Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.
- The sampling plan including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.
- Criteria that provide for a rational conclusion of whether the process consistently produces quality products. The criteria should include the following:
 - A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
 - Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PQ without a documented, science-based justification.
- Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and

verification of material sources (components and container/closures), if not previously accomplished.

- Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.
- Review and approval by appropriate departments and the quality unit.

d. Protocol Execution and Report

Protocol execution should not begin until the protocol has been reviewed and approved by all appropriate departments, including the quality unit. Departure from the established protocol must be made according to established procedure or provisions in the protocol. Such departures must be justified and approved by all appropriate departments and the quality unit before implementation (§ 211.100).

The commercial manufacturing process and routine procedures must be followed [§§ 211.100(b) and 211.110(a)]. The PQ lots should be manufactured under normal conditions by personnel expected to routinely perform each step of each unit operation in the process. Normal operating conditions should cover the utility systems (e.g., air handling and water purification), material, personnel, environment, and manufacturing procedures.

A report documenting and assessing adherence to the written protocol should be prepared in a timely manner after the completion of the protocol. This report should

- Discuss and cross-reference all aspects of the protocol.
- Summarize data collected and analyze the data, as specified by the protocol.
- Evaluate any unexpected observations and additional data not specified in the protocol.
- Summarize and discuss all manufacturing nonconformances such as deviations, aberrant test results, or other information that has bearing on the validity of process.
- Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls.
- State a clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a sufficient state of control. If not, the report should state what should be accomplished before such a conclusion can be reached. This conclusion should be based on a documented justification for the approval of the process, and release of lots produced by it to the market in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage.
- Include all appropriate department and quality unit review and approvals.

3. Stage 3—Continued Process Verification

The goal of the third validation stage is to continually assure that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the CGMP requirements, specifically including the collection and evaluation of information and data about the performance of the process (see below), will allow detection of process drift. The evaluation should determine whether action must be taken to prevent the process from drifting out of control [§ 211.180(e)].

An ongoing program to collect and analyze product and process data that relate to product quality must be established [§ 211.180(e)]. The data collected should include

relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the critical quality attributes are being controlled throughout the process.

It is recommended that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed. Procedures should guard against overreaction to individual events as well as against failure to detect process drift. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If done properly, these efforts can identify variability in the process and/or product; this information can be used to alert the manufacturer that the process should be improved.

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. However, a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. It is recommended that the manufacturer use quantitative, statistical methods whenever feasible. It is also recommended that it scrutinize intra-batch as well as inter-batch variation as part of a comprehensive continued process verification program.

It is recommended continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and sampling and/or monitoring adjusted accordingly.

Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance. Operator errors should also be tracked to measure the quality of the training program; to identify operator performance issues; and to look for potential batch record, procedural, and/or process improvements that could help to reduce operator error. It is recommended that the quality unit meet periodically with production staff to evaluate data, discuss possible trends or drifts in the process, and coordinate any correction or follow-up actions by production.

Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented (21 CFR 211.100). Depending on the significance to product quality, modifications may warrant performing additional process design and process qualification activities.

Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules (21 CFR part 211, subparts C and D). The data should be assessed periodically to determine whether requalification should be performed and the extent of that requalification. Maintenance and calibration frequency should be adjusted based on feedback from these activities.

V. CONCURRENT RELEASE OF PERFORMANCE QUALIFICATION BATCHES

In most cases, the PQ protocol needs to be completed before the commercial distribution of a product. In special situations, the PQ protocol can be designed to release a PQ batch for distribution before completion of the protocol. The conclusions about the manufacturing process should be made when the protocol is completed and the data is fully evaluated.

FDA expects that concurrent release will be used rarely. Concurrent release might be appropriate for processes used infrequently because of limited demand for the product (e.g., orphan drugs), processes with necessarily low production volume per batch (e.g., radiopharmaceuticals, including positron emission tomography drugs), and processes manufacturing medically necessary drugs to alleviate a short supply, which should be coordinated with the Agency (FDA).

When warranted and used, concurrent release should be accompanied by a system for careful oversight of the distributed batch to facilitate rapid customer feedback. For example, customer complaints and defect reports should be rapidly assessed to determine root cause and whether the process should be improved or changed. It is recommended that each batch in a concurrent release program also undergo stability testing and that this test data be promptly evaluated to ensure rapid detection and correction of any problems.

VI. DOCUMENTATION

Documentation at each stage of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. In addition to being a fundamental tenet of following the scientific method, information transparency and accessibility are essential so that organizational units responsible and accountable for the process can make informed, science-based decisions that ultimately support the release of a product to commerce.

The degree and type of documentation required by CGMP is greatest during stage 2, process qualification, and stage 3, continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (see 21 CFR 211.22 and 211.100). Viral and impurity clearance studies, even when performed at small scale, also require full quality unit oversight as is necessary during routine commercial production.

CGMP documents for commercial manufacturing [i.e., the initial commercial master batch production and control record (21 CFR 211.186) and supporting procedures] are key outputs of stage 1, process design. It is recommended that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision-making about their comparability.

VII. ANALYTICAL METHODOLOGY

Process knowledge is dependent on accurate and precise measuring techniques that are used to test and examine the quality of drug components, in-process materials, and finished products. For data to have value in predicting process outcomes, it is essential that the analytical tests be scientifically sound (as required under 21 CFR 211.160). While validated analytical methods are not required during product- and process-development activities, methods should be scientifically sound (e.g., specific, sensitive, and accurate), suitable, and reliable for the specified purpose. There should be assurance of proper equipment function for laboratory experiments. Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described. Analytical methods supporting clinical supply production, particularly stage 2 and 3 studies, must follow appropriate CGMPs in parts 210 and 211.

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Bioequivalence Regulatory Compliance

I. BACKGROUND

Bioequivalence (BE) is defined in 21 CFR 320.1 as “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 becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.” FDA usually considers that the plasma concentration of a drug is a surrogate for the concentration at the site of action for a systemically acting drug. 21 CFR 320.24 outlines options for BE testing. Proving equivalence therefore requires integration of several studies such as pharmacokinetic (PK), pharmacodynamic (PD), controlled-clinical, in vitro studies, and any other specific model or study that may prove useful in proving equivalence.

The concept of BE and the required proof by the regulatory agencies has evolved over the past several decades.

- In the United States, the 1902 federal law for biologics, particularly vaccines, required evaluation for “safety, purity and potency.”
- The 1906 Food and Drugs Act added drugs other than biologics.
- The 1938 FDC act created FDA and evaluation of new drugs based on data in a filed NDA.
- The 1962 law added effectiveness requirement for the approval of NDA.
- 1960s, FDA permits marketing of “similar” while corresponding pioneer products undergo DESI reviews. “Similar” came into market between 1938 and 1962.
- The 1970 FDA terminates marketing of “similar” unless
 - DESI pioneer showed safety and efficacy, and
 - “Similar” manufacturer submits aNDA with formulation and manufacture information (The Supreme Court in the United States v. Generix Drug Corporation supported FDA requirement for aNDA.).
 - The 1984 generic law in the United States (Waxman-Hatch) created a generic approval system for all new drugs, including those approved after 1962. FDA finalized the bioequivalence (BA/BE) regulations (21 CFR 320) wherein the pioneer shows BA in NDA; “similar” to DESI-effective pioneers show BE leading to first U.S. first generics. Several revisions to 21 CFR 320 were made including the most recent one in April 2006. The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub.L. No. 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the act, which established the current aNDA approval process. The showing that must be made for an aNDA to be approved is quite different from what is required in an NDA. An NDA applicant must prove that the drug product is safe and effective. An aNDA does not have to prove the safety and effectiveness of the drug product because an aNDA

relies on the finding FDA has made that the reference-listed drug (RLD) is safe and effective. Instead, an aNDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD [21 USC 355(j)(2)(A)(iv)]. The scientific premise underlying the Hatch-Waxman amendments is that in most circumstances bioequivalent drug products may be substituted for each other. The Generic Animal Drug and Patent Term Restoration Act (GADPTRA) signed into law on November 16, 1988, permits sponsors to submit an abbreviated New Animal Drug Application (aNADA) for a generic version of any off-patent-approved animal drug (with certain exceptions noted in the law) regardless of whether the drug was approved prior to 1962 and subject to the National Academy of Sciences/National Research Council/Drug Effectiveness Study Implementation (NAS/NRC/DESI) review.

A generic drug is bioequivalent to the listed drug if “the rate and extent of the absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses” [21 USC 355(j)(8)(B)(i)].

In vivo and/or in vitro BE testing is required for most generic drug products submitted for marketing approval. A proposed generic drug product must be compared in vivo and/or in vitro to the officially designated reference drug product. Harmonized BE criteria for the interchangeability of pharmaceutical products address the issue of waivers for in vivo trials, which are expensive and, as recently concluded, not always discriminating enough to form the sole basis of approval of interchangeability. As discussed later, the worldwide requirements to demonstrate BE vary widely, mostly as a result of the ability of the regulatory authorities to enforce such requirements, both from an economic as well as ethical perspective.

Drug regulatory authorities must ensure that all pharmaceutical products, including generic drug products, conform to the same standards of quality, efficacy, and safety required of innovator drug products. Therefore, regulatory frameworks must be able to respond to varied and emerging drugs and dosage forms where BE demonstration is required; issues such as BE of topical products, products acting locally, endogenous therapeutic proteins, and more recently, botanical products now need regulatory pathways, besides streamlining and reducing cost of evaluation of more traditional dosage forms where cost considerations, especially in the Third World, and often a lack of good correlation between in vivo studies and clinical response are observed. This chapter addresses these issues and provides a pathway for the prospective filers of marketing approval applications worldwide.

Table 1 Data Requirement for Drug Approval in the United States

	FD&C505(b)(1)	FD&C505(b)(2)	FD&C505(j)	PHS
Application	NDA	NDA	aNDA	BLA
Preclinical	Yes	Yes/No	No	Yes
Clinical	Yes	Yes/No	No	Yes
CMC	Yes	Yes	Yes (PE)	Yes
PK & bioequivalence	Yes	Yes		Yes
Labeling	Yes	Yes	Yes	Yes

Abbreviations: aNDA, abbreviated New Drug Application; CMC, chemistry, manufacturing, and control; FD&C, Food, Drug, and Cosmetic Act; NDA, New Drug Application PHS, Public Health Service; BLA, Biologic License Application.

II. REGULATORY ASPECTS

The regulation of drug quality involves three arrangements in this country. First, the U.S. Congress gave the *U.S. Pharmacopoeia* and the National Formulary revision committees the authority to set standards of strength, quality, and purity of drugs and their finished preparations. The FDA, also authorized by the U.S. Congress, establishes regulations for the development and manufacture of safe and effective drugs. Finally, in-house GMPs of the manufacturer, mostly dictated by the FDA regulations, ensure quality of drug products. The FDA has also decreed on the bioavailability (BA) and BE of drug products. All NDAs and amended NDAs must demonstrate in vivo BA of the drug product that is followed by an in vitro test, usually a dissolution test, of individual batches to ensure the quality. Table 1 shows a comparison of regulatory filing requirements under various applications.

Applicants submitting an NDA or New Animal Drug Application (NADA) under the provisions of section 505(b) in the Federal Food, Drug, & Cosmetic Act (the Act) are required to document BA [21 CFR 320.21(a)]. If approved, an NDA drug product may subsequently become an RLD. Under section 505(j) of the act, a sponsor of an aNDA or aNADA must document first pharmaceutical equivalence and then BE to be deemed therapeutically equivalent to an RLD. Defined as relative BA, BE is documented by comparing the performance of the generic (test) and listed (reference) products. (Pharmaceutical equivalents are drugs that have the same active ingredient; in the same strength; the same dosage form and route of administration; and have comparable labeling and meet compendia or other standards of identity, strength, quality, purity and potency.)

In addition to the standard CMC tests, the active bulk drug substance for an NDA should be studied and controlled via appropriate specifications for polymorphic form, particle size distribution, and other attributes important to the quality of the resulting drug product. To the extent possible and using compendial monographs where appropriate, sponsors of aNDAs should attempt to duplicate the specifications considered important for the RLD. Where the necessary information is not available, applicants may wish to rely on in vitro release to ensure batch-to-batch consistency. CMC guidelines available from FDA are generally applicable to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product for a topical dermatological drug product.

As stated in 21 CFR 320.24, approaches to document BE in order of preference are (1) PK measurements based on measurement of an active drug and/or metabolite in blood, plasma, and/or urine; (2) PD measurements; (3) comparative clinical trials; and (4) in vitro studies.

The science of BE is still undergoing major changes and final rules are established after years of debate and validation of protocols. The U.S. FDA has finalized or drafted several guidelines (Table 2).

III. EQUIVALENCE DOCUMENTATION FOR MARKETING AUTHORIZATION

Pharmaceutically equivalent multisource pharmaceutical products must be verified to be therapeutically equivalent

Table 2 Final and Draft-Stage Biopharmaceutics Guidelines of the U.S. FDA

Guideline	Date Finalized/Draft Issued
Bioanalytical method validation—final	23 May 2001
Bioavailability and bioequivalence studies for orally administered drug products—general considerations (revised)—final	19 March 2003
Cholestyramine powder in vitro bioequivalence—final	15 July 1993
Clozapine tablets: in vivo bioequivalence and in vitro dissolution testing—final	20 June 2005
Corticosteroids, dermatological (topical) in vivo—final	2 June 1999
Dissolution testing of immediate-release solid oral dosage forms—final	25 August 1997
Extended-release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations—final	26 September 1997
Metaproterenol sulfate and albuterol metered dose inhalers—final	27 June 1989
Statistical approach to establishing bioequivalence—final	2 February 2001
Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms on a biopharmaceutical classification system—final	31 August 2000
Potassium chloride (slow-release tablets and capsules) in vivo bioequivalence and in vitro dissolution testing	6 June 1994
Food-effect bioavailability and fed bioequivalence studies	December 2002
Antifungal (topical)—draft	24 February 1990
Antifungal (vaginal)—draft	24 February 1990
Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action—draft	3 April 2003

to one another to be considered interchangeable. Several test methods are available to assess equivalence, including:

- Comparative BA (BE) studies, in which the active drug substance or one or more metabolites is measured in an accessible biologic fluid such as plasma, blood or urine.
- Comparative PD studies in humans.
- Comparative clinical trials.
- In vitro dissolution tests in combination with the Biopharmaceutics Classification System (BCS, see below)

Acceptance of any test procedure in the equivalence documentation between two pharmaceutical products by a drug regulatory authority depends on many factors, including characteristics of the active drug substance and the drug product and the availability of resources to carry out a specific type of study. Wherever a drug produces meaningful concentrations in an accessible biological fluid, such as plasma, BE studies are preferred. Wherever a drug does not produce measurable concentrations in an accessible biological fluid, comparative clinical trials or PD studies may be necessary to document equivalence. In vitro testing, preferably based on a documented in vitro/in vivo correlation or on consideration based on the BCS, may sometimes provide an indication of equivalence between two pharmaceutical products

Oral drugs/drug products for which in vivo equivalence documentation is important: Regulatory authorities require equivalence documentation for multisource pharmaceutical products in which the product is compared to the reference pharmaceutical product. Studies must be carried out using the formulation proposed for marketing. For certain drugs and dosage forms, in vivo equivalence documentation, through either a BE study, a comparative clinical PD study, or a comparative clinical trial, is considered especially important. The following are the factors for oral drug products that should be considered when requiring in vivo equivalence documentation.

Immediate-release oral pharmaceutical products with systemic action when one or more of the following criteria apply.

1. Indicated for serious conditions requiring definite therapeutic response
2. Narrow therapeutic window /safety margin, steep dose-response curve
3. PKs complicated by variable or incomplete absorption or absorption window, nonlinear PKs, pre-systemic elimination/high first-pass metabolism >70%
4. Unfavorable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability
5. Documented evidence of BA problems related to the drug or drugs of similar chemical structure or formulations
6. Where there is a high ratio of excipients to active ingredients

Nonoral and nonparenteral pharmaceutical products designed to act through systemic absorption (such as transdermal patches, suppositories): Plasma concentration measurements over time (BE) are normally sufficient proof for efficacy and safety.

Sustained or otherwise modified-release pharmaceutical products designed to act through systemic absorption: Plasma concentration measurements over time (BE) are normally sufficient proof for efficacy and safety.

Fixed combination products (see WHO Technical Report Series No. 825, 1992) with systemic action: Plasma con-

centration measurements over time (BE) are normally sufficient proof for efficacy and safety.

Nonsolution pharmaceutical products for nonsystemic use (oral, nasal, ocular, dermal, rectal, vaginal application) and intended to act without systemic absorption: In these cases, the BE concept is not suitable and comparative clinical or PD studies are required to prove equivalence. This does not, however, exclude the potential need for drug concentration measurements to assess unintended partial absorption.

IV. THERAPEUTIC CLASSIFICATION

FDA has also provided a therapeutic classification of drugs and dosage forms for the purpose of BE testing (Table 3).

V. TOPICS RELATED TO REGULATORY COMPLIANCE

A. Is a BE Study Required?

The submission of an NDA, aNDA, or supplemental application requires that it contains in vivo BA and BE data either by direct measurement of in vivo BA of the drug product that is the subject of the application or information to permit FDA to waive the submission of evidence measuring in vivo BA. The supplemental application involves a change in the manufacturing site or a change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application, or a change in the labeling to provide for a new indication for use of the drug product, for which a new clinical trial may be required.

FDA may approve a full NDA, or a supplemental application proposing any of the changes set forth earlier that does not contain evidence of in vivo BA or information to permit waiver of the requirement for in vivo BA data.

- For certain drug products, the in vivo BA or BE of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the BA or demonstrating the BE of these drug products. A drug product's in vivo BA or BE may be considered self-evident based on other data in the application.
- If the drug product is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA or aNDA; or
- if the drug product is administered by inhalation as a gas, for example, a medicinal or an inhalation anesthetic, and contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full NDA or aNDA; or
- if the drug product is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form and contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full NDA or aNDA and contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full NDA or aNDA that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

Table 3 Therapeutic Equivalence Code Classifications of the U.S. FDA

Name	Definition	FDA code
Products in conventional dosage forms not presenting bioequivalence problems	Products coded as AA contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. However, all oral dosage forms must, nonetheless, meet an appropriate in vitro test(s) for approval.	AA
Products meeting necessary bioequivalence requirements	Products generally will be coded AB if a study is submitted demonstrating bioequivalence. Even though drug products of distributors and/or repackagers are not included in the list, they are considered therapeutically equivalent to the application holder's drug product if the application holder's drug product is rated AB or is single source in the List. The only instance in which a multisource product will be rated AB on the basis of bioavailability rather than bioequivalence is where the innovator product is the only one listed under that drug ingredient heading and has completed an acceptable bioavailability study. However, it does not signify that this product is therapeutically equivalent to the other drugs under the same heading. Drugs coded AB under an ingredient heading are considered therapeutically equivalent only to other drugs coded AB under that heading.	AB
Solutions and powders for aerosolization	Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded AN. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded BN, unless they have met an appropriate bioequivalence standard because drug products in their respective delivery systems are not necessarily pharmaceutically equivalent to each other and, therefore, are not therapeutically equivalent.	AN
Injectable oil solutions	The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.	AO
Injectable aqueous solutions	It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, Injectable; Injection. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are all considered to be pharmaceutically and therapeutically equivalent provided they are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to ensure that it is given only by the route(s) of administration stated in the labeling. Certain commonly used large volume intravenous products in glass containers are not included on the list (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.	AP
Topical products	There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including solutions, creams, ointments, gels, lotions, pastes, sprays, and suppositories. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and DESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of in vivo bioequivalence has been granted and for which chemistry and manufacturing processes are adequate, are considered therapeutically equivalent, and coded AT. Pharmaceutically equivalent topical products that raise questions of bioequivalence including all post 1962 topical drug products are coded AB when supported by adequate bioequivalence data, and BT in the absence of such data.	AT
Extended-release dosage forms (capsules, injectables, and tablets)	An extended-release dosage form is defined by the official compendia as one that allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form). Although bioavailability studies have been conducted on these dosage forms, they are subject to bioavailability differences, primarily because firms developing extended-release products for the same active ingredient rarely employ the same formulation approach. FDA, therefore, does not consider different extended-release dosage forms containing the same active ingredient in equal strength to be therapeutically equivalent unless equivalence between individual products in both rate and extent has been specifically demonstrated through appropriate bioequivalence studies. Extended-release products for which such bioequivalence data have not been submitted are coded BC, while those for which such data are available have been coded AB.	BC

(Continued)

Table 3 (Continued)

Name	Definition	FDA code
Active ingredients and dosage forms with documented bioequivalence problems	The BD code denotes products containing active ingredients with known bioequivalence problems and for which adequate studies have not been submitted to FDA demonstrating bioequivalence. Where studies showing bioequivalence have been submitted, the product has been coded AB.	BD
Delayed-release oral dosage forms	A delayed-release dosage form is defined by the official compendia as one that releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms. Drug products in delayed-release dosage forms containing the same active ingredients are subject to significant differences in absorption. Unless otherwise specifically noted, the agency considers different delayed-release products containing the same active ingredients as presenting a potential bioequivalence problem and codes these products BE in the absence of in vivo studies showing bioequivalence. If adequate in vivo studies have demonstrated the bioequivalence of specific delayed-release products, such products are coded AB.	BE
Products in aerosol nebulizer drug delivery systems	This code applies to drug solutions or powders that are marketed only as a component of, or as compatible with, a specific drug delivery system. There may, for example, be significant differences in the dose of drug and particle size delivered by different products of this type. Therefore, the agency does not consider different metered aerosol dosage forms containing the same active ingredient(s) in equal strengths to be therapeutically equivalent unless the drug products meet an appropriate bioequivalence standard.	BN
Active ingredients and dosage forms with potential bioequivalence problems	FDA's bioequivalence regulations (21 CFR 320.33) contain criteria and procedures for determining whether a specific active ingredient in a specific dosage form has a potential for causing a bioequivalence problem. It is FDA's policy to consider an ingredient meeting these criteria as having a potential bioequivalence problem even in the absence of positive data demonstrating inequivalence. Pharmaceutically equivalent products containing these ingredients in oral dosage forms are coded BP until adequate in vivo bioequivalence data are submitted. Injectable suspensions containing an active ingredient suspended in an aqueous or oleaginous vehicle have also been coded BP. Injectable suspensions are subject to bioequivalence problems because differences in particle size, polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption. FDA does not consider pharmaceutical equivalents of these products bioequivalent without adequate evidence of bioequivalence.	BP
Suppositories or enemas that deliver drugs for systemic absorption	The absorption of active ingredients from suppositories or enemas that are intended to have a systemic effect (as distinct from suppositories administered for local effect) can vary significantly from product to product. Therefore, FDA considers pharmaceutically equivalent systemic suppositories or enemas bioequivalent only if in vivo evidence of bioequivalence is available. In those cases where in vivo evidence is available, the product is coded AB. If such evidence is not available, the products are coded BR.	BR
Products having drug standard deficiencies	If the drug standards for an active ingredient in a particular dosage form are found by FDA to be deficient so as to prevent an FDA evaluation of either pharmaceutical or therapeutic equivalence, all drug products containing that active ingredient in that dosage form are coded BS. For example, if the standards permit a wide variation in pharmacologically active components of the active ingredient such that pharmaceutical equivalence is in question, all products containing that active ingredient in that dosage form are coded BS.	BS
Topical products with bioequivalence issues	This code applies mainly to post 1962 dermatologic, ophthalmic, otic, rectal, and vaginal products for topical administration, including creams, ointments, gels, lotions, pastes, and sprays, as well as suppositories not intended for systemic drug absorption. Topical products evaluated as having acceptable clinical performance, but that are not bioequivalent to other pharmaceutically equivalent products or that lack sufficient evidence of bioequivalence will be coded BT.	BT
Drug products for which the data are insufficient to determine therapeutic equivalence	The code BX is assigned to specific drug products for which the data that have been reviewed by the agency are insufficient to determine therapeutic equivalence under the policies stated in this document. In these situations, the drug products are presumed to be therapeutically inequivalent until the agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.	BX

Abbreviation: DESI, Drug Effectiveness Study Implementation.

FDA also waives the requirement for the submission of evidence measuring the in vivo BA or demonstrating the in vivo BE of a solid oral dosage form (other than a delayed-release or extended-release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation (DESI) notice or which is identical, related, or similar (IRS) to such a drug product unless FDA has evaluated the drug product, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential BE problem. A drug product so rated reflects a determination by FDA that an in vivo BE

study is required. [A DESI drug is any drug that lacks substantial evidence of effectiveness (less than effective [LTE]) and is subject by FDA to a Notice of Opportunity for Hearing (NOOH). This includes drugs, which are IRS to DESI drugs. Valid values: 2 = safe and effective or non-DESI drug; 3 = drug under review (no NOOH issued); 4 = LTE/IRS drug for some indications; 5 = LTE/IRS drug for all indications; 6 = LTE/IRS drug withdrawn from market.]

For certain drug products, BA may be measured or BE may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the BA or

demonstrating the BE of the drug product if the drug product meets one of the following criteria:

- The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the following conditions are met that the BA of this other drug product has been measured and both drug products meet an appropriate *in vitro* test approved by FDA and the applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients. (except for the delayed-release or extended-release products).
- The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an *in vitro* test that has been correlated with *in vivo* data.
- The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the BA of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met. The BA of the other product has been measured, and both drug products meet an appropriate *in vitro* test approved by FDA.

FDA, for good cause, may waive a requirement for the submission of evidence of *in vivo* BA or BE 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* BA if deferral is compatible with the protection of the public health.

FDA, for good cause, may require evidence of *in vivo* BA or BE for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the BA or BE of the drug product.

B. Prior Review

The Commissioner of Food and Drugs strongly recommends that, to avoid the conduct of an improper study and unnecessary human research, any person planning to conduct a BA or BE study submit the proposed protocol for the study to FDA for review prior to the initiation of the study. FDA may review a proposed protocol for a BE study and will offer advice with respect to whether the conditions are an appropriate design, the choice of reference product, and the proposed chemical and statistical analysis methods are met.

The Commissioner of Food and Drugs shall consider the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents and pharmaceutical alternatives that are not or may not be bioequivalent drug products.

- Evidence from well-controlled clinical trials or controlled observations in patients that such drug products do not give comparable therapeutic effects.
- Evidence from well-controlled BE studies that such products are not bioequivalent drug products.
- Evidence that the drug products exhibit a narrow therapeutic ratio, for example, there is less than a twofold difference in median lethal dose (LD₅₀) and median effective dose (ED₅₀) values, or have less than a twofold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring.

- Competent medical determination that a lack of BE would have a serious adverse effect in the treatment or prevention of a serious disease or condition.
- The physicochemical evidence that the active drug ingredient has a low solubility in water, for example, less than 5 mg/mL, or, if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose far exceeds the volume of fluids present in the stomach (taken to be 100 mL for adults and prorated for infants and children); or, the dissolution rate of one or more such products is slow, for example, less than 50% in 30 minutes when tested using either a general method specified in an official compendium or a paddle method at 50 revolutions/min in 900 mL of distilled or deionized water at 37°C, or differs significantly from that of an appropriate reference material such as an identical drug product that is the subject of an approved full NDA; or, the particle size and/or surface area of the active drug ingredient is critical in determining its BA; or, certain physical structural characteristics of the active drug ingredient, for example, polymorphic forms, conformers, solvates, complexes, and crystal modifications, dissolve poorly and this poor dissolution may affect absorption; or, such drug products have a high ratio of excipients to active ingredients, for example, greater than 5:1; or, specific inactive ingredients, for example, hydrophilic or hydrophobic excipients and lubricants, either may be required for absorption of the active drug ingredient or therapeutic moiety or, alternatively, if present, may interfere with such absorption.
- The PK evidence that the active drug ingredient, therapeutic moiety, or its precursor is absorbed in large part in a particular segment of the GI tract or is absorbed from a localized site, or, the degree of absorption of the active drug ingredient, therapeutic moiety, or its precursor is poor, for example, less than 50%, ordinarily in comparison to an intravenous dose, even when it is administered in pure form, for example, in solution; or, there is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the process of absorption (first-class metabolism) so the therapeutic effect and/or toxicity of such drug product is determined by the rate as well as the degree of absorption; or, the therapeutic moiety is rapidly metabolized or excreted so that rapid dissolution and absorption are required for effectiveness; or, the active drug ingredient or therapeutic moiety is unstable in specific portions of the GI tract and requires special coatings or formulations, for example, buffers, enteric coatings, and film coatings, to ensure adequate absorption; or, the drug product is subject to dose-dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important to BE.

VI. RECORD MAINTENANCE

All records of *in vivo* or *in vitro* tests conducted on any marketed batch of a drug product to ensure that the product meets a BE requirement shall be maintained by the manufacturer for at least 2 years after the approval of the application submitted and would be available to the FDA on request.

- If the formulation of the test article is the same as the formulation(s) used in the clinical studies demonstrating substantial evidence of safety and effectiveness for the test article's claimed indications, a reserve sample of the test article used to conduct an *in vivo* BA study comparing

the test article to a reference oral solution, suspension, or injection

- If the formulation of the test article differs from the formulation(s) used in the clinical studies demonstrating substantial evidence of safety and effectiveness for the test article's claimed indications, a reserve sample of the test article and of the reference standard used to conduct an in vivo BE study comparing the test article to the formulation(s) (reference standard) used in the clinical studies
- For a new formulation, new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing, a reserve sample of the test article and of the reference standard used to conduct an in vivo BE study comparing the test article to a marketed product (reference standard) that contains the same active drug ingredient or therapeutic moiety

Each reserve sample shall consist of a sufficient quantity to permit FDA to perform 5 times all of the release tests required in the application or supplemental application. Each reserve sample shall be adequately identified so that the reserve sample can be positively identified as having come from the same sample as used in the specific BA study. Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the BA study in which the sample from which the reserve sample was obtained was used.

Authorized FDA personnel will ordinarily collect reserve samples directly from the applicant or contract research organization at the storage site during a PAI. If authorized FDA personnel are unable to collect samples, FDA may require the applicant or contract research organization to submit the reserve samples to the place identified in the agency's request. If FDA has not collected or requested delivery of a reserve sample, or if FDA has not collected or requested delivery of any portion of a reserve sample, the applicant or contract research organization shall retain the sample or remaining sample for the 5-year period.

Upon release of the reserve samples to FDA, the applicant or contract research organization shall provide a written assurance that, to the best knowledge and belief of the individual executing the assurance, the reserve samples came from the same samples as used in the specific BA or BE study identified by the agency. The assurance shall be executed by an individual authorized to act for the applicant or contract research organization in releasing the reserve samples to FDA.

A contract research organization may contract with an appropriate independent third party to provide storage of reserve samples provided that the sponsor of the study has been notified in writing of the name and address of the facility at which the reserve samples will be stored. If a contract research organization conducting a BA or BE study that requires reserve sample retention goes out of business, it shall transfer its reserve samples to an appropriate independent third party, and shall notify in writing the sponsor of the study of the transfer and provide the study sponsor with the name and address of the facility to which the reserve samples have been transferred.

The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if BE, testing was performed under contract, the contract research organization shall retain reserve samples of any test article, and reference standard used in conducting an in vivo or in vitro BE study required for approval of the abbreviated application or supplemental application and beyond as required.

VII. CLARIFICATION ON REQUIREMENTS

After the revision of the note for guidance (NfG) on the Investigation on BA and Bioequivalence in 2002, (<http://www.emea.europa.eu/pdfs/human/qwp/140198enfin.pdf>), it appears that some harmonization in the interpretation of critical parts of the guideline is needed.

A. In Which Cases Is It Allowed to Use a Wider Acceptance Range for the Ratio of C_{max}?

NfG states under 3.6.2 "With respect to the ratio of C_{max} the 90% CI for this measure of relative bioavailability should lie within an acceptance range of 0.80 – 1.25. In specific cases, such as a narrow therapeutic range, the acceptance interval may need to be tightened."

NfG also states "In certain cases a wider interval may be acceptable. The interval must be prospectively defined, e.g. 0.75 – 1.33, and justified addressing in particular any safety or efficacy concerns for patients switched between formulations."

The possibility offered here by the guideline to widen the acceptance range of 0.80 to 1.25 for the ratio of C_{max} (not for AUC) should be considered exceptional and limited to a small widening (0.75–1.33). Furthermore, this possibility is restricted to those products for which at least one of the following criteria applies:

1. Data regarding PK/PD relationships for safety and efficacy are adequate to demonstrate that the proposed wider acceptance range for C_{max} does not affect PDs in a clinically significant way.
2. If PK/PD data are either inconclusive or not available, clinical safety and efficacy data may still be used for the same purpose, but these data should be specific for the compound to be studied and persuasive.
3. The reference product has a highly variable within-subject BA. Please refer to the question on highly variable drug or drug products for guidance on how to address this issue at the planning stage of the BE trial.

A post hoc justification of an acceptance range wider than defined in the protocol cannot be accepted. Information that would be required to justify results lying outside the conventional acceptance range at the post hoc stage should be utilized at the planning stage, either for a scientific justification of a wider acceptance range for C_{max}, or for selecting an experimental approach that allows the assessment of different sources of variability.

B. When Can Subjects Classified as Outliers Be Excluded from the Analysis in BE Studies?

Under 3.6.3 the NfG states "Post-hoc exclusion of outliers is generally not accepted" but at the same time acknowledges "the protocol should also specify methods for identifying biologically implausible outliers."

Unbiased assessment of results from randomized studies requires that all subjects are observed and treated according to the same rules that should be independent from treatment or outcome. In consequence, PK data can only be excluded based on nonstatistical reasons that have been either defined previously in the protocol or, at the very least, established before reviewing the data. Acceptable explanations to exclude PK data or to exclude a subject would be protocol violations like vomiting, diarrhea, analytical failure. The search for such explanations must apply to all subjects in all groups independently of the size of the observed PK parameters or its outlying position. Exclusion of data can never be accepted on the basis of statistical analysis or for PK reasons alone, because it is impossible to distinguish between formulation effects and PK effects.

Exceptional reasons may justify post hoc data exclusion but this should be considered with utmost care. In such a case, the applicant must demonstrate that the condition stated to cause the deviation is present in the outlier(s) only and absence of this condition has been investigated using the same criteria for all other subjects.

Results of statistical analyses with and without the group of excluded subjects should be provided.

C. If One Side of the 90% CI of a PK Variable for Testing BE Lies on 0.80 or 1.25, Can We Conclude that the Products Are Bioequivalent?

For establishing BE, the 90% CI should lie *within* the acceptance interval (in most cases, 0.80–1.25), the borders being included. The conclusion that products are bioequivalent is based on the overall scientific assessment of the PK studies, not only on meeting the acceptance range.

D. In Which Cases May a Nonparametric Statistical Model Be Used?

NfG states under 3.6.1, statistical analysis, “AUC and C_{max} should be analysed using ANOVA after log transformation.”

The reasons for this request are the following:

- The AUC and C_{max} values as biological parameters are usually not normally distributed.
- A multiplicative model may be plausible.
- After log transformation, the distribution may allow a parametric analysis.

However, the true distribution in a PK data set usually cannot be characterized due to the small sample size, so it is *not* recommended to have the analysis strategy depend on a pretest for normality. Parametric testing using analysis of variance (ANOVA) on log-transformed data should be the rule. Results from nonparametric statistical methods or other statistical approaches are nevertheless welcome as sensitivity analyses. Such analyses can provide reassurance that conclusions from the experiment are robust against violations of the assumptions underlying the analysis strategy.

For T_{max}, the use of nonparametric methods on the original data set is recommended.

E. When Should Metabolite Data Be Used to Establish BE?

According to the guideline, the only situations where metabolite data *can be used* to establish BE are

- “If the concentration of the active substance is too low to be accurately measured in the biological matrix, thus giving rise to significant variability.” Comments. Metabolite data can only be used if the applicant presents convincing, state-of-the-art

arguments that measurements of the parent compound are unreliable. Even so, it is important to point out that C_{max} of the metabolite is less sensitive to differences in the rate of absorption than C_{max} of the parent drug. Therefore, when the rate of absorption is considered of clinical importance, BE should, if possible, be determined for C_{max} of the parent compound, if necessary at a higher dose. Furthermore, when using metabolite data as a substitute for parent drug concentrations, the applicant should present data supporting the view that the parent drug exposure will be reflected by metabolite exposure.

- “If metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is nonlinear.” Comments. To evaluate the significance of the contribution of metabolites, relative AUCs and nonclinical or clinical PD activities should be compared with those of the parent drug. PK/PD modeling may be useful. If criteria for significant contribution to activity and PK nonlinearity are met, then “it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately.” Any discrepancy between the results obtained with the parent compound and the metabolites should be discussed based on relative activities and AUCs. If the discrepancy lies in C_{max}, the results of the parent compound should usually prevail. Pooling of the plasma concentrations or PK parameters of the parent drug and its metabolite for calculation of BE is not acceptable.

F. When Using Metabolite Data to Establish BE, May One Use the Same Justification for Widening the C_{max} Acceptance Criteria as in the Case of the Parent Compound?

In principle, the same criteria apply as for the parent drug (see question on widening the acceptance range for C_{max}). However, as stated earlier (see question regarding when metabolite data can be used), C_{max} of the metabolite is less sensitive to differences in the rate of absorption than C_{max} of the parent drug. Therefore, widening the C_{max} acceptance range when using metabolites instead of the parent compound is generally not accepted. When the metabolite has a major contribution to, or is completely responsible for, the therapeutic effect, and if it can be demonstrated that a widened acceptance range would not lead to any safety or efficacy concerns, which will usually prove more difficult than for the parent compound (see question on widening the acceptance range for C_{max}), then a widened acceptance range for C_{max} of metabolite may be accepted.

G. What is a “Highly Variable Drug or Drug Product”?

The standard approach to the analysis of a two-treatment, two-sequence, two-period crossover trial is an ANOVA for the log-transformed PK parameters, where the factors formulation, period, sequence, and subject nested within sequence are used to explain overall variability in the observations. The residual coefficient of variation (CV) is a measure of the variability that is unexplained by the aforementioned factors. Amongst others, within-subject variability, formulation variability, analytical errors, and subject by formulation interaction can contribute to this residual variance.

A drug product is called highly variable if its intra-individual (i.e., within-subject) variability is greater than 30%. A high CV as estimated from the ANOVA model is thus an indicator for high within-subject variability. However, a replicate design is needed to assess within-subject variability.

When testing for BE of a product with a nonlinear PK, how should one select the strengths with the largest sensitivity to detect differences in the two products?

Section 5.4 of the guideline states "If a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable" provided five conditions are fulfilled, among which, when PKs is not linear over the therapeutic dose range "the strengths where the sensitivity is largest to identify differences in the two products should be used". Nonlinear PK, in this case, should reflect a nonlinear drug input rate as stated in the guideline.

Generally, it is the studied dose and not the studied formulation strength that is of importance when considering BE for drugs with nonlinear PK characteristics. An exception is when BA is governed by the solubility of the active ingredient. Then BE studies should include the highest formulation strength.

When studies are warranted at the high dose range, they should be performed at the highest commonly recommended dose. If this dose cannot be administered to volunteers, the study may need to be performed in patients. If the study is conducted at the highest acceptable dose in volunteers, the applicant should justify this and discuss how BE determined at this dose can be extrapolated to the highest commonly recommended dose.

When proof of linear absorption or elimination kinetics is lacking, or if evidence of nonlinearity is available, BE between test and reference formulations should be established with both the lowest and the highest doses unless adequately justified by the applicant. This approach is the most sensitive for detecting differences in rate and extent of absorption for substances with dose-dependent PKs. On the other hand, if only one dose is chosen in the BE studies, which dose to choose depends on the cause of nonlinearity. For instance, single-strength studies may be conducted

- On the highest dose for drugs with a demonstrated greater than proportional increase in AUC or C_{max} with increasing dose during single or multiple dose studies. In this case an additional steady-state study may be needed if the drug accumulates (steady-state concentrations are higher than those reached after single dose administration).
- On the lowest dose (or a dose in the linear range) for drugs with a demonstrated less than proportional increase in AUC or C_{max} with increasing dose, for example, if this phenomenon is due to saturable absorption.

When BA of a substance with nonlinear PK is governed by the solubility of the active substance, resulting in a less than proportional increase in AUC with increasing dose, BE should be established with both the lowest and the highest dose (which may exceed the recommended initial dose) and should include the highest formulation strength.

It is worth mentioning that in case of linear kinetics but low or critical solubility, there is a similar need to test the highest strength and dose.

H. What Are the Conditions for Using Urinary PK Data for BE Assessment?

Section 3.3 of the guideline states "The use of urinary excretion data may be advantageous in determining the extent of drug input in case of products predominantly excreted renally, but has to be justified when used to estimate the rate of absorption."

The extent of drug input may be determined by the use of urinary excretion data provided elimination is dose-linear and is predominantly renal as intact drug. However, the use of urinary data has to be carefully justified when used to estimate the rate of absorption. If reliable plasma C_{max} can be determined, this should be combined with urinary data on the extent of absorption for assessing BE.

I. Standardization of BE Studies with Regard to Food Intake. How Strictly Should the Guideline Be Interpreted?

Section 3.2.2 of the guideline states "If the Summary of Product Characteristics (SPC) of the reference product contains specific recommendations in relation to food intake related to food interaction the study should be designed accordingly."

The recommendations concerning food intake in the SPC are not sufficient for regulatory decisions on the adequacy of BE studies. Preferably, the following conditions should be considered separately when the SPC recommends administration of the substance together with food intake.

- If the recommendation of food intake in the SPC is based on PK properties such as higher BA, then a BE study under fed conditions is generally required.
- If the recommendation of food intake is intended to decrease adverse events or improve tolerability, a BE study under fasting conditions is considered acceptable although it would be advisable to perform the study under fed conditions.
- If the SPC leaves a choice between fasting and fed conditions, then BE should preferably be tested under fasting conditions as this situation will be more sensitive to differences in PKs.

The composition of the meal should be described and taken into account, since a light meal might sometimes be preferable to mimic clinical conditions, especially when the fed state is expected to be less sensitive to differences in PKs. However, for modified-release products, a high fat meal is required.

For products with release characteristics differing from conventional immediate release (e.g., improved release, dissolution, or absorption), even if they cannot be classified as modified-release products with prolonged or delayed release, BE studies may be necessary in both the fasted and fed states.

J. Worldwide Considerations

Whereas there is a general consensus among the West European, North American, and Japanese regulatory authorities on the BE requirements for marketing authorization of generic products, such is not the case in the rest of the world. For example, the varied nature of the requirement in South America perhaps typifies the heterogeneity in other continents. For example, an examination of the regulatory systems of the ten South American agencies showed that out of the 96 active ingredients, only 4 active ingredients commonly require BE studies in all 10 countries: valproic acid, carbamazepine, cyclosporine, and phenytoin. All of them are considered high health risks. The countries with least number of active ingredients with BE study requirements are Colombia (only 5) followed by Costa Rica (only 7) and the countries with the highest number of requirements remain the United States and Canada. Chile is in the process of establishing the requirement for all active ingredients that require BE studies. Whereas the WHO has established certain guidelines, these are not widely followed in much of the Third World countries

and BE studies remain haphazardly managed. Following are some of the common occurrences in the marketing approvals of generic products in the Third World countries:

- Nonvalidated test methods
- Statistically incorrect experimental designs
- Lack of authenticity of study
- Lack of assurance that the study is conducted on the manufactured batches; the MNCs routinely submitting studies from their filings in the West in support of products to be manufactured locally

VIII. POSTAPPROVAL CHANGES

Information on the types of in vitro dissolution and in vivo BE studies that should be conducted for immediate-release and modified-release drug products approved as NDAs or aNDAs in the presence of specified postapproval changes is provided in the FDA guidance for industry titled *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* (November 1995) and *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* (September 1997). In the presence of certain major changes in components, composition, or methods of manufacture after approval, in vivo BE should be redemonstrated. For approved NDAs, the drug product after the change should be compared with the drug product before the change. For approved aNDAs, the drug product after the change should be compared with the RLD. Under section 506A(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 USC 356a(c)(2)(B)], postapproval changes requiring completion of studies in accordance with Part 320 must be submitted in a supplement and approved by FDA before distributing a drug product made with the change.

A. NDAs: BA and BE Studies

An NDA can be submitted for a previously unapproved new molecular entity or for a new salt, new ester, prodrug, or other noncovalent derivative of a previously approved new molecular entity, formulated as a modified-release drug product. The first modified-release drug product for a previously approved immediate-release drug product should be submitted as an NDA. Subsequent modified-release products that are pharmaceutically equivalent and bioequivalent to the listed drug product should be submitted as aNDAs. BA requirements for the NDA of an extended-release product are listed in 21 CFR 320.25(f). The purpose of an in vivo BA study for which a controlled-release claim is made is to determine if all the following conditions are met:

- The drug product meets the controlled-release claims made for it.
- The BA profile established for the drug product rules out the occurrence of any dose dumping.
- The drug product's steady-state performance is equivalent to a currently marketed noncontrolled-release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and is subject to an approved full NDA.
- The drug product's formulation provides consistent PK performance between individual dosage units.

As noted in 21 CFR 320.25(f)(2), "the reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled-release claims made for the drug product," such as the following:

- Solution or suspension of the active drug ingredient or therapeutic moiety
- Currently marketed noncontrolled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling
- Currently marketed controlled-release 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

This guidance recommends that the following BA studies be conducted for an extended-release drug product submitted as an NDA.

- Single-dose fasting study on all strengths of tablets and capsules and highest strength of beaded capsules
- Single-dose food-effect study on the highest strength
- Steady-state study on the highest strength

BE studies are recommended when substantial changes in the components or composition or method of manufacture for an extended-release drug product occur between the to-be-marketed NDA dosage form and the clinical trial material.

B. Waivers of In Vivo BE Studies (Biowaivers): NDAs and aNDAs

1. Beaded Capsules—Lower Strength

For modified-release beaded capsules, where the strength differs only in the number of beads containing the active moiety, a single-dose fasting BE study should be carried out only on the highest strength, with waiver of in vivo studies for lower strengths based on dissolution profiles. A dissolution profile should be generated for each strength using the recommended dissolution method. The f_2 test should be used to compare profiles from the different strengths of the product. An f_2 value of 50 can be used to confirm that further in vivo studies are not needed.

2. Tablets—Lower Strength

For modified-release tablets, when the drug product is in the same dosage form but in a different strength, is proportionally similar in its active and inactive ingredients, and has the same drug release mechanism, an in vivo BE determination of one or more lower strengths can be waived based on dissolution profile comparisons, with an in vivo study only on the highest strength. The drug products should exhibit similar dissolution profiles between the highest strength and the lower strengths, based on the f_2 test in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8). The dissolution profile should be generated on the test and reference products of all strengths.

C. Risk-Based BE

The guidance defines *narrow therapeutic range* drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and 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 PD monitoring

are narrow therapeutic range drugs, sponsors and applicants should contact the appropriate review division at CDER to determine whether a drug should or should not be considered to have a narrow therapeutic range.

The guidance recommends that sponsors consider additional testing and controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs. It is not designed to influence the practice of medicine or pharmacy.

Unless otherwise indicated by a specific guidance, this guidance recommends that the traditional BE limit of 80% to 125% for non-narrow therapeutic range drugs remain unchanged for the BA measures (AUC and C_{max}) of narrow therapeutic range drugs.

The selection of active ingredients for which BE studies should be required is a public health decision and as such should take into account the benefit/risk ratio of the same. This situation leads to the health risk concept, that is, which active ingredients require rigorous handling to prevent public health problems. One way of doing this is to take into account which active ingredients, because of their pharmacological characteristics, should be controlled through blood determinations.

As operational definition, the health risk concept should be established in the context of the problems of BE. For this purpose it would be reasonable to establish what are the health consequences when the drug is outside (under or above) the therapeutic window (the margin determined by the nontoxic maximum concentration and the effective minimum concentration). Thus, in relating the therapeutic window (the margin whose limits are the nontoxic maximum and effective minimum concentrations) and adverse effects of the drugs, three risk levels can be established, as described below.

High health risk: This is the probability of the appearance of threatening complications of the disease for the life or the psychophysical integrity of the person and/or serious adverse reactions (death, patient hospitalization, extension of the hospitalization, significant or persistent disability, disability or threat of death), when the blood concentration of the active ingredient is not within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 3 (three).

Intermediate health risk: This is the probability of the appearance of nonthreatening complications of the disease for the life or the psychophysical integrity of the person and/or adverse reactions, not necessarily serious, when the blood concentration of the active ingredient is not found within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 2 (two).

Low health risk: This is the probability of the appearance of a minor complication of the disease and/or mild adverse reactions, when the blood concentration of the active ingredient is not within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 1 (one).

While there are other factors to be considered such as the physicochemical and PK parameters, from the standpoint of public health, the most important element to take into account is the health risk. Table 4 lists the active ingredients classified in accordance with their health risk and the established scores.

Table 4 Classification of Active Ingredients According to Their Health Risk

Active Ingredient	Health Risk
Acetazolamide	1
Allopurinol	1
Calcium folinate	1
Captopril	1
Clomifene	1
Cloxacillin	1
Dexamethasone	1
Diazepam	1
Folic acid + ferrous sulfate	1
Ibuprofen	1
Isosorbide dinitrate	1
Levamisole	1
Mebendazole	1
Mefloquine	1
Nalidixic acid	1
Niclosamide	1
Nifedipine	1
Nystatin	1
Phenoxymethylpenicillin	1
Phytomenadione	1
Pyranatel	1
Praziquantel	1
Pyrazinamide	1
Sulfasalazine	1
Amiloride	2
Amitriptyline	2
Amoxicillin	2
Atenolol	2
Azathioprine	2
Biperiden	2
Chloramphenicol	2
Cimetidine	2
Ciprofloxacin	2
Clofazimine	2
Clomipramine	2
Chlorpromazine	2
Co-trimoxazole	2
Cyclophosphamide	2
Dapsone	2
Diethylcarbamazine	2
Doxycycline	2
Erythromycin	2
Ethinylestradiol	2
Etoposide	2
Flucytosine	2
Fludrocortisone	2
Furosemide	2
Haloperidol	2
Hydrochlorothiazide	2
Indometacin	2
Isoniazid	2
Ketoconazole	2
Levodopa + inhib. DDC	2
Levonorgestrel	2
Levotiroxina	2
6-Mercaptopurine	2
Methotrexate	2
Methylidopa	2
Metoclopramide	2
Metronidazole	2
Nitrofurantoin	2
Norethindrone	2
Oxamniquine	2

Table 4 (Continued)

Active Ingredient	Health Risk
Paracetamol	2
Penicillamine	2
Piperazine	2
Pyridostigmine	2
Procarbazine	2
Promethazine	2
Propranolol	2
Propylthiouracil	2
Pyrimethamine	2
Quinine	2
Rifampicin	2
Salbutamol, sulfate	2
Spironolactone	2
Tamoxifen	2
Tetracycline	2
Carbamazepine	3
Cyclosporine	3
Digoxin	3
Ethambutol	3
Ethosuximide	3
Griseofulvin	3
Lithium carbonate	3
Oxcarbazepine	3
Phenytoin	3
Procainamide	3
Quinidine	3
Theophylline	3
Tolbutamide	3
Valproic acid	3
Verapamil	3
Warfarin	3

D. Typical Examples of Complex BE

1. Digoxin

Digoxin in tablet form is not listed in the Orange Book, since this is a “grandfathered” dosage form of digoxin. Since the tablet formulation of digoxin was established in clinical use before the passage of the Federal Food, Drug, and Cosmetic Act of 1938, generic versions of digoxin tablets may be marketed without an approved aNDA. Data showing BE of generic digoxin tablet products to the innovator product Lanoxin are generally not available or forthcoming, so that comparable rate and extent of absorption between generic products and Lanoxin brand tablets, or between different generic products, is not ensured. Seventeen generic digoxin tablets (0.25 mg) have been listed as currently marketed, though some of these may be marketed by suppliers or distributors of another manufacturer’s product. Without PK data to verify the BE of these products to Lanoxin, the clinical responses (both therapeutic and toxic) from these generic products compared with Lanoxin are unpredictable. This inability to guarantee therapeutic equivalence to a reference product opposes the entire premise of generic substitution: the practitioner should expect the same responses (no more, no less) from a therapeutically equivalent generic product. Consequently, generic substitution is not advised. Use of a generic digoxin product as initial therapy may result in lower or higher than expected BA, requiring additional monitoring and dosage adjustment, and ultimately increasing costs of therapy far above the cost savings from a less expensive generic product.

2. Levothyroxine

Levothyroxine sodium tablets are also currently not listed in the Orange Book. In the words of FDA, levothyroxine sodium was first introduced into the market before 1962 without an approved NDA, apparently in the belief that it was not a new drug. The lack of BE data of generic preparations to the two major brand name products Synthroid and Levothroid has been noted, along with the adoption in 1984 of the *U.S. Pharmacopoeia* guidelines for potency of levothyroxine sodium tablets. However, between 1987 and 1994, a total of 58 adverse drug experience reports with levothyroxine sodium tablets were received by FDA, with 47 of the incidences apparently related to subpotency and 9 incidences related to superpotency. These adverse events were caused not only by switching product brands, but also by inconsistencies in BA between different lots from the same source. BE issues regarding levothyroxine sodium tablets were highlighted when the results of a BE study comparing the innovator product Synthroid with several generic brands finally appeared in the literature. The study sponsor (the marketer of Synthroid) attempted to prevent publication of these results, which claimed BE of Synthroid to three other levothyroxine sodium products. After publication of these study results, advertisements appeared in journals and trade magazines advocating the substitution of other brand name levothyroxine sodium products (e.g., Levothroid, Levoxyl) for Synthroid. In addition, statements were made such as “Feel comfortable using Levothroid, Levoxyl, or Synthroid in hypothyroid patients. These three are bioequivalent. . . even though they’re not AB-rated.”

Several points should be considered before routinely switching marketed brands of levothyroxine sodium tablets (at least 24 products for the 0.1 mg tablet are listed). First, although the conclusions stated in the peer-reviewed BE study cited appear to be generally accepted, the results of this study were not subjected to the scrutiny of the FDA review process. In view of significant stability and potency problems, FDA has issued a Federal Register notice stating that (1) orally administered levothyroxine sodium products are now considered new drugs and (2) manufacturers who intend to continue marketing these products must submit an NDA within 3 years to obtain approval. Recently, FDA extended this deadline for an additional year. Second, the impression that all levothyroxine sodium tablet formulations are likely to be bioequivalent is not currently supported with FDA-substantiated BE data; routine substitution of these products for refills of existing prescriptions is not advisable until FDA review is complete. Third, practitioners must always comply with the substitution laws in their individual states. If a statute mandates substitution of a therapeutically equivalent or bioequivalent product, reliance upon data reported in the scientific literature may not always guarantee these requirements will be satisfied.

3. Warfarin Sodium

Three approved generic versions of warfarin sodium tablets (seven strengths) are currently listed in the Orange Book. Before approval of these generic warfarin sodium products, several states either enacted or were considering legislation to require pharmacists to obtain prescriber and patient approval for generic substitution of drugs with a narrow therapeutic index (NTI). In response, FDA issued a position statement. FDA’s position is clear with regard to the issue of tightening CIs and changing study designs for BE determinations of NTI drugs. The present requirements to prove BE, at least in the

United States and Canada, are already so difficult and constrained that there is no possibility, even for NTI drugs, that dosage forms meeting the criteria could lead to therapeutic problems. Drugs approved through the NDA process with NTIs, by definition, must have low intrasubject variability. Otherwise, patients would have cycles of toxicity and lack of efficacy, and therapeutic drug monitoring would be useless. The low intrasubject variability associated with NTI drugs ensures that patient response to a specific drug should be consistent, and the statistical criteria required by FDA for BE appear more than adequate for confidence in generic substitution. This is especially true in light of the notable absence of data that prove otherwise. For the most part, the arguments against generic substitution of NTI drugs appear to be based on economic considerations. Commentaries debating the suitability of generic warfarin products have focused on the results from reports of clinical studies with generic warfarin and the content uniformity requirements for warfarin sodium tablets. As indicated in a letter addressing these issues, no convincing and substantiated scientific data have been published showing bioinequivalence of generic warfarin products or product failure of these products in clinical studies. Recently, an evidence-based medicine approach was used to compare the results reported with Coumadin and a generic warfarin product in clinical studies. No significant differences were found in the international normalized ratio (INR), number of dosage changes to adjust INR in range, or number of hospitalizations or incidences of bleeding between the reference and generic warfarin products. Physicians may sometimes encounter difficulties in maintaining stabilized INR in patients anticoagulated with warfarin, because multiple drug interactions and patient variables affect warfarin levels and create difficulty in achieving consistently therapeutic INR values. However, factors such as diet, concurrent illnesses, interacting drugs, and noncompliance are *intersubject* variables that are unrelated to the BE issue. For crossover studies using log-transformed data, it is largely the within-subject distribution of values (*intrasubject* variability) that determines the validity and efficiency of the standard parametric methods of analysis. For NTI drugs such as warfarin, intrasubject variability, by definition, is low and the available clinical data indicate that lack of BE does not appear to be the explanation for problems experienced during warfarin therapy. Another article introduces the concept of “switchability,” that is, the substitution of one approved generic product for another generic product. BE studies submitted to FDA through an aNDA are conducted by comparing data from the proposed generic product and a reference product. The reference product is selected by FDA and is typically the innovator or pioneer product that was originally introduced into the market. Suppose approved generic product A differed from the reference product in at least one parameter (e.g., mean AUC values) by +4%, and that approved generic product B differed from the reference product by -4%. The net difference of generic products A and B would then be 8%; could this magnitude of difference result in bioinequivalence and lack of equivalent therapeutic response for an NTI drug? No data were presented from any clinical studies that could support the contention that switchability for NTI drugs is problematic. Rather, phrases such as “...with NTI drugs, small variations in bioavailability can potentially pose problems” and conceptual arguments are used to suggest the need for special BE criteria to be applied to NTI drugs. Reference is made to the FDA’s draft guidance for population and individual BE studies, which propose the use of reference scaling (essentially, modifying the BE criteria to account for the vari-

ability of the reference product) for NTI drugs, regardless of the intrasubject variability of the reference product. Since NTI drugs have low intrasubject variability as discussed, this approach would likely result in narrower CI requirements. Finally, a recent report further confirms the BE of generic warfarin to the innovator product. More than 100 subjects anticoagulated with Coumadin were switched to a generic warfarin product for 8 weeks in a nonrandomized comparative clinical observational study. The overall conclusion was that the variability in INR in patients receiving generic warfarin was not statistically significant from that seen in the control group receiving Coumadin. These investigators identified associated factors not related to the product change in subjects whose INR varied by >1.0 from baseline. This further emphasizes the critical role of interpatient factors (physical activity, dietary vitamin K, noncompliance, drug interactions, congestive heart failure, diarrhea, alcohol consumption) affecting the anticoagulant response with warfarin.

4. Albuterol Metered-Dose Inhalers

Four approved generic versions of albuterol metered-dose inhalers are currently listed in the Orange Book as therapeutically equivalent (AB-rated) to the reference product Ventolin. The Proventil product is rated BN, or not therapeutically equivalent to Ventolin or the four generic products. For products administered by metered-dose inhalation and intended for local therapeutic effects, the typical PK methods for evaluating BE cannot be used. Rather, an approach based on acute PD response (forced expiratory volume in 1 second, FEV₁) was proposed, with asthmatic patients as subjects. The statistical criteria and appropriate CIs for BE determination are not as rigidly defined for PD methods as for PK methods. Consequently, variability in patient response may be of slightly greater concern, since albuterol metered-dose inhalers are used as “rescue inhalers” for nocturnal asthma attacks (even though they are not considered NTI drugs). However, FDA is satisfied that these products will produce equivalent therapeutic responses.

E. General PK Study Design and Data Handling

For replicate and nonreplicate *in vivo* PK BE studies, the following general approaches are recommended, recognizing that the elements may be adjusted for certain drug substances and drug products.

1. Study Conduct

- The test or reference products should be administered with approximately 8 oz (240 mL) of water to an appropriate number of subjects under fasting conditions, unless the study is a food-effect BA and BE study.
- Generally, the highest marketed strength should be administered as a single unit. If warranted for analytical reasons, multiple units of the highest strength can be administered, providing the total single dose remains within the labeled dose range.
- An adequate washout period (e.g., more than five 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. The drug content of the test product should not differ from that of the reference-listed 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, samples of the test and reference-listed product must be retained for 5 years.

- Before and during each study phase, subjects should be allowed water, as desired, except for 1 hour before and after drug administration; be provided standard meals no less than 4 hours after drug administration; and abstain from alcohol for 24 hours before each study period and until after the last sample from each period is collected.

2. Sample Collection and Sampling Times

- Under normal circumstances, blood, rather than urine or tissue, should be used. In most cases, drug or metabolites are measured in serum or plasma. However, in certain cases, whole blood may be more appropriate for analysis. Blood samples should be drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, 12 to 18 samples, including a predose sample, should be collected per subject per dose. This sampling should continue for at least three or more terminal half-lives of the drug. The exact timing for sample collection depends on the nature of the drug and the input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration of the drug in the blood (C_{max}) and terminal elimination rate constant ($t_{1/2}$) can be estimated accurately. At least three to four samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of $t_{1/2}$ from linear regression. The actual clock time when samples are drawn as well as the elapsed time related to drug administration should be recorded.

3. Subjects with Predose Plasma Concentrations

- If the predose concentration is less than or equal to 5% of the C_{max} value in that subject, the subject's data, without any adjustments, can be included in all PK measurements and calculations. If the predose value is greater than 5% of C_{max} , the subject should be dropped from all BE study evaluations.

4. Data Deletion due to Vomiting

- Data from subjects who experience emesis during the course of a BE study for immediate-release products should be deleted from statistical analysis if vomiting occurs at or before two times median T_{max} . In the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval should be deleted.

5. PK Information Recommended for Submission

- Plasma concentrations and time points
- Subject, period, sequence, treatment
- AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} , k_z , and $t_{1/2}$
- Intersubject, intrasubject, and total variability, if available
- Concentration at the end of a dosing interval (C_{min}), average concentration during a dosing interval (C_{av}), degree of fluctuation $[(C_{max} - C_{min})/C_{av}]$, and swing $[(C_{max} - C_{min})/C_{min}]$, if steady-state studies are employed
- Partial AUC, if justified.

6. BE Demonstration Measures

- Logarithmic transformation should be provided for measures used for BE demonstration.

7. CI Values

- CI values should not be rounded off; therefore, to pass a CI limit of 80 to 125; the value should be at least 80 and not more than 125.

8. Statistical Information for AUC_{0-T} , $AUC_{0-\infty}$, and C_{max}

- Geometric mean
- Arithmetic mean
- Ratio of means
- CIs

F. Measurement Indices

Whenever comparison of the test product and the reference material is to be based on blood concentration-time curves or cumulative urinary excretion-time curves at steady state, appropriate dosage administration and sampling should be carried out to document attainment of steady state. A more complete characterization of the blood concentration or urinary excretion rate during the absorption and elimination phases of a single dose administered at steady state is encouraged to permit estimation of the total area under concentration-time curves or cumulative urinary excretion-time curves and to obtain PK information, for example, half-life or blood clearance, that is essential in preparing adequate labeling for the drug product.

When comparison of the test product and the reference material is to be based on acute pharmacological effect-time curves, measurements of this effect should be made with sufficient frequency to demonstrate a maximum effect and a lack of significant difference between the test product and the reference material.

G. Dose Selection

Dose selection will depend upon the label claims, consideration of assay sensitivity, and relevance to the practical use conditions of the reference product. A blood level BE study should generally be conducted at the highest dose approved for the pioneer product.

However, FDA will consider a BE study conducted at a higher than approved dose in certain cases. Such a study may be appropriate when a multiple of the highest approved dose achieves measurable blood levels, but the highest approved dose does not. In general, the study would be limited to 2 to 3 times the highest dose approved for the pioneer product. The pioneer product should have an adequate margin of safety at the higher than approved dose level. The generic sponsor should also confirm (e.g., through literature) that the drug follows linear kinetics. A higher than approved dose BE study in food animal species would be accompanied by a tissue residue withdrawal study conducted at the highest approved dose for the pioneer product.

For products labeled for multiple claims involving different pharmacological actions at a broad dose range (e.g., therapeutic and production claims), a single BE study at the highest approved dose will usually be adequate. However, multiple BE studies at different doses may be needed if the drug is known to follow nonlinear kinetics. The sponsor should consult with FDA to discuss the BE study or studies appropriate to a particular drug.

H. Multiple Strengths of Solid Oral Dosage Forms

The generic sponsor should discuss with FDA the appropriate *in vivo* BE testing and *in vitro* dissolution testing to obtain approval for multiple strengths (or concentrations) of solid oral dosage forms. FDA will consider the ratio of active to inactive ingredients and the *in vitro* dissolution profiles of

the different strengths, the water solubility of the drug, and the range of strengths for which approval is sought. One in vivo BE study with highest strength product may suffice if the multiple strength products have the same ratio of active to inactive ingredients and are otherwise identical in formulation. In vitro dissolution testing should be conducted using an FDA approved method, to compare each strength of the generic product to the corresponding strength of the reference product.

I. Manufacturing of Pilot Batch (“Biobatch”)

A pilot batch or “biobatch” should be the source of the finished drug product used in the pivotal studies (i.e., BE studies and tissue residue studies), stability studies, and the validation studies for the proposed analytical and stability indicating methods. Batch testing Individual batch testing is necessary to ensure that all batches of the same drug product meet an appropriate in vitro test. The Commissioner will ordinarily terminate a requirement for a manufacturer to submit samples for batch testing on a finding that the manufacturer has produced four consecutive batches that were tested by the FDA and found to meet the BE requirement, unless the public health requires that batch testing be extended to additional batches.

If a BE requirement specifies a currently available in vitro test or an in vitro BE standard comparing the drug product to a reference standard, the manufacturer shall conduct the test on a sample of each batch of the drug product to ensure batch-to-batch uniformity.

J. Dosing by Labeled Concentration

The potency of the pioneer and generic products should be assayed prior to conducting the BE study to ensure that FDA or compendial specifications are met. The center recommends that the potency of the pioneer and generic lots should differ by no more than $\pm 5\%$ for dosage form products.

The animals should be dosed according to the labeled concentration or strength of the product rather than the assayed potency of the individual batch (i.e., the dose should not be corrected for the assayed potency of the product). The BE data or derived parameters should not be normalized to account for any potency differences between the pioneer and generic product lots.

K. Single Dose vs. Multiple Dose Studies

A single dose study at the highest approved dose will generally be adequate for the demonstration of BE. A single dose study at a higher than approved dose may be appropriate for certain drugs.

A multiple dose study may be appropriate when there are concerns regarding poorly predictable drug accumulation, (e.g., a drug with nonlinear kinetics) or a drug with a narrow therapeutic window. A multiple dose study may also be needed when assay sensitivity is inadequate to permit drug quantification out to three terminal elimination half-lives beyond the time when maximum blood concentrations (C_{max}) are achieved, or in cases where prolonged or delayed absorption exist. The determination of prolonged or delayed absorption (i.e., flip-flop kinetics) may be made from pilot data, from the literature, or from information contained with FOI summaries pertaining to the particular drug or family of drugs.

L. Guidelines on the Design of a Single-Dose Study

A BE study should be a single-dose comparison of the drug product to be tested and the appropriate reference material

conducted in normal adults. The test product and the reference material should be administered to subjects in the fasting state, unless some other approach is more appropriate for valid scientific reasons. A single-dose study should be crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons, and should provide for a drug elimination period. Unless some other approach is appropriate for valid scientific reasons, the drug elimination period should be either at least 3 times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured in the blood or urine or at least 3 times the half-life of decay of the acute pharmacological effect.

When comparison of the test product and the reference material is to be based on blood concentration-time curves, unless some other approach is more appropriate for valid scientific reasons, blood samples should be taken with sufficient frequency to permit an estimate of both the peak concentration in the blood of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured; and the total AUC for a time period at least 3 times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured.

In a study comparing oral dosage forms, the sampling times should be identical. In a study comparing an intravenous dosage form and an oral dosage form, the sampling times should be those needed to describe both the distribution and elimination phase of the intravenous dosage form; and the absorption and elimination phase of the oral dosage form.

In a study comparing drug delivery systems other than oral or intravenous dosage forms with an appropriate reference standard, the sampling times should be based on valid scientific reasons.

When comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves, unless some other approach is more appropriate for valid scientific reasons, samples of the urine should be collected with sufficient frequency to permit an estimate of the rate and extent of urinary excretion of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured.

When comparison of the test product and the reference material is to be based on acute pharmacological effect-time curves, measurements of this effect should be made with sufficient frequency to permit a reasonable estimate of the total AUC for a time period at least 3 times the half-life of decay of the pharmacological effect, unless some other approach is more appropriate for valid scientific reasons.

The use of an acute pharmacological effect to determine BA may further require demonstration of dose-related response. In such a case, BA may be determined by comparison of the dose-response curves as well as the total area under the acute pharmacological effect-time curves for any given dose.

M. Guidelines for Multiple-Dose Study

In selected circumstances it may be necessary for the test product and the reference material to be compared after repeated administration to determine steady-state levels of the active drug ingredient or therapeutic moiety in the body. The test product and the reference material should be administered to subjects in the fasting or nonfasting state, depending upon the conditions reflected in the proposed labeling of the test product.

A multiple-dose study may be required to determine the BA of a drug product in the following circumstances that

there is a difference in the rate of absorption but not in the extent of absorption., there is excessive variability in BA from subject to subject.; 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; the drug product is an extended-release dosage form.

A multiple-dose study should be crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons, and should provide for a drug elimination period if steady-state conditions are not achieved. A multiple-dose study is not required to be of crossover design if the study is to establish dose proportionality under a multiple-dose regimen or to establish the PK profile of a new drug product, a new drug delivery system, or an extended-release dosage form.

If a drug elimination period is required, unless some other approach is more appropriate for valid scientific reasons, the drug elimination period should be either at least 5 times the half-life of the active drug ingredient or therapeutic moiety, or its active metabolite(s), measured in the blood or urine; or at least 5 times the half-life of decay of the acute pharmacological effect.

Whenever a multiple-dose study is conducted, unless some other approach is more appropriate for valid scientific reasons, sufficient doses of the test product and reference material should be administered in accordance with the labeling to achieve steady-state conditions.

N. Fed vs. Fasted State

Feeding may either enhance or interfere with drug absorption, depending upon the characteristics of the drug and the formulation. Feeding may also increase the inter- and intra-subject variability in the rate and extent of drug absorption. The rationale for conducting each BE study under fasting or fed conditions should be provided in the protocol. Fasting conditions, if used, should be fully described, giving careful consideration to the PKs of the drug and the humane treatment of the test animals. The protocol should describe the diet and feeding regime, which will be used in the study.

If a pioneer product label indicates that the product is limited to administration either in the fed or fasted state, then the BE study should be conducted accordingly. If the BE study parameters pass the agreed upon CIs, then the single study is acceptable as the basis for approval of the generic drug.

However, for certain product classifications or drug entities, such as enteric-coated and oral sustained-release products, demonstration of BE in both the fasted and the fed states may be necessary, if drug BA is highly variable under feeding conditions, as determined from the literature or from pilot data. A BE study conducted under fasted conditions may be necessary to pass the CIs. A second smaller study may be necessary to examine meal effects. FDA will evaluate the smaller study with respect to the means of the pivotal parameters (AUC, C_{max}). The sponsors should consult with FDA prior to conducting the studies.

O. Pharmacological End-Point Studies

Where the direct measurement of the rate and extent of absorption of the new animal drug in biological fluids is inappropriate or impractical, the evaluation of a pharmacological end point related to the labeled indications for use will be acceptable.

Typically the design of a pharmacological end-point study should follow the same general considerations as the

blood level studies. However specifics such as the number of subjects or sampling times will depend on the pharmacological end point monitored. The parameters to be measured will also depend upon the pharmacological end points and may differ from those used in blood level studies. As with blood level studies, when pharmacological end-point studies are used to demonstrate BE, a tissue residue study will also be required in food-producing animals.

For parameters which can be measured over time, a time versus effect profile is generated, and equivalence is determined with the method of statistical analysis essentially the same as for the blood level BE study.

For pharmacological effects for which effect versus time curves cannot be generated, then alternative procedures for statistical analysis should be discussed with FDA prior to conducting the study.

P. Clinical End-Point Studies

If measurement of the drug or its metabolites in blood, biological fluids, or tissues is inappropriate or impractical, and there are no appropriate pharmacological end points to monitor (e.g., most production drugs and some coccidiostats and anthelmintics), then well-controlled clinical end-point studies are acceptable for the demonstration of BE.

Generally, a parallel group design with three treatment groups should be used. The groups should be a placebo (or negative) control, a positive control (reference/pioneer product), and the test (generic) product. The purpose of the placebo (or negative) control is to confirm the sensitivity or validity of the study. Dosage(s) approved for the pioneer product should be used in the study. Dosage(s) should be selected following consultation with FDA and should reflect consideration for experimental sensitivity and relevance to the common use of the pioneer product.

Studies should generally be conducted using the target animal species, with consideration for the sex, class, body weight, age, health status, and feeding and husbandry conditions, as described on the pioneer product labeling. In general, the length of time that the study is conducted should be consistent with the duration of use on the pioneer product labeling.

In general, the response(s) to be measured in a clinical end-point study should be based upon the labeling claims of the pioneer product and selected in consultation with the Center for Veterinary Medicine (CVM, FDA). It may not be necessary to collect data on some overlapping claims (e.g., for a production drug which is added at the same amount per ton of feed for both growth rate and feed efficiency, data from only one of the two responses need be collected).

When considering sample size, it is important to note that the pen, not the individual animal, is often the experimental unit. As with blood level BE studies, FDA is advocating the use of 90% CIs as the best method for evaluating clinical end-point studies. The bounds for confidence limits [e.g., $\pm 20\%$ of the improvement over placebo (or negative) control] for the particular drug should be agreed upon with FDA prior to initiation of the study.

The analysis should be used to compare the test product and the reference product. In addition, a traditional hypothesis test should be performed comparing both the test and reference products separately to the placebo (or negative) control. The hypothesis test is conducted to ensure that the study has adequate sensitivity to detect differences when they actually occur. If no significant improvement ($\alpha = .05$) is seen in the parameter [i.e., the mean of the test and the mean of the reference products are each not significantly better than

the mean of the placebo (or negative) control], generally, the study will be considered inadequate to evaluate BE.

Assuming that the test and reference products have been shown to be superior to the placebo (or negative) control, the determination of BE is based upon the CI of the difference between the two products.

Some clinical end-point studies may not include a placebo (or negative) control for ethical and/or practical considerations. If the placebo is omitted, then the response(s) to the test and reference products should each provide a statistically significant improvement over baseline.

If the results are ordered categorical data (e.g., excellent, good, fair, or poor), a nonparametric hypothesis test of no difference between test product and placebo (or negative) control and between the reference product and placebo (or negative) control should be performed. As above, if these tests result in significant differences between the test product and control and the reference product and control, then a nonparametric CI on the difference between the test and reference products is calculated.

Another acceptable approach for categorical data is to calculate the CI on the odds ratio between the test and reference products after showing that the test and reference products are significantly better than the control.

Q. Analytical Methods

The analytical method used in an *in vivo* BA or BE study to measure the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products, or the method used to measure an acute pharmacological effect shall be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), achieved in the body. When the analytical method is not sensitive enough to measure accurately the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products produced by a single dose of the test product, two or more single doses may be given together to produce higher concentration.

1. Assay Consideration

A properly validated assay method is pivotal to the acceptability of any PK study. Sponsors should discuss any questions or problems concerning the analytical methodology with CVM before undertaking the BE studies. The aNADA submission should contain adequate information necessary for the CVM reviewer to determine the validity of the analytical method used to quantitate the level of drug in the biological matrix (e.g., blood).

The following aspects should be addressed in assessing method performance.

Concentration range and linearity

The quantitative relationship between concentration and response should be adequately characterized over the entire range of expected sample concentrations. For linear relationships, a standard curve should be defined by at least five concentrations. If the concentration response function is nonlinear, additional points would be necessary to define the nonlinear portions of the curve. Extrapolation beyond a standard curve is not acceptable.

Limit of detection

The standard deviation of the background signal and limit of detection (LoD) should be determined. The LoD is estimated

as the response value calculated by adding 3 times the standard deviation of the background response to the average background response.

Limit of quantitation

The initial determination of limit of quantitation (LoQ) should involve the addition of 10 times the standard deviation of the background response to the average background response. The second step in determining LoQ is assessing the precision (reproducibility) and accuracy (recovery) of the method at the LoQ. The LoQ will generally be the lowest concentration on the standard curve that can be quantified with acceptable accuracy and precision.

Specificity

The absence of matrix interferences should be demonstrated by the analysis of six independent sources of control matrix. The effect of environmental, physiological, or procedural variables on the matrix should be assessed. Each independent control matrix will be used to produce a standard curve, which will be compared to a standard curve produced under chemically defined conditions. The comparison of curves should exhibit parallelism and superimposability within the limits of analytical variation established for the chemically defined standard curve.

Accuracy (Recovery)

This parameter should be evaluated using at least three known concentrations of analyte freshly spiked in control matrix, one being at a point two standard deviations above the LoQ, one in the middle of the range of the standard curve ("midrange") and one at a point two standard deviations below the upper quantitative limit of the standard curve. The accuracy of the method, based upon the mean value of six replicate injections, at each concentration level, should be within 80% to 120% of the nominal concentration at each level (high, midrange, and LoQ).

Precision

This parameter should be evaluated using at least three known concentrations of analyte freshly spiked in control matrix, at the same points used for determination of accuracy. The CV of six replicates should be $\pm 10\%$ for concentrations at or above 0.1 ppm (0.1 $\mu\text{g}/\text{mL}$). A CV of $\pm 20\%$ is acceptable for concentrations below 0.1 ppm.

Analyte stability

Stability of the analyte in the biological matrix under the conditions of the experiment (including any period for which samples are stored before analyses) should be established. It is recommended that the stability be determined with incurred analyte in the matrix of dosed animals in addition to, or instead of, control matrix spiked with pure analyte. Also, the influence of three freeze-thaw cycles at two concentrations should be determined.

Stability samples at three concentrations should be stored with the study samples and analyzed through the period of time in which study samples are analyzed. These analyses will establish whether or not analyte levels have decreased during the time of analysis.

Analytical system stability

To ensure that the analytical system remains stable over the time course of the assay, the reproducibility of the standard curve should be monitored during the assay. A minimal

design would be to run analytical standards at the beginning and at the end of the analytical run.

QC samples

The purpose of QC samples is to ensure that the complete analytical method, sample preparation, extraction, cleanup, and instrumental analysis perform according to acceptable criteria. The stability of the drug in the test matrix for the QC samples should be known and any tendency for the drug to bind to tissue or serum components over time should also be known.

Drug-free control matrix, for example, tissue, serum, that is freshly spiked with known quantities of test drug, should be analyzed contemporaneously with test samples, evenly dispersed throughout each analytical run. This can be met by the determination of accuracy and precision of each analytical run.

Replicate and repeat analyses

Single rather than replicate analyses are recommended, unless the reproducibility and/or accuracy of the method are borderline. Criteria for repeat analyses should be determined prior to running the study and recorded in the method SOP.

Summary of samples to be run with each analysis

- a. Accuracy estimate
- b. Precision estimate
- c. Analytical system stability
- d. Analyte stability samples

R. Sampling Time Considerations

The total number of sampling times necessary to characterize the blood level profiles will depend upon the curvature of the profiles and the magnitude of variability associated with the BA data (including PK variability, assay error, and interproduct differences in absorption kinetics).

The sampling times should adequately define peak concentration(s) and the extent of absorption. The sampling times should extend to at least three terminal elimination half-lives beyond T_{max} . The sponsor should consult with FDA prior to conducting the pivotal BE study if the assay is unable to quantify samples to three half-lives.

Maximum sampling time efficiency may be achieved by conducting a pilot investigation. The pilot study should identify the general shapes of the test and reference curves, the magnitude of the difference in product profiles, and the noise associated with each blood-sampling time (e.g., variability attributable to assay error and the variability between subjects, for parallel study designs, or within subjects, for crossover study designs). This information should be applied to the determination of an optimum blood-sampling schedule. Depending upon these variability estimates, it may be more efficient to cluster several blood samples rather than to have samples which are periodically dispersed throughout the duration of blood sampling.

S. Protein Binding

In general, product BE should be based upon total (free plus protein bound) concentrations of the parent drug (or metabolite, when applicable). However, if nonlinear protein binding is known to occur within the therapeutic dosing range (as determined from literature or pilot data), then sponsors may need to submit data on both the free and total drug concentrations for the generic and pioneer products.

Similarly, if the drug is known to enter blood erythrocytes, the protocol should address the issue of potential

nonlinearity in erythrocyte uptake of the drug administered within the labeled therapeutic dosing range.

The BE protocol or completed study report should provide any information available from the literature regarding erythrocyte uptake and protein binding characteristics of the drug or drug class, including the magnitude of protein binding and the type of blood protein to which it binds.

T. Subject Number

Pilot studies are recommended as a means of estimating the appropriate sample size for the pivotal BE study. Estimated sample size will vary depending upon whether the data are analyzed on a log or linear scale. Useful references for sample size estimates include Hauschke et al., 1992.

U. Crossover and Parallel Design Considerations

A two-period crossover design is commonly used in blood level studies. The use of crossover designs eliminates a major source of study variability: between subject differences in the rates of drug absorption, drug clearance, and the volume of drug distribution.

In a typical two-period crossover design, subjects are randomly assigned to either sequence A or sequence B with the restriction that equal numbers of subjects are initially assigned to each sequence. The design is as follows:

	Sequence A	Sequence B
Period 1	Test	Reference
Period 2	Reference	Test

A crucial assumption in the two-period crossover design is that of equal residual effects. Unequal residual effects may result, for example, from an inadequate washout period. Another assumption of the crossover (or extended period) design is that there is no subject by formulation interaction. In other words, the assumption is that all subjects are from a relatively homogeneous population and will exhibit similar relative BA of the test and reference products. If there are subpopulations of subjects, such that the relationship between product BA is a function of the subpopulation within which they are being tested, then a subject by formulation interaction is said to exist.

A one-period parallel design may be preferable in the following situations:

- The drug induces physiological changes in the animal (e.g., liver microsomal enzyme induction), which persist after total drug clearance and alter the BA of the product administered in the second period.
- The drug has a very long terminal elimination half-life, creating a risk of residual drug present in the animal at the time of the second period dosing.
- The duration of the washout time for the two-period crossover study is so long as to result in significant maturational changes in the study subjects.
- The drug follows delayed or prolonged absorption (flip-flop kinetics), where the slope of the beta-elimination phase is dictated by the rate of drug absorption rather than the rate of drug elimination from one or both products.

Other designs, such as the two-period design with four treatment sequences (test/test, reference/reference, test/reference, and reference/test) or the extended period design may be appropriate depending on the circumstances. The use of alternative study designs should be discussed with

FDA prior to conducting the BE study. Pilot data or literature may be used in support of alternative study designs.

V. Duration of Washout Time for Crossover Study

For drugs which follow a one- or two-compartment open body model, the duration of the washout time should be approximately 10 times the plasma apparent terminal elimination half-life, to provide for 99.9% of the administered dose to be eliminated from the body. If more highly complex kinetic models are anticipated (e.g., drugs for which long withdrawal times have been assigned due to prolonged tissue binding), or for drugs with the potential for physiologic carryover effects, the washout time should be adjusted accordingly. The washout period should be sufficiently long to allow the second period of the crossover study to be applicable in the statistical analysis. However, if sequence effects are noted, the data from the first period may be evaluated as a parallel design study.

W. Fed BE Studies

Food-effect BA studies are usually conducted for new drugs and drug products during the IND period to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. Fed BE studies, on the other hand, are conducted for aNDAs to demonstrate their BE to the RLD under fed conditions. Food can influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by various means, including:

- Delay gastric emptying.
- Stimulate bile flow.
- Change GI pH.
- Increase splanchnic blood flow.
- Change luminal metabolism of a drug substance.
- Physically or chemically interact with a dosage form or a drug substance.

Food effects on BA are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. It is recommended to use high-calorie and high-fat meals during food-effect fed BE studies.

X. Food Effects on Drug Products

Administration of a drug product with food may change the BA by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies. Important food effects on BA are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution. However, for some drugs in this class, food can influence BA when there is a high first-pass effect, extensive adsorption, complexation, or instability of the drug substance in the GI tract. In some cases, excipients or interactions be-

tween excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of BE. For rapidly dissolving formulations of BCS Class I drug substances, food can affect C_{max} and the time at which this occurs (T_{max}) by delaying gastric emptying and prolonging intestinal transit time. However, we expect the food effect on these measures to be similar for test and reference products in fed BE studies.

For other immediate-release drug products (BCS Class II, III, and IV) and for all modified-release drug products, food effects are most likely to result from a more complex combination of factors that influence the *in vivo* dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on formulation BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a fed BE study.

Y. Recommendations for Immediate-Release Drugs:

- For uncomplicated drugs in immediate-release dosage forms, BE must be demonstrated under fasted conditions. In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions.

When both test products and RLDs are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I), or

when the Dosage and Administration section of the RLD label states that the product should be taken only on an empty stomach, or

when the RLD label does not make any statements about the effect of food on absorption or administration.

When the reference-listed product label does not make any statements about the effect of food on absorption or administration.

- For complicated drugs in immediate-release dosage forms, for example, narrow therapeutic range drugs (drugs with a steep dose—response curve, critical drugs), highly toxic drugs, and drugs known to have nonlinear PKs. BE must be demonstrated under both fasted and fed conditions.
- Nonlinear drugs. BE must be demonstrated under both fasted and fed conditions unless the nonlinearity occurs after the drug enters the systemic circulation and there is no evidence that the product exhibits a food effect.
- Drugs in modified-release dosage forms. BE must be demonstrated under both fasted and fed conditions.

Z. Recommendations For Modified-Release Products

In addition to a BE study under fasting conditions, a BE study under fed conditions should be conducted for all orally administered modified-release drug products. It is recommended that food-effect BA and fed BE studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report.

For fasting administration, following an overnight fast of at least 10 hours, subjects should be administered the drug

product with 240 mL (8 fluid oz) of water. No food should be allowed for at least 4 hours post dose. Water may be allowed as desired, except 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

For fed administration, following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to the administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid oz) of water. No food should be allowed for at least 4 hours post dose. Water may be allowed as desired, except 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

1. Study Design

A sponsor may propose any study designs and data analyses. The scientific rationale and justification for these study designs and analyses should be provided in the study protocol. Sponsors may choose to conduct additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g., different meals and different times of drug intake in relation to meals). In studying modified-release dosage forms, consideration should be given to the possibility that coadministration with food can result in *dose dumping*, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects.

2. General Design

A randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design is recommended for studying the effects of food on the BE of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered following a test meal (fed condition). The treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BE studies.

3. Subject Selection

Fed BE studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects. A minimum of 12 subjects should complete the fed BE studies.

4. Dosage Strength

In general, the highest strength of a drug product intended to be marketed should be tested in fed BE studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For aNDAs, the same lot and strength used in the fasting BE study should be tested in the fed BE study. For products with multiple strengths in aNDAs, if a fed BE study has been performed on the highest strength, BE determination of one or more lower strengths can be waived based on dissolution profile comparisons.

5. Test Meal

The fed BE studies can be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. (An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 oz of hash brown potatoes and 8 oz of whole milk.) Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. 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 here, the sponsor should provide a scientific rationale for this difference.

6. Administration

a. Fed Treatments

Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid oz) of water. No food should be allowed for at least 4 hours post dose. Water can be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

7. Sample Collection

Timed samples in biological fluid, usually plasma, should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. It may be advisable to measure other moieties in the plasma, such as active metabolites. Consideration should be given to the possibility that coadministration of a dosage form with food can alter the time course of plasma drug concentrations so that fasted and fed treatments can have different sample collection times.

8. Data Analysis and Labeling

The following exposure measures and PK parameters should be obtained from the resulting concentration-time curves for the test and reference products.

- Total exposure, or area under the concentration-time curve ($AUC_{0-\text{inf}}$, AUC_{0-t})
- Peak exposure (C_{max})
- Time to peak exposure (T_{max})
- Lag-time (t_{lag}) for modified-release products, if present
- Terminal elimination half-life
- Other relevant PK parameters

Individual subject measurements, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation) should be reported. An equivalence approach is recommended analyzing data using an average criterion. Log transformation of exposure measurements (AUC and C_{max}) prior to analysis is recommended. The 90% CI for the ratio of population geometric means between test and

reference products should be provided for AUC_{0-inf} , AUC_{0-t} , and C_{max} . For an NDA-fed BE studies, the RLD administered under fed condition serves as the reference treatment.

For an NDA, BE of a test product to the RLD product under fed conditions is concluded when the 90% CI for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the BE limits of 80% to 125% for AUC and C_{max} . Although no criterion applies to T_{max} , the T_{max} values for the test and reference products are expected to be comparable based on clinical relevance. The conclusion of BE under fed conditions indicates that with regard to food, the language in the package insert of the test product can be the same as the reference product.

Parent Drug vs. Metabolites

The moieties to be measured in biological fluids collected in BA and BE studies are either the active drug ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolites [21 CFR 320.24(b)(1)(i)]. This guidance recommends the following approaches for BA and BE studies.

For BA studies (see section II.B), determination of moieties to be measured in biological fluids should take into account concentration and activity. *Concentration* refers to the relative quantity of the parent drug or one or more metabolites in a given volume of an accessible biological fluid, such as blood or plasma. *Activity* refers to the relative contribution of the parent drug and its metabolite in the biological fluids to the clinical safety and efficacy of the drug. For BA studies, the parent drug and its major active metabolite should be measured, if analytically feasible.

For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. The following are exceptions to this general approach.

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. The metabolite data obtained from these studies should be subject to a CI approach for BE demonstration. If there is clinical concern related to efficacy or safety for the parent drug, sponsors and applicants should contact the appropriate review division to determine whether the parent drug should be measured and analyzed statistically.
- Metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and efficacy, the metabolite and the parent drug should be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and efficacy, it does not need to be measured. The parent drug measured in these BE studies should be analyzed using a CI approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

Enantiomers vs. Racemates

For BA studies, the measurement of individual enantiomers may be important. For BE studies, this guidance recommends measurement of the racemate using an achiral assay. Mea-

surement of individual enantiomers in BE studies is recommended only when all the following conditions are met.

- Enantiomers exhibit different pharmacodynamic characteristics.
- Enantiomers exhibit different PK characteristics.
- Primary efficacy and safety activity reside with the minor enantiomer.
- Nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with a change in the input rate of the drug) for at least one of the enantiomers.

In such cases, BE criteria should be applied to the enantiomers separately.

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 natural source components). Some or all the components of these complex drug substances cannot be characterized with regard to chemical structure or biological activity. Quantification of all active or potentially active components in pharmacokinetic studies to document BA and BE is neither necessary nor desirable. Rather, BA and BE studies should be based on a small number of markers of rate and extent of absorption. Although necessarily a case-by-case determination, criteria for marker selection include the amount of the moiety in the dosage form, plasma or blood levels of the moiety, and biological activity of the moiety relative to other moieties in the complex mixture. Where pharmacokinetic approaches are not feasible to assess the rate and extent of absorption of a drug substance from a drug product, *in vitro* approaches may be preferred. Pharmacodynamic or clinical approaches may be called for if no quantifiable moieties are available for *in vivo* pharmacokinetic or *in vitro* studies.

Long Half-Life Drugs

In a BA or PK study involving an oral product with a long half-life drug, adequate characterization of the half-life calls for blood sampling over a long period of time. For a BE determination of an oral product with a long half-life drug, a nonreplicate, single-dose crossover study can be conducted, provided an adequate washout period is used. If the crossover study is problematic, a BE study with a parallel design can be used. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of GI transit (approximately 2–3 days) of the drug product and absorption of the drug substance. The 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, an AUC truncated at 72 hours (AUC_{0-72h}) can be used in place of AUC_{0-t} or $AUC_{0-\infty}$. For drugs demonstrating high intrasubject variability in distribution and clearance, AUC truncation warrants caution. In such cases, sponsors and applicants should consult the appropriate review staff.

First-Point C_{max}

The first point of a concentration-time curve in a BE study based on blood and plasma measurements is sometimes the highest point, which raises a question about the measurement of true C_{max} because of insufficient early sampling times. A carefully conducted pilot study may avoid this problem. Making collections at an early time point, between 5

and 15 minutes after dosing, followed by making additional sample collections (e.g., two to five) in the first hour after dosing may be sufficient for assessing early peak concentrations. If this sampling approach is followed, data sets should be considered adequate, even when the highest observed concentration occurs at the first time point.

Orally Administered Drugs Intended for Local Action

Documentation of product quality BA for NDAs, where the drug substance produces its effects by local action in the GI tract, can be achieved using clinical efficacy and safety studies or suitably designed and validated *in vitro* studies. Similarly, documentation of BE for aNDAs and for NDAs, as well as for aNDAs in the presence of certain postapproval changes, can be achieved by using BE studies with clinical efficacy and safety end points or suitably designed and validated *in vitro* studies, if the latter studies are reflective of important clinical effects or are more sensitive to changes in product performance compared with 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 GI tract.

Sprinkles

In aNDAs, BE of the test to the RLD is demonstrated in a single-dose crossover study. Both treatments should be sprinkled on one of the soft foods mentioned in the labeling, usually applesauce. The BE data should be analyzed using average BE and the 90% CI criteria should be used to declare BE. If there are questions about other foods, the design, or the analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.

Special Vehicles

In aNDAs, BE of the test to the RLD is demonstrated in a single-dose crossover study. Both treatments should be mixed with one of the beverages mentioned in the labeling. Sponsors should provide evidence that BE differences would not be expected from the use of other listed vehicles. The BE data should be analyzed using average BE, and the 90% CI criteria should be used to declare BE.

Locally Acting GI Drugs

For drugs whose site of action is the GI tract, determination of BE is more complicated because local drug concentrations cannot be measured directly requiring evaluation of PKs, its relationship *in vitro* tests including dissolution and binding assays and correlation with clinical studies.

The PK studies for locally acting drugs provide safety data and whereas PK studies may not correlate with therapeutic effectiveness, the relationship with BE is not so straightforward. If a drug is acting locally and also absorbed in the systemic circulation, the PK studies would still reflect the dosage form factors even though the site of action is also local. The premise here remains same; any differences noted in the C_{max} of AUC is due to differences in absorption rates and extent attributable to dosage form differences such as release of drug. However, when plasma levels can be connected to product effectiveness then we can determine the significance of differences in product performance. When the connection to efficacy is broken, we do not have a simple way to say what difference in PK is significant. In this sense,

downstream PK is similar to a PD end point for which a dose-response curve needs to be established. Another concern about PK studies on locally acting drugs is that the drug may be able to reach the plasma without passing the site of action. An example is an inhalation product for which some of the dose is swallowed and potentially absorbed orally. An important distinction is between parallel and sequential absorption paths. In the inhalation example, the drug either goes to the lung or to the stomach or could appear in plasma at the same time by either path. In a locally acting GI drug the absorption process is sequential, so the drug absorbed from the intestine appears before the drug absorbed in the colon and thus can be distinguished.

The PK studies often fail for locally acting drugs because of the very low concentration observed in plasma and even at the site of local action. For example, mesalamine must reach the mucosal surface lining the GI tract to exert its pharmacological effect, which is dependent on the dissolution rate; for other dosage forms, which dissolve instantly, the rate-limiting factor would be the transit rate in the GI tract. The use of dissolution thus becomes an important tool to demonstrate BE. Some GI acting drugs are formulated to target different regions of the GI tract, often via coatings that lead to pH-dependent dissolution. Comparative dissolution testing at different pH could demonstrate that test and reference products are targeting the same region of the GI tract. Biowaivers for BCS Class I drugs formulated in rapidly dissolving immediate-release solid oral dosage forms are well established. Since a GI acting drug does not need to be absorbed, application of the scientific basis of the BCS would suggest that a high solubility drug in a rapidly dissolving formulation with no excipients that affect product performance may be eligible for a biowaiver.

Generally, studies that measure the concentration of drug in the small intestinal mucosa could provide more direct evidence of equivalent tissue concentration at the site of action. But those studies are difficult to conduct and interspecies correlations often add a lot of variability; as a result, there is a consensus developing that comparative clinical trials be conducted to demonstrate BE but only in those situations where other methods fail since not only are these expensive to conduct, these can often be insensitive to formulation differences—the purpose of the study.

Animal Drug BE Testing

A BE study may also be part of a NADA or supplemental NADA for approval of an alternative dosage form, new route of administration, or a significant manufacturing change, which may affect drug BA. Many requirements described earlier for human studies also apply to animal studies; various descriptions of experimental design and data handling are common to both. FDA has concluded that the tissue residue depletion of the generic product is not adequately addressed through BE studies. Therefore, sponsors of aNADA for drug products for food-producing animals will generally be asked to include BE and tissue residue studies [21 USC 360b(n)(1)(E)]. A tissue residue study should generally accompany clinical end-point and pharmacological end-point BE studies, and blood level BE studies that cannot quantify the concentration of the drug in blood throughout the established withdrawal period [21 USC 360b(n)(1)(A)(ii)]. BE studies (i.e., blood level, pharmacological end-point and clinical end-point studies) and tissue residue depletion studies should be conducted in accordance with GLP regulations (21 CFR Part 58). Whereas the focus of the guidance is BE

testing for aNADA approval, the general principles also apply to relative BA studies conducted for NADAs.

Reference Product

As a general rule, the proposed generic product should be tested against the original pioneer product. If the original pioneer product is no longer marketed, but remains eligible to be copied, then the first approved and available generic copy of the pioneer should be used as the reference product for BE testing against the proposed new generic product.

If several approved NADAs exist for the same drug product, and each approved product is labeled differently (i.e., different species and/or claims), then the generic spon-

sor must clearly identify which product label is the intended pioneer. BE testing should be conducted against the single approved product which bears the labeling that the generic sponsor intends to copy. The generic sponsor should consult with CVM regarding selection of the appropriate reference product before conducting the BE study.

REFERENCE

1. Hauschke D, Steinjans VW, Diletti M, Burke M (1992). Sample size determination for bioequivalence assessment using a multiplicative model. *J Pharm Biopharm* 20:557–561.

Bioequivalence Regulatory Review Process and Audit

BACKGROUND

The Food and Drug Administration (FDA) requires an applicant to provide detailed information to establish bioequivalency. Applicants may request a waiver from performing in vivo (testing done in humans) bioequivalence studies for certain drug products where bioavailability (the rate and extent to which the active ingredient or active moiety is absorbed from the drug product and becomes available at the site of action) may be demonstrated by submitting data such as (1) a formulation comparison for products whose bioavailability is self-evident, for example, oral solutions, injectables, or ophthalmic solutions where the formulations are identical or (2) comparative dissolution.

Alternatively, in vivo bioequivalence testing comparing the rate and extent of absorption of the generic versus the reference product is required for most tablet and capsule dosage forms. For certain products, a head-to-head evaluation of comparative efficacy based upon clinical endpoints may be required.

The Manual of Policies and Procedures of the CDER (Generic Drugs) (MAPP 5210.6) describes the following procedures for review of bioequivalence study protocols.

PROTOCOLS

When a protocol is received in the DBE, the PM assigns it randomly to the next available reviewer. All protocols received are entered in the protocol tracking system and assigned a control number. The protocol receipt date, firm name, drug name, reviewer assigned, and date of assignment are recorded. The reviewer searches the literature and the Agency's databases [e.g., Excalibur, WinBio, drug files (hard copy and electronic)]. If a protocol has been previously submitted and found acceptable by the Division, this should be used as a model in the preparation of responses to subsequent protocols for the same drug. The reviewer should state in the review whether other protocols for the same drug have been previously reviewed. If no other protocols have been reviewed for the product, a statement to that effect should be included in the review. The reviewer prepares a review with recommendations to the requestor. The review must have the concurrence of the team leader and Division Director. If the reviewer discovers discrepancies in bioequivalence criteria or appropriate study design in recommendations provided to industry in previous protocols or correspondence for the same drug product, the reviewer prepares a memorandum to the team leaders and Division Director. The memo should specify the name of the sponsor or CRO that received conflicting information/guidance in protocol responses. Abbreviated new drug applications (ANDAs) affected by this information should also be noted. Once the review is finalized and has the concurrence of the Division Director, it is

forwarded to the PM. The PM or TIA drafts a letter based on the reviewer's recommendation. The PM ensures that all recommendations are provided to the firm. The letter will be routed through the team leader for corrections and endorsement, and to the Division Director for signature. Once the letter is signed by the Division Director, the PM or TIA enters into the protocol tracking system the date the review was finalized and the date the letter was issued. The protocol is then forwarded to the Document Room. Document Room personnel mail the letter and store the protocol in the designated area. The PM drafts letters to sponsors or CROs that have received outdated information to ensure that consistent information is provided to industry.

PRODUCTIVITY DOCUMENTATION

When the Document Room assigns an ANDA to the DBE, a description of the bioequivalence section is entered into the bioequivalence data entry screen in COMIS, using the study types below.

A. Bioequivalence Studies

1. **Fasting Study (STF)**. This includes replicate study designs and combined studies (e.g., combined fasting and multiple-dose studies where the same subjects are used).
2. **Food Study (STP)**.
3. **Multiple-Dose Study (STM)**.
4. **Study (STU)**. This category is generally used for a bioequivalence study with clinical endpoints, in vitro studies for metered-dose inhalers and nasal sprays, pilot and pivotal studies for vasoconstrictors, or any pharmacokinetic/pharmacodynamic study other than a standard bioequivalence study (such as 1–3 above).

- B. **Dissolution Data (DIS)**. This code is usually used when dissolution data are the only basis for approval. Examples are AA drugs and supplements for which changes in formulation or manufacturing require dissolution data only. In vitro release data for topical products may also be coded under DIS. *Note:* Dissolution data submitted for the same strength drug that was the subject of a bioequivalence study are not separately coded. The dissolution information is considered part of the study.

C. Other (OTH):

Study Amendment (STA). This category is for responses to deficiency comments. Whether the amendment contains dissolution data or addresses a deficiency such as incomplete information on analytical methods or a study, the submission should be coded as STA unless a new study is submitted for review. In that case, the appropriate code under BE studies should be selected. If an amendment to a previously submitted BE study is included with a new, not previously submitted BE study required to establish BE, then STA should be coded for

the amendment, and the new study should be coded separately. Retesting of subjects classified as outliers in the original submission should not be classified as a separate study, but as part of the original study. Frequently, the Division telephones sponsors to request information needed to finalize the review. These requests should be made for information the sponsor can respond to within 10 working days, and should be coded as STA. If the sponsor submits incorrect information or partial data, the submission should be coded as new correspondence (NC). Once the correct information is received, the submission should be coded as STA.

Waiver (WAI). This category is used for injectable, ophthalmic, otic, oral, and topical solutions. A formulation in the same concentration packaged in different sizes is not coded separately, but different concentrations of the same product are coded separately.

Dissolution Waiver (DIW). This code is used for lower strengths that can be approved based on proportionality of the formulation and an acceptable study on the highest strength or the strength of the reference listed drug. A dissolution waiver should be coded for each strength for which dissolution data are submitted, except the strength for which bioequivalence studies have been conducted.

Other (OTH). This category is used for correspondence or addenda revising the original review. The Division of Scientific Investigations (DSI) inspection reports may generate an addendum to the review. If a significant statistical analysis is needed based on the recommendation of the DSI, or if the issuance of a Form 483 (Inspectional Observations) indicates serious violations by the laboratory, then the review of the DSI report may be coded as OTH. If the DSI report is acceptable, the DSI report should be filed in the ANDA, and no addendum to the review is necessary. Addenda to the reviews are entered as US documents (FDA generated), because these reviews are not prompted by industry submissions, but are due to internal policy changes or inspection reports. Diskettes containing the data already coded in a previous submission will not be coded separately.

Methods Validation for Abbreviated New Drug Applications

A request for validation of the applicant's proposed regulatory analytical methods is sent by the review chemist to the Office of Regulatory Affairs (ORA) coordinator in the Division of Field Science (DFS) using form FDA 2871a. This action should be taken as soon as the need is identified and the test methods are determined to be adequate by the review chemist.

A copy of the methods, testing specifications, and composition statement is to be included with the request. The package is sent to DFS by current procedures.

Requests are processed and carried out as detailed in the Supplement to the Compliance Program on Preapproval Inspections CP7346.832.

The chemistry/microbiology review is included in the approval package, along with the bioequivalence and labeling reviews. Upon concurrence by the chemistry team leader, the package proceeds through the final administrative review channels. If, after administrative review, the application

remains approvable (including an acceptable EER and office-level bioequivalence endorsement), the project manager determines the status of the methods validation process. The application can be approved with or without results of the methods validation, except under the circumstances noted below.

There was an undue delay in sample submission by the applicant.

There are problems identified in the course of methods validation by the servicing laboratory.

There is no commitment from the applicant to resolve any problems subsequently found by the FDA laboratory.

Any problem identified with the method or the product is evaluated by the review chemist for its significance. Any problem that potentially affects the quality of the drug product must be resolved before application approval. When approval is granted in the absence of a completed methods validation, the approval letter is revised to include the following statement as the last paragraph. *Validation of the regulatory methods has not been completed. It is the general policy of the OGD not to withhold approval until the validation is complete.*

The approval letter is endorsed by the chemistry reviewer and team leader as well as the division director. If the laboratory results are received during the administrative review process for approval and they reveal problems with the methods or the product, the approval of the application is delayed and the results transmitted to the applicant. The applicant is asked to address these issues as soon as possible in an amendment to the application. This amendment is given priority review in consultation, if necessary, with the servicing laboratory. If the amended methods are satisfactory to OGD and they address the concerns of the laboratory, the application can then be approved, provided all other aspects of the application are acceptable. Out-of-specification results on products already expired at the time of testing are evaluated for their significance and relevance. Any product failures must be satisfactorily resolved before application approval. Routine revalidation can be done after approval of the application. The review chemist can request testing at a second FDA laboratory to resolve conflicting results obtained by an applicant and by the FDA servicing laboratory. The team leader and the division director must concur with the request. For methods validation completed after an application is approved, any deficiencies identified are communicated promptly to the applicant. Generally, the response addressing the deficiencies can be submitted as a changes-being-effected supplement. If the methods validation is waived, this fact must be documented and filed in the ANDA.

Good Laboratory Practices

In the 1970s, FDA inspections of nonclinical laboratories revealed that some studies submitted in support of the safety of regulated products had not been conducted in accord with acceptable practice, and that accordingly data from such studies was not always of the quality and integrity to assure product safety. As a result of these findings, FDA promulgated the Good Laboratory Practice (GLP) Regulations, 21 CFR part 58, on December 22, 1978 (43 FR 59986). The regulations became effective June 1979. The regulations establish standards for the conduct and reporting of nonclinical laboratory studies and are intended to assure the quality and integrity of safety data submitted to FDA.

FDA relies on documented adherence to GLP requirements by nonclinical laboratories in judging the acceptability of safety data submitted in support of research and/or marketing permits. FDA has implemented this program of regular inspections and data audits to monitor laboratory compliance with the GLP requirements.

The objective of this program is

- to verify the quality and integrity of data submitted in a research or marketing application,
- to inspect (approximately every 2 years) nonclinical laboratories conducting safety studies that are intended to support applications for research or marketing of regulated products, and
- to audit safety studies and determine the degree of compliance with GLP regulations.

Types of Inspections

1. **Surveillance Inspections.** Surveillance inspections are periodic, routine determinations of a laboratory's compliance with GLP regulations. These inspections include a facility inspection and audits of on-going and/or recently completed studies.
2. **Directed Inspections.** Directed inspections are assigned to achieve a specific purpose, such as:
 - Verifying the reliability, integrity, and compliance of critical safety studies being reviewed in support of pending applications.
 - Investigating issues involving potentially unreliable safety data and/or violative conditions brought to FDA's attention.
 - Reinspecting laboratories previously classified OAI (usually within 6 months after the firm responds to a Warning Letter).
 - Verifying the results from third party audits or sponsor audits submitted to FDA for consideration in determining whether to accept or reject questionable or suspect studies.

Inspections

1. The investigator will determine the current state of GLP compliance by evaluating the laboratory facilities, operations, and study performance.
2. **Organization Chart**—If the facility maintains an organization chart, obtain a current version of the chart for use during the inspection and submit it in the EIR.
3. **Facility Floor-plan Diagram**—Obtain a diagram of the facility. The diagram may identify areas that are not used for GLP activities. If it does not, request that appropriate facility personnel identify any areas that are not used for GLP activities. Use during the inspection and submit it in the EIR.
4. **Master Schedule Sheet**—Obtain a copy of the firm's master schedule sheet for all studies listed since the last GLP inspection or last 2 years and select studies as defined in 21 CFR 58.3(d). If the inspection is the first inspection of the facility, review the entire master schedule. If studies are identified as non-GLP, determine the nature of several studies to verify the accuracy of this designation. See 21 CFR 58.1 and 58.3(d). In contract laboratories determine who decides if a study is a GLP study.

Identification of Studies

 - a. **Directed Inspections**—Inspection assignments will identify studies to be audited.
 - b. **Surveillance inspections**—Inspection assignments may identify one or more studies to be audited. If

the assignment does not identify a study for coverage, or if the referenced study is not suitable to assess all portions of current GLP compliance, the investigator will select studies as necessary to evaluate all areas of laboratory operations. When additional studies are selected, first priority should be given to FDA studies for submission to the assigning Center.

5. **Ongoing Studies**—Obtain a copy of the study protocol and determine the schedule of activities that will be underway during the inspection. This information should be used to schedule inspections of on-going laboratory operations, as well as equipment and facilities associated with the study. If there are no activities underway in a given area for the study selected, evaluate the area based on on-going activities.
6. **Completed Studies**—The data audit should be carried out as outlined in part III, D. If possible, accompany laboratory personnel when they retrieve the study data to assess the adequacy of data retention, storage, and retrieval as described in part III, C 10.

The facility inspection should be guided by the GLP regulations. The following areas should be evaluated and described as appropriate.

1. **Organization and Personnel** (21 CFR 58.29, 58.31, 58.33)
 - a. **Purpose:** To determine whether the organizational structure is appropriate to ensure that studies are conducted in compliance with GLP regulations, and to determine whether management, study directors, and laboratory personnel are fulfilling their responsibilities under the GLPs.
 - b. **Management Responsibilities** (21 CFR 58.31)—Identify the various organizational units, their role in carrying out GLP study activities, and the management responsible for these organizational units. This includes identifying personnel who are performing duties at locations other than the test facility and identifying their line of authority. If the facility has an organization chart, much of this information can be determined from the chart.
2. **Determine if management has procedures for assuring that the responsibilities in 58.31 can be carried out.** Look for evidence of management involvement, or lack thereof, in the following areas:
 - a) Assigning and replacing study directors.
 - b) Control of study director workload (use the Master Schedule to assess workload).
 - c) Establishment and support of the Quality Assurance Unit (QAU), including assuring that deficiencies reported by the QAU are communicated to the study directors and acted upon.
 - d) Assuring that test and control articles or mixtures are appropriately tested for identity, strength, purity, stability, and uniformity.
 - e) Assuring that all study personnel are informed of and follow any special test and control article handling and storage procedures.
 - f) Providing required study personnel, resources, facilities, equipment, and materials.
 - g) Reviewing and approving protocols and standard operating procedures (SOPs).
 - h) Providing GLP or appropriate technical training.
3. **Personnel** (21 CFR 58.29)—Identify key laboratory and management personnel, including any consultants or

- contractors used, and review personnel records, policies, and operations to determine if
- a. Summaries of training and position descriptions are maintained and are current for selected employees.
 - b. Personnel have been adequately trained to carry out the study functions that they perform.
 - c. Personnel have been trained in GLPs.
 - d. Practices are in place to ensure that employees take necessary health precautions, wear appropriate clothing, and report illnesses to avoid contamination of the test and control articles and test systems.
4. If the firm has computerized operations, determine the following:
 - a. Who was involved in the design, development, and validation of the computer system?
 - b. Who is responsible for the operation of the computer system, including inputs, processing, and output of data?
 - c. Whether computer system personnel have training commensurate with their responsibilities, including professional training and training in GLPs?
 - d. Whether some computer system personnel are contractors who are present on-site full-time, or nearly full-time. The investigation should include these contractors as though they were employees of the firm. Specific inquiry may be needed to identify these contractors, as they may not appear on organization charts.
 - e. Interview and observe personnel using the computerized systems to assess their training and performance of assigned duties.
 5. Study director (21 CFR 58.33)
 - a. Assess the extent of the study director's actual involvement and participation in the study. In those instances when the study director is located off-site, review any correspondence/records between the testing facility management and quality assurance unit and the off-site study director. Determine that the study director is being kept immediately apprised of any problems that may affect the quality and integrity of the study.
 - b. Assess the procedures by which the study director
 - i. assures the protocol and any amendments have been properly approved and are followed,
 - ii. assures that all data are accurately recorded and verified,
 - iii. assures that data are collected according to the protocol and SOPs,
 - iv. documents unforeseen circumstances that may affect the quality and integrity of the study and implements corrective action,
 - v. assures that study personnel are familiar with and adhere to the study protocol and SOPs, and
 - vi. assures that study data are transferred to the archives at the close of the study.
 6. EIR Documentation and Reporting—Collect exhibits to document deficiencies. This may include SOPs, organizational charts, position descriptions, and curriculum vitae (CVs), as well as study-related memos, records, and reports for the studies selected for review. **The use of outside or contract facilities must be noted in the EIR. The assigning Center should be contacted for guidance on inspection of these facilities.**
 7. Quality Assurance Unit (QAU; 21 CFR 58.35)

Purpose: To determine if the test facility has an effective, independent QAU that monitors significant study events and facility operations, reviews records and reports, and assures management of GLP compliance.

QAU Operations—(21 CFR 58.35(b-d))—Review QAU SOPs to assure that they cover all methods and procedures for carrying out the required QAU functions, and confirm that they are being followed. Verify that SOPs exist and are being followed for QAU activities including, but not limited to, the following:

 - a) Maintenance of a master schedule sheet.
 - a) Maintenance of copies of all protocols and amendments.
 - a) Scheduling of its in-process inspections and audits.
 - a) Inspection of each nonclinical laboratory study at intervals adequate to assure the integrity of the study, and maintenance of records of each inspection.
 - a) Immediately notify the study director and management of any problems that are likely to affect the integrity of the study.
 - a) Submission of periodic status reports on each study to the study director and management.
 - a) Review of the final study report.
 - a) Preparation of a statement to be included in the final report that specifies the dates inspections were made and findings reported to management and to the study director.
 8. Inspection of computer operations.
 - a) Verify that, for any given study, the QAU is entirely separate from and independent of the personnel engaged in the conduct and direction of that study. Evaluate the time QAU personnel spend in performing in-process inspection and final report audits. Determine if the time spent is sufficient to detect problems in critical study phases and if there are adequate personnel to perform the required functions.
 - b) *Note:* The investigator may request the firm's management to certify in writing that inspections are being implemented, performed, documented, and followed-up in accordance with this section [see 58.35(d)].
 9. EIR Documentation and Reporting—Obtain a copy of the master schedule sheet dating from the last routine GLP inspection or covering the past 2 years. If the master schedule is too voluminous, obtain representative pages to permit headquarters review. When master schedule entries are coded, obtain the code key. Deficiencies should be fully reported and documented in the EIR. Documentation to support deviations may include copies of QAU SOPs, list of QAU personnel, their CVs or position descriptions, study-related records, protocols, and final reports.
 10. Facilities (21 CFR 58.41 – 51)

Purpose: Assess whether the facilities are of adequate size and design.

Facility Inspection

 - a) Review environmental controls and monitoring procedures for critical areas (i.e., animal rooms, test article storage areas, laboratory areas, handling of bio-hazardous material, etc.) and determine if they appear adequate and are being followed.
 - b) Review the SOPs that identify materials used for cleaning critical areas and equipment, and assess the facility's current cleanliness.
 - c) Determine whether there are appropriate areas for the receipt, storage, mixing, and handling of the test and control articles.

- d) Determine whether separation is maintained in rooms where two or more functions requiring separation are performed.
 - e) Determine that computerized operations and archived computer data are housed under appropriate environmental conditions (e.g., protected from heat, water, and electromagnetic forces).
11. EIR Documentation and Reporting—Identify which facilities, operations, SOPs, etc., were inspected. Only significant changes in the facility from previous inspections need be described. Facility floor plans may be collected to illustrate problems or changes. Document any conditions that would lead to contamination of test articles or to unusual stress of test systems.
12. Equipment (21 CFR 58.61 – 63)
- Purpose: To assess whether equipment is appropriately designed and of adequate capacity and is maintained and operated in a manner that ensures valid results.
- Equipment Inspection—Assess the following:
- a) The general condition, cleanliness, and ease of maintenance of equipment in various parts of the facility.
 - b) The heating, ventilation, and air conditioning system design and maintenance, including documentation of filter changes and temperature/humidity monitoring in critical areas.
 - c) Whether equipment is located where it is used and that it is located in a controlled environment, when required.
 - d) Nondedicated equipment for preparation of test and control article carrier mixtures is cleaned and decontaminated to prevent cross-contamination.
 - e) For representative pieces of equipment check the availability of the following:
 - i) SOPs and/or operating manuals.
 - ii) Maintenance schedule and log.
 - iii) Standardization/calibration procedure, schedule, and log.
 - iv) Standards used for calibration and standardization.
 - f) For computer systems, assess that the following procedures exist and are documented:
 - i. Validation study, including validation plan and documentation of the plan's completion.
 - ii. Maintenance of equipment, including storage capacity and backup procedures.
 - iii. Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change.
 - iv. Evaluation of test data to assure that data are accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer.
 - v. Procedures for emergency backup of the computer system (e.g., backup battery system and data forms for recording data in the event of a computer failure or power outage).
13. EIR Documentation and Reporting—The EIR should list which equipment, records, and procedures were inspected and the studies to which they are related. Detail any deficiencies that might result in contamination of test articles, uncontrolled stress to test systems, and/or erroneous test results.
14. Testing Facility Operations (21 CFR 58.81)

Purpose: To determine if the facility has established and follows written SOPs necessary to carry out study operations in a manner designed to ensure the quality and integrity of the data.

SOP Evaluation

- a. Review the SOP index and representative samples of SOPs to ensure that written procedures exist to cover at least all of the areas identified in 58.81(b).
 - b. Verify that only current SOPs are available at the personnel workstations.
 - c. Review key SOPs in detail and check for proper authorization signatures and dates, and general adequacy with respect to the content (i.e., SOPs are clear, complete, and can be followed by a trained individual).
 - d. Verify that changes to SOPs are properly authorized and dated and that a historical file of SOPs is maintained.
 - e. Ensure that there are procedures for familiarizing employees with SOPs.
 - f. Determine that there are SOPs to ensure the quality and integrity of data, including input (data checking and verification), output (data control), and an audit trail covering all data changes.
 - g. Verify that a historical file of outdated or modified computer programs is maintained. If the firm does not maintain old programs in digital form, ensure that a hard copy of all programs has been made and stored.
 - h. Verify that SOPs are periodically reviewed for current applicability and that they are representative of the actual procedures in use.
 - i. Review selected SOPs and observe employees performing the operation to evaluate SOP adherence and familiarity. EIR Documentation and Reporting - Submit SOPs, data collection forms, and raw data records as exhibits that are necessary to support and illustrate deficiencies.
15. Reagents and Solutions (21 CFR 58.83)
- Purpose: To determine that the facility ensures the quality of reagents at the time of receipt and subsequent use.
- Review the procedures used to purchase, receive, label, and determine the acceptability of reagents and solutions for use in the studies.
- Verify that reagents and solutions are labeled to indicate identity, titer or concentration, storage requirements, and expiration date.
- Verify that for automated analytical equipment, the profile data accompanying each batch of control reagents are used.
- Check that storage requirements are being followed.
16. Test and Control Articles (21 CFR 58.105 – 113)
- Purpose: To determine that procedures exist to assure that test and control articles and mixtures of articles with carriers meet protocol specifications throughout the course of the study, and that accountability is maintained.
- Characterization and Stability of Test Articles (21 CFR 58.105)—The responsibility for carrying out appropriate characterization and stability testing may be assumed by the facility performing the study or by the study sponsor. When test article characterization and stability testing is performed by the sponsor, verify that the test facility has received documentation that this testing has been conducted.

Verify that procedures are in place to ensure that

- a) the acquisition, receipt and storage of test articles, and means used to prevent deterioration and contamination are as specified;
- b) the identity, strength, purity, and composition, (i.e., characterization) to define the test and control articles are determined for each batch and are documented;
- c) the stability of test and control articles is documented;
- d) the transfer of samples from the point of collection to the analytical laboratory is documented;
- d) storage containers are appropriately labeled and assigned for the duration of the study; and
- f) reserve samples of test and control articles for each batch are retained for studies lasting more than 4 weeks.

Test and Control Article Handling (21 CFR 58.107)

- a) Determine that there are adequate procedures for:
 - i. documentation for receipt and distribution;
 - ii. proper identification and storage; and
 - iii. precluding contamination, deterioration, or damage during distribution.
- a. Inspect test and control article storage areas to verify that environmental controls, container labeling, and storage are adequate.
- b. Observe test and control article handling and identification during the distribution and administration to the test system.
- c. Review a representative sample of accountability records and, if possible, verify their accuracy by comparing actual amounts in the inventory. For completed studies verify documentation of final test and control article reconciliation.

17. Protocol and Conduct of Nonclinical Laboratory Study (21 CFR 58.120 – 130)

Purpose: To determine if study protocols are properly written and authorized, and that studies are conducted in accordance with the protocol and SOPs.

Study Protocol (21 CFR 58.120)

- a) Review SOPs for protocol preparation and approval and verify they are followed.
- b) Review the protocol to determine if it contains required elements.
- c) Review all changes, revisions, or amendments to the protocol to ensure that they are authorized, signed, and dated by the study director.
- d) Verify that all copies of the approved protocol contain all changes, revisions, or amendments.

18. Conduct of the Nonclinical Laboratory Study (21 CFR 58.130)—Evaluate the following laboratory operations, facilities, and equipment to verify conformity with protocol and SOP requirements for

Test system monitoring.

Recording of raw data (manual and automated).

Corrections to raw data (corrections must not obscure the original entry and must be dated, initialed, and explained).

Randomization of test systems.

Collection and identification of specimens.

Authorized access to data and computerized systems.

19. Records and Reports (21 CFR 58.185 – 195)

Purpose: To assess how the test facility stores and retrieves raw data, documentation, protocols, final reports, and specimens.

Reporting of Study Results (21 CFR 58.185)—Determine if the facility prepares a final report for each study conducted. For selected studies, obtain the final report, and verify that it contains the following:

- a) Name and address of the facility performing the study and the dates on which the study was initiated and completed.
- b) Objectives and procedures stated in the approved protocol, including any changes in the original protocol.
- c) Statistical methods used for analyzing the data.
- d) The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.
- e) Stability of the test and control articles under the conditions of administration.
- f) A description of the methods used.
- g) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.
- h) A description of the dosage, dosage regimen, route of administration, and duration.
 - i) A description of all circumstances that may have affected the quality or integrity of the data.
 - j) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.
 - k) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
 - l) The signed and dated reports of each of the individual scientists or other professionals involved in the study.
 - m) The locations where all specimens, raw data, and the final report are to be stored.
 - n) The statement prepared and signed by the quality assurance unit as described in section 58.35(b)(7).
 - i. The final report shall be signed and dated by the study director.
 - ii. Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

20. Storage and Retrieval of Records and Data (21 CFR 58.190)

Verify that raw data, documentation, protocols, final reports, and specimens have been retained.

Identify the individual responsible for the archives. Determine if delegation of duties to other individuals in maintaining the archives has occurred.

Verify that archived material retained or referred to in the archives is indexed to permit expedient retrieval. It is not necessary that all data and specimens be in the same archive location. For raw data and specimens retained elsewhere, the archives index must make specific reference to those other locations.

Verify that access to the archives is controlled and determine that environmental controls minimize deterioration.

- Ensure that there are controlled procedures for adding or removing material. Review archive records for the removal and return of data and specimens. Check for unexplained or prolonged removals.
- Determine how and where computer data and backup copies are stored, that records are indexed in a way to allow access to data stored on electronic media, and that environmental conditions minimize deterioration.
- Determine to what electronic media such as tape cassettes or ultra high capacity portable discs the test facility has the capacity of copying records in electronic form. Report names and identifying numbers of both copying equipment type and electronic medium type to enable agency personnel to bring electronic media to future inspections for collecting exhibits.
21. **Data Audit.** In addition to the procedures outlined above for evaluating the overall GLP compliance of a firm, the inspection should include the audit of at least one completed study. Studies for audit may be assigned by the Center or selected by the investigator as described in part III, A. The audit will include a comparison of the protocol (including amendments to the protocol), raw data, records, and specimens against the final report to substantiate that protocol requirements were met and that findings were fully and accurately reported. For each study audited, the study records should be reviewed for quality to ensure that data are:
- Attributable—the raw data can be traced, by signature or initials and date to the individual observing and recording the data. Should more than one individual observe or record the data, that fact should be reflected in the data.
 - Legible—the raw data are readable and recorded in a permanent medium. If changes are made to original entries, the changes
 - a) must not obscure the original entry,
 - b) indicate the reason for change, and
 - c) must be signed or initialed and dated by the person making the change.
 - Contemporaneous—the raw data are recorded at the time of the observation.
 - Original—the first recording of the data.
 - Accurate—the raw data are true and complete observations. For data entry forms that require the same data to be entered repeatedly, all fields should be completed or a written explanation for any empty fields should be retained with the study records.
22. **General**
- Determine if there were any significant changes in the facilities, operations, and QAU functions other than those previously reported.
 - Determine whether the equipment used was inspected, standardized, and calibrated prior to, during, and after use in the study. If equipment malfunctioned, review the remedial action, and ensure that the final report addresses whether the malfunction affected the study.
 - Determine if approved SOPs existed during the conduct of the study.
 - Compare the content of the protocol with the requirements in 21 CFR
 - Review the final report for the study director's dated signature and the QAU statement as required in 21 CFR 58.35(b)(7).
23. **Protocol Versus Final Report—**Study methods described in the final report should be compared against the protocol and the SOPs to confirm those requirements were met. Examples include, but are not limited to, the following:
24. **Final Report Versus Raw Data—**The audit should include a detailed review of records, memorandum, and other raw data to confirm that the findings in the final report completely and accurately reflect the raw data. Representative samples of raw data should be audited against the final report.
25. **Samples—**Collection of samples should be considered when the situation under audit or surveillance suggests that the facility had, or is having, problems in the area of characterization, stability, storage, contamination, or dosage preparation.
26. **Inspectional Observations—**A FDA 483 listing inspectional observations will be issued under this program. Findings should not be listed on the FDA 483 if in the opinion of the field investigator:
- The findings are problems that have been observed and corrected by the firm through its internal procedures.
 - The findings are minor and are one-time occurrences that have no impact on the firm's operations, study conduct, or data integrity.
 1. Findings that are not considered significant enough to be listed on the FDA 483 may be discussed with the firm's management. Such discussions must be reported in the EIR. Analyzing Laboratories

FDA Audit Plans

When bioequivalence studies are submitted as part of an ANDA, the US FDA inspections include an audit of the studies submitted under the Compliance Program 7348.001. It is important to review these directives since it allows firms to prepare studies and have them ready for presentation in a format that is readily accessible and comprehensible. This applies to both domestic and international inspections. When the clinical and analytical portions of a study have been performed at separate locations, separate reports should be prepared and submitted for each site

PART I—BACKGROUND

The Bioequivalence Regulations (21 CFR 320) of January 7, 1977 and its amendments stated the requirements for submission of in vivo bioavailability and bioequivalence data as a condition of marketing a new (i.e., new chemical compound; new formulation, new dosage form, or new route of administration of a marketed drug) or generic drug. 21 CFR 320 also provided general guidance concerning the design and conduct of bioavailability/bioequivalence studies. However, it should be noted that bioequivalence studies conducted to support ANDAs involve testing of already approved drug entities and therefore, generally do not require an investigational new drug application (IND). However, sponsors of generic drugs need to file INDs when studies involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product [21 CFR 312.2(b)(iii)].

The FDA does not require bioequivalence studies on pre-1938 drug products. It is however the responsibility of the firm to assure that the studies are submitted in accordance with the most current guidelines as amended.

Bioequivalence studies involve both a clinical component and an analytical component. The objective of a typical

bioequivalence study is to demonstrate that the test and reference products achieve a similar pharmacokinetic profile in plasma, serum, and/or urine. Bioequivalence studies usually involve administration of test and reference drug formulations to 18 to 36 normal healthy subjects, but patients with a target disease may also be used. Formulations to be tested are administered either as a single dose or as multiple doses. Sometimes formulations can be labeled with a radioactive component to facilitate subsequent analysis. In a bioequivalence study, serial samples of biological fluid (plasma, serum, or urine) are collected just before and at various times after dose administration. These samples are later analyzed for drug and/or metabolite concentrations. The study data are used in subsequent pharmacokinetic analyses to establish bioequivalence.

In some situations, the clinical and analytical facilities for a study may be part of the same organization and therefore may be covered by one District. In other situations, the two facilities may be located in different Districts. For the purpose of this program, the District where the clinical facility is located will be referred to as the Clinical Component District, and the District where the analytical facility is located will be referred to as the Analytical Component District.

PART II—IMPLEMENTATION

Objective

1. To verify the quality and integrity of scientific data from bioequivalence studies submitted to the Center for Drug Evaluation and Research (CDER);
2. To ensure that the rights and welfare of human subjects participating in drug testing are protected; and
3. To ensure compliance with the regulations (21 CFR 312, 320, 50, and 56) and promptly follow-up on significant problems, such as research misconduct or fraud.

Program Management Instructions

A. Coverage

It is important to draw distinctions between a clinical laboratory, a clinical facility, and an analytical facility. A clinical laboratory generally uses blood and/or urine to conduct medical screening or diagnostic tests such as blood counts (CBC), liver function tests (ALT, AST) or kidney function (BUN, creatinine clearance, etc.) tests. Clinical laboratories are usually certified under programs based on the Clinical Laboratories Improvement Act (42 USC 263a) and are not routinely inspected by the FDA. A clinical laboratory may be visited during a bioequivalence study audit to confirm that reported screening or diagnostic laboratory work was indeed performed. The clinical facility and the analytical facility as described above are the laboratories that will be routinely inspected under this program.

1. Clinical Facilities

Clinical facilities conduct bioequivalence studies (including screening, dosing, monitoring of subjects' safety, etc.) in order to obtain biological specimens (e.g., plasma, serum, urine) for analysis of drug and/or drug metabolite concentrations. Facilities that conduct bioequivalence studies in human research subjects for pharmacodynamic measurements (i.e., clinical or pharmacological effects) are also included.

2. Analytical Facilities

Analytical facilities analyze biological specimens collected in bioequivalence studies and other human clinical

studies for drug and/or metabolite concentrations to measure the absorption and disposition of the drug.

3. Clinical and Analytical Investigators

The clinical investigator in a bioequivalence study is involved in the screening and dosing of human subjects, and will ordinarily be a physician. PhD clinical pharmacologists and PharmDs are acceptable if a physician is available to cover medical emergencies. The clinical investigator may also perform pharmacodynamic measurement(s) and evaluation activities of clinical or pharmacological endpoints. The analytical investigator in a bioequivalence study is the scientist in the analytical facility responsible for assay development and validation, and analyses of biological specimens, for example, Scientific Director or Laboratory Director.

B. Process

Facilities where bioequivalence studies are conducted are to include a review of the clinical and analytical testing procedures plus an audit of source data from one or more specified studies.

C. Assignments under this program are of two basic categories:

1. *Directed Data Audit*—Covers studies and/or facilities in which gross problems/inadequacies are suspected (including, but not limited to research misconduct, or fraud). Such assignments require rapid evaluation and resolution.
2. *Routine Data Audit*—Covers (1) pivotal studies under current review in the Divisions of Pharmaceutical Evaluation I (HFD-860), II (HFD-870), or III (HFD-880) in the Office of Clinical Pharmacology and Biopharmaceutics (HFD-850); and (2) bioequivalence studies supporting the approval of a generic product.

Assignments will be issued by the GLP and Bioequivalence Investigations Branch (GBIB, HFD-48) to the field. For each assignment, a scientific reviewer in GBIB with expertise in chemical assays, bioavailability/bioequivalence, biopharmaceutics, pharmacokinetics, or pharmacodynamics will (1) assist the field in coordinating and as necessary conducting the inspection; (2) provide technical guidance and on-site support to the field as necessary; and (3) serve as the liaison between the field investigator(s) and the Review Divisions in CDER.

For all inspections in which a Form FDA-483 is issued, a copy of the Form FDA-483 should be forwarded by facsimile to the GBIB contact or the Branch Chief of GBIB.

PART III—INSPECTIONAL

Operations

A. Inspectional

A complete inspection report under this compliance program consists of inspectional findings covering:

1. *Clinical testing*, which includes the adequacy of facilities and procedures utilized by the clinical investigator along with a data audit of the specific study(ies) identified by GBIB; and
2. *Analytical testing*, which includes the adequacy of the facilities, equipment, personnel, and methods and procedures utilized at the analytical facility including an audit of the method validation and analytical data for the study(ies) identified by GBIB.

A full narrative report of any deviations from existing regulations is required. Deviation(s) must be documented sufficiently to support legal or administrative action. For

example, any records containing data that are inconsistent with data submitted to FDA should be copied and the investigator should identify the discrepancy. Generally, serious violations will require more extensive documentation a discussion between the inspector and his supervisor and the appropriate Center contact prior to embarking on this type of coverage.

B. Investigational

If inspections of institutional review boards and/or clinical laboratories are indicated, the inspector is required to contact his supervisor and GBIB for guidance prior to initiating the inspection.

C. Refusals

If access to, or copying of records is refused for any reason, the inspector promptly contacts his supervisor so that the GBIB contact can be advised of the refusal. Send follow-up information via EMS to GBIB, and ORO contacts. The same procedure is followed when it becomes evident that delays by the firm constitute a de facto refusal.

If actions by the firm take the form of a partial refusal for inspection of documents or areas to which FDA is entitled under the law, inspector calls attention to 301(e) and (f) and 505(k)(2) of the FD&C Act; if the refusal persists, he telephones his supervisor and the GBIB contact for instructions.

If the proper course of action to deal with a refusal cannot be resolved expeditiously by GBIB or ORO, GBIB will notify the Bioresearch Program Coordinator (HFC-230).

D. Findings

1. If the inspector encounters serious problems with the data, methodology, quality control practices, etc., he will continue with the originally assigned inspection, but contact GBIB for advice on possibly expanding the inspection. GBIB will determine if an in-depth inspection, involving additional bioequivalence studies, should be initiated.
2. If the inspector encounters questionable or suspicious records and is unable to review or copy them immediately and have reason to preserve their integrity by officially sealing them, the inspector contacts his supervisor immediately for instructions. Procedures exist for the inspector District to clear this type of action by telephone with the ORA/Bioresearch Program Coordinator (HFC-230). See *Inspection Operations Manual*, Section 453.5.
3. Issuance of a Form FDA-483, Inspectional Observations, is appropriate when (1) practice at the clinical site deviates from the standards for conduct of a clinical study as set forth in 21 CFR 312 and 320 and 361, (2) practice at the analytical site deviates from the standards of laboratory practices as set forth in 21 CFR 320, and (3) discrepancies have occurred between source data and reported data in the case report forms. Items that need to be checked for compliance to study standards are provided in Attachment A. Examples of noncompliance to study standards at the clinical and analytical sites are listed in part V of this guidance. Observed deficient practices should be discussed with the responsible officials.

PART IV—ANALYTICAL

Routine analytical work is anticipated for this compliance program. Collected study retention samples will be sent to the Division of Drug Testing and Applied Analytical Development, St. Louis, MO for screening. The sample size should be sufficient to allow the FDA laboratory to perform all of the release tests required in the ANDA, NDA, or supplemental applications five times. If the clinical investigator is not sure of the amount that constitutes the "five times quantity," the clinical investigator should contact the study sponsor. The clinical facility must provide a written assurance (e.g., an affidavit) that the retained samples are representative of those used in the specific bioavailability/bioequivalence study, and that they were stored under conditions specified in accompanying records.

opment, St. Louis, MO for screening. The sample size should be sufficient to allow the FDA laboratory to perform all of the release tests required in the ANDA, NDA, or supplemental applications five times. If the clinical investigator is not sure of the amount that constitutes the "five times quantity," the clinical investigator should contact the study sponsor. The clinical facility must provide a written assurance (e.g., an affidavit) that the retained samples are representative of those used in the specific bioavailability/bioequivalence study, and that they were stored under conditions specified in accompanying records.

PART V—REGULATORY/ADMINISTRATIVE STRATEGY

Clinical Testing

Examples of noncompliance are as follows:

1. Subjects not receiving the test or reference drug formulation according to the study randomization codes.
2. Biological samples compromised by improper identification, handling, or storage.
3. Failure to report adverse experiences, such as vomiting, and diarrhea, which may affect absorption and elimination of drugs.
4. Inadequate drug accountability records.
5. Inadequate medical supervision and coverage.
6. Significant problems/protocol deviations/adverse events not reported to the sponsor.
7. Failure to adhere to the inclusion/exclusion criteria of the approved protocol.
8. Inadequate or missing informed consent for participating subjects.
9. Any other situation in which the health and welfare of the subjects are compromised.

Analytical Testing

Examples of noncompliance are as follows:

1. Inconsistencies between data reported to FDA and at the site.
2. Inadequate or missing validation of assay methodology with respect to specificity (related chemicals, degradation products, metabolites), linearity, sensitivity, precision, and reproducibility.
3. Failure to employ standard, scientifically sound quality control techniques, such as use of appropriate standard curves and/or analyte controls that span the range of subjects' analyte levels.
4. Failure to include all data points, not otherwise documented as rejected for a scientifically sound reason, in determination of assay method precision, sensitivity, accuracy, etc.
5. Samples are allowed to remain for prolonged periods of time without proper storage.
6. Failure to maintain source data, for example, source data written on scrap paper and/or discarded in trash after transferring to analytical documents.
7. Lack of objective standard for data acceptance of calibration standards, quality controls, etc.
8. Unskilled personnel conducting analytical procedures.
9. No documentation of analytical findings.
10. Inadequate or no written procedures for drug sample receipt and handling.
11. Inadequate or missing standard operating procedures.

Note: The above are not all-inclusive lists of examples of clinical and analytical noncompliance.

Bioequivalence Inspection Report**PART I—FACILITIES AND PROCEDURES (Clinical and Analytical)****A. Facilities (Clinical and/or Analytical)**

1. Evaluate the general facilities for adequate space, work-flow patterns, separation of operations, etc.
2. Comment on potential or actual problems, such as:
 1. adjacent clinic rooms housing concurrent studies;
 2. open windows allowing ingress of unauthorized food, drugs, etc., into clinic rooms;
 3. are dropped ceilings sealed or monitored to prevent storage of nonpermitted materials;
 4. other conditions that may compromise study security, contribute to the potential for sample mix-up, sample contamination/degradation, etc.
3. Comment if the facilities do not appear adequate to support their normal workload.
4. Are there written, dated, and approved standard operating procedures, readily available to all personnel in their work areas? Are working copies kept current?
5. Are outdated procedures archived for future reference?
6. Are visitors to the clinical facility permitted? How are visitors monitored to prevent passage of nonpermitted materials to the study subjects?
7. Are off-site trips for smoking or other reasons monitored to prevent consumption of nonpermitted materials or passage of such materials to or from unauthorized persons?

B. Personnel

1. Check the relevant qualifications, training, and experience of personnel. Assess staff's ability to perform assigned functions. Document any deficiencies that relate to the audited study(ies).

C. Specimen Handling and Integrity

In the Clinic. Check and describe:

1. Procedures for positive subject and sample identification so that study, drug, subject, sampling time, etc., are linked.
2. Procedures for adherence to processing time, temperature, and light conditions as specified by analytical method.
3. Storage conditions before and after processing, as well as during transit to the laboratory.
4. Precautions against sample loss and mix-up during storage, processing and transit to the laboratory.

In the Analytical Laboratory

1. Determine if the analytical facility receives bioequivalence samples from other locations. If yes:
 - a. Are there freight receipts for sending/receiving samples?
 - b. Is a documented history of sample integrity available (e.g., the sample storage time and conditions prior to shipment)?
 - c. Is the length of time in shipment recorded?
 - d. Evaluate the type of transportation employed, and type of protection provided (e.g., shipped by air in insulated containers of dry ice). Report any questionable practices.
 - e. What arrangement(s) can be made for receiving shipments outside of normal working hours?
 - f. Are the conditions of the samples noted upon arrival at the analytical laboratory, along with the identity of the person(s) receiving the samples?

- g. Are there procedures and documentation to assure that the samples remained at the proper temperature during shipment and holding?
2. Describe the storage equipment for bioequivalence samples until analysis (e.g., GE Freezer, chest type, Model #417, etc.)
3. Evaluate the equipment and procedures (e.g., ultraviolet light protection) for storing and maintaining bioequivalence samples, prior to and during analysis.
 - a. Compare storage capacity versus number of samples in storage.
 - b. Examine set points for alarms and temperature controlling/recording devices.
 - c. Review procedures for calibration and maintenance of alarms and controllers/recorders.
 - d. Determine practices for monitoring, review, and storage of temperature records.
 - e. Report any evidence of sample thawing.
 - f. Check integrity of study samples.
 - g. Determine if action plans are in place in case of power loss leading to abnormal storage conditions, that is, emergency procedures.
4. Determine if samples are labeled and separated in storage and during analysis to prevent sample loss or mix-up between studies, subjects, and test/reference drug?
5. Examine how sample identification is maintained through transfer steps during analysis.
6. Is there accurate documentation to show how many freeze and thaw cycles the samples have been subjected to, including accidental thawing due to equipment failure(s)?

Electronic Records and Signatures

FDA published the Electronic Records; Electronic Signatures; Final Rule (21 CFR 11) on March 20, 1997. The rule became effective on August 20, 1997. Records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirement set forth in agency regulations must comply with 21 CFR 11. The following questions are provided to aid evaluation of electronic records and electronic signatures:

1. Are electronic data systems used to gather clinical (e.g., adverse experiences, concomitant medications) and analytical data (e.g., peak heights, peak areas of chromatograms)? Are such systems used to store, analyze, and/or calculate pharmacokinetic/pharmacodynamic modeling, or to transmit clinical and analytical data to the sponsor? If so, identify the system(s), and summarize the system(s)' capabilities. If electronic data systems are not used, omit coverage of the remainder of this section.
2. Determine the source(s) of data entered into the computer for accuracy, security, and traceability.
 - a. Direct electronic transfer of on-line instrument data.
 - b. Case report forms, analytical worksheets, or similar records requiring manual data entry.
 - c. Chromatograms requiring evaluation prior to manual extraction of data.
 - d. Other.
3. Determine the following:
 - a. Who enters data and when?
 - b. Who verifies data entry and when?
 - c. Who has access to computer and security codes?
 - d. How are data in computers changed? By whom? Audit trail?

4. Determine if the sponsor gets source data or tabulated, evaluated data.
5. Determine how data are transmitted to sponsor (hard copy, computer disk, fax, modem, etc.)
6. If the *sponsor* discovers errors, omissions, etc., in the final report, what contacts are made with the investigator; how are corrections effected, and how are they documented?
7. Determine how data are retained by the investigator? (Hard copy, electronic, etc.)
8. Determine if the firm has SOPs for validation of computer systems involved in storing, analyzing, calculating, modeling, and/or transmitting clinical and analytical data. Have the computer systems been validated according to the SOPs? Are results of the validations documented and available for audit? Summarize the validated capabilities of the computer systems with respect to their effect on the validity of the study data.

Clinical Data and Operations

General

Inspections of clinical facilities should include a comparison of the practices and procedures of the clinical investigator with the requirements of 21 CFR 312, 320.

Inspections should also include a comparison of the source data in the clinical investigator's files with the data submitted to the FDA. Original records should be reviewed, including medical records, dosing records, clinical laboratory test reports, adverse reaction reports, concomitant medications records, nurses' notes, etc.

Inspection Procedures

This part identifies the minimum information that must be obtained during an inspection to determine if the clinical investigator is complying with the regulations. Each FDA investigator should expand the inspection as facts emerge. The inspections should be sufficient in scope to determine the clinical investigator's general practices for each point identified, as well as the particular practices employed for the study(ies) under audit.

Study Responsibility and Administration

1. Determine if the clinical investigator was aware of the status of the test article(s), nature of the protocol, and the obligations of the clinical investigator.
2. Determine whether authority for the conduct of various aspects of the study was delegated properly so that the investigator retained control and knowledge of the study.
3. Determine if the investigator discontinued the study before completion. If so, provide reason.
4. Determine the name and address of any clinical laboratory performing clinical laboratory tests for qualifying and/or safety monitoring of study subjects.
 - a. If any clinical laboratory testing was performed in the investigator's own facility, determine whether that facility is equipped to perform each test specified.
 - b. Determine if individuals performing the clinical tests are adequately qualified.

Protocol

Obtain a copy of the written protocol. Unavailability should be reported and documented. If a copy of the protocol is sent with the assignment background material, it should be compared to the protocol on site. If the protocols are identical, a duplicate copy does not need to be obtained. The narrative should note that the protocols were identical. If the protocol

has been accepted by a Review Division in CDER, a copy of the acceptance letter should be attached to the EIR. If the Agency has recommended the incorporation of additional material, method, or information into the protocol, verify that appropriate modifications were made.

1. Compare the written protocol and all Institutional Review Board (IRB) approved modifications against the protocol provided with the assignment package. Report and document any differences.
2. Determine if the approved protocol was followed with respect to:
 - a. Subject selection (inclusion/exclusion criteria).
 - b. Number of subjects.
 - c. Drug dose form, strength and route of administration.
 - d. Frequency of subject dosing, monitoring, and sampling.
 - e. Washout period between study arms (test vs. reference drug)
 - f. Other (specify)?
3. Determine whether all significant changes to the protocol were:
 - a. documented by an approved amendment that is maintained with the protocol;
 - b. dated by the investigator;
 - c. approved by the IRB and reported to the sponsor before implementation except where necessary to eliminate apparent immediate hazard to human subjects.
 - d. implemented after IRB approval.

Note: Changes in protocol are not violations of protocol.

Subjects' Records

1. Describe the investigator's source data files in terms of their organization, condition, accessibility, completeness, and legibility.
2. Determine whether there is adequate documentation to assure that all audited subjects did exist and were alive and available for the duration of their stated participation in the study.
3. Compare the source data in the clinical investigator's records with the case reports completed for the sponsor. Determine whether clinical laboratory testing (including blood work, EKGs, X-rays, eye examinations, etc.), as noted in the case report forms, was documented by the presence of completed laboratory records among the source data.
4. Determine whether all adverse experiences were reported in the case report forms. Determine whether they were regarded as caused by or associated with the test article and if they were previously anticipated (specificity, severity) in any written information regarding the test article.
5. Concomitant therapy and/or intercurrent illnesses might interfere with the evaluation of the effect of the test article. Check whether concomitant therapy or illness occurred. If so, was such information included in the case report forms?
6. Determine whether the number and type of subjects entered into the study were confined to the protocol limitations and whether each record contains:
 - a. Observations, information, and data on the condition of each subject at the time the subject entered into the clinical study;
 - b. Records of exposure of each subject to the test article;
 - c. Observations and data on the condition of each subject throughout participation in the investigation including time(s) of drug administration; dosing according to

preestablished, randomization schedules; results of laboratory tests; development of unrelated illness; bleeding times and any other specimen collections; wash-out periods for subjects; and other factors which might alter the effects of the test article; and

- d. The identity of all persons and locations obtaining source data or involved in the collection or analysis of such data.

Other Study Records

Review information in the clinical investigator's records that would be helpful in assessing any under-reporting of adverse experiences by the sponsor to the agency. The following information will ordinarily be obtained from the sponsor and sent with the assignment:

- a. The total number of subjects entered into the study;
- b. The total number of dropouts from the study (identified by subject number);
- c. The number of evaluable subjects and the number of nonevaluable subjects (the latter identified by subject number); and
- d. The adverse experiences identified by subject number and a description of the adverse experience.

Compare the information submitted to the sponsor according to the clinical investigator's files with the information obtained from the sponsor, and document any discrepancies found.

Consent of Human Subjects

1. Obtain a copy of the consent form actually used.
2. Determine whether proper informed consent was obtained from *all* subjects *prior* to their entry into the study. Identify the staff who obtain and witness the signing of informed consent for study subjects.

Institutional Review Board

1. Identify the name, address, and chairperson of the Institutional Review Board for this study.
2. Determine whether the investigator maintains copies of all reports submitted to the IRB and reports of all actions by the IRB. Determine the nature and frequency of periodic reports submitted to the IRB.
3. Determine whether the investigator submitted reports to the IRB of all deaths and serious adverse experiences and unanticipated problems involving risk to human subjects (21 CFR 312.66).
4. Determine if the investigator submitted to and obtained IRB approval of the following *before* subjects were allowed to participate in the investigation:
 - a. Protocol.
 - b. Modifications to the protocol.
 - c. Materials to obtain human subject consent.
 - d. Media advertisements for subject recruitment.
5. Determine if the investigator disseminated any promotional material or otherwise represented that the test article was safe and effective for the purpose for which it was under investigation. Were the promotional material(s) submitted to the IRB for review and approval before use?

Sponsor

1. Did the investigator provide a copy of the IRB approved consent form to the sponsor?
2. Determine whether the investigator maintains copies of all reports submitted to the sponsor.

3. Determine if and how the investigator submitted any report(s) of deaths and adverse experiences to the sponsor.
4. Determine whether all intercurrent illnesses and/or concomitant therapy(ies) were reported to the sponsor.
5. Determine whether all case report forms on subjects were submitted to the sponsor shortly (within 6 months) after completion.
6. Determine whether all dropouts, and the reasons therefore were reported to the sponsor.
7. Did the sponsor monitor the progress of the study to assure that investigator obligations were fulfilled? Briefly describe the method (on-site visit, telephone, contract research organization, etc.) and *frequency* of monitoring. Do the study records include a log of on-site monitoring visits and telephone contacts?

Test Article Accountability

1. Determine whether unqualified or unauthorized persons administered or dispensed the test article(s).
2. What names are listed on the FDA-1571 (for Sponsor-Investigator) and FDA-1572 (for studies conducted under an IND)? Obtain a copy of all FDA-1572s.
3. Determine accounting procedures for test articles:
 - A. Receipt date(s) and quantities.
 - B. Dates and quantities dispensed.
 - C. Quantities of bioequivalence testing samples retained (see section "Sample Collection" under part III).
4. Inspect storage area.
 - a. Reconcile amounts of test article used with amounts received, returned, and retained. Report any discrepancy.
 - b. If not previously sampled under CP 7346.832, collect samples of both the test and reference products for FDA analysis.
5. If test articles are controlled substances, determine if proper security is provided.

Records Retention

1. Determine who maintains custody of the required records and the means by which prompt access can be assured.
2. Determine whether the investigator notified the sponsor in writing regarding alternate custody of required records, if the investigator does not maintain them.
3. Be aware that records should be retained at the study site for the specified time as follows:
 - a. Two years following the date on which the test article is approved by FDA for marketing for the purposes, which were the subject of the clinical investigation; or
 - b. Two years following the date on which the entire clinical investigation (not just the investigator's part in it) is terminated or discontinued *by the sponsor*. If the investigator was terminated or discontinued, was FDA notified?

Abbreviated Report Format

For inspection of a clinical facility, abbreviated report is allowed if (1) there are no significant violations and no FDA Form 483 is issued, and (2) in cases where there are objectionable findings but the findings are not serious and clearly do not have any impact on data integrity and study outcomes. The following is a guideline for preparation of the abbreviated report:

1. Reason for inspection
 - a. Identify the headquarters unit that initiated and/or issued the assignment.
 - b. State the purpose of the inspection.

2. What was covered
 - a. Identify the clinical study, protocol number, sponsor, NDA, ANDA, etc.
 - b. Location of study.
3. Administrative procedures
 - a. Report the name, title, and authority of the person to whom credentials were shown and FDA-482 Notice of Inspection was issued.
 - b. Persons interviewed.
 - c. Who accompanied the inspector during establishment inspection.
 - d. Who provided relevant information.
 - e. Identify the IRB.
 - f. Prior inspectional history.
4. Individual responsibilities
 - a. Identify study personnel and summarize their responsibilities relative to the clinical study (e.g., who screened the subjects, who administered the drugs, who supervised collection, identification, and processing of samples, etc.).
 - b. A statement about (i) who obtained informed consent, (ii) how it was obtained, and (iii) was informed consent signed by each subject?
 - c. Identify by whom the clinical study was monitored, and when, etc.
5. Inspectional findings
 - a. A statement regarding the comparison of data on the case report forms to the source data at the investigator's site. Indicate the number of records compared and what was compared (patient charts, hospital records, lab slips, etc.), and specific information about any discrepancies.
 - b. A statement indicating if the drug accountability records were sufficient to reconcile the amount of drug received, dispensed, returned, and retained.
 - c. A statement about protocol adherence. Describe in detail any nonadherence.
 - d. A statement concerning doses in accordance with preestablished, randomization schedules.
 - e. The EIR should identify the IRB and state if it approved the study and was kept informed of the progress of the study.
 - f. A statement on (i) follow-up activities in response to reports of adverse experiences (including death) if any occurred; (ii) whether there was evidence of under reporting of adverse experiences/events.
 - g. Discussion of 483 observations, reference the exhibits/documentation collected.
6. Discussion with Management
 - a. Discussion of 483 observations and non-483 observations.
 - b. Clinical investigator's response to observations.

Remember that the above deals with abbreviated reports, not abbreviated inspections. All assignments issued for cause must have full reporting. The assignment EMS or memo will indicate the need for full reporting for any special inspection.

I. ANALYTICAL DATA AND OPERATIONS

Information required by this section must be obtained with the assistance of a qualified analyst from the field and/or a reviewer in GBIB with expertise in the type of analysis used in the bioequivalence study under review.

At random, compare the analytical source data with data provided in the inspection assignment for accuracy of transference and for scientific soundness/bearing on the validity of the study. Analytical source data are codes used to blind samples; data establishing the sensitivity, linearity, specificity, and precision of the analytical assay; data determining the stability of the drug in the biological specimen; all standard curves; blinded and unblinded spiked control samples; blanks; data on reagent preparation; instrumental readings; calculations; etc. The data comparison and the testing procedural review should include an evaluation of any discrepancies found.

A. Prestudy analysis

If the analytical laboratory is involved in analysis of drug standards and products employed in the bioequivalence studies, determine if:

1. Appropriate samples were analyzed by the laboratory to determine potency and content uniformity for tablets and capsules. Include a description of procedures used to prepare the sample(s) used in the study.
2. If testing of the samples described above was not performed by the analytical laboratory, did the sponsor provide test results to the laboratory?
3. For both the test and reference drug products studied, were the products' appearance, potency, dosage form (capsule, tablet, suspension, controlled release, etc.), lot numbers and expiration dates the same as that reported to FDA?

B. Protocol acceptance

If the Review Division reviewed the protocol and recommended protocol modifications, verify that the modifications were incorporated into the protocol.

C. Equipment

Check on the following with respect to both current equipment and practices and those in place at the time of the study:

1. Does the laboratory have the same type, brand, and model (not serial) numbers of all major pieces of analytical equipment and instrumentation used in their testing procedures, as reported in the ANDA or NDA? (e.g., gas chromatographs, high-performance liquid chromatographs, ultraviolet spectrophotometers, colorimeter, fluorescence or atomic absorption spectrophotometer, pH meter, etc.). If not, describe the discrepancy and include its effect on the validity of the study data.
2. Assess the general condition of the major pieces of equipment (e.g., gross mistreatment), which may render them inaccurate or unreliable. Examples: damaged gas chromatograph inlet port, dry pH meter electrodes, etc. Review maintenance and repair logs for indications of past problems.
3. Are there written operating instructions for these major pieces of equipment, and are they available to the laboratory personnel?
4. Are there written and scheduled calibration/standardization procedures, and preventative maintenance procedure for all analytical instruments employed in the study? Determine whether these calibration/standardization procedures are actually employed and documented? If not, describe the deficiencies and determine whether the instruments have been calibrated during the time of the study.
5. Were specific instrument operating parameters documented during the study? If so, where?

- D. Analytical methods validation—determine through data and procedural review if
1. The analytical laboratory has scientifically sound data to support claims for the specificity of the assay employed in this study. Ascertain the laboratory's justification for noninterferences, both endogenous and exogenous (e.g., metabolites, solvent contamination, etc.) in measuring the analytes (drug, metabolites, etc.) studied.
 2. The analytical laboratory has data to support the claims for the linearity of the assay employed in this study.
 3. The laboratory analyst who analyzed the biological samples has generated data demonstrating the sensitivity of the assay using the same instrumentation as that employed in the bioequivalence study. The sensitivity of the assay (or limit of detection) may be defined as the lowest quantifiable limit that can be *reproducibly determined* for the measured analyte(s) being carried through the method.
 4. The laboratory analyst who analyzed the biological specimen has generated data demonstrating the precision of the assay using the instrumentation employed in the bioequivalence study. The data should be available for both standard and quality control samples and should include the consistency of precision of the standard and control samples carried through the assay procedure. Ascertain the laboratory's justification for the precision based on the separation procedure, instrumentation, and analyte concentration levels in the biological fluids.
 5. The laboratory has data to demonstrate drug recoveries (percent recovery) for the measured analyte(s). This should include both analyte extraction efficiency from the biological fluid *and* recovery of the analyte(s) carried through the analytical testing procedure.
 6. The analytical laboratory determined the stability of the drug both in the biological specimen and in the sample preparation medium under the same condition as in actual analysis of subject samples.
 7. The analytical laboratory showed that the storage procedures (e.g., freezing and number of freeze/thaw cycles) have no adverse effect on drug stability for the period of time the samples were stored, from subject dosing until last sample analysis.
 8. The water quality specified for sample and reagent preparation is consistently and readily available in the laboratory.
- E. Sample analyses—determine if
1. The analytical assay employed was the same as that specified in the ANDA or NDA.
 2. The assay parameters observed for the study's sample analysis are similar to those (e.g. specificity, precision, etc.) obtained during method validation. Review study subjects' source analytical data to check this; pay particular attention to analytical runs determined toward the end of analytical testing.
 3. Coding techniques were used to blind the analytical laboratory to the sample. Was the code available to the analytical chemist?
 4. The samples were analyzed in a randomized fashion or in some specific order. Were samples of test and reference products for the same subject analyzed at the same time under identical conditions with the same standard curve, same control, and same instrument?
 5. Standard curves are prepared each time a batch of unknown samples is assayed. If not, how often are standards run? Have all the standard curves run during the study been reported? How many standards are used to define each standard curve? (Should be 5–8, excluding blank.) Does the laboratory have scientifically sound procedures for acceptance or rejection of a standard point and/or a standard curve?
 6. The standard curve encompasses the concentration values reported. Were any values reported which were derived from points extrapolated on the standard curve?
 7. The laboratory has a scientifically sound SOP in place to guide the acceptance/rejection of data. Did the laboratory adhere to the SOPs in the reporting of repeated determinations, or was supervisory discretion used to accept/reject data points?
 8. Blinded or nonblinded spiked control samples have been included and reported with each run. Who prepared these samples? Were the controls made from a standard weight different from the standard weight used to prepare standards for the standard curve (i.e., two separate independent weighings for calibration standards and QC stock solutions)? Do the controls span the expected analyte concentration range (low, midrange, and high) found in the subjects' samples? Have all control values been reported individually, as opposed to averages?
 9. The control samples were processed and analyzed exactly the same as the unknown samples. Were the controls interspersed throughout the entire analytical run?
 10. The source of blank biological fluids. (Was each subject's zero hour serum used as the blank, pooled plasma, etc.?) Were interferences noted in the analytical source data for these samples? Specifications should be established to assure that blank biological fluids are as similar as possible to the biological matrix for the subject samples.
 11. The source of the drug standards used for the in vivo sample analysis. If not compendial standards, how was the quality and purity of the standard assured?
 12. All sample values were recorded and reported. If not, were reasons for rejection documented and justified? Were any samples rerun? When repeated determinations were made, were new standard curves and control samples run concurrently?
 13. The procedure employed for determining which value of a rerun sample is reported. Was this procedure scientifically sound and consistently followed? Was an established written procedure followed?
 14. The submitted chromatograms are representative of the quality of the chromatograms generated throughout the study.
 15. There are written procedures for preparing reagents used in these assays. Are reagents properly labeled with date of preparation, storage requirements, as well as chemist who prepared them? Were the original weighings for calibration standard and QC stock solutions checked and countersigned by a second party?
 16. Copies of the following chromatograms are available: (If not submitted by the applicant, the Field investigator or chemist should obtain copies.)
 - a. Reagent blank
 - b. Sample blank
 - c. Internal standard
 - d. A standard run
 - e. A quality control run
 - f. A set of chromatograms for one subject over the entire span of the study

- F. For antibiotic analyses—determine:
1. Are incubators available? Specify dimensions and type.
 2. Whether
 - a. the bench tops are level;
 - b. the room temperature is controlled and, if so, what are the temperature tolerances;
 - c. agar, propagation cultures, and other necessary resources are available and properly monitored;
 - d. zone readers are available, if so, specify type; and
 - e. autoclaves are available and, if so, specify type and determine if the autoclave sterilization process has been validated.
 3. The room where these studies are conducted is “environmentally sterile” and what monitoring is done to determine the degree of “environmental sterility.”
 4. Whether the samples were run properly through the incubator, that is, times and temperatures are controlled to desired specifications and properly documented.
 5. Whether the standards, controls and samples are incubated at the same time, in the same incubator.
 6. Whether the microorganisms used in the media are the same as described in the AADA.
 7. Whether a burner is used to heat the wire for transfer purposes.
 8. Whether calibrated zone readers were used for zone size determinations.
 9. Whether turbidimetric methodology was employed. Also, determine the type of spectrophotometry used.
 10. Whether the turbidimetric standardization procedure was the same as that specified in the AADA. If not, describe differences.
 11. Whether all samples were read in duplicate. Were all samples read by the same person? Did zone diameters or turbidimetric readings correlate with drug concentration levels?
 12. Are standard operating procedures in place to calibrate the incubator, autoclave, etc., used in antibiotic analysis? Are the SOPs readily available to laboratory personnel?
- G. For radiometric analyses—in addition to the general guidance above, determine:
1. How the specific activity of the radiochemical standards employed was determined.
 2. Whether all counts specified in records submitted to the Agency were actually counted for the time interval specified.
 3. Whether an inventory of all radiolabeled compounds is maintained by the laboratory.
 4. If the background level has been determined? If yes, by what method?
 5. For RIA methodology, determine if a commercial kit was used in the analysis. If so, report the type of kit, the expiration date and whether the laboratory validated the accuracy, specificity, precision, sensitivity and linearity of the kit assay in relation to the reported study assay procedure.

- H. Data handling and storage—determine:
1. Whether bound notebooks and/or source data worksheets are used by the laboratory.
 2. If bound notebooks are used, are the pages filled in sequentially on a chronological basis? Does the analyst sign the notebook/worksheets daily? Does a supervisor initial the notebook/worksheets after checking it for accuracy?
 3. Whether the laboratory retains all source data, such as notebooks, worksheets, chromatograms, standard curves, etc. Is there justification for source data excluded from the study report, such as rejected runs, missing samples, etc.?
 4. Whether the analyst(s) sign and date all source data records.
 5. How long the source data is retained.
 6. Describe the maintenance and accessibility of laboratory source data (e.g., repeated determinations, rejected analytical runs, etc.). Document problems with data recording and verification, such as lack of dates and signatures, erasures, white-out, etc.

REFERENCES

1. FD & C Act Section 301 (e), 505 and 510
2. Code of Federal Regulations, Title 21: Part 11, “Electronic Records; Electronic Signatures,” Part 50, “Protection of Human Subjects,” Part 56, “Institutional Review Boards,” Part 200.10, “Contract Facilities (Including Consulting Laboratories) Utilized as Extramural Facilities by Pharmaceutical Manufacturers,” Part 207, “Registration of Producers of Drugs,” Part 312, “Investigational New Drug Application,” Part 314, “Applications for FDA Approval to Market a New Drug or An Antibiotic Drug,” Part 314.125, “Refusal to Approve an Application or Abbreviated Antibiotic Application,” Part 320, “Bioavailability and Bioequivalence Requirements,” Part 361.1, “Radioactive Drugs for Certain Research Uses.”
3. Compliance Program Guidance Manual (CPGM), CPGM 7348.811, “Clinical Investigators”
4. 21 CFR 11—Electronic Records. Electronic Signatures Regulation effective August 1997.
5. 21 CFR 58.1 – 58.219 Good Laboratory Practice Regulations effective June 1979, and amended effective October 1987
6. Good Laboratory Practice Regulations, Management Briefings, Post Conference Report, August 1979
7. Good Laboratory Practice Regulations, Questions and Answers, June 1981
8. “Guide to Inspection of Computerized Systems in Drug Processing,” February 1983
9. “Software Development Activities, Technical Report” July 1987
10. “Guide For Detecting Fraud in Bioresearch Monitoring Inspections,” April 1993
11. 21 CFR part 54, Financial Disclosure by Clinical Investigators
12. 21 CFR part 314, Applications for FDA Approval to Market a New Drug
13. 21 CFR part 320, Bioavailability and Bioequivalence Requirements
14. The Federal Food, Drug, and Cosmetic Act, Section 505(k)(2)
15. FDA Compliance Program Guidance Manual (CPGM), Compliance Program 7348.001 – Bioresearch Monitoring – In Vivo Bioequivalence

EU Guidelines to Good Manufacturing Practice

Basic Requirements for Active Substances Used as Starting Materials

1.1. Objective

These guidelines are intended to provide guidance regarding good manufacturing practice (GMP) for the manufacture of active substances under an appropriate system for managing quality. It is also intended to help ensure that active substances meet the requirements for quality and purity that they purport or are represented to possess.

In these guidelines "manufacturing" includes all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of active substances and the related controls. The term "should" indicates recommendations that are expected to apply unless shown to be inapplicable, modified in any relevant annexes to the GMP guide, or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

The GMP guide as a whole does not cover safety aspects for the personnel engaged in manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by other parts of the legislation.

These guidelines are not intended to define registration requirements or modify pharmacopoeial requirements and do not affect the ability of the responsible competent authority to establish specific registration requirements regarding active substances within the context of marketing/manufacturing authorizations. All commitments in registration documents must be met.

1.2. Scope

These guidelines apply to the manufacture of active substances for medicinal products for both human and veterinary use. They apply to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile. The sterilization and aseptic processing of sterile active substances are not covered, but should be performed in accordance with the principles and guidelines of GMP as laid down in Directive 2003/94/EC and interpreted in the GMP guide including its Annex 1.

In the case of ectoparasiticides for veterinary use, other standards than these guidelines, that ensure that the material is of appropriate quality, may be used.

These guidelines exclude whole blood and plasma, as Directive 2002/98/EC and the technical requirements supporting that directive lay down the detailed requirements for the collection and testing of blood; however, it does include active substances that are produced using blood or plasma as raw materials. Finally, these guidelines do not apply to bulk-packaged medicinal products. They apply to all other active starting materials subject to any derogations described in the annexes to the GMP guide, in particular Annexes 2 to 7 where supplementary guidance for certain types of active substance may be found. The annexes will consequently

undergo a review but in the meantime and only until this review is complete, manufacturers may choose to continue to use Part I of the basic requirements and the relevant annexes for products covered by those annexes, or may already apply Part II.

Section 19 contains guidance that only applies to the manufacture of active substances used in the production of investigational medicinal products, although it should be noted that its application in this case, though recommended, is not required by community legislation.

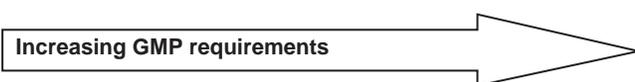
An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance. An "Active Substance Starting Material" can be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

The manufacturer should designate and document the rationale for the point at which production of the active substance begins. For synthetic processes, this is known as the point at which "Active Substance Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc.), this rationale should be established on a case-by-case basis. Table 7.1 gives guidance on the point at which the "Active Substance Starting Material" is normally introduced into the process. From this point on, appropriate GMP as defined in these guidelines should be applied to these intermediate and/or active substance manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the active substance. However, it should be noted that the fact that a manufacturer 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 7.1. It does not imply that all steps shown should be completed. The stringency of GMP in active substance manufacturing should increase as the process proceeds from early steps to final steps, purification, and packaging. Physical processing of active substances, such as granulation, coating, or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of these guidelines. These guidelines do not apply to steps prior to the first introduction of the defined "Active Substance Starting Material."

In the remainder of this guideline, the term active pharmaceutical ingredient (API) is used repeatedly and should be considered interchangeable with the term "Active Substance." The glossary in section 20 of Part II should only be applied in the context of Part II. Some of the same terms are already defined in Part I of the GMP guide and these therefore should only be applied in the context of Part I.

Table 7.1 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 plant	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



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 quality assurance (QA) and quality control (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

- releasing or rejecting all APIs;
- releasing or rejecting intermediates for use outside the control of the manufacturing company;
- establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials;
- reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
- making sure that critical deviations are investigated and resolved;
- approving all specifications and master production instructions;

approving all procedures impacting the quality of intermediates or APIs;
 making sure that internal audits (self-inspections) are performed;
 approving intermediate and API contract manufacturers;
 approving changes that potentially impact intermediate or API quality;
 reviewing and approving validation protocols and reports;
 making sure that quality-related complaints are investigated and resolved;
 making sure that effective systems are used for maintaining and calibrating critical equipment;
 making sure that materials are appropriately tested and the results are reported;
 making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
 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

preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures;
 producing APIs and, when appropriate, intermediates according to preapproved instructions;
 reviewing all production batch records and ensuring that these are completed and signed;
 making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
 making sure that production facilities are clean and when appropriate disinfected;
 making sure that the necessary calibrations are performed and records kept;
 making sure that the premises and equipment are maintained and records kept;
 making sure that validation protocols and reports are reviewed and approved;
 evaluating proposed changes in product, process, or equipment; and
 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.

3.2. 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; and
- 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, and 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 following list:

- 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.
- 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 following points

- 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 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
- 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 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 is 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 Out-of-specification (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 out-dated 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 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/biologic 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 (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and (2) 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 (PV) 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 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; and
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. A 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 and 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 by-products 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

- name and address of the consignee;
- intermediate or API, batch number, and quantity returned;
- reason for return; and
- 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 Relabellers

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 relabellers 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 relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include

- 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, and
- retest or expiry date.

17.2. Quality Management

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

17.3. 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.

17.4. 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.

17.5. Transfer of Information

17.60 Agents, brokers, distributors, repackers, or relabellers 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 relabeller 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 relabellers 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 relabellers 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 relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).

17.6. Handling of Returns

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

Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

18. 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 the following 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.

18.1. 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.

18.2. 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, e.g.) 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 assess-

ments 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.

18.3. 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.

18.4. 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 postviral 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.

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

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

Authorized person—The person recognized by the national regulatory authority as having the responsibility for

ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of 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, etc.

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 onto a starting material or intermediate 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.

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

Drug Substance—See Active Pharmaceutical Ingredient

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

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

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

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

In-Process Control—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 which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.
- Packaging**—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized would not normally be regarded as part of packaging.
- Packaging Material**—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.
- Pharmaceutical Product**—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.
- Procedure**—A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.
- Process Aids**—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc.).
- 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 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. This standard can be used to prepare secondary reference standard.
- 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 is 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).
- 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.

Preapproval Inspections

I. INTRODUCTION

A preapproval inspection is a visit by regulatory authority inspectors (generally from the District office of FDA) to review the compliance, in terms of adequacy and accuracy of the information included in a regulatory submission (Compliance Program Guidance Manual, Program 7346.832). The preapproval inspection program has evolved over the years in response to the fraudulent submissions to the U.S. Food and Drug Administration (FDA) by the generic drug industry.

A. Background

The Food, Drug, and Cosmetic Act provides that the FDA may approve a new drug application (NDA) or an abbreviated new drug application (ANDA) only if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality, and purity. The applicant is required to submit information in the NDA/ANDA to the Center for Drug Evaluation and Research (CDER), which contains among other things a method of analysis and details as to how the firm proposes to manufacture—and control the manufacture—of the product that is the subject of the application. This information is reviewed by CDER scientists (chemists, microbiologists, etc.) to determine whether the specifications in the application meet the FDA's standards. The CDER's role in the preapproval process is to review data submitted to the agency as part of premarket NDAs and generic drug applications and to establish specifications for the manufacture and control of the resulting drug product on the basis of the submitted data.

The investigator's role is to ensure current good manufacturing practice (cGMP) compliance, verify the authenticity and accuracy of the data contained in these applications, and report any other data that may affect the firm's ability to manufacture the product in compliance with GMPs. This program is designed to provide close inspectional and analytical attention to the authenticity and accuracy of data in applications and to provide information regarding facilities. Such coverage is necessary to ensure that applications are not approved if the applicant has not demonstrated an ability to operate with integrity and in compliance with all applicable requirements.

B. Objective

The objective of the compliance program is to ensure that establishments involved in the manufacturing, testing, or other manipulation of new drug dosage forms and new drug substances are audited

1. through on-site inspections for compliance with cGMPs;
2. for conformance with application commitments;
3. to ensure data is authentic and accurate; and
4. through laboratory testing of products, including evaluations of the adequacy of analytical methodology.

Both foreign and domestic establishments are covered by this program. Such coverage is intended to be consistent to the extent possible. This program provides guidance for establishment inspections and related investigations and for laboratory evaluations of methods of analysis proposed by applicants in NDA and ANDA submissions.

Before any application is approved by the CDER, a determination will be made of whether all establishments that will participate in the manufacture, packaging, or testing of the finished dosage form or new drug substance are in compliance with cGMP and application commitments. This determination may be made by conducting preapproval inspections. Method validations, method verifications, and forensic analyses will be performed to confirm the authenticity of the preapproval product and to ensure that it can be accurately assayed with the proposed regulatory methods. Postapproval inspections will monitor and enforce what is submitted in an application. "Application" means NDA, ANDA, antibiotic drug application, or abbreviated antibiotic drug application (AADA) and their supplements. CDER will request inspections in accordance with preestablished criteria. Optional preapproval inspections may be requested where circumstances warrant. The scope of preapproval inspections, compared with the responsibilities assigned to CDER scientists, is set forth below:

- **Biobatch manufacturing:** Inspection to determine the establishment's compliance with cGMP requirements, including a data audit of the specific batches on which the application is based (e.g., pivotal clinical, bioavailability, bioequivalence, and stability) is a field office responsibility. CDER scientists are responsible for the review and evaluation of the records and data submitted in the application, including the components, composition, batch instructions, in-process and finished product test points, and specifications established for the resulting drug product.
- **Manufacture of drug substance or substances:** Inspection to determine cGMP compliance of the establishment is a Field responsibility. CDER chemists are responsible for the scientific review and evaluation of the records and data associated with the manufacture of the active drug substance submitted in the application or of a properly referenced Type II Drug Master File (DMF). The review will include starting materials, key intermediates, reagents, and solvents. CDER reviewers are also responsible for the review of process validation required for the manufacturing of biotechnological and certain natural substances.
- **Excipients manufacture:** The manufacture of novel excipients may be provided in an application or supporting DMF. Typically, these excipients are noncompendial and are used in specialized dosage forms and drug delivery systems. CDER chemists are responsible for the scientific reviews and evaluation of the records and data associated with the manufacture of these novel excipients. The review will include starting materials, key intermediates, reagents, and

solvents. cGMP inspections by the Field usually will be performed on request from CDER.

- Raw materials (cGMP controls): Inspection of the establishment for the drug substance and review of data on raw materials to determine compliance with cGMP requirements is a Field responsibility.
- Raw materials (tests, methods, and specifications): Audit of the data submitted for CDER review in the application is a Field responsibility. CDER chemists are responsible for the scientific review of the associated data, evaluations of the adequacy of the submitted data, and ultimate approval of the tests, methods, and specifications established for the raw materials in the application.
- Composition and formulation of finished dosage form: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER reviewers are responsible for the scientific review of the composition and formulation to determine, qualitatively and quantitatively, the acceptability of the information submitted in the application.
- Container/closure system or systems: CDER is responsible for the scientific review of the container/closure system or systems to be used to package the drug product as indicated in the application. The Field may audit this data.
- Labeling and packaging controls: Inspection to determine the establishment's compliance with cGMP requirements and audit of the data submitted for CDER review in the application are Field responsibilities.
- Labeling and packaging materials: CDER reviewers are responsible for the scientific review of the labeling and packaging components associated with the drug product.
- Laboratory support of methods validation: On CDER request, Field laboratory analysts will conduct laboratory validation of the analytical methods proposed by the applicant. CDER laboratories may participate in certain instances abbreviated antibiotic drug application [(AADA) validations, etc.]. CDER chemists are responsible for the review and acceptance/rejection of the analytical methods based on the laboratory results and the established specifications. Contacts between field laboratory analysts and the applicant will include the CDER chemist.
- Product (cGMP) controls: Inspection of the establishment to determine compliance with cGMP requirements, and review and audit of the data furnished to CDER in the application, are Field responsibilities. CDER scientists will request information on sterile processes, for example, laboratory controls for environmental monitoring, sterile fill operations, and evaluation and reduction of microbial contamination, to be submitted to the application for CDER review.
- Product tests, methods, and specifications: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER is responsible for the scientific review of the associated data and for the ultimate approval of the tests, methods, and specifications established for the drug product in the application. The Field will advise the center when it finds a questionable specification.
- Product stability: Inspection of the establishment to determine compliance with cGMP requirements and to conduct an audit of the data furnished to CDER in the application is a Field responsibility. This requirement applies to both the relevant preapproval batches, as discussed above, and the proposed commercial batches. CDER application review chemists are responsible for review of the proposed drug product stability protocol, specifications, and evaluation of the data submitted in support of the expiration dating period proposed for the drug product in the application.
- Comparison of the relevant preapproval batch or batches and proposed commercial production batches: CDER chemists are responsible for the comparison of the formulation, manufacturing instructions, and associated in-process and finished product tests and specifications established for the relevant preapproval batch or batches with the proposed commercial production batch to determine the acceptability of the firm's proposed scale-up procedure. The Field will compare the process used to make the preapproval batches with the actual process used to manufacture the validation batches. Significant differences in these processes will be evaluated by CDER's Office of Compliance, to determine whether the differences constitute fraud, and by the reviewing officers, to determine whether differences in the processes will affect the safety and effectiveness of the resulting product.
- Facilities, personnel, and equipment qualification: Review of the information and inspection of the establishment to determine compliance with cGMP requirements is a Field responsibility.
- Equipment specification or specifications: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER scientists are responsible for the review of equipment specifications furnished to the center in the application.
- Packaging and labeling (cGMP controls): Review of the controls information and inspection of the establishment to determine compliance with cGMP requirements is a Field responsibility.
- Process validation: Inspection of the establishment to determine compliance with cGMP requirements and adherence to application requirements is a Field responsibility. CDER may request data to support validation of sterile processing operations; for example, environmental monitoring, equipment validation, sterile fill validation, and associated sterile operations.
- Reprocessing: Inspection of the establishment to determine compliance with cGMP requirements and to conduct an audit of the data submitted to the center in the application is a Field responsibility. CDER application review chemists are responsible for review of reprocessing protocols proposed in the application. All reprocessing procedures must be validated, or scientific data must be available to justify the reprocessing procedure. The Field will audit the validation of these procedures.
- Ancillary facilities: Ancillary facilities (contract testing laboratories and contract packagers and labelers) will be inspected to determine compliance with cGMP requirements at the discretion of CDER. The name, address, and function of each ancillary facility will be indicated in the drug application, and CDER will review biological and immunological test methods and results submitted. These facilities shall also provide a certification in the drug application regarding compliance with the conditions of approval of the application.

C. Triggering of Inspections

There are two types of events that trigger inspection: categories that will regularly prompt an inspection request, and categories in which the district office may elect to perform an inspection at their discretion for elements of applications—filed or otherwise.

The following categories will regularly prompt a preapproval or cGMP:

1. New molecular entities (includes finished drug product and the active pharmaceutical ingredient)
2. Priority NDAs
3. First application filed by an applicant
4. For-cause inspection
5. For original applications, if the current cGMP status is unacceptable or greater than 2 years
6. For certain preapproval supplements, such as site change or major construction, if the cGMP status is unacceptable
7. Treatment IND inspections (information is available to CDER indicating that an inspection of a clinical supplies manufacturer is warranted to protect the health of patients)

D. Inspections/Audits

1. Manufacturing Process

i. Drug Product (Dosage Form)

In many cases, clinical production or trial runs of a new drug are produced in facilities other than the ones used for full-scale production. The facilities and controls used for the manufacture of the batch or batches are audited. For a generic drug product, the biobatch or biobatches are required to be manufactured in production facilities, using production equipment, by production personnel, and the facility is to be in conformance with cGMPs. Accurate documentation is essential so that the production process can be defined and related to the batch or batches used for the early clinical, bioavailability, or bioequivalence studies of new drug or generic drug products. Generic product biobatches are ANDA batches that are compared to the originator/reference product to establish their equivalence. NDA biobatches are NDA batches comparing the product planned for marketing with that studied during clinical trials to establish their equivalence. The batch records submitted in the application must be audited as part of the inspection to ensure that the proposed production process is the process that was used for the manufacture of the bio/stability batches. Some manufacturers have historically made small batches that were used for biostudies and stability studies and misrepresented them as larger batches in submissions. Documentation sometimes has included research and development notebooks or batch records. Inventory records or receiving records of drug substances have been found to be of value in documenting the accountability of drug substances used in the early batches.

ii. Drug Substance (Bulk Drug Chemical)

The *Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing* (http://www.fda.gov/ora/inspect_ref/igs/bulk.html) and Compliance Program 7356.002F (http://www.fda.gov/cder/dmpq/compliance_guide.htm) covering bulk pharmaceutical chemicals (BPCs) provide details of inspections covering bulk drug chemical manufacturing processes.

2. Reprocessing

The GMP regulations require reprocessing procedures to be written, and it is customary but not required that NDAs/ANDAs contain procedures covering foreseeable deviations from physical specifications (e.g., color, capped tablets, deviations from hardness specifications, etc.). If the NDA/ANDA contains a reprocess provision, the applicant must produce scientific data to establish that the procedure will result in a product that is equivalent to the original product.

3. Laboratory

Laboratory equipment and procedures must be qualified and validated. Every NDA/ANDA inspection will include both an evaluation of laboratory controls and procedures and an audit of some of the raw data used to generate results. These data may be located in research and development test logs. The authenticity and accuracy of data used in the development of a test method should be established. (See the *Guide to Inspection of Pharmaceutical Quality Control Laboratories*, July 1993.)

4. Components

The supplier and source of the active drug substance used in the manufacturing of the biobatch or clinical batch should be identified. When the manufacturer changes suppliers of drug substance from that supplier used for the manufacture of the biobatch or clinical batches, then the application should include data demonstrating that the dosage forms produced from the drug substances from the two different suppliers are equivalent in terms of conformance with established specifications, including those stated in the application. The data used to determine the adequacy of the physical specifications established for the subsequent suppliers or suppliers of the drug substance should be established.

5. Building and Facilities

The addition of any new drug to a production environment must be carefully evaluated as to its effect on other products already under production and as to changes that will be necessary to make to the building and facility. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their effect on the overall compliance with GMP requirements. For example, new products, such as cephalosporins, would require that the firm demonstrate through appropriate separation and controls that cross-contamination cannot occur with regard to other products being made in the same facility. In addition, facilities that may already be operating at full capacity may not have adequate space for additional products.

6. Equipment

New products, particularly potent drug products, can present cleaning problems in existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

7. Packaging and Labeling Controls

Packaging and labeling control procedures must be adequately written. Poor label control and accountability for other products may have an adverse effect on the firm's ability to ensure that the new drug will always be properly labeled. The label and packaging controls should take into account considerations of past label mix-ups and recalls.

II. REGULATORY/ADMINISTRATIVE STRATEGY

A. General

The plant should be in substantial compliance with GMP regulations and should have the necessary facilities and equipment in place to manufacture the specific product in the pending application. Some significant problems include, but are not limited to

- Application misrepresents data or conditions relating to preapproval batches; there are other inconsistencies or

discrepancies raising significant questions about the validity of records

- Preapproval batches are not made in accordance with GMPs
- There is a failure to report adverse findings or test data without adequate justification: If applications are withheld because of significant cGMP noncompliance, and the GMP deficiencies also apply to commercially marketed products, then action must be taken to ensure that the deficiencies are corrected

B. Process Validation

Approvals are not generally withheld on the basis of a lack of complete, full-scale, multiple-batch process validation. Although the agency does not require the manufacturer to fully validate the manufacturing process and control procedures of the commercial batch production before approval, the CDER will require that certain data be filed to demonstrate that a plant's sterilization and aseptic fill process has been qualified. These filing issues are under the control of the CDER's reviewing divisions. Because complete process validation is not required before approval, it is not required to audit complete process validation for sterile and nonsterile processes until the application has been approved. However, if the plant has already validated the process before the preapproval inspection, the validation is evaluated during the preapproval inspection. The inspection team lists deficiencies in the validation process on the FDA-483 and advises the plant official that complete validation must be completed before shipment. Applicants and sponsors must be able to justify filed specifications with scientific data. In other words, the sponsor should have conducted sufficient research on the test batches to establish specifications for the manufacturing and control procedures listed in the application. These data form the basis for the review and evaluation of the application, and these specifications form the basis of the validation protocol that may be developed following the approval of the application. The final step in the product development process is validation that the process will perform consistently. Companies are expected to validate the process using the specifications listed in the filing. Process validation requirements for the manufacture of BPCs differ somewhat from those involving dosage forms. The *Guide to Inspection of BPCs* issued in 1991 states that BPC manufacturers are expected to adequately determine and document that significant manufacturing processes perform consistently. The type of BPC, the range of specifications, and other factors determine the extent of the process development and documentation required. The documentation system required for early process steps must provide a chain of documentation, and although it need not be as comprehensive as in the later parts of the process, the manufacturer is required to identify and control the key steps in the process. Though many BPC manufacturers have recently initiated validation programs, not all BPCs can be validated simultaneously. Therefore, the inspections do not recommend taking any legal action where a firm has an adequate program in place, including reasonable milestones. Regulatory actions are recommended where there is a lack of validation and where there is evidence of a significant number of failed batches.

C. Key Elements

The key elements of an inspection are to ensure that the facility is capable of fulfilling the application commitments to manufacture, process, control, package, and label a drug product following GMP; the adequacy and accuracy of ana-

lytical methods submitted, to ensure that these methods are proper for the testing proposed; correlation between the manufacturing process for clinical trial material, bioavailability study material, and stability studies and submitted process; that the scientific data support full-scale production procedures and controls; that only factual data have been submitted; and that the protocols are in place to validate the manufacturing process.

The CDER, which governs the preapproval inspections, can additionally require preapproval inspections in the case of drugs with narrow therapeutic range, where new chemical entities are involved, where drugs are difficult to manufacture, in the case of drugs that represent a new dosage form for the application, where it is the first approval for the company, in the case of a poor GMP track record, and where generic versions of one of the 200 most prescribed drugs is involved (see Table 8.1).

D. Strategies for Preinspection

Preinspection preparation involves developing both short-term and long-term strategies. The short-term strategy may comprise

- Determining the state of cGMP compliance of all of the manufacturing and development facilities listed in the NDA for the product under review: This should be carried out by the quality assurance division of the firm.
- Compiling all relevant regulatory documents for use by the FDA inspectors at the potential inspection sites: This should be done by the regulatory affairs group of the firm; the efforts also include a summary of the commitments made to the FDA.
- Identification of key batch records: These documents are then compared with the commitments that are contained in the Regulatory Commitment Document (see above). Any discrepancies identified are resolved, and explanations are documented when appropriate. This is done by the product development group in collaboration with the quality control and regulatory affairs departments.
- The history of analytical methods used to control the product is prepared: The analytical development department prepares a chronological history of the various analytical methods used during the product development. This includes justifications for any changes made in the methods during the development process and a comparison of the methods used to release clinical batch vis-à-vis the commercial batches.
- Transfer of analytical methods to the site or sites where they are used: This is the responsibility of the analytical development division. Raw data supporting a successful transfer should be readily available to the inspectors.
- Scale-up ensuring that installation qualification, operational qualification, performance qualification (IQ/OQ/PQ) activities are properly conducted: These include cleaning validation, process validation, sterilization validation, and so forth, according to established corporate procedures.
- The development report has two main sections, one that addresses the dosage form and one that deals with the bulk drug substance: The product development scientist compiles the experimental evidence to demonstrate bioequivalency for the first clinical trial lot through those lots that will be used for launch. The report further includes a description of the current process along with a description of the chemical/physical characteristics, purity, related substances, specifications, and stability of the drug substance.

Table 8.1 Active Pharmaceutical Ingredients from the Top 200 Prescription Drugs in 2002

Acetaminophen+codeine	Fluconazole	Omeprazole
Acyclovir	Fluoxetine	Oxybutynin
Albuterol	Fluticasone	Oxycodone
Alendronate	Folic acid	Oxycodone+APAP
Allopurinol	Fosinopril	Pantoprazole
Alprazolam	Furosemide	Paroxetine
Amitriptyline	Gabapentin	Penicillin VK
Amlodipine	Gemfibrozil	Phenytoin
Amlodipine/benazepril	Glimepiride	Pioglitazone
Amoxicillin	Glipizide	Potassium chloride
Amoxicillin+clavulanate	Glyburide	Pravastatin
Amphetamine mixed salts	Glyburide+metformin	Prednisone
Aspirin	Human insulin 70/30	Promethazine
Atenolol	Human insulin NPH	Promethazine+codeine
Atorvastatin	Hydrochlorothiazide	Propoxyphene N+APAP
Azithromycin	Hydrocodone+APAP	Propranolol
Benazepril	Hydroxyzine	Quetiapine
Bisoprolol+hydrochlorothiazide	Ibuprofen	Quinapril
Budesonide	Insulin lispro	Rabeprazole
Bupropion hydrochloride	Ipratropium+albuterol	Raloxifene
Buspirone	Irbesartan	Ramipril
Captopril	Isosorbide mononitrate S.A.	Ranitidine
Carbidopa+levodopa	Lansoprazole	Risedronate
Carisoprodol	Latanoprost	Risperidone
Carvedilol	Levofloxacin	Rofecoxib
Cefprozil	Levonorgestrel+ethinyl estradiol	Rosiglitazone maleate
Celecoxib	Levothyroxine	Salmeterol
Cephalexin	Lisinopril	Salmeterol+fluticasone
Cetirizine	Lisinopril+HCTZ	Sertraline
Ciprofloxacin	Loratadine	Sildenafil Citrate
Citalopram	Loratidine+pseudoephedrine	Simvastatin
Clarithromycin	Lorazepam	Spironolactone
Clindamycin	Losartan	Sumatriptan
Clonazepam	Losartan+hydrochlorothiazide	Tamoxifen
Clonidine	Meclizine	Tamsulosin
Clopidogrel	Medroxyprogesterone	Temazepam
Conjugated estrogens+medroxyprogesterone	Metaxalone	Terazosin
Conjugated estrogens	Metformin	Tetracycline
Cyclobenzaprine	Methylphenidate extended release	Timolol maleate
Desloratadine	Methylprednisolone	Tolterodine
Desogestrel+ethinyl estradiol	Metoclopramide	Topiramate
Diazepam	Metoprolol	Tramadol
Diclofenac	Metronidazole	Tramadol+acetaminophen
Digoxin	Minocycline	Trazodone
Diltiazem	Mirtazapine	Triamcinolone
Divalproex	Mometasone	Triamterene+HCTZ
Doxazosin	Montelukast	Trimethoprim+sulfamethoxazole
Doxycycline	Mupirocin	Valacyclovir
Enalapril	Naproxen	Valdecoxib
Esomeprazole	Nifedipine	Valsartan
Estradiol	Nitrofurantoin	Valsartan+HCTZ
Ethinyl estradiol+norethindrone	Norethindrone+ethinyl estradiol	Venlafaxine
Famotidine	Norgestimate+ethinyl estradiol	Verapamil
Fenofibrate	Nortriptyline	Warfarin
Fexofenadine	Nystatin	Zolpidem
Fexofenadine+pseudoephedrine	Olanzapine	

The long-term strategy of preparing for a pre-NDA approval inspection generally comprises

- Incorporating drug development process in the preparation to allow the FDA to review the documents from the earliest stages of development.
- Establishing measures of cGMP for the production and distribution of clinical trial material; this may be different from the commercial production systems and addresses the iss-

ues of stability guidelines developed by the analytical laboratory in consultation with the quality assurance, the policy on the management of deviations (fully justified), batch disposition of clinical trial lots, change documentation—which is another critically important part of a quality system for product development, process validation, training, management notification—which sets the standard for notification of corporate research management in the event that a quality issue occurs with clinical trial materials.

E. International Inspection

The FDA inspections are conducted in the same manner for both domestic and international firms, but in practice there are legal and logistic reasons for the FDA to follow different procedures when scheduling and conducting international inspections for the purpose of verifying integrity of information submitted and ascertaining compliance with the cGMP regulations. There are four differences between domestic and international inspections: international inspections are nearly always scheduled in advance, language barriers pose unique challenges during international inspections, international inspections are typically of shorter duration than domestic inspections that are conducted for the same purpose, and international firms are reinspected less often than are domestic facilities.

When inspecting domestic firms, the FDA has the responsibility over all products manufactured, and thus inspections are often extended to include other products as well. At foreign facilities, the FDA generally has interest only in products that will be marketed in the United States, and it is likely that the firm inspected may only be marketing a handful of products in the United States, though it may have a large presence. In addition, most international inspections are completed within a fixed duration, as the inspection may be heading for similar audits in the region elsewhere and it is not often possible to make last-minute changes to itinerary. In domestic audits, the inspectors routinely interrupt the audit and return later to complete it; such is not the case with the foreign inspections.

Unless a firm has previous experience with such audits, it is highly recommended that the firm assign responsibilities for PAI readiness, determine the PAI schedule, anticipate FDA needs, verify application integrity, and verify GMP compliance on their own before the visit.

Whereas the regulatory submissions must be in English, the FDA expects that raw data and original records may be in the native language, and this is acceptable: there is no need to translate documents that are created in the native language. In fact, it is ill-advised to convert documents, as this may result in errors that can unnecessarily create confusion in the inspection. However, the summary documents as requested by the FDA may be translated before the arrival of inspectors. Where attachments were included in the regulatory submissions, these should be available with proper certification for their authenticity.

Foreign inspections almost always follow a preset routine, despite individual style, which depends on the qualification of the inspector (whether he or she is a microbiologist or a chemist, for example).

Summary documents are critical to a successful start of the audit; the FDA would rely heavily on the development reports, particularly as they pertain to early development phases of development, scale-up, and the development of analytical methods. Information contained in the development report is also useful for the firm's management to present overviews to the FDA about key development activities at the start of an inspection. Well-written, comprehensive reports may be sufficient for the purpose of the inspection without the FDA getting into inquiry about the raw data. Because the FDA is short of time in foreign inspections, they are more likely to accept the report in lieu of a larger number of support documents; as a result, the importance of a well-written, comprehensive development report is the most important tool for foreign firms. A lack of reports or incomplete reports will almost always cause the FDA inspectors to inquire about the raw data—something that should be

avoided, if at all possible. Raw data always spells trouble in every inspection. An unnoticed peak in the active pharmaceutical ingredient (API) thin layer chromatography (TLC), a missing signature, numbers changed without crossing it out, and so forth, are some of the common occurrences that raise flags as the audit gets deeper.

Next to the preparation of the development report, the most important thing for the foreign firm to do is to "break ice" with the FDA inspectors. Almost always there are cultural and etiquette differences that must be overcome immediately. Although there is no need for an elaborate protocol, the firm is expected to inform the FDA inspectors about the matters indigenous to the region, such as traffic problems, hotel accommodation, food availability, and most important, any local customs that may adduce a behavior with which the inspectors may not be familiar. It is also a good idea to start the meeting with the inspectors by expressing a desire to be apprised of any findings as they occur, as it is easier to rebut or explain the situation at that moment. These situations often arise as a result of different systems of document keeping, document routing, and personnel management.

Where deficiencies are found, the firm should attempt to rectify them during the visit while keeping the FDA inspectors informed of the changes made to overcome the objections. Know that the FDA personnel are expected to report corrective actions in the Environmental Impact Report (EIR). When it is not possible to complete the corrective actions before the FDA leaves the premises, it is in the firm's best interest to report steps that have already been taken toward initiating a corrective action plan. In addition, the FDA is concerned about the steps taken to prevent recurrence of such problems and the evaluations made to determine whether the objectionable conditions may apply to other areas of the facility, as well as the steps taken by the company to determine the cause of specific objections found by the FDA. Also, falsification of documentation that a corrective action has been taken when it may not have been can land the firms in deep trouble in the follow-up inspections. The FDA becomes suspicious when the firm provides evasive or inconsistent answers, shows unexpected body language or behavior in responding, or an inconsistent response is received from different employees. It is important, therefore, that the firm go through a mock-up exercise involving all those employees who may eventually end up talking to the FDA inspectors.

At the end of inspection, the FDA conducts an exit discussion with management to deliberate on the inspection findings. Should there be any GMP-related deviations or other objectionable conditions, they will leave with the company a written list of observations (FDA-483) and will provide management with the opportunity to discuss the FDA findings. The purpose of the FDA-483 is to list objectionable conditions and practices found by the FDA investigator; it is not intended to report any favorable or acceptable conditions that may have been observed during the inspection. Each of the FDA-483s issued is subjected to further review by FDA management in the field offices or at headquarters units to determine the validity and significance of each item. It is imperative that personnel completely understand the reason or reasons that the FDA considers a condition or practice to be objectionable before the inspection team departs. As mentioned earlier, it is in the best interest of the FDA as well that issues are closed before their departure, as the inspectors may not be able to return soon, and it will create a substantial burden on the firm if the approval is withheld; this is a significant benefit in international inspections of which the firms should take full advantage.

Management should verbally respond to the inspection findings during the discussion of the FDA-483. Each item should be discussed individually, and the company personnel should provide additional explanations where appropriate and should state their intentions for items where they have made or intend to make improvements. When companies have initiated corrective actions, it is imperative that the FDA be informed of the actions taken (especially corrections that have already been completed). The company should request that the FDA team report in their EIR the corrections that have been accomplished. If the FDA has had the opportunity to verify the corrections, it would be appropriate to ask them to comment on the adequacy of the actions taken by the company (i.e., Were they satisfied with the corrective actions, or should the firm consider further actions?).

To demonstrate to the FDA that corrective actions have been taken, firms should provide to the FDA team the copies of documents that show corrections such as revised standard operating procedures (SOPs), change control records for facility improvements, training documentation, and results of analytical testing. In those situations in which the firm may need some time to decide appropriate corrective actions, it is advisable to inform the FDA team that a written response will be provided within a reasonable period (ideally within 2 weeks). It is extremely important to stick to this timeline, as it takes about 2 weeks for the inspector to file his or her EIR: It is most beneficial, strategically, to have the response of the firm be recorded in the EIR. The firm, however, should not make promises that it knows cannot be fulfilled, such as requiring substantial financial outlay that the firm may not be able to afford, or giving a timeline that is too restrictive or unrealistic. The firms should not risk creating a credibility problem in the follow-up visits. The FDA encourages an open discussion of each item listed on the FDA-483, and the FDA team should be able to defend its observations. If management believes that an item listed on the FDA-483 is incorrect or does not accurately reflect the true conditions found by the FDA investigator, this should be discussed in sufficient detail until the issue can be resolved to mutual satisfaction. If the observation is an error caused by misunderstandings, it is essential that there be full discussions to ensure that the FDA has accurate and complete information. This is why it was earlier recommended that the firm develop an open communication with the FDA, finding out the deviations as they are discovered rather than in the end-of-visit reporting. If the FDA has all of the relevant information and facts, but the FDA team has reached the conclusion that the firm's practices or conditions are unacceptable, then the FDA-483 observation will remain. The FDA does routinely alter its FDA-483; however, where disputes remain on how the FDA has interpreted a finding vis-à-vis the position firm takes, it is important to identify which data were used by the FDA that formed the basis of their decision; these data should then be verified, and if it is discovered that discrepancies occurred that were unintentional, the FDA inspectors should be informed as soon as possible after they leave the firm's premises.

When the FDA team has not found objectionable conditions, they will terminate the inspection (an FDA-483 will not be issued). In such cases, the company will not receive anything in writing from the FDA team. The firm, however, reserves the right to request the FDA to issue a statement to this effect and to ask for an exit discussion.

However, one should be extremely careful about engaging the FDA inspectors in discussions that are superfluous, to prevent any inadvertent disclosure that might change their opinion about the inspection.

The Application Integrity Policy (AIP) is a formal administrative program that the FDA uses to deal with fraud, scientific misconduct, or other instances in which wrongful acts have been committed or are suspected. The AIP, introduced in 1990 as consequence of the generic drug scandal, was formerly called the "fraud policy." The AIP is invoked when the integrity of data or information in applications filed with the FDA has been compromised or questioned. Examples of actions that may prompt investigations include submission of false or fraudulent data, making untrue statements to the FDA officials, offering illegal gratuities, and other actions that subvert the integrity of an application. The primary enforcement options that are available to the FDA under the AIP program include withholding of approvals, product recalls, and civil and criminal penalties. However, note that the FDA may not have a legal jurisdiction over a foreign establishment, and thus the penalties are mainly the rejection of application and banning the firm from submitting future applications.

F. Product Stability Data

One of the most widely cited observations in the FDA audits is the lack of or inadequate data to support the stability of the product. This applies to domestic as well as international audits, though more problems arise in international audits, where the firm may have used a different climatic zone for testing the product. A robust stability program includes study of loss of active ingredient (potency), increase in concentration of active ingredient, alteration of bioavailability, loss of content uniformity, decline in microbiological status, increase in possibly toxic decomposition product, loss of pharmaceutical elegance, and modification in any other factor of functional relevance (e.g., loss of adhesion strength in a transdermal). The stability data that should be available at the time of preapproval inspection include

- Adequate test method: The assays of the active component should be stability-indicating; that is, they can be separated from the degradation products and other components of the formulation. Furthermore, the degradation products should be quantitated and all methods should be validated not only at the beginning of the testing but also through the testing period.
- Characterization of drug substance: Where a reference standard is used in an ANDA, this aspect is set aside. However, where a new chemical entity (NCE) is involved, a large volume of data would generally be required to establish the degradation profile of the new drug, especially if this happens to be a macromolecule; when the testing requires evaluation by a biological response, the difficulties in validating the test method rise exponentially. Where an entirely new stability-indicating assay is established, it is necessary to demonstrate that the procedure is indeed stability-indicating by forced degradation studies. For protein drugs, incomplete knowledge of the molecule makes it difficult to demonstrate the stability-indicating nature of the assay.
- Calibration of equipment: This is a routine requirement, and the FDA inspectors may not review these data if they find that the firm is in general good compliance with the cGMP. However, these data should be updated and current at all times.
- Assay validation parameters: The common parameters that require attention include accuracy, limit of detection, limit of quantification, linearity, precision, range, recovery, robustness, sample stability (on storage and during

assay), specificity and selectivity, and systems suitability. Two additional parameters that may need special attention are transferability and comparability. This applies to both chemical and physical testing where used. Because stability-indicating methods evolve over time, revalidation is critical. Partial revalidation is required whenever significant changes are made either in the method itself or in the material analyzed, which could reasonably be expected to affect the results obtained (e.g., changes in equipment or suppliers of critical supplies).

- Preformulation studies (bulk drug substance): Stability data of the bulk drug substance alone or in model test systems is required, and most companies find this to be weakest point of their presentation to the FDA.
- SOPs: During the PAI, the FDA investigators routinely examine the SOPs that relate to the development and operation of the stability program to ascertain the strengths and weaknesses of the program, as well as ensuring compliance with the SOPs. Firms should understand that there are no official guidelines on how to write an SOP, what methods to use, and who should be responsible for doing it. What the FDA looks for is that, given an approved SOP, the firm adheres to its own guidance. Should doubts arise that the firm is not following its own guidelines, suspicion grows about the firm's overall ability to comply with the cGMP regulations.
- Room temperature and accelerated test data: For products that will be labeled to require storage at controlled room temperature, long-term studies at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ with 60% relative humidity (RH; $\pm 5\%$) with at least 12 months of data are needed. Accelerated studies at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 75% $\pm 5\%$ RH with at least 6 months of data are also normally required. However, the ICH does allow for a less rigorous accelerated test if the 40°C test cannot be passed. When "significant change" occurs during the 40°C accelerated study, an intermediate test, such as $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and 60% RH $\pm 5\%$ for 12 months, can be used. Significant change is defined as a 5% loss of potency, exceeding pH limits, dissolution failure, and failures of physical specifications (hardness, color, etc.). If products are to be labeled with instructions for storage at a temperature of less than 25°C , then the accelerated studies can be performed at a temperature less than 40°C ; however, the conditions should be at least 15°C above those used for long-term evaluation. Products for which water loss may be more important, such as liquids or semisolids in plastic containers, it can be appropriate to replace high-RH conditions by lower RH, such as 10% to 20%. If, during clinical trials, a number of different formulations have been used that differ in either formulation or processing variables from the product intended for the market, it may be appropriate to "build bridges" between the various formulations if there is reason to believe that the changes in the formulation or processing variables are such that might reasonably be expected to significantly modify stability. The FDA SUPAC (scale-up and postapproval changes) Guideline should be consulted about the importance of such changes.
- Contract laboratory stability testing: Where contract work is involved, complete details about the facility conducting the testing should be available. The FDA may choose to visit that facility as well, unless it is an approved facility that has undergone several FDA inspections in the past.

Developing stability data for an ANDA product generally requires fewer laboratory studies than those required with an NCE. The primary goal of an ANDA should be to

mimic the stability profile of the innovator product, barring any intellectual property issues that might prevent the generic manufacturer from formulating a similar product. (Of course, there is nothing to prevent an ANDA sponsor from trying to formulate a product with a longer shelf life than that of the innovator, and this idea has been considered by some companies.) The formulation of generic products requires developing a source of API—a DMF source—that is substantially identical in its stability profile to the innovator API; where reference standards are not yet available, this may create serious problems. In addition, it is often difficult to obtain impurities in sufficient quantity to validate the test methods. As a result, much effort is needed in making this part of the stability profile appear as comprehensive as possible. Firms often use bracketing, or matrixing—a form of partial factorial experimental design—to reduce their experimental load, and it is well accepted; however, before adopting this method, the firm is advised to consult with the FDA, as the power of test required may change with the type of API involved. Also, normalization of stability results is not usually desirable, and the plots of percentage of label claim as a function of time should not be normalized so that all batches originate at 100% of label claim. In considering batch-to-batch variability in three or more batches, the FDA is interested in both intercepts and slopes. The arguments often adduced by European companies that the slope is more important in establishing shelf life are not acceptable to the FDA. The FDA also considers delay in testing of samples a serious issue in the stability profiling in addition to the calibration and validation of the stability chambers. Know that the FDA takes a hard-line approach when it comes to the conduct of stability testing. Firms often are greatly surprised by how important the FDA considers these "nuts and bolts" issues, such as crowded stability chambers with poor air circulation, lack of proper calibration, and evidence that the temperature fluctuation is not more than 2°C .

G. Validation of Processes

Next to the problems frequently recorded in stability profiles of drug products is the lack of or inadequacy of the documents that affirm that the process used for the manufacture of a biobatch of the commercial batch was fully validated. Validation is a requirement of both the development stage and the final batches. Process validation is defined as establishing documented evidence, which provides a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. To provide the FDA with sufficient documentation, firms should prepare a flow diagram of the process in a logical flow, identifying various unit operations. Firms are required to perform validation of three formal batches.

The general principles of process validation involve prospective process validation (also called premarket validation), retrospective process validation, revalidation, and concurrent process validation. Prospective process validation is the most important for an FDA pre-NDA approval inspection of a NCE or API in a dosage form or delivery system.

Prospective validation is conducted before the distribution of either a new product or an existing product made under a revised manufacturing process where such revisions may affect product specifications or quality characteristics (attributes). This involves documenting critical step analysis, in which the unit operations are challenged during the process qualification stage to determine, using either "worst case" analysis or a fractional factorial design, critical process variables that may affect overall process performance.

During formal, three-batch, prospective validation, critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should fall well within finished product specifications.

Retrospective validation involves using the accumulated in-process production and final product testing and control (numerical) data to establish that the product and its manufacturing process are in a state of control. Valid in-process results should be consistent with the drug products' final specifications and should be derived from previous acceptable process average and process variability estimates, where possible, and determined by the application of suitable statistical procedures, that is, quality control charting, where appropriate. The retrospective validation option is selected when manufacturing processes for established products are considered to be stable and when, on the basis of economic considerations and resource limitations, prospective qualification and validation experimentation cannot be justified.

Before undertaking either prospective or retrospective validation, the facilities, equipment, and subsystems used in connection with the manufacturing process must be qualified in conformance with cGMP requirements.

Concurrent validation is conducted under a protocol during the course of normal production. The first three production-scale batches must be monitored as comprehensively as possible. The evaluation of the results is used in establishing the acceptance criteria and specifications of subsequent in-process control and final product testing. Some form of concurrent validation, using statistical process control techniques (quality control charting), may be used throughout the product manufacturing life cycle.

Revalidation is required to ensure that changes in-process or in the process environment, whether introduced intentionally or unintentionally, do not adversely affect product specifications and quality characteristics. Firms should put a quality assurance system (change control) in place that requires revalidation whenever there are significant changes in formulation, equipment, process, and packaging that may affect product and manufacturing process performance. Furthermore, when a change is made in a raw material supplier, the supplier of API should be apprised of the critical requirements of impurities. Revalidation is often required in following conditions:

- Change in an API or a key excipient, or primary packaging.
- Change or replacement in a critical piece of equipment.
- Significant change in processing conditions that are known to affect either subsequent unit operations or product quality.
- Change in a location, site, or support system (e.g., utilities).
- Significant change in batch size from what was validated and that affects the operation of or selection of manufacturing equipment.
- Where several batches fail sequentially.

Process performance requalification studies before revalidation assignments are currently required for sterile products only; some of these issues can be covered in the yearly filings. However, firms are urged to review the most current SUPAC guidelines for the specific type of product manufactured.

An important document that all firms must have is the validation master plan, which enables creation of an overview of the validation effort. This plan should be put together early in the drug development process and updated on a regular basis as the drug product enters various stages of

development. The plan is basically a layout of how the various activities will be performed against a predetermined timeline [perhaps using Gantt or Program Evaluation and Review Technique (PERT) chart format]. Of significance are the critical paths in the plan and how they are linked to objective achievement.

The validation program generally follows the following order:

- Selection of raw materials and components
- IQ/OQ of facilities, equipment, and systems
- Performance and process qualification stages
- Protocol-driven, three-batch, formal process validation

Running these in series and in parallel, much time can be conserved. The three stages with respect to equipment qualification are sometimes referred to as Equipment Validation, comprising IQ, which ensures that a piece of equipment has been correctly calibrated and installed in accordance with the equipment manufacturer's recommendations (proper voltage, amperage, clearance from wall, exhaust requirements, etc.). It is important to understand that IQ is also required for all utility systems. In most instances, once the installation is complete, IQ cannot be performed retroactively, such as in the case of heating, ventilation, and air-conditioning or water systems; the FDA considers this phase of planning crucial in evaluating the readiness for compliance with GMP regulations. The next phase is OQ, comprising procedures and documentation that show that the facility, support system, or piece of equipment performed as intended throughout all anticipated operating ranges under a suitable load. In this phase the systems or equipment are challenged to the limits of operation. The final phase is PQ, which demonstrates that the facility, support system, or piece of equipment performed according to a predefined protocol and achieved process reproducibility and product acceptability.

Given below is a proposed outline for a prototype validation protocol:

1. Purpose of the entire validation and prerequisites
2. Description of the entire process and subprocesses, including flow diagram and critical step analysis
3. Validation protocol approvals
4. IQ and OQ, including blueprints or drawings
5. Qualification report or reports for each subprocess
 - a. Purpose
 - b. Methods/procedures
 - c. Sampling and testing procedures, release criteria; for example, reporting function
 - d. Calibration of test equipment used; for example, test data
 - e. Summary of results
 - f. Approval and requalification procedure
6. Product qualification, test data from prevalidation batches
7. Product validation, test data from three formal validation batches
8. Evaluation and recommendations (including revalidation/requalification requirements)
9. Certification (approval)
10. Summary report with conclusions

The validation protocol and report may also include the product stability data or a summary and documentation concerning cleaning and analytical validation.

The pilot-production program is generally a result of cooperation between the development laboratories and the manufacturing department. Technology transfer documentation applies to processes as well as to the systems being

qualified and validated and their testing standards and testing methods. This documentation is important, particularly where an NDA is involved.

The concept of validation should be incorporated during every phase of product and process development:

1. Preformulation studies incorporate API qualification and evaluation of key excipients. Studies should incorporate studies of combinations of API and excipients and a rationale developed for the levels of various excipients chosen. Interactions between the API and excipients are expected and should not form the basis of altering the choice so long as data can be collected to show that the API is available through the shelf life.
2. Once a selection of ingredients is made, the work is transferred to the formulation laboratory to establish preliminary product design as well as prototype formulations. If the product manufactured at this level is to be used in humans, the manufacturing should be done at a GMP level.
3. Once a laboratory batch (often called 1 \times) has been determined to be both physically and chemically stable based on accelerated, elevated-temperature testing (i.e., 1 month at 45°C or 3 months at 40°C or 40°C/80% RH), the next step is to scale the product and its process to a (10 \times) pilot-laboratory-size batch or batches. The pilot-laboratory-size batch represents the first replicated scale-up of the designated formula. The size of the pilot-laboratory batch will usually range between 10 and 100 kg, 10 and 100 L, or 10,000 and 100,000 U. These pilot-laboratory batches are often used in clinical trials and bioequivalency studies. According to the FDA, the minimum requirement for a biobatch is 100,000 U. The pilot-laboratory batches are usually prepared in small pilot equipment within a designated cGMP-ready facility. Process-development (process-qualification) or process-capability studies are normally started in this important stage of the scale-up sequence. To evaluate the critical control parameters and their unit operation, constraint analysis techniques followed by fractional factorial designs are often used to challenge the tentative control limits (so-called “worst-case analysis”) established for the process at this intermediate stage.
4. A pilot production is at about a 100 \times level; in general, the full-scale batch and the technology transfer at this stage should comprise preformulation information, product development report, and product stability and analytical methods reports. This is the time to finalize the batch production documentation for the 100 \times level. The objectives of prevalidation trials at this stage are to qualify and optimize the process in full-scale production equipment and facilities. These studies should not be rushed, as they are followed by a formal validation cycle, and rushing the prevalidation protocols may result in costly errors later on.
5. The formal validation is often completed after the PAI, where three-batch process validation will be conducted in accordance with the protocol approved during the preapproval inspection. The primary objective of the formal process validation exercise is to establish process reproducibility and consistency. Such validation must be completed before entering the market. The formal validation studies continue through packaging and labeling operations (in whole or in part), so that machinability and stability of the finished product can be established and documented in the primary container-closure system.

H. Change Control

Changes in the processes, systems, and formulations are inevitable. However, procedures for change control should be in place before, during, and after the completion of the formal validation program—to ensure that the process continues in a validated, operational state even when small noncritical adjustments and changes have been made to the process. These changes should be critically reviewed by the validation or CMC committee. The change control system allows innovation and process improvements, making it more flexible without prior formal review on the part of the NDA- and ANDA-reviewing function of the FDA. The supplemental procedures with respect to the Chemistry and Manufacturing Control sections of NDAs and ANDAs are covered through annual SUPAC review documentation procedures, with change control procedures providing assurance that process validation will remain more proinnovative.

1. Cleaning Validation

According to section 211.67 Equipment Cleaning and Maintenance of cGMP regulations, equipment and utensils should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product. This includes materials used in clinical trials as well as the commercial drug product. Written SOPs must ensure that cleaning and maintenance of equipment in both product development laboratories and manufacturing facilities is strictly adhered to. Records should be kept of maintenance, cleaning, sanitizing, and inspection. These records are likely to be requisitioned by the FDA during the course of the preapproval inspection. The objective of cleaning validation of equipment and utensils is to reduce the residues of one product below established limits so that the residue of the previous product does not affect the quality and safety of the subsequent product manufactured in the same equipment. Some of the equipment design considerations include type of surface to be cleaned (stainless steel, glass, plastic), use of disposables or dedicated equipment and utensils (bags, filters, etc.), use of stationary equipment (tanks, mixers, centrifuges, presses, etc.), use of special features (clean-in-place systems, steam-in-place systems), and identification of the difficult-to-clean locations on the equipment (so-called “hot spots” or critical sites). It is important to realize that the FDA has tightened significantly the cleaning validation policies, particularly if there are biological products involved; the therapeutic proteins and peptides are specifically the target of FDA inspection.

The cleaning procedures define in certain terms the amounts and the specific type of cleaning agents or solvents used, and the procedure includes complete details about what is to be cleaned and how it is to be cleaned. As always, the methods focus on the worst-case conditions, such as the higher-strength, least soluble, most difficult-to-clean formulations manufactured within the facility that may be alternated. Cleaning procedures should identify the time between processing and cleaning, cleaning sequence, equipment dismantling procedure, need for visual inspection, and provisions for documentation.

The analytical methods chosen to validate the cleaning process may include the HPLC, TLC, spectrophotometry, TOC (total organic carbon), pH, conductivity, gravimetric, and so forth. The sampling techniques chosen may include direct surface sampling, using swabs and gauze or rinsing, depending on the residue limit to be established on the basis of the sampling site, type of residue sought, and equipment

configuration (critical sites vis-à-vis large surface area) consideration. The analytical and sampling methods should be challenged in terms of specificity, sensitivity, and recovery. The residue limits to validate the cleaning must be practical, achievable, and verifiable, and they must ensure safety. The potency of the selected drug and the presence of degradation products, cleaning agents, and microorganisms should be taken into consideration.

As a general rule, use these limits: not more than 10 ppm, not more than 0.001 of the dose of any product will appear in the maximum daily dose of another product, and no physical or chemical residue will be visible on the equipment after cleaning procedures have been performed.

2. Analytical Methods Validation

Nothing is more critical to a successful PAI than an elegant presentation of analytic methods validation in the eyes of the FDA investigators. Not only does this tell the investigators about the assurance provided for the correct testing of the product, but this also reflects on the overall understanding of the firm on compliance with the cGMP. Analytical methods go to the heart of a validated process for drug product manufacture. To establish what is tested and what the amounts involved are may appear a simple process at the outset, yet there remain many elaborate steps that will ensure that every time an analysis is performed, the test results can be relied on. Analytical methods that form the technical package for a product include not only the API but also inert excipients, the impurities in both, the residue from previously used materials and operations, the composition of in-process blends and compositions, and obviously the finished product before its release. To ascertain that the methods used are qualified for each of these phases of testing, a large volume of data is generally collected at all stages of product development, for scale-up and final manufacturing batches, and at all stages of validation and stability protocol development.

While validating a production process, several steps were listed as they pertained to each of the components of manufacturing: equipment, process conditions, personnel, and so forth. These key elements multiply rapidly when it comes to analytical methods validation. Take, for example, HPLC—the most commonly used method of analysis. A typical analytical method would involve use of columns, pumps, heaters, detectors, controllers, samplers, sensors, recorders, computers, reagents, standards, and operators—put together as a system. Each of these components and systems needs independent validation, followed by a validation of the system. Note that when this equipment is used to manufacture a product such as therapeutic proteins wherein HPLC techniques are used for the purification purpose, then all additional requirements of a manufacturing system also apply, including, but not limited to, the requirement that the equipment be of a sanitary kind. This limits the choice for manufacturers, and these considerations should be taken into account in the first selection of equipment.

The suitability of analytic method must be clearly demonstrated. This involves developing data on accuracy, precision, and linearity over the range of interest; that is, 80% to 120% of label potency. Data demonstrating the specificity, sensitivity, and ruggedness of the method and the limits for degradation products or impurities should be included. It is also important to study degradation products and impurities, which should be adequately identified and characterized. Data collected must demonstrate recovery of actives and lack of interference from other components, reagents, and standards. In addition, data characterizing day-to-day,

laboratory-to-laboratory, analyst-to-analyst, and column-to-column variability should be developed to supplement reproducibility and ruggedness information. The validated analytical method should be stability-indicating. Recognition by an official compendium will often simplify the requirements listed above, but it still requires a verification process. Biological assay methods as well as the identification and analysis of microorganisms should be held to similar but reasonable standards in conformance with the limitation of biological testing.

3. Computer System Validation

New to the industry is the requirement that all electronically kept records be validated in accordance with the CFR (title 21, volume 1, part 11 revised April 1, 2003 requirement). This is particularly true of instances in which the systems are custom-designed and, furthermore, where computer-controlled automated processes are used. There remain many misconceptions about what makes up computer validation. The CFR guideline as listed below should be well understood:

PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Subpart A—General Provisions

Sec. 11.1 Scope.

- (a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.
- (b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.
- (c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.
- (d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with sec. 11.2, unless paper records are specifically required.
- (e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

Sec. 11.2 Implementation.

- (a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

- (b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:
- (1) The requirements of this part are met; and
 - (2) The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

Sec. 11.3 Definitions.

- (a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.
- (b) The following definitions of terms also apply to this part:
 - (1) Act means the Federal Food, Drug, and Cosmetic Act [secs. 201-903 (21 U.S.C. 321-393)].
 - (2) Agency means the Food and Drug Administration.
 - (3) Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.
 - (4) Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.
 - (5) Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.
 - (6) Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
 - (7) Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.
 - (8) Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.
- (9) Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B—Electronic Records

Sec. 11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

- (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.
- (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.
- (c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.
- (d) Limiting system access to authorized individuals.
- (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.
- (f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
- (g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
- (h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
- (i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.
- (j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.
- (k) Use of appropriate controls over systems documentation including:
 - (1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
 - (2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Sec. 11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from

the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in sec. 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Sec. 11.50 Signature manifestations.

- (a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
 - (1) The printed name of the signer;
 - (2) The date and time when the signature was executed; and
 - (3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.
- (b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Sec. 11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C—Electronic Signatures

Sec. 11.100 General requirements.

- (a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.
- (b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.
- (c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
 - (1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.
 - (2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

Sec. 11.200 Electronic signature components and controls.

- (a) Electronic signatures that are not based upon biometrics shall:
 - (1) Employ at least two distinct identification components such as an identification code and password.
 - (i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only

executable by, and designed to be used only by, the individual.

- (ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.
 - (2) Be used only by their genuine owners; and
 - (3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.
- (b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Sec. 11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

- (a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.
- (b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).
- (c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.
- (d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.
- (e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

To understand fully the importance of computer validation, one must realize that computers can perform the functions humans used to. Instructions such as SOPs are needed to instruct humans as to what functions to perform and in what order. When computers are used, these instructions are programmed. Computer systems are extensions of the processes that they are designed to control or monitor; as a result, all computer-controlled manufacturing is subject to validation. With exponential increase in PLC-based manufacturing systems, the FDA has begun to place strict requirements on computer validation. A computer system consists of hardware, that is, physical and calibration devices, sensors, input/output devices, transducers, or equipment, and its companion software, which is used to generate records, instructions, or data. Source codes and supporting software documentation used in drug process control is considered to be part of the master production and control records under cGMP interpretation. The computer systems may comprise

- computer-integrated manufacturing,
- analytical instrumentation and automated laboratory practices,

- computer-controlled electronic signature systems,
- computer-integrated packaging operations,
- laboratory information-management systems,
- computer systems for good clinical practice, and
- computer-assisted medical devices.

The categories listed above require qualification and validation documentation. It is advisable that process automation and companion computer-integrated manufacturing operations not be initiated until sufficient prospective and concurrent validation studies have been completed.

The requirements for hardware validation are identical to those of any other equipment in use, comprising the OQ/IQ/PQ cycle, except that in the PQ, it is the test of software used. The software validation comprises functional testing, in which defined inputs produce outputs that meet expectations or specifications; a thorough examination of source codes, database designs, programming standards, control methods, and support documentation; or a quality-assurance program that includes alternate plans, contingency practices, record retrieval, and security practices

I. Documentation Standards

The cliché of the three Ds—documents, documents, and more documents—is apt for FDA PAI inspections. Historically, the regulatory agencies have relied heavily on cross-checking documents to ascertain the state of compliance with the cGMP regulations. The documents of critical importance are the batch records that contain detailed information about the batch history. It is often difficult for a firm to “fudge” these documents, although many have tried. What is important to understand here is that the entire batch record is cross-checked with the purchase requisitions, delivery documents, testing documents, and final release documents. It is almost impossible to create a system that would fool the FDA inspectors. The firms are advised that a low level of due diligence will expose the trial of doing paperwork. Included in the batch records are the date of manufacture, the identity of major equipment and lines used, specific identification of each batch of component or in-process material used, weights and measures of components used in the course of processing, in-process and laboratory control results, inspection of the packaging and labeling area before and after use, a statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing, complete labeling control records, including specimens or copies of all labeling used, description of drug product containers and closures, any sampling performed, identification of the persons performing and directly supervising or checking each significant step in the operation, any deviation report resulting from an investigation made according to 21 CFR 211.192, and results of examinations made in accordance with 21 CFR 211.134 (packaging and labeling inspections).

Change control is the procedural system through which changes are reviewed, justified, documented, approved, and implemented in conformance with regulatory and corporate requirements. To support a strong change control system, the firms must have a series of documents available that includes a summary of all changes made to date that affect the manufacturing process being considered for approval; individual reports that are written to review, justify, approve, and implement specific changes that affect the manufacturing process being considered for approval; any change control reports for facilities, manufacturing processes, and cleaning processes; or analytical laboratory methods that are related to the NDA/ANDA process being submitted. As it is a routine

that changes are made in the development timeline, a rigid change control system may not work all the time. It is therefore recommended that the firms must have available for the FDA investigators a history of changes made, along with justification for the changes. It is important for the firms to know that the investigators arriving at the site may not have a copy of the filing made to the FDA, such as the CMC section of the application. Firms are advised to have a “third” copy available. The requirements of the CMC section are given below; these requirements also apply to supplements, except that the information required in the supplement is limited to that needed to support the change being submitted.

1. Batch production record
2. Specifications and test procedures for each component and for the drug product
3. Names and addresses of the sources of the active and non-compensial inactive components and of the container closure system for the drug product
4. Results of any test performed on the components used in the manufacture of the drug product and on the drug product
5. Name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility
6. Proposed or actual master production record, including a description of the equipment to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product must be provided for all initial NDAs; ANDAs must contain a proposed or actual master production record

1. Development History Report

A historic summary of the development of the product serves many purposes. The foremost purpose is to apprise the investigators of the scope of inspection. The investigators learn more about the product from the history of its development than from the analysis report of the finished product. This shows the awareness of the firm about the development process. This document should include a description of the API, the formulation, and the analytical methods. These sections should be clearly marked or presented in separate binders. The summary section should highlight how the biobatch is linked to the full-scale batch with respect to validation and scale-up of production. This section also offers an opportunity for the firm to address the issues that it considers critical.

2. Deviation Records

Deviations are inevitable, whether they occur in the production or the testing of the product; obviously, a broader standard is used during development than in full-scale production. The important thing is that all deviations should be recorded, a justification should be provided for the decision to deviate, and a description of its potential effect on the quality of product should be provided. Of most significance to the FDA is the reason for entering into a deviation: Is it because the process was not adequately characterized or validated? Or was it because of inevitable circumstances, such as a breakdown in the system? A logbook describing deviations is one way the firm may show to the FDA is diligence in ensuring compliance with the cGMP regulations. Nothing makes the FDA more suspicious than a blank log stating that there were no deviations. In addition, these log reports offer an excellent medium for internal QA audits. Firms need to understand

that the purpose of cGMP compliance is ensuring the quality and safety of the product, not necessarily adhering to a particular process or composition. Obviously, the requirements of validation make it necessary that any deviation converted into regular practice must be properly validated.

3. Installation, Operational, and Performance Qualification

The IQ/OQ/PQ documents pertaining to all manufacturing equipment, analytical equipment, or systems should be available for inspection. In many instances, firms consider their development laboratories as not needing to be as rigidly compliant for these documentation requirements as their manufacturing facilities are. This creates serious problems at PAI if the development laboratory produces a biobatch. Furthermore, the process or method transfer becomes a serious problem if unqualified equipment or processes are used in the development cycle. Firms are strongly urged to treat their development laboratory as if they were cGMP-compliant facilities.

4. Organizational Chart

Organizational charts establish that an adequate number of personnel are available to perform and supervise the manufacture, processing, packaging, or holding of a drug product (21 CFR 211.25), that a proper chain of responsibility has been established in supervisors of manufacturing processes, and that there is appropriate separation of responsibilities for manufacturing operations and the quality unit. These charts should be available for both the development organizations and the commercial manufacturing organizations.

5. Products List

To evaluate how the product submitted may be affected by the manufacturing of other products in the same premises, a complete list of all products manufactured should be provided to the PAI team on the first day of inspection. The FDA considers cross-contamination issues critical; should there be a serious objection raised, the PAI team will refuse to continue the audit. Firms are strongly urged to review the cGMP guidelines and the guidance documents provided by the FDA: Some basic rules about the cephalosporins, penicillins, hormones, and biological products are well known; however, when in doubt, do not hesitate to write the FDA to seek clarification before beginning the production of a new product. It is noteworthy that a single batch of a forbidden entity in the premises may render the premises unsuitable forever if proper validation could not be performed. For example, if a penicillin or cephalosporin product is manufactured on the premises, this premises can no longer be used for any other product, as it would be difficult to prove the absence of contaminants.

6. Drawings

Site plan drawings should be available for facilities used in clinical trial material production as well as for those at which commercial products will be produced. These drawings quickly show how the facility is constructed and controlled and include the floor plan, which shows the proper segregation of areas by walls, airlocks, and doors; these plans are useful to demonstrate people and equipment flow, showing that clean personnel and equipment do not cross paths with dirty personnel and equipment. Also, there should be a broader facility and grounds plan showing the relative position and location of various buildings in the facility. This is particularly useful where multiple building are used to finish the product or to test it, as the security of the batch in transit and the possibility of contamination are key issues to be resolved. In addition, drawings of the utility systems, such

as the heating, ventilation, and air-conditioning systems and water systems, should be available. Firms are advised that they may request the FDA to review these drawings before the visit, perhaps at the time of installation, to make sure that the basic guidelines are adhered to.

7. Stability Data

Some of the most significant data that the PAI team confirm is the stability profile of the product; most likely the raw data would be examined if the presentation of the summary data appears flawed.

8. SOPs

SOPs relevant to basic systems and operations should be provided in a neatly arranged folder starting with the master validation plan, product, personnel, and process management. A comprehensive index should be attached.

9. Training Records

It is a cGMP requirement (21 CFR 211.25 a, b) that personnel have education, training, or experience that enables them to perform their assigned task. These training records should include the training curriculum for each individual, as well as the list of completed courses. These records should be made available for all personnel who manufacture, process, package, test, or release clinical trial materials and the commercial product. Firms are strongly reminded that in most inspections the FDA finds this to be one of the weakest areas. For example, some of the common FDA citations for training violations include lack of formal training documentation, lack of training in GMP regulations on an ongoing basis, lack of a formal job function training program, lack of a system for evaluating or monitoring employees to ensure that training was effective, no provision for retraining individuals on a periodic basis to ensure that employees remain familiar with the requirements applicable to them, no provision for training employees on recently revised procedures, and no provision for ensuring that employees were trained before they perform job functions. Training records should also include details about how the new employees are trained to follow the company's SOPs, rules, and other regulations. The SOP reading and understanding records, therefore, form vital evidence that the FDA examines to ensure that all employees have received adequate training in performing their tasks. Awareness and understanding of what is considered critical depends on the role the employee plays; for example, compliance with good laboratory practices or good clinical practice may be relevant to some, but not all, employees. Safety training, job function training, and documentation training are additional requirements.

10. Validation Records

Validation protocols may include test parameters, product characteristics, production equipment specifications and settings, and decision points on what constitutes acceptable test results. Three types of validation protocols should be available during the PAI: cleaning, manufacturing process, and analytical methods. Any data associated with a completed protocol should also be made available. Also, if there had been any retrospective validation, these data should also be available.

11. Technology Transfer and Scale-Up

The goal of technology transfer and scale-up is to show, through process control, that any modifications made from conception to implementation have been appropriately

evaluated and documented and that the product is safe, pure, and effective. The technology transfer master plan comprises three components: the documents, the writing style, and the illustration of equivalents. The development stage documents are often abbreviated, and the files are not necessarily as complete as in the case of full-scale production; also in addition, the language used often differs as the audience changes from a scientist to a line worker. It is important also to show how the equivalent processes were selected; for example, when using a small dryer, how can the use of large fluid bed dryer be labeled as equivalent?

12. Quality Policy

The quality policy is a global document for the company that covers such issues as recalls, employee training and certification, and overall impact analysis of product and process changes. Customer expectations, materials specifications, and laws and regulations may also affect the number of personnel needed and the way quality functions are subdivided into manageable work units. Of importance for inclusion in the quality systems description are the documenting controls, including clearance and issuance of production records, procedures, specifications, and so forth; internal and vendor audits; sampling, examination, and approval of materials, including packaging and labeling (often administered by the laboratory component of the department); Material Review Board representatives; verifying yields and other critical production data through production record audits; finished product release; accompanying FDA investigators and external auditors; administering or contributing to cGMP, safety, or other required training programs; ensuring the investigations of product failures, process deviations, laboratory out-of-specification findings, and consumer complaints; monitoring approval and implementation of corrective action plans and change controls; on-site verification of the performance of critical production operations such as clearing labeling equipment and lines; review and approval of the product development records and documents transferring a product from development to commercial production; validation/qualification protocols and sum-

mary reports acceptance; and annual cGMP review. In addition, some functions are delegated to the engineering group to complete, and these include statistical process control and trend analyses; calibration of instruments and equipment, including out-of-specification follow-up; and analysis of reports of extraordinary maintenance and preventative maintenance failures.

13. Vendor Approval

The ISO 9001 and ISO 9002 Quality Standards require manufacturers to select vendors on the basis of their ability to meet purchase specifications. By ISO 9004 definition, this includes meeting regulatory requirements and safety standards. The FDA's cGMP regulations 21 CFR 211.84(a) through (e) require a manufacturer to test and approve or reject components, drug product containers, and closures. 21 CFR 211.84(d)(2) requires the manufacturer to test each component for conformity with written specifications for purity, strength, and quality or to accept the supplier's report of analysis. 21 CFR 211.84(d)(3) requires the manufacturer to test containers and closures for conformance with all appropriate written procedures or to accept the supplier's report of analysis. Reports showing compliance with firm's vendor approval policy are required at the time of PAI.

14. Outside Contractors

When any work is contracted out, whether in manufacture or testing phase, the FDA will hold the firm where the deviation or deviations occurred responsible for violations of the cGMP regulations (21 CFR 210 and 211) that pertain to those services. However, the contractor and the application holder will be held jointly responsible for processes performed by the contractor to the extent that each party contributed to the violations. Performance of each party will be considered in determining whether one or both parties are subject to regulatory action for failure to comply with cGMPs. It is in the best interest of the applicant to perform due diligence in the selection of any contractor, as well as to audit the contractors to ensure they meet the regulatory requirements and the contractual commitments.

Formulation Factors in Uncompressed Dosage Forms

I. RELATIVE HUMIDITY

Relative humidity in the filling and storage areas is more important for powders than for other dosage forms because of the large specific surface area (area/weight), which can result in significant moisture uptake. The gelatin capsule shells are also susceptible to moisture and degradation at high moisture. In addition, at very low moisture, gelatin in capsules can become very brittle; therefore, an appropriate humidity level must be maintained.

II. SURFACE AREA

The large surface area of powders provides greater opportunity for the production of static electricity during the friction of flow and handling. Make sure all equipment is well grounded or else significant segregation and impeded flow of powder can result. Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be described completely by a single parameter; however, when either nonuniform size distribution or anisometric shapes exist, any single parameter is incapable of totally defining the powder. In addition to a value for the average particle size, often we use frequency histograms to help describe the powder. We also use other measures of powder characteristics such as angle of repose and bulk or tap density. Lastly, we use compressibility and the powder's ability to undergo plastic deformation.

III. SIEVE ANALYSIS

Dry sieving allows the fractionation of relatively coarse powders and granules. Sieves are stacked (*nested*) with the largest apertures at the top and the smallest at the bottom. A sample of powder is placed on the top sieve and shaken for a fixed time period at a given amplitude and pulse frequency.

The weight of powder on each sieve can then be calculated and the particle size distribution obtained. Particles must have a two-dimensional profile smaller than the sieve aperture in order to pass through a particular sieve. A *mean sieved diameter* is calculated. Because the weight of particles on each sieve is determined, the mean sieved diameter represents a *mass distribution*.

A mesh number denotes the size of the apertures in each sieve. The mesh number is the number of wire strands (of constant diameter) per inch used to weave the square mesh pattern. The side length of the aperture in microns is inversely related to the mesh number.

Whereas the specifications of starting materials are specified, the powders often form aggregates during storage; a point of use check of aggregation is needed. It is a good idea to sift all ingredients through specified sieves prior to adding them to mixing or blending vessels. For most raw materials,

sifting through a No. 60 sieve (250 μm) is desirable; however, passing materials through finer sieves can generate electrostatic charges. Wet mass is passed through a No. 8 (2.38 mm) sieve and dried granules are passed through a No. 16 (1.19 mm) mesh sieve. Lubricants should be sieved through No. 60 mesh, except for magnesium stearate, which should not be shifted through an opening smaller than the opening in a No. 35 mesh. This is necessary to avoid building up electrical charges. A conversion chart for sieve sizes from U.S. Mesh to inches and microns (or millimeters) is presented next.

U.S. Mesh	Inches	Microns	Millimeters
3	0.2650	6730	6.730
4	0.1870	4760	4.760
5	0.1570	4000	4.000
6	0.1320	3360	3.360
7	0.1110	2830	2.830
8	0.0937	2380	2.380
10	0.0787	2000	2.000
12	0.0661	1680	1.680
14	0.0555	1410	1.410
16	0.0469	1190	1.190
18	0.0394	1000	1.000
20	0.0331	841	0.841
25	0.0280	707	0.707
30	0.0232	595	0.595
35	0.0197	500	0.500
40	0.0165	400	0.400
45	0.0138	354	0.354
50	0.0117	297	0.297
60	0.0098	250	0.250
70	0.0083	210	0.210
80	0.0070	177	0.177
100	0.0059	149	0.149
120	0.0049	125	0.125
140	0.0041	105	0.105
170	0.0035	88	0.088
200	0.0029	74	0.074
230	0.0024	63	0.063
270	0.0021	53	0.053
325	0.0017	44	0.044
400	0.0015	37	0.037

IV. PARTICLE SIZE DISTRIBUTION

Sieving is a common method for establishing the distribution of particle size in a powder sample. It is a simple method that works well for powders in the size ranges used most often in the pharmaceutical industry. Sieves are limited in that they cannot be made with very small openings. The current lower limit is 43 μm , which corresponds to a No. 325 sieve. The sieve number or mesh number refers to the number of openings per linear inch. You can easily calculate the opening

size in millimeters. For example, a No. 2 sieve has an opening of 9.52 mm, while a No. 200 sieve has an opening of 0.074 mm.

A frequency histogram is a useful tool in understanding the nature of a sample of powder. It is a bar graph with the size range on the x-axis and the number or weight of each segment of the powder on the y-axis. The particle size distribution can be determined by a sample of coarse powder using a nest of sieves shaken in a sonic sifter:

1. Using at least a three-decimal-place electronic balance, record the weight of each empty sieve and the collection pan. Also record the sieve size.
2. Arrange the sieves in a sequential nest: smallest mesh number (largest aperture) at the top, largest mesh number (smallest aperture) at the bottom. Add the collection pan to the bottom of the nest.
3. Add approximately 5 g of accurately weighed coarse powder to the top sieve, and cover with the rubber cap.
4. Shake the sample for 5 minutes with a sieve "amplitude" greater than 3.
5. Reweigh each sieve and the collection pan. Calculate the weight and percentage of powder on each sieve and in the collection pan. Then calculate the cumulative weight percentage of powder that is finer than the aperture.
6. Use the probability paper to calculate the mean diameter and standard deviation; alternately, calculate the geometric mean and standard deviation for the coarse and fine powder particles.

V. POWDER FLOW PROPERTIES

During many pharmaceutical production processes, it is necessary to transfer large quantities of powder from one location to another in a controlled manner, for example, in powder blending, powder filling into containers (e.g., dusting powders), powder flow into capsules, and powder filling into the dies of a tablet press.

One method of assessing flow properties is the *Angle of repose*, which is another measure of the nature of the powder. It estimates the adhesive force between the particles. Uniform glass beads, which will show good flow properties, have an angle of repose of 23 degrees. As the adhesive force between the particles increases, the angle increases. In rare cases, it can exceed 90 degrees.

Powder is allowed to flow freely through a funnel onto the center of an upturned petri dish of known radius. When the powder reaches the side of the petri dish, the height of the cylindrical cone is determined. From the petri dish radius (r , cm) and cone height (h , cm), the angle of repose (between the petri dish and base of the powder cone) can be calculated. *Flow rate* can also be determined by measuring how fast a powder flows through an aperture. Free-flowing powders exhibit a high flow rate and a smaller angle of repose. Angle of repose and flow rate depend on particle size, shape, and surface roughness. Flow properties are frequently enhanced by the use of *glidants*.

Several commercial instruments are available to evaluate angle of repose. Follow the instructions from the supplier of instrument and test methods. A simple method is given in the following list:

1. Measure the external diameter of a petri dish; position the bottom of a funnel or paper cone approximately 5 to 15 cm above the center of the upturned petri dish using a ring

stand. Be sure, a piece of paper is under the petri dish so you can pick up the powder and reuse the powder for all your replicates.

2. Slowly pour the *coarse powder* sample into the funnel, tapping the funnel as necessary to ensure that powder flows through the hole.
3. Continue this process until the bottom of the powder pile just begins to fall over the edge of the petri dish.
4. Measure the height of the pile using a ruler.
5. If the powder is lumpy, sieve it before beginning the experiment.
6. Repeat step 2 until you consistently obtain the same answer.
7. Calculate the mean height of the coarse powder pile and the mean angle of repose (ϕ).
Note: Remember that $\tan \phi = \text{Opposite/Adjacent}$; therefore, $\tan \phi = 2 h/D$.
8. Repeat steps 2 and 3 using both *fine powder* and *fine powder with glidant*, if the purpose is to select an appropriate glidant.
9. Plot angle of repose (x-axis) against Carr's index (y-axis).

VI. REAL, TAPPED, AND BULK DENSITY

Bulk or *tapped density* is a measure of the degree of packing or, conversely, the amount of space between the particles in the powder. Bulk density is determined by placing a sample of powder of known weight in a graduated cylinder. Tap density is determined by tapping the powder in the graduate until it no longer settles.

Many methods are also used to determine the true density of the powder (e.g., helium pycnometer or gas adsorption). Dividing the true density by the bulk or tap density yields a number that is related to the amount of space in the powder. If the particles are sphere, the value is approximately 0.53, while irregular shaped particles can have values of 0.74 or more.

The *real density* of a powder sample is the weight per unit volume of the material with no air spaces between particles. Therefore, if a material has a true density of 1 g/cm^3 , 100 g of material will occupy 100 mL, assuming individual particles fit together exactly. In practice, most powders do not fit together very well. Therefore, if one fills a graduated cylinder to 100 mL with a powder, the weight of powder required may only be 70 g. This apparent density is known as the *bulk* or *expanded density* (0.7 g/cm^3). If the 100-mL cylinder is subsequently tapped, the particles slide past each other and become consolidated. The 70 g of particles that once occupied 100 mL may now only occupy 80 mL. They have an apparent *packed* or *tapped density* (g/cm^3) of 0.875 g/cm^3 . Carr's index is a measure of interparticulate forces. If the interparticulate forces are high, powders will have a low bulk density because bridging will occur between particles. This results in a large Carr's index and a large change in volume caused by tapping. If the interparticulate forces are low, particles will have little affinity for one another and will compact spontaneously. Under these circumstances, Carr's index is small and little change in apparent density is induced by tapping. Porosity is the volume ratio occupied by air spaces (voids) between particles of a powder sample.

VII. SOLID HANDLING

A sample of powder is the most complex physical system. No two particles are identical. The properties of the powder

are dependent on both the chemical and physical nature of the component and the nature of the interactions between the particles in the powder.

The ability of a powder to pack is dependent on the shape, size, and porosity of the particle.

VIII. MIXING OF POWDERS

Three primary mechanisms are responsible for mixing:

1. convective movement of relatively large portions of the powder;
2. shear failure, which primarily reduces the scale of segregation; and
3. diffusive movement of individual particles.

Large-scale mixers

- Rotating shell
- Fixed shell

Vertical impeller

- Fluid bed

Small-scale mixing

- Mortar and pestle
- Spatula and surface
- Paper bag

Extemporaneous techniques for mixing

- Geometric dilution
- Uniform particle size

Trituration

Sieving

- Pulverization by intervention

Levigation

IX. ORAL POWDERS

Oral powders include headache powders, dusting powders (such as antifungal powders), powders to be reconstituted (such as antibiotics), and insufflations, which are powders intended to be blown into a body cavity such as in the ear or nose. Powder mixtures as a means of measuring small quantities of powders are called triturations.

X. CAPSULES

Capsules are solid dosage forms in which one or more medicinal ingredients and/or inert substances are enclosed within a small shell or container generally prepared from a suitable form of gelatin. Some of the best sources of information about capsules are the companies that manufacture capsule shells. For example, Capsugel® (<http://www.capsugel.com/contact.html>) provides a lot of very useful information.

What goes into the capsule plays a role in proper capsule selection. Although the industry-leading Coni-Snap® (<http://www.capsugel.com/products/conisnap.html>) capsule is extremely versatile for many formulations, other capsule types are used specifically with liquids or with materials with unique moisture retention properties.

The amount of active ingredient per dose has a direct bearing on the proper size capsule to use. Because capsules usually require less excipients and additives, it is easier to get a more potent dosage without having to use a large-size capsule.

For broad-based appeal, the Coni-Snap capsule is a proven winner; however, for targeting select con-

sumer segments, such as vegetarians, Vcaps (<http://www.capsugel.com/products/vcaps.html>) capsules, which are of plant origin, may better meet customer needs.

Very often, strict governmental regulations are placed on products that are being consumed by the public for health reasons. In most cases, pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) face different regulatory constraints than do dietary supplements (http://www.capsugel.com/services/ds_dpstdy.html). Capsule shell manufacturers are well acquainted with Regulatory Information and Certification (<http://www.capsugel.com/services/regulatory.html>) and can alert you to important areas of consideration.

Adding to the complexity to the aforementioned regulatory issue, different countries have varying regulations that need to be considered. For example, regarding the issue of color selection (<http://www.capsugel.com/services/color.html>), countries have their own specific lists of colorants that can be legally used for capsules.

The appearance of the capsule itself is an important consideration. Colors are known to impact user perception, and the printing of logos on the capsule can increase brand recognition. Because capsules have a long and successful history as the dosage form of choice for pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) as well as for dietary supplement applications (<http://www.capsugel.com/services/dsproduct.html>), many options are available for locating capsule-filling-machinery (<http://www.capsugel.com/equipment/index.html>).

XI. FDA CLASSIFICATION OF CAPSULE TYPES

Capsule 600	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin.
Capsule, coated 602	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; additionally, the capsule is covered in a designated coating.
Capsule, coated, extended release 611	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.
Capsule, coated pellets 603	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which varying amounts of coating have been applied.
Capsule, delayed release 620	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms.

Capsule, delayed-release pellets 621	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which enteric coating has been applied, thus delaying release of the drug until its passage into the intestines.
Capsule, extended release 610	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) in such a manner to allow a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.
Capsule, film coated, extended release 612	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated film coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.
Capsule, gelatin coated 605	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin; through a banding process, the capsule is coated with additional layers of gelatin so as to form a complete seal.
Capsule, liquid filled 606	A solid dosage form in which the drug is enclosed within a soluble, gelatin shell that is plasticized by the addition of a polyol, such as sorbitol or glycerin, and is therefore of a somewhat thicker consistency than that of a hard shell capsule; typically, the active ingredients are dissolved or suspended in a liquid vehicle.

XII. FDA CLASSIFICATION OF POWDERS

Powder (PWD 110)	An intimate mixture of dry, finely divided drugs or chemicals that may be intended for internal or external use.
Powder, dentifrice (PWD DENT 115)	A powder formulation intended to clean and polish the teeth, and may contain certain additional agents.
Powder, for solution (PWD F/SOL 833)	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yield a solution.
Powder, for suspension (PWD F/SUSP 834)	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yield a suspension (a liquid preparation containing the solid particles dispersed in the liquid vehicle).
Powder, metered (PWD MET 841)	A powder dosage form that is situated inside a container, which has a mechanism to deliver a specified quantity.

XIII. INHALERS AND LUNG DELIVERY

Key factors that contribute to the aerodynamic properties of aerosol particles are found in Stokes' law. These factors may

be monitored or controlled to optimize drug delivery to the lungs. Predictions of the aerodynamic behavior of therapeutic aerosols can be derived in terms of the physical implications of particle slip, shape, and density. The manner in which each of these properties has been used or studied by pharmaceutical scientists to improve lung delivery of drugs is readily understood in the context of aerosol physics. Additional improvement upon current aerosol delivery of particulates may be predicted by further theoretical scrutiny (Crowder TM et al 2002).

The history of inhaler development in modern times can be traced to the metering valve and propellants (metered dose inhalers, pMDI) used in the treatment of asthma in the 1950s. This was followed closely by somewhat primitive dry powder inhalers (DPIs) in the 1970s. Throughout this period, nebulizers were employed to deliver drugs in aqueous solution. In the past decade, research and development in the field has broadened. This may be explained, in part, by the demise of the Kyoto Treaty on Global Warming (1997), which has refocused activities in the area of alternative propellant formulation. More significantly, there has been an increase in research into alternative approaches to powder and solution formulation and stability. This review is intended to reflect the interest and growth that has occurred in the field of pharmaceutical inhalation aerosol technology in the last 4 years (Crowder TM et al, 2001).

The field of inhalation science is expanding rapidly as scientists are designing delivery systems for proteins and peptides using nanoparticle inhalation systems; the quick absorption through lung surface offers an excellent administration route.

XIV. PROBLEMS IN POWDER HANDLING

Powder materials exhibit a number of technological challenges with their manufacture, storage, transportation, mixing, dusting, characterization, packing, crushing, and milling.

Symptoms of a nonoptimized product system utilizing a powder include unacceptable rehydration, dissolution, and solubility rate/reproducibility of the powder mixture; degradation, loss of drug activity, and reduction of product shelf life; drug mixture heterogeneity both before and during use; clogging of spray nozzle; and loss of delivered drug. The following can have a significant impact on the performance of a product using a powder:

- Utilization of the appropriate binders and adhesives
- Disintegrating agents
- Fillers
- Lubricants
- Wetting agents/surfactants
- Glidants
- Flavoring and sweetening agents

Typical powder dispersion problems include the following:

- Chemical and morphological heterogeneity of the surface
- Dissolution or isomorphous substitution of constituent components (metals)
- Dependency of the surface and solution (dissolved or added) ion species

A number of interrelated physicochemical properties, such as pH (acidity), pI (ionic strength), pe (redox), and pc

(concentration) influence the properties of the dispersion beside of the pressure and temperature.

XV. CAPSULATION EQUIPMENT

Significant advances have been made within the recent years in automating and validating capsule filling equipment. For example, the German packaging company, Bosch Packaging Technology recently introduced a new generation of capsule-filling machines. A main feature of the models GKF 701, GKF 1400, and GKF 2500 ASB 100% is the dosing station on the slide-gate principle, which, according to the company, ensures low-loss processing, even for difficult powders. The machine is controlled by an industrial personal computer (PC), using software that complies with the FDA 21 CFR part 11 federal regulations. In response to harmful dust that occurs in all areas of pharmaceutical production, Bosch has developed a containment system for its standard blister machine TLT 1400. The system, which produces 400 blisters per minute, protects the operator while processing toxic contents, according to the company. (No endorsement of any manufacturer or product is intended here.) Major suppliers of capsule-filling equipment include Farmatic, Hofliker and Karg, macofar, mGw, and Zanasi.

XVI. CAPSULE FINISHING

Capsules coming off the filling line require dedusting and polishing. These can be done by pan polishing, cloth dusting, and brushing. Commercial equipment to do this includes RotosortTM, Erwek DedusterTM and the equipment from SeidenaderTM. Imprinting on capsules serves many purposes including ready identification. The choice of ink is important.

XVII. MODIFIED-RELEASE PRODUCTS

The capsulation process offers many advantages for designing modified-release products. The simple process of loading the drug onto nonpareil sugar beads and then coating them with a variety of release profiles offers the opportunity of not only separating the incompatible components, but also mixing granules that provide different release profiles, from instant release to step release to prolonged release. Equipment is available to fill several beads simultaneously into capsules, thus assuring dosing accuracies. (If granules with different coatings are mixed, segregation is likely because of the differences in their density.) Coated granules, if compressed, lose their release profiles.

XVIII. CLINICAL TEST SUPPLIES AND PLACEBOS

Encapsulation is the preferred form of drug delivery in preparing placebos and clinical test supplies wherein small runs are planned.

XIX. COATED PARTICLES

Use of hard gelatin capsules allows for the preparation of coated particles to provide modified release or stability; these

particles are prepared generally by the method described in section XVII; however, the possibilities of creating innovative dosage forms using different size of particles makes this dosage form highly desirable for many unstable drugs.

XX. MIXING MECHANISMS

Mixing solids involves a combination of one or more mechanisms of convection, shear, and diffusive mixing. Convection mixing is achieved by the transport of solids such as by blades or screws. Shear mixing results from the forces within the particulate mass; slip planes are set up. This can take place singularly or as a laminar flow. When shear occurs between regions of different composition and parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers. Shear occurring in a direction normal to the interface of such layers is also effective because it reduces segregation. The diffusive mixing is the random motion of particles.

XXI. SEGREGATION MECHANISMS

Particulate solids tend to segregate by virtue of differences in the size, density, shape, and other properties; it can happen during mixing or subsequent storage handling as well. It is important to note that powders that are difficult to flow do not segregate easily because of high interparticulate adhesion; however, because powders must be rendered flowable for the purpose of filling capsules or in bottles or sachet, the segregation phenomenon because very important. Note that often after the addition of magnesium stearate, it is advisable to mix the product only for a limited time because electrical charges on the particles may cause segregation. Often, additives are included in formulations to reduce the tendency of segregation; these components have polarity similar to the components of the formulation. A variety of mixers are designed to counter the segregation during mixing. Regardless of the formulation or equipment used, however, the formulator must conduct a validation study to assure that the product before filling is not segregated and that detailed Manufacturing Directions consequently include conditions such as humidity, mixing speeds, mixing times, and grounding of equipment. It is often said that longer mixing causes unmixing; this occurs because of segregation as well as abrasion of particles, which alters the particle size distribution profile.

XXII. MIXING EQUIPMENT

Batch mixing is the most common practice using twin-shell, cubic, and cylindrical tumbling mixers on a common shaft. The speed of rotation (generally 30–100 rpm) for these mixers is crucial to good mixing. Other mixers of the same type take the shape of cylinders, cubes, or hexagonal cylinders. The stationary container mixers do not depend on gravity for tumbling as for the preceding mixers; these are useful for mixing sticky, wetted, or plastic mass where shear force is needed to impart mixing. Stationary container mixers include the ribbon blender and the helical flight mixer.

Large mixers produce continuous mixing; large mixers are less consistent in producing uniform mixing and are more useful in the stages, where such consistency is not critical.

Selection of equipment depends on the measure of mixing degree required. Manufacturing process validation should include a definition of segregation where large-scale segregation is not present. A large volume of data on the statistics of "degree of mixing" is available where samples are drawn from the mix at various times, and the samples must be of a sufficiently large size to contain enough particles. Perfect mixtures, in statistical terms, are random mixtures. In capsules where pellets of different types are included, these considerations become critical. Let us take the example of a binary mixture, where n is the number of particles in the sample and p is the fraction of particles of interest. For example, if a capsule contains 30% of type A pellets, then the average number is 150 in a 500-pellet capsule with standard deviation of:

$$\sigma = \bar{A}(\text{average})(1 - p)$$

Thus, for the preceding composition, a deviation of 10.2 counts for 150 pellets occurs in each capsule when there is perfect mixing; in this instance, each capsule must be individually sampled because large bulk samples would not reveal the variations.

XXIII. MILLING

Mixing of powders is easier if all components are of the same dimension in particle size. Granulation of powders is done to provide a more uniform particle size; this is a common practice in tablet, capsule, and powder suspension formulations. Milling of granulated mass produces uniform particle size, where dyes are used, milling provides a more uniform mixing and spread of dyes. Lubricants act by coating the particles and require the presence of a certain amount of fines. Size distribution profiles are routinely prepared as part of the development pharmaceuticals process, especially where high-

speed filling machines are used. Frequency and cumulative plots are made to validate the process. Probability function values found in statistics books should be consulted when designing a robust evaluation program. Particles are measured either microscopically or by weight fractions through a stack of sieves. A sedimentation method is also used for particles in the range of 1 to 200 μm to obtain a size-weight distribution. Other methods include adsorption, electrical conductivity, light and X-ray scattering, permeametry, and particle trajectory.

During the process of milling or comminution, the particles undergo transformation based on the strain applied, which produces stress, and size reduction begins with the opening of new cracks. If the force applied is not sufficient, then the particle returns to its original state from a stressed state and does not yield. The type of mill used is important, such as a cutter, fluid energy, hammer, or roller, because each provides a special pattern of comminution. For example, it is useful for fibrous material, but not for friable material; it produces a product size of 20 to 80 mesh. The fluid energy mill can produce 1- to 30- μm -particles, and is more suitable for soft and sticky materials. The most common mill is the hammer mill, which is useful for abrasive materials and produces 4- to 325-mesh particles. In a hammer mill, it matters whether the blades are forward or reversed.

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Bioequivalence Testing Protocols

To receive approval for an ANDA, applicants generally must demonstrate, among other things, that their product has the same 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)]. BE drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 USC 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320.

The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). Given below are the current recommendations for the products of relevance to this specific volume of the book:

Acitretin Capsules/Oral. *Recommended studies:* Two studies.

(1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 25 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Pregnant female subjects should be excluded from the bioequivalence studies. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 25 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure:* All-trans-acitretin and 13-cis-acitretin in plasma. Since acitretin undergoes extensive presystemic metabolism and interconversion by isomerization to 13-cis-acitretin, measurement of all-trans-acitretin and 13-cis-acitretin in plasma is recommended. The pharmacokinetic parameters for all-trans-acitretin should meet the current bioequivalence criteria. The 13-cis-acitretin data will be used as supportive evidence. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. *Bioequivalence based on (90% CI):* All-trans-acitretin. *Waiver request of in vivo testing:* 10 mg based on (i) acceptable bioequivalence studies on the 25-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Amlodipine Besylate; Benazepril Hydrochloride Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 10 mg/40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Female subjects should be excluded from the bioequivalence studies, if they are pregnant. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo.

Strength: 10 mg/40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure:* Amlodipine, benazepril, and active metabolite benazeprilat in plasma. *Bioequivalence based on (90% CI):* Amlodipine and benazepril. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. *Waiver request of in vivo testing:* 2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, and 10 mg/20 mg, based on (i) acceptable bioequivalence studies on the 10-mg strength/40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Amprenavir Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Single dose of 200 mg (4×50 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Single dose of 200 mg (4 × 50 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluids):* Amprenavir in plasma. *Bioequivalence based on (90% CI):* Amprenavir. *Waiver request of in vivo testing:* Not applicable.

Anagrelide Hydrochloride Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 1 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 1 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Anagrelide in plasma. *Bioequivalence based on (90% CI):* Anagrelide. *Waiver request of in vivo testing:* 0.5 mg based on (i) acceptable bioequivalence studies on the 1-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Aprepitant Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 125 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 125 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Aprepitant in plasma. *Bioequivalence based on (90% CI):* Aprepitant. *Waiver request of in vivo testing:* 40 mg and 80 mg based on (i) acceptable bioequivalence studies on the 125-mg strength, (ii) proportionally similar to the

125-mg strength, and (iii) acceptable in vitro dissolution testing.

Atazanavir Sulfate Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Atazanavir in plasma. *Bioequivalence based on (90% CI):* Atazanavir. *Waiver request of in vivo testing:* 100 mg, 150 mg, and 200 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Atomoxetine Hydrochloride Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 60 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* 60 mg is studied, because higher doses may cause unacceptable side effects in normal healthy subjects. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 60 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Atomoxetine in plasma. *Bioequivalence based on (90% CI):* Atomoxetine. *Waiver request of in vivo testing:* 5, 10, 18, 25, 40, 80, and 100 mg based on (i) acceptable bioequivalence studies on the 60-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. The 5-mg strength of Strattera(tm) is currently not marketed. If a firm is interested in seeking approval for this strength, please submit a citizen petition requesting the U.S.FDA make a determination that this particular strength was not withdrawn for reasons of safety or effectiveness, or check the Federal Register for a previously submitted citizen petition. Submission of the citizen petition to the FDA should be done prior to an ANDA submission.

Balsalazide Disodium Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 2250-mg dose (3 × 750 mg). *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 2250-mg dose (3 × 750 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Balsalazide and mesalamine in plasma. *Bioequivalence based on (90% CI):* Balsalazide and mesalamine. *Waiver request of in vivo testing:* Not applicable. In vitro dissolution testing under the following conditions should be submitted to support documentation of bioequivalence. *Apparatus and rotation speed:* USP apparatus I (basket), at 100 rpm. *Medium:* (1) 0.1N HCl, (2) pH 4.5 buffer, (3) pH 6.8 buffer, (4) pH 7.4 buffer. *Volume:* 900 mL. *Temperature:* 37°C. *Sample times:* 5, 10, 15, 20, 30, 45, and 60 minutes and until at least 80% of the labeled content is dissolved.

Benzonatate Capsule/Oral. *Recommended studies:* Benzonatate capsules, 100 mg and 200 mg, may be considered for waiver of in vivo bioequivalence testing pursuant to 21 CFR 320.22(c) provided the in vitro dissolution profiles of your benzonatate capsules, 100 mg and 200 mg, and the

reference listed drugs (RLDs) are comparable. *Analytes to measure (in appropriate biological fluid):* Not applicable. *Bioequivalence based on (90% CI):* Not applicable. *Waiver request of in vivo testing:* Not applicable.

Carbamazepine Extended-Release Capsules/Oral. *Recommended studies:* Three studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Female subjects should not be enrolled in bioequivalence studies of carbamazepine, if they are pregnant. Only females who are either surgically sterile or practicing a recognized safe method of contraception should be included in a study. You should clearly define in the study protocol what is considered a "safe method of contraception." Bioequivalence studies conducted for this product, may be referenced to support a request for a waiver of evidence of in vivo bioequivalence for generic products referencing Equetro. Please submit separate applications for each RLD. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see above comment. (3) *Type of study:* Fasting (capsule compared to RLD, sprinkled on a spoonful of applesauce). *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see above comment. *Analytes to measure (in appropriate biological fluid):* Carbamazepine in plasma. *Bioequivalence based on (90% CI):* Carbamazepine. *Waiver request of in vivo testing:* 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Cefdinir Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Cefdinir in plasma. *Bioequivalence based on (90% CI):* Cefdinir. *Waiver request of in vivo testing:* Not applicable.

Celecoxib Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 400 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 400 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Celecoxib in plasma. *Bioequivalence based on (90% CI):* Celecoxib. *Waiver*

request of *in vivo* testing: 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.

Cevimeline Hydrochloride Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover *in vivo*. *Strength:* 30 mg. *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover *in vivo*. *Strength:* 30 mg. *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Cevimeline in plasma. *Bioequivalence based on (90% CI):* Cevimeline. *Waiver request of in vivo testing:* Not applicable.

Danazol Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover *in vivo*. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Because of teratogenicity concerns, females in these studies should not be pregnant. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover *in vivo*. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Because of teratogenicity concerns, females in these studies should not be pregnant. *Analytes to measure:* Danazol in plasma. *Bioequivalence based on (90% CI):* Danazol. *Waiver request of in vivo testing:* 50 mg and 100 mg based on (i) acceptable bioequivalence studies on the 200-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.

Dantrolene Sodium Capsules/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* single-dose, two-way crossover *in vivo*. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Dantrolene in plasma. *Bioequivalence based on (90% CI):* Dantrolene. *Waiver request of in vivo testing:* 25 mg and 50 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.

Dicloxacillin Sodium Capsules/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* Single-dose, two-way crossover *in vivo*. *Strength:* 500 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Dicloxacillin in plasma. *Bioequivalence based on (90% CI):* Dicloxacillin. *Waiver request of in vivo testing:* 125 mg and 250 mg based on (i) acceptable bioequivalence study on the 500 mg, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.

Didanosine Delayed-Release Capsules Enteric-Coated Beadlets/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover *in vivo*. *Strength:* 400 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Didanosine in plasma using an achiral method *Bioequivo-*

alence based on (90% CI): Didanosine. *Waiver request of in vivo testing:* 125 mg, 200 mg, and 250 mg, based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths.

Diltiazem Hydrochloride Extended-Release Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way, crossover *in vivo*. *Strength:* 360 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way, crossover *in vivo*. *Strength:* 360 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Diltiazem and the active metabolites desacetyldiltiazem and desmethyl diltiazem in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. *Bioequivalence based on (90% CI):* Diltiazem. *Waiver request of in vivo testing:* 120 mg, 180 mg, 240 mg, and 300 mg based on (i) acceptable bioequivalence studies on the 360-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable *in vitro* dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Diltiazem Hydrochloride Extended-Release Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover *in vivo*. *Strength:* 240 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover *in vivo*. *Strength:* 240 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. *Analytes to measure (in appropriate biological fluid):* Diltiazem and the active metabolites desacetyldiltiazem and desmethyl diltiazem in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. *Bioequivalence based on (90% CI):* Diltiazem. *Waiver request of in vivo testing:* 120 mg, and 180 mg based on acceptable (i) bioequivalence studies on the 240-mg strength, and (ii) proportional similarity of the formulations, and (iii) acceptable *in vitro* dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three

dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Diltiazem Hydrochloride Extended-Release Capsules/Oral.

Recommended studies: Three studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 420 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 420 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. (3) *Type of study:* Fasting, sprinkle-in-applesauce. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 420 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the RLD. *Analytes to measure (in appropriate biological fluid):* Diltiazem and the active metabolites desacetyldiltiazem and desmethyl diltiazem in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. *Bioequivalence based on (90% CI):* Diltiazem. *Waiver request of in vivo testing:* 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg based on acceptable (i) bioequivalence studies on the 420-mg strength, and (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 units.

Divalproex Sodium Delayed-Release Pellets Capsule/Oral.

Recommended studies: Three studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 125 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Normal liver function test should be required prior to dosing with divalproex sodium in bioequivalence studies. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 125 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. (3) *Type of study:* Fasting sprinkle-

in-applesauce. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 125 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure:* Valproic acid in plasma. It is not necessary to measure plasma concentrations of the metabolites. *Bioequivalence based on (90% CI):* Valproic acid. *Waiver request of in vivo testing:* Not applicable.

Dofetilide Capsules/Oral.

Recommended studies: Two studies. (1) *Type of study:* Fasting. *Design:* Single dose, two-way crossover in vivo. *Strength:* 0.5 mg. *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* A black box warning concerns the risk of drug-induced arrhythmia. The study should be conducted in a facility that can provide continuous cardiac monitoring in the presence of personnel trained in management of serious ventricular arrhythmias. Any subject that develops a prolonged QTc interval should be monitored until the QTc is within normal limits. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 0.5 mg. *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* Please see comments above. *Analytes to measure (in appropriate biological fluid):* Dofetilide in plasma. *Bioequivalence based on (90% CI):* Dofetilide. *Waiver request of in vivo testing:* 0.25 mg, 0.125 mg based on (i) acceptable bioequivalence studies on the 0.5-mg strength, (ii) proportionally similar to the 0.5-mg strength, and (iii) acceptable in vitro dissolution testing.

Doxycycline Delayed-Release Capsules/Oral.

Recommended studies: Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Doxycycline in plasma. *Bioequivalence based on (90% CI):* Doxycycline. *Waiver request of in vivo testing:* Not applicable.

Duloxetine Hydrochloride Delayed-Release Pellets Capsule/Oral.

Recommended studies: Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 60 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. Because of the need to maintain the enteric coating, the subjects in a BE study should be advised not to crush or chew the enteric-coated pellets. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 60 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see above. *Analytes to measure (in appropriate biological fluid):* Duloxetine in plasma. *Bioequivalence based on (90% CI):* Duloxetine. *Waiver request of in vivo testing:* 20 mg, 30 mg based on (i) acceptable bioequivalence studies on the 60-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dutasteride Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 0.5 mg. *Subjects:* Normal healthy males. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 0.5 mg. *Subjects:* Normal healthy males. *Additional comments:* *Note:* As an option, because of the relatively long half-life, the firm may wish to conduct these studies using a parallel design. As an additional option for either the crossover or parallel design, the firm may wish to truncate the AUC at 72 hours. *Analytes to measure (in appropriate biological fluid):* Dutasteride in plasma. *Bioequivalence based on (90% CI):* Dutasteride. *Waiver request of in vivo testing:* Not applicable.

Efavirenz Capsules/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Efavirenz in plasma. *Bioequivalence based on (90% CI):* Efavirenz. *Waiver request of in vivo testing:* 50 mg and 100 mg based on (i) acceptable bioequivalence study on the 200-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Emtricitabine Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. *Analytes to measure:* Emtricitabine in plasma. *Bioequivalence based on (90% CI):* Emtricitabine. *Waiver request of in vivo testing:* Not applicable.

Esomeprazole Magnesium Delayed-Release Capsules/Oral. *Recommended studies:* Three studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (3) *Type of study:* Sprinkle. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Fasting study, with treatments sprinkled over a spoonful of applesauce. *Analytes to measure:* Esomeprazole using an achiral assay. *Bioequivalence based on (90% CI):* Esomeprazole. *Waiver request of in vivo testing:* 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For dissolution method development, please refer to USP, "Delayed-Release (Enteric-Coated) Articles-General Drug Release Standard." Esomeprazole is an acid labile drug substance; therefore, please measure esomeprazole from the beadlets of the EC capsule and not from the dissolution medium (0.1N HCl) during the acid stage; using 12 additional capsules of the test and reference products, proceed to the buffer stage.

Fenofibrate Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 150 mg. *Subjects:* Normal

healthy males and females, general population. *Additional comments:* Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 150 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Fenofibric acid, the active metabolite of fenofibrate in plasma. *Bioequivalence based on (90% CI):* Fenofibric acid. *Waiver request of in vivo testing:* 50 mg and 100 mg based on (i) acceptable bioequivalence studies on the 150-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Fenofibrate Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 130 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 130 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Fenofibric acid in plasma. *Bioequivalence based on (90% CI):* Fenofibric acid. *Waiver request of in vivo testing:* 43 mg based on (i) acceptable bioequivalence studies on the 130-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Fexofenadine Hydrochloride Capsules/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 60 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Fexofenadine in plasma. *Bioequivalence based on (90% CI):* Fexofenadine. *Waiver request of in vivo testing:* Not applicable.

Fluoxetine Hydrochloride; Olanzapine Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 50 mg/6 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 50 mg/6 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Fluoxetine and olanzapine in plasma. *Bioequivalence based on (90% CI):* Fluoxetine and olanzapine. *Waiver request of in vivo testing:* 25 mg/3 mg, 25 mg/6 mg, 25 mg/12 mg, and 50 mg/12 mg based on (i) acceptable bioequivalence studies on the 50-mg strength/6-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Fluvastatin Sodium Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Because of teratogenicity concerns, female subjects enrolled in these studies should not be pregnant. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Fluvastatin in plasma (achiral assay). *Bioequivalence based on (90% CI):* Fluvastatin. *Waiver request of in vivo testing:* 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Gabapentin Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 400 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 400 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Gabapentin in plasma. *Bioequivalence based on (90% CI):* Gabapentin. *Waiver request of in vivo testing:* 100 mg and 300 mg based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Galantamine Hydrobromide Extended-Release Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 8 mg. *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* The most frequent adverse events leading to drug discontinuation are nausea, vomiting, dizziness, and syncope. Please include appropriate safety precautions in your protocols. These include adequate monitoring of vital signs and adverse events, stopping criteria in the event of an unacceptable degree of hypotension or bradycardia, and appropriate evaluation and management of adverse events. Please assure that the investigator(s) will be vigilant in recognizing and managing any unacceptable clinical or laboratory findings. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 8 mg. *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* Please see comments above. *Analytes to measure (in appropriate biological fluid):* Galantamine in plasma. *Bioequivalence based on (90% CI):* Galantamine. *Waiver request of in vivo testing:* 16 mg, 24 mg based on (i) acceptable bioequivalence studies on the 8-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Ganciclovir Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 500 mg. *Subjects:* Because of safety concerns with the use healthy subjects, the study population should be patients with advanced HIV positive infection, who are at risk for developing cytomegalovirus disease. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 500 mg. *Subjects:* There are safety concerns with using healthy subjects. Therefore, the study population should be patients with advanced HIV positive infection who are at risk for developing cytomegalovirus disease. *Additional comments:* *Analytes to measure:* Ganciclovir in plasma. *Bioequivalence based on (90% CI):* Ganciclovir. *Waiver request of in vivo test-*

ing: 250 mg based on (i) acceptable bioequivalence studies on the 500-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Hydrochlorothiazide Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 12.5 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 12.5 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Hydrochlorothiazide in plasma. *Bioequivalence based on (90% CI):* Hydrochlorothiazide. *Waiver request of in vivo testing:* Not applicable.

Ibandronate Sodium Tablets/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, parallel design, or two-way crossover in vivo. *Strength:* 2.5 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please include as many postmenopausal women as possible in the studies. (2) *Type of study:* Fasting. *Design:* Single-dose, parallel design, or two-way crossover in vivo. *Strength:* 150 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please include as many postmenopausal women as possible in the studies. *Analytes to measure:* Ibandronate in plasma. *Bioequivalence based on (90% CI):* Ibandronate. *Waiver request of in vivo testing:* Not applicable.

Indinavir Sulfate Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 400 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 400 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Indinavir in plasma. *Bioequivalence based on (90% CI):* Indinavir. *Waiver request of in vivo testing:* 100 mg, 200 mg, and 333 mg based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Isradipine Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 5 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 5 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Isradipine in plasma. *Bioequivalence based on (90% CI):* Isradipine. *Waiver request of in vivo testing:* 2.5 mg based on (i) acceptable bioequivalence studies on the 5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Itraconazole Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Itraconazole and its active metabolite, hydroxyitraconazole, in plasma.

Bioequivalence based on (90% CI): Itraconazole. Waiver request of in vivo testing: Not applicable.

Miglustat Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* single-dose, two-way crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* Pregnancy category X. Miglustat may cause fetal harm when administered to a pregnant woman. The drug is contraindicated in women who are or may become pregnant. (2) *Type of study:* Fed. *Design:* single-dose, two-way crossover in vivo. *Strength:* 100 mg *Subjects:* Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* Please see comments above. *Analytes to measure (in appropriate biological fluid):* Miglustat in plasma. *Bioequivalence based on (90% CI):* Miglustat. *Waiver request of in vivo testing: Not applicable.*

Morphine Sulfate Extended-Release Capsules/Oral. *Recommended studies:* Three studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way, crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please use a narcotic antagonist such as naltrexone if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. (2) *Type of study:* Fed. *Design:* Single-dose, two-way, crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please use a narcotic antagonist such as naltrexone, if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. (3) *Type of study:* Sprinkle. *Design:* Single-dose, two-way, crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please use a narcotic antagonist such as naltrexone, if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. *Analytes to measure:* morphine and morphine-6-glucuronide *Bioequivalence based on (90% CI):* Morphine. *Waiver request of in vivo testing:* 20 mg, 30 mg, 50 mg, and 60 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Because of concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows: *Testing conditions:* 900 mL, 0.1 N HCl, apparatus I (basket) at 100 rpm, with and without the alcohol (see below): Test 1: 12 units tested according

to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours. Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on both strengths.

Mycophenolate Mofetil Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, randomized, two-treatment, two-period, two sequence, crossover in vivo. *Strength:* 250 mg. *Subjects:* Normal healthy males and females, general population. *Additional Comments:* (2) *Type of study:* Fed. *Design:* Single-dose, randomized, two-treatment, two-period, two sequence, crossover in vivo. *Strength:* 250 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Mycophenolate mofetil, and the active metabolite, mycophenolic acid (MPA) in plasma. *Bioequivalence based on (90% CI):* Mycophenolate mofetil. If mycophenolate mofetil plasma concentrations can be reliably measured and its pharmacokinetics accurately determined, please analyze the data for the parent compound using the confidence interval approach. The data for the active metabolite can be used as supportive evidence. However, if you can demonstrate that it is not possible to measure mycophenolate mofetil in plasma accurately and reliably, please analyze the metabolite using the confidence interval approach. *Waiver request of in vivo testing: Not applicable.*

Olsalazine Sodium Capsule/Oral. *Recommended studies:* One study. *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 250 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please use the lowest single dose possible to obtain accurate pharmacokinetic parameters for both olsalazine and mesalamine. Please enroll enough subjects to achieve adequate statistical power to demonstrate bioequivalence to the RLD. A pilot study may be necessary to assist in the determination of the appropriate number of subjects to enroll in the pivotal study. The number of subjects should be sufficient to allow for dropouts. You may also refer to Appendix C of the Guidance for Industry, "Statistical Approaches to Establishing Bioequivalence" at <http://www.fda.gov/cder/guidance/index.htm>. *Analytes to measure (in appropriate biological fluid):* Olsalazine and mesalamine in plasma. *Bioequivalence based on (90% CI):* Olsalazine and mesalamine. *Waiver request of in vivo testing: Not applicable.* In addition, please perform dissolution testing over a range of pH values comparing the test and reference products. Varying pH conditions should be studied to approximate the pH conditions that olsalazine sodium capsules will be subjected to in the GI tract. Therefore, the following pH conditions should be used using 12 dosage units of the test and reference products: *Apparatus:* USP apparatus I (basket). *Speed:* 100 rpm. *Medium:* 0.1N HCl; pH 4.5 buffer; pH 6.8 buffer. *Volume:* 900 mL *Sampling times:* 5, 10, 15, 20, 30, 45, and 60 minutes and until at least 80% of the labeled content is dissolved.

Omeprazole Delayed-Release Capsule/Oral. *Recommended studies:* Four studies (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fasting, sprinkle. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the RLD. (3) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (4) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 20 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Omeprazole in plasma. *Bioequivalence based on (90% CI):* Omeprazole. *Waiver request of in vivo testing:* 10 mg based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportional similarity of the formulations on 10- and 20-mg strengths, and (iii) acceptable in vitro dissolution testing of 10 mg and 20 mg strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.

Paricalcitol Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 4 µg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 4 µg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Paricalcitol in plasma. *Bioequivalence based on (90% CI):* Paricalcitol. *Waiver request of in vivo testing:* 2-µg, 1-µg tablets, based on (i) acceptable bioequivalence studies of the 4-µg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Phenytoin Sodium Extended-Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Single dose of 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Washout period of at least 14 days. The single dose studies for fasting and fed can be conducted as single dose, two-treatment, four periods, replicated design. The strength(s) designated in the Orange Book as the RLD should be used in the studies. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Singledose of 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. *Analytes to measure:* Phenytoin in plasma. *Bioequivalence based on (90% CI):* Phenytoin. *Waiver request of in vivo testing:* 200 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method. In addition to

the method above, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Phenytoin Sodium Extended-Capsule/Oral. *Recommended studies:* Four studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Single dose of 300 mg (3 × 100 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Washout period of at least 14 days. The single dose studies for fasting and fed can be conducted as single dose, two-treatment, four periods, replicated design. The strength(s) designated in the Orange Book as the RLD should be used in the studies. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Single dose of 300 mg (3 × 100 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. (3) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Single-dose of 300 mg (10 × 30 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. (4) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* Single dose of 300 mg (10 × 30 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. *Analytes to measure:* Phenytoin in plasma. *Bioequivalence based on (90% CI):* Phenytoin. *Waiver request of in-vivo testing:* Not applicable. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method. In addition to the method above, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Quinine Sulfate Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 324 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. Subjects with a QTc interval of >480 msec by ECG should also be excluded. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 324 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. *Analytes to measure (in appropriate biological fluid):* Quinine in plasma. *Bioequivalence based on (90% CI):* Quinine. *Waiver request of in vivo testing:* Not applicable.

Ramipril Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 10 mg.

Subjects: Normal healthy males and females, general population. *Additional comments:* Female subjects enrolled in the BE studies should not be pregnant, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 10 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Ramipril and the metabolite, ramiprilat in plasma. *Bioequivalence based on (90% CI):* Ramipril. If ramipril can be reliably measured, a confidence interval approach for bioequivalence determination should be used for ramipril. If ramipril cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for ramiprilat. *Waiver request of in-vivo testing:* 1.25 mg, 2.5 mg, and 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Ribavirin Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Ribavirin in plasma. *Bioequivalence based on (90% CI):* Ribavirin. *Waiver request of in-vivo testing:* Not applicable.

Rifampin Capsule/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Rifampin in plasma. *Bioequivalence based on (90% CI):* Rifampin. *Waiver request of in-vivo testing:* 150 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please submit separate applications for each strength. You may cross-refer the study submitted in the application for the higher strength to request waivers of in vivo testing for the lower strength. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method.

Ritonavir Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Ritonavir in plasma. *Bioequivalence based on (90% CI):* Ritonavir. *Waiver request of in-vivo testing:* Not applicable.

Saquinavir Mesylate Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 200 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 200 mg. *Subjects:* Normal healthy males

and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Saquinavir in plasma. *Bioequivalence based on (90% CI):* Saquinavir. *Waiver request of in-vivo testing:* Not applicable.

Sibutramine Hydrochloride Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 15 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Because of safety concerns, studies should not be conducted using doses higher than 15 mg. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 15 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure:* Sibutramine, and the major first-generation active (desmethyl) metabolites M1 and M2, using an achiral assay. *Bioequivalence based on (90% CI):* Sibutramine. If sibutramine can be reliably measured, a confidence interval approach for bioequivalence determination should be used for sibutramine. If sibutramine cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for major first-generation active (desmethyl) metabolites M1 and M2. *Waiver request of in vivo testing:* 5 mg and 10 mg based on (i) acceptable bioequivalence studies on the 15-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Stavudine Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 40 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Stavudine in plasma. *Bioequivalence based on (90% CI):* Stavudine. *Waiver request of in-vivo testing:* 15 mg, 20 mg, and 30 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) acceptable dissolution testing of the 15-, 20-, 30-mg, and 40-mg strengths, and (iii) proportional similarity in the formulations of the 15-, 20-, 30-, and 40-mg strengths.

Tacrolimus Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 5 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 5 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. *Analytes to measure (in appropriate biological fluid):* Tacrolimus in whole blood. *Bioequivalence based on (90% CI):* Tacrolimus. *Waiver request of in-vivo testing:* 0.5 mg and 1 mg, based on (i) acceptable bioequivalence studies on the 5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Tamsulosin Hydrochloride Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 0.4 mg. *Subjects:* Normal, healthy, males and females, general

population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 0.4 mg. *Subjects:* Normal, healthy, males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Tamsulosin in plasma. *Bioequivalence based on (90% CI):* Tamsulosin. *Waiver request of in vivo testing:* Not applicable.

Terazosin Hydrochloride Capsules/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 2 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Because of safety concerns, the studies should be conducted using the 2-mg strength. *Analytes to measure:* Terazosin in plasma. *Bioequivalence based on (90% CI):* Terazosin. *Waiver request of in vivo testing:* 1 mg, 5 mg, and 10 mg based on (i) acceptable bioequivalence studies on the 2-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Tipranavir Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 250 mg (please administer a 500-mg dose; 2 × 250 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 250 mg (please administer a 500-mg dose; 2 × 250 mg). *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure (in appropriate biological fluid):* Tipranavir in plasma. *Bioequivalence based on (90% CI):* Tipranavir. *Waiver request of in vivo testing:* Not applicable.

Tizanidine Hydrochloride Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 6 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 6 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Tizanidine in plasma. *Bioequivalence based on (90% CI):* Tizanidine. *Waiver request of in vivo testing:* 2 mg and 4 mg based on (i) acceptable bioequivalence studies on the 6-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Tolterodine Tartrate Extended-Release Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 4 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 4 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Tolterodine and the 5-hydroxymethyl tolterodine (5-OHM) metabolite in plasma. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. *Bioequivalence based on (90% CI):* Tolterodine. *Waiver*

request of in vivo testing: 2 mg, based on (i) acceptable bioequivalence studies on the 4-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Topiramate Sprinkle Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 25 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 25 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comments above. *Analytes to measure (in appropriate biological fluid):* Topiramate in plasma. *Bioequivalence based on (90% CI):* Topiramate. *Waiver request of in vivo testing:* 15 mg based on (i) acceptable bioequivalence studies on the 25-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Triamterene Capsule/Oral. *Recommended studies:* One study. *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Triamterene in plasma. *Bioequivalence based on (90% CI):* Triamterene. *Waiver request of in vivo testing:* 50 mg based on (i) acceptable bioequivalence study on the 100-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method.

Venlafaxine Hydrochloride Extended-Release Capsule/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 150 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Because of safety concerns, bioequivalence studies under fasting conditions are not recommended. (2) *Type of study:* Fed, Sprinkle. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 150 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the reference product under fed conditions. Please see comment above. *Analytes to measure:* Venlafaxine, and its metabolite O-desmethylvenlafaxine, in plasma. *Bioequivalence based on (90% CI):* Venlafaxine. *Waiver request of in vivo testing:* 37.5 mg and 75 mg based on (i) acceptable

bioequivalence studies on the 150-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Verapamil Hydrochloride Extended-Release Capsules/Oral. *Recommended studies:* Three studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 360 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 360 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (3) *Type of study:* Fasting, sprinkled over applesauce. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 360 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure:* Verapamil and its metabolite, norverapamil, in plasma. Please submit the metabolite data as supportive evidence of the comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. *Bioequivalence based on (90% CI):* Verapamil. *Waiver request of in vivo testing:* 120 mg, 180 mg, and 240 mg based on (i) acceptable bioequivalence studies on the 360-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4, and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Verapamil Hydrochloride Extended-Release Capsules/Oral. *Recommended studies:* Three studies. (1) *Type of study:* Fasting, bedtime (PM) dosing. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Bedtime (PM) dosing. (2) *Type of study:* Fed, morning (AM) dosing. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Morning (AM) dosing. (3) *Type of study:* Fasting, sprinkled over applesauce, morning (AM) dosing. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 300 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Morning (AM) dosing. *Analytes to measure:* Verapamil and its metabolite, norverapamil in plasma utilizing a validated LC/MS/MS method.

For norverapamil, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. The following sampling times are recommended: pre-dose and 2, 3, 4, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post dose. *Bioequivalence based on (90% CI):* Verapamil. *Waiver request of in vivo testing:* 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4, and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Zidovudine Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* (2) *Type of study:* Fed. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* *Analytes to measure (in appropriate biological fluid):* Zidovudine in plasma. *Bioequivalence based on (90% CI):* Zidovudine. *Waiver request of in vivo testing:* Not applicable. Please conduct dissolution testing on 12 dosage units each of the test and reference products using the USP method.

Ziprasidone Hydrochloride Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 20 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Given that the risk of QT prolongation is associated with higher doses and little, if any, such effect is expected with a 20-mg dose, a screening EKG to exclude subjects with prolonged QT, or other EKG abnormality is recommended, along with monitoring of vital signs and adverse events. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study:* Fed. *Design:* Single-dose, two-way crossover in vivo. *Strength:* 20 mg. *Subjects:* Normal healthy males and females, general population. *Additional comments:* Please see comment above. *Analytes to measure:* Ziprasidone in plasma. *Bioequivalence based on (90% CI):* Ziprasidone. *Waiver request of in vivo testing:* 40 mg, 60 mg, and 80 mg based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Zonisamide Capsules/Oral. *Recommended studies:* Two studies. (1) *Type of study:* Fasting. *Design:* Single-dose, two-treatment, two-period crossover in vivo. *Strength:* 100 mg. *Subjects:* Normal healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. *Additional comments:* Since zonisamide has a long

half-life, you can consider performing a parallel design study, truncating the AUC at 72 hours. If you choose to do a crossover design study, the washout period should be adequate to provide for drug elimination. Please verify that zonisamide's clearance has low intrasubject variability. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should

not be pregnant or lactating, and if applicable, should practice abstinence or contraception during the study. *Additional comments*: Please see *Additional comments* above. *Analytes to measure (in appropriate biological fluid)*: Zonisamide in serum *Bioequivalence based on (90% CI)*: Zonisamide. *Waiver request of in vivo testing*: 25 mg and 50 mg, based on acceptable (i) bioequivalence studies on the 100-mg capsule, and (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution Testing of Uncompressed Solid Dosage Forms

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Acetaminophen/butalbital/caffeine/codeine phosphate	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	03/04/2006
Acetaminophen/caffeine/dihydrocodeine bitartrate	Capsule	I (Basket)	100	Water	900	10, 20, 30, 45, and 60	01/03/2007
Acitretin	Capsule	I (Basket)	100	3% SLS in water, pH 9.6	900	10, 20, 30, and 45	01/12/2004
Acrivastine/pseudoephedrine HCl	Capsule	II (Paddle)	50	0.01 N HCl	900	5, 10, 15, and 30	01/12/2004
Amlodipine besylate/benazepril HCl	Capsule	I (Basket)	100	0.01 N HCl	500	10, 20, 30, 45, and 60	06/20/2007
Amphetamine ER	Capsule	II (Paddle)	50	750 mL of dilute HCl, pH 1.1 for the first 2 hr, then add 200 mL of 200 mM phosphate buffer, and adjust to pH 6 (w/HCl or NaOH) for the remainder	750 mL of dilute HCl, 200 mL of phosphate buffer	1, 2, 3, 4, and 6 hr	08/17/2006
Amprenavir	Capsule	II (Paddle)	50	0.1 N HCl	900	10, 15, 30, and 45	02/19/2008
Anagrelide HCl	Capsule	I (Basket)	100	0.1 N HCl	900	5, 10, 15, 30, and 45	01/14/2004
Aprepitant	Capsule	II (Paddle)	100	2.2% sodium dodecyl sulfate in distilled water	900	10, 15, 20, 30, and 45	01/20/2006
Aspirin/dipyridamole	Capsule	I (Basket)	100	0.01 N HCl for first hour, 0.1 M phosphate buffer, pH 5.5, thereafter	0-1 hr: 900 mL. 900 mL thereafter	Acid stage: 10, 20, 30, 45, and 60 min. Buffer stage: 1, 2, 5, and 7 hr	10/09/2007
Atazanavir sulfate	Capsule	II (Paddle)	50	0.025 N HCl	1000	10, 20, 30, and 45	01/20/2006
Atomoxetine HCl	Capsule	II (Paddle)	50	0.1 N HCl	1000	10, 20, 30, and 45	12/20/2005
Auranofin	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/15/2004
Balsalazide disodium	Capsule	II (Paddle) with sinker	50	pH 6.8 buffer	900	10, 20, 30, and 45	01/26/2006
Benzonatate	Capsule			Refer to USP			
Bexarotene	Capsule	II (Paddle)	50	Tier 1 medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5. Tier 2 medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme	900	15, 30, 45, and 60	08/17/2006

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Cefdinir	Capsule	II (Paddle)	50	Phosphate buffer, pH 6.8	900	5, 10, 15, 30, and 45	07/25/2007
Celecoxib	Capsule	II (Paddle)	100 mg and 200 mg: 50 rpm; 400 mg: 75 rpm	Tier 1 medium: 0.04 M tribasic sodium phosphate (pH 12) with 1% SLS. Tier 2 initial medium: 750 mL of simulated gastric fluid, USP (includes pepsin) At 20 min, 180 mL of 5% SLS solution and 70 mL of 1.2 N NaOH are added to initial medium. Tier 2 final medium: 1% SLS, pH 12	Tier 1: 1000 mL. Tier 2: 750 mL (initial) 1000 mL (final)	15, 30, 45, and 60	08/17/2006
Cevimeline HCl	Capsule	II (Paddle) with option to use a sinker	50	0.1 N HCl	900	5, 10, 15, and 30	01/26/2006
Cysteamine bitartrate	Capsule	I (Basket)	75	0.1 N HCl	900	10, 20, 30, and 45	01/24/2004
Danazol	Capsule			Refer to USP			06/18/2007
Dantrolene sodium	Capsule	I (Basket)	100	0.5% hyamine 10 times in water, adjust to pH 6.8 with 0.1 N KOH or 0.1 N HCl	900	10, 20, 30, 40, and 60	01/27/2004
Demeclocycline HCl	Capsule			Refer to USP			07/25/2007
Dicloxacillin sodium	Capsule			Refer to USP			06/18/2007
Diphenhydramine hydrochloride/ ibuprofen	Capsule	I (Basket)	100	200 mM phosphate buffer, pH 7.2	900	10, 20, 30, and 45	01/14/2008
Dofetilide	Capsule	I (Basket)	100	0.001 M HCL	900	10, 15, 30, and 45	01/20/2006
Dronabinol	Capsule	II (Paddle)	100 and 150	10% labrasol in water; (In addition, the USP capsule rupture test should also be conducted)	500	5, 10, 15, 30, 45, 60, and until at least 80% of the labeled content is released	01/31/2007
Efavirenz	Capsule	II (Paddle). A sinker may be used with justification if necessary.	50	1% sodium lauryl sulfate in water	900	15, 30, 45, and 60	03/22/2006
Emtricitabine	Capsule	II (Paddle)	50	Tier 1: 0.1 N HCl. Tier 2: 0.1 N HCl containing pepsin 750,000 USP units/L. Tier 2 is used after failure of tier 1 testing	900	10, 20, 30, and 45	12/16/2005
Fenofibrate	Capsule	II (Paddle)	75	Phosphate buffer w/2% between 80 and 0.1% pancreatin, pH 6.8	900	15, 30, 45, 60, 90, and 120	02/19/2008
Fexofenadine HCl	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	01/29/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Fluoxetine/olanzapine	Capsule	II (Paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	08/17/2006
Fluvastatin sodium	Capsule			Refer to USP			01/14/2008
Gabapentin	Capsule	II (Paddle)	50	0.06 N HCl	900	5, 10, 20, and 30	01/30/2004
Ganciclovir	Capsule	II (Paddle)	60	Water (deaerated)	900	10, 20, 30, 45, and 60	02/02/2004
Hydrochlorothiazide	Capsule	I (Basket)	100	0.1 N HCl	900	10, 20, 30, and 45	02/03/2004
Ibuprofen/diphenhydramine	Capsule	I (Basket)	100	Phosphate buffer (200 mM), pH 7.2	900	10, 20, 30, and 45	01/03/2007
Ibuprofen/pseudoephedrine HCl	Capsule	I (Basket)	150	Tier 1: 0.05 M phosphate buffer, pH 7.2. Tier 2: 0.05 M phosphate buffer, pH 7.2 with NMT 1750 USP protease units/L of 1 time USP pancreatin	900	10, 20, 30, and 45	03/04/2006
Imipramine pamoate	Capsule	I (Basket)	100	0.1 N HCl without pepsin and with 0.3% pepsin (addition of pepsin is recommended only when significant slow dissolution is observed)	900	30, 60, 90, 120, 150, and 180	01/14/2008
Indinavir sulfate	Capsule	II (Paddle)	50	0.1 M citrate buffer, pH 3.8	900	10, 15, 20, and 30	02/04/2004
Isradipine	Capsule	II (Paddle)	50	0.1% lauryl dimethylamine oxide (LDAO) in water	500	10, 20, 30, 45, and 60	02/25/2004
Itraconazole	Capsule	II (Paddle)	100	SGF without enzyme	900	10, 20, 30, 45, 60, and 90	02/04/2004
Ketoprofen	Capsule	II (Paddle)	50	0.05 M phosphate buffer pH 7.4	1000	10, 20, 30, and 45	07/25/2007
Lithium carbonate	Capsule			Refer to USP			07/25/2007
Metronidazole	Capsule	I (Basket)	100	0.1 N HCl	900	10, 20, 30, and 45	02/09/2004
Miglustat	Capsule	I (Basket)	100	0.1 N HCl	1000	10, 20, 30, and 45	01/03/2007
Mycophenolate mofetil	Capsule	II (Paddle)	40	0.1 N HCl	900	5, 10, 20, and 30	02/10/2004
Nicardipine HCl	Capsule	II (Paddle)	50	0.033 M citric acid buffer, pH 4.5	900	10, 20, 30, and 45	02/11/2004
Nimodipine	Capsule	II (Paddle)	50	0.5% SDS in water	900	10, 20, 30, and 45	04/09/2007
Nizatidine	Capsule			Refer to USP			01/14/2008
Olsalazine sodium	Capsule	I (Basket)	100	Phosphate buffer, pH 7.5	900	10, 20, 30, and 45	02/12/2004
Orlistat	Capsule	II (Paddle)	75	3% SLS in 0.5% sodium chloride, pH 6.0	900	10, 20, 30, 45, and 60	02/12/2004
Oseltamivir phosphate	Capsule	II (Paddle)	50	0.1 N HCl	900	5, 10, 20, and 30	01/03/2007
Paricalcitol	Capsule	I (Basket)	100	4 mg/mL (0.4%) lauryldimethylamine N-oxide (LDAO)	500	20, 30, 45, 60	06/18/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Paromomycin sulfate	Capsule	I (Basket)	50	0.05 M phosphate buffer, pH 6.8	900	5, 10, 15, 20, 30, and 45	02/13/2004
Phentermine HCl	Capsule			Refer to USP			01/14/2008
Phenytoin sodium	Capsule			Refer to USP			06/18/2007
Pregabalin	Capsule	II (Paddle)	50	0.06 N HCl	900	10, 20, 30, and 45	03/22/2006
Quinine sulfate	Capsule			Refer to USP			01/14/2008
Ramipril	Capsule	II (Paddle)	50	0.1 N HCl	500	10, 20, 30, and 45	02/18/2004
Ranitidine HCl	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	02/18/2004
Ribavirin	Capsule	I (Basket)	100	Water (deaerated)	900	10, 20, 30, and 45	02/18/2004
Rifampin	Capsule			Refer to USP			06/18/2007
Ritonavir	Capsule	II (Paddle)	50	0.1 N HCl with 25 mM polyoxyethylene 10 laurylether (POE10LE)	900	10, 20, 30, and 45	02/18/2004
Rivastigmine tartrate	Capsule	II (Paddle)	50	Water (deaerated)	500	10, 20, 30, and 45	01/03/2007
Saquinavir mesylate	Capsule			Refer to USP			09/13/2007
Sibutramine HCl	Capsule	II (Paddle)	50	0.05 M acetate buffer, pH 4.0	500	10, 20, 30, 45, and 60	02/25/2004
Stavudine	Capsule			Refer to USP			06/18/2007
Succimer	Capsule	II (Paddle)	50	0.01 N phosphoric acid	900	10, 20, 30, 45, 60, and 90	02/20/2004
Tacrolimus	Capsule	II (Paddle)	50	Hydroxypropyl cellulose solution (1 in 20,000). Adjust to pH 4.5 by phosphoric acid	900	30, 60, 90, and 120	02/20/2004
Tamsulosin HCl	Capsule	II (Paddle)	100	0-2 hr: 0.003% polysorbate 80, pH 1.2 2-8 hr: phosphate buffer, pH 7.2	500	1, 2, 3, 6, 8, and 10 hr	03/26/2007
Temazepam	Capsule			Refer to USP			01/14/2008
Temozolomide	Capsule	I (Basket)	100	Distilled water	500	10, 20, 30, and 45	01/03/2007
Terazosin HCl	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, 60, and 90	02/20/2004
Thalidomide	Capsule	II (Paddle)	100	1.5% (w/v) SLS (pH 3.0, adj w/HCl)	900	10, 20, 30, 60, and 90	03/04/2006
Tipranavir	Capsule	II (Paddle)	50	0.05 M phosphate buffer pH 6.8	900	15, 30, 45, and 60	12/03/2007
Tizanidine HCl	Capsule	II (Paddle)	50	0.01 N HCl	500	5, 10, 15, and 30	02/20/2004
Triamterene	Capsule			Refer to USP			06/18/2007
Trimipramine maleate	Capsule	I (Basket)	100	Water (deaerated)	1000	10, 20, 30, 45, 60, and 90	03/04/2006
Vancomycin hydrochloride	Capsule			Refer to USP			01/14/2008
Zaleplon	Capsule	II (Paddle)	75	Deionized water	900	5, 10, 20, and 30	01/03/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Zidovudine	Capsule			Refer to USP			06/18/2007
Zinc acetate	Capsule	II (Paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	02/19/2004
Ziprasidone HCl	Capsule	II (Paddle)	75	Tier 1: 0.05 M Na phosphate buffer, pH 7.5 + 2% SDS (w/w). Tier 2: 0.05 M Na phosphate buffer, pH 7.5 (700 mL) + 1% pancreatin. After 15-min incubation, add 200 mL of phosphate buffer containing 9% SDS	900	10, 20, 30, 45, and 60	03/04/2006
Zonisamide	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/03/2007
Didanosine	Capsule (delayed-release pellets)	I (Basket)	100	Acid stage: 0.1 N HCl. Buffer stage: 0.1 N HCl: 0.2 M tribasic sodium phosphate (3:1), pH 6.8	1000	Acid stage: 60, 90 and 120. Buffer stage: 10, 20, 30, 45, and 60	01/26/2004
Duloxetine HCl	Capsule (delayed-release pellets)	I (Basket)	100	Gastric challenge: 0.1 N HCl. Buffer medium: pH 6.8 phosphate buffer (USP)	1000	Acid stage: 120 min. Buffer stage: 15, 30, 45, 60, and 90 min	03/22/2006
Esomeprazole magnesium	Capsule (delayed-release pellets)	II (Paddle)	100	Acid stage: 0.1 N HCl. Buffer stage: sodium phosphate buffer, pH 6.8	Acid stage: 300. Buffer stage: 1000	Acid stage: 60, 90, and 120. Buffer stage: 10, 20, 30, 45, and 60	02/26/2004
Doxycycline	Capsule (delayed release)	II (Paddle)	75	Dilute HCl, pH 1.1 for 2 hr and then add 200 mL of 0.1 N NaOH in 200 mM phosphate buffer. Adjust pH to 6.0 using 2 N HCl and/or 2 N NaOH	Acid stage: 750. Buffer stage: 950.	0.5, 1, 2, 2.5, 3, and 4 hr	02/19/2008
Omeprazole	Capsule (delayed release)			Refer to USP			06/18/2007
Amphetamine aspartate/amphetamine sulfate/dextroamphetamine saccharate/dextroamphetamine sulfate	Capsule (extended release)	II (Paddle)	50	Dilute HCl, pH 1.1 for first 2 hr, then add 200 mL of 200 mM phosphate buffer and adjust to pH 6.0 for the remainder	0–2 hr: 750 mL. After 2 hr: 950 mL	0.5, 1, 2, 3, and 4 hr	07/25/2007
Carbamazepine	Capsule (extended release)	II (Paddle)	75	First 4 hr: Dilute acid, pH 1.1 with 1.8% <i>B</i> -cyclodextrin. After 4 hr: 50 mM phosphate buffer, pH 7.5 with 1.1% <i>B</i> -cyclodextrin.	First 4 hr: 600 mL. After 4 hr: 1000 mL	1, 2, 4, 8, and 10 hr	07/25/2007
Dexmethylphenidate HCl	Capsule (extended release)	I (Basket)	100	First 2 hr: 0.01 N HCl, Hours 2–10: phosphate buffer, pH 6.8	Acid stage: 500. Buffer stage: 500	0.5, 1, 2, 4, 6, and 10 hr	01/14/2008
Diltiazem HCl (AB2)	Capsule (extended release)			Refer to USP			02/19/2008

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Diltiazem HCl (AB3)	Capsule (extended release)			Refer to USP			02/19/2008
Diltiazem HCl (AB4)	Capsule (extended release)			Refer to USP			02/19/2008
Galantamine HBr	Capsule (extended release)	II (Paddle)	50	50 mM potassium dihydrogen phosphate buffer pH 6.5 comparative dissolution data should also be provided in 900 mL pH 0.1 HCl, pH 4.5 buffer, and water using apparatus II (Paddle) at 50 rpm.	900	1, 4, 10, and 12 hr	01/20/2006
Indomethacin	Capsule (extended release)			Refer to USP			07/25/2007
Methylphenidate HCl	Capsule (extended release)	I (Basket)	75	0–2 hr: 0.01 N HCl. 2–10 hr: phosphate buffer, pH 6.8.	0–2 hrs: 500. 2–10 hr: 500	0.5, 1, 3, 6, 8, and 10 hr	07/25/2007
Morphine sulfate	Capsule (extended release)	II (Paddle)	50	Phosphate buffer, pH 6.8	900	1, 3, 6, 12, 24 hr	01/14/2008
Morphine sulfate	Capsule (extended release)	I (Basket)	100	Acid stage: 0.1 N HCl. Buffer stage: phosphate buffer, pH 7.5	Acid stage: 600. Buffer stage: 500	1, 4, 6, 9, and 12 hr	01/14/2008
Propafenone HCl	Capsule (extended release)	II (Paddle)	50	0–2 hr: 0.08 N HCl. 2–15 hr: phosphate buffer, pH 6.8	900	1, 2, 4, 8, 10, 12, and 15 hr	03/11/2008
Propranolol HCl	Capsule (extended release)			Refer to USP			07/25/2007
Tolterodine tartrate	Capsule (extended release)	I (Basket)	100	Phosphate buffer (pH 6.8)	900	1, 3, 7 hr	06/18/2007
Venlafaxine HCl	Capsule (extended release)	I (Basket)	100	Water	900	2, 4, 8, 12, and 20 hr	01/03/2007
Verapamil HCl (100, 200, 300 mg)	Capsule (extended release)	I (Basket)	75	Water, pH 3.0 (adjusted with 0.1 N or 2 N HCl)	1000	1, 4, 8, 11, and 24 hr	01/03/2007
Cyclosporine (100 mg) (AB1)	Capsule (liquid filled)	II (Paddle)	75	0.1 N HCl containing 4 mg of <i>N,N</i> -dimethyldodecylamine- <i>N</i> -oxide per mL	1000	10, 20, 30, 45, 60, and 90	01/14/2008
Cyclosporine (25 mg) (AB1)	Capsule (liquid filled)	II (Paddle)	75	0.1 N HCl containing 4 mg of <i>N,N</i> -dimethyldodecylamine- <i>N</i> -oxide per mL	500	10, 20, 30, 45, 60, and 90	01/14/2008
Fenofibrate (AB)	Capsule (Micronized)	II (Paddle)	75	0.05 M SLS in water	1000	10, 20, 30, 40, and 60	01/29/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Dutasteride	Capsule (soft gelatin)	II (Paddle)	50	Tier 1: dissolution medium: 0.1 N HCl with 2% (w/v) sodium dodecyl sulfate (SDS) (900 mL). Tier 2: dissolution medium: 0.1 N HCl with pepsin (1.6 g/L, label activity 1:3000) (450 mL) for the first 25 min, followed by addition of 0.1 N HCl with SDS (4% w/v) (450 mL) for the remainder of the dissolution test.	900	15, 30, 45, and 60	01/26/2006
Ibuprofen potassium (Soft gelatin cap gel—liquid filled)	Capsule (soft gelatin/liquid fill)	I (Basket)	150	Phosphate buffer, pH 7.2	900	5, 10, 20, and 30	02/04/2004
Lopinavir/ritonavir	Capsule (soft gelatin)	II (Paddle)	50	Tier 1: 0.05 M polyoxyethylene 10 lauryl ether with 10 mM sodium phosphate monobasic (pH 6.8). Tier 2: same as above with NMT 1750 USP units/L of pancreatin	900	10, 15, 30, and 45	06/18/2007
Divalproex sodium	Capsule (sprinkle)	II (Paddle)	50	0.05 M phosphate buffer, pH 7.5	500	2, 4, 6, 8, and 10 hr	03/04/2006
Topiramate	Capsule (sprinkle)	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	02/19/2004
Verapamil HCl (120, 180, 240, 360 mg)	Capsule (sustained release)	I (Basket)	75	Water, pH 3.0 (adjusted with 0.1 N or 2 N HCl)	1000	1, 4, 8, 11, and 24 hr	01/03/2007
Procarbazine HCl	Capsules	II (Paddle)	50	Water	900	10, 20, 30, 45, and 60	01/14/2008
Fluoxetine	Capsules (delayed release)			Refer to USP			07/25/2007
Nelfinavir mesylate	Powder for suspension	II (Paddle)	50	0.1 N HCl	900	5, 10, 15, 20, 30, and 45	09/13/2007
Omeprazole sodium bicarbonate	Powder for suspension (immediate release)	II (Paddle)	50	0.25 mM sodium phosphate buffer, pH 7.4	900	5, 10, 15, and 30	06/20/2007

Approved Excipients in Uncompressed Solid Dosage Forms

Ingredient	Dosage Form	Qty	Unit
Acacia	Oral; capsule, sustained action	11.77	mg
Acacia	Oral; powder, for oral suspension	64.8	%
Acacia	Oral; powder	80	%
Acacia syrup	Oral; capsule, sustained action	69.64	mg
Acesulfame potassium	Oral; powder, for suspension	0.9	%
Acesulfame potassium	Oral; powder, for oral solution	117	mg
Acetophenone	Oral; capsule, soft gelatin	0.01	mg
Acetylated monoglycerides	Oral; capsule, sustained action	0.593	mg
Acetylated monoglycerides	Oral; capsule, extended release	2.37	mg
Acetyltributyl citrate	Oral; capsule, enteric-coated pellets	7.6	mg
Acetyltributyl citrate	Oral; capsule, sustained action	18.98	mg
Alcohol	Oral; capsule	0.058	mg
Alcohol	Oral; capsule, soft gelatin	15.36	mg
Alcohol, dehydrated	Oral; capsule, soft gelatin	159.6	mg
Alcohol, dehydrated	Oral; capsule	200	mg
Alcohol, diluted	Topical; powder, for solution	40	%
Alginic acid	Oral; capsule	80	mg
Alpha-tocopherol	Oral; capsule	0.5	mg
Alpha-tocopherol	Oral; capsule, soft gelatin	5	mg
Aluminum stearate	Oral; capsule, sustained action	0.4	mg
Amberlite	Oral; capsule	4.86	mg
Amberlite IR-120	Oral; capsule, sustained action	12	mg
Ammonia solution, strong	Oral; capsule, sustained action	0.05	mg
Ammonio methacrylate copolymer	Oral; capsule, sustained action	81.1	mg
Ammonio methacrylate copolymer type A	Oral; capsule, extended release	4.2	mg
Ammonio methacrylate copolymer type B	Oral; capsule, extended release	37.48	mg
Ammonium glycyrrhizate	Oral; granule	3.125	mg
Anidrisorb 85/70	Oral; capsule	35.09	mg
Anidrisorb 85/70	Oral; capsule, soft gelatin liquid-filled	93.4	mg
Anidrisorb 85/70	Oral; capsule, soft gelatin	123	mg
Antifoam	Oral; capsule, sustained action	0.16	mg
Ascorbic acid	Oral; capsule	7	mg
Ascorbyl palmitate	Oral; capsule	12	mg
Aspartame	Oral; powder, for oral suspension	1	%
Aspartame	Oral; powder, for reconstitution	1.25	%

Ingredient	Dosage Form	Qty	Unit
Aspartame	Oral; powder, for suspension	2	%
Aspartame	Oral; powder, for solution	4.7	%
Aspartame	Oral; granule, for suspension	35	mg
Aspartame	Oral; powder	45	%
Aspartame	Oral; powder, for oral solution	233	mg
Beeswax	Oral; capsule	2	mg
Beeswax	Oral; capsule, sustained action	15.7857	mg
Beeswax	Oral; capsule, soft gelatin	16.8	mg
Bentonite	Topical; powder	66.64	%
Benzyl alcohol	Oral; capsule, sustained action	1.231	mg
Benzyl alcohol	Oral; capsule	15	mg
Benzyl benzoate	Oral; capsule	0.6084	mL
Beta-naphthol	Oral; capsule	0.3	mg
Betose	Oral; capsule	0.0487	mg
Butylated hydroxyanisole	Oral; capsule	0.08	mg
Butylated hydroxyanisole	Oral; capsule, soft gelatin	1	mg
Butylated hydroxytoluene	Oral; capsule	0.2	mg
Butylated hydroxytoluene	Oral; capsule, soft gelatin	0.25	mg
Butylparaben	Oral; capsule	0.002	mg
Calcium carbonate	Oral; capsule, sustained action	4	mg
Calcium carbonate	Oral; capsule, hard gelatin	62.84	mg
Calcium carbonate	Oral; capsule	349.9	mg
Calcium citrate	Oral; powder	42.9	%
Calcium phosphate, dibasic	Oral; capsule, sustained action	287.6	mg
Calcium phosphate, dibasic	Oral; capsule	401	mg
Calcium phosphate, dibasic, dihydrate	Oral; capsule	400	mg
Calcium phosphate, tribasic	Oral; capsule, sustained action	32.727	mg
Calcium silicate	Oral; capsule, soft gelatin	1.03	mg
Calcium stearate	Oral; capsule, hard gelatin	1	mg
Calcium stearate	Oral; powder	3	%
Calcium stearate	Oral; capsule	21.1	mg
Calcium stearate	Oral; capsule, sustained action	91.9	mg
Calcium sulfate	Oral; capsule, sustained action	1.54	mg
Calcium sulfate	Oral; capsule	74.68	mg
Calcium sulfate dihydrate	Oral; capsule	370	mg
Calcium sulfate hemihydrate	Oral; capsule	10	mg
Calcium sulfate, anhydrous	Oral; capsule	50	mg
Canola oil	Oral; capsule, soft gelatin	165.55	mg
Caprylic/Capric triglyceride	Oral; powder, for suspension	67.8	%
Caprylic/Capric triglyceride	Oral; capsule	140.56	mg
Caprylic/Capric triglyceride	Oral; capsule, soft gelatin	250	mg
Caramel	Oral; granule	2.5	mg
Carbomer 934p	Oral; capsule	14.2	mg

Ingredient	Dosage Form	Qty	Unit
Carbon black	Oral; capsule, sustained action	0.2	mg
Carboxymethyl starch	Oral; capsule	15	mg
Carboxymethylcellulose calcium	Oral; capsule, hard gelatin	36	mg
Carboxymethylcellulose calcium	Oral; capsule	70	mg
Carboxymethylcellulose sodium	Oral; powder, for solution	0.2625	%
Carboxymethylcellulose sodium	Oral; capsule, sustained action	0.469	mg
Carboxymethylcellulose sodium	Oral; powder, for suspension	2	%
Carboxymethylcellulose sodium	Oral; capsule, enteric-coated pellets	4.2	mg
Carboxymethylcellulose sodium	Oral; granule	25.7	mg
Carboxymethylcellulose sodium	Oral; capsule	160	mg
Carnauba wax	Oral; capsule, sustained action	0.75	mg
Carrageenan	Oral; capsule	0.1534	mg
Carrageenan	Oral; powder, for suspension	1.5	%
Carrageenan	Oral; granule, for reconstitution	6	mg
Carrageenan	Oral; granule, for suspension	20.15	mg
Castor oil	Oral; capsule	0.03	mg
Castor oil	Oral; capsule, sustained action	1.756	mg
Castor oil	Oral; granule, for suspension	32	mg
Castor oil, hydrogenated	Oral; capsule	8	mg
Castor oil, hydrogenated	Oral; capsule, sustained action	410.82	mg
Cellacefate	Oral; capsule, sustained action	9.42	mg
Cellacefate	Oral; capsule, enteric-coated pellets	28.2	mg
Cellulose	Oral; capsule, hard gelatin	140	mg
Cellulose	Oral; capsule	405	mg
Cellulose acetate	Oral; capsule	18.08	mg
Cellulose microcrystalline, aqueous	Oral; capsule	47.85	mg
Cellulose microcrystalline, aqueous	Oral; capsule, hard gelatin	141	mg
Cellulose microcrystalline/Carboxymethylcellulose sodium	Oral; powder, for suspension	2.26	%
Cellulose microcrystalline/Carboxymethylcellulose sodium	Oral; powder, for oral suspension	2.5	%
Cellulose microcrystalline/Carboxymethylcellulose sodium	Oral; granule, for suspension	50	mg
Cellulose, microcrystalline	Oral; capsule, coated pellets	8.03	mg
Cellulose, microcrystalline	Oral; capsule, enteric-coated pellets	14	mg
Cellulose, microcrystalline	Oral; granule, for reconstitution	25	mg
Cellulose, microcrystalline	Oral; capsule, extended release	41.67	mg
Cellulose, microcrystalline	Oral; capsule (immed./comp. release), hard gelatin	44.33	mg
Cellulose, microcrystalline	Oral; powder, for suspension	58.65	%
Cellulose, microcrystalline	Oral; capsule, coated, soft gelatin	60	mg
Cellulose, microcrystalline	Oral; capsule, soft gelatin	105	mg
Cellulose, microcrystalline	Oral; capsule, hard gelatin	154.3	mg
Cellulose, microcrystalline	Oral; capsule, sustained action	186	mg
Cellulose, microcrystalline	Oral; capsule, sustained action, hard gelatin	282.6	mg
Cellulose, microcrystalline	Oral; capsule	363.75	mg
Cellulose, microcrystalline	Oral; granule, enteric coated	789.6	mg

Ingredient	Dosage Form	Qty	Unit
Cellulose, microcrystalline 101	Oral; capsule	39.1	mg
Cellulose, powder	Oral; capsule	170	mg
Cetyl alcohol	Oral; capsule, enteric-coated pellets	1	mg
Cetylpyridinium chloride	Oral; capsule, soft gelatin	0.0043	mg
Cetylpyridinium chloride	Oral; capsule, sustained action	0.02	mg
Cetylpyridinium chloride	Oral; capsule	1.5	mg
Chartreuse-colored spheres	Oral; capsule, sustained action	35.14	mg
Citric acid	Oral; for suspension	0.1	%
Citric acid	Oral; powder, for reconstitution	0.25	%
Citric acid	Oral; capsule, soft gelatin	1	mg
Citric acid	Oral; capsule, enteric-coated pellets	4.9	mg
Citric acid	Oral; granule, for oral suspension	4.9	mg
Citric acid	Oral; granule, for reconstitution	6	mg
Citric acid	Oral; granule	6.25	mg
Citric acid	Oral; powder, for oral suspension	8.1	%
Citric acid	Oral; granule, for suspension	9.1	mg
Citric acid	Oral; powder	9.5	%
Citric acid	Oral; capsule, extended release	18.8	mg
Citric acid	Oral; capsule, sustained action, hard gelatin	18.8	mg
Citric acid	Oral; capsule	30.75	mg
Citric acid	Oral; powder, for suspension	60	%
Citric acid, hydrous	Oral; granule, for suspension	14.1	mg
Coconut oil, fractioned	Oral; capsule, soft gelatin	99.77	mg
Coconut oil, fractioned	Oral; capsule	124.9497	mg
Compressible sugar	Oral; powder, for oral suspension	49.73	%
Compressible sugar	Oral; capsule, sustained action	75	mg
Compressible sugar	Oral; capsule	270	mg
Corn glycerides	Oral; capsule, soft gelatin	344	mg
Corn oil	Oral; capsule, soft gelatin	416	mg
Corn oil	Oral; capsule	918	mg
Corn oil PEG-6 esters	Oral; capsule, soft gelatin	300	mg
Cottonseed oil, hydrogenated	Oral; capsule	15	mg
Cottonseed oil, hydrogenated	Oral; capsule, sustained action	58	mg
Croscarmellose sodium	Oral; capsule, enteric-coated pellets	20	mg
Croscarmellose sodium	Oral; capsule, hard gelatin	20	mg
Croscarmellose sodium	Oral; capsule (immed./comp. release), hard gelatin	30	mg
Croscarmellose sodium	Oral; granule, for suspension	35.3	mg
Croscarmellose sodium	Oral; capsule	50	mg
Croscarmellose sodium	Oral; granule, for reconstitution	143.5	mg
Crospovidone	Oral; powder, for suspension	5	%
Crospovidone	Oral; capsule, sustained action	10.71	mg
Crospovidone	Oral; capsule, coated, soft gelatin	14	mg
Crospovidone	Oral; capsule	30	mg

Ingredient	Dosage Form	Qty	Unit
Crospovidone	Oral; capsule, hard gelatin	70	mg
Crospovidone	Oral; capsule, enteric-coated pellets	75	mg
Crospovidone	Oral; granule, for oral suspension	75	mg
D&C green no. 4	Oral; capsule	40	mg
D&C green no. 5	Oral; capsule, sustained action	0.0029	mg
D&C red no. 28	Oral; powder, for suspension	0.07	%
D&C red no. 28	Oral; capsule	0.2241	mg
D&C red no. 3 lake	Oral; capsule	0.005	mg
D&C red no. 30 lake	Oral; capsule, enteric-coated pellets	0.3	mg
D&C red no. 30 lake	Oral; powder	0.3	%
D&C red no. 30 lake	Oral; granule, for suspension	0.85	mg
D&C red no. 33	Oral; capsule, soft gelatin	0.0001	mg
D&C red no. 33	Oral; capsule, soft gelatin liquid-filled	0.0113	mg
D&C red no. 33	Oral; capsule, sustained action	0.134	mg
D&C red no. 33	Oral; capsule	0.39	mg
D&C red no. 40	Oral; capsule, sustained action	0.2	mg
D&C yellow no. 10	Oral; capsule, coated pellets	0.0145	mg
D&C yellow no. 10	Oral; capsule, coated, soft gelatin	0.047	mg
D&C yellow no. 10	Oral; capsule, enteric-coated pellets	0.0525	mg
D&C yellow no. 10	Oral; capsule (immed./comp. release), soft gelatin, perle	0.09	mg
D&C yellow no. 10	Oral; capsule, sustained action	0.491	mg
D&C yellow no. 10	Oral; powder	0.6	%
D&C yellow no. 10	Oral; capsule, soft gelatin	1.51	mg
D&C yellow no. 10	Oral; capsule	331	mg
D&C yellow no. 10–aluminum lake	Oral; capsule, sustained action	0.22	mg
D&C yellow no. 10–aluminum lake	Oral; capsule, enteric-coated pellets	0.3	mg
D&C yellow no. 10–aluminum lake	Oral; capsule	1.2	mg
D&C yellow no. 10–aluminum lake	Oral; powder	4.3	%
D&C yellow no. 6	Oral; capsule, sustained action	0.2	mg
D&C yellow no. 6 lake	Oral; capsule, enteric-coated pellets	0.5	mg
DC antifoam AF trituration 1% on sucrose	Oral; powder, for solution	0.2625	%
Dibutyl phthalate	Oral; capsule, extended release	11.18	mg
Dibutyl sebacate	Oral; capsule, enteric-coated pellets	0.893	mg
Dibutyl sebacate	Oral; capsule, sustained action	8.82	mg
Dibutyl sebacate	Oral; granule, enteric coated	43.2	mg
Diethyl phthalate	Oral; capsule, sustained action	3.6	mg
Diethyl phthalate	Oral; capsule, extended release	5.93	mg
Diethyl phthalate	Oral; capsule, enteric-coated pellets	12	mg
Dimethicone 350	Oral; capsule, sustained action	0.114	mg
Dimethicone 350	Oral; capsule	3.7	mg
Docosate sodium	Oral; capsule, sustained action	0.001	mg
Docosate sodium	Oral; capsule, hard gelatin	0.64	mg
Docosate sodium	Oral; capsule	8.2	mg

Ingredient	Dosage Form	Qty	Unit
Docusate sodium/Sodium benzoate	Oral; capsule	85	mg
Dye blue #1	Oral; capsule	0.027	mg
Dye casing 27-75	Oral; powder, for suspension	0.0014	%
Dye chromatone	Oral; capsule	29.6	mg
Dye DC red #27 lake	Oral; capsule	1.31	mg
Dye DC red #33 lake	Oral; capsule	0.0046	mg
Dye FDC yellow #10 lake	Oral; capsule, sustained action	0.28	mg
Dye FDC yellow #6 ht lake	Oral; capsule	0.8	mg
Dye yellow #62	Oral; capsule	5.1	mg
Edetate calcium disodium	Oral; powder, for solution	0.022	%
Edetate calcium disodium	Oral; capsule	0.272	mg
Edetate disodium	Topical; powder, for solution	0.01	%
Edetate disodium	Oral; powder, for suspension	0.06	%
Edetate disodium	Oral; capsule	1	mg
Edetate disodium	Oral; capsule, soft gelatin	1.004	mg
Edetate sodium	Oral; capsule, soft gelatin	1	mg
Ethyl acetate	Oral; capsule, sustained action	382.257	mg
Ethyl vanillin	Oral; capsule, coated, soft gelatin	0.124	mg
Ethyl vanillin	Oral; capsule	0.341	mg
Ethyl vanillin	Oral; capsule, soft gelatin	0.64	mg
Ethylcellulose	Oral; capsule	6	mg
Ethylcellulose	Oral; capsule, extended release	25.2	mg
Ethylcellulose	Oral; capsule, sustained action, hard gelatin	27.04	mg
Ethylcellulose	Oral; capsule, sustained action	39.2	mg
Ethylcellulose	Oral; granule, for suspension	85	mg
Ethylene glycol monoethyl ether	Oral; capsule	0.009	mg
Ethylparaben sodium	Oral; capsule, soft gelatin	1.004	mg
Eudragit E 100	Oral; capsule, sustained action	1.63	mg
Eudragit L 100	Oral; capsule, sustained action	22.08	mg
Eudragit L 100	Oral; capsule, enteric-coated pellets	93.36	mg
Eudragit L 30 D	Oral; capsule, sustained action	2.16	mg
Eudragit L 30 D	Oral; capsule, enteric-coated pellets	28	mg
Eudragit L 30D - 55	Oral; capsule, sustained action, hard gelatin	10.9	mg
Eudragit L 30D - 55	Oral; capsule, extended release	40.414	mg
Eudragit L 30D - 55	Oral; capsule, sustained action	48.1	mg
Eudragit L 30D - 55	Oral; capsule	75.18	mg
Eudragit L 30D - 55	Oral; capsule, enteric-coated pellets	80.36	mg
Eudragit NE 30 D	Oral; capsule, extended release	30.062	mg
Eudragit NE 30 D	Oral; capsule, enteric-coated pellets	93.36	mg
Eudragit NE 30 D	Oral; capsule, sustained action	187.3	mg
Eudragit RL 12.5	Oral; powder, for suspension	3.22	%
Eudragit RL 12.5	Oral; capsule, sustained action	25.59	mg
Eudragit RL 30 D	Oral; capsule, sustained action, hard gelatin	4.2	mg

Ingredient	Dosage Form	Qty	Unit
Eudragit RL 30 D	Oral; capsule, sustained action	4.706	mg
Eudragit RS 30 D	Oral; capsule, extended release	35.7	mg
Eudragit RS 30 D	Oral; capsule, sustained action	91.88	mg
Eudragit S 100	Oral; capsule, sustained action	28.38	mg
Fatty acid esters, saturated	Oral; capsule, enteric-coated pellets	0.2	mg
FD&C blue no. 1	Oral; capsule, coated pellets	0.0002	mg
FD&C blue no. 1	Oral; capsule, soft gelatin liquid-filled	0.017	mg
FD&C blue no. 1	Oral; powder, for suspension	0.02	%
FD&C blue no. 1	Oral; capsule, soft gelatin	0.04	mg
FD&C blue no. 1	Oral; capsule, sustained action	0.9	mg
FD&C blue no. 1	Oral; capsule, hard gelatin	3.708	mg
FD&C blue no. 1	Oral; capsule	26.3	mg
FD&C blue no. 1–aluminum lake	Oral; capsule	0.0412	mg
FD&C blue no. 1–aluminum lake	Oral; capsule, sustained action	0.095	mg
FD&C blue no. 1–aluminum lake	Oral; capsule, enteric-coated pellets	4	mg
FD&C blue no. 2	Oral; capsule, hard gelatin	0.0114	mg
FD&C blue no. 2	Oral; capsule, sustained action	0.03	mg
FD&C blue no. 2	Oral; capsule, delayed action	0.0769	mg
FD&C blue no. 2	Oral; capsule	0.218	mg
FD&C blue no. 2–aluminum lake	Oral; capsule	0.218	mg
FD&C blue no. 2–aluminum lake	Oral; capsule, enteric-coated pellets	3.5	mg
FD&C green no. 3	Oral; capsule, sustained action	0.067	mg
FD&C green no. 3	Oral; capsule, soft gelatin	0.17	mg
FD&C green no. 3	Oral; capsule, enteric-coated pellets	0.2192	mg
FD&C green no. 3	Oral; capsule	40	mg
FD&C red no. 2	Oral; capsule, soft gelatin	0.092	mg
FD&C red no. 2	Oral; capsule, sustained action	0.1	mg
FD&C red no. 2	Oral; capsule	0.101	mg
FD&C red no. 28	Oral; capsule	0.004	mg
FD&C red no. 3	Oral; powder, for oral suspension	0.008	%
FD&C red no. 3	Oral; powder, for suspension	0.1	%
FD&C red no. 3	Oral; capsule, soft gelatin	0.217	mg
FD&C red no. 3	Oral; granule	0.25	mg
FD&C red no. 3	Oral; capsule, sustained action	0.58	mg
FD&C red no. 3	Oral; capsule	59.16	mg
FD&C red no. 33	Oral; capsule	262	mg
FD&C red no. 3–aluminum lake	Oral; powder, for suspension	0.03	%
FD&C red no. 3–aluminum lake	Oral; capsule, sustained action	0.29	mg
FD&C red no. 3–aluminum lake	Oral; granule	50	mg
FD&C red no. 4	Oral; capsule	0.64	mg
FD&C red no. 40	Oral; powder, for oral suspension	0.003	%
FD&C red no. 40	Oral; capsule, coated, soft gelatin	0.0125	mg
FD&C red no. 40	Oral; powder, for reconstitution	0.0292	%

Ingredient	Dosage Form	Qty	Unit
FD&C red no. 40	Oral; powder, for suspension	0.0375	%
FD&C red no. 40	Oral; powder	0.05	%
FD&C red no. 40	Oral; capsule, soft gelatin	0.52	mg
FD&C red no. 40	Oral; powder, for solution	1.3325	%
FD&C red no. 40	Oral; capsule, sustained action	1.36	mg
FD&C red no. 40	Oral; capsule	73.2	mg
FD&C red no. 40–aluminum lake	Oral; powder, for oral suspension	0.008	%
FD&C red no. 40–aluminum lake	Oral; powder, for suspension	0.01	%
FD&C red no. 40–aluminum lake	Oral; capsule, sustained action	0.05	mg
FD&C red no. 40–aluminum lake	Oral; powder	0.1	%
FD&C yellow no. 10	Oral; capsule, sustained action	0.2	mg
FD&C yellow no. 10	Oral; capsule	0.34	mg
FD&C yellow no. 5	Oral; capsule, sustained action	0.065	mg
FD&C yellow no. 5	Oral; capsule, enteric-coated pellets	0.12	mg
FD&C yellow no. 5	Oral; capsule	652	mg
FD&C yellow no. 5–aluminum lake	Oral; capsule	0.09	mg
FD&C yellow no. 6	Oral; capsule, coated pellets	0.0017	mg
FD&C yellow no. 6	Oral; powder, for suspension	0.04	%
FD&C yellow no. 6	Oral; capsule, soft gelatin	0.8	mg
FD&C yellow no. 6	Oral; powder	2	%
FD&C yellow no. 6	Oral; capsule, sustained action	4.5	mg
FD&C yellow no. 6	Oral; capsule	327.6	mg
FD&C yellow no. 6–aluminum lake	Oral; powder, for suspension	0.032	%
FD&C yellow no. 6–aluminum lake	Oral; powder	0.15	%
FD&C yellow no. 6–aluminum lake	Oral; capsule, sustained action	0.24	mg
FD&C yellow no. 6–aluminum lake	Oral; capsule	0.385	mg
FD&C yellow no. 6–aluminum lake	Oral; capsule, enteric-coated pellets	1.25	mg
Ferric oxide	Oral; capsule	0.63	mg
Ferric oxide	Oral; capsule, enteric-coated pellets	2	mg
Ferric oxide, red	Oral; capsule, soft gelatin	2.28	mg
Ferric oxide, red	Oral; capsule	2.64	mg
Ferric oxide, yellow	Oral; granule, for reconstitution	0.25	mg
Ferric oxide, yellow	Oral; capsule	1.05	mg
Ferric oxide, yellow	Oral; capsule, soft gelatin	1.23	mg
Ferric oxide, yellow	Oral; capsule, enteric-coated pellets	1.8	mg
Ferric oxide, yellow	Oral; granule, for oral suspension	1.8	mg
Ferric oxide, yellow	Oral; capsule, sustained action	3.04	mg
Ferric oxide, brown	Oral; capsule	0.0983	mg
Ferric oxide, brown	Oral; capsule, soft gelatin	0.7	mg
Ferrosoferric oxide	Oral; capsule, soft gelatin	0.3	mg
Ferrosoferric oxide	Oral; capsule	0.82	mg
Ferrosoferric oxide	Oral; capsule, sustained action	1.492	mg
Flavor aromalok 182608	Oral; powder, for suspension	0.72	%

Ingredient	Dosage Form	Qty	Unit
Flavor banana 15223	Oral; powder, for oral suspension	23	%
Flavor banana 501013 ap0551	Oral; powder, for oral suspension	0.3906	%
Flavor black cherry 501027 ap0551	Oral; powder, for oral suspension	0.2344	%
Flavor cheri-beri PFC-8573	Oral; powder, for suspension	0.5	%
Flavor cherry 11929	Oral; powder, for oral suspension	14	%
Flavor cherry 594 S.D.	Oral; powder, for suspension	0.15	%
Flavor cherry 594 S.D.	Oral; granule, for reconstitution	7.5	mg
Flavor cherry-beri PFC-8573	Oral; granule	16.7	mg
Flavor cherry R-6556	Oral; powder, for suspension	0.05	%
Flavor cream EP-17688	Oral; powder, for suspension	0.08	%
Flavor creme de vanilla 28156	Oral; powder, for suspension	0.002	%
Flavor fruit gum 912	Oral; powder, for oral suspension	0.36	%
Flavor fruit gum 912	Oral; powder, for suspension	0.4	%
Flavor fruit gum 912	Oral; granule, for reconstitution	20	mg
Flavor grape 59.145/apo5.51	Oral; powder, for suspension	0.1	%
Flavor grape 59.266/apo5.51	Oral; powder, for suspension	0.1	%
Flavor grape micron ZD-3876	Oral; powder, for solution	0.3	%
Flavor kiwi S-718	Oral; powder	0.63	%
Flavor lemon spray V3938-1N1	Oral; powder, for oral solution	340	mg
Flavor mandarin 15228-71	Oral; granule, for suspension	70	mg
Flavor mask rbt-NV-7759	Oral; powder, for suspension	0.224	%
Flavor orange 249792	Oral; powder, for reconstitution	0.3	%
Flavor orange 57.458/apo5.51	Oral; powder, for oral suspension	6	%
Flavor orange 739 K (pb82)	Oral; powder, for reconstitution	0.625	%
Flavor orange 74016-71	Oral; granule, for suspension	70	mg
Flavor orange 9/79j839	Oral; powder, for reconstitution	0.225	%
Flavor perlarom strawberry	Oral; powder, for oral suspension	1.2	%
Flavor pharmaceutical 182608	Oral; powder, for suspension	0.72	%
Flavor prosweet 694	Oral; powder, for suspension	0.5	%
Flavor raspberry 954 K (bk77)	Oral; powder, for reconstitution	1.25	%
Flavor raspberry dy-04447	Oral; powder, for reconstitution	0.45	%
Flavor root beer 180339	Oral; powder, for suspension	0.042	%
Flavor strawberry 052311 ap0551	Oral; for suspension	0.5	%
Flavor strawberry 52.311ap	Oral; powder, for reconstitution	0.2	%
Flavor strawberry 52.311ap	Oral; powder, for suspension	0.5	%
Flavor strawberry 52312/ap	Oral; powder, for suspension	0.3	%
Flavor strawberry DY-04359	Oral; powder, for suspension	0.12	%
Flavor strawberry guarana 586.997/apo5.51	Oral; powder, for reconstitution	0.2	%
Flavor strawberry guarana 586.997/apo5.51	Oral; powder, for suspension	0.4	%
Flavor strawberry microseal	Oral; powder, for suspension	0.08	%
Flavor sweet-AM 918.005	Oral; granule, for suspension	30	mg
Flavor tutti frutti 51.880/apo5.51	Oral; powder, for suspension	2.04	%
Flavor tutti frutti permaseal 77919-31	Oral; powder, for solution	0.015	%

Ingredient	Dosage Form	Qty	Unit
Flavor tutti frutti WL-18481	Oral; powder, for suspension	0.6	%
Flavor vanilla 501441 ap2004	Oral; powder, for oral suspension	0.547	%
Flavor veralock bubble gum	Oral; powder, for suspension	0.167	%
Flavor wild cherry givaudan F-1813	Oral; powder, for solution	3.704	%
Flavor wild cherry givaudan F-1813	Oral; powder, for suspension	6.82	%
Flavor wild cherry NV-101-1489	Oral; powder, for suspension	0.05	%
Fluorescein	Oral; capsule	0.0068	mg
Fumaric acid	Oral; capsule, sustained action	150	mg
Gelatin	Oral; capsule (immed./comp. release), soft gelatin, perle	50	mg
Gelatin	Oral; capsule, hard gelatin	50.5	mg
Gelatin	Oral; capsule, enteric-coated pellets	60.7595	mg
Gelatin	Oral; capsule, coated pellets	65	mg
Gelatin	Oral; capsule, coated, soft gelatin	67.71	mg
Gelatin	Oral; capsule, extended release	96	mg
Gelatin	Oral; capsule, delayed action	97.012	mg
Gelatin	Oral; capsule, sustained action, hard gelatin	107	mg
Gelatin	Oral; capsule (immed./comp. release), soft gelatin	117.5	mg
Gelatin	Oral; capsule, soft gelatin liquid-filled	164	mg
Gelatin	Oral; capsule, sustained action	217.859	mg
Gelatin	Oral; capsule, soft gelatin	733	mg
Gelatin	Oral; capsule	756	mg
Gelucire 33/01	Oral; capsule, soft gelatin	114	mg
Glucose, liquid	Oral; pastille	826	mg
Glycerin	Oral; capsule (immed./comp. release), soft gelatin, perle	25	mg
Glycerin	Oral; capsule, coated, soft gelatin	31.2	mg
Glycerin	Oral; capsule (immed./comp. release), soft gelatin	75	mg
Glycerin	Oral; capsule, sustained action	132.31	mg
Glycerin	Oral; capsule	197.88	mg
Glycerin	Oral; capsule, soft gelatin	223.8	mg
Glyceryl behenate	Oral; capsule, enteric-coated pellets	1.7496	mg
Glyceryl behenate	Oral; capsule	5.7	mg
Glyceryl caprylate	Oral; capsule, soft gelatin	400	mg
Glyceryl caprylate/Caprato	Oral; capsule, soft gelatin	765	mg
Glyceryl distearate	Oral; capsule, sustained action	39.2	mg
Glyceryl stearate	Oral; capsule, enteric-coated pellets	0.95	mg
Glyceryl stearate	Oral; capsule, delayed action	1.896	mg
Glyceryl stearate	Oral; granule, for oral suspension	1.9	mg
Glyceryl stearate	Oral; capsule, sustained action	27	mg
Glycine	Oral; powder, for oral suspension	0.1	%
Glycine	Oral; powder, for suspension	1	%
Glycine	Oral; capsule, soft gelatin	3.6	mg
Glycine	Oral; powder, for solution	9.08	%
Glycine	Oral; capsule	25	mg

Ingredient	Dosage Form	Qty	Unit
Guar gum	Oral; for suspension	0.2	%
Guar gum	Oral; powder, for suspension	0.2	%
Guar gum	Oral; capsule	3.3	mg
Hydroxyethyl cellulose	Oral; capsule	2.98	mg
Hydroxymethyl cellulose	Oral; capsule, sustained action	1.6	mg
Hydroxymethyl cellulose	Oral; powder, for reconstitution	7.5	%
Hydroxypropyl cellulose	Oral; powder, for suspension	0.0004	%
Hydroxypropyl cellulose	Oral; capsule, coated pellets	3.96	mg
Hydroxypropyl cellulose	Oral; powder, for oral suspension	6.7	%
Hydroxypropyl cellulose	Oral; capsule, delayed action	8.88	mg
Hydroxypropyl cellulose	Oral; granule	10.4	mg
Hydroxypropyl cellulose	Oral; granule, for reconstitution	20	mg
Hydroxypropyl cellulose	Oral; granule, for suspension	31.4	mg
Hydroxypropyl cellulose	Oral; capsule	36	mg
Hydroxypropyl cellulose	Oral; granule, for oral suspension	39	mg
Hydroxypropyl cellulose	Oral; capsule, enteric-coated pellets	41.4	mg
Hydroxypropyl cellulose	Oral; capsule, sustained action	41.5	mg
Hydroxypropyl cellulose	Oral; capsule, hard gelatin	71.3	mg
Hydroxypropyl cellulose, low substituted	Oral; capsule, hard gelatin	6	mg
Hydroxypropyl cellulose, low substituted	Oral; capsule, enteric-coated pellets	20	mg
Hydroxypropyl methylcellulose 2208	Oral; capsule, sustained action, hard gelatin	2.771	mg
Hydroxypropyl methylcellulose 2208	Oral; capsule	80.25	mg
Hydroxypropyl methylcellulose 2208	Oral; capsule, sustained action	336	mg
Hydroxypropyl methylcellulose 2906	Oral; capsule	3.5	mg
Hydroxypropyl methylcellulose 2906	Oral; granule, enteric coated	33.2	mg
Hydroxypropyl methylcellulose 2910	Oral; powder, for reconstitution	1.593	%
Hydroxypropyl methylcellulose 2910	Oral; capsule, hard gelatin	2	mg
Hydroxypropyl methylcellulose 2910	Oral; powder, for suspension	3	%
Hydroxypropyl methylcellulose 2910	Oral; capsule, sustained action, hard gelatin	4.772	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, extended release	10.6	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, sustained action	10.88	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, enteric-coated pellets	13.82	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, delayed action	33.42	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule	40.5519	mg
Hydroxypropyl methylcellulose 4000	Oral; capsule, sustained action	100.4	mg
Hydroxypropyl methylcellulose acetate succinate	Oral; capsule	44.6	mg
Hydroxypropyl methylcellulose acetate succinate	Oral; capsule, delayed action	66.78	mg
Hydroxypropyl methylcellulose E5	Oral; capsule	9	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule, coated pellets	13.26	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule	16.8	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule, sustained action	19.63	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule, enteric-coated pellets	76.4	mg
Hydroxypropyl methylcellulose phthalate	Oral; granule, for suspension	302.4	mg

Ingredient	Dosage Form	Qty	Unit
Ink black GG-606	Oral; capsule	37	mg
Ink edible black	Oral; capsule	0.05	mg
Ink edible white	Oral; capsule	0.0005	mg
Ink red and aqua imprinting GG-827	Oral; capsule	95	mg
Ink red and caramel imprinting GG-825	Oral; capsule	62	mg
Ink red imprinting GG-826	Oral; capsule	78	mg
Ink white 21-K	Oral; capsule, sustained action	0.5	mg
Ink white A-8154	Oral; capsule	0.8	mg
Isopropyl alcohol	Oral; capsule	46.4	mg
Isopropyl alcohol	Oral; capsule, sustained action	392.8	mg
Kaolin	Oral; capsule, enteric-coated pellets	14.61	mg
Karion 83 (D-sorbitol content 19–25%)	Oral; capsule	55.79	mg
Lac resin	Oral; capsule, sustained action	31.2	mg
Lactic acid	Oral; capsule, soft gelatin liquid-filled	44	mg
Lactitol monohydrate	Oral; capsule	133	mg
Lactose	Oral; capsule, hard gelatin	100	mg
Lactose	Oral; capsule, coated pellets	102.44	mg
Lactose	Oral; capsule, soft gelatin	115.75	mg
Lactose	Oral; capsule, sustained action	120	mg
Lactose	Oral; capsule, enteric-coated pellets	135.2	mg
Lactose	Oral; capsule	530	mg
Lactose monohydrate	Oral; powder, for inhalation	1.25	%
Lactose monohydrate	Oral; capsule, sustained action, hard gelatin	18.8	mg
Lactose monohydrate	Oral; capsule, extended release	23.3	mg
Lactose monohydrate	Oral; capsule, sustained action	67	mg
Lactose monohydrate	Oral; capsule, hard gelatin	161.8	mg
Lactose monohydrate	Oral; capsule, coated, soft gelatin	178.90	mg
Lactose monohydrate	Oral; capsule	427.26	mg
Lactose, anhydrous	Oral; powder, for inhalation	0.1161	%
Lactose, anhydrous	Oral; granule, for reconstitution	15.688	mg
Lactose, anhydrous	Oral; capsule, coated, soft gelatin	71.906	mg
Lactose, anhydrous	Oral; capsule, enteric-coated pellets	117	mg
Lactose, anhydrous	Oral; capsule, sustained action	300.8	mg
Lactose, anhydrous	Oral; capsule	402.5	mg
Lactose, anhydrous	Oral; granule	433	mg
Lactose, hydrous	Oral; capsule, hard gelatin	141	mg
Lactose, hydrous	Oral; capsule, sustained action	147.6	mg
Lactose, hydrous	Oral; capsule	430.42	mg
Lauroyl polyoxylglycerides	Oral; capsule, hard gelatin	218	mg
Lauryl sulfate	Oral; capsule	0.15	mg
Lecithin	Oral; capsule, coated, soft gelatin	1	mg
Lecithin	Oral; powder, for suspension	3.34	%
Lecithin	Oral; capsule	15	mg

Ingredient	Dosage Form	Qty	Unit
Lecithin, soybean	Oral; capsule	5	mg
Lecithin, soybean	Oral; capsule, soft gelatin	20	mg
Lemon oil	Oral; capsule	5	mg
Lemon oil	Oral; capsule, soft gelatin	8.5	mg
Light mineral oil	Oral; capsule	0.8	mg
Lubritab	Oral; capsule	1.5	mg
Magnasweet 135	Oral; powder	20	%
Magnasweet 135	Oral; granule, for suspension	60	mg
Magnasweet 185	Oral; powder, for solution	53	%
Magnesium acetate	Oral; capsule	1.475	mg
Magnesium aluminum silicate	Oral; granule	8.3	mg
Magnesium aluminum silicate hydrate	Oral; granule, for suspension	11	mg
Magnesium aluminum silicate hydrate	Oral; granule	12.5	mg
Magnesium aluminum silicate hydrate	Oral; capsule	19.8	mg
Magnesium carbonate	Oral; capsule	19.44	mg
Magnesium carbonate	Oral; capsule, enteric-coated pellets	22.4	mg
Magnesium carbonate	Oral; capsule, sustained action	22.4	mg
Magnesium hydroxide	Oral; powder, for oral suspension	25	%
Magnesium oxide	Oral; capsule	10	mg
Magnesium silicate	Oral; capsule	40	mg
Magnesium stearate	Oral; powder, for inhalation	0.0028	%
Magnesium stearate	Oral; capsule, coated pellets	0.15	mg
Magnesium stearate	Oral; powder, for suspension	0.65	%
Magnesium stearate	Oral; granule	1.25	mg
Magnesium stearate	Oral; granule, for oral suspension	2.6	mg
Magnesium stearate	Oral; capsule, delayed action	2.604	mg
Magnesium stearate	Oral; capsule, coated, soft gelatin	3	mg
Magnesium stearate	Oral; capsule, soft gelatin	9	mg
Magnesium stearate	Oral; capsule, extended release	9.157	mg
Magnesium stearate	Oral; capsule (immed./comp. release), hard gelatin	10	mg
Magnesium stearate	Oral; capsule, hard gelatin	11.4	mg
Magnesium stearate	Oral; capsule, enteric-coated pellets	34.87	mg
Magnesium stearate	Oral; capsule, sustained action	100	mg
Magnesium stearate	Oral; capsule	256.4	mg
Magnesium sulfate, anhydrous	Oral; capsule	29.8	mg
Maleic acid	Oral; capsule	2	mg
Maltodextrin	Oral; powder, for suspension	19	%
Maltodextrin	Oral; powder	26.68	%
Maltodextrin	Oral; granule, for suspension	238.1	mg
Mannitol	Oral; powder, for suspension	20	%
Mannitol	Oral; powder, for reconstitution	29.362	%
Mannitol	Oral; capsule, sustained action	56.1	mg
Mannitol	Oral; capsule, hard gelatin	92	mg

Ingredient	Dosage Form	Qty	Unit
Mannitol	Oral; capsule, enteric-coated pellets	170.7	mg
Mannitol	Oral; capsule	297.2	mg
Mannitol	Oral; granule	484.2	mg
Mannitol	Oral; granule, for suspension	500	mg
Menthol	Oral; capsule	0.87	mg
Methacrylic acid copolymer	Oral; capsule, extended release	18.04	mg
Methacrylic acid copolymer	Oral; capsule, delayed action	37.916	mg
Methacrylic acid copolymer	Oral; capsule, sustained action	44.6	mg
Methacrylic acid copolymer	Oral; capsule, enteric-coated pellets	95.876	mg
Methacrylic acid copolymer	Oral; granule, enteric coated	430.8	mg
Methacrylic acid copolymer type A	Oral; capsule, extended release	37.48	mg
Methacrylic acid copolymer type B	Oral; capsule, extended release	5.39	mg
Methacrylic acid copolymer type C	Oral; capsule, delayed action	15.82	mg
Methacrylic acid copolymer type C	Oral; capsule, enteric-coated pellets	25.6	mg
Methacrylic acid copolymer type C	Oral; granule, for oral suspension	38	mg
Methyl acrylate – methyl methacrylate	Oral; capsule, extended release	37.5	mg
Methyl alcohol	Oral; capsule, sustained action	0.03	mL
Methyl salicylate	Oral; capsule	16	mg
Methylated spirits	Oral; capsule	0.101	mg
Methylcellulose	Oral; powder, for suspension	1.19	%
Methylcellulose	Oral; capsule, extended release	2.67	mg
Methylcellulose	Oral; capsule, sustained action	3.2	mg
Methylcellulose	Oral; capsule	13.5	mg
Methylene chloride	Oral; capsule	69.658	mg
Methylparaben	Oral; powder, for suspension	0.1	%
Methylparaben	Oral; capsule, coated, soft gelatin	0.156	mg
Methylparaben	Oral; powder, for solution	0.1575	%
Methylparaben	Oral; capsule, soft gelatin	0.48	mg
Methylparaben	Oral; capsule, sustained action	0.864	mg
Methylparaben	Oral; capsule	1	mg
Methylparaben	Oral; granule	50	mg
Methylparaben sodium	Oral; powder, for suspension	0.1	%
Microcrystalline wax	Oral; capsule, sustained action	6	mg
Mineral oil	Oral; capsule	5	mg
Mineral oil	Oral; capsule, sustained action	50	mg
Monosodium citrate	Oral; powder, for reconstitution	0.12	%
Monosodium citrate	Oral; powder, for suspension	2.2	%
N-Decyl-methyl sulfoxide	Topical; powder, for solution	0.125	%
Neutral oil	Oral; capsule, sustained action	240	mg
Nonpareil seeds	Oral; capsule, coated pellets	122.191	mg
Nonpareil seeds	Oral; capsule	299.9	mg
Nonpareil seeds	Oral; capsule, sustained action	823.5	mg
Nonpareil seeds blue	Oral; capsule	65	mg

Ingredient	Dosage Form	Qty	Unit
Nonpareil seeds orange	Oral; capsule, sustained action	35	mg
Nonpareil seeds white	Oral; capsule	43	mg
Oleic acid	Oral; capsule, soft gelatin	598.6	mg
Opacode S-1-1681 red	Oral; capsule	1	mg
Opacode S-1-7085 white	Oral; capsule, sustained action	0.028	mg
Opacode S-1-7085 white	Oral; capsule	0.0332	mg
Opacode S-1-8090 black	Oral; capsule	0.05	mg
Opacode S-1-8114 black	Oral; capsule	0.0275	mg
Opacode S-1-8114 black	Oral; capsule, sustained action	0.033	mg
Opacode S-1-8115 black	Oral; capsule, sustained action	0.0232	mg
Opacode S-1-8115 black	Oral; capsule	0.0275	mg
Opacode S-1-9460hv brown	Oral; capsule	0.15	mg
Opacode S-19-7014 white	Oral; capsule, sustained action	0.5	mg
Opadry 03F12920 yellow	Oral; capsule	5.4	mg
Opadry II Y-19-19054 clear	Oral; capsule, sustained action	45.14	mg
Opadry II Y-19-7483 clear	Oral; capsule, sustained action	5.74	mg
Opadry II Y-22-7719 white	Oral; capsule	4.44	mg
Opadry YS-1-17274 A beige	Oral; capsule, delayed action	1.49	mg
Opadry YS-1-17274 A beige	Oral; capsule, sustained action	9.1	mg
Opadry YS-1-19025-A clear	Oral; capsule, sustained action	2.76	mg
Opadry YS-1-7003 white	Oral; capsule	7	mg
Opadry YS-1-7003 white	Oral; capsule, extended release	10.7	mg
Opadry YS-1-7006 clear	Oral; capsule, extended release	4.29	mg
Opadry YS-1-7006 clear	Oral; capsule, sustained action	12.156	mg
Opadry YS-1-7552 gray	Oral; capsule	7.3	mg
Opalux AS 4151 blue	Oral; capsule	2.76	mg
Opalux AS 8050-L black	Oral; capsule	2	mg
Opaque white 001	Oral; capsule	78	mg
Opaque white 002	Oral; capsule	62	mg
Opaque white 535	Oral; capsule	45	mg
Opaque white 536	Oral; capsule	65	mg
Opaque white 538	Oral; capsule	38	mg
Opaspray K-1-1414 pink	Oral; capsule, sustained action	1.112	mg
Opaspray K-1-5024 red	Oral; capsule, sustained action	0.75	mg
Orange juice	Oral; powder	1.25	%
Palm oil—soybean oil, hydrogenated	Oral; capsule	4	mg
Parabens	Oral; capsule (immed./comp. release), soft gelatin, perle	0.16	mg
Paraffin	Oral; capsule, sustained action	50	mg
PD base-1000	Oral; capsule, sustained action	225	mg
Peanut oil	Oral; capsule, coated, soft gelatin	149	mg
Peanut oil	Oral; capsule	313.8	mg
Pectin	Oral; powder	25.5	%
Peg-8 caprylic/Capric glycerides	Oral; capsule, soft gelatin	70	mg

Ingredient	Dosage Form	Qty	Unit
Peppermint oil	Oral; capsule	1.01	mg
Peppermint oil	Oral; capsule, soft gelatin	1.02	mg
Petrolatum	Oral; capsule, sustained action	0.07	mg
Pharmaceutical glaze	Oral; capsule, coated pellets	0.429	mg
Pharmaceutical glaze	Oral; capsule	34.48	mg
Pharmaceutical glaze	Oral; capsule, sustained action	75.01	mg
Polacrillin potassium	Oral; capsule	23	mg
Poloxamer 188	Oral; powder, for oral suspension	0.34	%
Poloxamer 331	Oral; powder, for suspension	0.5286	%
Poloxamer 331	Oral; powder, for solution	2.5926	%
Poloxamer 407	Oral; powder, for oral suspension	12.6	%
Polyethylene	Oral; capsule	2	mg
Polyethylene glycol 20000	Oral; capsule, hard gelatin	13.5	mg
Polyethylene glycol 20000	Oral; capsule	18	mg
Polyethylene glycol 3350	Oral; capsule	27.2	mg
Polyethylene glycol 3350	Oral; capsule, soft gelatin	76.92	mg
Polyethylene glycol 400	Oral; capsule, extended release	1.7	mg
Polyethylene glycol 400	Oral; capsule, sustained action, hard gelatin	1.7	mg
Polyethylene glycol 400	Oral; capsule, coated, soft gelatin	103.55	mg
Polyethylene glycol 400	Oral; capsule	500	mg
Polyethylene glycol 400	Oral; capsule, soft gelatin	960.78	mg
Polyethylene glycol 4000	Oral; capsule, soft gelatin	15	mg
Polyethylene glycol 4000	Oral; capsule	449.6	mg
Polyethylene glycol 600	Oral; capsule, soft gelatin	324	mg
Polyethylene glycol 600	Oral; capsule	448.4	mg
Polyethylene glycol 600	Oral; capsule, soft gelatin liquid-filled	580.6	mg
Polyethylene glycol 6000	Oral; capsule	10	mg
Polyethylene glycol 6000	Oral; capsule, extended release	12	mg
Polyethylene glycol 6000	Oral; capsule, sustained action	17.46	mg
Polyethylene glycol 6000	Oral; capsule, hard gelatin	450	mg
Polyethylene glycol 8000	Oral; capsule, sustained action	1.39	mg
Polyethylene glycol 8000	Oral; capsule	10	mg
Polyethylene glycol 8000	Oral; capsule, hard gelatin	27.8	mg
Polygalacturonic acid	Oral; powder, for solution	14.5	%
Polyglyceryl-10 oleate	Oral; capsule, soft gelatin	199.9	mg
Polyglyceryl-3 oleate	Oral; capsule, soft gelatin	330.7	mg
Polyoxyl 35 castor oil	Oral; capsule	120	mg
Polyoxyl 35 castor oil	Oral; capsule, soft gelatin	599.4	mg
Polyoxyl 40 hydrogenated castor oil	Oral; capsule	200	mg
Polyoxyl 40 hydrogenated castor oil	Oral; capsule, soft gelatin	405	mg
Polyoxyl 40 stearate	Oral; capsule, hard gelatin	0.6	mg
Polyoxyl 40 stearate	Oral; capsule	2.4	mg
Polysorbate 20	Oral; powder, for suspension	0.026	%

Ingredient	Dosage Form	Qty	Unit
Polysorbate 20	Oral; capsule	56.25	mg
Polysorbate 80	Oral; powder, for suspension	0.2	%
Polysorbate 80	Oral; capsule, soft gelatin	0.41	mg
Polysorbate 80	Oral; capsule, extended release	0.528	mg
Polysorbate 80	Oral; capsule, delayed action	1.064	mg
Polysorbate 80	Oral; granule, for oral suspension	1.1	mg
Polysorbate 80	Oral; capsule, enteric-coated pellets	2	mg
Polysorbate 80	Oral; capsule, sustained action	2.6	mg
Polysorbate 80	Oral; powder	3	%
Polysorbate 80	Oral; granule	20	mg
Polysorbate 80	Oral; capsule	418.37	mg
Polyvinyl acetal	Oral; capsule, sustained action	5	mg
Potassium carbonate	Oral; capsule	27.69	mg
Potassium chloride	Oral; capsule	62	mg
Potassium hydroxide	Oral; capsule, soft gelatin	25.6	mg
Potassium hydroxide	Oral; capsule, soft gelatin liquid-filled	25.6	mg
Potassium phosphate, dibasic	Oral; powder, for suspension	5	%
Potassium phosphate, dibasic	Oral; capsule	30	mg
Potassium phosphate, monobasic	Oral; capsule, enteric-coated pellets	17	mg
Potassium sorbate	Oral; granule, for suspension	20	mg
Povidone K25	Oral; capsule	1.5	mg
Povidone K25	Oral; capsule, extended release	12.6	mg
Povidone K25	Oral; capsule, sustained action, hard gelatin	12.6	mg
Povidone K25	Oral; capsule, sustained action	17.79	mg
Povidone K29-32	Oral; capsule, extended release	6.19	mg
Povidone K29-32	Oral; granule	6.7	mg
Povidone K29-32	Oral; capsule, sustained action	10.05	mg
Povidone K29-32	Oral; capsule, enteric-coated pellets	14.2	mg
Povidone K29-32	Oral; capsule	15	mg
Povidone K30	Oral; powder, for suspension	0.26	%
Povidone K30	Oral; capsule, extended release	5.625	mg
Povidone K30	Oral; capsule, sustained action	6.875	mg
Povidone K30	Oral; capsule, hard gelatin	8	mg
Povidone K30	Oral; capsule, soft gelatin liquid-filled	17.7	mg
Povidone K30	Oral; capsule	20	mg
Povidone K30	Oral; capsule, soft gelatin	30	mg
Povidone K90	Oral; capsule, hard gelatin	5.95	mg
Povidone K90	Oral; capsule	16	mg
Povidone K90	Oral; capsule, extended release	18.8	mg
Povidone K90	Oral; capsule, sustained action, hard gelatin	18.8	mg
Povidone K90	Oral; granule, for suspension	32	mg
Propyl gallate	Oral; capsule, soft gelatin	2	mg
Propylene glycol	Oral; capsule, sustained action	0.7954	mg

Ingredient	Dosage Form	Qty	Unit
Propylene glycol	Oral; capsule, enteric-coated pellets	1.7	mg
Propylene glycol	Oral; powder	5.5	%
Propylene glycol	Oral; capsule, soft gelatin liquid-filled	17.7	mg
Propylene glycol	Oral; capsule	52	mg
Propylene glycol	Oral; capsule, soft gelatin	148.31	mg
Propylene glycol alginate	Oral; powder	50.248	%
Propylparaben	Oral; powder, for solution	0.0158	%
Propylparaben	Oral; capsule, coated, soft gelatin	0.041	mg
Propylparaben	Oral; powder, for suspension	0.08	%
Propylparaben	Oral; capsule, soft gelatin	0.12	mg
Propylparaben	Oral; capsule	0.21	mg
Propylparaben	Oral; capsule, sustained action	0.216	mg
Propylparaben sodium	Oral; powder, for suspension	0.1	%
Propylparaben sodium	Oral; capsule, soft gelatin	0.35	mg
Quatrimycin hydrochloride	Topical; powder, for solution	0.28	%
Saccharin	Oral; granule, for suspension	16	mg
Saccharin sodium	Oral; powder, for oral suspension	0.0666	%
Saccharin sodium	Oral; powder, for reconstitution	0.312	%
Saccharin sodium	Oral; capsule, soft gelatin	0.51	mg
Saccharin sodium	Oral; powder, for suspension	1.3354	%
Saccharin sodium	Oral; capsule	2.02	mg
Saccharin sodium	Oral; powder, for solution	53.32	%
Saccharin sodium, anhydrous	Oral; powder, for suspension	1.875	%
Sea spon	Oral; powder, for suspension	1.5	%
Sesame oil	Oral; capsule	162.5	mg
Shellac	Oral; capsule	24.83	mg
Shellac	Oral; capsule, enteric-coated pellets	29	mg
Shellac	Oral; capsule, sustained action	60	mg
Shellac P.V.P. solution no. 4	Oral; capsule, sustained action	87	mg
Silica, diatomaceous	Oral; capsule	3.4	mg
Silicon	Oral; capsule	15	mg
Silicon dioxide	Oral; powder, for oral suspension	0.4	%
Silicon dioxide	Oral; capsule, hard gelatin	2	mg
Silicon dioxide	Oral; powder, for reconstitution	4	%
Silicon dioxide	Oral; powder, for suspension	4.5	%
Silicon dioxide	Oral; capsule, sustained action	5.26	mg
Silicon dioxide	Oral; capsule, enteric-coated pellets	9.635	mg
Silicon dioxide	Oral; granule, for suspension	10	mg
Silicon dioxide	Oral; capsule	22	mg
Silicon dioxide, colloidal	Oral; for suspension	0.3	%
Silicon dioxide, colloidal	Oral; capsule, coated, soft gelatin	0.5	mg
Silicon dioxide, colloidal	Oral; capsule, enteric-coated pellets	0.6	mg
Silicon dioxide, colloidal	Oral; capsule, extended release	1.7	mg

Ingredient	Dosage Form	Qty	Unit
Silicon dioxide, colloidal	Oral; capsule, sustained action, hard gelatin	1.7	mg
Silicon dioxide, colloidal	Oral; capsule, soft gelatin	1.73	mg
Silicon dioxide, colloidal	Oral; powder, for reconstitution	2.5	%
Silicon dioxide, colloidal	Oral; granule, enteric coated	3.2	mg
Silicon dioxide, colloidal	Oral; powder, for suspension	5.5	%
Silicon dioxide, colloidal	Oral; capsule, hard gelatin	5.8	mg
Silicon dioxide, colloidal	Oral; capsule, sustained action	7.02	mg
Silicon dioxide, colloidal	Oral; powder	10	%
Silicon dioxide, colloidal	Oral; powder, for oral suspension	11	%
Silicon dioxide, colloidal	Oral; capsule	11.66	mg
Silicon dioxide, colloidal	Oral; granule, for reconstitution	16.25	mg
Silicon dioxide, colloidal	Oral; granule, for suspension	25	mg
Silicon dioxide, colloidal	Oral; granule	100	mg
Silicone	Oral; powder, for suspension	0.1	%
Silicone	Oral; capsule, sustained action	0.14	mg
Silicone	Oral; capsule, hard gelatin	0.42	mg
Silicone	Oral; capsule	10	mg
Silicone emulsion	Oral; capsule, sustained action	0.078	mg
Silicone emulsion	Oral; powder, for suspension	1.24	%
Simethicone	Oral; capsule, extended release	0.0446	mg
Simethicone	Oral; capsule, sustained action	0.062	mg
Simethicone	Oral; capsule, enteric-coated pellets	0.61	mg
Simethicone	Oral; powder, for suspension	0.666	%
Simethicone	Oral; granule	3.3	mg
Simethicone	Oral; capsule	5.7	mg
Simethicone	Oral; granule, effervescent	36	mg
Simethicone emulsion	Oral; powder, for suspension	0.5	%
Simethicone emulsion	Oral; capsule	14.4	mg
Simethicone emulsion	Oral; capsule, sustained action	15.63	mg
Sodium acetate	Oral; powder, for solution	9.93	%
Sodium alginate	Oral; capsule	80	mg
Sodium aminobenzoate	Oral; capsule	0.0017	mg
Sodium benzoate	Oral; powder, for reconstitution	0.1	%
Sodium benzoate	Oral; capsule, hard gelatin	0.11	mg
Sodium benzoate	Oral; for suspension	0.2	%
Sodium benzoate	Oral; capsule	0.3	mg
Sodium benzoate	Oral; powder, for oral suspension	3.6	%
Sodium benzoate	Oral; powder, for suspension	8	%
Sodium benzoate	Oral; powder, for solution	9.332	%
Sodium benzoate	Oral; granule, for reconstitution	10	mg
Sodium benzoate	Oral; granule, for suspension	10	mg
Sodium bicarbonate	Oral; capsule, hard gelatin	2	mg
Sodium bicarbonate	Oral; powder, for solution	8.72	%

Ingredient	Dosage Form	Qty	Unit
Sodium bicarbonate	Oral; capsule	26.5	mg
Sodium bisulfite	Topical; powder, for solution	0.1	%
Sodium bisulfite	Oral; capsule	0.36	mg
Sodium carbonate	Oral; capsule, sustained action	6	mg
Sodium carbonate hydrate	Oral; powder, for oral suspension	0.6	%
Sodium cellulose	Oral; capsule	150	mg
Sodium chloride	Oral; powder, for oral suspension	0.1	%
Sodium chloride	Oral; powder, for suspension	0.25	%
Sodium chloride	Oral; granule, for suspension	13.5	mg
Sodium citrate	Oral; powder, for reconstitution	0.04	%
Sodium citrate	Oral; granule, for reconstitution	0.7	mg
Sodium citrate	Oral; powder, for suspension	3.5	%
Sodium citrate	Oral; powder, for oral suspension	4.5	%
Sodium citrate	Oral; granule, for suspension	15	mg
Sodium citrate	Oral; granule	210.625	mg
Sodium citrate, anhydrous	Oral; for suspension	0.18	%
Sodium citrate, anhydrous	Oral; powder, for reconstitution	0.75	%
Sodium citrate, anhydrous	Oral; powder, for solution	4.8	%
Sodium citrate, anhydrous	Oral; powder, for suspension	6.67	%
Sodium citrate, anhydrous	Oral; granule	1250	mg
Sodium hydroxide	Oral; capsule	0.74	mg
Sodium laureth sulfate	Oral; capsule	3.5	mg
Sodium lauryl sulfate	Oral; powder, for suspension	0.066	%
Sodium lauryl sulfate	Oral; capsule, delayed action	0.118	mg
Sodium lauryl sulfate	Oral; capsule, enteric-coated pellets	0.6	mg
Sodium lauryl sulfate	Oral; capsule, sustained action	1.6	mg
Sodium lauryl sulfate	Oral; capsule, extended release	1.7	mg
Sodium lauryl sulfate	Oral; capsule, sustained action, hard gelatin	1.7	mg
Sodium lauryl sulfate	Oral; capsule, hard gelatin	6	mg
Sodium lauryl sulfate	Oral; capsule	15	mg
Sodium lauryl sulfate	Oral; capsule, soft gelatin	24	mg
Sodium metabisulfite	Topical; powder, for solution	0.1	%
Sodium metabisulfite	Oral; capsule	0.36	mg
Sodium phosphate	Oral; capsule	36	mg
Sodium phosphate, dibasic, anhydrous	Oral; capsule	300	mg
Sodium phosphate, dibasic, dihydrate	Oral; capsule, enteric-coated pellets	0.9	mg
Sodium phosphate, dibasic, heptahydrate	Oral; capsule, sustained action	92	mg
Sodium phosphate, dibasic, heptahydrate	Oral; capsule	500	mg
Sodium phosphate, monobasic, monohydrate	Oral; capsule	109.5	mg
Sodium phosphate, tribasic, anhydrous	Oral; powder, for oral suspension	35.3	%
Sodium phosphate, tribasic, hydrate	Oral; powder, for suspension	8.8	%
Sodium propionate	Oral; powder, for suspension	0.25	%
Sodium propionate	Oral; capsule	0.362	mg

Ingredient	Dosage Form	Qty	Unit
Sodium starch glycolate	Oral; capsule, soft gelatin	7.75	mg
Sodium starch glycolate	Oral; capsule, coated pellets	16.714	mg
Sodium starch glycolate	Oral; capsule, enteric-coated pellets	16.8	mg
Sodium starch glycolate	Oral; capsule, sustained action	18.6	mg
Sodium starch glycolate	Oral; capsule, hard gelatin	20	mg
Sodium starch glycolate	Oral; capsule	180	mg
Sodium stearyl fumarate	Oral; capsule	7.263	mg
Sodium thiosulfate	Oral; capsule	20	mg
Sorbitan monooleate	Oral; capsule, soft gelatin	153.9	mg
Sorbitan trioleate	Oral; capsule	0.0244	mL
Sorbitol	Oral; granule, for suspension	28	mg
Sorbitol	Oral; powder, for suspension	34.284	%
Sorbitol	Oral; capsule, soft gelatin	66.82	mg
Sorbitol	Oral; capsule	185.18	mg
Sorbitol solution	Oral; capsule	3.112	mg
Sorbitol solution	Oral; capsule, coated, soft gelatin	3.114	mg
Sorbitol solution	Oral; capsule, soft gelatin	28.9	mg
Sorbitol-glycerin blend	Oral; capsule	61.232	mg
Soybean oil	Oral; capsule, soft gelatin	227	mg
Soybean oil	Oral; capsule	263	mg
Soybean oil, hydrogenated	Oral; capsule	1	mg
Soybean oil, hydrogenated	Oral; capsule, soft gelatin	15.3	mg
Soybean oil, refined	Oral; capsule	101	mg
Starch	Oral; capsule, soft gelatin	15.5	mg
Starch	Oral; capsule, hard gelatin	33.5	mg
Starch	Oral; capsule, enteric-coated pellets	36.4	mg
Starch	Oral; capsule, sustained action	65.2	mg
Starch	Oral; capsule	605	mg
Starch 1500 pregelatinized	Oral; capsule	294	mg
Starch 1500, pregelatinized	Oral; capsule	365.1	mg
Starch 1551	Oral; capsule	30	mg
Starch 21	Oral; capsule	150	mg
Starch 7150	Oral; capsule	0.44	mg
Starch 825	Oral; capsule	217	mg
Starch 826	Oral; capsule	237	mg
Starch, corn	Oral; capsule, sustained action	27	mg
Starch, corn	Oral; capsule, hard gelatin	289.2	mg
Starch, corn	Oral; capsule	1135	mg
Starch, corn 21	Oral; capsule	125	mg
Starch, modified	Oral; powder, for suspension	0.2	%
Starch, modified	Oral; capsule	23	mg
Starch, pregelatinized	Oral; capsule, coated, soft gelatin	15	mg
Starch, pregelatinized	Oral; capsule, hard gelatin	128.75	mg

Ingredient	Dosage Form	Qty	Unit
Starch, pregelatinized	Oral; capsule, sustained action	141.75	mg
Starch, pregelatinized	Oral; capsule	600	mg
Starch, pregelatinized corn	Oral; capsule, coated, soft gelatin	27.75	mg
Starch, pregelatinized corn	Oral; capsule	195.9	mg
Starch, pregelatinized tapioca	Oral; capsule	100	mg
Starch, wheat	Oral; capsule, sustained action	0.75	mg
Stearic acid	Oral; capsule, coated, soft gelatin	3	mg
Stearic acid	Oral; capsule, sustained action	9.32	mg
Stearic acid	Oral; capsule, hard gelatin	15	mg
Stearic acid	Oral; powder, for suspension	24.06	%
Stearic acid	Oral; capsule	52	mg
Stear-O-wet M	Oral; capsule, hard gelatin	0.25	mg
Stear-O-wet M	Oral; capsule, coated, soft gelatin	1.5	mg
Stear-O-wet M	Oral; capsule, sustained action	6	mg
Stear-O-wet M	Oral; capsule	14	mg
Stearyl polyoxyglycerides	Oral; capsule	260	mg
Stearyl alcohol	Oral; capsule, sustained action	72	mg
Succinic acid	Oral; powder, for reconstitution	0.15	%
Sucralose	Oral; powder, for oral suspension	8	%
Sucrose	Oral; powder	25.61	%
Sucrose	Oral; powder, for solution	48.4	%
Sucrose	Oral; powder, for oral suspension	90.274	%
Sucrose	Oral; powder, for suspension	93.237	%
Sucrose	Oral; capsule, enteric-coated pellets	140.758	mg
Sucrose	Oral; capsule, delayed action	175.14	mg
Sucrose	Oral; capsule, extended release	396.14	mg
Sucrose	Oral; capsule	413.655	mg
Sucrose	Oral; capsule, sustained action	481.7	mg
Sucrose	Oral; granule, for suspension	1052.9	mg
Sucrose palmitate	Oral; powder, for suspension	1	%
Sucrose polyesters	Topical; powder, for solution	0.125	%
Sucrose stearate	Oral; capsule, extended release	31.835	mg
Sucrose stearate	Oral; capsule, sustained action	44.569	mg
Sugar confectioners	Oral; powder, for suspension	3.32	%
Sugar confectioners	Oral; capsule, sustained action	17.6	mg
Sugar confectioners	Oral; capsule	527.425	mg
Sugar fruit fine	Oral; powder, for suspension	27.52	%
Sugar/Starch insert granules	Oral; capsule, sustained action	254.49	mg
Surelease E-719010 clear	Oral; capsule, sustained action	37.44	mg
Surelease E-7-7050	Oral; capsule, enteric-coated pellets	28.331	mg
Talc	Oral; capsule, soft gelatin	0.1	mg
Talc	Oral; capsule, coated pellets	0.257	mg
Talc	Oral; capsule, sustained action, hard gelatin	16.7	mg

Ingredient	Dosage Form	Qty	Unit
Talc	Oral; capsule, enteric-coated pellets	17	mg
Talc	Oral; granule, for oral suspension	34	mg
Talc	Oral; capsule, extended release	39	mg
Talc	Oral; capsule, delayed action	70.46	mg
Talc	Topical; powder	98	%
Talc	Oral; capsule, hard gelatin	108	mg
Talc	Oral; capsule, sustained action	122.06	mg
Talc	Oral; granule, enteric coated	215.2	mg
Talc	Oral; capsule	220.4	mg
Talc triturate	Oral; capsule	1.92	mg
Tartaric acid	Oral; capsule	9	mg
Tartaric acid	Oral; capsule, sustained action	215.1	mg
Timing solution clear N-7	Oral; capsule, sustained action	26.2	mg
Titanium dioxide	Oral; capsule, extended release	0.7305	mg
Titanium dioxide	Oral; capsule, delayed action	0.7625	mg
Titanium dioxide	Oral; capsule, coated, soft gelatin	0.78	mg
Titanium dioxide	Oral; capsule, hard gelatin	0.8512	mg
Titanium dioxide	Oral; capsule, enteric-coated pellets	4.4	mg
Titanium dioxide	Oral; capsule, sustained action	4.4	mg
Titanium dioxide	Oral; capsule, soft gelatin	6	mg
Titanium dioxide	Oral; powder, for suspension	9	%
Titanium dioxide	Oral; granule, for suspension	35.7	mg
Titanium dioxide	Oral; powder, for oral suspension	40	%
Titanium dioxide	Oral; capsule	1387	mg
Tocophersolan	Oral; capsule, soft gelatin	282	mg
Tocophersolan	Oral; capsule	300	mg
Tragacanth	Oral; powder, for suspension	24	%
Triacetin	Oral; capsule	1.08	mg
Triacetin	Oral; capsule, coated pellets	1.205	mg
Triacetin	Oral; capsule, sustained action	2.76	mg
Triacetin	Oral; capsule, enteric-coated pellets	5.1	mg
Triethyl citrate	Oral; capsule, sustained action, hard gelatin	3.3	mg
Triethyl citrate	Oral; granule, for oral suspension	3.8	mg
Triethyl citrate	Oral; capsule, delayed action	3.848	mg
Triethyl citrate	Oral; capsule, sustained action	7.5	mg
Triethyl citrate	Oral; capsule	8.9	mg
Triethyl citrate	Oral; capsule, enteric-coated pellets	9.16	mg
Triethyl citrate	Oral; capsule, extended release	15.03	mg
Triglyceride, synthetic	Oral; capsule, soft gelatin	160	mg
Triglycerides, medium chain	Oral; capsule	159.9764	mg
Tristearin	Oral; capsule	225	mg
Tromethamine	Oral; capsule, soft gelatin	15	mg
Vanillin	Oral; powder, for suspension	0.666	%

Ingredient	Dosage Form	Qty	Unit
Vegetable oil	Oral; capsule	2	mg
Vegetable oil, hydrogenated	Oral; capsule	82	mg
Vegetable oil, hydrogenated	Oral; capsule, soft gelatin	82.8	mg
Vegetable shortening	Oral; capsule	10.56	mg
Vitamin E	Oral; capsule	1	mg
Vitamin E	Oral; capsule, soft gelatin	1	mg
Vitamin E acetate	Oral; capsule	2	mg
Wax, white	Oral; capsule	3	mg
Wax, white	Oral; capsule, sustained action	7.183	mg
Wax, white	Oral; capsule, soft gelatin	18.36	mg
Wax, yellow	Oral; capsule	2.72	mg
Xanthan gum	Oral; for suspension	0.075	%
Xanthan gum	Oral; powder, for reconstitution	2.5	%
Xanthan gum	Oral; powder, for solution	4.1	%
Xanthan gum	Oral; powder, for oral suspension	6.7	%
Xanthan gum	Oral; powder, for suspension	8	%
Xanthan gum	Oral; powder	9	%
Xanthan gum	Oral; granule, for suspension	15	mg
Xanthan gum	Oral; capsule, enteric-coated pellets	75	mg
Xanthan gum	Oral; granule, for oral suspension	75	mg
Zinc stearate	Oral; capsule	2.04	mg

Part II

Manufacturing Formulations

Uncompressed Solids Formulations

Acebutolol Hydrochloride Capsules

The capsules are provided in two dosage strengths, which contain 200 or 400 mg of acebutolol as the hydrochloride salt. The inactive ingredients present are D&C red No. 22, FD&C blue No. 1, FD&C yellow No. 6, gelatin, povidone,

starch, stearic acid, and titanium dioxide. The 200-mg dosage strength also contains D&C red No. 28; the 400-mg dosage strength also contains FD&C red No. 40.

Aceclofenac Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
50.00	1	Aceclofenac	50.00
165.83	2	Orange Flavor	165.83
3292.30	3	Sorbitol	3292.30
169.23	4	Lutrol F 68	169.23
169.23	5	Cremophor RH 40	169.23
QS	6	Deionized water	~2 kg

Manufacturing Directions

1. Granulate items 1 to 3 with a solution of items 4 to 6. Pass through a 0.8-mm screen, dry, and sieve again.
2. Fill 3.9 g in sachets corresponding to 50 mg aceclofenac.

Acetaminophen and Diphenhydramine Hydrochloride Hot Therapy Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
650.00	1	Acetaminophen (micronized)	650.00
250.00	2	Diphenhydramine hydrochloride	250.00
0.90	3	FD&C yellow dye No. 10 lake	0.90
0.0005	4	FD&C red dye No. 40	0.0005
18081.10	5	Castor sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Maize starch (dried)	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
240.00	11	Honey flavor (dry)	240.00
100.00	12	Lemon flavor (dry)	100.00
QS	13	Purified water	QS

Manufacturing Directions

- Mix items 1 and 2 well, then pass through 0.8-mm sieves.
- Mix items 3, 5, and 13 to make a clear solution.
- Add mixture of items 1 and 2 to second step mixture and mix well.
- Add this mixture to item 4 and mix. Take care to avoid lump formation.
- Dry in an oven and maintain a constant temperature.
- Sieve and add items 6 to 12. Mix well. Make sure all the solids added are in fine powder form.
- Fill 20 g of powder into sachets and seal.

Acetaminophen Capsules (500 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Acetaminophen powder	500.00
30.00	2	Sodium starch glycolate	30.00
1.00	3	Aerosil [®] 200	1.00
2.00	4	Magnesium stearate	2.00
17.00	5	Starch dried	15.00

Manufacturing Directions

- Charge all items after passing through No. 60 screen mesh and mix for 1 hour.
- Fill 550 mg in size 0 capsule.

Acetaminophen, Doxylamine, and Caffeine Effervescent

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
500.00	1	Acetaminophen powder	500.00
5.00	2	Doxylamine succinate	5.00
33.00	3	Caffeine (knoll)	33.00
391.00	4	Tartaric acid	391.00
417.00	5	Sodium hydrogen carbonate	417.00
6.00	6	Kollidon [®] 30	6.00
–	7	Isopropanol (or ethanol)	QS
30.00	8	Sodium citrate	30.00
707.00	9	Sugar	707.00

Manufacturing Directions

1. Granulate a mixture of items 1 to 5 with a solution of items 6 and 7. Dry at 60°C under vacuum conditions. Sieve and mix with items 8 and 9.
2. Fill 2.1 g in sachets at a maximum 30% of relative atmospheric humidity. If the solvent isopropanol is replaced by water, the granulation should be done in a fluidized bed.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
166.66	1	Acetaminophen fine powder	166.66
426.64	2	Sucrose fine powder	426.64
300.00	3	Kollidon [®] CL-M	300.00
23.33	4	Aspartame	23.33
16.66	5	Orange flavor	16.66
16.66	6	Strawberry flavor	16.66
40.00	7	Kollidon 30	40.00
250.00	8	Ethanol 96%	250.00

Manufacturing Directions

1. Granulate items 1 to 6 with solution made from items 7 and 8 and pass through a 0.8-mm sieve.
2. Fill 1.5 or 3.0 g in sachets (for 250- or 500-mg strength, respectively). The free-flowing granules are well dispersible in cold water. Suspend 1.5 or 3.0 g of the granules (=250 or 500 mg acetaminophen, respectively) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
192.30	1	Acetaminophen fine powder	192.30
500.00	2	Sorbitol instant (Merck)	500.00
192.30	3	Kollidon CL-M	192.30
27.00	4	Aspartame	27.00
19.23	5	Orange flavor	19.23
19.23	6	Strawberry flavor	19.23
11.53	7	Sodium citrate	11.53
11.53	8	Citric acid	11.53
30.76	9	Kollidon [®] 90 F	30.76
192.30	10	Ethanol 96%	192.30

Manufacturing Directions

- Granulate items 1 to 8 with a solution made from items 9 and 10 and pass through a 0.8-mm sieve.
- Fill 1.3 or 2.6 g in sachets (for 250- or 500-mg strength, respectively).
- The free-flowing granules are well dispersible in cold water. Suspend 1.2 or 2.6 g of the granules (=250 or 500 mg acetaminophen, respectively) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
500.00	1	Acetaminophen fine powder	500.00
1300.00	2	Sorbitol instant (Merck)	1300.00
500.00	3	Lutrol F 127	500.00
30.00	4	Citric acid powder	30.00
30.00	5	Sodium citrate	30.00
80.00	6	Kollidon 90 F	80.00
500.00	7	Ethanol 96%	500.00

Manufacturing Directions

- Granulate a mixture of items 1 to 5 in a solution of item 6 in item 7. Fill 2.44 g in sachets (=500 mg acetaminophen).
- The free-flowing granules are well dispersible in cold water.
- The taste of the suspension is only slightly bitter (2.44 g in a glass of water).

Acetaminophen, Pseudoephedrine Hydrochloride, Chlorpheniramine Hot Therapy Sachet

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
650.00	1	Acetaminophen micronized	650.00
60.00	2	Pseudoephedrine hydrochloride	60.00
4.00	3	Chlorpheniramine maleate	4.00
1.20	4	Dispersed orange	1.20
18081.10	5	Castor sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Cornstarch dried	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
400.00	11	Blood orange dry flavor	400.00
QS	12	Purified water	QS

Manufacturing Directions

- Items 1 and 2 are mixed well, followed by passing through sieves and adding to items 3 and 12 premixed and made into a clear solution.
- Take care to avoid lump formation.
- Dry in an oven.
- Sieve and add items 6 to 11. Mix well.
- Make sure all the solids added are in fine powder form. Fill 20 g powder into sachets and seal.

Acetaminophen, Pseudoephedrine Hydrochloride Hot Therapy Sachet

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
650.00	1	Acetaminophen micronized	650.00
260.00	2	Pseudoephedrine hydrochloride	260.00
0.90	3	FD&C yellow No. 10 lake	0.90
18081.10	4	Castor sugar	18081.10
200.00	5	Aspartame	200.00
250.00	6	Cornstarch dried	250.00
180.00	7	Citric acid	180.00
38.00	8	Sodium citrate	38.00
200.00	9	Sodium chloride	200.00
240.00	10	Apple dry flavor	240.00
100.00	11	Cinnamon dry flavor	100.00
QS	12	Purified water	QS

Manufacturing Directions

- Items 1 and 2 are mixed well, followed by passing through sieves and added to items 3 and 12 premixed and made into a clear solution.
- Take care to avoid lump formation.
- Dry in an oven.
- Sieve and add items 6 to 11. Mix well.
- Make sure all the solids added are in fine powder form. Fill 20 g powder into sachets and seal.

Acetaminophen Swallow Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
325.00	1	Acetaminophen fine powder	325.00
409.50	2	Sodium carbonate fine powder	409.50
13.91	3	Cornstarch	13.91
32.50	4	Starch pregelatinized	32.50
1.30	5	Polyvinylpyrrolidone K25	1.30
0.39	6	Potassium sorbate	0.39
9.75	7	Talc	9.75
3.25	8	Stearic acid	3.25
23.86	9	Ac-Di-Sol [®]	23.86
QS	10	Water purified	QS

Manufacturing Directions

- Sift items 1 to 6 through a 16-mesh sieve into a suitable mixer and granulate with a suitable quantity of item 10 to form a medium/heavy granule.
- Dry the granules in a suitable oven at 45°C until the water content is <1%.
- Pass the dried granule through a 12-mesh sieve to produce a white granule (yield 20.250 kg).
- Fill 819.46 mg in a suitable capsule size.

Acetazolamide Sustained-Release Capsules

Each sustained-release capsule, for oral administration, contains 500 mg of acetazolamide and the following inactive ingredients: ethyl vanillin, FD&C blue No. 1, FD&C yellow

No. 6, gelatin, glycerin, microcrystalline cellulose, methylparaben, propylene glycol, propylparaben, silicon dioxide, and sodium lauryl sulfate.

Acetylcysteine Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
66.66	1	Acetylcysteine BP (200 mg/sachet)	66.66
914.16	2	Sugar (18–60 mesh)	914.16
3.33	3	Saccharin sodium	3.33
0.66	4	Silicon dioxide (colloidal)	0.66
0.16	5	FD&C yellow dye No. 6	0.16
QS	6	Mandarin flavor (e.g., Naarden)	~13.00 mL

Manufacturing Directions

- Load the acetylcysteine and half the amount of sugar and saccharin sodium into a suitable blender and premix for 30 minutes.
- Sift the premix through a 0.8-mm screen.
- Load again into the blender.
- Add the remaining amount of sugar and colloidal silicon dioxide and blend until uniform (typically this is achieved on the PK processor[®] by heating the envelope to 40°C and mixing until the product cools to 30–35°C).
- Dissolve the dye in 13 mL of distilled water.
- Continue mixing the blended powders and slowly add the solution from step above.
- When addition of the solution is complete, continue massing until the granulation is evenly wetted and colored. If necessary, complete massing by adding additional quantities of distilled water (approximately 1 mL increments).
- Verify that massing is adequate and note the total quantity of added water. Record the total quantity of water added. Do not overmass.
- Spread the wet granules on trays and dry at 50°C until loss on drying (LOD) is NMT 1% (3 hours at 60°C at 5 mm Hg).
- Allow the granules to cool, then sift on an oscillating granulator fitted with 1.18-mm aperture screen.
- Load the granules from step above into a suitable blender, add the flavor, and blend until uniform (15 minutes), passing it through a 1.18-mm screen if necessary.
- Fill into suitable approved sachets at a theoretical fill weight of 3 g per sachet.

Acitretin Capsules

Acitretin, a retinoid, is available in 10- and 25-mg gelatin capsules for oral administration. Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink, and maltodextrin (a mixture of polysac-

charides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, and edetate calcium disodium.

Acrivastine and Pseudoephedrine Hydrochloride Capsules

Acrivastine and pseudoephedrine hydrochloride is a fixed combination product formulated for oral administration. Acrivastine is an antihistamine and pseudoephedrine is a decongestant. Each capsule contains 8 mg of acrivastine and 60 mg of pseudoephedrine hydrochloride and the following inactive ingredients: lactose, magnesium stearate, and

sodium starch glycolate. The green and white capsule shell consists of gelatin, D&C yellow No. 10, FD&C green No. 3, and titanium dioxide. The yellow band around the capsule consists of gelatin and D&C yellow No. 10. The capsules may contain one or more parabens and are printed with edible black and white inks.

Acrivastine and Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
8.00	1	Acrivastine	8.00
60.00	2	Pseudoephedrine	60.00
440.00	3	Lactose	440.00
5.00	4	Magnesium stearate	5.00

Manufacturing Directions

1. Blend items 1 to 3 after sifting through an 80-mesh screen.

2. Pass item 4 through a 100-mesh screen and add to step 1. Blend for 2 minutes.
3. Fill 513 mg in size 0 capsules.

Acyclovir Capsules

Each capsule contains 200 mg of acyclovir and the inactive ingredients cornstarch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of

gelatin, FD&C blue No. 2, and titanium dioxide. It may contain one or more parabens and is printed with edible black ink.

Acyclovir Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
200.00	1	Acyclovir, USE acyclovir micronized	212.00
3.00	2	Sodium lauryl sulfate	3.00
20.00	3	Cornstarch	20.00
52.00	4	Lactose monohydrate	52.00
2.00	5	Magnesium stearate	2.00
—	6	Ethanol	60 mL

Manufacturing Directions

1. Charge items 1 to 4 in a suitable mixer and mix for 5 minutes with slow chopper speed.
2. Add item 6 slowly with mixing at slow speed. Mix and chop for 2 to 3 minutes.
3. Check for satisfactory massing. Use additional item 6 if necessary.

4. Spread granules to $1/4$ -inch thick layer on paper trays and dry at 50°C for 4 hours to a moisture of not more than (NMT) 1%. Dry further if required after testing.
5. Pass the dried granules through a granulator equipped with a 0-mm sieve.
6. Pass item 5 through 250-mm sieve and add to step 5. Mix for 3 minutes.
7. Use size 1 capsules to fill 289 mg.

Adenosine Monophosphate Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	DBcAMP ^a	30.00
920.00	2	Polyethylene glycol 6000	920.00
30.00	3	Talc	30.00
20.00	4	Colloidal silica Aerosil 200	20.00

^aSodium N⁶, 2'-O-dibutyryladenosine-3',5'-cyclic phosphate.

Manufacturing Directions

1. Pass all items through a 100-mesh sieve and blend.
2. Pack in a bottle. Topical powder for treatment of dermatosis.

Aluminum Acetate Powder

Each powder packet, when dissolved in water and ready for use, provides the active ingredient aluminum acetate, resulting from the reaction of calcium acetate (938 mg) and

aluminum sulfate (1191 mg). The resulting astringent solution is buffered to an acid pH.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	Aluminum hydroxide dry gel (Giulini)	200.00
200.00	2	Basic magnesium carbonate	200.00
240.00	3	Kollidon CL-M	240.00
211.50	4	Sorbitol, crystalline	211.50
41.30	5	Orange flavor	41.30
82.60	6	Kollidon 30	82.60
3.30	7	Coconut flavor	3.30
4.13	8	Banana flavor	4.13
4.13	9	Saccharin sodium	4.13
8.26	10	Water	8.26

Manufacturing Directions

Granulate mixture of items 1 to 5 with solution of items 6 to 10, pass through a sieve, and dry. Shake 58 g of the granules with 100 mL of water.

Aminosalicic Acid Granules

Delayed-release granule preparation of aminosalicic acid (p-aminosalicylic acid: 4-aminosalicylic acid) for use with other antituberculosis drugs for the treatment of all forms of active tuberculosis due to susceptible strains of tubercle bacilli. The granules are designed for gradual release to avoid high peak levels that are not useful (and perhaps toxic) with bacteriostatic drugs. Aminosalicic acid is rapidly degraded in acid media; the protective acid-resistant outer coating is rapidly dissolved in neutral media such that a mildly acidic food, such as orange, apple, or tomato juice or yogurt or applesauce should be consumed. PASER granules are the free base of aminosalicic acid and do *not* contain sodium

or sugar. With heat p-aminosalicylic acid is decarboxylated to produce CO₂ and m-aminophenol. If the airtight packets are swollen, storage has been improper. Supply warning: DO NOT USE if packets are swollen or the granules have lost their tan color and are dark brown or purple. The granules are supplied as off-white, tan-colored granules with an average diameter of 1.5 mm and an average content of 60% aminosalicic acid by weight. The acid-resistant outer coating will be completely removed after a few minutes at a neutral pH. The inert ingredients are colloidal silicon dioxide, dibutyl sebacate, hydroxypropyl methylcellulose, methacrylic acid copolymer, microcrystalline cellulose, and talc.

Amlodipine Besylate and Benazepril Hydrochloride Capsules

The capsules are formulated for oral administration with a combination of amlodipine besylate equivalent to 2.5 or 5 mg of amlodipine and 10 or 20 mg of benazepril hydrochloride. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon

dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate, starch, talc, and titanium dioxide.

Amlodipine Besylate and Benazepril Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Benazepril hydrochloride	20.00
32.92	2	Lactose monohydrate	32.92
5.00	3	Pregelatinized starch	5.00
1.00	4	Colloidal silica	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline cellulose	10.00
4.00	7	Hydrogenated castor oil	4.00
–	8	Water purified	QS
4.88	9	Hydroxypropyl methylcellulose 2910, 3 cps	4.88
0.12	10	Polysorbate 80	0.12
–	11	Water purified	QS
QS	12	Talc	QS
5.00	13	Amlodipine, USE amlodipine besylate	6.94
124.05	14	Microcrystalline cellulose, Avicel PH102	124.05
63.00	15	Dibasic calcium phosphate	63.00
4.00	16	Sodium starch glycolate	4.00
2.00	17	Magnesium stearate	2.00

Manufacturing Directions

1. Mill items 1 to 3 and blend together.
2. Add water (item 8) to granulate the blend.
3. Screen the wet granules and dry them in oven.
4. Mill the dried granules and then mill together with items 5 to 7.
5. Screen item 4 and mix in step 4.
6. Compress into a core.
7. Dissolve item 10 in item 11 and add item 9 to it.
8. Coat the core prepared in step 6 using item 12 to dust the cores.
9. Mix items 13 to 16, then blend and screen. Blend again in a separate vessel.
10. Screen item 17 separately and add to step 9.
11. Fill in size 1 hard gelatin capsules the coated cores with 200 mg of the powder in step 10.

Amlodipine Besylate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Amlodipine, USE amlodipine besylate	7.00
93.00	2	Microcrystalline cellulose, Avicel PH102	93.00
65.00	3	Dibasic calcium phosphate	65.00
8.00	4	Sodium starch glycolate	8.00
0.50	5	Colloidal silicon dioxide Aerosil 200	0.50
1.50	6	Magnesium stearate	1.50
1	7	Empty hard gelatin shell, size 3	1000.00

Manufacturing Directions

1. Sift amlodipine besylate, Avicel PH102, dibasic calcium phosphate, and Primojel[®] through a 0.5-mm sieve and mix well in a mixer.
2. Lubricate the powder mixture in step 1 with magnesium stearate and Aerosil 200 that has been previously sieved. Mix for 2 minutes to get a homogeneous powder.
3. Fill the capsule in the capsule-filling machine to a weight adjusted to provide 5 mg amlodipine per capsule.

Amlodipine Free Base Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
5.00	1	Amlodipine base	5.00
20.00	2	Predried potato starch	20.00
72.60	3	Microcrystalline cellulose	72.60
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. The amlodipine base was sieved through a 500-micron screen.
2. The other excipients have been sieved through an 850-micron screen.
3. All excipients except magnesium stearate have been mixed in a free fall mixer for 15 minutes at approximately 25 rpm.
4. Magnesium stearate was added and the powder blend was mixed for another 5 minutes at approximately 25 rpm and fill gelatin capsules.

Amlodipine Maleate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
6.42	1	Amlodipine maleate	6.42
72.60	2	Microcrystalline cellulose	72.60
20.00	3	Predried potato starch	20.00
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. The amlodipine maleate was sieved through a 500-micron screen. The other excipients have been sieved through an 850-micron screen.
2. All excipients except magnesium stearate have been mixed in a free fall mixer for 15 minutes at approximately 25 rpm.
3. Magnesium stearate was added and the powder blend was mixed for another 5 minutes at approximately 25 rpm.
4. Gelatin capsules filled at approximately 100 mg weight.

The pH value was checked in 20% aqueous slurry (pH around 5.9).

Amoxicillin and Bromhexine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Amoxicillin, USE amoxicillin trihydrate	290.00
8.00	2	Bromhexine, USE bromhexine hydrochloride	8.80
34.00	3	Starch dried	34.00
3.00	4	Magnesium stearate	3.00
3.50	5	Aerosil 200	3.50
40.00	6	Talc	40.00
1.00	7	Hard gelatin capsule, size 1	1000.00

Manufacturing Directions

1. Charge items 1 and 3 to 6 in a suitable blender and mix for 10 minutes.
2. In a separate mixer, add small portion of step 1 and add by geometric dilution item 2 and mix well.
3. Sift through No. 60 mesh screen.
4. Fill 398 mg in each capsule.

Amoxicillin and Clavulanic Acid Powder for Suspension, 125 mg and 31.25 mg per 5 mL (Amoxil)*

Each capsule, with a royal blue opaque cap and pink opaque body, contains 250 or 500 mg of amoxicillin as the trihydrate. The cap and body of the 250-mg capsule are imprinted with the product name and 250; the cap and body of the 500-mg

capsule are imprinted with AMOXIL and 500. The inactive ingredients are D&C red No. 28, FD&C blue No. 1, FD&C red No. 40, gelatin, magnesium stearate, and titanium dioxide.

Amoxicillin and Clavulanic Acid Powder for Suspension

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
19.00	1	Amoxicillin trihydrate	19.00
10.60	2	Potassium clavulanate (eq. clavulanic acid) 1:1 in syloid	10.60
15.00	3	Aerosil 200	15.00
48.80	4	Mannitol	48.80
0.50	5	Citric acid monohydrate	0.50
1.90	6	Sodium citrate	1.90
1.20	7	Xanthan gum	1.20
2.00	8	Powdered flavor	2.00
0.45	9	Sweetener	0.45

Manufacturing Directions

1. Charge items 1 to 9 after passing through a No. 60 screen mesh at a temperature of 25°C and RH of NMT 30% in a suitable blender-mixer.

2. Fill 5 g in a 30-mL bottle. Reconstitution with water gives 125 mg of item 1 and 31.25 mg of item 2 per 5 mL.

Amoxicillin and Clavulanate Potassium for Suspension*

The inactive ingredients are powder for oral suspension (i.e., colloidal silicon dioxide, flavorings, succinic acid, xanthan

gum, and aspartame) hydroxypropyl methylcellulose, mannitol, silica gel, silicon dioxide, and sodium saccharin.

Amoxicillin and Clavulanate Potassium for Suspension*

Bill of Materials			
Scale (mg/bottle) (7 g/60 mL)	Item	Material Name	Qty/1000 Bottle (g)
1500.00	1	Amoxicillin trihydrate (equivalent to 1250 g of amoxicillin)	1500.00
393.60	2	Potassium clavulanate	393.60
150.00	3	Xanthan gum	150.00
1800.00	4	Hydroxypropyl methylcellulose dried	1800.00
150.00	5	Saccharin sodium	150.00
300.00	6	Silicon dioxide colloidal	300.00
10.00	7	Succinic acid	10.00
1500.00	8	Silica gel	1500.00
183.60	9	Peach dry flavor	183.60
236.40	10	Strawberry dry flavor	236.40
731.14	11	Lemon dry flavor	731.14

Note: 156 mg/5 mL syrup 60 mL (125 mg amoxicillin and 31.25 mg clavulanic acid.) 6.95 g/60 mL: Each 5 mL of reconstituted syrup contains 156.25 mg of amoxicillin and clavulanic acid.

Manufacturing Directions

Note: Throughout the process of manufacturing and filling, maintain a relative humidity (RH) of NMT 40%.

I. Preparation of powder mix

- A. Mill 50% of amoxicillin trihydrate, saccharin sodium (dried to NMT 2% moisture by the Karl Fischer method), succinic acid through a 250-mm sieve or using a Fitz mill or equivalent with blades forward. Transfer to a blending mixer and mix for 15 minutes.
- B. Mill remaining amoxicillin trihydrate through a No. 100 mesh using a Fitz mill or equivalent and mix with above screened powders. Mix for 15 minutes.

- C. Mill xanthan gum, hydroxypropyl methylcellulose (dried to NMT 2% moisture dried at 105°C for 2 hours), colloidal silica, and silica gel through a No. 250-mm sieve or using a Fitz mill or equivalent with knives forward. Add to above mixture in step band mix for 15 minutes at medium speed.
- D. Screen all dry flavors through a 250-mm mesh screen and add to above mixture from step C.

II. Finishing

- A. Fill dry powder approximately 7 g in dry 60-mL glass bottles at a fill weight based on the assay of the active constituent.

Amoxicillin Powder for Suspension (125 and 250 mg)

Bill of Materials			
Scale (mg/5 mL) ^a	Item	Material Name	Qty/5 l (g)
125.00	1	Amoxicillin, USE amoxicillin trihydrate with 8% excess	143.50
1.04	2	Simethicone A	1.04
111.11	3	Castor sugar	111.11
444.44	4	Castor sugar	444.44
2479.86	5	Castor sugar	2479.86
23.33	6	Sodium citrate	23.33
1.67	7	Xanthan gum	1.67
13.33	8	Blood orange dry flavor	13.33
0.74	9	Vanilla dry flavor	0.74
4.44	10	Orange banana dry flavor	4.44
14.44	11	Aerosil 200	14.44

^aAfter reconstitution.

Manufacturing Directions

- Charge item 3 and item 2 in a mixer and mix for 2 minutes.
- Add item 4 and items 6 to 11 and mix for 5 minutes.
- Pass through a Fitz mill; impact forward at high speed using sieve 24228.

- In a separate mixer, charge item 5 and item 1 and mix well, passing through a sifter.
- Add to step 3 and mix for 20 minutes.
- Fill 65 g for 100-mL and 39 g for 60-mL pack size.

Amoxicillin Trihydrate Capsules (250 and 500 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Amoxicillin, USE amoxicillin trihydrate	576.00
1.20	2	Aerosil 200	1.20
7.72	3	Magnesium stearate	7.72
8.91	4	Sodium lauryl sulfate	8.91

Manufacturing Directions

- All operations are to be completed at RH 40% to 45% and temperature 20°C to 25°C.
- Pass item 1 through a 1-mm sieve in a mixing vessel.

- Pass items 2 to 4 after passing through a 250-mm sieve; add one-third portion of item 1 from step 2 and mix for 10 minutes; add another one-third item 1 and mix; and finally, add balance and mix.
- Fill 594 mg in size 0 capsules.

Ampicillin Dry Syrup (5% = 500 mg/10 mL)**Formulation**

Ampicillin trihydrate, 5.0 g; sodium citrate, 5.0 g; citric acid, crystalline, 2.1 g; sodium gluconate, 5.0 g; sorbitol crystalline [10], 40.0 g; Kollidon CL-M [1], 6.0 g; orange flavor, 1.5 g; lemon flavor, 0.5 g; saccharin sodium, 0.4 g.

Manufacturing

Mix all components and fill in a bottle.

Preparation of the Suspension for Administration

To 66 g of the powder, add water to fill to a total volume of 100 mL shaking well.

Ampicillin Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/5 l (g)
125.00	1	Ampicillin, USE ampicillin trihydrate 8% excess	144.25
1.00	2	Simethicone A	1.00
138.90	3	Castor sugar	138.90
27.44	4	Sodium citrate	27.44
7.00	5	Xanthan gum	7.00
15.00	6	Blood orange dry flavor	15.00
0.78	7	Vanilla dry flavor	0.78
7.55	8	Strawberry dry flavor	7.55
10.00	9	Aerosil 200	10.00
138.90	10	Castor sugar	138.90
2747.90	11	Castor sugar	2747.90

Manufacturing Directions

- All operations should be completed in a RH of 45% to 55% and a temperature of 23°C to 25°C.
- Charge items 2 and 3 in a suitable blender and mix for 5 minutes.
- Charge items 1 and 4 to 10 in a separate mixer and mix for 5 minutes.
- Add step 2 into step 3 and mix for 10 minutes.
- Add item 11 and mix for 10 minutes.
- Fill 65 g for a 100-mL pack and 39 g for a 60-mL pack. For 250-mg strength, adjust active ingredient and adjust with item 11.

Ampicillin Trihydrate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Ampicillin, USE ampicillin trihydrate compacted	582.13
1.17	2	Aerosil 200	1.17
11.69	3	Magnesium stearate	11.69

Manufacturing Directions

- Pass item 1 through a 1-mm sieve into a double-cone blender, except approximately 5% of the quantity.
- In a separate container, pass and collect items 2 and 3 through a 250-µm sieve.
- Add the balance of item 1 retained in step 1 into step 2 and blend for 10 minutes; pass through a 900-µm sieve if necessary.
- Add to step 2 and blend for 10 minutes.
- Fill 223.125 mg in size 0 capsules.

Ampicillin Trihydrate Capsules for Suspension

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Ampicillin, USE ampicillin trihydrate	250.00
2.50	2	Magnesium stearate	2.50
–	3	Gelatin capsule, size 2	1000.00

Manufacturing Directions

1. Dry blend ampicillin trihydrate and magnesium stearate in Baker Perkins mixer; bag off into polyethylene-lined drums.

2. Fill on Zanasi AZ20 capsule-filling machine. The average fill weight is 295 ± 9 mg; the average total weight is 360 mg. For a 500-mg capsule (size 0 capsules), the average fill weight is 593 ± 15 mg; the average total weight is 690 mg.

Ampicillin Trihydrate Powder for Suspension

Bill of Materials			
Scale (mg/bottle) (15 mL)	Item	Material Name	Qty/1000 Bottles (g)
1500.00	1	Ampicillin, USE ampicillin trihydrate (assuming potency 871; adjust amount accordingly)	1722.22
3072.10	2	Sucrose (adjust amount based on item 1 potency)	3072.10
372.53	3	Sodium citrate Dihydrate	372.53
31.93	4	Saccharin sodium	31.93
2.12	5	Acid citric anhydrous	2.12
45.23	6	Sodium carboxymethyl cellulose	45.23
22.61	7	Magnesium aluminum silicate Veegum [®] F	22.61
7.98	8	Dye	7.98
26.60	9	Flavor	26.60
18.00	10	Sodium benzoate	18.00
QS	11	Water purified	400.00

Note: Simethicone 0.15% can be added to reduce foaming during reconstitution. Adjust fill volume for the final size of reconstitution container, such as 60 mL or different strength desired, e.g., 250 mg/5 mL upon reconstitution.

Manufacturing Directions

Caution: Handle with extreme care. Protect face and hands from amoxicillin because some individuals may be sensitive and reactions may occur.

1. Mixing

- Pass sugar through a 2.38-mm aperture screen using an oscillating granulator.
- Pass the following ingredients through a 595- μ m aperture screen in a Fitz mill (high speed, impact forward): Sodium citrate, acid citric, saccharin sodium, carboxymethylcellulose, amoxicillin, and magnesium aluminum silicate.
- Charge ingredients from steps A and B into a suitable mixer and mix for 10 minutes until uniform.

- Dissolve yellow dye in approximately 60 g of purified water.
 - Mass mixture from step C with dye solution from step D. If necessary, pass wet mass through a 4.76-mm aperture screen. *Caution:* Do not overwet or overmass. Product must remain as wet granules.
 - Spread evenly on stainless steel trays. If necessary, pass wet mass through a 4.76-mm aperture screen.
 - Oven dry granules at 45°C until LOD is NMT 0.6% (vacuum 60°C, 2 hours).
- ##### 2. Finishing
- Fill product into suitable containers. Theoretical fill weight is 5.32 g (+3% fill excess) per 15-mL container, requiring approximately 12 mL of water for reconstitution.

Antibacterial and Bacterial Culture Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
125–500 mg	1	Penicillin, cephalosporin, or macrolide	125–500
10–100 million	2	<i>Lactobacillus acidophilus</i> ^a	10–100 B

^aSubstitute with *Lactobacillus* spores, 300–600 million; *Streptococcus thermophilus*, 10 million; *Lactobacillus lactis*, 10–500 million; *Streptococcus lactis*, 10 million; *Saccharomyces cerevisiae*, 10 million; lactobacilli, GG 10¹⁰ units. This formulation includes the anti-infective agent, which can be penicillin, a cephalosporin, or a macrolide in doses ranging from 125 to 500 mg per capsule. Also included in the same capsule is a granulation of the bacteria, which is known to be eradicated during the therapy with these antibiotics. The bacterial are coated to protect them from the effect of coadministered antibiotic and last in the intestine for over 3 months replenishing the lost flora and reduce many side effects related to use of antibiotics.

Manufacturing Directions

- Granules of one of the active ingredients (e.g., microorganisms) are first prepared by the following process.

Ingredients Parts by weight

Microorganism: 42.86%
 Microcrystalline cellulose: 53.93%
 Magnesium stearate: 1.07%
 Colloidal silicone dioxide: 0.71%
 Cross carmellose sodium: 1.43%

The granules formed are compressed into a tablet-by-tablet compression machine heaving a laying facility at a temperature less than 25°C and RH NMT 50%.

Tablets are transferred to a coating pan for coating using the following formulation.

Ingredients Parts by weight

Hydroxypropyl methylcellulose phthalate: 4.37%

Titanium dioxide: 0.96%

Purified talc: 0.19%

Polyethylene glycol: 0.99%

Isopropyl alcohol: 34.95%

Dichloromethane: 58.54%

- The remaining active ingredient (antibacterial agent) is mixed with excipients and filled into gelatin capsules. Before sealing of capsules the coated tablet containing active ingredients is introduced into capsules. The relative proportion of antiinfective agent and excipients for filling in capsule:

Ingredients Parts by weight

Anti-infective agent: 91.94%

Pregelatinized starch: 6.24%

Magnesium stearate: 1.44%

Sodium lauryl sulfate: 0.38%

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

- Mix all ingredients using the geometric dilution technique.
- Fill.

Antioxidant Eye Nutrition Supplement Capsules

This is an antioxidant supplement formulated to provide nutritional support for the eye. It contains essential antioxidant vitamins, minerals, and 6 mg of lutein. Each capsule contains ascorbic acid, 60 mg; DL-alpha-tocopheryl acetate, 30 IU; zinc

oxide, 15 mg (elemental); cupric oxide, 2 mg (elemental). The inactive ingredients are lactose monohydrate, crospovidone, magnesium stearate, and silicone dioxide.

Aspartame Granules in Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
30.00	1	Aspartame	30.00
2.00	2	Silicon dioxide colloidal	2.00
968.00	3	Cerelose powder No. 60 ^a	1052.00

^a Std. qty. of cerelose powder allows for loss on drying.

Manufacturing Directions

1. Protect from moisture; 40% RH at 25°C.
2. Oven dry cerelose powder at 50°C overnight until LOD is no more than 3% (3 hours, vacuum at 60°C). Pass dried cerelose powder through 595- μ m aperture screen in oscillating granulator.
3. Charge the following ingredients into suitable blender: aspartame, half the amount dried of cerelose powder

(milled), and silicon dioxide colloidal. Add balance of dried cerelose powder (total amount of dried powder is 968 g/kg) and blend for 15 minutes.

4. Pass blended powders through an 840-mm aperture screen using an oscillating granulator and discharge into polyethylene-lined drums. Fill weight of 1 g/sachet.

Aspartame Powder in Sachets

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
47.50	1	Aspartame	47.50
2.50	2	Silicon dioxide (colloidal)	2.50
950.00	3	Mannitol granules	950.00

Manufacturing Directions

1. Protect from humidity. Maintain a RH of 40% and a temperature of 25°C.
2. Pass mannitol granules and colloidal silicon dioxide through an 840- μ m screen in oscillating granulator.
3. Charge the following ingredients into suitable blender: aspartame, half of the amount of mannitol granules, and colloidal silicon dioxide.

4. Add balance of mannitol granules and blend for 15 minutes.
5. Pass blended powders through an 840- μ m screen using an oscillating granulator and discharge into polyethylene-lined drums.
6. Fill weight is 0.8 g/sachet.

Aspirin and Chlorpheniramine Powder

The active ingredients are aspirin (650 mg) and chlorpheniramine maleate (4 mg) per powder. The inactive ingredients are fumaric acid, glycine, lactose, potassium chloride, silica, and sodium lauryl sulfate.

Aspirin-Coated Crystals

Formulation: aqueous-based polymeric coating solution: hydroxypropylmethylcellulose (HPMC E5) 6%, propylene glycol 1%, FD&C red No. 3 0.01%, and distilled Water QS to 100.

Manufacturing Directions

1. A standard coating pan and an air suspension 6-inch column are used to coat aspirin crystals of 100 to 200 mesh using top-spray, bottom-spray, and tangential-spray fluid bed coating processes.

2. Aspirin crystal load is placed in the product container.
3. The crystals are fluidized in an expansion chamber.
4. The spray nozzle is located low in the expansion chamber so that liquid is applied when the crystals are moving at a higher velocity.
5. This serves to minimize surface wetting and to inhibit agglomeration.
6. A filter is used to separate entrained crystals from the exiting process air stream.
7. The pump is calibrated with coating solution prior to start-up of the coating process.
8. The turbine is activated and the process air is heated to 55°C.
9. The spray and shake cycle is started and ran continually until the coating solution is completely depleted.
10. The coated aspirin crystal bed is dried for 10 minutes and the product is cooled to 35°C.

- The product is removed, weighed, and passed through a 20-mesh screen to remove any agglomerates.
- Aspirin-coated crystals can be used to make tablets or capsules. Tablets are prepared containing five components: 50% by weight aspirin crystals (100–200 mesh) coated previously with 3% to 6% polyvinylpyrrolidone; 25% calcium carbonate buffer, 5% to 15% hydroxypropyl-

methylcellulose (K100LV) as the gel forming hydrophilic matrix material; 14.5% to 19.5% microcrystalline cellulose (Avicel PH 101) as the excipient/binder; and 0.5% stearic acid as the hydrophobic lubricant.

- 650-mg samples are either compressed in 1/2 inch punches or filled in size 0 capsules.

Aspirin and Phenylpropanolamine Powder

The active ingredients are aspirin (650 mg), phenylpropanolamine hydrochloride (25 mg) per powder, and pseu-

doephedrine hydrochloride (60 mg) per powder sachet. The inactive ingredients are fumaric acid, glycine, lactose, potassium chloride, silica, and sodium lauryl sulfate.

Aspirin Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
320.00	1	Aspirin	320.00
480.00	2	Gelatin	480.00
QS	3	Water purified	QS
QS	4	Corn oil	QS
QS	5	Petroleum ether	QS
QS	6	Isopropyl alcohol	QS
QS	7	Glutaraldehyde 1%	QS

Manufacturing Directions

- Item 2 is added to 0.8 L of item 3 and the mixture is allowed to stand at 25°C for 1 hour while the gelatin hydrates and swells.
- This preparation is then heated to 60°C while it is stirred at 300 rpm for 30 minutes; 0.5 L of distilled water, previously heated to 60°C, is then added, and the solution is stirred at 500 rpm for an additional 5 minutes.
- Item 1, as finely powdered aspirin, is then added to the solution while stirring is continued to give a uniform suspension.
- After 1 minute, the warm suspension is poured without delay into 5 L of a rapidly stirred (500 rpm) solution of 20% corn oil in petroleum ether, which has been previously brought to 25°C, and the resulting emulsion is rapidly (i.e., over a period of no more than 5 minutes) cooled to 5°C while the stirring is continued.
- L of cold (5°C) isopropyl alcohol is then added to dehydrate the gelatin microspheres while the preparation is stirred for another 10 minutes.

- The microspheres are then collected by filtration and washed 3 times with cold (5°C) isopropyl alcohol.
- They are then immersed in 0.8 L of a 1% solution of glutaraldehyde in cold (5°C) isopropyl alcohol for 8 hours and then washed 3 times with isopropyl alcohol, collected by filtration, and vacuum dried for 24 hours.
- The microspheres, which average 300 to 400 μm in diameter, are filled into gelatin capsules for administration as a safer, long-acting analgesic product (800 mg of the microsphere mix, which contains 320 mg of aspirin, is filled into each size 0 capsule). The capsules, when released into the stomach following ingestion, provide for sustained release of the drug for from 1 to 4 hours and also ensure that the drug reaches the gastrointestinal mucosa while in the solution state, instead of the more deleterious solid state that is characteristic of conventional dosage forms of this drug. Physical integrity of the matrix is maintained for 1 to 4 hours after the release of its drug content, after which time the matrix dissolves.

Aspirin, Salicylamide, and Caffeine Powder

Each powder contains aspirin (650 mg), salicylamide (195 mg), and caffeine (33.3 mg). The inactive ingredients are dioctyl sodium sulfosuccinate, fumaric acid, lactose, and potassium chloride. For arthritis strength powder, the active ingredients in each powder are aspirin (742 mg), salicylamide (222 mg), and caffeine (38 mg). The inactive ingredients are dioctyl sodium sulfosuccinate, fumaric acid, lactose, and potassium chloride.

nesium oxide (280 g) were placed in a blender and blended for 15 minutes.

- The blend was passed through a sieve and blended for another 15 minutes. To the blend were added aspartame (100 g), artificial cherry flavor (8 g), artificial cream flavor (8 g), and artificial strawberry flavor (8 g) and the mixture was blended for 10 minutes.
- To the blend was added magnesium stearate (30 g) and the mixture was further blended for 5 minutes. The contents of the blender were removed from the blender and packaged for constitution with water.

Azithromycin Suspension

Manufacturing Directions

- Sucrose (1433.216 g), azithromycin dihydrate (530.784 g), mannitol (1200 g), pregelatinized starch (200 g), and mag-

Azithromycin Capsules

Each capsule contains azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard gelatin capsules (containing FD&C red No. 40).

They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate.

Azithromycin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Azithromycin, USE azithromycin dihydrate ^a	263.00
196.00	2	Anhydrous lactose	196.00
50.00	3	Starch (cornstarch dried)	50.00
9.00	4	Magnesium stearate	9.00
2.00	5	Sodium lauryl sulfate	2.00
–	6	Empty hard gelatin capsules, size 0	1000.00

Note: Weight of one capsule = 520 mg + shell.

^aConsidering the potency of the active ingredient is 1000 µg/mg (anhydrous basis) with water content 5%, the required quantity of azithromycin dihydrate depends on the provided potency.

Manufacturing Directions

Note: Processing should be done under a controlled room temperature and humidity area. The limits are room temperature: 20°C to 25°C, RH: 40% to 45%.

- Mix items 1 and 2 in a polyethylene bag. Pass through a 500-mm stainless steel sieve. Collect in a stainless steel drum lined with a polyethylene bag.
- Mix items 3 to 5 in a polyethylene bag. Pass through a 250-mm stainless steel sieve. Collect in a polyethylene bag.
- Take a polyethylene bag. Check if there is any leakage. Add the powder mix from steps 1 and 2. Mix manually for 1 minute.
- Unload the powder in a stainless steel drum.
- Check the temperature and RH of the room before beginning encapsulation. The limits are RH: 40% to 45%, temperature: 20°C to 25°C.
- Load the empty capsule shells, size 0, in the hopper.
- Switch the power to "ON." Check the locking of the capsules without powder. The locking length is 21.1 to 21.7 mm.
- Load the powder in the hopper by scoop. Switch the power to "ON." Adjust the fill net weight to 520 mg per capsule. Nominal weight of one capsule: 520 mg + weight of one empty shell (95 mg). Target weight: 520 mg±2% + weight of one empty shell (95 mg).

Azithromycin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Azithromycin base, USE azithromycin monohydrate	263.72
149.88	2	Lactose anhydrous	149.88
9.40	3	Magnesium stearate/Sodium lauryl sulfate (90/10)	9.40

Note: Based on bulk potency of 94.8%, adjust with item 2.

Manufacturing Directions

- Sift items 1 and 2 through an 80-mesh screen and blend.
- Add item 3 and mix for 3 minutes.
- Fill 470 mg in size 0 capsules.

Azithromycin Capsules and Oral Suspension

Capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard gelatin capsules (containing FD&C red No. 40). They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate. It is also supplied as a powder for oral suspen-

sion in bottles containing azithromycin dihydrate powder equivalent to 300, 600, 900, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate tribasic anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C red No. 40; and spray-dried artificial cherry, creme de vanilla, and banana flavors. After constitution, each 5 mL of suspension contains 100 or 200 mg of azithromycin.

Azithromycin for Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/Bottles (g)
200.00	1	Azithromycin, USE azithromycin dihydrate ^a	1.263
3861.50	2	Castor sugar	23.169
18.00	3	Tribasic sodium phosphate	0.108
15.00	4	Sodium benzoate	0.090
2.50	5	Hydroxypropyl cellulose (Klucel EF)	0.015
2.50	6	Xanthan gum	0.015
15.00	7	Cherry dry flavor	0.090
33.33	8	Vanilla dry flavor	0.200
25.00	9	Banana dry flavor	0.150

^aConsidering the potency of the active ingredient is 1000 µg/mg (anhydrous basis) with water content 5%, the required quantity of azithromycin dihydrate depends on the provided potency.

Manufacturing Directions

Note: Processing should be done under controlled room temperature and humidity conditions. The limits are room temperature: 20°C to 25°C, RH: 40% to 45%.

1. Dry item 3 at 90°C for 2 hours.
2. Sift item 2 through a Fitz mill, impact forward, medium speed using sieve No. 24228.
3. Collect in a stainless steel drum.
4. Sift 12 g of item 2 (From step 2) and item 1 through 630-µm s.s. sieve in sifter. Load into a drum blender. Mix for 3 minutes.
5. Mix 5 g of item 2 (from step 2), item 3 from step 1, and items 4 to 9 in a polyethylene bag. Sift through 630-µm s.s. sieve in sifter. Collect in a polyethylene bag.
6. Load the powder mix from step 4 into step 3 in a drum blender. Mix for 3 minutes.
7. Load 6.17 g of item 2 (from step 2) into step 5 in a drum blender. Mix for 3 minutes.
8. The fill weight for a 30-mL pack is 25.10 g.

Azithromycin for Oral Suspension

Bill of Materials			
Scale (mg/bottle)	Item	Material Name	Qty/1000 Bottles (g)
838.57	1	Azithromycin dihydrate	838.57
15487.74	2	Sucrose	15487.74
70.01	3	Sodium phosphate tribasic anhydrous	70.01
26.62	4	Hydroxypropyl cellulose (Klucel EF)	26.62
26.62	5	Xanthan gum (Keltrol)	26.62
0.67	6	FD&C red No. 40	0.67
59.94	7	Cherry flavor spray-dried artificial No. 11929	59.94
133.28	8	Vanilla flavor artificial No. 11489	133.28
99.96	9	Banana flavor spray-dried artificial No. 15223	99.96

Note: Based on bulk potency of 95.4%, adjust with item 2.

Manufacturing Directions

1. Sift all ingredients through an 80-mesh screen and mix well.
2. Fill 16.743 g per bottle.
3. To reconstitute, add 0.52 mL/g of dry suspension.

Azithromycin Sachets for Oral Suspension

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
1.000	1	Azithromycin base, USE azithromycin dihydrate	1.048
9.707	2	Sucrose	9.707
0.088	3	Sodium phosphate tribasic anhydrous	0.088
0.055	4	Colloidal silicon dioxide	0.055
0.038	5	Cherry flavor spray-dried artificial	0.038
0.064	6	Banana flavor spray-dried artificial	0.064

Note: Based on bulk potency of 95.4% of azithromycin, adjust for potency using item 2.

Manufacturing Directions

1. Sift items 1 to 4 through an 80-mesh screen into a blender. Blend.
2. Sift items 5 and 6 and add to step 1. Blend.
3. Fill 11 g in one sachet, approximately 3.25 in × 4 in, polyethylene-lined. To reconstitute, add contents to 60 mL water and stir well.

Balsalazide Disodium Capsules

Each capsule contains 750 mg of balsalazide disodium. The inactive ingredients are colloidal silicon dioxide and magnesium stearate. The sodium content of each capsule is approximately 86 mg.

Benazepril Hydrochloride and Amlodipine Besylate Capsules

These capsules are a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated for

oral administration with a combination of amlodipine besylate equivalent to 2.5 or 5 mg of amlodipine and 10 or 20 mg of benazepril hydrochloride. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.

Benazepril Hydrochloride and Amlodipine Besylate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Benazepril hydrochloride	20.00
32.90	2	Lactose monohydrate	32.90
5.00	3	Pregelatinized starch	5.00
1.00	4	Colloidal silicon dioxide	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline cellulose	10.00
4.00	7	Hydrogenated castor oil	4.00
QS	8	Water purified	QS
4.88	9	Hydroxypropyl methylcellulose 2910, 3 cps	4.88
0.19	10	Polysorbate 80	0.19
QS	11	Purified water	QS
QS	12	Talc	QS
5.00	13	Amlodipine, USE amlodipine besylate	6.94
124.05	14	Microcrystalline cellulose	124.05
63.00	15	Calcium phosphate dibasic	63.00
4.00	16	Sodium starch glycolate	4.00
2.00	17	Magnesium stearate	2.00

Manufacturing Directions

- Benazepril hydrochloride cores are prepared using the following:
 - Items 1 to 3 are milled and blended together and water is added to granulate the blend.
 - The wet granules are screened and oven dried. The dried granules are then milled together with items 5 to 7.
 - Item 4 is screened and then mixed with the other ingredients. The resulting mixture is then compressed into a core.
- The resulting cores are coated with a coating solution prepared as follows: Item 10 is dissolved in the water and item 9 is added thereto.
 - The previously made cores are then coated with this solution and the wet coated tablets are dried.
 - The dried tablets are then dusted with item 12.
- Amlodipine besylate for incorporation into the formulation is prepared as follows:
 - Items 13 to 16 are mixed together and the blended mixture is screened and reblended.
 - Item 17 is separately screened and then blended with the reblended mixture containing the amlodipine.
- No. 1 hard gelatin capsules are used to encapsulate benazepril hydrochloride containing coated core along with 200 mg of the amlodipine besylate containing powder per capsule.

Bisacodyl Colonic Delivery Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
210.00	1	Sugar sphere	210.00
5.00	2	Hydroxypropyl methylcellulose	5.00
3.00	3	Bisacodyl micronized	3.00
1.00	4	Hydroxypropyl methylcellulose	1.00
18.00	5	Eudragit [®] L100-55	18.00
5.00	6	Eudragit S	5.00
4.00	7	Dibutyl phthalate	4.00
8.00	8	Talc	8.00
1.00	9	Red ferric oxide	1.00
2.00	10	Talc	2.00

Manufacturing Directions

1. Bisacodyl is micronized in a fluid energy mill using a grinding pressure of 50 psi to produce a powder with 90% of the particles below 10 μm .
2. It is dispersed in water at a level of 2.7% by weight, with 0.9% by weight of hydroxypropyl methylcellulose (HPMC) as a binding polymer sprayed onto sugar spheres (6.53–6.63 mm diameter) in a perforated pan coater maintaining an outlet air/bed temperature of approximately 40°C.
3. Barrier coat: HMPC is dissolved in water to produce 4% by weight solution, which is coated on the substrates described above in a perforated pan coater maintaining an outlet air/bed temperature of approximately 40°C.
4. Inner enteric coat: Eudragit L100-55 and dibutyl phthalate are dissolved in a solution of isopropanol, acetone, and

- water (37:9:1) at levels of 8.0% and 1.6% (total weight percent) respectively. Talc is then suspended in the solution at a level of 3.3% by weight. The resulting mixture is coated onto the barrier-coated substrates in step 4 in a perforated pan coater maintaining an outlet air/bed temperature of approximately 30°C.
5. Outermost enteric coat: Eudragit S and dibutyl phthalate are dissolved in a solution of isopropanol, acetone, and water (37:9:1) at levels of 8.0% and 1.6% (total weight percent) respectively. Red ferric oxide and talc are then suspended in the solution at levels of 1.2% and 2.1% by weight respectively. The resulting mixture is coated onto the barrier-coated substrates above in a perforated pan coater maintaining an outlet air/bed temperature of approximately 30°C.
6. Appropriate theoretical quantity is filled in hard capsules.

Brompheniramine and Pseudoephedrine Capsules

These capsules are light green and clear, and contain white beads. The extended-release capsule contains brompheniramine maleate (12 mg) and pseudoephedrine hydrochloride (120 mg) in a specially prepared base to provide prolonged action. Alternate strength is 6 mg and 60 mg respectively. The

capsules also contain the following inactive ingredients: calcium stearate, D&C yellow No. 10, FD&C blue No. 1, FD&C yellow No. 6, gelatin, pharmaceutical glaze, starch, sucrose, and talc.

Budesonide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
1.00	1	Budesonide micronized	1.00
321.00	2	Sugar spheres	321.00
6.60	3	Aquacoat ECD30	6.60
0.50	4	Acetyltributyl citrate	0.50
0.10	5	Polysorbate 80	0.10
17.50	6	Eudragit L100-55	17.50
1.80	7	Triethylcitrate	1.80
8.80	8	Talc	8.80
0.01	9	Antifoam MMS	0.01

Manufacturing Directions

1. Budesonide (32.2 g) is suspended in the Aquacoat ECD30 dispersion (0.70 kg) with the aid of the polysorbate 80 (0.42 g) together with acetyltributyl citrate (15.8 g).
2. The mixture is sprayed onto sugar spheres (10.2 kg) in a fluid bed apparatus.
3. The enteric coating, consisting of the Eudragit L100-55 dispersion [Eudragit L100-55 (0.558 kg), triethylcitrate (55.8 g), talc (0.279 kg), antifoam MMS (0.44 g), and polysorbate 80 (2.79 g)] is then sprayed on the spheres.
4. The pellets are dried in the fluid bed apparatus, sieved, and filled in hard gelatin capsules.

Budesonide Inhalation Powder

The inhalation-driven, multidose dry powder inhaler contains only micronized budesonide. Each actuation of container provides 200 µg budesonide per metered dose, which delivers approximately 160 µg budesonide from the mouth-piece (based on in vitro testing at 60 L/min for 2 sec).

Butalbital and Acetaminophen Capsules

Each capsule contains butalbital (50 mg) and acetaminophen (325 mg). In addition, each capsule may also contain the following inactive ingredients: benzyl alcohol, butylparaben, D&C red No. 28, D&C red No. 33, edetate calcium disodium, FD&C blue No. 1, FD&C red No. 40, gelatin, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, sodium propionate, and titanium dioxide.

The fluid bed sprayer/dryer is operated with the following parameters.

Flow rate: 1.5 mL/min
 Inlet air temperature: 25°C
 Outlet air temperature: 25°C
 Air flap: 35
 Atomizer: 2 bar

1. A size 0 capsule after the enteric coating will typically have the following composition.
 Preemulsion solution: 0.589 g
 Undercoat polymer: 0.027 g
 Enteric coat polymer: 0.032 g, 0.648 g

Calcitonin (Salmon) Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500 IU	1	Salmon calcitonin	500000 IU
0.048	2	Dimyristoyl phosphatidic acid	0.048
3.44	3	Aprotinina	3.44
3.78	4	Hydroxypropyl cellulose-LF	3.78
3.78	5	Polyoxy-40 stearate	3.78
140.97	6	Polyethylene glycol 400	140.97
15.55	7	Propylene glycol	15.55
8.83	8	Citrate buffer	8.83
31.49	9	Cholesterol	31.49
17.40	10	Tween 80	17.40
63.69	11	Egg yolk lecithin	63.69
19.79	12	D-Alpha-tocopherol	19.79
28.15	13	Glyceryl monooleate	28.15
251.45	14	Isostearic acid	251.45

Note: Human Growth Hormone: 2.6 IU = 1 mg.

^aAprotinin: 7500 KIU = 1 mg.

Manufacturing Directions

1. Polyoxy-40 stearate is dispersed in the solvent mixture of polyethylene glycol 400 and propylene glycol.
2. Sodium cholate is also separately dispersed in the mixture.
3. A water solution containing recombinant human growth hormone, phospholipid, and aprotinin is then added to the solvent mixture from step 1 and the pH is adjusted to 2.5 with the help of buffer.
4. The lipid solution is made separately in another vessel.
5. To the oil solution, the polyol solution is added drop-wise while mixing continuously. While mixing, it is suggested that the vessel be ice jacketed to prevent the denaturation of the protein in the formulation.
6. Clear transparent liquid, which is called the preemulsion solution, is obtained after approximately 5 minutes of mixing at low speed. An in situ emulsion can be made by mixing any ratio of the preemulsion solution with the simulated intestinal fluid.
7. The preemulsion solution is filled in a size 0 hard gelatin capsule, and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
8. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, a 3.5% to 4.5% weight gain of the capsules is a good indication of the amount required as an undercoat.
9. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers, such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, are used.
10. Anionic copolymers, which are based on methacrylic acid and methyl methacrylate and are commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, or isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% of the weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows: methacrylic acid and methyl, 10% w/w; methacrylate copolymer (polymer); diethyl butyl phthalate (plasticizer), 2% w/w; acetone, 22% w/w; isopropanol, 66% w/w.
11. Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
12. For size 0 capsules, the above-mentioned enteric coating solution can be sprayed using fluidizing.

Calcitriol Capsules

It is available as capsules containing 0.25 or 0.50 µg calcitriol, BHA, and BHT as antioxidants. The capsules contain a fractionated triglycerides of palm seed oil. Gelatin capsule shell

contains glycerin, methyl, and propyl parabens, and sorbitol, with the following dye system: 0.25 µg of FE&C red No. 3, FD&C yellow No. 6, and titanium dioxide.

Calcium Carbonate Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
600.00	1	Calcium carbonate	600.00
900.00	2	Gelatin	900.00
QS	3	Water purified	1.5 l
QS	4	Corn oil	QS
QS	5	Petroleum ether	QS
QS	6	Isopropyl alcohol	QS
QS	7	Glutaraldehyde 1%	QS

Manufacturing Directions

- Item 2 is added to 1.5 L of item 3 and the mixture is allowed to stand at 25°C for 1 hour while the gelatin hydrates and swells.
- To this mixture is added item 1 and the preparation is heated to 60°C while it is stirred at 300 rpm for 30 minutes to effect dissolution of the gelatin and to ensure even suspension of the calcium carbonate. Additional distilled water, previously heated to 60°C, is then added to bring the total volume to 100°C while the stirring is continued.
- This preparation is slowly poured into 12 L of a mixture consisting of 20% by volume of corn oil in petroleum ether, which has previously been heated to 60°C while the petroleum ether solution is stirred at 500 rpm. This preparation is then cooled to 5°C with continued stirring and the stirring is continued at 500 rpm for 1 hour after the lower temperature is reached.
- While stirring of the preparation at 5°C is continued, 6 L of isopropanol is then added.
- The solid microspheres are then collected by filtration and washed 3 times with isopropyl alcohol.
- The capsules are then immersed in 1.5 L of a 1% solution of glutaraldehyde in isopropyl alcohol for 8 hours at 5°C.
- The capsules are then washed again 3 times with isopropyl alcohol, filtered, and vacuum dried for 24 hours.
- The microspheres, which average between 200 and 300 µm in diameter, are filled into gelatin capsules for administration as a long-acting antacid product (1.5 g of the microsphere mix, which contains 600 mg calcium carbonate, are filled into each size 0 capsule).
- The microcapsules, when released into the stomach following ingestion, delay the reaction of the calcium carbonate with the acid of the stomach for a useful period of time (between 3 and 6 hours), which provides for sustained antacid protection for the patient.
- Physical integrity of the matrix is maintained from 1 to 4 hours after the release of its drug contents, after which the matrix dissolves through hydrolytic cleavage of its bonds and proteolytic digestion.

Camptothecin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	CPT-11	100.00
470.00	2	Polyethylene glycol 13000	470.00
50.00	3	Triacetin	50.00
5.00	4	Polysorbate 80	5.00
QS	5	Capsule shell HPMC	1000.00

Manufacturing Directions

- Items 2 to 4 are melted and item 1 is added and admixed thoroughly; the mixture is allowed to cool and solidify.
- Mill the step 1 mixture into a suitable size and fill in an HPMC shell capsules.

Carbamazepine Extended-Release Capsules

The capsule is a multicomponent capsule formulation consisting of three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice daily dosing of carbamazepine. The inactive ingredients are citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate, and other ingredients. The 200-mg capsule shells contain gelatin, FD&C red No. 3, FD&C yellow No. 6, yellow iron oxide, FD&C blue

No. 2, and titanium dioxide, and are imprinted with white ink. The 300-mg capsule shells contain gelatin, FD&C blue No. 2, FD&C yellow No. 6, red iron oxide, yellow iron oxide, and titanium dioxide, and are imprinted with white ink.

Manufacturing Directions

This product is made from three types of pellets, one with instant-release profile and two with sustained-release profile; generally, an equal component of each pellet is used but other variations may be used as well.

	Percent	Kilograms
Pellet A: Immediate-Release Component		
Microcrystalline cellulose, N.F. (MCC) (Avicel PH-101/102, Emcocel)	40.0	40.0
Hydroxypropyl methylcellulose (HPMC) (Methocel E5/E50/K5/K50)	2.5	0.025
Croscarmellose, type A, N.F. (Ac-Di-Sol)	2.0	0.020
Sodium lauryl sulfate (SLS)	0.1	0.001
Carbamazepine	55.4	0.554
Total	100.0	1.000
Pellet B: Sustained-Release Component		
Microcrystalline cellulose	30.0	0.300
Hydroxypropyl methylcellulose	5.0	0.050
Sodium monoglycerate	8.0	0.080
Tartaric acid	5.0	0.050
Sodium lauryl sulfate	0.2	0.002
Carbamazepine	51.8	0.518
Total	100.0	1.000
Coating		
Ethacrylic/Methacrylic acid esters (Eudragit RS100)	45.0	0.450
Ethacrylic/Methacrylic acid esters (Eudragit RL100)	45.0	0.450
Propylene glycol	9.0	0.090
Talc	1.0	0.010
Total	100.0	1.000
Pellet C: Delayed-Release Component		
Microcrystalline cellulose	25.0	0.250
Hydroxypropyl methylcellulose phthalate	10.0	0.100
Tartaric acid	10.0	0.100
Sodium monoglycerate	7.5	0.075
Diethyl sodium sulfosuccinate	0.5	0.005
Carbamazepine	47.0	0.470
Total	100.0	1.000
Coating		
Cellulose acetate phthalate (CAP)	60.0	0.600
Ethylcellulose	25.0	0.250
PEG400	15.0	0.150
Total	100.0	1.000

Cefaclor Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Cefaclor	250.00
15.00	2	Starch	15.00
5.00	3	Silicon fluid 350 CS	5.00
4.00	4	Magnesium stearate	4.00

Note: For 500-mg strength, fill proportionally higher quantity.

Manufacturing Directions

1. Mix cefaclor with silicon fluid and magnesium stearate.
2. Slug and granulate if necessary for flow.

3. Mix with starch powder.
4. Fill in appropriate size 2 capsules. Finish capsules with polishing methods.

Cefdinir Capsules and Oral Suspension*

Capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, polyoxyl 40 stearate, magnesium stearate, and silicon dioxide. The capsule shells contain FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, gelatin, and sodium lauryl sulfate. Powder for oral suspension, after reconstitution, contains 125 mg/5 mL cefdinir and the following inactive ingredients: sucrose, citric acid, sodium citrate, sodium benzoate, xanthan gum, guar gum, artificial strawberry and cream flavors, silicon dioxide, and magnesium stearate.

Cefixime for Oral Suspension*

Powder for oral suspension, when reconstituted, provides 100 mg/5 mL. The powder for oral suspension is strawberry flavored and contains sodium benzoate, sucrose, and xanthan gum.

Cefpodoxime Proxetil for Oral Suspension*

Each 5 mL of oral suspension contains cefpodoxime proxetil equivalent to 50 or 100 mg of cefpodoxime activity after

constitution and the following inactive ingredients: artificial flavorings, butylated hydroxy anisole (BHA), carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

Cefprozil for Oral Suspension*

Cefprozil for oral suspension contains cefprozil equivalent to 125 or 250 mg of anhydrous cefprozil per 5 mL of constituted suspension. In addition, the oral suspension contains the following inactive ingredients: aspartame, cellulose, citric acid, colloidal silicone dioxide, FD&C red No. 3, flavors (natural and artificial), glycine, polysorbate 80, simethicone, sodium benzoate, sodium carboxymethylcellulose, sodium chloride, and sucrose.

Ceftibuten Capsules and Oral Suspension*

Capsules contain ceftibuten dihydrate equivalent to 400 mg of ceftibuten. Inactive ingredients contained in the capsules formulation include magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell and band contain gelatin, sodium lauryl sulfate, titanium dioxide, and polysorbate 80. The capsule shell may also contain benzyl alcohol, sodium propionate, edetate calcium disodium, butyl-

paraben, propylparaben, and methylparaben. Oral suspension after reconstitution contains ceftibuten dihydrate equivalent to 90 mg of ceftibuten per 5 mL. Oral suspension is cherry flavored and contains the following inactive ingredients: cherry flavoring, polysorbate 80, silicon dioxide, simethicone, sodium benzoate, sucrose (approximately 1 g/5 mL), titanium dioxide, and xanthan gum.

Ceftibuten for Oral Suspension

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
72.00	1	Ceftibuten trihydrate	72.00
0.40	2	Polysorbate 80	0.40
0.80	3	Simethicone	0.80
16.00	4	Xanthan gum	16.00
10.00	5	Silicone dioxide	10.00
18.00	6	Titanium dioxide	18.00
8.00	7	Sodium benzoate	8.00
3.66	8	Cherry flavor, natural and artificial (microencapsulated)	3.66
QS	9	Sucrose QS to 1 kg	QS

Manufacturing Directions

Note: This formulation, upon reconstitution, gives a final concentration of 19 mg/mL. For 36 mg/mL, use 144.00 g of item 1 and 4 g of item 7. Adjust quantity of item 1 based on mois-

ture content. The quantity given here is for anhydrous form; adjust with item 9.

1. Pass all items through an 80-mesh screen and blend.
2. Fill into 60-mL bottles at either 5, 7.5, or 15 g, or 120-mL bottles at 25 or 30 g aliquots.

Cefuroxime for Oral Suspension*

The oral suspension, when reconstituted with water, provides the equivalent of 125 or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. It contains the following in-

active ingredients: povidone K30, stearic acid, sucrose, and tutti-frutti flavoring.

Celecoxib Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
200.00	1	Celecoxib	200.00
204.00	2	Lactose	204.00
12.00	3	Sodium lauryl sulfate	12.00
7.00	4	Polyvinyl pyrrolidone potassium 30	7.00
—	5	Isopropyl alcohol	45.00 L
6.00	6	Polyvinyl pyrrolidone potassium 30	6.00
6.00	7	Magnesium stearate	6.00
15.00	8	Talc	15.00
50.00	9	Croscarmellose sodium	50.00

Manufacturing Directions

- Charge items 1 to 3 in suitable vessel after passing through a No. 60 mesh and mix for 15 minutes.
- In a separate container, mix and prepare a solution of items 4 and 5.
- Add step 2 into step 1 and mix, pass the granules through a 2.5-mm sieve, dry the granules at 40°C in an open room or a fluid-bed dryer to moisture of NMT 1%.
- Pass the dried granules through a No. 30 sieve and recycle through 1.5-mm sieve to size all granules through No. 30 mesh.
- Pass items 7 to 9 through No. 40 mesh and add to step 4; mix for 5 to 10 minutes.
- Tap density is NMT 0.80 g/cc; fines are NMT 10%.
- Fill 600 mg in size 0 capsules.

Celecoxib Tablets Celebrex*

Celebrex oral capsules contain 100 and 200 mg of celecoxib. The inactive ingredients in Celebrex capsules include croscarmellose sodium, edible inks, gelatin, lactose monohy-

drate, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

Cellulose Triacetate Liquefiable Topical Powder

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
120.00	1	Cellulose triacetate	120.00
880.00	2	Dow Corning [®] 345	880.00

Manufacturing Directions

- A liquefiable powder was prepared by evaporative spray drying. Dow Corning 345, a slightly volatile cyclic silicone liquid, was used as the porogen.
- Cellulose triacetate (40 g) was dissolved in 3000 g of methylene chloride by moderate stirring for 4 hours. To that solution was added 270 g of the porogen dissolved in 1000 g of methylene chloride.
- The resulting homogeneous solution was sprayed at 1000 psi from a 0.0135-in nozzle, downward into a tower 100 cm in diameter and 300 cm tall, through which 1250 L/min of solvent-free air was passing from top to bottom.
- The evaporatively formed powder was collected on a fabric filter spanning the bottom of the tower and the solvent-laden air was passed through carbon beds to collect and recover solvent.
- The product was transferred to a steel tray and exposed as a 1-cm deep layer in a ventilated hood for 25 minutes to remove residual solvent.
- An analysis showed 12% cellulose triacetate, 88% DC 345, and less than 4 ppm of residual methylene chloride.
- The white powder readily could be dusted onto the feet and made to liquefy and vanish by gentle rubbing.

Cephalexin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Cephalexin, USE cephalexin monohydrate (0–2% excess)	526.31
2.50	2	Magnesium stearate	2.50
QS	3	Cornstarch	600.00

Manufacturing Directions

- Charge magnesium stearate, cornstarch, and one-tenth part of cephalexin into a suitable mixer. Mix well.
- Pass blend from step 1 and balance of cephalexin through an 840-mm aperture screen by hand or with a mechanical shaker.
- Charge into a suitable mixer and mix well. Discharge into polyethylene-lined drums.

- Note:* For slugging, first use 624 mg of magnesium stearate; balance after milling slugs through a 1.2-mm aperture screen in an oscillating granulator.
- Machine fill using either size 00 or size 0 capsules; the theoretical weight of 10 capsules is 6 g. Sort and final clean with sodium chloride.

Cephalexin Powder for Oral Suspension

Bill of Materials			
Scale (mg/5 mL) ^a	Item	Material Name	Qty/5 l (g)
125.00	1	Cephalexin, USE cephalexin monohydrate, 1.5% excess	131.50
0.50	2	FD&C No. 6	0.50
10.00	3	Orange flavor	10.00
5.00	4	Vanilla dry flavor	5.00
5.00	5	Raspberry dry flavor	5.00
277.54	6	Castor sugar	277.54
2844.80	7	Castor sugar	2844.80

^aUpon reconstitution as recommended. For 250-mg strength, adjust with items 6 and 7.

Manufacturing Directions

- Charge items 2 to 6 in a suitable mixer and mix for 5 minutes.
- Add item 1 in portions and mix well.
- Pass through a Fitz mill, impact forward at high speed using sieve 24338.

- Collect milled powder in step 3 in a suitable mixer and mix for 10 minutes.
- Pass item 7 through 900-mm sieve, add 15% of quantity to step 4, and mix for 10 minutes.
- Load in a double-cone blender. Add the balance of item 7 from step 5 and mix for 20 minutes.
- Fill appropriate quantity in bottles.

Cephadrine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Cephadrine, USE cephadrine compacted (1000 µg/mg with 5% moisture) ^a	526.00
7.00	2	Magnesium stearate	7.00
8.40	3	Talc	8.40
18.60	4	Lactose monohydrate ^b	18.60

^aAdjust according to potency; taken as 105.2% of label.

^bAdjust according to quantity of item 1.

Manufacturing Directions

- Process limits are relative humidity: 40% to 45%, temperature: 20°C to 25°C.
- Pass item 1 through 630-µm sieve; crush larger particles in a Frewitt mill using a 1-mm sieve.
- Load approximately half of item 1 from steps 1 and 2 into a mixer.

- Sift items 2 to 4 through a 250-mm sieve in a suitable blender; blend for 5 minutes at slow speed.
- Charge balance of item 1 to step 4 and blend for 5 minutes at slow speed.
- Fill 560 mg per capsule.

Cephadrine Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/5 L (g)
125.00	1	Cephadrine, USE cephradine monohydrate with 10.8% excess ^a	131.50
8.00	2	Sodium citrate	8.00
4.00	3	Citric acid anhydrous	4.00
10.00	4	Guar gum	10.00
5.00	5	Methylcellulose, 15 cps	5.00
2.00	6	Yellow FD&C No. 6	2.00
20.00	7	Blood orange flavor	20.00
10.00	8	Orange banana flavor	10.00
3095.28	9	Castor sugar	3095.28

^aFor 250 mg/5 mL, adjust active ingredient and adjust with item 9.

Manufacturing Directions

1. Pass item 9 through a 500-mm sieve for use in later steps.
2. Charge items 1 to 6 in a mixing vessel and add approximately 10% of item 9 from step 1; mix for 5 minutes.
3. Pass the powder mixture in step 2 through a Fitz mill.
4. Charge 10% of item 9 from step 1 in a separate mixing vessel and add items 7 and 8; blend for 5 minutes.
5. Add to step 3 and blend for 5 minutes.
6. Pass step 5 through a 500-mm sieve.
7. Add item 9 (about 15%) and mix for 5 minutes; transfer to a double-cone blender.
8. Add 40% of item 9 and mix for 10 minutes.
9. Add the balance of item 9 and mix for another 15 minutes.
10. Fill weight for 100 mL = 66 g; fill weight for 60 mL = 39.60 g.

Cevimeline Capsules

Each capsule contains 30 mg of active ingredient. The inactive ingredients are lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate.

Cevimeline Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
30.00	1	Cevimeline	30.00
60.00	2	Hydroxypropyl cellulose	50.00
15.00	3	Sodium carboxymethyl cellulose cross-linked	15.00
189.00	4	Lactose	189.00
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Sift items 1 to 3 through an 80-mesh screen and blend.
2. Pass item 5 through a 100-mesh screen and add to step 1 and blend for 3 minutes.
3. Fill 300 mg in size 0 capsules.

Chlordiazepoxide Hydrochloride Capsules*

It is available as capsules containing 5, 10, or 25 mg chlordiazepoxide HCl. Each capsule also contains cornstarch, lactose, and talc. Gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, with the following dye systems: for 5-mg capsules—FD&C yellow No. 6 plus

D&C yellow No. 10, and either FD&C blue No. 1 or FD&C green No. 3; for 10-mg capsules—FD&C yellow No. 6 plus D&C yellow No. 10, and either FD&C blue No. 1 plus FD&C red No. 3 or FD&C green No. 3 plus FD&C red No. 40; for 25-mg capsules—D&C yellow No. 10 and either FD&C green No. 3 or FD&C blue No. 1.

Chlordiazepoxide Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Chlordiazepoxide hydrochloride	5.10
114.00	2	Starch dried	114.00
26.00	3	Dicalcium phosphate	26.00
40.00	4	Talc	40.00

Manufacturing Directions

1. Charge all ingredients in a suitable mixer after passing through a No. 60 mesh and mix for 30 minutes.

2. Fill 185 mg in size 4 capsules.

Chloroxylenol and Chlorhexidine Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Chloroxylenol	10.00
10.00	2	Chlorhexidine diacetate	10.00
30.00	3	Magnesium-L-lactate	30.00
10.00	4	Allantoin	10.00
100.00	5	Zinc stearate	10.00
840.00	6	Cornstarch	840.00

Manufacturing Directions

1. Pass all items through a 100-mesh screen and blend.

2. Fill; for use as a topical anti-infective formulation.

Chlorpromazine Sustained-Release Capsules*

Each capsule, with opaque orange cap and natural body, contains chlorpromazine hydrochloride as follows: 30 or 75 or 150 mg. Inactive ingredients consist of benzyl alcohol, calcium sulfate, cetylpyridinium chloride, FD&C yellow No. 6,

gelatin, glyceryl distearate, glyceryl monostearate, iron oxide, povidone, silicon dioxide, sodium lauryl sulfate, starch, sucrose, titanium dioxide, wax, and trace amounts of other inactive ingredients.

Cimetidine Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
275.00	1	Cimetidine	275.00
525.00	2	Sodium alginate	525.00
QS	3	Calcium chloride 2%	QS
QS	4	Poly-L-glycine 0.05%	QS

Manufacturing Directions

- Item 2 is dissolved in 17.5 L of distilled water at 25°C and item 1 is added to this solution with constant mixing.
- This preparation is added drop-wise to a 2% calcium chloride solution through a small orifice that delivers droplets that are 1 mm in diameter. The spherical beads of cimetidine-containing calcium alginate thus formed are collected by filtration and washed 3 times with distilled water.
- The beads are then immersed in a 0.05% aqueous solution of poly-L-lysine (molecular weight 14000) for 4 hours, then

- washed again 3 times with distilled water, collected by filtration, and dried under vacuum for 24 hours. The beads thus produced are filled into gelatin capsules (800 mg per capsule, providing a dose of 275 mg of cimetidine).
- This dosage form for the delivery of cimetidine over an extended time period allows for through-the-night protection for patients who suffer from excess gastric acidity without the high bedtime dose that conventional dosage forms require for this duration of protection. The high bedtime dose otherwise required for such protection is associated with untoward side effects, which are reduced through use of the dosage form described in this example.

Citrate Effervescent Powder

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/kg (g)
0.50	1	Oil lemon terpeneless	0.50
10.00	2	Lemon flavor (natural microseal)	10.00
QS	3	Alcohol dehydrated (absolute, doubly rectified)	6.50
440.33	4	Sodium bicarbonate	440.33
0.35	5	Saccharin sodium	0.35
157.50	6	Anhydrous sodium citrate	157.50
178.82	7	Anhydrous citric acid (powder)	178.82
222.50	8	Acid tartaric	222.50

Manufacturing Directions

- All processing should be done in controlled humidity at a maximum relative humidity of 40% at 25°C.
- Sodium citrate and citric acid are anhydrous.
- Dissolve lemon oil in dehydrated alcohol with stirring in a suitable container (do not follow this step if using powdered lemon flavor).
- Sift sodium bicarbonate, if necessary, through a 595- μ m screen.
- Charge into a suitable mixer and mix for 10 minutes.
- Very slowly add solution from first step to the mixer while mixing; continue mixing for at least 10 minutes and up to a total of 30 minutes, depending on equipment.
- Screen the massed granulation mixture through a 595- μ m screen and divide approximately in half.
- Premix saccharin sodium into sodium citrate (and lemon powder, if used) and sift through a 595- μ m screen or

- mill fitted with a 595- μ m screen (knives forward, medium speed).
- Sift both citric acid and tartaric acid separately through a 595- μ m screen or mill separately using a comminuting mill with a 595- μ m aperture (knives forward, medium speed).
 - Load materials into a suitable blender, preferably in the following order: milled tartaric acid, milled citric acid, half of granulation mixture, milled saccharin sodium, sodium citrate, and remaining granulation mixture.
 - Blend for 20 minutes and pack into double plastic bags inside fiber drums.
 - Provide silica gel protection to maintain low humidity in drums.
 - If blended material is lumpy, pass through a 1.2-mm screen before bagging.

Clindamycin Capsules*

Clindamycin hydrochloride capsules contain clindamycin hydrochloride equivalent to 150 mg of clindamycin. The inactive ingredients are cornstarch, FD&C blue No. 1, FD&C

yellow No. 5, gelatin, lactose, magnesium stearate, talc, and titanium dioxide.

Clindamycin Capsules (150 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Clindamycin, USE clindamycin hydrochloride	163.00
12.00	2	Lactose	12.00
3.00	3	Magnesium stearate	3.00
24.00	4	Talc	24.00
2.00	5	Aerosil 200	2.00
65.00	6	Starch dried	65.00

Manufacturing Directions

1. Pass all items through a No. 60 mesh and mix well for 30 minutes.

2. Fill 270 mg in size 2 capsules.

Clofibrate Capsules

Each capsule contains 500 mg of clofibrate for oral administration. Capsules also contain the following inactive ingredients: D&C red No. 28, D&C red No. 30, D&C yellow No. 10,

FD&C blue No. 1, FD&C red No. 28, FD&C red No. 40, FD&C yellow No. 6, and gelatin.

Clonidine Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.10	1	Clonidine hydrochloride (equivalent to 0.087 mg clonidine base) 100 μ m or finer	0.10
70.00	2	Methocel [®] E4M ^a	70.00
129.90	3	Lactulose ^b	129.90

^aThis formulation is intended to provide an 8-hour release pattern; for an extended release pattern of 12 hours, use Methocel[®] K100M.

^bCornstarch can be used in place of lactulose.

Manufacturing Directions

1. This is a low-dose product that requires a careful geometric dilution of item 1 with portions of item 3.

2. Add the triturate in step 1 in one-half of item 3 and mix well.
3. Add item 2 and mix well; add balance of item 3.
4. Fill 200 mg in an appropriate capsule size.

Clorazepate Dipotassium Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
7.50	1	Clorazepate dipotassium	7.50
10.00	2	Potassium carbonate dried	10.00
0.45	3	Silicon dioxide colloidal	0.45
168.00	4	Talc	168.00
QS	5	Sodium chloride granules (for cleaning)	QS

Manufacturing Directions

Note: Avoid exposing clorazepate to light and moisture; process in low humidity area (46 grains, 35% RH at 76°F).

1. Blending
 - a. Determine LOD (1 hour Brabender or equivalent at 105°C) of potassium carbonate dried (NMT 0.5%), silicon dioxide (NMT 2.5%), and talc (NMT 0.3%).
 - b. Mill while mixing the potassium carbonate and silicon dioxide through a 60-mesh (250-mm aperture) screen using a Fitz mill or a similar mill, impact forward, high speed.
 - c. Premix screened clorazepate with the milled mixture of potassium carbonate and silicon dioxide in a suitable container. Pass the mix through a 40-mesh (420-mm) screen by hand. Clean the screen with a small portion of talc (approximately 0.63 g). Use rubber gloves when handling clorazepate.
- d. Charge about half of the remaining talc into a V-blender or a similar blender. Add the preblend from step C and, finally, the remaining talc. Blend for 30 minutes. Discharge into polyethylene-lined drums, tightly tie, and seal.
2. Filling
 - a. Fill blended material into hard gelatin capsules; fill weight for 10 caps is 1.85 g (± 0.06 g). Sort capsules on sort vibrator, clean with sodium chloride, and store in polyethylene-lined drums.
3. Printing
 - a. Print capsules using edible ink.

Coated Spheroids

Uncoated spheroids (24% w/w vinpocetine)	3.00 kg
Hydroxypropyl methylcellulose 2910, 4000 cps	0.075 kg
Methylene chloride	4.98 kg
Methanol anhydrous	2.96 kg
Eudragit E30D aqueous dispersion	1.00 kg
Calcium stearate	0.03 kg
Simethicone emulsion	0.0025 kg
Water purified	0.50 kg

Manufacturing Directions

1. Vinpocetine hydrochloride (10 kg), microcrystalline cellulose (Avicel-PH-101, 80 kg), and citric acid monohydrate (10 kg) are blended together in a 450-L planetary mixer. Water (100 kg) is added and the mixer is run for 10 minutes until a homogeneous plastic mass is obtained. The mass is extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1 mm in diameter.
2. The damp extrudates (in batches of 15–20 kg) are placed in a spheronizer in which the rotating disc (diameter 68 cm) is rotated at 300 to 400 rpm. The rotation is continued for 20 minutes and the resulting spheroids are then dried at 80°C in a fluidized bed drier. The dried spheroids are passed over a 1.2-mm screen and those that passed through are subjected to a 0.5-mm screen. The over- and undersized spheroids are discarded.
3. The finished dosage form consists of a hard gelatin capsule containing a powder blend of vinpocetine and two types of spheroids. The formulation particulars are based on 30 mg per capsule, although they can be designed to provide other dosage strengths.
4. The vinpocetine powder blend (or first group of spheroids) provides the loading dose (e.g., 5 mg of vinpocetine).
 - a. Blend the vinpocetine, lactose microcrystalline cellulose, starch, glutamic acid, sodium starch glycolate, talc triturate, and the sodium lauryl sulfate into the PK[®] blender for 20 minutes with intensifier bar running.
 - b. Pass the step 1 blend through a Fitz mill using a No. 1B screen, medium speed, knives forward.
 - c. Return the granulation from step 2 to the PK blender and add the magnesium stearate and blend for 2 minutes without the intensifier bar on.
5. The second and third types of spheroids are categorized as
 - a. pH-sensitive coated spheroids to provide a second dose (pH >6.5) (e.g., 12 mg vinpocetine). Uncoated spheroids are placed in a fluidized bed coater. The Eudragit S solution is applied using a peristaltic pump. The spheroids are dried.
 - b. Coated spheroids to provide a third dose 4 to 10 hours post ingestion (e.g., 13 mg vinpocetine). Process for applying undercoat: The uncoated spheroids are placed in a fluidized bed coater. Methocel E4MP solution is

sprayed using a peristaltic pump. The spheroids are dried. Process for applying overcoat: Eudragit E30D suspension containing calcium stearate is sprayed on the Methocel E4MP-coated spheroids using a peristaltic pump. The spheroids are dried.

- Capsules are filled with the powder blend, pH-sensitive coated spheroids, and coated spheroids on an encapsulating machine capable of dual filling powders and spheroids.

Crospovidone Water-Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1000.00	1	Crospovidone M (BASF)	1000.00
50.00	2	Aerosil 200	50.00
250.00	3	Sucrose (crystalline)	250.00
5.00	4	Saccharin sodium	5.00
2.00-3.00	5	Flavors	2.00-3.00
380.00	6	Water	380.00
5.00	7	Magnesium stearate	5.00

Manufacturing Directions

- Granulate mixture of items 1 to 5 with item 6, dry, and pass through a sieve.
- Mix the dry granules with item 7 and press with low compression force.

- The dosage may be increased to 2000 mg crospovidone by increasing the tablet weight to 2600 mg.
- Compress 1280-mg tablets using 20-mm biplanar punches.

Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00 µg	1	Cyanocobalamin; use gelatin-coated cyanocobalamin (0.1%)	50.00
150.00	2	Ludipress [®]	150.00
1.50	3	Magnesium stearate	1.50
2.00	4	Sicovit Quinoline lake, yellow	2.00
3.00	5	Sicovit yellow lake, orange	3.00

Manufacturing Directions

- Prepare a premix of item 1 and 2 and add to items 3 to 5.
- Pass through a 0.5-mm sieve and press with low compression force.

- Compress into 209-mg tablets using 8-mm biplanar punches.

Cyclosporin A Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Cyclosporin A	100.00
300.00	2	Crephor RH (or Tween)	300.00

Manufacturing Directions

Mix ingredients and fill in hard gelatin capsules of a type that will not interact with ingredients. Optionally, the com-

position may contain ethanol 8%, propylene glycol 8%, or polyethylene glycol 300, 30% by weight.

Dantrolene Sodium Capsules*

It is supplied in capsules of 25, 50, and 100 mg. Each capsule contains the following inactive ingredients: edible black ink, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, starch, synthetic iron oxide red, synthetic iron oxide yellow, talc, and titanium dioxide.

Dextroamphetamine Sulfate Capsules*

Each sustained-release capsule is so prepared that an initial dose is released promptly, and the remaining medication is

released gradually over a prolonged period. Each capsule containing 5 to 15 mg of active and inactive ingredients consist of cetyl alcohol, D&C yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C blue No. 1, FD&C blue No. 1 aluminum lake, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres, and trace amounts of other inactive ingredients.

Diclofenac and Misoprostol Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Diclofenac delayed-release beads (47% diclofenac)	214.00
0.20	2	Misoprostol (dilute 1:100 on HPMC)	20.00
150.00	3	Microcrystalline cellulose	150.00
4.00	4	Stearic acid	4.00
9.00	5	Talc	9.00

Manufacturing Directions

- Item 1 beads are prepared by spray coating a suspension or solution of diclofenac sodium onto a nonpareil sugar core, together with a binder (e.g., polyvinylpyrrolidone or hydroxypropyl methylcellulose).
- The beads are subsequently coated with a delayed-release coating (e.g., methylmethacrylate, e.g., Eudragit). Mixtures of beads with various levels of coating are used to give the required therapeutic release pattern.
- In a fluidized-bed apparatus, uniform spherical inert sugar sphere cores are coated with a first layer consisting of the compounds, an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, and talc.
- The second layer consists of an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydrox-

ypropyl cellulose, talc, and a pigment, such as titanium dioxide.

- The third and enteric coating layer consists of an enteric coating polymer, such as copolymerized methacrylic acid/methacrylic acid methyl esters, a plasticizer, such as triethyl acetate or similar plasticizers, and talc.
- The layers are applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions. Pseudozero release is obtained by the use of a mixture of beads.
- The beads in item 1 contain 47% diclofenac, giving a dose per capsule of 75 mg.
- The mixture of items 1 to 4 is filled into suitable hard gelatin capsules.

Diclofenac Spheronized Pellets for Sustained-Release Coating (30%)**Formulation**

Diclofenac sodium, 300 g; Avicel PH101 (5), 438 g; granulac 230 (8), 237 g; Kollidon VA64 (1), 25 g; water, approximately 580 g.

Manufacturing Directions

- Granulate the mixture (I) in a Diosna granulator with water (II) and press the humid granules through a sieve of

1.5 mm. Form pellets in a spheronizer during 10 minutes with the rotation speed of 380 to 420 rpm. Dry the pellets in a fluidized bed at 70°C.

- Fill at relative humidity that does not exceed 45% and a temperature of 20°C to 25°C.
- Calculate exact amount based on quantity of active ingredient in uncoated beads.
- Fill 192.5 mg based on 100% potency basis.

Diclofenac Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Diclofenac, USE diclofenac sodium pellets (520 mg/g)	192.50

Diclofenac Granules

1. Preparation of uncoated granules:
 - a. 800 g of diclofenac sodium, 200 g of citric acid, and 200 g of cornstarch are mixed and pulverized.
 - b. The fine powders thus prepared are processed to produce spherical granules, using 600 g of purified sucrose that was obtained by shifting through 20 to 28 mesh as a core, while spraying a solution of 25 g of hydroxypropyl cellulose in 475 g of ethyl alcohol.
 - c. The granules are then dried for 3 hours at 55°C.
 - d. These dried granules are then passed through a 14 mesh, followed by passage through a 28 mesh. The granules that do not go through the 28 mesh are taken as uncoated granules A. The formulation of uncoated granules A is as follows.

Component	% by weight
Diclofenac sodium	43.7
Citric acid	11.0
Cornstarch	11.0
Purified sucrose	32.9
Hydroxypropyl cellulose	1.4
Total	100.0

- e. Alternate method of preparing uncoated granules:
 - i. 1000 g of diclofenac sodium, 30 g of fumaric acid, and 170 g of cornstarch are mixed and pulverized.
 - ii. The fine powders thus produced are processed to produce spherical granules, using 600 g of purified sucrose that is obtained by shifting through a 20 to 28 mesh as a core, while spraying a solution of 25 g of hydroxypropyl cellulose in 475 g of ethyl alcohol.
 - iii. The granules are then dried for 3 hours at 55°C.
 - iv. These dried granules are then passed through a 14 mesh followed by passage through a 28 mesh. The granules that do not go through the 28 mesh are taken as uncoated granules. The formulation of this uncoated granules B is as follows.

Component	% by weight
Diclofenac sodium	54.8
Fumaric acid	1.6
Cornstarch	9.3
Purified sucrose	32.9
Hydroxypropyl cellulose	1.4
Total	100.0

2. Preparation of long-acting granules:
 - a. 600 g of uncoated granules are placed into a coating apparatus with a fluidized bed.
 - b. The granules are spray-coated with 1263 g of a coating liquid having the following composition according to a conventional method to produce long-acting granules. The weight of the coat was approximately 8% of the weight of the uncoated granules.

Component	% by weight
Ethylcellulose	2.7
Polyvinyl pyrrolidone K30	0.9
Talc	0.2
Ethyl alcohol	96.2
Total	100.0

3. Preparation of long-acting granules, alternate method:
 - a. 600 g of uncoated granules B are placed into a coating apparatus with fluidized bed.
 - b. The granules are spray-coated with 1667 g of a coating liquid having the following composition according to a conventional method to produce long-acting granules. The amount of the coat is approximately 20% based on the weight of the uncoated granules.

Component	% by weight
Methacrylic acid copolymer S	6.5
Glycerin fatty acid ester	0.5
Talc	0.2
Ethyl alcohol	92.8
Total	100.0

4. Preparation of long-acting granules having an exterior rapid-releasing layer:
 - a. 50.7 g of diclofenac sodium and 149.3 g of cornstarch are mixed and pulverized.
 - b. The fine powders thus produced are processed to produce spherical granules, using 500 g of the long-acting granules (step 6) as a core, while spraying a solution of 4 g of hydroxypropyl cellulose in 76 g of ethyl alcohol.
 - c. The granules are then dried for 2 hours at 55°C to produce long-acting granules. These granules have an exterior rapid-releasing layer.

Didanosine Delayed-Release Capsules*

The delayed-release capsules, which contain enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine Delayed-Release Capsules Enteric-Coated Beadlets*

Delayed-release capsules, containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the

beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine for Oral Suspension

The powder for oral solution is supplied for oral administration in single-dose packets containing 100, 167, or 250 mg of didanosine. Packets for each product strength also contain a citrate-phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose. Pediatric powder for oral solution is supplied for oral administration in 4- or 8-oz glass bottles containing 2 or 4 g of didanosine respectively. The chemical name for didanosine is 2c,3c-dideoxyinosine.

Diethyl Toluamide Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
552.00	1	<i>N, N</i> -diethyl- <i>m</i> -toluamide (DEET)	600.00
368.00	2	2-Octyldodecanol	400.00
QS	3	Methylene chloride	QS
80.00	4	Cellulose triacetate	400.00

Manufacturing Directions

1. A liquefiable powder was prepared by spray evaporative drying. A liquid porogen was prepared from 60 parts by weight of *N, N*-diethyl-*m*-toluamide (DEET) and 40 parts by weight of 2-octyldodecanol, a heavy secondary alcohol commonly used in cosmetic formulations.
2. Cellulose triacetate (40 g) was dissolved in 3000 g of methylene chloride by moderate stirring for 4 hours. To that solution was added 460 g of the previously prepared porogen diluted with 1000 g of methylene chloride.
3. The resulting homogeneous solution was sprayed at 1000 psi from a 0.0135-in nozzle, downward into a tower (100 cm in diameter × 300 cm tall), through which 1250 L/min of solvent-free air was passing from top to bottom.
4. The evaporatively formed powder was collected on a fabric filter spanning the bottom of the tower and the solvent-laden air was passed through carbon beds to collect and recover solvent.
5. The product was transferred to a steel tray and exposed as a 1-cm deep layer in a ventilated hood for 25 minutes to remove residual solvent. Analysis showed 8% cellulose triacetate, 36.8% octyldodecanol, and 55.2% DEET, with less than 5 ppm or residual methylene chloride.
6. The resulting white powder could be readily dusted onto the skin and made to liquefy and vanish by gentle rubbing without any perceptible grit or stickiness.

Difluoromethylornithine-Alpha Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/2000 Caps (g)
		Rapid-release granules	
50.00	1	Difluoromethylornithine-alpha (DFMO)	100.00
50.00	2	Microcrystalline cellulose (MCC) Avicel PH101	100.00
QS	3	Water purified	QS
		Slow-release granules	
250.00	4	Difluoromethylornithine-alpha	500.00
250.00	5	Microcrystalline cellulose PH101	500.00
15-25.00	6	Eudragit RS 30D	30-50
QS	7	Triethyl citrate	QS
QS	8	Water purified	QS

Manufacturing Directions

- Rapid-release granules: DFMO (100 g) and microcrystalline cellulose (MCC, Avicel PH101, 100 g) are mixed thoroughly. A sufficient amount of water to make a wet mass is added to the mixture, which is subsequently extruded and spheronized. The pellets are screened (size 14–20 mesh) and dried at 40°C for 24 hours. Polyvinyl pyrrolidone (PVP, 2% by weight of total mass) can optionally be included in the formulation. Increasing PVP will generally lengthen the release profile of the formulation.
- Slow-release granules: DFMO (500 g), MCC (500 g), and Eudragit (35–50 g) are mixed. To this mixture is added sufficient water to yield a 30% weight suspension. To the suspension is added triethylcitrate (10% weight based on dry polymer weight of Eudragit) to yield a dispersion that is wet granulated and dried to remove as much water as possible. The particles are then ground into a fine powder.
- Fill the rapid-release granules (500 g prepared according) and slow-release granules (750 g prepared) after thoroughly mixing.
- Gastric-release granules: A slow gastric-release granule can be prepared as follows. DFMO (600 g), MCC (350 g), and HPC (50 g) are mixed thoroughly. To the mixture is added sufficient water to make a wet mass that is extruded and then spheronized using procedures well known in the art. The particles are then dried and ground.
- Enteric-release granules: A latex dispersion is prepared as follows. To Eudragit L 30D–55 (1000 g, 15% weight in water) is added a plasticizer (15% weight of dry polymer weight in the Eudragit) while mixing for 1 to 24 hours. Plasticizers, such as triethylcitrate, tributylcitrate, acetyl-tributylcitrate, or dibutylsebacate, can be used. To this mixture is added talc (50% weight of dry polymer in the Eudragit) or glycerylmonostearate (10% weight of dry polymer in the Eudragit) to form a dispersion. The rapid-release granules are coated in a fluidized bed with the latex dispersion until a 10% to 15% weight increase in granule weight is achieved. The fluidized bed inlet air temperature is adjusted to approximately 40°C to 45°C and the outlet air temperature is adjusted to approximately 30°C to 35°C with a spray rate of about 2 g/min.
- Slow-release granules: Granules previously prepared are coated with Eudragit L 30D (10–12% weight) or Aquateric (CAP, 10% weight, plasticized with TEC) until a 25% to 30% weight increase in granule weight is achieved.
- Colorectal-release granules: A dispersion is prepared as follows. To Eudragit S100 (1000 g, 10% weight in water) is added a plasticizer (10% weight of dry polymer weight in the Eudragit) while mixing for 1 to 24 hours. Plasticizers, such as triethylcitrate, tributylcitrate, acetyl-tributylcitrate, or dibutylsebacate, can be used. To this mixture is added talc (50% weight of dry polymer in the Eudragit) to form a dispersion. The rapid-release granules previously prepared are coated in a fluidized bed with this dispersion until a 15% weight increase in granule weight is achieved.
- Slow-release granules: A mixture is prepared as follows. Eudragit RS 30D (1000 g, 15% weight aqueous dispersion, Aquacoat[®] or Surelease[®]) is plasticized with triethylcitrate (TEC, 20% wt of dry polymer in the Eudragit) for 1 to 24 hours. Talc (50% weight of dry polymer in the Eudragit) is added with mixing to form the mixture. The rapid-release granules are coated with this mixture until a 10% to 15% weight increase in granule weight is achieved. The coated granules are then coated with a Eudragit S100 dispersion as done immediately above until a 10% to 15% weight increase in granule weight is achieved.
- Sustained-release granules: This procedure employs a double granulation. Thus, DFMO (500 g), MCC (500 g), and Eudragit RS 30D (75–100 g) are mixed. To this mixture is added sufficient water to yield a 30% weight suspension. To the suspension is added TEC (10% weight based on dry polymer weight of Eudragit) to yield a dispersion that is wet granulated and dried to remove as much water as possible. The granules are then ground into a fine powder. To the powder is added sufficient water to make a wet mass that is extruded, spheronized, dried, ground, and screened (size 14–20 mesh).
- Gastric-, enteric-, and colorectal-release granules: The following procedure details the preparation of the dosage form. Rapid gastric-release granules (450 g, prepared previously), rapid enteric-release granules (100 g, prepared previously), and slow colorectal-release granules (450 g, prepared previously) are mixed thoroughly. Hard gelatin capsules are then filled with the mixture.

Diltiazem Hydrochloride Extended-Release Capsules*

The extended-release capsules contain diltiazem hydrochloride in extended-release beads in doses of 120, 180, 240, 300, 360, and 420 mg. They also contain microcrystalline cellulose, sucrose stearate, Eudragit, povidone, talc, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polysorbate, simethicone, gelatin, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, FD&C green No. 3, black iron oxide, and other solids.

In another formulation, the 120-, 180-, 240-, and 300-mg capsules also contain black iron oxide, ethylcellulose, FD&C blue No. 1, fumaric acid, gelatin, sucrose, starch, talc, titanium dioxide, white wax, and other ingredients. The 360-mg capsule also contains black iron oxide, diethyl phthalate, FD&C blue No. 1, gelatin, povidone K17, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other ingredients.

Manufacturing Directions

The rapid-release pellets of diltiazem can be manufactured by the following procedure: 2 kg of microgranules composed of sucrose and starch, with a particle size of 0.500 to 0.710 mm, are rotated in a trough with a stainless steel basket that is 450 mm in diameter. The rotating mass is sprayed, by means of a membrane-type proportioning pump, with 26 g of a 40% strength solution of shellac in ethanol and sprinkled with 80 g of diltiazem with a particle size of 40 to 80 mm.

The sustained-release pellets can be manufactured by following procedure: 2 kg of saccharose/starch pellets having a particle size between 0.500 and 0.710 mm are put in rotation in a suitable coating pan. The rotating mass is sprayed with 27.2 g of an ethanolic solution containing 9.79 g of shellac and 1.09 g of polyvinylpyrrolidone, and 80 g of diltiazem HCl are added. This operation is repeated 50 times. These pellets are then coated with the same amount of solution of ethylcellulose N100 and talc, respectively, 80 g of 0.5% solution of ethylcellulose N100, and 54 g of talc. This operation is repeated 25 times. The proportion of soluble versus insoluble coating materials can be altered to obtain the best release profile. All the formulations are tested for in vitro dissolution, in the range of pH between 1 and 7.5, using the method described in the USP, paddle apparatus.

Alternate methods of preparing coated beads include first preparing beads and then coating them. The plain beads are prepared by

Formula 1

Diltiazem hydrochloride	1120.00 g
Lactose	119.00 g
Microcrystalline cellulose (Avicel pH101)	140.00 g
Povidone K30	21.00 g

After introducing the powders into a planetary mixer and granulating same through the obtained plastic, mass is extruded through a cylinder with 1-mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60°C for 12 hours, the beads are sifted and the fraction with size comprised between 0.7 and 1.4 mm are retained. 1179 g of beads was obtained yield (84%).

Formula 2

Diltiazem HCl	560.00 g
Crodesta F 160	59.50 g
Microcrystalline cellulose (Avicel pH101)	70.00 g
Povidone K30	10.50 g

The ingredients are introduced in a planetary mixer and dry mixed for approximately 15 minutes. Thereafter, 100 mL purified water is added, and the mixing is pursued for 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal[®] extruder equipped with a 1-mm screen to obtain "spaghetti." A spheronizer-type caleva is used to transform the extruded product into beads. After drying for 12 hours on trays in an oven at 60°C, the beads are sieved to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with sizes between 0.7 and 1.4 mm was 639.1 g (yield 91.3%).

The beads prepared previously are then coated in a STREA-1 (Aeromatic-Fielder) fluidized bed using the "top spraying" technique, and 440 g of coating suspension from the following composition is applied on 500 g of beads. Thereafter, the coated beads are dried at 50°C for 16 hours.

Coating Suspension Composition

Magnesium stearate	12.50 g
Titanium dioxide	5.00 g
Povidone K30	5.00 g
Eudragit NE30D	620.00 g
Talc	17.50 g
Water	338.00 g
Simethicone	1.00 g
Tween 80	0.80 g

Diphenhydramine Hydrochloride Capsules*

Each capsule contains diphenhydramine hydrochloride 25 mg. Each capsule contains lactose and magnesium stearate. The banded capsule shell contains D&C red No. 28, FD&C red No. 3, FD&C red No. 40, FD&C blue No. 1, gelatin, glyceryl monooleate, and titanium dioxide.

Dipyridamole and Aspirin Extended-Release Capsules*

This is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg of dipyridamole in an extended-release form and 25 mg of aspirin as an immediate-release sugar-coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, aluminum stearate, colloidal silicon dioxide, cornstarch, dimethicone, hydroxypropyl methylcellulose, hy-

droxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin. Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide, and water.

Divalproex Sodium Capsules*

The sprinkle capsules are for oral administration and contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in hard gelatin capsules. The inactive ingredients in the 125-mg sprinkle capsules are cellulosic polymers, D&C red No. 28, FD&C blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

Divalproex Sodium Coated Particle Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
125.00	1	Valproic acid, USE divalproex sodium-coated particles	134.50
0.53	2	Magnesium stearate	0.53
1.00	3	Silica gel (Syloid 244)	1.00

Manufacturing Directions

1. Prepare coated particles of divalproex sodium by coating with ethylcellulose (34.34 mg), triethyl citrate (5.8 mg), and magnesium citrate (35 mg), using a mixture of alcohol and acetone in an air suspension system; screen particles us-

ing 20- and 40-mesh screens; particles larger than 20 and smaller than 40 must be reworked.

2. Make the granules by wet granulation of divalproex sodium and silica gel, using alcohol.
3. Collect 20- to 40-mesh granules after drying NMT 50°C to LOD of NMT 0.5%.

Dofetilide Capsules*

Each capsule contains the following inactive ingredients: microcrystalline cellulose, cornstarch, colloidal silicon dioxide, and magnesium stearate. It is supplied for oral administration in three dosage strengths: 125 µg (0.125 mg) orange and white capsules, 250 µg (0.25 mg) peach capsules, and 500 µg (0.5 mg) peach and white capsules.

40, yellow No. 10, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, and starch.

Doxycycline Capsules*

Available as 100- and 50-mg capsules, they contain doxycycline monohydrate equivalent to 100 or 50 mg of doxycycline for oral administration. The inert ingredients are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

Doxepin Hydrochloride Capsules*

Inert ingredients for the capsule formulations are hard gelatin capsules (which may contain blue No. 1, red No. 3, red No.

Doxycycline Hyclate Capsules*

These capsules contain specially coated pellets of doxycycline hyclate for oral administration. They also contain lactose, microcrystalline cellulose, and povidone. The capsule shell and

band contain FD&C blue No. 1, FD&C yellow No. 6, D&C yellow No. 10, gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide.

Doxycycline Hyclate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
122.00	1	Doxycycline hyclate (22% excess)	122.00
26.00	2	Microcrystalline cellulose (Avicel PH 102)	26.00
4.00	3	Starch (cornstarch dried)	4.00
0.60	4	Sodium lauryl sulfate	0.60
0.60	5	Colloidal silicon dioxide (Aerosil 200)	0.60
2.00	6	Magnesium stearate	2.00
—	7	Hard gelatin capsules, Size 3	1000.00

Manufacturing Directions

Note: Processing should be conducted in a controlled room temperature and humidity area. The limits are room temperature 20°C to 27°C, RH 40% to 45%.

- Mix items 1, 2, and 4 in a stainless steel drum. Pass the mixed material through a 500- μ m sieve using a sifter. Collect in stainless steel drum.
- Mix items 3, 5, and 6 in a polyethylene bag. Pass the mixed material through a 250- μ m sieve using a sifter. Pass two times. Collect in the polyethylene bag and transfer to step 1 in a stainless steel drum.
- Mix the material in a drum mixer for 3 minutes.
- Take a sample for assay and moisture content.
- Load the empty capsule shells (size 3) in the hopper; cap and body are ivory opaque.
- Run the machine and check the locking of shells. Run the machine. Check the fill weight (155 mg) and locking of the capsules. Collect the filled capsules from polyethylene-lined stainless steel container in silica bags and close tightly.
- Store the containers in a controlled room temperature and humidity area. The limits are RH 45% to 50% at a temperature of 25°C to 27°C.

Doxycycline Hydrochloride Capsules and Oral Suspension*

Inert ingredients in the capsule formulations are hard gelatin capsules (which may contain blue 1 and other inert ingredients; magnesium stearate; microcrystalline cellulose; and sodium lauryl sulfate).

Efavirenz Capsules*

It is available as capsules for oral administration containing either 50, 100, or 200 mg of efavirenz as well as the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate.

Enalapril Maleate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
10.00	1	Enalapril maleate	10.00
235.00	2	Lactose anhydrous	235.00
1.25	3	Magnesium stearate	1.25

Manufacturing Directions

- Pass all items through No. 60 mesh into blender; mix for 10 minutes.
- Fill 250 mg in size 00 capsules.

The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue, FD&C blue No. 2, and titanium dioxide.

Enalapril Maleate Capsules

Inactive ingredients: magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Inert ingredients for the oral suspension formulation are carboxymethylcellulose sodium, blue 1, methylparaben, microcrystalline cellulose, propylparaben, raspberry flavor, red 28, and simethicone.

Eplerenone Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
10.00	1	Eplerenone	10.00
306.80	2	Lactose hydrous NF	306.80
60.00	3	Microcrystalline cellulose NF	60.00
10.00	4	Talc	10.00
1.20	5	Croscarmellose sodium NF	1.20
2.00	6	Sodium lauryl sulfate NF	2.00
2.00	7	Colloidal silicon dioxide NF	2.00
1.20	8	Magnesium stearate NF	1.20

*adjust for higher dose fill.

Directions

Total capsules fill weight 400 mg, hard gelatin capsules, size
250 mg, white opaque.

Erythromycin and Bromhexine Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/l (g)
21.00	1	Sodium carboxymethylcellulose	0.42
6.55	2	Dye red	0.131
4735.00	3	Sugar granular 39075 mesh	94.70
2650.00	4	Sodium citrate dihydrate	53.00
659.00	5	Sodium carboxymethylcellulose high viscosity	13.18
393.50	6	Magnesium aluminum silicate Veegum F	7.87
78.50	7	Saccharin sodium dihydrate	1.57
200.00	8	Erythromycin, USE erythromycin ethylsuccinate ^a citrate washed	123.58
0.80	9	Bromhexine, USE bromhexine hydrochloride	2.10
QS	10	Flavor	3.95
QS	11	Water purified, ca	67 mL

^aErythromycin ethylsuccinate is factored = $(123.58 \times 850)/\text{potency}$, $\mu\text{g/g}$.

Manufacturing Directions

1. Granulation

- Dissolve the sodium carboxymethylcellulose (item 1) and the dye in approximately 67 mL of purified water with heat while stirring. Allow to cool. Ensure that the sodium carboxymethylcellulose is completely in solution.
- Pass sugar cane through a 2.38-mm aperture screen using an oscillating granulator.
- Pass the following through a 1.27-mm aperture or similar screen: sodium CMC (item 5), Veegum F, sodium saccharin, bromhexine HCl, and erythromycin ethylsuccinate. Use a Fitz mill or a similar mill, high speed, impact forward.
- Load the ingredients from steps B and C into the mixer and blend for 30 minutes.
- Mass with the solution from step A. If necessary, add purified water to form a cohesive granule with even color dispersion.
- If necessary, pass the wet mass through a 4.76-mm aperture screen and spread on stainless steel trays.
- Load trays of granulation into the oven and dry at 49°C to LOD of less than 0.5% (60°C/5 mm). *Note:* Stir granulation during drying.
- Allow granulation to cool in low humidity area before passing through a 1.7-mm aperture screen. *Note:* Precooling in a low humidity area prevents condensation when later packed in polyethylene-lined bags.
- Request samples.
- Charge part of dry granulation and sodium citrate into a mixer. Slowly add flavor while mixing. Mix for a few minutes. Hand screen through a 1.2-mm aperture screen.
- Charge the screened granulation into a suitable blender and add flavor mixture from step J. Mix well (approximately 30 minutes).
- Take samples.
- Discharge blended granulation into tared polyethylene-lined drums; seal and weigh. Store until needed for filling.

2. Finishing

- At filling, weight for a 60-mL bottle should be 22.85 g, weight for a 100-mL bottle should be 39.08 g.

Erythromycin and Sulfisoxazole Granules for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/kg (g)
180.63	1	Sodium citrate dihydrate	66.90
600.00	2	Sulfisoxazole, USE sulfisoxazole acetyl	222.30
13.50	3	Sodium carboxymethylcellulose high viscosity	5.00
10.80	4	Magnesium aluminum silicate Veegum F	4.00
5.40	5	Citric acid	2.00
0.54	6	Polaxamer 188 (Pluronic F68)	0.20
200.00	7	Erythromycin, USE erythromycin ethylsuccinate citrate washed ^a (850 µg/mg) 5% excess	75.29
1661.28	8	Sucrose	615.29
QS	9	Water purified	55 mL
7.56	10	Flavor	2.80
3.24	11	Flavor	1.20
10.80	12	Flavor	4.00
2.70	13	Ammonium glycyrrhizinate	1.00

^aFactored according to potency. Adjust with sugar.

Manufacturing Directions**I. Premixing**

Note: This milling step is hazardous. *Caution:* Equipment must be grounded or bonded.

A. Mill sodium citrate, sodium carboxymethylcellulose, magnesium aluminum silicate, citric acid, poloxamer, and erythromycin ethylsuccinate through a No. 2 band (1.59-mm aperture) using a Fitz mill or similar mill, at high speed, impact forward.

B. Load milled materials from step A into a suitable blender. Mix for 15 minutes.

C. Screen the sulfisoxazole acetyl through a 4.76-mm aperture screen and add to the blender. Blend for 15 minutes.

D. Discharge blender into polyethylene-lined drums.

II. Granulation

A. Load mass mixer with the premix blend. Add the sucrose to mixer by hand screening through a 2.00-mm aperture screen. Dry mix for not less than 5 minutes.

B. QS to mass using approximately 51 mL of purified water.

C. Granulate the wet mass through a $\frac{5}{8}$ -in band (15.88-mm aperture or similar) on a rotary granulator or

similar granulator. Spread on paper-lined trays, no more than one scoopful per tray. Place granulation in oven set at 49°C.

D. Dry to NMT 0.7% LOD.

E. Sift dried granulation through a 1.19-mm aperture screen and grind coarse granulation through a No. 2 AA band (1.98-mm aperture or similar) in a Fitz mill or a similar mill, medium speed, knives forward into polyethylene-lined drums.

III. Blending

A. Load approximately one-half of the granulation from step II-E into a suitable blender.

B. Screen flavors and ammonium glycyrrhizinate through a 600-µm aperture screen into a portion of the granulation; mix and add to the blender.

C. Add the remaining granulation into the blender. Blend for 20 minutes.

D. Discharge mixture into polyethylene-lined drums.

IV. Finishing

A. Fill into suitable approved bottles at a theoretical weight of 62.5 g/100 mL, requiring approximately 50 mL of water for reconstitution.

Erythromycin Delayed-Release Capsules*

Erythromycin delayed-release capsules contain enteric-coated pellets of erythromycin base for oral administration. Each erythromycin delayed-release capsule contains 250 mg

of erythromycin base. The inactive ingredients are cellulosic polymers, citrate ester, D&C red No. 30, D&C yellow No. 10, magnesium stearate, and povidone. The capsule shell contains FD&C blue No. 1, FD&C red No. 3, gelatin, and titanium dioxide.

Erythromycin Delayed-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Erythromycin, USE erythromycin 66.7% pellets (label claim is 667 mg/g)	375.00 ^a
—	2	Empty hard gelatin capsules, Size 0	1000.00

^aQuantity of pellets for 1000 capsules will be adjusted based on the pellets assay results.

Manufacturing Directions

Note: Processing should be done under controlled room temperature and relative humidity. The limits are room temperature 20°C to 25°C, RH 40% to 45%.

1. Load the empty capsule shells (size 0) in the hopper.
2. Fill.

Erythromycin Ethylsuccinate for Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/1 kg (19 units) (g)
125.00	1	Erythromycin ethylsuccinate ^a	55.860
2168.00	2	Sucrose ^b	823.840
250.25	3	Sodium citrate	95.095
2.97	4	Saccharin sodium	1.128
0.27	5	FD&C red No. 40	0.104
1.43	6	Carmellose sodium (sodium CMC 7 MFD)	0.543
21.45	7	Simethicone emulsion 30% (simethicone M30)	8.151
12.98	8	Xanthan gum	4.932
6.27	9	Cherry dry flavor	2.382
—	10	Purified water	15.200

^aPotency: 850 µg/mg, as is.

^bSucrose quantity to be adjusted accordingly. The weight of sucrose may be adjusted to compensate for potency variation of erythromycin ethylsuccinate to maintain the standard batch size (1 kg). Fill weight: 52.5 g for 100-mL pack.

Manufacturing Directions

Precautions: Handle erythromycin ethylsuccinate carefully to avoid any cross-contamination. The processing area must be under controlled room temperature and humidity. The limits are RH: 45% to 55%, temperature: 23°C to 25°C.

1. Preparation of solution: Dissolve item 5 in item 10 (25–30°C). Add item 6 slowly while stirring with stirrer at medium speed until gel is formed. Check the weight; theoretical weight is 15.84 g. If required, adjust with item 10.
2. Dry mixing: Pass item 2 (calculated quantity) through sifter using a 900-µm sieve. Crush the larger crystals of item 2 using a Fitz mill, impact forward, high speed.
3. Load item 2 from step 2 into the mixer and start mixing at high speed. Add item 7 while mixing. Mix for 10 minutes with the mixer and chopper at high speed.
4. Mix items 3, 4, 8, 1, and the mixture from step 3 in a clean, dry stainless steel container using a clean, dry stainless steel scoop.
5. Pass the material through a Fitz mill, impact forward, high speed.
6. Add the milled material to the mixer; mix for 5 minutes with the mixer and chopper at high speed.
7. Scrap down the sides and blades and again mix for 2 minutes with the mixer and chopper at high speed.
8. Wet granulation: Very slowly add the solution from step 1 to step 5 in mixer. Mix at low speed, until a satisfactory mass is obtained. Mix and chop for 1 minute only. Do not overwet the mass.
9. Drying: Dry the wet granules in the fluid-bed dryer at 55°C to reach an LOD of no more than 0.4%.
10. Grinding: Pass the dried granules through a 1-mm sieve using Frewitt[®] granulator. Collect in a stainless steel drum.
11. Final mixing: Pass item 9 through 250-µm sieve using a sifter. Collect in a polyethylene-lined bag.
12. Load sieved material from step 8 into the blender.
13. Add sieved flavor (item 9) from step 11 to the blender.
14. Blend the powders for 5 minutes.
15. Unload the blended powder in stainless steel drums.

Erythromycin Ethylsuccinate for Oral Suspension (200 mg/5 mL)

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/1 kg (18 Units) (g)
200.00	1	Erythromycin, USE erythromycin ethylsuccinate ^a	89.3700
1342.00	2	Sucrose	483.1200
880.00	3	Sucrose ^b	316.8000
250.25	4	Sodium citrate	90.0900
2.97	5	Saccharin sodium	1.0692
0.27	6	FD&C red No. 40	0.0990
1.43	7	Carmellose sodium (Sodium CMC 7 MFD)	0.5148
21.45	8	Simethicone emulsion 30% (simethicone M30)	7.7220
12.98	9	Xanthan gum	4.6728
6.27	10	Cherry dry flavor	2.2572
–	11	Purified water	15.8400

^aPotency: 850 µg/mg, as is.

^bThe weight of sucrose may be adjusted to compensate for potency variation of erythromycin ethylsuccinate to maintain the standard batch size (1 kg). Fill weight: 55 g for 100-mL pack.

Erythromycin Stearate for Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	Erythromycin stearate 600 µg/mg, 5% excess	43.75
1.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
10.00	4	Magnesium aluminum silicate	10.00
1.15	5	Sodium carboxymethylcellulose (CMC), low viscosity	1.15
4.00	6	Alcohol 190 proof	4.00
120.00	7	Sodium citrate dihydrate	120.00
0.20	8	Saccharin sodium	0.20
700.00	9	Sugar granular	700.00
0.07	10	Yellow dye	0.07
2.76	11	Chocolate flavor	2.76
0.54	12	Orange flavor	0.54
1.25	13	Sodium lauryl sulfate	1.25
QS	14	Water purified	QS

Manufacturing Directions**I. Mixing**

- A. Place sodium CMC and 40 g of sugar in a mixing drum. (If using alcohol, add it to the drum to wet the mixture and indicate use on the work order.) Roll for 2 hours to blend.
- B. Measure 350 mL of purified water into a jacketed mixing tank and heat the water to 95°C. Maintain at this temperature.
- C. Add methyl paraben to the water at 95°C. Stir until completely dissolved.
- D. Add propyl paraben to the solution at 95°C. Stir until completely dissolved.
- E. Cool to 60°C and maintain temperature. Stir the solution and slowly sprinkle in Veegum. Stir until Veegum is completely dispersed. Check by passing quantity of the batch through a 350-µm aperture or similar screen and watch for any undissolved residue.
- F. While stirring, add the blended powders from step A slowly to the solution. Stir until completely dissolved. Screen a quantity through a 350-µm aperture or similar screen to check for undissolved sodium CMC.
- G. Maintain the batch at 50°C to 55°C and gradually add the remaining sugar (item 9) with stirring. Stir until completely dissolved. Check for any undissolved sugar by passing a quantity of the bulk through a 350-mm aperture or similar screen.
- H. Dissolve the saccharin sodium in approximately 5 mL of purified water and add the solution to the batch.
- I. While stirring, add the sodium citrate to the batch. Stir under maximum vacuum until completely dissolved. Check by passing a quantity of the bulk through a 350-mm aperture or similar screen.
- J. Dissolve FD&C yellow No. 6 in approximately 5 mL of purified water and add the solution to the batch. Cool the batch to 30°C (chilled water may be used).
- K. In a separate tank, stir approximately 85 mL of purified water and slowly, taking care to avoid a vortex, add and dissolve sodium lauryl sulfate. When dissolved, gradually sprinkle in the erythromycin stearate and mix into a smooth slurry. Mix for half hour.
- L. While stirring the batch from step J, slowly add the slurry from step K. Take care not to aerate the batch. Wash thoroughly into the batch with approximately 10 mL of purified water.
- M. With continual stirring, add the flavors (items 11 and 12) to the batch.
- N. Pass the whole batch through a homogenizing mill using a suitable setting such that crystal fracture is minimized. Rinse the mill with purified water and add the rinsing to the batch.
- O. Return the milled batch back into the mixing tank. Gradually increase the application of vacuum as allowed by the level in the tank. Stir under a 28-in Hg vacuum for 1 hour. Adjust the batch volume to 1 L using purified water.
- P. Repeat step O until the volume is constant and specific gravity meets specifications.

Erythromycin Stearate for Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/l (g)
25.00	1	Erythromycin stearate 600 µg/mg, 5% excess	43.75
1.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
2.00	4	Xanthan gum	2.00
120.00	5	Sodium citrate dihydrate	120.00
0.20	6	Saccharin sodium	0.20
100.00	7	Sorbitol solution	100.00
4.50	8	Antifoam emulsion Dow Corning	4.50
0.07	9	Dye yellow	0.07
2.76	10	Flavor chocolate	2.76
700.00	11	Sugar granular	700.00
0.54	12	Flavor orange	0.54
1.25	13	Sodium lauryl sulfate	1.25
QS	14	Water purified	QS

Manufacturing Directions**I. Mixing**

- A. Heat 600 mL of purified water in a jacketed mixing tank to 95°C to 100°C.
- B. Add the methyl paraben and propyl paraben and mix to dissolve.
- C. Withdraw the following preserved purified water:
 1. 200 mL and dissolve the sodium citrate.
 2. 150 mL and dissolve the sodium lauryl sulfate.
 3. 5 mL and dissolve the sodium saccharin and the dye yellow.
- D. In a plastic bag, mix together the xanthan gum and 20 g of sucrose (item 11) for 10 minutes.
- E. Maintaining the batch at 50°C to 60°C while mixing, slowly add the dry mixture from step D until a clear gel is obtained.
- F. Add the sorbitol and mix.
- G. While mixing, slowly add the solution obtained from step C-1.
- H. Add the disperse 380 g of sucrose (item 11) while mixing. Make sure that the temperature will not go over 60°C. Stop heating when all dissolved.
- I. Without producing the vortex, add erythromycin stearate to the solution from step C-2 and continue mixing until smooth slurry is formed. Continue mixing for 15 to 30 minutes and then pass slurry through a homogenizer. Add the antifoam C to the slurry and mix; rinse the homogenizer with purified water and add the rinsings to the slurry. Mix.
- J. While mixing, add the slurry obtained from step I to the batch; rinse the vessel with 5 mL of purified water and add the rinsings to the batch.
- K. Add and disperse the solution from step C-3 and continue mixing.
- L. Mix under vacuum for 1 hour. Release the vacuum and record the volume. *Caution:* Do not adjust volume at this stage.
- M. Repeat step L until no further volume change is noticed.
- N. Add the flavors (items 10 and 11) and bring to volume with purified water.

Erythropoietin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
14000 IU	1	Erythropoietin ^a	140000000 IU
0.047	2	Dimyristoyl phosphatidyl choline	0.047
3.42	3	Aprotinin ^b	3.42
3.78	4	Hydroxypropyl cellulose-LF	3.78
3.78	5	Polyoxy-40 stearate Myrj-52 [®]	3.78
141.1	6	Polyethylene glycol 400	141.1
15.72	7	Propylene glycol	15.72
8.83	8	Phosphate buffer	8.83
31.49	9	Cholesterol	31.49
17.72	10	Tween 80	17.72
63.68	11	Egg yolk lecithin	63.68
28.15	12	Glyceryl amino oleate	28.15
19.78	13	d-Alpha Tocopherol	19.78
251.42	14	Oleic acid	251.42

^aErythropoietin: 1000 IU = 8 µg

^bAprotinin: 7500 KIU = 1 mg

Manufacturing Directions

- Erythropoietin is a 165-amino acid glycoprotein of approximately 34000 daltons. It is an endogenous protein, which is involved in the production of red blood cells. It is indicated for the treatment of anemia associated with chronic renal failure, in AIDS patients, and also to maintain or elevate the red blood cell level in the human body. In its preparations, there can be no use of heat or alcohol that can denature it.
- The overall method is as follows: The high HLB surfactant polyoxy-40 stearate is slowly dispersed into the mixture of polyethylene glycol 400 and propylene glycol. Once it dissolves, hydroxypropyl cellulose as a stabilizer is also added which is dispersed slowly into the above mixture. A separate solution of the proteinaceous material along with the phospholipid and the protease inhibitor is made in a portion of the above solvent mixture. The solution can then be added to the PEG/PG mixture at room temperature. The amount of any water is limited to 5% of the polyol solvent. When the water solution is used, citrate buffer is used to maintain the pH at a point where the protein is most stable. For erythropoietin, pH can be adjusted to 7.0 to 7.5 with a phosphate buffer. The amount of aqueous buffer solution would still be 5% of the hydrophilic phase. At a pH of 7.0 to 7.5, erythropoietin has its maximum stability. It is known that in formulating proteins, the pH of the formulation should be distant from the isoelectric point of the protein, which would not precipitate the protein from the solution. Separately, the ingredients of the lipid solvent are mixed together. Under gentle and constant stirring, the polyol solution is dispersed with the lipid solution.
- The surfactant (polyoxy-40 stearate) is slowly dispersed into a mixture of polyethylene glycol and propylene glycol. Once it is dissolved, small amounts of hydroxypropyl cellulose are then added and dispersed into the same mixture. Erythropoietin is dissolved in the phosphate buffer/water/saline, along with aprotinin and dimyristoyl phosphatidyl choline. The aqueous solution is then added to the polyethylene glycol mixture at room temperature. The pH of the solution should be adjusted at 7.5 for maximum stability.
- In a separate vessel, dissolve all the lipid-liking ingredients in oleic acid. Cholesterol is added slowly to achieve faster dissolution. Once both the phases are ready, the lipid solution is added slowly to polyol solution while mixing at low speed. Preferably, the vessel should be ice jacketed because mixing produces heat. Once the mixing is achieved, a transparent yellowish-brown preemulsion solution is obtained.
- The preemulsion solution is filled in a size 0 hard gelatin capsule and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
- The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, a 3.5% to 4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
- Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers, such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate, are used.
- Anionic copolymers that are based on methacrylic acid and methyl methacrylate, commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% of the weight gain of the capsules from the original weight of the capsules before applying an enteric coat.

A typical enteric coating solution is made as follows: methacrylic acid and Methacrylate copolymer 10% w/w, diethyl butyl phthalate (plasticizer) 2% w/w, acetone 22% w/w, isopropanol 66% w/w.

- Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.

For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid bed sprayer/dryer is operated with the following parameters.

Flow rate: 1.5 mL/min

Inlet air temperature: 25°C

Outlet air temperature: 25°C

Air flap: 35

Atomizer: 2 bar

A size 0 capsule after the enteric coating will typically have the following composition: preemulsion solution: 0.589 g, undercoat polymer: 0.027 g, enteric coat polymer: 0.032 g, 0.648 g.

Esomeprazole Magnesium Capsules*

Each delayed-release capsule contains 20 or 40 mg of esomeprazole (present as 22.3 or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40 to 50, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C yellow No. 10.

Estramustine Phosphate Capsules*

The capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate that is equivalent to 140 mg estramustine phosphate for oral administration. Each capsule also contains magnesium stearate, silicon dioxide, sodium lauryl sulfate, and talc. Gelatin capsule shells contain titanium dioxide.

Ethosuximide Capsules*

Each capsule contains 250 mg ethosuximide and the inactive ingredient polyethylene glycol. The capsule contains D&C yellow No. 10; FD&C red No. 3, gelatin, glycerin, and sorbitol.

Etodolac Capsules*

The inactive ingredients in the capsules are cellulose, gelatin, iron oxides, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide.

Felbamate for Oral Suspension*

The inactive ingredients for felbamate suspension (600 mg/5 mL) are sorbitol, glycerin, microcrystalline cellulose, carboxy methylcellulose sodium, simethicone, polysorbate 80, methylparaben, saccharin sodium, propylparaben, FD&C yellow No. 6, FD&C red No. 40, flavorings, and purified water.

Fenofibrate Capsules*

Each capsule contains 67, 134, or 200 mg of micronized fenofibrate. Each capsule also contains the following inactive ingredients: crospovidone, iron oxide, lactose, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide.

Fenofibrate Capsules

- According to the preparation example I in Japanese Examined Patent Publication No. Hei 7-14876 (hereinafter referred to "PREPARATION I"), granules are prepared via a co-micronizing process of fenofibrate and sodium lauryl sulfate.
- The formulation used is as follows (in a capsule; total amount: 250 mg): Fenofibrate 200 mg, sodium lauryl sulfate 7 mg, lactose 3 mg, magnesium stearate 3 mg, alpha, modified starch 30 mg, crospovidone 7 mg.
- The granules thus obtained were filled into size No. 2 capsules.

Fenofibrate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Fenofibrate micronized (5 mm)	100.00
2.00	2	Sodium lauryl sulfate	2.00
100.00	3	Polyvinylpyrrolidone K 25, 100–400 mm	100.00
QS	4	Water purified	1750.00
114.28	5	Lactose monohydrate, 100–400 mm	114.28

Note: This formulation is expected to provide enhanced bioavailability of item 1, thus the dose may be reduced by 33% for all strengths.

Manufacturing Directions

1. Examine item 1 using a Coulter[®] counter to make sure 90% of particles are within the 5-mm range.
2. Add and dissolve item 2 in item 4; item 1 is then added to make a smooth suspension using a high-speed stirrer and then passing it through a high-speed mill.
3. Add item 3 while agitating until it is dissolved and ensure that no agglomerates are present.
4. Pass step 3 through a 350- μ m sieve.
5. Separately, item 5 is charged in a fluid-bed granulator and brought into suspension and the temperature is raised to 40°C.
6. Add step 3 into step 5 gradually at a spraying pressure of 2.1 bar, air throughput of 70 m³/h, air inlet temperature of 45°C, air outlet temperature of 33°C, product temperature of 34°C, and a spraying duration of 3 hours.
7. The granulate thus obtained is filled in a suitable size capsule.

Fexofenadine Hydrochloride Capsules*

Each capsule contains 60 mg of fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin,

lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

Fexofenadine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
60.00	1	Fexofenadine hydrochloride ^a	60.00
141.00	2	Microcrystalline cellulose	141.00
141.00	3	Lactose	141.00
40.00	4	Pregelatinized starch	40.00
20.00	5	Croscarmellose sodium	20.00
14.70	6	Gelatin capsules	14.70

^aParticle surface area of 2–4 m²/g.

Manufacturing Directions

1. Combine fexofenadine hydrochloride (item 1), microcrystalline cellulose (item 2), lactose (item 3), and pregelatinized starch (item 4) and blend in a mixer for 5 minutes.
2. To this mixture, add a solution of gelatin (item 6) in purified water (prepared by adding the gelatin to the water and heating the dispersion with mixing until solution of the gelatin is attained) and continue mixing until a good granulation is formed.
3. Pass the granulation through a 0.375-in screen and dry at 60°C until moisture content of less than 3.0% is achieved as determined by a Computrac moisture balance at 125°C.
4. Mill the dried granulation through a 0.065-in screen.
5. To the granulation, add croscarmellose sodium and mix for approximately 10 minutes.
6. Fill the granulation into size 0 hard gelatin capsules to a total fill weight of 416.7 mg granulation per capsule.

Fluconazole for Oral Suspension*

The oral suspension contains 350 or 1400 mg of fluconazole and the following inactive ingredients: sucrose, sodium citrate dihydrate, citric acid anhydrous, sodium benzoate, titanium dioxide, colloidal silicon dioxide, xanthan gum, and natural orange flavor. After reconstitution with 24 mL of distilled water or purified water, each milliliter of reconstituted suspension contains 10 or 40 mg of fluconazole.

Flucytosine Capsules*

Each capsule also contains cornstarch, lactose, and talc. Gelatin capsule shells contain parabens (butyl, methyl, propyl) and sodium propionate, with the following dye systems: 250-mg capsules contain black iron oxide, FD&C blue No. 1, FD&C yellow No. 6, D&C yellow No. 10, and titanium dioxide; 500-mg capsules contain black iron oxide and titanium dioxide.

Fluoxetine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Fluoxetine, USE fluoxetine hydrochloride	22.36
80.14	2	Starch (cornstarch)	80.14
10.00	3	Simethicone, USE simethicone M30	35.00
42.00	4	Starch (cornstarch dried)	42.00
0.50	5	Colloidal Silicon dioxide (Aerosil 200)	0.50
1.00	6	Empty hard gelatin capsule, shell size 3	1000.00

Manufacturing Directions

Note: The processing area must be under controlled room temperature and humidity. The limits are RH 40% to 50%, temperature NMT 27°C.

- Dry powder mixing
 - Sift items 1 and 2 through a stainless steel sieve (630 μm) in a sifter.
 - Load the powder mix in the mixer. Mix for 5 minutes at low speed.
 - Wet massing
 - Add item 3 suspension into the powder mix while mixing at low speed for 3 minutes. Scrape sides and blades. Mix for another 3 minutes at low speed.
 - Drying and grinding
 - Spread the moist mass thinly on stainless steel trays. Break the big lumps if any.
- Dry the mass in oven at 55°C for 10 hours.
 - Check LOD (limit between 1.5% and 2.0%). If required, dry further for 1 hour.
 - Grind the dried granules through a granulator using a stainless steel sieve (1 mm). Collect in a stainless steel drum.
- Lubrication
 - Sift items 4 and 5 through a stainless steel sieve (500 μm) using a sifter. Collect in a stainless steel drum. Add into the drum blender (step III-D). Mix for 5 minutes.
 - Unload the final blend.
 - Take sample for analyzing fluoxetine hydrochloride content in the granules to fill. *Note:* Encapsulation is recommended within 7 days after lubrication.

Fluoxetine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Fluoxetine, USE fluoxetine hydrochloride	22.40
160.00	2	Talc	160.00
100.00	3	Starch dried	100.00
4.00	4	Magnesium stearate	4.00
1.00	5	Aerosil 200	1.00

Manufacturing Directions

- Charge items 1 to 5 in a suitable blender after passing through a No. 60 mesh.
- Mix for 30 minutes.
- Fill 350 mg in size 2 capsules.

Fluoxetine Hydrochloride Instant and Weekly Capsules*

Each capsule contains fluoxetine hydrochloride equivalent to 10 mg (32.3 mmol), 20 mg (64.7 mmol), or 40 mg (129.3 mmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and optionally other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C blue No. 1 and the 40-mg Pulvule also contains FD&C blue No. 1 and FD&C yellow No. 6. The capsules intended for weekly administration, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 mmol) of fluoxetine. The capsules also contain FD&C yellow No. 10, FD&C blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and optionally other inactive ingredients.

Flutamide Capsules*

Each capsule contains 125 mg of flutamide. The inactive ingredients include cornstarch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may also contain benzyl alcohol, butylparaben, colloidal silicon dioxide, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate, as well as the following dye systems: FD&C blue No. 1, FD&C red No. 3, FD&C yellow No. 6, titanium dioxide, and black ink.

Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder*

This is a combination of fluticasone propionate and salmeterol xinafoate. These are specially designed plastic devices

containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 µg of microfine fluticasone propionate and 72.5 µg of microfine salmeterol xinafoate salt, equivalent to 50 µg of salmeterol base, in 12.5 mg of formulation containing lactose. Each blister contains one complete dose of both medications. After a blister containing the medication is opened by activating the device, the medication is dispersed into the air stream created by the patient inhaling through the mouthpiece. Under standardized in vitro test conditions, it delivers 93, 233, and 465 µg of fluticasone propionate and 45 µg of salmeterol base per blister, respectively, when tested at a flow rate of 60 L/min for 2 seconds.

Fluvastatin Sodium Capsules*

It is supplied in capsules containing fluvastatin sodium, equivalent to 20 or 40 mg of fluvastatin, for oral administration. The inactive ingredients in the capsules are gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, and yellow iron oxide. Capsules may also include benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

Fluvastatin Sodium Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Fluvastatin	20.00
62.84	2	Calcium carbonate heavy precipitated	62.84
2.00	3	Sodium bicarbonate	2.00
23.35	4	Microcrystalline cellulose Avicel PH102	23.35
20.95	5	Pregelatinized starch (starch 1500)	20.95
QS	6	Water purified	QS
33.88	7	Microcrystalline cellulose	33.38
20.95	8	Pregelatinized starch	20.95
9.43	9	Talc	9.43
1.05	10	Magnesium stearate	1.05

Manufacturing Directions

1. Fluvastatin (item 1), sodium bicarbonate (item 3), calcium carbonate (item 2), microcrystalline cellulose (item 4), and pregelatinized starch (item 5) are mixed for 5 minutes and the mixture is passed through a 40-mesh screen and blended for another 3 minutes.
2. Water is added to the mixture while blending for about 4 minutes to form a wet granulation.
3. The wet granulation is dried in a fluid bed dryer at 50°C inlet temperature to a loss on drying of 1.59%.
4. The dried granules are passed through a 20-mesh screen and blended with the microcrystalline cellulose and pregelatinized starch set-asides (items 7 and 8) for approximately 10 minutes.
5. Talc and magnesium stearate (each prescreened on a 60-mesh bolting cloth) are added to the mixture while blending for approximately 5 minutes. The resulting composition has a loss on drying of 2.65%.
6. A blue opaque capsule is filled with the composition and polished manually with salt.

Formoterol Fumarate Inhalation Powder*

This consists of a capsule dosage form containing a dry powder formulation of formoterol fumarate intended for oral inhalation only with the Aerolizer[®] inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 µg of formoterol fumarate and 25 mg of lactose as a carrier. The active component is formoterol fumarate—a racemate.

Formoterol Fumarate Inhaler Capsules*

The inhaler consists of a capsule dosage form containing a dry powder formulation of formoterol fumarate intended for oral inhalation only with the Aerolizer[®] inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 µg of formoterol fumarate and 25 mg of lactose as a carrier.

Fosfomycin Tromethamine Sachets*

Fosfomycin tromethamine sachet contains fosfomycin tromethamine, a synthetic, broad-spectrum bactericidal an-

tibiotic for oral administration. It is available as a single-dose sachet, which contains white granules consisting of 5.631 g of fosfomycin tromethamine (equivalent to 3 g of fosfomycin) and the following inactive ingredients: mandarin flavor, orange flavor, saccharin, and sucrose.

Gabapentin Capsules*

Gabapentin capsules are supplied as imprinted hard shell capsules containing 100, 300, and 400 mg of gabapentin. The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100-mg capsule shell contains gelatin and titanium dioxide. The 300-mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400-mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C blue No. 2 and titanium dioxide.

Gabapentin Capsules

Ingredients	Percent (w/w)
Gabapentin (Kemprotec)	75.00%
StarCap 1500 [®] (Colorcon)	24.75%
Magnesium stearate NF (Mallinckrodt)	0.25%
Total:	100.00%
Hard gelatin capsule shell No. 0, White/White	QS

Manufacturing Directions

1. Mix all ingredients.

2. Fill 400 mg in size 0 capsule.

Ganciclovir Capsules*

Each capsule contains 250 or 500 mg ganciclovir respectively and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and povidone. Both hard

gelatin shells consist of gelatin, titanium dioxide, yellow iron oxide, and FD&C blue No. 2.

Ganciclovir Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Ganciclovir	250.00
3.00	2	Magnesium stearate	3.00
30.00	3	Cornstarch	30.00
116.00	4	Lactose	116.00
4.00	5	Polyvinylpyrrolidone	3.00
QS	6	Methanol	QS

Manufacturing Directions

1. Items 1, 3, and 4 are granulated in a solution of item 5 in item 6.

2. Granules are dried, lubricated with item 2, and filled in capsules or tablets.

Gemfibrozil Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Gemfibrozil	100.00
248.80	2	Lactose anhydrous ^a	248.80
100.00	3	Cornstarch	100.00
25.00	4	Sodium starch glycolate	25.00
5.00	5	Povidone	5.00
15.00	6	Polysorbate 80	15.00
1.25	7	Colloidal silicon dioxide	1.25
5.00	8	Magnesium stearate	5.00
QS	9	Water purified	QS

^aThe quantity of lactose can be reduced to compensate if additional quantities of glycine 12.5 mg and citric acid 2.5 mg are used.

Manufacturing Directions

1. An aqueous wet granulation process is used whereby the respective active ingredients of lactose, cornstarch, sodium starch glycolate, colloidal silicon dioxide, and povidone are mixed and subsequently granulated with polysorbate dissolved in purified water.
2. Additional purified water is then added until granules form and no dry powder remains.
3. Wet granules are dried at 60°C until the loss on drying is NMT 2%.
4. The dried granules are milled with the sodium starch glycolate, blended, and lubricated with screened magnesium stearate in a twin-shell blender.
5. Size 0 capsules are used to fill 500 mg of granules.

Glycoprotein IIa/IIb Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.23	1	Glycoprotein IIa/IIb	0.23
53.77	2	Lactose anhydrous	53.77
2.70	3	Crospovidone	2.70
1.20	4	Povidone	1.20
1.50	5	Disodium citrate	1.50
0.60	6	Magnesium stearate	0.60
QS	7	Water purified	QS

Manufacturing Directions

1. Triturate item 1 with item 2 (portion) in a small mixing vessel or mortar.
2. Charge the balance of item 2 and two-thirds of the quantity of item 3 in a shear granulator and add step 1 into it with fast mixing.
3. Granulate step 2 using aqueous solution of balance of item 4 and item 5 (9.3% solids in item 7 and pH adjusted to 4 using 1 N-hydrochloric acid).
4. Screen the granulation through a No. 8 mesh and dry in vacuum at 40°C to moisture content of 0.7%.
5. Blend the granulation with remaining amount of items 3 and 6.
6. Fill 60 mg in size 3 capsules.

Guaifenesin Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Guaifenesin	150.00
26.60	2	Carbopol 934P (B. F. Goodrich)	26.60
172.10	3	PVP C-15 (GAF Corporation)	172.10
3.50	4	Talc	3.50
1.80	5	Zinc stearate	1.80

Manufacturing Directions

1. Carbopol 934P, PVP C-15, talc, and zinc stearate are combined in a mortar and triturated well.

2. The guaifenesin is added to this mixture in the mortar and triturated well until a substantially uniform particulate mixture is achieved.
3. The resulting particulate mixture is filled 354 mg into size 1 hard gelatin capsule shells.

Herbal AIDS Treatment Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
32.00	1	<i>Combretum quadrangulare</i>	32.00
20.00	2	<i>Houttuynia cordata</i>	20.00
20.00	3	<i>Mimusops elengi</i>	20.00
20.00	4	<i>Randia siamensis</i>	20.00
308.00	5	<i>Borassus flabellifer</i>	308.00

Manufacturing Directions

1. Items 1 to 5 are prepared by first making a powdered form of herbs, extracting them in water or hydroalcoholic solution, and drying the extract.

2. Powdered extracts 1 to 5 are admixed and filled in a gelatin capsule. Add magnesium stearate 1%, if necessary, to improve flow.

Histidine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Histidine	240.00
QS	2	Lactose	QS

Manufacturing Directions

1. Mix items 1 and 2 (using desired quantity of item 2 to fit the capsule size chosen) by process of trituration.

2. Fill in appropriate capsule.

Human Growth Hormone Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
28.00 IU	1	Human growth hormone ^a	28000 IU
0.047	2	Dimyristoyl phosphatidic acid	0.047
3.38	3	Aprotinin ^b	3.38
3.47	4	Sodium cholate	3.47
3.70	5	Polyoxy-23 lauryl ether	3.70
138.60	6	Polyethylene glycol 400	138.60
13.71	7	Propylene glycol	13.71
8.67	8	Water/pH adjuster	8.67
30.92	9	Cholesterol	30.92
17.40	10	Tween 80	17.40
62.53	11	Egg yolk lecithin	62.53
19.43	12	D-alpha-tocopherol	19.43
27.64	13	Sorbitan monooleate	27.64
246.90	14	Isostearic acid	246.90

^aHuman growth hormone 2.6 IU = 1 mg.

^bAprotinin: 7500 KIU = 1 mg.

Manufacturing Directions

- Polyoxy-23 lauryl ether (commercially available as BrijTM 35) is dispersed in the solvent mixture of polyethylene glycol 400 and propylene glycol.
- Sodium cholate is also separately dispersed in the mixture.
- A water solution containing recombinant human growth hormone, phospholipid, and aprotinin is then added to the solvent mixture in step 1 and the pH is adjusted to 7.5 to 7.8 with the help of a phosphate buffer.
- The lipid solution is made separately in another beaker.
- To the oil solution, the polyol solution is added drop-wise while mixing continuously. While mixing, it is suggested that the vessel be ice jacketed to prevent the denaturation of the protein in the formulation.
- A clear transparent liquid, which is called the preemulsion solution, is obtained after approximately 5 minutes of mixing at low speed. An in situ emulsion can be made by mixing any ratio of the preemulsion solution with the simulated intestinal fluid.
- The preemulsion solution is filled in a size 0 hard gelatin capsule and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
- The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually 3.5% to 4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
- Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate are used.
- Anionic copolymers, which are based on methacrylic acid and methyl methacrylate, commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, and isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows:
Methacrylic acid and methyl methacrylate copolymer 10% w/w
Diethyl butyl phthalate (plasticizer) 2% w/w
Acetone 22% w/w
Isopropanol 66% w/w
- Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
- For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid bed sprayer/dryer is operated with the following parameters:
Flow rate: 1.5 mL/min
Inlet air temperature: 25°C
Outlet air temperature: 25°C
Air flap: 35
Atomizer: 2 bar
A size 0 capsule, after the enteric coating, will typically have the following composition:
Preemulsion solution: 0.589 g
Undercoat polymer: 0.027 g
Enteric coat polymer: 0.032 g, 0.648 g

Hydrochlorothiazide and Triamterene Capsules*

This is a combination capsule with an opaque red cap and an opaque white body. It contains hydrochlorothiazide (25 mg) and triamterene (37.5 mg). Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red No. 33, FD&C yellow No. 6, gelatin, glycine, lactose, magnesium stearate, microcrystalline cellulose, povidone, polysorbate 80, sodium starch glycolate, titanium dioxide, and trace amounts of other inactive ingredients. These capsules meet Drug Release Test 3 as published in the USP monograph for triamterene and hydrochlorothiazide capsules.

Hydrochlorothiazide Capsules*

It is supplied as 12.5-mg capsules for oral use. Each capsule contains the following inactive ingredients: colloidal silicon dioxide, cornstarch, D&C red No. 28, D&C yellow No. 10, FD&C blue No. 1, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, and other optional ingredients.

Ibuprofen Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
450.00	1	Ibuprofen	450.00
450.00	2	Sodium alginate	450.00
4.50 mL	3	Zinc chloride solution 2%	451.00
QS	4	Hydrochloric acid	QS
0.22 mL	5	Glycerin	225.00 mL
—	6	Water purified	22.5 L

Manufacturing Directions

1. A mixture consisting of item 1, previously triturated in 225 mL of glycerin, is added with rapid stirring to an aqueous solution consisting of 450 g (w/v) of sodium alginate in 22.5 L of purified water.
2. This solution is then added to 45 L of a 2% (w/v) zinc chloride solution, which has previously been adjusted to pH 3 by the addition of HCl while the rapid stirring is continued for 10 minutes.
3. The preparation is then allowed to stand at room temperature for 4 hours, after which the drug-entrapped zinc alginate precipitate is collected by filtration, washed 3 times with distilled water, and dried under vacuum for 24 hours.
4. After drying, the residue is granulated using minimal amounts of glycerin/water and processed into 0.5-mm diameter microspheres by mechanical extrusion and spherization (Nica Extruder[®]; Aeromatic Ltd., Bubendorf, Switzerland), into which the slightly flexible

Hydroxyzine Pamoate Capsules and Oral Suspension*

The inert ingredients for the capsule formulations are hard gelatin capsules (which may contain FD&C yellow No. 10, FD&C green No. 3, FD&C yellow No. 6, FD&C red No. 33, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, starch, and sucrose. The inert ingredients for the oral suspension formulation are carboxymethylcellulose sodium, lemon flavor, propylene glycol, sorbic acid, sorbitol solution, and water.

Hyoscyamine Sulfate Capsules*

The sustained-release capsules contain 0.375 mg hyoscyamine sulfate in an extended-release formulation designed for oral bid dosage. Each capsule also contains the following inactive ingredients: FD&C blue No. 1, D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6, gelatin, lactose monohydrate, sodium lauryl sulfate, magnesium stearate, silicon dioxide, titanium dioxide, and other optional ingredients.

mass represented by the above residue is fed and which produces therefrom a continuous flow of cylindrical extrudate that is 0.5 mm in diameter.

5. This extrudate falls onto the spinning plate of a Nica Spheronizer[®] (Aeromatic Ltd.), where it is broken into cylinders of approximately 1:1 length:diameter ratio. Interaction then between the spinning disc and the wall of the spheronizer causes the cylinders to be worked into spheres of 0.5 mm diameter.
6. The spheres are then filled into gelatin capsules (1 g of spheres per size 0 capsule, which represents a total dose of 450 mg of ibuprofen). The capsules of spheres thus produced represent a sustained-release dosage form for analgesic-antipyretic activity with less propensity for gastrointestinal side effects than the conventional tablet form of ibuprofen. Upon ingestion, the spheres begin to release the incorporate drug almost immediately, but begin erosion in 3 to 5 hours. Total erosion time is approximately 8 hours.

Ibuprofen and Domperidone Maleate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
200.00	1	Ibuprofen	200.00
10.00	2	Domperidone maleate	10.00
100.00	3	Lactose	100.00
20.00	4	Croscarmellose	20.00

Manufacturing Directions

Items 1 to 4 are formed into a homogeneous blend and filled into a conventional hard gelatin capsule containing 200 mg ibuprofen and 10 mg domperidone.

Ibuprofen and Domperidone Maleate Effervescent Granules

Bill of Materials			
Scale (mg/10 g sachet)	Item	Material Name	Qty/kg (g)
20.00	1	Domperidone	2.00
400.00	2	Ibuprofen	40.00
250.00	3	Microcrystalline cellulose	25.00
5120.00	4	Pulverized sugar	512.00
2550.00	5	Malic acid	255.00
770.00	6	Sodium bicarbonate anhydrous	77.00
260.00	7	Sodium carbonate	26.00
10.00	8	Sodium lauryl sulfate	1.00
QS	9	Water	QS

Manufacturing Directions

1. The domperidone, ibuprofen, microcrystalline cellulose, and sugar are granulated with water and then thoroughly

dried. The remaining ingredients are added to form a powder mixture.

2. Fill 10 g into sachets each containing 400 mg ibuprofen and 20 mg domperidone maleate.

Ibuprofen Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
800.00	1	Ibuprofen	800.00
8.00	2	Aerosil R972	8.00
8.00	3	Beeswax	8.00

Manufacturing Directions

1. Charge items 1 and 3 in a jacketed kettle and heat to melt; stir until uniformly melted.
2. Add item 2, with stirring, to form a homogeneous suspension. Allow to cool.

3. Pass through sieve. If needed, a lubricant may be added to facilitate flow (1% magnesium stearate).

4. Fill size 00 capsules.

5. The 50% dissolution time is approximately 15 hours.

Given below are guidelines on controlling release rates of ibuprofen using different compositions of excipients. In all instances, ibuprofen is melted with the ingredient, allowed to congeal, sized, and filled in appropriate size capsules. T₅₀

represents time for 50% dissolution. A combination of these granules can be used to provide a wide range of ibuprofen release patterns that are particularly useful in arthritis therapy.

	Amount of			
	Ibuprofen (% w/w)	Excipient (% w/w)	T ₅₀ (hours)	
None	100	–	2.9	
Arachis oil	90	10	4.1	
Beeswax	90	10	>24.0	
Beeswax	90 ^a	10	9.5	
Colloidal silicon dioxide (Aerosil 200)	99	1	4.7	
	97	3	6.6	
	95	5	10.0	
Colloidal silicon dioxide (Aerosil R972)	99	1	5.9	
	95	5	20.5	
Croscarmellose sodium (Ac-Di-Sol)	99	1	0.4	
	97.5	2.5	0.13	
Glycerides	95	5	3.0	
	(Gelucire 50/13)	90	10	7.4
	(Gelucire 50/13)	90 ^a	10	2.9
Liquid paraffin	90	10	4.8	
Cornstarch	99	1	3.5	
	95	5	1.6	
	90	10	0.16	
Copolymer (Pluronic F68)	95	5	3.0	
PEG 400	90	10	3.5	
PEG 4000	90	10	3.3	
PEG 6000	90	10	4.2	
Polyvinylpyrrolidone (crospovidone)	90	10	4.0	
Sodium starch glycolate (Explotab [®])	99	1	1.8	
	95	5	0.3	
Stearic acid	99	1	4.2	
	95	5	7.8	
	90	10	>24.0	
Stearyl alcohol	99	1	10.0	
	95	5	14.0	
	90	10	>24.0	

^aIndicates S(+)-ibuprofen.

Ifosfamide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Ifosfamide	250.00
83.50	2	Microcrystalline cellulose, Avicel PH105	83.50
1.50	3	Colloidal silicon dioxide	1.50
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. Pass items 1 to 3 through a 0.8-mm sieve into a blender.
2. Blend for 4 minutes.
3. Add item 4, which has been sieved through a 0.8-mm sieve, to step 2; mix for another 1 minute.
4. Fill 340 mg in size 1 capsules. For a 500-mg capsule, fill 680 mg in size 00 capsules.
5. To impart enteric resistance to capsules, coat using a coating suspension. For example, to coat 2500 size 1 capsules containing 250 mg ifosfamide, use 3 kg of suspension con-

taining 1440 g anionic polymerizate of methacrylic acid and methacrylic acid esters with a mean molecular weight of, for example, 150000, to which a conventional softener has been added, 18 g of 1,2-propandiol, 36 g of magnesium stearate, and 1506 g of isopropanol. The copolymerizate of methacrylic acid and methylmethacrylate that may, for example, be considered is Eudragit[®] L, particularly in the form of a 12.5% solution in isopropanol (Eudragit[®] L/12.5%). Copolymerizates for this type are soluble in neutral to weak alkaline medium through salt formation with alkalis.

Imatinib Mesylate Capsules*

The capsules contain imatinib mesylate equivalent to 100 mg of imatinib freebase. The inactive ingredients are colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The capsule shell contains gelatin; iron oxide; red (E172); iron oxide, yellow (E172); and titanium dioxide (E171).

Indinavir Sulfate Capsules*

Capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide, and sodium lauryl sulfate.

Indinavir Sulfate Capsules

Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
400.00	1	Indinavir sulfate, USE indinavir sulphate	400.00
7.00	2	Sodium lauryl sulphate	7.00
1.50	3	Colloidal silicon dioxide (Aerosil 200)	1.50
6.50	4	Magnesium stearate	6.50
650.00	5	Lactose monohydrate dense	QS to 650.00
1.00	6	Empty hard gelatin capsule, size 00	1000.00

Manufacturing Directions

1. Sift indinavir sulphate, lactose anhydrous, and Aerosil 200 through a specified sieve.
2. Load the sifted powder into a blender and blend well.

3. Sift magnesium stearate and sodium lauryl sulphate through a specified sifter.
4. Mix step 3 with step 2 and blend well.
5. Encapsulate the powder to get the stated amount of indinavir per capsule.

Indomethacin Capsules**Directions**

1. Granules (per 100 mg), indomethacin 25 (mg), DL-tryptophan 35, hardened oil (hydrogenate soybean oil) 38, ethyl cellulose, total 100 mg.
2. A blender was charged with 750 g of indomethacin, 1050 g of DL-tryptophan, and 1140 g of the hardened oil (hydrogenated soybean oil) and mixing was conducted for 10 minutes.
3. Thereafter, 600 g of an ethanol solution of 10% ethyl cellulose (Ethocel 10CPS) was added and blending was conducted for an additional 10 minutes.

4. The blend was granulated in a rotary granulator equipped with a net (1 mm), dried at 45°C in a tray dryer for 6 hours, and classified on a 12-mesh sieve to make granules.
5. 2500 g of the granules prepared in step 4 were coated with 15% (w/w), based on the granules, of 6% hydroxypropyl methyl cellulose phthalate (HP-55) dissolved in a 1:1 mixture of methylene chloride and ethanol.
6. 300 g of the granules prepared in step 4 and 805 g of the enteric granules obtained in example 4 were mixed in a polyethylene bag and charged in No. 2 capsules in such a manner that each capsule contained 110.5 mg of the mixed granules.

Indomethacin Capsules*

Capsules for oral administration contain either 25 or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD&C blue No. 1, FD&C red No. 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide. Suspension for oral use contains 25 mg/5 mL of

indomethacin, alcohol 1%, and sorbic acid 0.1% added as a preservative. The suspension also contains the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, and tragacanth.

Indomethacin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
25.00	1	Indomethacin micronized	26.25
1.00	2	Lecithin (liquid)	1.00
–	3	Trichlorotrifluoroethane	17.00
218.25	4	Lactose monohydrate (dense)	218.25
1.50	5	Colloidal silicon dioxide (Aerosil 200)	1.50
2.00	6	Sodium lauryl sulfate	2.00
1.00	7	Magnesium stearate	1.00
1.00	8	Empty hard gelatin capsule, size 3	1000.00

Manufacturing Directions

1. Precautions

- The processing area must be under controlled room temperature and humidity. The limits are RH: 40% to 50%, temperature: 21°C to 27°C.
- Trichlorotrifluoroethane is a volatile substance when kept in open air. Always keep in covered containers.
- Do not expose the granules for a long time to light, as discoloration will occur.
- Mix item 2 with item 3 in a clean stainless steel container. Firmly cover to avoid any vaporization.

2. Blending

- Mix item 1 and 0.25 g of item 5 in a drum mixer.
- Sift the “mix” through 1250- μ m sieve using sifter. Collect in stainless steel drum and transfer to the mixer.
- Add item 2 solution from step 1 to the item 1 powder in mixer while mixing at high speed. When the addition is over, mix the moist mass at highest speed for 5 minutes.
- Scrape the sides of mixer and mix at highest speed for 5 minutes.
- Again scrape the sides of mixer and mix at highest speed for 10 minutes.

3. Drying

- Spread the moist mass thinly on stainless steel trays. Break the big lumps if any.

- Dry the mass in oven using only cold air (without temperature) for 6 hours.

4. Sifting

- Sift 168.25 g of item 4 through 630-mm sieve using a sifter. Collect in stainless steel drum. Keep aside.

5. Mixing

- Mix 50.0 g of item 4, the indomethacin–lecithin mixture (dried) and 1.25 g of item 5 in a drum mixer, for 10 minutes.
- Sift the mixture twice through 630-mm stainless steel sieve using a sifter.
- Use item 4 (approximately 2–4 g) to prevent the clogging of the sifter sieve, if required.
- Load sieved item 4 from step 4 into the blender.
- Add lactose–indomethacin–Aerosil mixture from step V-B to the blender. Mix for 10 minutes.

6. Lubrication

- Sift items 6 and 7 through a 630-mm sieve using a sifter.
- Add to the powder in blender. Mix for 2 minutes.
- Unload the granules in stainless steel drums.

7. Loading of empty shells

- Load the empty capsule shells (size 3) in the hopper.
- Run the machine and check the locking of shells.

8. Filling of powder

- Calculation: A fill weight of one capsule = 250 mg.

Indomethacin Capsules (25 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
25.00	1	Indomethacin	25.00
0.50	2	Lecithin Swiss	0.50
1.25	3	Colloidal silicon dioxide	1.25
1.67	4	Magnesium stearate	1.67
200.00	5	Lactose	200.00
—	6	Chloroform	QS

Manufacturing Directions

- Mix indomethacin with about one-half of the quantity of lactose and micronize.
- Dissolve lecithin in chloroform and wet this solution with the remaining half of the lactose.
- Dry the chloroform mixture in a drying oven at 4°C for 4 hours.
- Pass the dried granulate through a Fitz mill sieve No. 24228 at a low speed; add the mixture of indomethacin and lactose from step 1; add colloidal silicon dioxide and magnesium stearate and mix for 15 minutes.
- Fill into size 3 capsules as 200 mg ± 5%. For 50 mg capsules, fill into capsules as 325 mg ± 5%.

Indomethacin Capsules (50 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
50.00	1	Indomethacin	50.00
1.00	2	Lecithin Swiss	1.00
3.00	3	Colloidal silicon dioxide	3.00
4.00	4	Magnesium stearate	4.00
325.00	5	Lactose	325.00
—	6	Chloroform	QS

Manufacturing Directions

- Mix indomethacin with about one-half of the quantity of lactose and micronize.
- Dissolve lecithin in chloroform and wet this solution with the remaining half of the lactose.
- Dry the chloroform mixture in a drying oven at 4°C for 4 hours.
- Pass the dried granulate through a Fitz mill sieve No. 24228 at a low speed; add the mixture of indomethacin and lactose from step 1; add colloidal silicon dioxide and magnesium stearate and mix for 15 minutes.
- Fill into size 3 capsules as 200 mg ± 5%. For 50 mg capsules, fill into capsules as 325 mg ± 5%.

Indomethacin Powder for Hard Gelatin Capsules (160 mg)

Formulation

Indomethacin, 160 g; Kollidon CL, 320 g; Aerosil 200, QS.

Manufacturing Directions

Mix the components for approximately 10 minutes and fill in hard gelatin capsules to obtain 160 mg indomethacin in each capsule.

Indomethacin Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
45.00	1	Indomethacin	45.00
45.00	2	Sodium alginate	45.00
4.50 mL	3	Zinc chloride solution 2%	45 L
QS	4	Hydrochloric acid	QS
0.22	5	Glycerin	22.5 mL
–	6	Water purified	2.25

Manufacturing Directions

1. A mixture consisting of item 1 previously triturated in 22.5 mL glycerin is added with rapid stirring to an aqueous solution consisting of 45.00 g (w/v) of sodium alginate in 2.25 L of purified water.
2. This solution is then added to 4.5 L of a 2% (w/v) zinc chloride solution, which has previously been adjusted to pH 3 by the addition of HCl, while the rapid stirring is continued for 10 minutes.
3. The preparation is then allowed to stand at room temperature for 4 hours, after which the drug-entrapped zinc alginate precipitate is collected by filtration, washed 3 times with distilled water and dried under vacuum for 24 hours.
4. After drying, the residue is granulated using minimal amounts of glycerin/water and processed into 0.5-mm diameter microspheres by mechanical extrusion and spheronization (Nica Extruder; Aeromatic Ltd., Bubendorf, Switzerland), into which the slightly flexible mass represented by the above residue is fed and which produces therefrom a continuous flow of cylindrical extrudate that is 0.5 mm in diameter.
5. This extrudate falls onto the spinning plate of a Nica Spheronizer (Aeromatic Ltd.), where it is broken into cylinders of approximately 1:1 length:diameter ratio. Interaction between the spinning disc and the wall of the spheronizer then causes the cylinders to be worked into spheres of 0.5 mm in diameter.
6. The spheres are then filled into gelatin capsules (100 mg of spheres per size 1 capsule, which represents a total dose of 45.0 mg indomethacin). The capsules of the spheres thus produced represent a sustained-release dosage form for analgesic–antipyretic activity with less propensity for gastrointestinal side effects than the conventional tablet form of indomethacin. Upon ingestion the spheres begin to release the incorporated drug almost immediately, but begin to erode in 3 to 5 hours. Total erosion time is approximately 8 hours.

Indomethacin Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
75.00	1	Indomethacin	75.00
110.20	2	Sucrose	110.20
39.75	3	Cornstarch	39.75
36.20	4	Lactose	36.20
10.95	5	Polyvinylpyrrolidone	10.95
19.65	6	Talc	19.65
5.15	7	Magnesium stearate	5.15
1.10	8	Eudragit L	1.10
2.00	9	Eudragit S	2.00
–	10	Ethyl alcohol	98.55
–	11	Acetone	27.90

Manufacturing Directions

1. Pellets

- A. Weigh and mix in a stainless steel mixer suitable quantities of sucrose and cornstarch in the proportion of 3:1 w/w. Sift through a screen of suitable size to break up possible lumps.
- B. Transfer the mixture to a stainless steel coating pan and adjust rotary speed between 20 and 30 rpm so as to obtain good tumbling action.
- C. By means of a suitable spray gun, spray over the powder a quantity of water equal to 15% w/w in very minute drops.
- D. Place the wet pellets over a thermostatic tray dryer and dry at 37°C to complete evaporation of water.
- E. Pass the dried pellets through sieves of suitable screens to ensure removal of dust and selection of cores of desirable size.

2. Active pellets

- A. Dissolve polyvinylpyrrolidone in ethyl alcohol and add indomethacin previously mixed with lactose (No. 3) to it.
- B. Transfer 149.95 kg of neutral pellets obtained from step I-E to a stainless steel coating pan and adjust the rotary speed between 20 and 30 rpm so as to obtain good tumbling action.
- C. Spray over the neutral pellets the result of step II-A.

D. Keep the pan rotating to allow partial evaporation of the solvent.

E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.

3. Film-coated pellets

- A. Dissolve Eudragit L and Eudragit S in acetone.
- B. Transfer the active pellets obtained from step II-E to a stainless steel coating pan and adjust the rotary speed to obtain a good tumbling action.
- C. Spray the pellets as uniformly as possible with the solution obtained from step II-E.
- D. Spray the wet pellets with talc and magnesium stearate to prevent agglutination.
- E. Keep the pan rotating to achieve solidification of the film coating and partial evaporation of the solvent.
- F. Complete evaporation of the solvent by drying the pellets in a thermostat for 35°C for 3 days.

4. Blending of pellets

- A. Transfer the film-coated pellets obtained from step III-F to a stainless steel pan and add a suitable quantity of neutral pellets obtained from step I-E so as to obtain the required dosage.
- B. Add 0.5% w/w of talc to eliminate electrostatic charges and mix for 30 to 35 minutes.

5. Filling

- A. Fill the blended pellets obtained from step IV-B into capsules (size 2) at the dose of 300 mg each.

Insulin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
140.00 IU	1	Insulin ^a	140000 IU
0.047	2	Dimyristyl phosphatidyl choline	0.047
3.39	3	Aprotinin ^b	3.39
3.76	4	Hydroxypropyl cellulose-LF	3.76
3.76	5	Polyoxy-40 stearate Myrj-52	3.76
139.80	6	Polyethylene glycol 400	139.80
15.57	7	Propylene glycol	15.57
8.75	8	Water-citrate buffer for pH adjustment	8.75
31.20	9	Cholesterol	31.20
17.56	10	Tween 80	17.56
63.10	11	Egg yolk lecithin	63.10
27.90	12	Glyceryl amino oleate	27.90
19.60	13	D-alpha-tocopherol	19.60
249.10	14	Oleic acid	249.10

^aInsulin: 26 IU = 1 mg.

^bAprotinin: 7500 KIU = 1 mg.

Manufacturing Directions

- Insulin is a biologically active proteinaceous material. Insulin is a polypeptide consisting of 65 amino acids with an approximate molecular weight of 6000. In its preparations, there can be no use of heat or alcohol that can denature it.
- The overall method is as follows: The surfactant Myrj-52 is slowly dispersed into the mixture of polyethylene glycol 400 and propylene glycol. Once it dissolves, hydroxypropyl cellulose as a stabilizer is also added, which is dispersed slowly into the preceding mixture. A separate solution of the proteinaceous material along with the phospholipid and the protease inhibitor is made in a portion of the preceding solvent mixture. The solution can then be added to the PEG/PG mixture at room temperature. The amount of any water is limited to 5% of the polyol solvent. When the water solution is used, citrate buffer is used to maintain the pH at a point where the protein is most stable. In this particular example, if insulin is used, it is suggested that the pH be maintained with a citrate buffer at or around 2.5. Separately, the ingredients of the lipid solvent are mixed together. Under gentle and constant stirring, the polyol solution is dispersed with the lipid solution.
- The surfactant (polyoxy-40 stearate) is slowly dispersed into a mixture of polyethylene glycol and propylene glycol.
- Once it is dissolved, small amounts of hydroxypropyl cellulose are then added and dispersed into the same mixture.
- Insulin is dissolved in water and citric acid is dissolved in water for maintaining the pH at 2.5.
- The water solution is added to the polyethylene glycol mixture. In a separate vessel, dissolve all the ingredients of the oil phase in oleic acid.
- Cholesterol is added slowly to achieve faster dissolution.
- Once both the phases are ready, the polyol solution is added slowly to lipid phase while mixing at low speed. The vessel should be preferably ice jacketed because heat may be produced. Once the addition is achieved, a transparent yellowish-brown solution is obtained.
- The preemulsion solution is filled in a size 0 hard gelatin capsule and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
- The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, 3.5% to 4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
- Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate are used.
- Anionic copolymers that are based on methacrylic acid and methyl methacrylate, commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, and isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows:
Methacrylic acid and methyl methacrylate copolymer 10% w/w
Diethyl butyl phthalate (plasticizer) 2% w/w
Acetone 22% w/w
Isopropanol 66% w/w
- Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
- For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid bed sprayer/dryer is operated with the

following parameters: Flow rate: 1.5 mL/min, inlet air temperature: 25°C, outlet air temperature: 25°C, air flap: 35, atomizer: 2 bar.

Iron–Polysaccharide Complex Capsules*

Each bead-filled capsule contains 150 mg elemental iron as polysaccharide–iron complex, as cell-contracted akaganeite. Each capsule also contains the following inactive ingredients: D&C red No. 7, D&C red No. 28, D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydrogenated castor oil, polysorbate 80 pharmaceutical glaze, povidone, sodium lauryl sulfate, starch, sucrose, and titanium dioxide. Each capsule may contain silicon dioxide.

Isosorbide Mononitrate Capsules (20 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Isosorbide-5-mononitrate	20.00
60.00	2	Lactose	60.00
60.00	3	Sucrose and cornstarch microgranules	60.00
5.85	4	Shellac	5.85
1.20	5	Eudragit L 100	1.20
1.20	6	Eudragit RS 100	1.20
11.75	7	Talc	11.75
–	8	Alcohol	QS
–	9	Acetone	QD

Manufacturing Directions

- Charge neutral microgranules of item 3 in a coating pan.
- Prepare a 40% solution of shellac in alcohol together with item 1.
- Maintain the temperature of microgranules at 25°C ± 5°C. Apply step 2 and dry granules and repeat the process until the entire drug has been incorporated.
- Sieve granules using a 1-mm aperture and dry at 20°C to 30°C for 8 hours.

- A size 0 capsule after the enteric coating will typically have the following composition: Preemulsion solution: 0.589 g, undercoat polymer: 0.027 g, enteric coat polymer: 0.032 g, 0.648 g.

Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules*

Each red capsule with a pink band contains isometheptene mucate (65 mg), dichloralphenazone (100 mg), and acetaminophen (325 mg). Capsules contain FD&C yellow No. 6 as a color additive.

- Prepare a 12.5% solution of equal parts of items 5 and 6 in acetone. Spray the microgranules from step 4 and incorporate.
- Sieve the microgranules using a 1-mm aperture sieve.
- Dry microgranules at 20°C to 30°C for 8 hours.
- Spray the microgranules with balance of alcoholic shellac solution adding talc simultaneously.
- Adjust fill weight of granules based on assay.

Isradipine Capsules*

The inactive ingredients are colloidal silicon dioxide, D&C red No. 7 calcium lake, FD&C red No. 40 (5-mg capsule only), FD&C yellow No. 6 aluminum lake, gelatin, lactose, starch (corn), titanium dioxide, and other optional ingredients. The 2.5- and 5-mg capsules may also contain benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate.

Itraconazole Capsules*

The capsules contain 100 mg of itraconazole coated on sugar spheres. The inactive ingredients are gelatin, hydroxypropyl methylcellulose, polyethylene glycol (PEG) 20000, starch, sucrose, titanium dioxide, FD&C blue No. 1, FD&C blue No. 2, D&C red No. 22, and D&C red No. 28.

Itraconazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Itraconazole (used as pellets)	100.00
–	2	Empty hard gelatin capsule, size 0	1000
280.00	3	Sugar spheres	280.00
32.00	4	Hydroxypropyl cellulose	32.00
2.00	5	Polyethylene glycol 6000	2.00
30.00	6	Cornstarch	30.00
6.00	7	Titanium dioxide	6.00

Manufacturing Directions

1. Check the assay of pellets to calculate the exact amount needed. Calculate the dose per capsule to fill.
2. Charge items 1 and 3 to 7 in a suitable blender; mix for 10 minutes.
3. Set the capsule-filling machine with empty shells.
4. Fill the pellets as per assay.
5. Polish the capsules.

Ketoprofen and Misoprostol Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Ketoprofen delayed-release beads (40% Ketoprofen)	250.00
0.20	2	Misoprostol (dilute 1:100 on HPMC)	20.00
160.00	3	Lactose anhydrous	160.00
4.00	4	Hydrogenated vegetable oil	4.00

Manufacturing Directions

1. Item 1 beads are prepared by spray coating a suspension or solution of ketoprofen onto a nonpareil sugar core, together with a binder (e.g., polyvinyl pyrrolidone or hydroxypropyl methylcellulose). The beads are subsequently coated with a delayed release coating (e.g., methyl methacrylate, for instance, Eudragit). Mixtures of beads with various levels of coating were used to give the required therapeutic release pattern.
2. In a fluidized bed apparatus, uniform spherical inert sugar cores were coated with a first layer consisting of the compounds, an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, and talc. The second layer consists of an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, talc, and a pigment, such as titanium dioxide. The third and enteric coating layer consists of an enteric coating polymer such as copolymerized methacrylic acid/methacrylic acid methyl esters, a plasticizer, such as triethylacetate or similar plasticizers, and talc. The layers were applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions. Pseudo-zero release is obtained by the use of a mixture of beads.
3. The beads in item 1 contain 40% ketoprofen, giving a dose per capsule of 100 mg. The mix of items 1 to 4 is filled into suitable hard gelatin capsules.

Ketoprofen Capsules*

Capsules contain 25, 50, or 75 mg of ketoprofen for oral administration. The inactive ingredients present are D&C yellow No. 10, FD&C blue No. 1, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25-mg dosage strength also contains D&C red No. 28 and FD&C red No. 40. Each 100-, 150-, or 200-mg capsule contains ketoprofen in the form of hundreds of coated pellets. The dissolution of the pellets is pH-dependent, with optimum dis-

solution occurring at pH 6.5 to 7.5. There is no dissolution at a pH of 1. In addition to the active ingredient, each 100-, 150-, or 200-mg capsule of Oruvail contains the following inactive ingredients: D&C red No. 22, D&C red No. 28, FD&C blue No. 1, ethyl cellulose, gelatin, shellac, silicon dioxide, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other optional ingredients. The 100- and 150-mg capsules also contain D&C yellow No. 10 and FD&C green No. 3.

Lansoprazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
30.00	1	Lansoprazole	30.00
93.50	2	Neutral pellets	93.50
22.86	3	Magnesium carbonate	22.86
66.00	4	Sucrose	66.00
37.14	5	Cornstarch	37.14
46.34	6	Hydroxypropyl cellulose	46.34
79.68	7	Eudragit L	79.68
13.68	8	Talc	13.68
4.36	9	Titanium dioxide	4.36
4.36	10	Polyethylene glycol 6000	4.36
1.80	11	Polysorbate 80	1.80
—	12	Water purified	QS

Manufacturing Directions

- Charge items 1 and 3 to 5 and half of item 6 in a suitable mixer and confirm homogeneity of mixture.
- In a separate mixer, add and dissolve balance of item 6 and dissolve.
- In rotary fluid bed dryer, charge item 2 and incorporate step 2 into it.

- Prepare a suspension with item 9 in item 12 and items 8, 10, and 11 and keep agitating until dissolved or well dispersed.
- Add item 7 and mix until well suspended.
- Start spraying it onto the pellets from step 3 after passing the suspension before a fine mill.
- Fill 370 mg in capsules.

Lansoprazole Delayed-Release Capsules*

Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole (30 mg), hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid

copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, and FD&C red No. 40.

Lincomycin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Lincomycin, USE lincomycin hydrochloride	560.00
7.00	2	Lactose	7.00
2.00	3	Aerosil 200	2.00
2.00	4	Magnesium stearate	2.00
12.00	5	Sodium starch glycolate	12.00

Manufacturing Directions

- Charge all items after passing through No. 60 mesh in a low humidity room (NMT 40%).

- Mix for 30 minutes.
- Fill 590 mg in size 0 capsules.

Linezolid Oral Suspension

The oral suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 mL contains 100 mg of linezolid. The inactive ingredients are sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors. The sodium (Na⁺) content is 8.52 mg/5 mL (0.4 mEq/5 mL).

Lipase, Amylase, and Protease Capsules

The pancrelipase capsules are orally administered and contain enteric-coated mini-tablets of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. Each capsule contains lipase (12000 USP

units), amylase (39000 USP units), and protease (39000 USP units). Other combinations are 18000/58500/58500 or 20000/65000/65000. The capsules contain an amount of pancrelipase equivalent to but NMT 125% of the labeled lipase activity expressed in USP units. The inactive ingredients are hydrogenated castor oil, silicon dioxide, sodium carboxymethylcellulose, magnesium stearate, microcrystalline cellulose, methacrylic acid copolymer (type C), talc, simethicone, triethyl citrate, iron oxides, and titanium oxide.

Lithium Carbonate Capsules

Each capsule for oral administration contains lithium carbonate (150, 300, or 600 mg). The capsules contain talc, gelatin, FD&C red No. 40, titanium dioxide. The imprinting ink contains FD&C blue No. 2, FD&C yellow No. 6, FD&C red No. 40, synthetic black iron oxide, and pharmaceutical glaze.

Loperamide and Trimebutine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 capsules (g)
2.00	1	Loperamide	2.00
200.00	2	Trimebutine	200.00
122.47	3	Cornstarch	122.47
30.00	4	Talc	30.00
60.00	5	Lactose monohydrate	60.00

Manufacturing Directions

Mix and fill using into No. 2 size capsule.

Lopinavir–Ritonavir Capsules*

This is a coformulation of lopinavir and ritonavir. Capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

Loracarbef Capsules and Oral Suspension*

Each Pulvule contains loracarbef equivalent to 200 mg (0.57 mmol) or 400 mg (1.14 mmol) anhydrous loracarbef

activity. They also contain cornstarch, dimethicone, FD&C blue No. 2, gelatin, iron oxides, magnesium stearate, titanium dioxide, and other inactive optional ingredients. After reconstitution, each 5 mL of Lorabid for oral suspension contains loracarbef equivalent to 100 mg (0.286 mmol) or 200 mg (0.57 mmol) anhydrous loracarbef activity. The suspensions also contain cellulose, FD&C red No. 40, flavors, methylparaben, propylparaben, simethicone emulsion, sodium carboxymethylcellulose, sucrose, and xanthan gum.

Loxapine Succinate Capsules

Each capsule for oral administration contains loxapine succinate 6.8, 13.6, 34.0, or 68.1 mg equivalent to 5, 10, 25, or 50 mg of loxapine base respectively. It also contains the following inactive ingredients: gelatin, silicon dioxide, sodium lauryl sulfate, anhydrous lactose, D&C yellow No. 10, FD&C

blue No. 1, polacrillin potassium, magnesium stearate, talc, and titanium dioxide. Additionally, the 5-mg capsule contains D&C red No. 33, the 10-mg capsule contains D&C red No. 28 and D&C red No. 33, and the 25-mg capsule contains FD&C yellow No. 6.

Magaldrate Instant Powder or Dry Syrup

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
800.00	1	Magaldrate, USP	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol (crystalline)	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon 90 F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharine sodium	0.80
QS	9	Water	~280.00 mL

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with solution of items 5 to 9 and pass through a 0.8-mm sieve to obtain free-flowing granules.

2. Fill 2 g in sachets or 20 g in a 100-mL flask.
3. Instant granules in sachets: Suspend 2 g (=one sachet) in a glass of water (=800 mg magaldrate).

Magaldrate Instant Powder or Dry Syrup

Bill of Materials			
Scale (mg/sachet)	item	Material Name	Qty/1000 Sachets (g)
800.00	1	Magaldrate	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol, crystalline	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon 90 F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharin sodium	0.80
QS	9	Water	~280 mL

Manufacturing Directions

1. Granulate a mixture of items 1 to 4 with solution of items 5 to 9 and pass through a 0.8-mm sieve to obtain free-flowing granules.

2. Fill 2 g in sachets or 20 g in a 100-mL flask. For instant granules in sachets, suspend 2 g (=1 sachet) in a glass of water (=800 mg magaldrate).

Magnesium Oxide Capsules

Each capsule contains magnesium oxide [140 mg USP (heavy)] or 84.5 mg of elemental magnesium (6.93 mEq).

Mefenamic Acid Capsules

Mefenamic acid is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each blue-

banded ivory capsule contains 250 mg of mefenamic acid for oral administration. Each capsule also contains lactose. The capsule shell and band contain citric acid, D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 3, FD&C yellow No. 6, gelatin, glycerol monooleate, silicon dioxide, sodium benzoate, sodium lauryl sulfate, and titanium dioxide.

Mesalamine Capsules*

Each capsule contains 250 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and

white wax. The capsule shell contains D&C yellow No. 10, FD&C blue No. 1, FD&C green No. 3, gelatin, titanium dioxide, and other optional ingredients.

Mesalamine Colonic Delivery Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Mesalamine (5-ASA)	250.00
45.00	2	Lactose	45.00
5.20	3	Polyvinylpyrrolidone	5.20
10.80	4	Sodium starch glycolate	10.80
3.60	5	Magnesium stearate	3.60
36.80	6	Talc	36.80
18.40	7	Eudragit S100	18.40
43.20	8	Eudragit NE 30D	43.20
0.40	9	Antifoam emulsion SE 2	0.40

Manufacturing Directions

1. Add items 1 and 2 to a blending vessel; mix well.
2. Add item 4 and blend.
3. Prepare an aqueous solution of item 3 and granulate step 2.
4. Dry and compress; reduce size by passing through a 0.5- to 1.2-mm sieve.
5. The granules in step 4 are loaded into a fluid bed coater and then spray-coated with an aqueous suspension to provide a 20% or 25% dry weight gain based on an uncoated granule weight of a mixture of Eudragit S100 and Eudragit NE 30D (Rohm Pharma GmbH, Darmstadt, Germany) in the

ratio of 3:7. Eudragit S100 is a copolymer of methacrylic acid and methylmethacrylate in the ratio of 1:2 in powder form and Eudragit NE 30D is a 30% aqueous dispersion of a copolymer of ethylacrylate and methylmethacrylate in the ratio 2:1.

6. Coated granules are packed into size 00 hard gelatin capsules in an amount of 400 mg granules per capsule.
7. The capsules are then spray-coated with a coating solution of the following formula:
Eudragit L powder 3 g
Diethyl phthalate 0.75 mL
Silicone fluid 200 cs 0.75 mL
Acetone 100 mL

Methsuximide Capsules*

Each capsule contains 150 or 300 mg methsuximide as well as starch. The capsule contains colloidal silicon dioxide, D&C yellow No. 10, FD&C yellow No. 6, gelatin, and sodium lauryl sulfate.

Methylphenidate Capsules

It contains 20 mg of methylphenidate hydrochloride for oral administration. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose (6 mg) is provided by the IR component and 70% of the dose (14 mg) is provided by the ER component. It also contains the following inert ingredients: sugar spheres, povidone, hydroxypropyl methylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, and FD&C blue No. 2.

Methylphenidate Capsules**Manufacturing Directions**

1. Methylphenidate HCl (200 g) is slowly added to an aqueous solution (approximately 15% solids) of

polyvinylpyrrolidone (10 g povidone K-30) and mixed well.

2. About 25- to 30-mesh sugar spheres (770 g) were coated with the drug solution in a fluid bed granulator. The drug-containing pellets are dried and a seal coat of Opadry Clear[®] (20 g) is first applied to produce instant-release or IR beads.
3. ER beads are produced by taking IR beads and coating with the dissolution rate controlling polymer. A plasticized ethyl-cellulose coating is applied to the methylphenidate particles (893 g) by spraying Aquacoat ECD-30[®] (233 g) and dibutyl sebacate (16.8 g).
4. An outer seal coating formulation (20 g) of Opadry[®] is sprayed onto the coated active particles. The coated particles are cured at 60°C for 12 hours so that polymer particles coalesce to form a smooth membrane on ER beads. The IR and ER beads are then filled into hard gelatin capsules with dual bead-filling hoppers.

Methylphenidate Immediate- and Extended-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
25.00	1	Methylphenidate	25.00
1.25	2	Polyvinylpyrrolidone K-30	1.25
96.25	3	Sugar spheres 25–30 mesh	96.25
2.25	4	Opadry clear	2.25
29.12	5	Aquacoat ECD-30	29.12
2.10	6	Dibutyl sebacate	2.10
2.25	7	Opadry clear	2.25
—	8	Alcohol	QS

Manufacturing Directions

- This product consists of two types of beads: IR and ER. The ER beads are formed by further coating of IR beads.
- IR beads are produced by preparing a 15% solution of item 2 in item 8 and adding item 1 to it slowly.
- Charge item 3 in a fluid bed granulator and load drug solution in step 2 onto sugar pellets. Dry and apply seal coat of item 4. This completes the process of preparing IR beads.
- Take an appropriate quantity (893 g) of beads in step 3 and apply a coating of item 6 in item 8.
- Apply item 7 seal coat (as 15% aqueous solution), and cure at 60°C for 12 hours for polymer particles to coalesce into a uniform film.
- Fill in gelatin capsules using a 20:80, 30:70, or 40:60 mixture of IR to ER beads. Use equipment that is capable of filling beads simultaneously.

Methyltestosterone Capsules*

Each capsule contains 10 mg of methyltestosterone. Each capsule, for oral administration, contains 10 mg of methyltestosterone. In addition, each capsule contains the following inactive ingredients: cornstarch, gelatin, FD&C blue No. 1, FD&C

red No. 40. Each capsule also contains the following inactive ingredients: cornstarch, gelatin, FD&C blue No. 1, and FD&C red No. 40.

Metoclopramide Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Metoclopramide, USE metoclopramide hydrochloride	21.00
183.90	2	Sucrose and cornstarch microgranules, size 20	183.90
0.12	3	Disodium edetate	0.12
0.19	4	Stearic acid	0.19
1.30	5	Methacrylic acid copolymer Eudragit L100	1.30
0.42	6	Cornstarch	0.42
9.07	7	Shellac, bleached wax-free	9.07
15.00	8	Talc	15.00
1.00	9	Gelatin capsules, size 3	1000.00
—	10	Alcohol	QS
—	11	Water purified	11.00

Manufacturing Directions

- The neutral microgranules (item 2) are placed in an appropriate coating pan and the pan is rotated.
- In a separate vessel, prepare an alcoholic solution of item 5. Spray in step 1.
- Prepare alcohol solution of item 4 in alcohol and spray into step 2.
- Prepare aqueous solution of item 3 and spray into step 3.
- Mix item 1 with item 6 and add to step 4 alternating with an alcoholic solution of Eudragit until the entire drug has been incorporated.
- Sieve the microgranules.
- Apply aqueous solution of item 3 followed by an alcohol solution of Eudragit L and microgranules dried.
- Apply alcoholic solution of shellac alternating with talc until all shellac solution is used.
- Lubricate and fill in capsules; sieve and dry microgranules.

Metyrosine Capsules*

It is supplied as capsules for oral administration. Each capsule contains 250 mg of metyrosine. The inactive ingredients are colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, magnesium stearate, and titanium dioxide. The capsules may also contain any combination of D&C red No. 33, D&C yellow No. 10, FD&C blue No. 1, and FD&C blue No. 2.

Miconazole Nitrate Foot and Itch Powder

Spray powder for athlete's foot contains miconazole nitrate 2%. It also contains alcohol SD-40 (10% w/w), isobutane, starch/acrylates/acrylamide copolymer, stearalkonium hectorite, and talc. Spray powder for jock itch contains miconazole nitrate 2%. It also contains alcohol SD-40 (10% w/w), isobutane, stearalkonium hectorite, and talc. Spray deodorant powder contains miconazole nitrate 2%. It also contains isobutane, alcohol SD-40 (10% w/w), talc, starch/acrylates/acrylamide copolymer, stearalkonium hectorite, and fragrance. Powder contains miconazole nitrate 2%. It also contains benzethonium chloride, cornstarch, kaolin, sodium bicarbonate, starch/acrylates/acrylamide copolymer, and zinc oxide.

Midodrine Capsules

- The midodrine controlled-release product is prepared by manufacturing one type of pellet, which afterward is coated with different types of film coatings. The capsule ends up with three different types of pellets (noncoated pellet, CR-coated pellet, and EC-pellet).
- The pellet is prepared by the use of an extrusion/spheronization technique.
- Microcrystalline 2135.0 g, cellulose lactose monohydrate 1207.5 g, carmellose sodium 70.0 g, midodrine hydrochloride 87.50 g, purified water qs to 2000.
- The above ingredients are mixed and wetted in a Fielder high shear mixer in which the water is applied by a nozzle.
- The wetted mass is extruded in a Nica E 140 extruder with a screen size of 600 micron (those pellets which is being used for noncoated pellets and for CR-coating) or 800 micron (those pellets used for EC-coating). The extrudate is spheronized in a laboratory unit for 5 minutes. The pellets were dried in a laboratory scala fluid bed for approximately 75 minutes at 50°C.
- The dried pellets used for noncoated pellets and for CR-coating were screened through a screen of 700 micron and the dried pellets used for EC coating were fractionated with a lower screen of 500 micron and a upper screen of 1000 micron.
- One batch of these pellets is not coated because it is used as an immediate-release unit. The pellets are a part of the content in the capsule.
- One batch of these pellets is coated with an inner coat and an outer coat in a fluid bed (GPCG3) with a 0.8-mm spray nozzle and a spray pressure of 2.5 bar.
- Inner coat (batchsize 2000 g), hypromellose (viscosity 13.1 5 cps), purified water 1094.0 g, magnesium stearate 2.7 g, talc 26.2 g, polyacrylate dispersion 864.0 g, 30% Eudragit g, talc 40.0 g. In the coating process, the following amount of inner and outer coat was applied. The amount of dry matter applied calculated in percentage of the core weight also appears from below. Inner coat: 1788.1 g per 3000.0 g pellets (dry matter: 9% of the core weight). Outer coat: 375.0 g per 3000.0 g pellets (dry matter: 1% of the core weight). Throughout the coating process the bed temperature is maintained substantially in the interval from 20°C to 25°C by adjustment of the liquid flow rate or the inlet temperature. The inlet air temperature is kept at approximately 32°C. After the application of the coatings the coated pellets were cured at a bed temperature of approximately 70°C for 30 minutes. Then the pellets were screened through a screen 1 mm. Oversized material is discarded.
- One batch of these pellets is coated with an EC-coat in a fluid bed (Wurster technique) with a 0.8-mm spray nozzle and a spray pressure of 2.5 bar.

Ingredients	Amount (g/batch size)
Isopropyl alcohol	3852.0
Talc	100.0
Acetyltributyl citrate	99.2
Methacrylic acid/Methyl methacrylate	3948.8
Copolymer	1:2
Eudragit S	12.5

In the coating process the following amount of the coat were applied. The amount of dry matter applied calculated in percentage of the core weight also appears from below. 15517.2 g per 3000 g pellets (dry matter: 45% of the core weight). Throughout the coating process, the bed temperature is maintained substantially in the interval from 30°C to 38°C by adjustment of the liquid flow rate or the inlet temperature. The inlet air temperature is kept at approximately 49°C. After the application of the coating the pellets were screened through a screen 1.3 mm. Oversized material is discarded.

- The three different pellets (steps 1, 2, and 3) were filled into capsules : Unit amount (mg) per capsule capsule approx. 76.3 pellets step 1 approx. 50.4 corresp. to 1.25 mg midodrine hydrochloride Pellets step 2 approx. 110.6 corresp. to 2.5 mg midodrine hydrochloride Pellets step 3 approx. 72.7 corresp. to 25 mg midodrine hydrochloride Total weight of capsule approx. 310 corresponding to 5.0 mg midodrine hydrochloride

Mineral Powder for Topical Herpes Simplex

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
14.00	1	Calcium carbonate	14.00
14.00	2	Sodium carbonate	14.00
14.00	3	Sodium dihydrogen phosphate anhydrous	14.00
80.00	4	Calcium hypochlorite	80.00
818.00	5	Cornstarch	818.00

Manufacturing Directions

1. Mix all ingredients after passing through an 80-mesh screen.

2. Pack in bottles.

Minocycline Hydrochloride Capsules*

Each minocycline hydrochloride capsule for oral administration contains the equivalent of 50, 75, or 100 mg of minocycline. In addition, each capsule contains the following inactive ingredients: magnesium stearate and starch (corn). The 50-, 75-, and 100-mg capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The 75- and 100-mg capsule shells also contain black iron oxide.

Mixed Amphetamine Salt Capsules*

It is a once-daily, extended-release single-entity amphetamine product. It combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and *d,l*-amphetamine aspartate monohydrate. The capsule contains two types of drug-containing

beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine compared to the conventional immediate-release tablet formulation. Each capsule contains equal quantities of four salts of amphetamine to give a total of 10, 20, or 30 mg of content (total amphetamine base equivalence of 6.3, 12.5, and 18.8 mg): dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, amphetamine sulfate. The inactive ingredients in the capsules include gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, Opadry beige, sugar spheres, talc, and triethyl citrate. The gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 10-mg capsules also contain FD&C blue No. 2. The 20- and 30-mg capsules also contain red iron oxide and yellow iron oxide.

Mixed Amphetamine Salts Enteric-Release Capsules

Bill of Materials		
Item	Material Name	Qty/kg (g)
Immediate-release beads		
1	Amphetamine mixed salts ^a	88.00
2	Nonpareil seeds (30/35 Mesh, Paulaur)	6.80
3	Hydroxypropyl methylcellulose E5 premium	0.60
4	Water purified	QS
Enteric-release pellets		
5	Immediate-release beads (see items 1-4)	40.00
6	Eudragit L30-D-55	24.88
7	Triethyl citrate	2.52
8	Talc	2.60
9	Water purified	QS

^aMixed salts include amphetamine sulfate, amphetamine aspartate, and dextroamphetamine sulfate.

Manufacturing Directions

1. Charge item 2 in a fluid-bed processor and fluidize at 60°C.
 2. Prepare a suspension of item 3 (prepare a 1% solution) and item 1 using item 4; ensure it is free of agglomerates and contains no fines with a yield of at least 98%.
 3. Apply binder solution to step 1 and load the drug.
 4. Charge item 5 into a fluid bed processor.

5. Prepare the coating dispersion using items 6 to 8 in item 9 and mix for at least 30 minutes.
 6. Spray the coating solution in step 5 onto step 1 until a target level of 20 µm is achieved.
 7. Dry pellets at 30°C to 35°C for 5 minutes before stopping the processor.
 8. Fill to contain in each capsule base equivalent 10, 20, and 30 mg (Adderall XR[®]).

Morphine Sulfate Capsules*

Each capsule for oral administration contains morphine sulfate 15 or 30 mg. The inactive ingredients are FD&C blue No. 1, FD&C blue No. 2, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydroxypropyl methylcellulose, lactose, polyethy-

lene glycol, polysorbate 80, polyvinylpyrrolidone, starch, sucrose, titanium dioxide, and other optional ingredients. In addition, the 30-mg capsule contains black iron oxide and D&C red No. 28.

Morphine Sulfate Controlled-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
40.00	1	Morphine hydrochloride	40.00
40.00	2	Lactose	40.00
20.00	3	Microcrystalline cellulose	20.00
QS	4	Water purified	QS
3.50-5.30	5	Ethyl cellulose	3.50-5.30
2.20-3.40	6	Hydroxypropyl methylcellulose	2.20-3.40
0.60-1.0	7	Triethyl citrate	0.60-1.00
QS	8	Ethanol	QS
QS	9	Methyl isobutyl ketone	QS

Manufacturing Directions

- Mixing and granulating: Morphine hydrochloride (40% w/w), lactose (40% w/w), and microcrystalline cellulose (Avicel PH-101) (20% w/w) total 1500 g are dry-mixed in a planetary-type mixer (Kenwood Major[®]) at a low mixing speed (speed adjustment <1) for 10 minutes. Water (585 g) is added and the mass is granulated for 5 minutes at speed adjustment 2.
- Extrusion: Extrusion is performed in a Nica[™] E-140 Extruder (Lejus Medical AB, Sweden) through a perforated screen with drilled orifices of 1 mm in diameter. The speed of the agitator and the feeder is set on the lowest values.
- Spheronization: Spheronization is conducted in a mamerizer (Ferro Mecano AB, Sweden). The speed of the Marumerizer[™] plate is adjusted to 450 rpm. The number of spheronization rounds is 5 with about 400 g of wet extrudates on the plates at each run.
- Drying: Drying is performed in a fluid bed dryer (Aeromatic AG[®], West Germany) at an IN temperature of 50°C. The batch is divided into subbatches of 600 to 700 g wet particulate cores. Each subbatch is dried for 5 minutes at the air velocity adjustment 20 to obtain individual cores rather than aggregates. The subbatches are then mixed and the whole batch is dried at adjustment 12 for 65 minutes. The end OUT temperature is 36°C. The yield of dry cores after drying is 1437 g and 96% w/w.
- Sieving: Sieving is performed by using analytical sieves with sieve sizes of 0.71 mm and 1.40 mm respectively. The yield of dry cores after sieving is 1337 g and 89% w/w. The yields are 96% and 89% w/w after drying and sieving respectively.
- A sieving analysis before and after abrasion of the cores shows that about 93% of the cores have a size between 0.71 and 1.0 mm. A crushing strength analysis shows that the mean crushing strength of 1-mm particles is 4.71 N. A hardness value at this level makes it possible to coat the particles in small as well as in large equipment.
- Morphine hydrochloride cores manufactured as above are coated with controlled-release membranes. Hydroxypropyl methylcellulose (HPMC) (E5) and ethyl cellulose (EC) (10 cps) were used as film formers together with triethyl citrate (TEC) as a plasticizer. The coating solution contains 99.5% ethanol and methyl isobutyl ketone (MIBK).
- The coating is performed using a spray coating equipment (Nica[™] FB-coater, Sweden). The spray gun used is a Binks&Bullows with a J92R liquid nozzle and a J930 air nozzle. A net device is placed in the top of the fluidized bed to avoid loss of cores to the cyclone output. The spray gun is mounted on a height over the bottom of the bed for 185 minutes. Ethanol/MIBK mixture is pumped through the system before to the start of the coating and there is consequently liquid present between the pump housing and the spray gun. The morphine hydrochloride cores prepared above are loaded. The cores are preheated at 55°C with an air velocity of 20 to 25 m³/h for 4 minutes. At the start of the coating, the bed temperature is 32°C to 36°C. The coating is started using the following process parameters: atomizing pressure 500 kPa, air velocity 85 m³/h, and a solution flow of about 24 mL/min. The registered IN temperature varies between 53°C to 56°C, and the OUT temperature varies between 34°C and 38°C during the coating.
- The coated spheres are sieved through a 1.4-mm sieve and spheres with size less than 1.4 mm are collected.
- The collected spheres are filled into hard gelatin capsule (white) with a normal weight of 0.17 g (net 108 mg). The mean content of active component in the capsule is between 36 and 44 mg.

Morphine Sulfate Sustained-Release Capsules*

Each sustained-release capsule contains either 20, 30, 50, 60, or 100 mg of morphine sulfate and the following inactive ingredients that are common to all strengths: hydroxypropyl methylcellulose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, cornstarch, and sucrose. The 20-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, titanium dioxide, and black ink (SW-9009). The 30-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, FD&C red No. 3, FD&C blue No. 1, titanium dioxide, and black ink (S-1-8114 or S-1-8115).

The 50-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink (SW-9009). The 60-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink (S-1-8114 or S-1-8115). The 100-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, FD&C blue No. 1, titanium dioxide, and black ink (SW-9009).

Multivitamin Effervescent Granules

Bill of Materials			
Scale (mg/Sachet)	Item	Material Name	Qty/1000 Tabs (g)
2.600	1	Thiamin hydrochloride (BASF)	0.26
3.000	2	Riboflavin (BASF)	0.30
11.000	3	Nicotinamide	1.10
2.500	4	Pyridoxine hydrochloride (BASF)	0.25
15.000	5	Calcium D-pantothenate (BASF)	1.50
200.000	6	Ascorbic acid powder (BASF)	20.00
500.000	7	Citric acid	50.00
1300.000	8	Sucrose	130.00
800.000	9	Fructose	80.00
200.000	10	Kollidon CL-M	20.00
250.000	11	Flavors	25.00
20.000	12	Cyclamate sodium	2.00
1.000	13	Saccharine sodium	0.10
150.000	14	Kollidon VA 64	15.00
350.000	15	Isopropanol	35.00
15.000	16	Vitamin A acetate dry powder 325000 IU/g CWD (BASF)	1.50
8.000	17	Vitamin D ₃ dry powder 100000 IU/g CWD (BASF)	0.80
21.000	18	Vitamin E acetate dry powder 50%	2.10
0.066	19	Cyanocobalamin gelatin coated 0.1% (BASF)	0.66
400.000	20	Sodium bicarbonate	40.00

Manufacturing Directions

1. Granulate mixture of items 1 to 13 with solution of items 14 and 15; pass through a 0.8-mm sieve, dry well, and mix with items 16 to 20.

2. Fill 4 g in sachets.

Multivitamin Effervescent Granules

Bill of Materials			
Scale (mg/Sachet)	Item	Material Name	Qty/1000 Sachet (g)
2.60	1	Thiamin hydrochloride	0.26
3.00	2	Riboflavin	0.30
11.00	3	Nicotinamide	1.10
2.50	4	Pyridoxine hydrochloride	0.25
15.00	5	Calcium D-pantothenate	1.50
200.00	6	Ascorbic acid (powder)	20.00
500.00	7	Citric acid	50.00
1300.00	8	Sucrose	130.00
800.00	9	Fructose	80.00
200.00	10	Kollidon CL-M	20.00
250.00	11	Flavors	25.00
20.00	12	Cyclamate sodium	2.00
1.00	13	Saccharine sodium	0.10
150.00	14	Kollidon VA 64	15.00
350.00	15	Isopropanol	35.00
5000 IU	16	Vitamin A acetate (dry powder; 325000 IU/g CWD)	1.50
800 IU	17	Vitamin D ₃ (dry powder; 100000 IU/g CWD)	0.80
21.00	18	Vitamin E acetate (dry powder; 50%)	2.10
0.0660	19	Cyanocobalamin (gelatin-coated; 0.1%)	0.66
400.00	20	Sodium bicarbonate	40.00

Manufacturing Directions

1. Granulate mixture of items 1 to 13 with solution of items 14 and 15.

2. Pass through a 0.8-mm sieve, drywell, and mix with items 16 to 20.
3. Fill 4 g in sachets.

Multivitamin Instant Granules

Bill of Materials			
Scale (mg/6 g Sachet)	Item	Material Name	Qty/30 kg (g)
40.00	1	Vitamin A+D dry powder + 50000 IU/g CWD (BASF)	200.00
5.00	2	Thiamine mononitrate (BASF)	26.00
6.00	3	Riboflavin (BASF)	33.00
22.00	4	Nicotinamide	110.00
4.50	5	Pyridoxine hydrochloride (BASF)	22.00
30.00	6	Calcium D-pantothenate (BASF)	150.00
0.013	7	Cyanocobalamin, USE cyanocobalamin 0.1% gelatin coated (BASF)	66.00
230.00	8	Ascorbic acid powder (BASF)	1150.00
42.00	9	Vitamin E acetate dry powder	210.00
4000.00	10	Sucrose, finely ground	20000.00
1000.00	11	Kollidon CL-M	5000.00
200.00	12	Orange flavor	1000.00
400.00	13	Kollidon VA 64	2000.00
—	14	Ethanol or isopropanol	~7 L

Manufacturing Directions

1. Pass mixture through a 0.8-mm sieve and granulate with solution of items 13 and 14 in the fluidized bed.
2. Fill the granules in sachets. If the technology of a fluidized bed is not available, the dry powders of vitamin A, E, and

B₁₂ should be added after the granulation of the other components.

3. Suspend 6 to 12 g (=1 sachet) in a glass of water corresponding to 2 to 4 RDA of vitamins. Double-strength sachet filled at 12 g.

Multivitamin Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/30 kg (g)
40.00	1	Vitamin A and vitamin D (dry powder + 50000 IU/g CWD)	200.00
5.00	2	Thiamine mononitrate	26.00
6.00	3	Riboflavin	33.00
22.00	4	Nicotinamide	110.00
4.50	5	Pyridoxine hydrochloride	22.00
30.00	6	Calcium D-pantothenate	150.00
0.013	7	Cyanocobalamin; use cyanocobalamin (gelatin-coated, 0.1%)	66.00
230	8	Ascorbic acid powder	1150.00
–	9	Vitamin E acetate dry powder	210.00
4000	10	Sucrose (finely ground)	20000.00
1000	11	Kollidon CL-M	5000.00
200	12	Orange flavor	1000.00
400	13	Kollidon VA 64	2000.00
–	14	Ethanol or isopropanol	~7.00 L

Manufacturing Directions

1. Pass mixture through a 0.8-mm sieve and granulate with solution of items 13 and 14 in the fluidized bed.
2. Fill 6 to 12 g of the granules in sachets.

Mycophenolate Mofetil Capsules and Oral Suspension*

The inactive ingredients in 250-mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90), and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue No. 2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. The inactive ingredients in Cell-Sept oral suspension include aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin, and xanthan gum.

Nanoparticle Polymer Particle Powders

1. Preparation of polymer nanoparticles of ketorolac: To 900 mg *N*-isopropyl acrylamide (NIPAAm), 100 mL freshly distilled vinyl pyrrolidone (VP) and 50 mL freshly distilled acrylic acid (AA) in 100 mL of water, and 300 mL methylene bis acrylamide (MBA; MBA = 0.049 g/mL) are added to cross-link the polymer chain. The dissolved oxygen is removed by passing nitrogen gas for 30 minutes; 50 mL of 0.5% w/v ferrous ammonium sulphate (FAS) and 50 mL saturated ammonium persulfate (APS) solutions are then added to initiate the polymerization reaction. The polymerization is done at 30°C for 24 hours in nitrogen atmosphere. Total aqueous solution of polymer is then dialyzed overnight using a spectrapore membrane dialysis bag (12 kD cutoff). The dialyzed aqueous solution of polymeric micelles is frozen in liquid nitrogen and is lyophilized immediately to obtain dry powder

3. If the technology of a fluidized bed is not available, the dry powders of vitamins A, E, and B₁₂ should be added after granulation of the other components.
4. Suspend 6 to 12 g (=1 sachet) in a glass of water; corresponds to 2 to 4 RDA of vitamins.

- for subsequent use. The yield of micelle nanoparticles is more than 80%. The lyophilized powder is easily redispersible in aqueous buffer; 100 mg of lyophilized powder of polymeric micelles is dispersed in 10 mL of water and is stirred well to disperse the micelles. The free acid form of ketorolac is dissolved in absolute ethanol (ketorolac = 50 mg/mL) and the alcoholic solution is added in polymeric micelles slowly with constant stirring. Ketorolac got directly loaded into hydrophobic core of micelles. The drug-loaded polymeric micelles are then lyophilized to get dry powder for subsequent use.
2. Preparation of polymeric nanoparticles containing indomethacin: In 100 mg of the lyophilized powder of the polymeric micelle nanoparticles, an alcoholic solution of indomethacin (indomethacin = 33 mg/mL) is added with constant stirring to get clear solution of polymeric micelles containing the drug of desired concentration dispersed in aqueous buffer. Maximum 10% w/w of the drug can be dissolved in polymeric micelles at room temperature. The drug-loaded polymeric micelles are then lyophilized to get dry powder for subsequent use.
 3. Preparation of polymeric micelles containing nimesulide: In 100 mg of dry powder of polymeric micelles, an alcoholic solution of nimesulide (nimesulide = 10 mg/mL) is added with constant stirring to get a clear solution. Maximum 8% w/w of nimesulide could be dissolved in polymeric micelles at room temperature. The drug-loaded micelles are then lyophilized to get dry powder for subsequent use.

Nelfinavir Mesylate Oral Powder*

Oral powder is available for oral administration in a 50-mg/g strength (as nelfinavir freebase) in bottles. The oral powder also contains the following inactive ingredients: microcrys-

talline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame, sucrose palmitate, and natural and artificial flavors.

Nelfinavir Mesylate Oral Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Nelfinavir mesylate	50.00
50.00	2	Sodium carboxymethylcellulose	50.00
1.25 mL	3	Syrup	1.25 L
0.10 mL	4	Benzoic acid solution	0.10 L
QS	5	Flavor	QS
QS	6	Dye	QS
QS to 5 mL	7	Purified water	5 L

Manufacturing Directions

- The active ingredient is passed through a No. 45 mesh sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste.
- The benzoic acid solution, flavor, and color are diluted with a portion of the water and added with stirring. Sufficient water is then added to produce the required volume.

Nilvadipine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
14.00	1	Nilvadipine	14.00
166.00	2	Polyethylene glycol 400	166.00
20.00	3	Hydroxypropyl methylcellulose	10.00

Manufacturing Directions

- Add and dissolve item 1 in item 2.
- Add item 3 and fill 200 mg in a size 4 hard gelatin capsule.

Nitrofurantoin Capsules*

Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, and may contain FD&C yellow No. 6 and D&C yellow No. 10. Nitrofurantoin is an antibacterial agent specific for urinary tract infections. Another formulation of nitrofurantoin capsule is a hard gelatin capsule shell containing the equivalent of 100 mg of nitrofurantoin in the

form of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate. Inactive ingredients: Each capsule contains carbomer 934P, cornstarch, compressible sugar, D&C yellow No. 10, edible gray ink, FD&C blue No. 1, FD&C red No. 40, gelatin, lactose, magnesium stearate, povidone, talc, and titanium dioxide.

Nitrofurantoin Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Nitrofurantoin monohydrate (Norwich Eaton Pharmaceuticals, Inc.)	150.00
17.70	2	Carbopol 934P (B. F. Goodrich)	17.70
181.00	3	PVP C-15 (GAF Corporation)	181.00
3.50	4	Talc	3.50
1.80	5	Zinc stearate	1.80

Manufacturing Directions

- Carbopol 934P, PVP C-15 (mean molecular weight of approximately 8000), talc, and zinc stearate are combined in a mortar and triturated well.
- The nitrofurantoin monohydrate is added to this mixture in the mortar and triturated well until a substantially uniform particulate mixture is achieved.
- The resulting particulate mixture (354 mg) is filled into size 1 hard gelatin capsule shells.

Nizatidine Capsules*

Each capsule contains pregelatinized starch, dimethicone, starch, titanium dioxide, yellow iron oxide, 150 mg (0.45 mmol) or 300 mg (0.91 mmol) of nizatidine, and

other inactive ingredients. The 150-mg capsule also contains magnesium stearate and the 300-mg capsule also contains croscarmellose sodium, povidone, red iron oxide, and talc.

Nizatidine Capsules*

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Nizatidine	150.00
33.70	2	Cornstarch	33.70
15.00	3	Pregelatinized starch (starch 1500)	15.00
0.70	4	Magnesium stearate	0.70
0.60	5	Simethicone	0.60
	6	Empty hard gelatin shell, size 2 (bovine origin)	1000.00

Manufacturing Directions

1. Add and blend items 1 to 3 in a suitable blender and mix for 20 minutes.

2. Add item 4 and blend for 10 minutes
3. Add item 5 and blend for 4 minutes.
4. Fill in 200 mg of hard gelatin capsules.

Nystatin Powder*

Nystatin topical powder is for dermatologic use and contains 100,000 USP nystatin units per gram dispersed in talc.

Omeprazole and Piroxicam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
95.70	1	Omeprazole enteric-coated pellets	95.70
122.70	2	Piroxicam enteric-coated pellets	122.70

Manufacturing Directions

1. This product requires preparation of enteric-coated pellets of omeprazole and piroxicam separately.
2. The omeprazole pellets are prepared by applying drug solution (in HPMC) on nonpareil sugar beads, applying a separating layer consisting of HPMC alone and then applying an enteric coating that comprises methylacrylic acid copolymer 30% suspension with triethyl citrate, mono- and diglycerides, and polysorbate 80 in purified water. Finally an overcoat is applied.

Core material (omeprazole)

Magnesium omeprazole: 5.00 kg
 Nonpareil cores: 10.00 kg
 Hydroxypropyl methylcellulose: 0.75 kg
 Water purified: 19.65 kg

Separating layer (omeprazole)

Core material (acc. to above): 14.60 kg
 Hydroxypropyl cellulose: 1.46 kg
 Talc: 2.5 kg
 Magnesium stearate: 0.21 kg
 Water purified: 29.2 kg

Enteric coating layer (omeprazole)

Pellets with separate layer (acc. to above): 9.00 kg
 Methacrylic acid copolymer (30% suspension): 15.00 kg
 Triethyl citrate: 1.35 kg
 Mono- and diglycerides: 0.22 kg
 Polysorbate 80: 0.02 kg
 Water purified: 8.8 kg

Overcoating layer (omeprazole)

Enteric coating layered pellets: 9.0 kg
 Hydroxypropyl methylcellulose: 0.18 kg
 Magnesium stearate: 0.005 kg
 Water purified: 3.6 kg

3. The piroxicam pellets are prepared by a similar method except using a hydroalcoholic solution in the first instance, not using a separating layer, and performing enteric coating using HPMC succinate.

Core material (piroxicam)

Piroxicam micronized: 35 g
 Sugar seeds: 100 g
 Hydroxypropyl methylcellulose: 6 cps, 25 g

Water purified: 250 g

Ethanol 99% (w/v): 250 g enteric coating layer (piroxicam)
 Piroxicam pellets (acc. to above): 100 g
 Hydroxypropyl methylcellulose acetate-succinate: 14.38 parts

Triethyl citrate: 2.87 parts

Sodium lauryl sulphate: 0.43 parts

Talc: 4.32 parts**Water purified: 183.3 parts**

4. Coat with a suspension of the preceding composition to give a product with a content of 163 mg/g; suspension layering is performed in fluid bed equipment. Micronized piroxicam is sprayed onto inert nonpareil cores from a water suspension containing the dissolved binder.

Omeprazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
20.00	1	Omeprazole	20.00
5.33	2	Hydroxymethylcellulose	5.33
6.00	3	2910 hydroxypropyl cellulose	6.00
8.00	4	Lactose	8.00
0.64	5	Disodium phosphate anhydrous	0.64
0.50	6	Sodium lauryl sulfate	0.50
		Enteric coating layer	
21.00	7	HPMCAS	21.00
6.00	8	Triethyl citrate	6.00
0.66	9	Sodium lauryl sulfate	0.66
11.00	10	Talc	11.00
1.12	11	Sodium hydroxide	1.12

Directions

1. First, sugar spheres 20/25 (700–850 microns, 161.63 mg) were placed in a fluid bed coating chamber equipped with a Wurster bottom-spraying device.
2. A suspension of the ingredients in water is then prepared so that the concentration is approximately 20% of total solids in water.
3. This active coating suspension is sprayed onto the sugar spheres. A suspension of the enteric coating is then sprayed onto the substrate to form the finished pellets. The pellets were then placed in capsules.

Omeprazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
40.00	1	Omeprazole	40.00
68.00	2	Sucrose and cornstarch neutral microgranules, size 26	68.00
4.00	3	Sodium starch glycolate (Explotab)	4.00
6.00	4	Sodium lauryl sulfate	6.00
7.12	5	Polyvidone	7.00
5.96	6	Hydroxypropyl methylcellulose	5.96
36.15	7	Eudragit L30D	36.15
3.62	8	Triethyl citrate	3.62
15.40	9	Talc	15.40
–	10	Alcohol	QS

Omeprazole Delayed-Release Capsules*

Each delayed-release capsule contains either 10, 20, or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate, and other ingredients. The capsule shells have the following inactive

ingredients: gelatin NF, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C blue No. 2, D&C red No. 7, calcium lake, and, in addition, the 10- and 40-mg capsule shells also contain D&C yellow No. 10

Oral Rehydration Salt (45 mEq)

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
811.90	1	Cerelose powder	811.90
66.57	2	Sodium chloride	66.57
31.82	3	Sodium citrate dihydrate	31.82
70.14	4	Potassium citrate monohydrate/food grade	70.14
19.57	5	Povidone (K 29–32)	19.57
–	6	Alcohol	500.00 mL
–	7	Water purified	50.00 mL

Manufacturing Directions

1. Mill the dextrose through a 1.2-mm aperture screen or similar on a comminuting mill, medium speed, knives forward.
2. Individually mill the sodium chloride, sodium citrate, and potassium citrate through a 1.2-mm aperture screen on a comminuting mill, medium speed, knives forward.
Note: Do not mix the milled items until ready to add them to the dextrose.
3. Charge the powders from steps above into a suitable mass mixer and mix for 10 minutes. Screen the povidone through a 1.2-mm aperture screen and transfer to the mixer. Mix all the powders for 5 minutes.
4. Mix 500 mL of alcohol with 50 mL of water and slowly add to the mixer while mixing. Continue to mix for 5 to 10 minutes. Do not overwet the mass.
5. Granulate the wet mass through a 4.76-mm aperture screen using an oscillating granulator and spread on stainless steel trays.
6. Dry the granules at 45°C for approximately 16 hours or until loss on drying is less than 0.8%.
7. Turn the granules over after 3 to 4 hours drying.
8. Screen dry granules through an 840- μ m aperture screen.
9. Transfer the fine powder to a suitable blender.
10. Pass coarse granules through an 840- μ m aperture screen using an oscillating granulator and transfer to the blender. Blend for 5 to 10 minutes.
11. Discharge into polyethylene-lined drums.
12. Fill 3.08 g for 100 mL, 7.70 g for 250 mL, and 30.80 g for 1000 mL of reconstituted solution; prorate weights for different volumes.

Orlistat Capsules*

Orlistat is available for oral administration in dark blue hard gelatin capsules, with light blue imprinting. Each capsule contains 120 mg of the active ingredient orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate,

povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C blue No. 1, with printing of pharmaceutical glaze, titanium dioxide, and FD&C blue No. 1 aluminum lake.

Orlistat Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
120.00	1	Orlistat	120.00
93.60	2	Microcrystalline cellulose	93.60
7.20	3	Sodium starch glycolate	7.20
12.00	4	Polyvinylpyrrolidone	12.00
7.20	5	Sodium lauryl sulfate	7.20

Manufacturing Directions

1. Polyvinylpyrrolidone and sodium lauryl sulfate are dissolved in water.

2. Orlistat, microcrystalline cellulose, and sodium starch glycolate are mixed for 10 minutes and granulated with the solution of step 1.
3. Granules are dried at or below 30°C and passed through a No. 20 mesh screen.
4. Granules are filled in a size 1 hard gelatin capsule.

Oseltamivir Phosphate Capsules and Oral Suspension*

Oseltamivir phosphate is available as a capsule containing 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/mL oseltamivir. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, and sodium stearyl fumarate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains xanthan gum, monosodium citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide, and tutti-frutti flavoring.

Oxcarbazepine Oral Suspension*

The oral suspension contains the following inactive ingredients: ascorbic acid, dispersible cellulose, ethanol, macrogol stearate, methyl parahydroxybenzoate, propylene glycol, propyl parahydroxybenzoate, purified water, sodium saccharin, sorbic acid, sorbitol, yellow-plum-lemon aroma.

Oxycodone Hydrochloride and Acetaminophen Capsules

Each capsule contains oxycodone hydrochloride USP 5 mg and acetaminophen 500 mg. Inactive ingredients: Docusate sodium, gelatin, magnesium stearate, sodium benzoate, sodium metabisulfite, cornstarch, FD&C blue No. 1, FD&C red No. 3, FD&C red No. 40, and titanium dioxide.

Oxytetracycline Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Oxytetracycline, USE oxytetracycline HCl BP 80	275.00
30.00	2	Starch (cornstarch dried)	30.00
1.00	3	Colloidal silicon dioxide (Aerosil 200)	1.00
3.00	4	Magnesium stearate	3.00
3.00	5	Talc (fine powder)	3.00
1	6	Empty hard gelatin capsule, size 1	1000.00

Manufacturing Directions

Note: The processing area must be under controlled room temperature and humidity. The limits are RH 50% to 55%, temperature 22°C to 27°C.

1. Pass item 1 through a 630- μ m sieve using a sifter. Collect in stainless steel drum.
2. Mix items 5, 3, and 2 in stainless steel drum. Pass through a 250- μ m sieve using a sifter. Collect in a stainless steel drum.
3. Add 66.67 g of sieved item 1 (from step 1) to the drum at step 2 and mix for 5 minutes in drum blender.

4. Pass the mix through a 630- μ m stainless steel sieve using a sifter. Collect in stainless steel drum.
5. Pass item 4 through a 250- μ m sieve using a sifter. Collect in stainless steel drum.
6. Add 8.0 g of sieved item 1 (from step 1) to the drum at step 4 and mix for 5 minutes by rolling.
7. Pass the mix through a 630- μ m stainless steel sieve using a sifter. Collect in stainless steel drum.
8. Load the sieved powders to the blender. Mix for 5 minutes.
9. Unload the powder in stainless steel drum.
10. A fill weight of one capsule is 312 mg.

Oxytetracycline Hydrochloride, Sulfamethizole, and Phenazopyridine Hydrochloride Capsules*

Each capsule contains tetracycline hydrochloride equivalent to 250 mg oxytetracycline, sulfamethizole 250 mg, phenazopyridine hydrochloride 50 mg. Inert ingredients in the formulation are hard gelatin capsules (which may contain FD&C green No. 3, FD&C yellow No. 6, D&C yellow No. 10, and other inert ingredients); magnesium stearate, sodium lauryl sulfate, and starch.

Pancrelipase Capsules

The delayed-release microsphere capsules for delayed release of pancrelipase, which is of porcine pancreatic origin, contain lipase (5000 USP units), protease (18750 USP units), and amylase 16600 (USP units) or pancrelipase (10000 USP units), protease (37500 USP units), and amylase (33200 USP units) or contain lipase (20000 USP units), protease (75000 USP units), and amylase (66400 USP units). Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropyl methylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule shell contains FD&C blue No. 2. In addition, the 10000-unit capsule shell contains

black iron oxide and the imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide.

Pancrelipase Capsules Enteric-Coated Microspheres

Pancrelipase capsules are orally administered capsules containing enteric-coated microspheres of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. The inactive ingredients are povidone, talc, sugar, methacrylic acid copolymer (type C), triethyl citrate, and simethicone emulsion.

Penicillamine Capsules*

Capsules of penicillamine for oral administration contain either 125 or 250 mg of penicillamine. Each capsule contains the following inactive ingredients: D&C yellow No. 10, gelatin, lactose, magnesium stearate, and titanium dioxide. The 125-mg capsule also contains iron oxide.

Pentosan Polysulfate Sodium Capsules

It is supplied in white opaque hard gelatin capsules containing 100 mg of pentosan polysulfate sodium, microcrystalline cellulose, and magnesium stearate. It is formulated for oral use.

Pentostatin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Pentostatin	5.00
25.00	2	Gelatin	25.00
100.00	3	Lactose	100.00
2.00	4	Iron oxide red	2.00

Manufacturing Directions

1. Pass items 1 to 3 through an 80 mesh and blend.
2. Add item 4 and mix for 10 minutes.
3. Fill 132 mg in a size 1 capsule.

pH-Sensitive Coated Spheroids

Uncoated spheroids (60% w/w propranolol hydrochloride)	3.00 kg
Methacrylic acid copolymer type B Eudragit S	0.75 kg
Triacetin	0.112 kg
Isopropyl alcohol	1.64 kg
Methylene chloride	1.99 kg
Water	0.50 kg
Coated Spheroids	
Uncoated spheroids (60% w/w propranolol hydrochloride)	3.00 kg
Hydroxypropyl methylcellulose 2910, 4000 cps, Methocel	0.075 kg
Methylene chloride	4.98 kg
Methanol anhydrous	2.96
Eudragit E 30D aqueous dispersion	1.00 kg
Calcium stearate	0.03 kg
Simethicone emulsion	0.0025 kg
Water purified	0.50 kg

Manufacturing Directions

1. The finished dosage form consists of a hard gelatin capsule containing a powder blend of propranolol hydrochloride and two types of spheroids. The formulation particulars are based on 160 mg of propranolol hydrochloride per capsule, although they can be designed to provide other dosage strengths.
2. The propranolol hydrochloride powder blend (or first group of spheroids) provides the loading dose (e.g., 25 mg of propranolol HCl). The second and third types of spheroids are categorized as
 - a. Propranolol hydrochloride (60 kg) and microcrystalline cellulose (Avicel-PH101; 40 kg) are blended together in a 450 L planetary mixer. Water (50 kg) is added and the mixer is run for 10 minutes until a homogeneous plastic mass is obtained. The mass is extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1 mm in diameter. The damp extrudates (in batches of 15–20 kg) are placed in a spheronizer in which the rotating disc (diameter 68 cm) rotated at 300 to 400 rpm. The rotation is continued for 10 minutes and the resulting spheroids are then dried at 60°C in a fluidized bed dryer. The dried spheroids are passed over a 1.4-mm screen, and those which passed through are subjected to a 0.7-mm screen. The over- and undersized spheroids are discarded.
 - b. pH-sensitive coated spheroids are used to provide a second dose (pH 6.5) (e.g., 65 mg propranolol HCl). Uncoated spheroids are placed in a fluidized bed coater. The Eudragit S solution is applied using a peristaltic pump. The spheroids are dried.
 - c. Coated spheroids are used to provide a third dose (4–10 hours post ingestion; e.g., 70 mg propranolol HCl). The uncoated spheroids are placed in a fluidized bed coater. Methocel E4MP[®] solution is sprayed using a peristaltic pump. The spheroids are dried.
3. Process for applying overcoat: Eudragit E 30D suspension containing calcium stearate is sprayed on the Methocel E4MP coated spheroids using a peristaltic pump.
4. The spheroids are dried.
5. Capsules are filled with the powder blend, pH-sensitive coated spheroids, and coated spheroids on an encapsulating machine capable of dual filling powders and spheroids.

Phenobarbital and Hyoscyamine Sulfate Capsules

Each capsule contains phenobarbital (16.2 mg) and hyoscyamine sulfate (0.1037 mg). The inactive ingredients include cornstarch, edible ink, D&C yellow No. 10 and FD&C green No. 3, or FD&C blue No. 1 and FD&C yellow No. 6, FD&C blue No. 2 aluminum lake, gelatin, lactose, sucrose. Capsules may contain FD&C red No. 40 and yellow No. 6 aluminum lake.

Phenoxybenzamine Hydrochloride Capsules

Each capsule with a red cap and a red body contains phenoxybenzamine hydrochloride (10 mg). Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red No. 33, FD&C red No. 3, FD&C yellow No. 6, gelatin, lactose, sodium lauryl sulfate, and trace amounts of other inactive ingredients.

Phentermine Capsules

Each capsule contains 15 or 30 mg of phentermine as the cationic exchange resin complex. Phentermine is alpha, alpha-dimethyl phenethylamine (phenyl-tertiary-butylamine). The inactive ingredients are D&C yellow No. 10, dibasic calcium phosphate, FD&C yellow No. 6, gelatin, iron oxides (15-mg capsules only), lactose, magnesium stearate, and titanium dioxide.

Piroxicam and Beta-Cyclodextrin Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Piroxicam	100.00
900.00	2	Beta-cyclodextrin	900.00

Manufacturing Directions

- Items 1 and 2 are screened through a 60-mesh screen and fed into the grinding chamber of a high-energy vibration mill together.
- While maintaining the mill at its minimum vibrational frequency, the powders are exposed for 15 minutes to a flow

Phentermine Hydrochloride Capsules

It is available as a capsule or tablet containing 37.5 mg of phentermine hydrochloride (equivalent to 30 mg of phentermine base). The capsules contain the following inactive ingredients: cornstarch, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, black iron oxide, FD&C blue No. 1, FD&C red No. 40, and D&C red No. 33.

Phenytoin Sodium Extended-Release Capsules*

Each extended phenytoin sodium capsule contains 30 or 100 mg phenytoin sodium. The capsule also contains lactose, confectioner's sugar, talc, and magnesium stearate. The capsule shell and band contain colloidal silicon dioxide, FD&C red No. 3, gelatin, glyceryl monooleate, and sodium lauryl sulfate. The 30-mg capsule shell and band also contain citric acid, FD&C blue No. 1, sodium benzoate, and titanium dioxide. The 100-mg capsule shell and band also contain FD&C yellow No. 6, purified water, and polyethylene glycol 200. Product in vivo performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 hours as contrasted with prompt phenytoin sodium capsules with a rapid rate of absorption with peak blood concentration expected in 1¹/₂ to 3 hours.

- of steam by opening a connection valve between the chamber and a steam reservoir (mixing and activation stage).
- After this operation, the true cogrinding stage is continued for 4 hours.
- On termination, the product is discharged, screened through a 60-mesh screen, and homogenized by mixing.

Piroxicam Capsules

Each maroon and blue capsule contains 10 mg of piroxicam; each maroon capsule contains 20 mg of piroxicam for oral administration. The inactive ingredients in Feldene capsules

include FD&C blue No. 1, FD&C red No. 3, lactose, magnesium stearate, sodium lauryl sulfate, and starch.

Piroxicam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Piroxicam	20.00
233.23	2	Lactose	233.23
48.75	3	Cornstarch	48.75
1.36	4	Magnesium stearate	1.36
0.15	5	Sodium lauryl sulfate	0.15

Note: For 5- and 10-mg strength, adjust with item 2.

Manufacturing Directions

- Charge items 1 to 3 in a suitable blender in a low humidity area.
- Compress to make slugs; reduce slugs by passing through a No. 20 sieve.

- Add and blend items 4 and 5 and blend for 10 to 15 minutes.
- Fill 305 mg in hard gelatin capsules.

Piroxicam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
50.00	1	Piroxicam	50.00
124.40	2	Lactose anhydrous	124.40
50.00	3	Cornstarch	50.00
12.50	4	Sodium starch glycolate	12.50
2.50	5	Povidone	2.50
7.50	6	Polysorbate 80	7.50
0.625	7	Colloidal silicon dioxide	0.625
6.25	8	Glycine	6.25
1.25	9	Citric acid	1.25
QS	10	Water purified	QS

Manufacturing Directions

- An aqueous wet granulation process is whereby item 1, lactose, cornstarch, sodium starch glycolate, colloidal silicon dioxide, and povidone are mixed and subsequently granulated with polysorbate dissolved in purified water.
- Additional purified water is then added until granules form and no dry powder remains.

- Glycine and citric acid are dissolved in the additional purified water.
- Wet granules are dried at 60°C until loss on drying is NMT 2%.
- The dried granules are milled with the sodium starch glycolate, blended and lubricated with screened magnesium stearate in a twin-shell blender.
- Fill 250 mg in size 2 capsules.

Polyethylene Glycol 3350 Powder for Reconstitution

Each dose consists of 17 g of polyethylene glycol 3350.

Polythiazide Capsules

Inert ingredients in the formulations are hard gelatin capsules (which may contain FD&C blue No. 1, FD&C green No. 3, FD&C red No. 3, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, starch, and sucrose.

Potassium Chloride Extended-Release Capsules

The extended-release capsules contain microencapsulated potassium chloride 600 and 750 mg, respectively, of potassium chloride USP equivalent to 8 and 10 mEq of potassium. Dispersibility of potassium chloride (KCl) is accomplished by microencapsulation and a dispersing agent. The resultant flow characteristics of the KCl microcapsules and the controlled release of K⁺ ions by the microcapsular membrane are intended to avoid the possibility that excessive amounts of KCl can be localized at any point on the mucosa of the gastrointestinal tract. Each crystal of KCl is microencapsulated by a patented process with an insoluble polymeric coating

which functions as a semipermeable membrane; it allows for the controlled release of potassium and chloride ions over an 8- to 10-hour period. Fluids pass through the membrane and gradually dissolve the potassium chloride within the microcapsules. The resulting potassium chloride solution slowly diffuses outward through the membrane. The inactive ingredients present are edible ink, ethylcellulose, FD&C blue No. 2 aluminum lake, FD&C yellow No. 6, gelatin, magnesium stearate, sodium lauryl sulfate, and titanium dioxide. The capsules may contain FD&C red No. 40 and yellow No. 6 aluminum lake.

Potassium Chloride for Oral Solution

Natural fruit-flavored potassium chloride for oral solution, USP is an oral potassium supplement offered in individual packets as a powder for reconstitution. Each packet of powder contains potassium 20 mEq and chloride 20 mEq provided by potassium chloride 1.5 g. It is an electrolyte replenisher. Inactive ingredients: FD&C yellow No. 6, maltodextrin (contains corn derivative), malic acid, saccharin, silica gel, and natural flavoring.

Potassium Chloride Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
600.00	1	Potassium chloride	600.00
900.00	2	Gelatin	900.00
QS	3	Water purified	1.5 L
QS	4	Corn oil	QS
QS	5	Petroleum ether	QS
QS	6	Isopropyl alcohol	QS
QS	7	Glutaraldehyde 1%	QS

Manufacturing Directions

- Item 2 is added to 1.5 L of item 3 and the mixture is allowed to stand at 25°C for 1 hour while the gelatin hydrates and swells.
- To this mixture is added item 1 and the preparation is heated to 60°C while it is stirred at 300 rpm for 30 minutes to effect dissolution of the gelatin and to ensure even suspension of the calcium carbonate. Additional distilled water previously heated to 60°C is then added to bring the total volume to 100°C while the stirring is continued.
- This preparation is slowly poured into 12 L of a mixture consisting of 20% by volume of corn oil in petroleum ether, which has previously been heated to 60°C while the petroleum ether solution is stirred at 500 rpm. This preparation is then cooled to 5°C with continued stirring and the stirring is continued at 500 rpm for 1 hour after the lower temperature is reached.
- Isopropanol (6 L) is then added while stirring of the preparation at 5°C is continued. The solid microspheres are then collected by filtration and washed 3 times with isopropyl alcohol. The capsules are then immersed in 1.5 L of a 1% solution of glutaraldehyde in isopropyl alcohol for 8 hours at 5°C, then washed again 3 times with isopropyl alcohol, filtered, and vacuum dried for 24 hours.
- The microspheres, which average between 200 and 300 μm in diameter, are filled into gelatin capsules for administration as a long-acting antacid product (1.5 g of the microsphere mix, which contains 600 mg of potassium chloride, are filled into each size 00 capsule). This final dosage form delivers a total dose of 600 mg of KCl, but over a sustained time period of 1 to 4 hours and in such a way that the potassium chloride is in the solution state, rather than the more injurious solid state, when it contacts the gastrointestinal mucosa. Total dissolution of the microspheres occurs from 1 to 5 hours after the drug content is depleted.

Potassium Chloride Powder (20 mEq)

Bill of Materials			
Scale (g/3 g pack)	Item	Material Name	Qty/kg (g)
1.50	1	Potassium chloride powder	500.00
0.40	2	Calcium cyclamate granules	130.00
4.00 mg	3	Dye yellow	1.33
0.16	4	Malic acid	51.67
0.50	5	Hydrolyzed cereal solids	165.00
–	6	Alcohol anhydrous	90.00
–	7	Water purified	10.00
15.00	8	Silicon dioxide colloidal	15.00
0.25	9	Flavor	81.66
0.20	10	Flavor	65.33

Manufacturing Directions

1. Pass items 1 to 4 and, if necessary, item 5 through a 686-mm mesh using a comminuting mill with impact forward.
2. Charge the materials from step 1 and item 5 in a suitable mixer and mix for 20 minutes.
3. Mix items 6 and 7 separately and add to step 2; mix for 5 minutes or until satisfactory mass is obtained.
4. Spread wet granules on paper-lined trays and dry at 40°C to 60°C to NMT 1.5% loss on drying.
5. Sift granules through an 840- μ m aperture and grind through a 1.27-mm aperture.
6. Screen the flavors and, if necessary, item 8 through a 20 mesh.
7. Load half the granulation in a blender and add step 6 followed by remainder granules and blend for 20 to 30 minutes.
8. Fill in suitable sachet 3 g.

Prazosin and Polythiazide Capsules*

Each 1-mg capsule of contains drug equivalent to 1-mg free base. Inert ingredients in the formulations are hard gelatin capsules (which may contain FD&C blue No. 1, FD&C red

No. 3, FD&C red No. 28, FD&C red No. 40, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, starch, and sucrose.

Prednisolone Targeted-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
10.00	1	Prednisolone	10.00
100.00	2	Succinic acid	100.00
30.00	3	Eudragit E100 (5%)	30.00
100.00	4	Hydroxypropyl methylcellulose acetate succinate	100.00
QS	5	Ethanol	QS
QS	6	Purified water	QS
QS	7	Talc	QS

Manufacturing Directions

1. Add items 1 and 2 to a suitable mixer and blend well. Fill in a size 2 capsule the core capsule.
2. Spray-coat the core capsule with a 5% by weight solution of Eudragit E100 dissolved in ethanol, in a coating amount of 30 mg/capsule (48% by weight, based on the weight of the used empty hard capsule) as Eudragit E100 to obtain a capsule coated with a low pH-soluble polymer film.
3. The coated capsule is further spray-coated with a coating solution prepared by dissolving item 4 in a mixture of ethanol and water [5:3 (w/w)] to obtain a 5% by weight item 4 solution and adding thereto talc in an amount of 2.5% by weight, based on the total weight of the 5% item 4 solution, in a coating amount of 100 mg/capsule (159% by weight, based on the weight of the used empty hard capsule) as item 4 by means of an appropriate coater.
4. The formulation described above releases in the lower part of the digestive tract.

Procarbazine Hydrochloride Capsules*

Procarbazine hydrochloride, a hydrazine derivative antineoplastic agent, is available as capsules containing the equivalent of 50 mg of procarbazine as the hydrochloride. Each capsule also contains cornstarch, mannitol, and talc. Gelatin capsule shells contain parabens (methyl and propyl), potassium sorbate, titanium dioxide, FD&C yellow No. 6, and D&C yellow No. 10.

Prochlorperazine Sustained-Release Capsules

Spanule sustained-release capsules—each Compazine Spanule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period. Inactive ingredients consist of ammonio methacrylate copolymer, D&C green No. 5, D&C yellow No. 10, FD&C blue No. 1, FD&C blue No. 1 aluminum lake, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, silicon dioxide, simethicone emulsion, sodium lauryl sulfate, sorbic acid, sugar spheres, talc, triethyl citrate, and trace amounts of other inactive ingredients.

Propoxyphene Hydrochloride, Caffeine, and Aspirin Capsules*

Each capsule contains 65 mg (172.9 mmol) of propoxyphene hydrochloride, 389 mg (2159 mmol) of aspirin, and 32.4 mg (166.8 mmol) of caffeine. It also contains FD&C red No. 3, FD&C yellow No. 6, gelatin, glutamic acid hydrochloride, iron oxide, kaolin, silicone, titanium dioxide, and other inactive ingredients.

Propranolol Hydrochloride Multiple Bead Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
160.00	1	Propranolol hydrochloride [total]	160.00
		Powder Blend	
30.00	2	Propranolol hydrochloride powder	30.00
54.00	3	Lactose	54.00
15.00	4	Microcrystalline cellulose	15.00
1.00	5	Magnesium stearate	1.00

Propoxyphene Hydrochloride Capsules

Each Pulvule contains 65 mg (172.9 mmol) (No. 365) of propoxyphene hydrochloride. It also contains D&C red No. 33, FD&C yellow No. 6, gelatin, magnesium stearate, silicone, starch, titanium dioxide, and other inactive ingredients.

Propranolol Hydrochloride and Hydrochlorothiazide Capsules

Each capsule contains propranolol (80 mg) and hydrochlorothiazide (50 mg); alternately, the capsule may contain 120/50 or 160/50 mg, respectively. It contains the following inactive ingredients: calcium carbonate, ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, and D&C yellow No. 10. In addition, 80/50-mg and 120/50-mg capsules contain D&C red No. 33; 120/50- and 160/50-mg capsules contain FD&C blue No. 1 and FD&C red No. 40.

Propranolol Hydrochloride Long-Acting Capsules*

It is available as 60-, 80-, 120-, and 160-mg capsules. The capsules contain the following inactive ingredients: cellulose, ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, and titanium dioxide. In addition, Inderal LA[®] 60-, 80-, and 120-mg capsules contain D&C red No. 28 and FD&C blue No. 1; Inderal LA 160-mg capsules contain FD&C blue No. 1. These capsules comply with USP Drug Release Test 1.

Propranolol Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
160.00	1	Propranolol hydrochloride	160.00
128.92	2	Sucrose	128.92
42.97	3	Cornstarch	42.97
22.86	4	Shellac	22.86
35.25	5	Talc	35.25
–	6	Ethyl alcohol	91.44
–	7	Water purified	QS

Manufacturing Directions

1. Neutral pellets

- A. Weigh and mix in a stainless steel mixer suitable quantities of sucrose and cornstarch in the proportion of 3:1 w/w. Sift through a screen of suitable size to break up possible lumps.
- B. Transfer the mixture to a stainless steel coating pan and adjust rotary speed between 20 and 30 rpm to obtain a good tumbling action.
- C. By means of a suitable spray gun, spray over the powder a quantity of water equal to 15% w/w in very minute drops.
- D. Place the wet pellets over a thermostatic tray dryer and dry at 37°C for complete evaporation of water.
- E. Pass the dried pellets through sieves of suitable screens to ensure removal of dust and selection of cores of desired size.

2. Active pellets

- A. Dissolve shellac in ethyl alcohol. To 65% of this solution, add propranolol hydrochloride. (Reserve the remaining 35% of the solution for the film coating.)
- B. Transfer 171.89 kg of neutral pellets obtained from step I-E to a stainless steel coating pan and adjust the rotation speed between 20 and 30 rpm so as to obtain good tumbling action.
- C. Spray over the neutral pellets the result of step II-A.

D. Keep the pan rotating to allow partial evaporation of the solvent.

E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.

3. Film-coated pellets

- A. Transfer the active pellets obtained from step II-E to a stainless steel coating pan and adjust the rotatory speed so as to obtain a good tumbling action.
- B. Spray the pellets as uniformly as possible with the alcoholic solution of shellac reserved from step II-A.
- C. Spread the wet pellets with talc to prevent agglutination.
- D. Keep the pan rotating to achieve solidification of the film coating and partial evaporation of the solvent.
- E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.

4. Blending of pellets

- A. Transfer the film-coated pellets obtained from step III-E to a stainless steel pan and add a suitable quantity of neutral pellets obtained from step III-E to obtain the required dosage.
- B. Add 0.5% w/w talc to eliminate electrostatic charges and mix for 30 to 35 minutes.

5. Assembly

- A. Fill the blended pellets obtained from step IV-B into capsules of size 1 at the weight of 390 mg.

Propranolol Timed- and Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
80.00	1	Propranolol	80.00
4.14	2	Polyvinylpyrrolidone K-30	4.14
55.85	3	Nonpareil sugar beads 25–30 mesh	55.85
2.80	4	Opadry clear	2.80
2.33	5	Ethyl cellulose	2.33
0.23	6	Diethyl phthalate	0.23
–	7	Water purified	QS
–	8	Acetone	QS
9.75	9	Ethyl cellulose	9.75
8.57	10	Hydroxypropyl methylcellulose phthalate	8.57
3.10	11	Diethyl phthalate	3.10

Manufacturing Directions

1. Prepare a solution of item 2 in item 7 and add item 1 slowly; mix well. This is the drug solution.
2. In a Glatt fluid bed dryer, charge item 3 and coat with step 1 slowly and then dry to less than 2% moisture.
3. Apply item 4 coating to dried granules from step 2 to obtain 2% weight gain.
4. In a separate vessel, prepare a solution of items 5 and 6 in 98 parts of item 8 and 2 parts of item 7. Spray this inner coating on to step 3.
5. Prepare an acetone:water solution of items 9 to 11 and coat on step 4.
6. Dry and fill in capsules to yield 80, 120, and 160 mg of item 1. This product provides drug loading of 56% w/w based on core composition corresponding to 45.7% drug based on final time and sustained-release beads.

Proton Pump Inhibitor Powder for Reconstitution for Oral Use

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
20.00	1	Omeprazole (or another PPI)	20.00
20.00	2	Calcium acetate	175.00
	3	Calcium glycerophosphate	175.00
	4	Sodium bicarbonate	500.00
	5	Calcium hydroxide	50.00
	6	Glycerin	200.00

Note: This formula can be used for most proton pump inhibitor drugs.

Manufacturing Directions

1. Granulate active drug with items 2 to 6.
2. Dry sieve.
3. Pack in moisture-resistant container.

Proton Pump Inhibitor Powder for Reconstitution for Oral Use

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
10.00	1	Lansoprazole or other PPI equipotent	10.00
200.00	2	Calcium lactate	200.00
200.00	3	Calcium glycerophosphate	200.00
400.00	4	Sodium bicarbonate	400.00
12.00	5	Croscarmellose sodium	12.00
3.00	6	Pregelatinized starch	3.00

Note: This formula can be used for most proton pump inhibitor drugs.

Manufacturing Directions

1. Granulate active drug with items 2 to 6.
2. Dry sieve.
3. Pack in moisture-resistant container.

Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
24.00	1	Pseudoephedrine hydrochloride	24.00
15.00	2	Hydroxyethylcellulose, NF	15.00
60.00	3	Anhydrous lactose	60.00
1.00	4	Magnesium stearate	1.00

Manufacturing Directions

1. Blend all the ingredients in a twin-shell blender for 10 minutes.
2. Fill No. 0 capsules with fill weight of 500 mg using a tamping force of 200 N.

Pseudoephedrine Hydrochloride Capsules

1. Composition by weight: Pseudoephedrine HCl, USP 60 mg, yellow beeswax 10 to 20 mg, partially hydrogenated vegetable oil 15 to 25 mg, lecithin, NF 2 to 8 mg, colloidal silicon dioxide 2 to 8 mg, soybean oil, USP 150 to 250 mg.
2. Fill.

Pseudoephedrine and Guaifenesin Capsules

Each capsule contains pseudoephedrine hydrochloride 120 mg in a specially prepared base to provide prolonged action and guaifenesin 250 mg designed for immediate release to provide rapid action. Alternate dosing is 60 mg and 300 mg respectively. The capsules also contain as inactive ingredients calcium stearate, FD&C blue No. 1 (for higher strength identification), gelatin, pharmaceutical glaze, starch, sucrose, talc, and titanium dioxide.

Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
24.00	1	Pseudoephedrine hydrochloride	24.00
15.00	2	Hydroxyethylcellulose NF	15.00
60.00	3	Lactose anhydrous	60.00
1.00	4	Magnesium stearate	1.00

Manufacturing Directions

1. Blend all the ingredients in a twin-shell blender for 10 minutes.
2. Fill size 0 capsules with fill weight of 500 mg using tamping force of 200 N.

Psyllium and Dioctyl Sodium Sulfosuccinate Powder

Manufacturing Directions

1. Psyllium husk 5.1 g, dioctyl sodium sulfosuccinate 240 mg.
2. The psyllium husk is milled to a small particle size, no more than 4% on 100 mesh and between 25% and 50% through 200 mesh.
3. These psyllium particles are then agglomerated with maltodextrin and citric acid is sprayed on.
4. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for dioctyl sodium sulfosuccinate, or two or three of these can be combined.
5. Methylcellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium.
6. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied within the ranges specified herein.

Psyllium and Docusate Sodium Wafer

Formulation

Ascorbic acid 0.15%, natural and artificial flavors 1.54%, corn oil 14.80%, cornstarch 1.97%, fructose crystalline 6.82%, lecithin oil 0.99%, molasses granular light 0.39%, oat hull fiber 6.42%, psyllium husk 13.32%, sodium bicarbonate 0.20%, sucrose white granulated 17.40%, table oats 8.89%, water purified USP QS, wheat flour 19.21%, docusate sodium 0.63%, sorbitan tristearin 0.20%.

Manufacturing Directions

1. In an appropriate mixer, add corn oil and lecithin and mix for 1 minute using low speed.
Note: Preheat (microwave) lecithin, if necessary.
2. Add psyllium, docusate (which has been coated with the sorbitan tristearin) and mix for 1 minute using low speed.
3. Into a separate bowl, add part of the sucrose, fructose, molasses, and half of the water.
4. Mix for 1 minute using low speed.
5. Add psyllium/oil/lecithin premix and oat fiber.
6. Mix for 1 minute. Add rest of water, soda, flavors, ascorbic acid, and starch.
7. Mix for 1 minute at low speed.
8. Add flour to the mixer and mix for 1 minute at low speed.
9. Roll dough into sheets approximately 0.1 in thick.
10. Cut dough into rectangles (approximately 2.5-in length × 1.6-in width).
11. Place bars on baking trays and bake at 375°C for 10 to 12 minutes.
12. Ethylcellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied within the ranges specified herein. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for dioctyl sodium sulfosuccinate, or two or three of these can be combined.

Psyllium Husk Granules

1. Raw, unmilled psyllium seed husk (2 g) is stirred with 0.2 N sodium hydroxide (400 mL) containing sodium borohydride (400 mg) in a nitrogen atmosphere at ambient temperature for 90 minutes.
2. The pH of the solution is from 10 to 11.
3. The solution is passed through a pasteurizer at a temperature of 100°C for a period of 50 seconds.
4. Once pasteurized, the mixture is centrifuged for 20 minutes at 23500 × g.

5. The supernatant is decanted from an insoluble fraction that settles out in the centrifuge bottle.
6. The insoluble fraction is mixed with fresh sodium hydroxide/sodium borohydride solution (100 mL) and re-centrifuged for 15 minutes to increase yield of the soluble fraction.
7. The pH of the supernatant is adjusted to 5.5 by the addition of acetic acid at ambient temperature with stirring forming a gel.
8. The gel is desiccated with isopropanol added with high shear mixing.
9. The isopropanol solution is then decanted from the gel.
10. The solids content of the gel is 30%.
11. The gel material is passed through an extruder and extruded into individual particles with an average particle size of 500 microns.
12. The extruded particles enter a fluidized bed dryer fitted with a cyclonic airflow screen, such as a Conidur screen.
13. The air temperature is maintained at 80°C.
14. The gel temperature remains below 70°C throughout the drying process.
15. The particles are dried to a powder with 90% of the water being removed.
16. The yield of the gel-forming polysaccharide is 85%.
17. The final compositions comprise the following components by weight: gel-forming 50.0%, polysaccharide sorbitol neosorb p20 48.16%, magnesium stearate 0.5%, flavorant 0.4%, colorant 0.14%, citric acid 0.8%.
18. The granules can be coated using the coating formulation: Isopropanol 94.5% Eudragit RD100 5%, polyethylene glycol 0.5%.
19. The coated gel-forming polysaccharide particles are dried and combined with the excipients as described above.

Ranitidine Effervescent Granules*

Granules for oral administration are effervescent formulations of ranitidine; these must be dissolved in water before use. Each packet contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate.

Ribavirin Capsules

Capsules consist of a white powder in a white opaque gelatin capsule. Each capsule contains 200 mg of ribavirin and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink, which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C blue No. 2 aluminum lake.

Rifabutin Capsules

The antimycobacterial agent rifabutin is a semisynthetic ansamycin antibiotic derived from rifamycin S. The capsules contain 150 mg of rifabutin, USP, per capsule, along with the following inactive ingredients: microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

Rifampicin Capsules

Rifampicin (rifampin) capsules contain 150 or 300 mg of rifampin per capsule. The 150- and 300-mg capsules also contain as inactive ingredients cornstarch, D&C red No. 28,

FD&C blue No. 1, FD&C red No. 40, gelatin, magnesium stearate, and titanium dioxide.

Rifampin and Isoniazid Capsules

This is a combination capsule containing 300 mg of rifampin and 150 mg of isoniazid. The capsules also contain as inactive ingredients colloidal silicon dioxide, FD&C blue No. 1, FD&C red No. 40, gelatin, magnesium stearate, sodium starch glycolate, and titanium dioxide.

Salmeterol Xinafoate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
2.00	1	Salmeterol xinafoate	2.00
97.00	2	Starch 1500 DC	97.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

Blend and fill 100 mg in each capsule.

Salmeterol Xinafoate Inhalation Powder*

It is a specially designed plastic device containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50 µg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg

Rivastigmine Tartrate Capsules*

It is supplied as capsules containing rivastigmine tartrate, equivalent to 1.5, 3, 4.5, and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard gelatin capsule contains gelatin, titanium dioxide, and red and/or yellow iron oxides.

of formulation containing lactose. When a blister containing medication is opened by activating the device, the medication is dispersed into the air stream created when the patient inhales through the mouthpiece.

Salmeterol Xinafoate Inhalation Powder

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.05	1	Salmeterol xinafoate micronized	0.05
12.50	2	Lactose anhydrous	12.50

Saquinavir Mesylate Capsules*

It is available as light brown and green opaque hard gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients: lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc, and magnesium stearate. Each capsule shell contains gelatin and water with the following dye systems: red iron oxide, yellow iron oxide, black iron oxide, FD&C blue No. 2, and titanium dioxide. Another formulation contains inactives. Each capsule also contains the inactive ingredients: medium chain mono- and diglycerides, povidone, and DL-alpha-tocopherol. Each capsule shell contains gelatin and glycerol 85% with the following colorants: red iron oxide, yellow iron oxide, and titanium dioxide.

Selegiline Hydrochloride

Each aqua blue capsule contains 5 mg of selegiline hydrochloride. The inactive ingredients are citric acid, lactose, magnesium stearate, and microcrystalline cellulose.

Sevelamer Hydrochloride Capsules*

Each hard gelatin capsule of Renagel[®] contains 403 mg of sevelamer hydrochloride on an anhydrous basis. The inactive ingredients are colloidal silicon dioxide and stearic acid. The capsule and imprint contain titanium dioxide and indigo carmine ink.

Sibutramine Hydrochloride Capsules*

Each capsule contains 5, 10, or 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C blue No. 2 (5- and 10-mg capsules only); D&C yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

Sibutramine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Sibutramine hydrochloride	5.00
78.50	2	Lactose anhydrous	78.50
5.00	3	Polyvinylpyrrolidone	5.00
15.00	4	Cornstarch	15.00
1.50	5	Magnesium stearate	1.50
QS	6	Alcohol	QS

Manufacturing Directions

1. Mix items 1, 2, and 4 and granulate with alcoholic solution of item 3.

2. Dry, size, and blend with item 5.

3. Fill 105 mg; adjust for higher dose with item 2.

Simethicone Instant Granules (60 mg and 120 mg)**Formulation**

Simethicone (Abil[®] 200, Goldschmidt), 10.0 g; cremophor RH 40 [1], 5.0 g; Kollidon VA 64, 3.0 g; ethanol, 40.0 g; sorbitol, crystalline 50.0 g; fructose, 50.0 g; Kollidon CL-M [1], 50.0 g; orange flavor (Dragoco), 0.5 g.

Manufacturing Directions

Introduce solution II into the mixture I.

1. Granulate the powder mixture III with the well-stirred mixture I/II; dry and pass through a 1-mm sieve.
2. Fill 1 or 2 g in sachets.

Stavudine Capsules*

The stavudine capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides.

Succimer Capsules*

Each opaque white capsule for oral administration contains beads coated with 100 mg of succimer and is imprinted in black with CHEMET 100[®]. The inactive ingredients in medicated beads are povidone, sodium starch glycolate, starch, and sucrose. The inactive ingredients in the capsule are gelatin, iron oxide, titanium dioxide, and other ingredients.

Sucralafate Granules

Bill of Materials			
Scale (mg/sachet) (2 g)	Item	Material Name	Qty/2 kg (g)
1000.00	1	Sucralafate	1000.00
100.00	2	Cornstarch	100.00
240.00	3	Povidone	240.00
QS	4	Lactose, QS to 2000	QS
—	5	Alcohol	QS

Manufacturing Directions

1. Charge items 1 and 2 in a fluid bed granulator (e.g., Glatt) and mix for 5 minutes at inlet temperature of 30°C.
2. Dissolve item 3 in a separate container in item 5 and spray into step 1 to granulate.

3. Dry granules at 50°C until the temperature reaches 30°C.

4. Sieve through No. 18.

5. Fill 1.9 to 2.1 g per sachet.

**Sulfamethoxazole + Trimethoprim Dry Syrup
(400 mg + 80 g/10 mL)****Formulation**

Sulfamethoxazole, 4 g; trimethoprim, 0.8 g; sorbitol, crystalline [10], 30 g; sodium citrate, 5 g; sodium gluconate, 5 g; Kollidon CL-M [1], 10 g; vanillin, 0.1 g; saccharin sodium, 0.1 g; chocolate flavor, 0.1 g; sodium benzoate, 0.1 g.

Manufacturing Directions

Mix all components and sieve for administration. Fill 55 g of the mixture in a 100-mL flask.

Tacrine Hydrochloride Capsules

Each capsule contains tacrine as the hydrochloride. Inactive ingredients are hydrous lactose, magnesium stearate, and microcrystalline cellulose. The hard gelatin capsules contain gelatin, silicon dioxide, sodium lauryl sulfate, and the following dyes: 10 mg: D&C yellow No. 10, FD&C green No.

3, titanium dioxide; 20 mg; D&C yellow No. 10, FD&C blue No. 1, titanium dioxide; 30 mg; D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, titanium dioxide; 40 mg; D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, and titanium dioxide. Each 10-, 20-, 30-, and 40-mg capsule for oral administration contains 12.75, 25.50, 38.25, and 51.00 mg of tacrine hydrochloride respectively.

Tacrolimus Capsules*

Tacrolimus is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5, 1, or 5 of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide; the 1-mg capsule shell contains gelatin and titanium dioxide; and the 5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide.

Tacrolimus Capsules*

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
1.00	1	Tacrolimus	1.00
1.00	2	Hydroxypropyl methylcellulose 2910	1.00
QS	3	Ethanol	QS
58.00	4	Lactose	58.00

Manufacturing Directions

- Item 1 is mixed with items 2 and 3. The mixture is kneaded and granulated to pass through sieves to collect particle size 180 to 250 mm; the other particle size is regranulated.
- Dry granulation in step 1 is dried at room temperature.
- In a suitable blending vessel, add item 4 and gradually add the step 2 granulation. Mix for 10 minutes and fill in size 0 capsules.

Talc, Crospovidone, and Starch Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Croscarmellose sodium (crospovidone)	100.00
800.00	2	Cornstarch	800.00
100.00	3	Talc	100.00

Manufacturing Directions

Mix and fill in bottles.

Tamsulosin Hydrochloride Capsules*

Each capsule for oral administration contains tamsulosin HCl 0.4 mg and the following inactive ingredients: methacrylic acid copolymer; microcrystalline cellulose; triacetin; polysorbate 80; sodium lauryl sulfate; calcium stearate; talc; FD&C

blue No. 2; titanium dioxide; ferric oxide; gelatin; and trace amounts of shellac, industrial methylated spirit 74 OP, *n*-butyl alcohol, isopropyl alcohol, propylene glycol, dimethylpolysiloxane, and black iron oxide (E172).

Tamsulosin Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.40	1	Tamsulosin hydrochloride	0.40
35.60	2	Crystalline cellulose	35.60
13.32	3	Eudragit L30D-55	13.32
4.00	4	Magnesium stearate	4.00

Manufacturing Directions

1. After sufficiently mixing item 1, crystalline cellulose, and magnesium stearate, a mixture of Eudragit L30D-55 and 40 mL of water is added to the aforementioned mixture,

and the resultant mixture is kneaded and granulated by a centrifugal fluidized bed granulator.

2. The granules obtained were spheres having particle sizes of 0.1 to 1.5 mm, mainly 0.2 to 1.0 mm.

Temazepam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
7.50	1	Temazepam micronized	7.50
7.50	2	Lactose anhydrous	7.50
232.50	3	Lactose anhydrous	232.50
2.50	4	Magnesium stearate	2.50

Manufacturing Directions

1. Item 1 is processed as follows: White crystalline temazepam having a purity of not less than 98% is fed into an Alpine 160 UPZ mill with a stainless steel pin at a rate of about 40 kg/h using a mill speed of about 11000 rpm to obtain temazepam particles having a specific surface area of 0.65 to 1.1 m²/g area and 95% of the particles having a particle size diameter of less than 65 μm. The surface area measurement is made with the Quantector Gas Flow System and Quantasorb Surface Area Analyser at the temperature of liquid nitrogen (-196°C) using krypton as the absorbent and helium as the carrier gas. The particle size diameter is determined with the Malverne Particle Sizer at an obscuration value of 0.2 to 0.25 using a 0.1%

Tween 80 solution in water saturated with temazepam in which 1 to 2 g of temazepam sample to be tested has been dispersed. After the feed rate and mill speed of the Alpine mill have been set, they are monitored at regular intervals to maintain the required particle size and surface area.

2. To prepare hard gelatin capsules containing 7.5 mg of the temazepam processed as in step 1, charge items 1 and 2 in a mill and pass through an 18-mesh screen.

3. Pass item 3 through 18-mesh screen and add to step 2.

4. Pass item 4 through 18-mesh screen and add to step 3 in a PK Mixer[®] without an intensity bar.

5. Mix for 30 minutes using tumbling action only.

6. The capsule mix is encapsulated in number 3 Lock hard gelatin capsules. Each capsule contains 250 mg of capsule mix and 7.5 mg of temazepam.

Temozolomide Capsules*

Each capsule contains 5, 20, 100, or 250 mg of temozolomide. The inactive ingredients for Temodar[®] capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. The gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.

Terazosin Capsules (1–10 mg) Hytrin*

Hytrin capsules are supplied in four dosage strengths, containing terazosin hydrochloride equivalent to 1, 2, 5, or 10 mg of terazosin. Hytrin inactive ingredients: 1-mg capsules: gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 2-mg capsules: D&C yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene

glycol, povidone, propylparaben, titanium dioxide, and vanillin; 5-mg capsules: D&C red No. 28, FD&C red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 10-mg capsules: FD&C blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

Terazosin Capsules

1. Capsules containing 5 mg of terazosin are prepared by blending the following ingredients in No. 3 gelatin capsules.
2. Terazosin HCL anhydrous 5.471; lactose monohydrate, NF 174.529; microcrystalline cellulose, NF 28.000; crospovidone, NF 14.000; magnesium stearate, NF 3.000; total capsule fill weight 225.000.

Terazosin Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.000	1	Terazosin hydrochloride anhydrous	5.471
174.529	2	Lactose monohydrate	174.529
28.000	3	Microcrystalline cellulose	28.000
14.000	4	Crospovidone	14.000
3.000	5	Magnesium stearate	3.000

Manufacturing Directions

1. Add and blend all items 1 to 5 in a suitable blender.

2. Fill using size 3 capsules; fill weight of 225.00 mg.

Terfenadine Oral Granules Directions

1. Micronized terfenadine (30 g) and 15 g of the block copolymer wetting agent (Pluronic polyol F-68) were mixed slowly in a "V-blender" for about 5 minutes.
2. Sorbitol instant (300 g) is added to the mixture and blended therewith for another 5 minutes to form a blend of all three components.
3. Microcrystalline cellulose (30 g; Avicel CL-611), PVP (50 g, KOLLIDON K-90), maltodextrin (200 g, MALTRIN QD

M500), and 375 g of fine, granular fructose were added to the above blend and blending is continued for another 10 minutes to form a homogeneous, dry terfenadine composition that is a free-flowing powder.

4. The blended dry composition is thereafter packaged into 2 g sachets as unit doses to provide 60 mg of terfenadine.

Tetracycline Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Tetracycline, USE tetracycline	275.00
46.00	2	Lactose monohydrate (dense)	46.00
2.00	3	Colloidal silicon dioxide (Aerosil 200)	2.00
2.00	4	Magnesium stearate	2.00
1.00	5	Empty hard gelatin capsule, size 1	1000.00

Manufacturing Directions

1. Check the temperature and relative humidity of the room before start of processing. Limits: RH 50% to 55%, temperature: 22°C to 27°C.
2. Pass the items 1, 2, and 3 through a 630-mm sieve using a sifter. Collect in stainless steel drum.

3. Pass item 4 through a 250-mm sieve using a sifter. Collect in polythene bag. Load the sieved powder to the drum (step 1) and mix for 5 minutes using drum mixer.
4. Load the empty capsule shells (size 1) in the hopper.
5. Run the machine and check the locking of shells.
6. Fill weight of one capsule = 325 mg + average weight of one empty shell.

Thalidomide Capsules

Thalidomide capsules are available in 50-mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose,

polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

Theophylline Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Theophylline anhydrous (B. F. Goodrich)	150.00
26.60	2	Carbopol 934P (GAF Corporation)	26.60
172.10	3	PVP C-15	172.10
3.50	4	Talc	3.50
1.80	5	Zinc stearate	1.80

Manufacturing Directions

1. Carbopol 934P, PVP C-15 (mean molecular weight of about 8000) talc, and zinc stearate are combined in a mixer and mixed.

2. Theophylline anhydrous is added to this mixture and mixed well to achieve a uniform mixture.
3. The resulting particulate mixture, 354 mg, is filled into size 1 hard gelatin capsule shells.

Thiothixene Capsules*

Each capsule contains 1, 2, 5, or 10 mg of thiothixene and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium (type A), gelatin, magnesium stearate, microcrystalline cellulose, powdered cellulose, pregelatinized starch, sodium lauryl sulfate, titanium dioxide, and other inactive ingredients. The following coloring

agents are employed: 1 mg—FD&C blue No. 1, D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6; 2 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6, D&C yellow No. 10; 5 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6; 10 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6.

Tibolone Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.30	1	Tibolone (Org GD 14)	0.30
1.95	2	Hydroxypropyl cellulose	1.95
32.50	3	Cornstarch	32.50
0.32	4	Magnesium stearate	0.32
QS	5	Lactose	QS to 130.00
QS	6	Water purified	QS

Manufacturing Directions

1. Charge in a mixer items 3 and 5 and mix well.
2. Prepare a suspension of items 1 and 2 in item 6 and mix thoroughly; add to step 1 and granulate in a granulator by mixing for 2 to 3 minutes.
3. Dry the sieved wet material for 4 hours in a vacuum dryer at 40°C.

4. Screen the dried granules through a 710-mm sieve in the drum.
5. Load the empty capsule shells (size 1) in the hopper.
6. Run the machine and check the locking of shells.
7. Fill 130 mg in suitable capsules.

Tiotropium Inhalation Powder

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
21.70	1	Tiotropium bromide micronized	21.70
270.00	2	Endothelin antagonist 2	270.00
4708.30	3	Lactose	4708.30

Manufacturing Directions

- Item 1 should first be prepared in an inhalable powder form by the following method:
 - 150 kg of tiotropium bromide is placed in 25.7 kg of water in a suitable reaction vessel.
 - The mixture is heated to 80°C to 90°C and stirred at constant temperature until a clear solution is formed.
 - Activated charcoal (0.8 kg) moistened with water is suspended in 4.4 kg of water. This mixture is added to the solution containing the tiotropium bromide and the resulting mixture is rinsed with 4.3 kg of water.
 - The mixture thus obtained is stirred for at least 15 minutes at 80°C to 90°C. Then it is filtered through a heated filter into an apparatus preheated to an external temperature of 70°C.

- The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled at 3°C to 5°C for every 20 minutes to a temperature of 20°C to 25°C.
 - The apparatus is cooled further to 10°C to 15°C using cold water and crystallization is completed by stirring for at least another hour.
 - The crystals are isolated using a suction filter dryer. The crystals are washed with cold water (10–15°C) and cold acetone (10–15°C).
 - The crystals obtained are dried at 25°C in nitrogen current over a period of 2 hours. Yield: 13.4 µg of tiotropium bromide monohydrate (86% of theory).
- Add and mix all items and mix well.
 - Fill 5 g per unit dose.

Tolmetin Sodium Capsules*

Capsules for oral administration contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium and the following inactive ingredients: gelatin, magnesium stearate, cornstarch, talc, FD&C red No. 3, FD&C yellow No. 6, and titanium dioxide.

Tolterodine Capsules*

Capsules contain 2 or 4 mg of tolterodine tartrate. The inactive ingredients are sucrose, starch, hydroxypropylmethylcellulose, ethylcellulose, medium-chain triglycerides, oleic acid, gelatin, and FD&C blue No. 2. The 2-mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac, titanium dioxide, propylene glycol, and simethicone.

Tolterodine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
2.00	1	Tolterodine	2.00
186.00	2	Lactose anhydrous	186.00
20.00	3	Cornstarch	20.00
15.00	4	Talc	15.00
2.00	5	Magnesium stearate	2.00

Note: For 1-mg strength, adjust with item 2.

Manufacturing Directions

- Item 1 is accordingly mixed with items 2 and 3 and then milled.

- The resulting mixture is then mixed with ingredients 4 and 5 and then filled into capsules of appropriate size.

Topiramate Capsules*

Topiramate capsules, sprinkle capsules, are available as 15- and 25-mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food. Sprinkle capsules contain topiramate-coated beads in a hard gelatin capsule. The inactive ingredients are sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

Tretinoin Capsules

It is available in a 10-mg soft gelatin capsule for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils, and soybean oil. The gelatin capsule shell contains glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben, and propylparaben.

Triamterene and Hydrochlorothiazide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
23.01	1	Triamterene	23.01
15.34	2	Hydrochlorothiazide	15.34
2.50	3	Glycine	2.50
7.50	4	Polysorbate 80	7.50
QS	5	Water purified	QS
QS	6	Isopropyl alcohol	QS
52.15	7	Lactic acid	52.15

Manufacturing Directions

1. Add and dissolve item 3 in a suitable quantity of item 5.
2. Add items 1 and 2 and prepare a good wet mass.
3. Separately dissolve item 4 in item 6 and add to step 2 until granules are formed.
4. Dry granules in vacuum and mill.
5. Fill in size 4 capsules.

Triamterene Capsules*

Each capsule for oral use, with an opaque red cap and body, contains triamterene, 50 or 100 mg. The inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red

No. 33, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, titanium dioxide, and trace amounts of other inactive ingredients.

Triclosan and Zinc Foot Deodorant Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
3.00	1	Triclosan (Irgasan [®] DP300)	3.00
2.00	2	Zinc undecylenate, USP	2.00
0.20	3	Menthol (crystals), USP	0.20
926.80	4	Talc (powder), USP	926.80
30.00	5	Magnesium stearate	30.00
30.00	6	Cornstarch, NF	30.00
8.00	7	Perfume	8.00

Manufacturing Directions

1. Pass the following ingredients through a 250- μ m screen or similar: Irgasan DP300, zinc undecylenate, magnesium stearate, cornstarch, menthol, and approximately 10% of the total amount of talc.
2. Charge materials from first step into a suitable mixer.
3. Mix until uniform.
4. Discharge powder from second step into another suitable mixer.
5. Add and disperse perfume.
6. Mix until uniform.
7. Pass mixture from step above through a 250- μ m screen or similar.
8. Charge mixture from step above into a V-mixer or similar and add balance of talc powder.
9. Mix for 30 minutes or until homogeneous.

Triclosan and Zinc Undecylenate Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tabs (g)
3.0	1	Triclosan-Irgasan DP300	3.0
2.0	2	Zinc undecylenate	2.0
0.2	3	Menthol	0.2
926.8	4	Talc	926.8
30.0	5	Magnesium stearate	30.0
30.0	6	Cornstarch	30.0
8.0	7	Perfume	8.0

Manufacturing Directions

1. Pass the following ingredients through a 250-mm aperture screen or similar screen: Triclosan-Irgasan DP300, zinc undecylenate, magnesium stearate, cornstarch, menthol, and approximately 10% of the total amount of talc.
2. Charge materials from first step into a suitable mixer. Mix until uniform.
3. Discharge powder from second step into another suitable mixer. Add and disperse perfume. Mix until uniform. Pass mixture from step above through a 250-mm aperture screen or similar screen. Charge mixture from step 2 into a V-mixer or a similar mixer and add balance of talc powder.
4. Mix for 30 minutes or until homogeneous.

Trientine Hydrochloride Capsules*

It is available as 250-mg capsules for oral administration. It contains gelatin, iron oxides, stearic acid, and titanium dioxide as inactive ingredients.

Trimebutine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
25%	1	Trimebutine	25%
50%	2	Calcium	50%
7.5%	3	Polycarbophil microcrystalline cellulose (Avicel 102)	7.5%
25%	4	Talc	25%

Manufacturing Directions

Mix and fill in No. 2 hard gelating capsule.

Trimethoprim and Sulfamethoxazole Oral Suspension*

Trimethoprim–sulfamethoxazole is a combination product available in double strength (DS) pediatric suspension for oral administration. Each teaspoonful (5 mL) of the pediatric suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole in a vehicle containing 0.3% alcohol, edetate disodium, glycerin, microcrystalline cellulose, parabens (methyl and propyl), polysorbate 80, saccharin sodium, simethicone, sorbitol, sucrose, FD&C yellow No. 6, FD&C red No. 40, flavors, and water.

Trimipramine Maleate Capsules*

Each capsule contains trimipramine maleate equivalent to 25, 50, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25-mg dosage strength also contains D&C yellow No. 10 and FD&C yellow No. 6; the 50-mg dosage strength also contains D&C red No. 28, FD&C red No. 40, and FD&C yellow No. 6.

Troleandomycin Capsules

Inert ingredients in the formulation are hard gelatin capsules (which may contain inert ingredients), lactose, magnesium stearate, sodium lauryl sulfate, and starch.

Typhoid Vaccine Live Oral Capsules

The vaccine strain is grown in fermenters under controlled conditions in a medium containing a digest of yeast extract, an

acid digest of casein, dextrose, and galactose. The bacteria are collected by centrifugation, mixed with a stabilizer containing sucrose, ascorbic and amino acids, and lyophilized. The lyophilized bacteria are mixed with lactose and magnesium stearate and filled into gelatin capsules, which are coated with an organic solution to render them resistant to dissolution in stomach acid. The enteric-coated, salmon/white capsules are then packaged in four-capsule blisters for distribution. The contents of each enteric-coated capsule are

Viable <i>Staphylococcus typhi</i> Ty21 ^a	2–6 H 109 colony-forming units ^a
Nonviable <i>S. typhi</i> Ty21 ^a	5–50 H 109 bacterial cells
Sucrose	26–130 mg
Ascorbic acid	1–5 mg
Amino acid mixture	1.4–7.0 mg
Lactose	100–180 mg
Magnesium stearate	3.6–4.4 mg

^aVaccine potency (viable cell counts per capsule) is determined by inoculation of agar plates with appropriate dilutions of the vaccine suspended in physiological saline.

Valsartan and Hydrochlorothiazide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
80.00	1	Valsartan	80.00
12.50	2	Hydrochlorothiazide	12.50
1.50	3	Colloidal anhydrous silica Aerosil	1.50
31.50	4	Microcrystalline cellulose Avicel	31.50
20.00	5	Polyvinylpyrrolidone crospovidone	20.00
4.50	6	Magnesium stearate	4.50

Manufacturing Directions

1. The components, except for a portion of the magnesium stearate, are blended in a container mixer.
2. The blended material is sieved and preblended for an additional time period in a container mixer. The blended material is compacted using a roller compactor by apply-

ing a compaction force of 25 to 65 kN and a roller speed of 1.3 to 7.5 rpm.

3. The compacted material is sieved again and the remaining portion of the magnesium stearate is added and finally blended in a container mixer.
4. Then 150 mg of the homogeneous mixture is filled in capsules or compressed for tablets and subsequent coating.

Valsartan Capsules*

It is available as capsules for oral administration, containing either 80 or 160 mg of valsartan. The inactive ingredients contained in the capsules are cellulose compounds, crospovi-

done, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

Valsartan Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
80.00	1	Valsartan	80.00
1.50	2	Colloidal anhydrous silica Aerosil	1.50
31.50	3	Microcrystalline cellulose Avicel	31.50
20.00	4	Polyvinylpyrrolidone crospovidone	20.00
4.50	5	Magnesium stearate	4.50

Manufacturing Directions

1. The components, except for a portion of the magnesium stearate, are blended in a container mixer.
2. The blended material is sieved and preblended for an additional period of time in a container mixer. The blended material is compacted using a roller compactor by applying a compaction force of 25 to 65 kN and a roller speed of 1.3 to 7.5 rpm.

3. The compacted material is sieved again and the remaining portion of the magnesium stearate is added and finally blended in a container mixer.

4. Then 138.50 mg of the homogeneous mixture is filled in capsules or compressed for tablets and subsequent coating.

Vancomycin Hydrochloride Capsules*

Each capsule contains vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The Pulvules also contain FD&C blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.

Venlafaxine Capsules

37.5 mg venlafaxine capsule comprises nonpareil seeds 17.26%, venlafaxine HCl 44.24%, sodium alginate 17.91%, talc 5.6%, Kollicoat SR30 D (copolymer of polyvinyl acetate), 12.03%, and purified water in required quantity.

Ingredients	mg/cap
Nonpareil Seeds	16.546 Drug coating
Venlafaxine HCl	42.400
Sodium Alginate	11.660
Talc	1.930
Titanium Dioxide	1.250
Purified Water	QS
*Subtotal	73.786 Seal coating
Sodium Alginate	5.510
Talc	0.892
Titanium Dioxide	0.392
Purified Water	QS
*Subtotal	80.580 Functional coating
Kollicoat SR30D	11.535
Propylene Glycol	1.154
Talc	2.551
Purified Water	QS
*Total	95.82
*Does not remain in formulation.	

1. Load the drug on NPS using solution containing Venlafaxine HCl, sodium alginate, talc & titanium dioxide by fluid bed coating technique.
2. Seal coat the drug-coated pellets using solution containing sodium alginate, talc, and titanium dioxide by fluid bed coating technique
3. Functional coat the seal-coated pellets using solution containing Kollicoat SR 30D, propylene glycol, and talc by fluid bed coating technique.

Verapamil Hydrochloride Capsules*

It is available for oral administration as a 360-mg hard gelatin capsule (lavender cap/yellow body), a 240-mg hard gelatin capsule (dark blue cap/yellow body), a 180-mg hard gelatin capsule (light gray cap/yellow body), and a 120-mg hard gelatin capsule (yellow cap/yellow body). These pellet-filled capsules provide a sustained release of the drug in the gastrointestinal tract. In addition to verapamil HCl, the capsule contains the following inactive ingredients: fumaric acid, talc, sugar spheres, povidone, shellac, gelatin, FD&C red No. 40, yellow iron oxide, titanium dioxide, methylparaben, propylparaben, silicon dioxide, and sodium lauryl sulfate. In addition, the 240-mg and 360-mg capsules contain FD&C blue No. 1 and D&C red No. 28; and the 180-mg capsule contains black iron oxide.

Verapamil Hydrochloride Capsules

Manufacturing Directions

1. Verapamil hydrochloride (30 kg), malic acid (10 kg), and talc (2.4 kg) are blended and passed through a No. 100 mesh screen using a conventional milling machine.
2. A polymer suspension is prepared containing 5% hydroxypropyl methylcellulose in methanol/methylene chloride 60/40.
3. Sugar/Starch seeds (0.4–0.5 mm, 9 kg) are placed in a standard coating pan and rotation commenced.
4. The seeds are wetted with sufficient polymer suspension to dampen them thoroughly and then an amount of the powder blend is dusted on until no more adhered. This step is repeated until the entire powder blend has been applied.
5. The coated seeds are allowed to dry after each application of polymer suspension.
6. When all of the powder has been applied, the coated seeds are dried at 40°C to 60°C until all of the solvent has been driven off.
7. A membrane suspension is prepared from the following components: two parts by volume 5% hydroxypropyl methylcellulose in methanol/methylene chloride 60/40, eight parts by volume 5% ethylcellulose in methanol/methylene chloride 60/40, and five parts by weight talc.
8. The coated seeds, which are prepared previously and which define the active core of the pellets being prepared, are placed in a coating pan and rotation commenced. The membrane suspension is applied to the coated seeds in separate coats, each coat corresponding to 10 mL of the membrane suspension per kg of coated seeds. After each coat had been applied, the pellets are air dried in the coating pan.
9. After the final coat has been applied, the pellets are dried at 40°C to 60°C to evaporate all traces of solvent. Rapid-release pellets as used in the controlled absorption pharmaceutical formulation of the invention are prepared by forming active cores without the subsequent application of a membrane thereto.

Verapamil Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
120.00	1	Verapamil hydrochloride	120.00
20.00	2	Sucrose and cornstarch neutral microgranules	20.00
11.30	3	Shellac, bleached, wax-free	11.30
0.75	4	Eudragit L100	0.75
3.60	5	Eudragit L30D	3.60
1.23	6	Eudragit NE30D	1.23
0.37	7	Diethyl phthalate	0.37
1.60	8	Talc	1.60
–	9	Alcohol	QS
–	10	Acetone	QS
–	11	Water purified	QS

Note: For 240-mg strength, scale to twice the formula.

Manufacturing Directions

- The neutral microgranules (item 2) are placed in a coating pan and pan started.
- Prepare a 20% solution of item 3 in a mixture of acetone and alcohol.
- Set temperature of step 1 to 25°C ± 5°C. Apply shellac solution alternating with item 1 powder until the entire active ingredient is incorporated.
- Sieve microgranules through a 0.85-mm aperture. Dry microgranules at 30°C to 40°C for 8 hours.
- Sieve dried microgranules and dry again at 30°C to 40°C for 8 hours.
- Prepare a 15% alcoholic solution of Eudragit L100 and apply with talc; dry and apply until all solution is incorporated.
- Sieve microgranules using a 1.18-mm aperture sieve.
- Prepare an aqueous dispersion of item 5 (L30D) and item 7. Apply part of suspension to microgranules together with part of item 8. Allow to dry. Repeat operation until desired dissolution rate is obtained.
- Sieve microgranules using 1.18-mm sieve and then dry at 30°C to 40°C for 12 hours.
- Prepare aqueous solution of NE30D and item 7, apply in parts with remaining talc, and then dry. Repeat until desired dissolution rate is obtained.
- Sieve using a 1.18-mm sieve. Dry at 30°C to 40°C for 12 hours.
- Fill appropriate quantity based on assay. Use approximately 158.85 mg for 120-mg strength and 317.70 mg for 240-mg strength.

Vincamine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
30.00	1	Vincamine	30.00
17.50	2	Lactose	17.50
166.80	3	Sucrose and cornstarch microgranules, size 20	166.80
3.30	4	Polyvinyl pyrrolidone	3.30
1.30	5	Shellac	1.30
3.60	6	Eudragit L	3.60
7.50	7	Talc	7.50
—	8	Alcohol	QS

Manufacturing Directions

- Charge item 3 in a coating pan and run the pan.
- Prepare solution of item 4 in item 8.
- Add and mix items 1 and 2 in a separate container.
- Heat step 1 to 25°C ± 5°C; apply solution in Step 2 and alternate with powder mixture in step 3 until all of step 3 is incorporated.
- Sieve granules through a 1.18-mm sieve in step 4 and dry at 30°C to 40°C for 8 hours.
- Prepare an alcoholic solution of item 5 in item 8 and apply to step 5 until all incorporated.
- Sieve microgranules through a 1.18-mm sieve and dry at 30°C to 40°C for 8 hours.
- Prepare a solution of item 6 in item 8 and apply in steps until all solution is incorporated.
- Sieve microgranules through a 1.18-mm sieve and dry at 30°C to 40°C for 8 hours.
- Fill appropriate quantity in capsules, approximately 230 mg.

Vinpocetine Multiple Bead Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
160.00	1	Vinpocetine	160.00
	Powder Blend		
5.00	1	Vinpocetine	5.00
0.10	2	Sodium lauryl sulfate	0.10
3.0	3	Sodium starch glycolate	3.00
6.00	4	Glutamic acid	6.00
7.00	5	Cornstarch	7.00
62.00	6	Lactose	62.00
13.00	7	Microcrystalline cellulose	13.00
1.00	8	Magnesium stearate	1.00

Vitamin B Complex, Amino Acids, and Magnesium Effervescent Granules (Sugar-Free)

Bill of Materials			
Scale (mg/Tab)	Item	Material Name	Qty/1000 Tabs (g)
2.00	1	Thiamin hydrochloride	2.00
2.00	2	Pyridoxine hydrochloride	2.00
5.00	3	Cyanocobalamin dry powder 0.1%	5.00
20.00	4	L-Glutamine	20.00
10.00	5	Inositol	10.00
10.00	6	Potassium L-aspartate	10.00
500.00	7	DL-Carnitine hydrochloride	500.00
350.00	8	Magnesium L-aspartate	350.00
600.00	9	Citric acid, anhydrous	600.00
500.00	10	Sodium bicarbonate	500.00
QS	11	Flavors	QS
50.00	12	Kollidon VA 64	50.00
—	13	Isopropanol	80.00

Manufacturing Directions

- Mix items 1 to 6, add the mixture of items 7 to 12, granulate mixture of these two combinations with item 13, pass through a 0.8-mm sieve, dry well, and mix.

- Fill 2.1 g of the granules in sachets.

Vitamin B Complex + Amino Acid + Magnesium Effervescent Granules (Sugar-free)

(1 RDA of vitamins + 500 mg carnitine + 20 mg glutamine)

Formulation

Thiamin hydrochloride, 2 g; pyridoxine hydrochloride, 2 g; cyanocobalamin dry powder 0.1%, 5 g; L-glutamine, 20 g; inositol, 10 g; potassium L-aspartate, 10 g; DL-carnitine hydrochloride, 500 g; magnesium L-aspartate, 350 g; citric acid, anhydrous, 600 g; sodium bicarbonate, 500 g; flavors, QS; Kollidon VA 64 50 g; isopropanol, 80 g.

drochloride, 500 g; magnesium L-aspartate, 350 g; citric acid, anhydrous, 600 g; sodium bicarbonate, 500 g; flavors, QS; Kollidon VA 64 50 g; isopropanol, 80 g.

Manufacturing Directions

- Mix the components I, add the mixture II, granulate mixture I+II with the liquid III, pass through a 0.8-mm sieve, dry well, and mix with III.
- Fill 2.1 g of the granules in sachets.

Vitamin B Complex and Vitamin C Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
3.60	1	Thiamine hydrochloride	3.60
5.70	2	Riboflavin phosphate sodium	5.70
45.00	3	Nicotinamide	45.00
4.50	4	Pyridoxine hydrochloride	4.50
15.0	5	Cyanocobalamin (gelatin-coated, 0.1%)	15.00
150.0	6	Ascorbic acid (powder)	150.00
723.00	7	Sucrose	723.00
51.00	8	Kollidon 30	51.00
QS	9	Ethanol	180.00 mL

Manufacturing Directions

- Mix items 1 to 7, granulate with solution of items 8 and 9, dry, and pass through a 0.8-mm sieve.
- Fill 1 g of the granules in sachets (or 10 g in 100 mL flakes as dry syrup) to produce yellow homogeneous granules dispersible in cold water.

- Approximately 1 g of the granules (=1 sachet) corresponds to two daily vitamin B and vitamin C requirements of adults.
- Because of the high loss of riboflavin phosphate sodium, it should be substituted by riboflavin.

Vitamin C and Calcium Carbonate Effervescent Powder

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tabs (g)
300.00	1	Calcium, USE calcium carbonate	315.00
450.00	2	Sodium tartaric acid, powder bicarbonate	450.00
600.00	3	Kollidon 30	600.00
35.00	4	Kollidon 30	35.00
200.00	5	Isopropanol	200.00
400.00	6	Sucrose crystalline	400.00
500.00	7	Ascorbic acid, crystalline, with excess	550.00
120.00	8	Kollidon CL	120.00
60.00	9	Polyethylene glycol 6000, powder	60.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 and 5, mix with item 6, and dry.
2. Add items 7 to 9 and press with a high compression force at maximum 30% of relative atmospheric humidity.
3. Package 2500 mg in aluminum-lined sachet.

Zanamivir Powder*

It is for administration to the respiratory tract by oral inhalation only. Each disc contains four regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose. The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the Diskhaler[®]. The drug is also administered as aqueous solution (10%) with

0.04% benzalkonium chloride and 0.40% phenylethyl alcohol. In an aqueous cosolvent system, it contains 10% active drug, 0.04% benzalkonium chloride, 10% PEG 400, and 30% propylene glycol (balance purified water). In an aerosol formulation, there is 7.5% active drug, 25.6% propellant 11, and 66.5% propellant 12.

Zanamivir Powder

Bill of Materials			
Scale (mg/disk)	Item	Material Name	Qty/1000 Disks (g)
5.00	1	Zanamivir	5.00
20.00	2	Lactose anhydrous	20.00

Zidovudine Capsules

Each capsule contains 100 mg of zidovudine and the inactive ingredients cornstarch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists

of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C blue No. 2.

Zidovudine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Zidovudine (3'-azido-3'-deoxythymidine)	100.00
200.00	2	Lactose	200.00
50.00	3	Cornstarch	50.00
5.00	4	Polyvinylpyrrolidone	5.00
4.00	5	Magnesium stearate	4.00

Manufacturing Directions

1. Sieve items 1 to 4 through 80-mesh sieve and blend.
2. Pass item 5 through a 100-mesh sieve and add to step 1 and blend for 2 minutes.
3. Fill 359 mg in capsules.

Zinc Oxide and Cornstarch Powder

Cornstarch baby powder combines zinc oxide (10%) with topical starch (cornstarch) for topical application. Also contains fragrance and tribasic calcium phosphate.

Ziprasidone Hydrochloride Capsules*

Capsules are supplied for oral administration in 20-, 40-, 60-, and 80-mg doses. Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

Ziprasidone Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Ziprasidone, USE ziprasidone hydrochloride	22.65
66.10	2	Lactose monohydrate	66.10
10.00	3	Pregelatinized cornstarch	10.00
0.75	4	Magnesium stearate	0.75

Manufacturing Directions

1. Pass items 1 to 3 through 80-mesh screen and blend.
2. Pass item 4 through 100-mesh screen and add and blend for 2 minutes.
3. Fill in size 4 capsules (100 mg). For higher strengths, scale up the quantity and size of capsule. The lactose monohydrate weight is adjusted according to small potency changes in the ziprasidone hydrochloride monohydrate to maintain a constant capsule weight.

Zonisamide Capsules*

Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose,

hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

Zonisamide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Zonisamide	100.00
35.00	2	Lactose anhydrous	35.00
17.00	3	Cornstarch	17.00
40.00	4	Crystalline cellulose	40.00
6.00	5	Hydroxypropyl cellulose	6.00
1.00	6	Light anhydrous silicic acid	1.00
1.00	7	Magnesium stearate	1.00
QS	8	Water purified	QS

Manufacturing Directions

1. Among the preceding components, zonisamide, lactose, cornstarch, and crystalline cellulose are blended and thereto is added hydroxypropyl cellulose being dissolved in water. The mixture is kneaded, dried, and granulated.
2. To these granules are added magnesium stearate and light anhydrous silicic acid and the mixture is filled (200 mg) in each capsule.
3. A 20% powder formulation contains zonisamide, 200 g; lactose, 719 g; hydroxypropyl cellulose, 20 g; light anhydrous silicic acid, 1 g. Total, 940 g.
4. Using a high-shear granulator, all the preceding components for powder formulation are blended, sprayed with an ethanolic solution (200 g) containing ethylcellulose (40 g) and hydroxypropyl cellulose (20 g) for granulation, and are then made into granules. These are dried and regulated in size to give 20% powders.

COMMERCIAL PHARMACEUTICAL FORMULATIONS

14 L-Crystalline amino acid formula—700 mg/cap—L-lysine HCL, L-isoleucine, L-glutamine, L-tyrosine, L-threonine, L-alanine, L-leucine, L-histidine, L-arginine HCL, L-aspartic acid, L-valine, L-methionine, L-cystine, L-glutamic acid, glycine, L-phenylalanine, N-acetyl-L-tyrosine, L-serine, L-proline plus ornithine alpha-ketoglutarate, and dipeptides; L-alanyl-L-glutamine and L-glycyl-L-glutamine. 20 L-Crystalline amino acid formula helps reverse negative nitrogen balance. 677 mg. L-Crystalline amino acids including neurotransmitter precursors, sulfur, and branched chain amino acids plus alpha-lipoic acid: L-lysine HCL, L-isoleucine, L-glutamine, L-tyrosine, L-threonine, L-alanine, L-leucine, L-histidine, L-arginine HCL, L-aspartic Acid, L-valine, ornithine alpha-ketoglutarate, L-methionine, L-cystine, L-glutamic acid, glycine, L-phenylalanine, N-acetyl-L-tyrosine, L-serine, L-proline, alpha-lipoic acid.

- Adipex-P capsules contain the inactive ingredients cornstarch, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, black iron oxide, FD&C blue No. 1, FD&C red No. 40, and D&C red No. 33.
- Aggrenox[®] (aspirin/extended-release dipyridamole) is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg dipyridamole in an extended-release form and 25 mg aspirin as an immediate-release sugar-coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, aluminum stearate, colloidal silicon dioxide, cornstarch, dimethicone, hypromellose, hypromellose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin. Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide, and water.
- Amitiza[™] (lubiprostone) is available for oral administration in an imprinted, oval, orange soft gelatin capsule containing 24 µg lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C red No. 40, D&C yellow No. 10, and purified water.
- Amnesteem contains isotretinoin, a retinoid, and is available in 10-, 20-, and 40-mg soft gelatin capsules for oral administration. Each capsule contains yellow wax, butylated hydroxyanisole, edetate disodium, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin with the following dye systems: 10 mg—red iron oxide paste and black ink; 20 mg—red iron oxide paste, yellow iron oxide paste, titanium dioxide, and black ink; 40 mg—red iron oxide paste, yellow iron oxide paste, titanium dioxide, and black ink.
- Benefiber[®] is a 100% natural fiber that can be mixed with almost anything. Ingredients: partially hydrolyzed guar gum (a 100% natural fiber). Guar gum is derived from the seed of the cluster bean.
- Biaxin for suspension, clarithromycin suspension (clarithromycin for oral suspension, USP), contains 125 or 250 mg of clarithromycin. Each bottle of Biaxin granules contains 1250 mg (50-mL size), 2500 mg (50- and 100-mL sizes), or 5000 mg (100-mL size) of clarithromycin and the following inactive ingredients: carbomer, castor oil, citric acid, hypromellose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide, and fruit punch flavor.
- Brevibloc (esmolol hydrochloride) premixed injection is a clear, colorless to light yellow, sterile, nonpyrogenic isoosmotic solution of esmolol hydrochloride in sodium chloride. 2500-mg, 250-mL single use premixed bag—Each milliliter contains 10 mg esmolol hydrochloride, 5.9 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 5.0 (4.5–5.5). The calculated osmolarity is 312 mOsmol/L. The 250-mL bag is a nonlatex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical compounds from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. 2000-mg, 100-mL single use premixed bag double strength—Each milliliter contains 20 mg esmolol hydrochloride, 4.1 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 5.0 (4.5–5.5). The calculated osmolarity is 312 mOsmol/L. The 100-mL bag is a nonlatex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Brevibloc injection is a clear, colorless to light yellow, sterile, nonpyrogenic isoosmotic solution of esmolol hydrochloride in sodium chloride. 100-mg, 10-mL single dose vial—Each milliliter contains 10 mg esmolol hydrochloride, 5.9 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary to adjust pH to 5.0 (4.5–5.5). 100-mg, 5-mL double-strength single-dose vial—Each milliliter contains 20 mg esmolol hydrochloride, 4.1 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary to adjust pH to 5.0 (4.5–5.5). Brevibloc Concentrate is a clear, colorless to light yellow, sterile nonpyrogenic concentrate. 2500-mg, 10-mL Ampul—Each milliliter contains 250 mg esmolol hydrochloride in 25% propylene glycol, USP, 25% alcohol, USP, and water for injection, USP, buffered with 17.0 mg sodium acetate trihydrate, USP, and 0.00715 mL glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 3.5 to 5.5.
- Buphenyl[®] (sodium phenylbutyrate) powder for oral, nasogastric, or gastrostomy tube administration contains sodium phenylbutyrate. Each gram of Buphenyl powder contains 0.94 g of sodium phenylbutyrate and the inactive ingredients calcium stearate and colloidal silicon dioxide.
- Ceftin for oral suspension when reconstituted with water provides the equivalent of 125 or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. Ceftin for oral suspension contains the inactive ingredients acesulfame potassium, aspartame, povidone K30, stearic acid, sucrose, tutti-frutti flavoring, and xanthan gum.
- Cevimeline (30 mg) The pH of a 1% solution ranges from 4.6 to 5.6. Inactive ingredients include lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate.
- Chemet (succimer) opaque white capsule for oral administration contains beads coated with 100 mg of succimer and is imprinted black with CHEMET 100. Inactive ingredients in medicated beads are povidone, sodium starch glycolate, starch, and sucrose. Inactive ingredients in

capsule are gelatin, iron oxide, titanium dioxide, and other ingredients.

- Colace[®] (docusate sodium) active ingredient: Colace capsules 100 mg contains 100 mg of docusate sodium. Inactive ingredients: D&C red No. 33, FD&C red No. 40, FD&C yellow No. 6, gelatin, glycerin, methylparaben, polyethylene glycol 400, propylene glycol, propylparaben, sorbitol, titanium dioxide. Colace capsules 50 mg contains 50 mg of docusate sodium.
- Colyte[®] with flavor packs is a colon lavage preparation provided as water-soluble components for solution. In solution this preparation with one flavor pack added delivers the following in grams per liter. Polyethylene glycol 3350 60.00, sodium chloride 1.46, potassium chloride 0.745, sodium bicarbonate 1.68, sodium sulfate 5.68, flavor ingredients 0.805. When dissolved in sufficient water to make 4 L, the final solution contains 125 mEq/L sodium, 10 mEq/L potassium, 20 mEq/L bicarbonate, 80 mEq/L sulfate, 35 mEq/L chloride, and 18 mEq/L polyethylene glycol 3350. The reconstituted solution is isoosmotic and has a mild salty taste. This preparation can be used without the flavor packs and is administered orally or via nasogastric tube. Each orange flavor pack (3.22 g) contains hypromellose, natural and artificial orange powder, saccharin sodium, colloidal silicon dioxide. Each citrus berry flavor pack (3.22 g) contains hypromellose, artificial citrus berry powder, saccharin sodium, colloidal silicon dioxide. Each lemon lime flavor pack (3.22 g) contains hypromellose, natural and artificial lemon lime powder, Prosweet[®] powder natural, saccharin sodium, colloidal silicon dioxide. Each cherry flavor pack (3.22 g) contains hypromellose, artificial cherry powder, saccharin sodium, colloidal silicon dioxide. Each pineapple flavor pack (3.22 g) contains hypromellose, artificial pineapple flavor powder, Magna Sweet[™], saccharin sodium, colloidal silicon dioxide.
- Creon[®] 20 capsules are orally administered and contain 497 mg of delayed-release Minimicrospheres[®] of pancrelipase, which is of porcine pancreatic origin. Each Creon 20 capsule contains lipase 20,000 USP units, protease 75,000 USP units, and amylase 66,400 USP units. Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropylmethylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide. Creon[®] 10 capsules are orally administered and contain 249 mg of delayed-release Minimicrospheres of pancrelipase, which is of porcine pancreatic origin. Each Creon 10 capsule contains lipase 10,000 USP units, protease 37,500 USP units, and amylase 33,200 USP units. Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropylmethylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide. Creon[®] 5 capsules are orally administered and contain 124 mg of delayed-release Minimicrospheres of pancrelipase, which is of porcine pancreatic origin. Each Creon 5 capsule contains lipase 5,000 USP units, protease 18,750 USP units, and amylase 16,600 USP units. Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropylmethylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain gelatin, red iron oxide, titanium dioxide, yellow iron oxide, and
- FD & C blue No. 2. The capsule imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide.
- Crixivan^{*} (indinavir sulfate) capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide, and sodium lauryl sulfate.
- Cuprimine, penicillamine, for oral administration contain either 125 or 250 mg of penicillamine. Each capsule contains the following inactive ingredients: D&C yellow No. 10, gelatin, lactose, magnesium stearate, and titanium dioxide. The 125-mg capsule also contains iron oxide.
- Cymbalta[®] (duloxetine hydrochloride) capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C blue No. 2, gelatin, hypromellose, hydroxypropylmethylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20- and 60-mg capsules also contain iron oxide yellow.
- Dalmane is available as capsules containing 15- or 30-mg flurazepam hydrochloride. Each 15-mg capsule also contains cornstarch, lactose, magnesium stearate, and talc; gelatin capsule shells contain the following dye systems: D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6, and D&C yellow No. 10. Each 30-mg capsule also contains cornstarch, lactose, and magnesium stearate; gelatin capsule shells contain the following dye systems: FD&C blue No. 1, FD&C yellow No. 6, D&C yellow No. 10, and either FD&C red No. 3 or FD&C red No. 40. Flurazepam hydrochloride is chemically 7-chloro-1-[2-(diethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride.
- Dantrium (dantrolene sodium) is supplied in capsules of 25 mg, 50 mg, and 100 mg. Inactive ingredients: Each capsule contains edible black ink, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, starch, synthetic iron oxide red, synthetic iron oxide yellow, talc, and titanium dioxide.
- DDS[®]-*Acidophilus* is the source of a special strain of *Lactobacillus acidophilus* free of dairy products, corn, soy, and preservatives. Each capsule or tablet contains 1 billion viable DDS-1 *L. acidophilus* at the time of manufacturing. 1 g of powder contains two billion viable DDS-1 *L. acidophilus*.
- Demser^{*} (Metyrosine) capsule contains 250 mg metyrosine. Inactive ingredients are colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, magnesium stearate, titanium dioxide, and FD&C blue 2.
- Depakene (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. Depakene capsules and syrup are antiepileptics for oral administration. Each soft elastic capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt. Inactive ingredients 250-mg capsules: corn oil, FD&C yellow No. 6, gelatin, glycerin, iron oxide, methylparaben, propylparaben, and titanium dioxide.
- Detrol LA capsules contain tolterodine tartrate. Detrol LA for oral administration contains 2 or 4 mg of tolterodine tartrate. Inactive ingredients are sucrose, starch, hypromellose, ethylcellulose, medium-chain triglycerides, oleic acid,

- gelatin, and FD&C blue No. 2. The 2-mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.
- **Dexedrine (dextroamphetamine sulfate)** Spansule sustained-release capsule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period. Each capsule, with brown cap and clear body, contains dextroamphetamine sulfate. The 5-mg capsule is imprinted 5 mg and 3512 on the brown cap and is imprinted 5 mg and SB on the clear body. The 10-mg capsule is imprinted 10 mg and 3513 on the brown cap and is imprinted 10 mg and SB on the clear body. The 15-mg capsule is imprinted 15 mg and 3514 on the brown cap and is imprinted 15 mg and SB on the clear body. A narrow bar appears above and below 15 mg and 3514. Product reformulation in 1996 has caused a minor change in the color of the time-released pellets within each capsule. Inactive ingredients now consist of cetyl alcohol, D&C yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C blue No. 1, FD&C blue No. 1 aluminum lake, FD&C red No. 40, FD&C yellow No. 6, gelatin, hypromellose, propylene glycol, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres, and trace amounts of other inactive ingredients.
 - **Divalproex sodium** is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Divalproex sodium occurs as a white powder with a characteristic odor. Depakote Sprinkle Capsules are for oral administration. Depakote Sprinkle Capsules contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in a hard gelatin capsule. Inactive ingredients 125-mg Depakote Sprinkle Capsules: cellulosic polymers, D&C red No. 28, FD&C blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.
 - **Dyazide capsule** for oral use, with opaque red cap and opaque white body, contains hydrochlorothiazide 25 mg and triamterene 37.5 mg. Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red No. 33, FD&C yellow No. 6, gelatin, glycine, lactose, magnesium stearate, microcrystalline cellulose, povidone, polysorbate 80, sodium starch glycolate, titanium dioxide, and trace amounts of other inactive ingredients. Dyazide capsules meet Drug Release Test 3 as published in the USP 23 monograph for triamterene and hydrochlorothiazide capsules.
 - **Edecrin, ethacrynic acid**, is supplied as 25-mg tablets for oral use. The tablets contain the following Inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, starch and talc. Intravenous sodium Edecrin* (ethacrynate sodium) is a sterile freeze-dried powder and is supplied in a vial containing ethacrynate sodium equivalent to ethacrynic acid 50 mg. Inactive ingredient: Mannitol 62.5 mg.
 - **EES (erythromycin ethylsuccinate) granules** are intended for reconstitution with water. Each 5-mL teaspoonful of reconstituted cherry-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin. The pleasant-tasting, fruit-flavored liquids are supplied ready for oral administration. Inactive: EES granules: citric acid, FD&C red No. 3, magnesium aluminum silicate, sodium carboxymethylcellulose, sodium citrate, sucrose, and artificial flavor.
 - **Effexor XR** is an extended-release capsule for oral administration. Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5-mg, 75-mg, or 150-mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.
 - **Eldepryl (selegiline hydrochloride)** contains 5 mg selegiline hydrochloride. Inactive ingredients are anhydrous citric acid, lactose, magnesium stearate, and microcrystalline cellulose.
 - **EMCYT (estramustine phosphate sodium)** capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate equivalent to 140 mg estramustine phosphate for oral administration. Each capsule also contains magnesium stearate, silicon dioxide, sodium lauryl sulfate, and talc. Gelatin capsule shells contain the pigment titanium dioxide.
 - **EMEND* (aprepitant)** capsule contains either 80 or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose, and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 125-mg capsule also contains red ferric oxide and yellow ferric oxide.
 - **Encora™** is a prescription vitamin and mineral nutritional supplement with essential fatty acids consisting of two capsules and two tablets on each blister card designated for AM and PM oral administration as follows. The AM tablet is an oval-shaped, light pink film-coated tablet containing the following ingredients: calcium (calcium carbonate) 400 mg, vitamin D₃ (cholecalciferol) 200 IU, vitamin C (as Ester-C®) 25 mg, folic acid USP 2 mg, vitamin B₆ (pyridoxine hydrochloride, USP 25 mg). The PM tablet is an oval-shaped, purple film-coated tablet containing the following ingredients: calcium (calcium carbonate) 600 mg, vitamin D₃ (cholecalciferol) 600 IU, vitamin C (as Ester-C) 25 mg, folic acid USP 0.5 mg, vitamin B₆ (pyridoxine hydrochloride, USP) 12.5 mg. The AM and PM capsules are a pink soft gelatin capsule containing the following ingredients: essential fatty acids (omega-3) 650 mg, DHA and EPA 550 mg, alpha-linolenic acid (ALA) 100 mg, linoleic acid (LA) 10 mg, vitamin E (DL-alpha-tocopheryl acetate) 50 IU. Ester-C is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) ratio is approximately 2.7:1. Inactive ingredients: Tablets: acacia, butylated hydroxyanisole, butylated hydroxytoluene, colloidal silicon dioxide, cornstarch, croscarmellose sodium, D&C red No. 27 aluminum lake, hydrolyzed gelatin, lecithin, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, stearic acid, sucrose, talc, titanium dioxide, and vegetable oil. The AM tablet also contains FD&C blue No. 2 aluminum lake. The PM tablet also contains FD&C blue No. 1 aluminum lake. Capsules: D&C red No. 33, ethyl vanillin, FD&C red No. 40, gelatin, glycerine, soybean oil, and titanium dioxide.
 - **Entocort® EC capsules** contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have

the following inactive ingredients: gelatin, iron oxide, and titanium dioxide.

- EryPed 200 and EryPed Drops (erythromycin ethylsuccinate for oral suspension) when reconstituted with water forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 mL (teaspoonful) or 100 mg/2.5 mL (dropperful) with an appealing fruit flavor. EryPed 400 when reconstituted with water forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 mL (teaspoonful) with an appealing banana flavor. Inactives: EryPed 200, EryPed 400, and EryPed. Drops: Caramel, polysorbate, sodium citrate, sucrose, xanthan gum, and artificial flavors.
- Erythromycin delayed-release capsules contain enteric-coated pellets of erythromycin base for oral administration. Each erythromycin delayed-release capsule contains 250 mg of erythromycin base. Inactive ingredients: cellulosic polymers, citrate ester, D&C red No. 30, D&C yellow No. 10, magnesium stearate, and povidone. The capsule shell contains FD&C blue No. 1, FD&C red No. 3, gelatin, and titanium dioxide.
- Eskalith contains lithium carbonate, a white, light alkaline powder. Eskalith capsules with opaque gray cap and opaque yellow body are imprinted with the product name **ESKALITH** and **SB** and contain lithium carbonate 300 mg. Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C yellow No. 10, FD&C green No. 3, FD&C red No. 40, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, titanium dioxide, and trace amounts of other inactive ingredients.
- Eulexin capsules contain flutamide and cornstarch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may also contain benzyl alcohol, butylparaben, colloidal silicon dioxide, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate, and the following dye systems: FD&C blue No. 1, FD&C red No. 3, FD&C yellow No. 6, titanium dioxide, black ink, and other inactive ingredients.
- Exelon[®] (rivastigmine tartrate) capsules contain rivastigmine tartrate, equivalent to 1.5, 3, 4.5, and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard gelatin capsule contains gelatin, titanium dioxide, and red and/or yellow iron oxides.
- Exubera[®] consists of blisters containing human insulin inhalation powder, which are administered using the Exubera inhaler. Each unit dose blister of Exubera contains a 1- or 3-mg dose of insulin in a homogeneous powder formulation containing sodium citrate (dihydrate), mannitol, glycine, and sodium hydroxide.
- Ferrochel[®] soft gelatin capsule for oral administration contains iron (as Ferrochel ferrous bis-glycinate chelate elemental iron) 70 mg; vitamin C as Ester-C patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate; ascorbic acid (as calcium ascorbate) 150 mg; threonic acid (as calcium threonate) 2 mg; vitamin B₁₂ (cyanocobalamin) 10 µg; desiccated stomach substance 100 mg. Inactive ingredients: soybean oil, gelatin, glycerine, yellow beeswax, lecithin (unbleached), titanium dioxide, methyl-/propylparaben blend, ethyl vanillin, FD&C red No. 40, FD&C yellow No. 6, FD&C blue No. 1.
- Focalin[™] XR (dexmethylphenidate hydrochloride) extended-release capsules are an extended-release formulation of dexmethylphenidate with a bimodal release profile. Focalin XR uses the proprietary SODAS[®] (spheroidal oral drug absorption system) technology. Each bead-filled Focalin XR capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate. Focalin XR 5-, 10-, and 20-mg capsules provide in a single dose the same amount of dexmethylphenidate as dosages of 2.5, 5, or 10 mg of Focalin[™] tablets given bid. Inactive ingredients: ammonio methacrylate copolymer, FD&C blue No. 2 (5-mg strength), FDA/E172 yellow iron oxide (10-mg strength), gelatin, ink tan SW-8010, methacrylic acid copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide, and triethyl citrate.
- Foradil[®] Aerolizer[®] consists of a capsule dosage form containing a dry powder formulation of Foradil (formoterol fumarate) intended for oral inhalation only with the Aerolizer inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 µg of formoterol fumarate and 25 mg of lactose as a carrier.
- Geodon[®] is available as Geodon capsules (ziprasidone hydrochloride) for oral administration and as Geodon for injection (ziprasidone mesylate) for intramuscular injection.
- Geodon capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Geodon capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. Geodon capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.
- Hep-Forte capsule contains vitamin A (palmitate) 1, 200 IU, vitamin E (d-alpha tocopherol) 10 IU, vitamin C (ascorbic acid) 10 mg, folic acid 0.06 mg, vitamin B₁ (thiamine mononitrate) 1 mg, vitamin B₂ (riboflavin) 1 mg, niacinamide 10 mg, vitamin B₆ (pyridoxine HCl) 0.5 mg, vitamin B₁₂ (cobalamin) 1 µg, biotin 3.3 µg, pantothenic acid 2 mg, choline bitartrate 21 mg, zinc (zinc sulfate) 2 mg, desiccated liver 194.4 mg, liver concentrate 64.8 mg, liver fraction number 2 64.8 mg, yeast (dried) 64.8 mg, DL-methionine 10 mg, inositol 10 mg. Other ingredients: microcrystalline cellulose, stearic acid, croscarmellose sodium, silicon dioxide, magnesium stearate, titanium dioxide coating.
- Hexalen (altretamine) capsules contain 50 mg of altretamine for oral administration. Inert ingredients include lactose, anhydrous and calcium stearate. Altretamine is a white crystalline powder melting at 172°C ± 1°C.
- Hytrin (terazosin hydrochloride) is supplied in four dosage strengths containing terazosin hydrochloride equivalent to 1 mg, 2 mg, 5 mg, or 10 mg of terazosin. Inactive ingredients: 1-mg capsules: gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. 2-mg capsules: D&C yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. 5-mg capsules: D&C red No. 28, FD&C red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. 10-mg capsules: FD&C blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

- Imodium[®] (loperamide hydrochloride) is available in 2-mg capsules. The inactive ingredients are lactose, cornstarch, talc, and magnesium stearate. Imodium capsules contain FD&C yellow No. 6.
- Indocin for oral administration contain either 25 or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD&C blue 1, FD&C red 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide.
- Inspira for oral administration contains 25 or 50 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, talc, magnesium stearate, titanium dioxide, polyethylene glycol, polysorbate 80, and iron oxide yellow and iron oxide red.
- Kadian[®] capsules 20, 30, 50, 60 and 100 mg contain identical polymer-coated sustained-release pellets of morphine sulfate for oral administration. Each Kadian sustained-release capsule contains either 20, 30, 50, 60, or 100 mg of morphine sulfate USP and the following inactive ingredients common to all strengths: hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, cornstarch, and sucrose. The 20-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, titanium dioxide, and black ink SW-9009. The 30-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, FD&C red No. 3, FD&C blue No. 1, titanium dioxide and black ink S-1-8114 or S-1-8115. The 50-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink SW-9009. The 60-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink S-1-8114 or S-1-8115. The 100-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, FD&C blue No. 1, titanium dioxide, and black ink SW-9009.
- K-LOR (potassium chloride for oral solution, USP) packet of 20 mEq powder contains potassium 20 mEq and chloride 20 mEq provided by potassium chloride 1.5 g. Inactive ingredients: FD&C yellow No. 6, maltodextrin (contains corn derivative), malic acid, saccharin, silica gel, and natural flavoring.
- Kristalose[™] (lactulose) is a synthetic disaccharide in the form of crystals for reconstitution prior to use for oral administration. Each 10 g of lactulose contains less than 0.3 g galactose and lactose as a total sum. The pH range is 3 to 7. Lactulose is a colonic acidifier, which promotes laxation.
- Lanoxicaps (digoxin) is a stable solution of digoxin enclosed within a soft gelatin capsule for oral use. Each capsule contains the labeled amount of digoxin USP dissolved in a solvent comprised of polyethylene glycol 400 USP, 8 percent ethyl alcohol, propylene glycol USP, and purified water USP. Inactive ingredients in the capsule shell include D&C yellow No. 10 (0.1-mg and 0.2-mg capsules), FD&C blue No. 1 (0.2-mg capsule), gelatin, glycerin, methylparaben and propylparaben (added as preservatives), purified water, and sorbitol. Capsules are printed with edible ink.
- Lescol[®] (fluvastatin sodium) is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration. Active ingredient: fluvastatin sodium. Inactive ingredients in capsules: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients. Capsules may also include benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate. Inactive ingredients in extended-release tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide, and polyethylene glycol 8000.
- Lotrel is a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated in four different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5, 5, or 10 mg of amlodipine, with 10 or 20 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg, and 10/20 mg. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.
- Lyrica (pregabalin) capsules are supplied as imprinted hard shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.
- Marinol[®] capsule, dronabinol, is supplied as round, soft gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each Marinol capsule is formulated with the following inactive ingredients: FD&C blue No. 1 (5 mg), FD&C red No. 40 (5 mg), FD&C yellow No. 6 (5 mg and 10 mg), gelatin, glycerin, methylparaben, propylparaben, sesame oil, and titanium dioxide.
- Matulane (procarbazine hydrochloride) is available as capsules containing the equivalent of 50 mg procarbazine as the hydrochloride. Each capsule also contains cornstarch, mannitol, and talc. Gelatin capsule shells contain parabens (methyl and propyl), potassium sorbate, titanium dioxide, FD&C yellow No. 6, and D&C yellow No. 10.
- Maxair Autohaler (pirbuterol acetate) is a pressurized metered-dose aerosol unit for oral inhalation. It provides a fine-particle suspension of pirbuterol acetate in the propellant mixture of trichloromonofluoromethane and dichlorodifluoromethane with sorbitan trioleate. Each actuation delivers 253 µg of pirbuterol (as pirbuterol acetate) from the valve and 200 µg of pirbuterol (as pirbuterol acetate) from the mouthpiece. The unit is breath-actuated such that the medication is delivered automatically during inspiration without the need for the patient to coordinate actuation with inspiration. Each 14.0 g canister provides 400 inhalations and each 2.8 g canister provides 80 inhalations.
- Meridia[®] (sibutramine hydrochloride monohydrate) capsule contains 5 mg, 10 mg, and 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains

- titanium dioxide, USP; gelatin; FD&C blue No. 2 (5- and 10-mg capsules only); D&C yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].
- Metadate CD is a central nervous system (CNS) stimulant. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose is provided by the IR component and 70% of the dose is provided by the ER component. Metadate CD is available in three capsule strengths containing 10 mg (3 mg IR; 7 mg ER), 20 mg (6 mg IR; 14 mg ER), or 30 mg (9 mg IR; 21 mg ER) of methylphenidate hydrochloride for oral administration. Metadate CD also contains the following inert ingredients: sugar spheres, povidone, hydroxypropylmethylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, FD&C blue No. 2, FDA/E172 yellow iron oxide (10-mg capsules), FDA/E172 red iron oxide (30-mg capsules).
 - Metamucil contains psyllium husk (from the plant *Plantago ovata*). Each dose of Metamucil powder and Metamucil fiber wafers contains approximately 3.4 g of psyllium husk (or 2.4 g of soluble fiber). A listing of ingredients and nutrition information is available in the listing of Metamucil fiber laxative in the Nonprescription Drug section. Metamucil smooth texture sugar-free regular flavor and Metamucil capsules contain no sugar and no artificial sweeteners. Metamucil smooth texture sugar-free orange flavor contains aspartame (phenylalanine content of 25 mg per dose). Metamucil powdered products are gluten-free.
 - Nalfon[®] (fenoprofen calcium capsules, USP) contain fenoprofen calcium as the dihydrate in an amount equivalent to 200 mg (0.826 mmol) or 300 mg (1.24 mmol) of fenoprofen. The capsules also contain cellulose, gelatin, iron oxides, silicone, titanium dioxide, and other inactive ingredients. The 300-mg capsules also contain D&C yellow No. 10 and FD&C yellow No. 6.
 - Neurontin[®] (gabapentin) capsules are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin. The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100-mg capsule shell contains gelatin and titanium dioxide. The 300-mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400-mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C blue No. 2 and titanium dioxide.
 - Nexium[®] (esomeprazole magnesium) delayed-release capsules contain 20 or 40 mg of esomeprazole (present as 22.3 or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40–50, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C yellow No. 10.
 - Nimotop[®] (nimodipine) capsules are formulated as soft gelatin capsules for oral administration. Each liquid-filled capsule contains 30 mg of nimodipine in a vehicle of glycerin, peppermint oil, purified water, and polyethylene glycol 400. The soft gelatin capsule shell contains gelatin, glycerin, purified water, and titanium dioxide.
 - Norvasc[®] is the besylate salt of amlodipine. Norvasc (amlodipine besylate) tablets are formulated as white tablets equivalent to 2.5, 5, and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.
 - Norvir (ritonavir) soft gelatin capsules are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide.
 - Omnicel[®] (cefdinir) capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, NF; polyoxyl 40 stearate, NF; and magnesium stearate, NF. The capsule shells contain FD&C blue No. 1; FD&C red No. 40; D&C red No. 28; titanium dioxide, NF; gelatin, NF; silicon dioxide, NF; and sodium lauryl sulfate, NF.
 - OxyIR[®] oxycodone is 14-hydroxydihydrocodeinone, a white odorless crystalline powder which is derived from the opium alkaloid thebaine. OxyIR oral capsules: Each 5 mg of OxyIR capsules contains oxycodone hydrochloride. 5 mg; Inactive ingredients: FD&C blue No. 2, FD&C yellow No. 6, gelatin, hypromellose, maize starch, polyethylene glycol, polysorbate 80, red iron oxide, silicon dioxide, sodium laurel sulfate, sucrose, titanium dioxide, and yellow iron oxide.
 - Pentasa (mesalamine) for oral administration is a controlled-release formulation of mesalamine. Each 250-mg capsule contains 250 mg of mesalamine and acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains D&C yellow No. 10, FD&C blue No. 1, FD&C green No. 3, gelatin, titanium dioxide, and other ingredients. Each 500-mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C blue No. 1, gelatin, titanium dioxide, and other ingredients.
 - Phenytek[®] (phenytoin sodium) capsule (extended phenytoin sodium capsule, USP) for oral administration contains 200 or 300 mg of phenytoin sodium. Each capsule also contains the following inactive ingredients: black iron oxide, colloidal silicon dioxide, D&C yellow no. 10 aluminum lake, FD&C blue No. 1, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, gelatin, hydroxyethyl cellulose, magnesium oxide, magnesium stearate, microcrystalline cellulose, pharmaceutical glaze, povidone, propylene glycol, silicon dioxide, sodium lauryl sulfate and titanium dioxide. Phenytek capsules, 200 mg and 300 mg, meet USP Dissolution Test 3.
 - PhosLo Gelcaps (calcium acetate) contains 667 mg calcium acetate, USP [anhydrous; Ca (CH₃COO)₂; MW = 158.17 g] equal to 169 mg (8.45 mEq) calcium, and 10 mg of the inert binder, polyethylene glycol 8000 NF. The gelatin cap and body have the following inactive ingredients: FD&C blue No. 1, D&C red No. 28, titanium dioxide, USP, and gelatin, USP.
 - Precare. Each powder-filled capsule for oral administration contains Ferrochel* (elemental iron) 80 mg, polysaccharide

- iron (elemental iron) 70 mg, vitamin C as Ester-C, ascorbic acid (as calcium ascorbate) 60 mg, threonic acid (as calcium threonate) 0.8 mg, folic acid, USP 1 mg, vitamin B₁₂ (cyanocobalamin) 25 µg. Ferrochel (ferrous bisglycinate chelate) is a registered trademark of Albion International, Inc., Clearfield, Utah, and is protected under U. S. Patent Nos. 4, 599, 152 and 4, 830, 716. Ester-C is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Ester-C is a licensed trademark of Zila Nutraceuticals, Inc. Inactive ingredients: Magnesium stearate, silicon dioxide, gelatin, titanium dioxide, FD&C red No. 40, D&C red No. 28, FD&C blue No. 1, pharmaceutical glaze.
- **Prelief powder:** Each one-fourth teaspoon usage of powder is comparable to two tablets. The powder dissolves rapidly in food or nonalcoholic beverages. Tablets are recommended for taking with alcoholic beverages.
 - **Prevacid[®] (lansoprazole) delayed-release capsules** contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropylcellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, FD&C green No. 3*, and FD&C red No. 40.
 - **Prevacid NapraPAC[™] 375** is a combination package containing Naprosyn 375-mg tablets and Prevacid 15-mg capsules. **Prevacid NapraPAC[™] 500** is a combination package containing Naprosyn 500-mg tablets and Prevacid 15-mg capsules. Naprosyn tablets contain 250 mg, 375 mg, or 500 mg of naproxen (active ingredient) and croscarmellose sodium, iron oxides, povidone, and magnesium stearate (inactive ingredients). Prevacid capsules contain enteric-coated granules consisting of active ingredient, lansoprazole (15 mg), and inactive ingredients, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, FD&C green No. 3, and FD&C red No. 40 (inactive ingredients).
 - **Prevpac** consists of a daily administration pack containing two Prevacid 30-mg capsules, four amoxicillin 500-mg capsules, USP, and two clarithromycin 500-mg tablets, USP, for oral administration. Prevacid (lansoprazole) delayed-release capsules. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole (30 mg), hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, and FD&C red No. 40. The yellow opaque capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin. Inactive ingredients: Capsule shells—yellow ferric oxide, titanium dioxide, gelatin, black ferric oxide. Capsule contents—cellulose microcrystalline and magnesium stearate.
 - **PrimaCare[®]** is a prescription prenatal/postnatal multivitamin/mineral capsule and tablet combination with essential fatty acids that consists of two dosage forms on each blister card designated as AM and PM, as follows: The AM dose is a dye-free, white soft gelatin capsule containing the following ingredients: essential fatty acids (as OmegaNate[™]): omega-3 fatty acids 300 mg, linoleic acid 30 mg, linolenic acid 30 mg, vitamin D₃ (cholecalciferol), 170 IU vitamin E (DL-alpha-tocopheryl acetate) 30 IU, calcium (calcium carbonate) 150 mg. The PM dose is a dye-free, oval shaped pink film-coated tablet containing the following ingredients: biotin 35 µg; folic acid, USP 1 mg; vitamin B₁ (thiamine mononitrate, USP) 3 mg; vitamin B₂ (riboflavin, USP) 3.4 mg; vitamin B₃ (niacinamide) 20 mg; vitamin B₆ (pyridoxine HCl, USP) 50 mg; vitamin B₁₂ (cyanocobalamin) 12 µg; vitamin C (as Ester-C) 100 mg; vitamin D₃ (cholecalciferol) 230 IU; vitamin K 90 µg; pantothenic acid 7 mg; calcium (as CalciPure[™] calcium carbonate) 250 mg; chromium 45 µg; copper (cupric oxide) 1.3 mg; iron (as MicroMask[®] ferrous fumarate) 30 mg; molybdenum 50 µg; selenium 75 µg; zinc (zinc oxide, USP) 11 mg.*Ester-C is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Ester-C is a licensed trademark of Zila Nutraceuticals, Inc. Inactive ingredients: Capsule: Natural wax, natural oils, and other ingredients. Dye free. Tablet: Cellulose polymers, flow agents, natural wax, natural oils, flavor, and other ingredients. Dye free.
 - **PrimaCare ONE** is a prescription prenatal/postnatal multivitamin/mineral capsule with essential fatty acids. Each purple soft gelatin capsule contains omega-3 fatty acids 300 mg, linoleic acid 30 mg, linolenic acid 30 mg. Folic acid, USP 1 mg; vitamin B₆ (as pyridoxine HCl) 25 mg; vitamin C (as Ester-C)* 25 mg; vitamin D₃ (from cholecalciferol) 170 IU; vitamin E (from DL-alpha-tocopheryl acetate) 30 IU; calcium 150 mg; iron (as carbonyl iron) 27 mg. Inactive ingredients: Gelatin, vegetable shortening, glycerin, soybean oil, yellow beeswax, lecithin, titanium dioxide, methylparaben, ethylvanillin, D&C red No. 33, propylparaben, FD&C blue No. 1.
 - **Prograf capsules (tacrolimus capsules)** contain the equivalent of 0.5 mg, 1 mg, or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide; the 1-mg capsule shell contains gelatin and titanium dioxide; and the 5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide.
 - **Prometrium[®] (progesterone, USP) capsules** contain micronized progesterone for oral administration. Prometrium capsules are available in multiple strengths to afford dosage flexibility for optimum management. Prometrium capsules contain 100 or 200 mg micronized progesterone. The inactive ingredients for Prometrium capsules 100 mg include peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C yellow No. 10, and FD&C red No. 40. The inactive ingredients for Prometrium capsules 200 mg include peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C yellow No. 10, and FD&C yellow No. 6.
 - **Prozac[®] (fluoxetine hydrochloride) Weekly[™] capsules**, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 µmol) of fluoxetine. The capsules also contain D&C yellow No. 10, FD&C blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl

- sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.
- Rebetol contains ribavirin. Each capsule consists of a white powder in a white, opaque gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C blue No. 2 aluminum lake.
 - ReishiMax[®] GLp is a proprietary, standardized extract of Reishi (*Ganoderma lucidum*) mushroom. ReishiMax supports healthy immune system function by stimulating cell-mediated immunity. Each capsule contains 495 mg of standardized Reishi mushroom extract and 5 mg of Reishi cracked spores standardized to 6% triterpenes and 13.5% polysaccharides.
 - Relenza is zanamivir. Rotadisk[®] contains four regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the Diskhaler. After a Relenza Rotadisk is loaded into the Diskhaler, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized *in vitro* testing, Relenza Rotadisk delivers 4 mg of zanamivir from the Diskhaler device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62–65 L/minutes) for 3 seconds.
 - Retrovir (zidovudine) capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients cornstarch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C blue No. 2.
 - Ritalin LA[®] (methylphenidate hydrochloride) extended-release capsules are an extended-release formulation of methylphenidate with a bimodal release profile. Ritalin LA uses the proprietary SODAS[™] (Spheroidal Oral Drug Absorption System) technology. Each bead-filled Ritalin LA capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of methylphenidate and a second delayed release of methylphenidate. Ritalin LA 10-, 20-, 30-, and 40-mg capsules provide in a single dose the same amount of methylphenidate as dosages of 5, 10, 15, or 20 mg of Ritalin[®] tablets given bid. Inactive ingredients: ammonio methacrylate copolymer, black iron oxide (10- and 40-mg capsules only), gelatin, methacrylic acid copolymer, polyethylene glycol, red iron oxide (10- and 40-mg capsules only), sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10-, 30-, and 40-mg capsules only).
 - Robitussin capsule. Active ingredients (in each capsule): guaifenesin, USP 200 mg, pseudoephedrine HCl USP 30 mg. Inactive ingredients: FD&C green no. 3, gelatin, glycerin, mannitol, pharmaceutical glaze, polyethylene glycol, povidone, propylene glycol, sorbitan, sorbitol, titanium dioxide, water. Active ingredients (in each capsule): acetaminophen, USP 250 mg; dextromethorphan HBr, USP 10 mg; guaifenesin, USP 100 mg; pseudoephedrine HCl, USP 30 mg. Inactive ingredients: D&C yellow no. 10, FD&C red no. 40, fractionated coconut oil, gelatin, glycerin, mannitol, pharmaceutical ink, polyethylene glycol, povidone, propylene glycol, purified water, sorbitol, sorbitol anhydrides. Active ingredients (in each capsule): dextromethorphan HBr, USP 10 mg; guaifenesin, USP 200 mg; pseudoephedrine HCl, USP 30 mg. Inactive ingredients (Capsules): FD&C blue no. 1, FD&C red no. 40, gelatin, glycerin, mannitol, pharmaceutical glaze, polyethylene glycol, povidone, propylene glycol, sorbitan, sorbitol, titanium dioxide, water.
 - Senokot[™] brand wheat bran, made with 100% natural bran, provides 4.6 g of wheat bran per serving. Ingredients: Orange flavor: fructose, wheat bran, sucrose, gum arabic, citric acid, locust bean gum, natural orange flavor, beta-carotene, xanthan gum. Calories 70, sodium 5 mg, total carbohydrates 16 g, dietary fiber 3 g, soluble fiber 1 g, insoluble fiber 2 g, sugars 12 g, iron 0.6 mg.
 - Serevent Diskus (salmeterol xinafoate inhalation powder) is a specially designed plastic inhalation delivery system containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. The Diskus[®], which is the delivery component, is an integral part of the drug product. Each blister on the double-foil strip within the unit contains 50 µg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister-containing medication is opened by activating the Diskus, the medication is dispersed into the air stream created by the patient inhaling through the mouthpiece. Under standardized *in vitro* test conditions, Serevent Diskus delivers 47 µg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function [mean forced expiratory volume in 1 second (FEV₁) 20–30% of predicted], mean peak inspiratory flow (PIF) through a Diskus was 82.4 L/min (range 46.1–115.3 L/min). The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.
 - Seromycin[®] (cycloserine capsules, USP) capsule contains cycloserine, 250 mg (2.45 mmol); D&C yellow No. 10; FD&C blue No. 1; FD&C red No. 3; FD&C yellow No. 6; gelatin; iron oxide; talc; titanium dioxide; and other inactive ingredients.
 - Soriatane (acitretin), a retinoid, is available in 10-mg and 25-mg gelatin capsules for oral administration. Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink, and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.
 - Sutent[®] (atomoxetine HCl) capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, or 60 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C blue No. 2, synthetic yellow iron oxide,

- titanium dioxide. The capsules are imprinted with edible black ink.
- Suprax (cefixime) for oral suspension is a semisynthetic cephalosporin antibiotic for oral administration. After reconstitution each teaspoonful (5 mL) of suspension contains 100 mg of cefixime as the trihydrate. In addition, the suspension contains the following inactive ingredients: strawberry flavor, sodium benzoate, sucrose, colloidal silicon dioxide, and xanthan gum.
 - Surmontil (trimipramine maleate) capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are black ink, FD&C blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25-mg dosage strength also contains benzyl alcohol, D&C yellow 10, edetate calcium disodium, FD&C yellow 6, parabens (butyl, propyl, and methyl), sodium lauryl sulfate, and sodium propionate; the 50-mg dosage strength also contains benzyl alcohol, D&C red 28, edetate calcium disodium, FD&C red 40, FD&C yellow 6, parabens (butyl, propyl, and methyl), sodium lauryl sulfate, and sodium propionate.
 - Sutent[®] (sunitinib malate) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5, 25, or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25), and magnesium stearate as inactive ingredients. The orange gelatin capsule shells contain titanium dioxide and red iron oxide. The caramel gelatin capsule shells also contain yellow iron oxide and black iron oxide. The printing ink contains shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide.
 - Symbyax[®] (olanzapine and fluoxetine HCl capsules) combines two psychotropic agents, olanzapine (the active ingredient in Zyprexa[®] and Zyprexa Zydis[®]) and fluoxetine hydrochloride (the active ingredient in Prozac, Prozac Weekly[™], and Sarafem[®]). Symbyax capsules are available for oral administration in the following strength combinations: 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, 12 mg/50 mg. Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.
 - Targretin[®] (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF; polysorbate 20, NF; povidone, USP; and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF; sorbitol special-glycerin blend; and titanium dioxide, USP.
 - Tegen[®] is a standardized decaffeinated polyphenol extract of the fresh green tea leaves with proven free radical scavenging and antioxidant properties. Each 250-mg capsule contains a 20:1 extract of green tea leaves (*Camellia sinensis*) standardized to a minimum 97% pure polyphenols including 162 mg catechins, of which 95 mg is ECGg, 37 mg is ECG, and 15 mg is EGC.
 - Tessalon Perle contains benzonatate, USP 100 mg. Each Tessalon capsule contains benzonatate, USP 200 mg. Tessalon capsules also contain D&C yellow 10, gelatin, glycerin, methylparaben, and propylparaben.
 - Thalomid[®] (thalidomide) is available in 50-mg, 100-mg and 200-mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: pregelatinized starch and magnesium stearate. The 50-mg capsule shell contains gelatin, titanium dioxide, and black ink. The 100-mg capsule shell contains black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black ink. The 200-mg capsule shell contains FD&C blue No. 2, titanium dioxide, gelatin, and white ink.
 - Thiothixene capsule contains 1 mg, 2 mg, 5, or 10 mg of thiothixene and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium (type A), gelatin, magnesium stearate, microcrystalline cellulose, powdered cellulose, pregelatinized starch, sodium lauryl sulfate, titanium dioxide, and other inactive ingredients. The following coloring agents are employed: 1 mg—FD&C blue No. 1, D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6; 2 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6, D&C yellow No. 10; 5 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6; 10 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6.
 - Tiazac[®] (diltiazem hydrochloride) capsules contain diltiazem hydrochloride in extended-release beads at doses of 120, 180, 240, 300, 360 and 420 mg. Tiazac also contains microcrystalline cellulose NF, sucrose stearate, Eudragit, povidone USP, talc USP, magnesium stearate NF, hypromellose USP, titanium dioxide USP, polysorbate NF, simethicone USP, gelatin NF, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, FD&C green No. 3, black iron oxide USP, and other solids.
 - Toprol-XL, metoprolol succinate tablets, comprises a multiple unit system containing metoprolol succinate in a multitude of controlled-release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 23.75, 47.5, 95 and 190 mg of metoprolol succinate equivalent to 25, 50, 100 and 200 mg of metoprolol tartrate, USP, respectively.
 - TriLyte[™] is a white powder for reconstitution containing 420 g polyethylene glycol 3350, 5.72 g sodium bicarbonate, 11.2 g sodium chloride, 1.48 g potassium chloride. Flavor packs, each containing 3.22 g of flavoring ingredients, are attached to the 4-L bottle. When dissolved in water to a volume of 4 L, TriLyte[™] with flavor packs (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution) is an isosmotic solution, for oral administration, having a pleasant mineral water taste. One flavor pack can be added before reconstitution to flavor the solution. TriLyte[™] with flavor packs is administered orally or via nasogastric tube as a gastrointestinal lavage.
 - Verelan[®] PM (verapamil hydrochloride) is available for oral administration as a 100-mg hard gelatin capsule (white opaque cap/amethyst body), a 200-mg hard gelatin capsule (amethyst opaque cap/amethyst body), and as a 300-mg hard gelatin capsule (lavender opaque cap/amethyst body). Verapamil is administered as a racemic mixture of the R and S enantiomers. In addition to verapamil HCl, the Verelan PM capsule contains the following inactive ingredients: D&C red No. 28, FD&C blue No. 1, FD&C red No. 40, fumaric acid, gelatin, povidone, shellac, silicon dioxide, sodium lauryl sulfate, starch, sugar spheres, talc, and titanium dioxide.
 - VFEND for oral suspension is a white to off-white powder providing a white to off-white orange-flavored suspension when reconstituted. Bottles containing 45 g powder for oral suspension are intended for reconstitution with water to produce a suspension containing 40 mg/mL voriconazole. The inactive ingredients include colloidal silicon dioxide, titanium dioxide, xanthan gum, sodium citrate dihydrate, sodium benzoate, anhydrous citric acid, natural orange flavor, and sucrose.

- Viracept oral powder is available for oral administration in a 50 mg/g strength (as nelfinavir free base) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor.
- Zavesca[®] (miglustat capsules, 100 mg) is supplied in hard gelatin capsules each containing 100 mg miglustat for oral administration. Each Zavesca 100-mg capsule also contains sodium starch glycolate, povidone (K30), and magnesium stearate. Ingredients in the capsule shell include gelatin and titanium dioxide, and the shells are printed with edible ink consisting of black iron oxide, shellac, soya lecithin, and antifoam.
- Zemplar (Paricalcitol, USP) is available as soft gelatin capsules for oral administration containing 1 µg, 2 µg, or 4 µg of paricalcitol. Each capsule also contains medium-chain triglycerides, alcohol, and butylated hydroxytoluene. The medium-chain triglycerides are fractionated from coconut oil or palm kernel oil. The capsule shell is composed of gelatin, glycerin, titanium dioxide, iron oxide red (2 µg capsules only), iron oxide yellow (2 µg and 4 µg capsules), iron oxide black (1 µg capsules only), and water.
- Zithromax[®] (azithromycin capsules, azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin. Zithromax capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C red No. 40). They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate.
- Zithromax for oral suspension is supplied in a single dose packet containing azithromycin dihydrate equivalent to 1 g azithromycin. It also contains the following inactive ingredients: colloidal silicon dioxide, sodium phosphate tribasic, anhydrous; spray-dried artificial banana flavor, spray-dried artificial cherry flavor, and sucrose.
- Zonegran[®] (zonisamide) capsules containing 25, 50, or 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

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about the book...

Providing methodologies that can serve as a reference point for new formulations, the second volume covers uncompressed solids, which include formulations of powders, capsules, powders ready for reconstitution, and other similar products.

Highlights from ***Uncompressed Solid Products, Volume Two*** include:

- the fundamental issues of good manufacturing practices
- formulations for more than 400 pharmaceutical products, including currently approved products and innovative products such as small proteins, instantly liquifiable powders, and nanoparticles
- access to US FDA guidelines, as well as all major guidelines around the world
- identification and inclusion of the most often approved capsules and powders in the US

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Printed in the United States of America

informa

healthcare

www.informahealthcare.com

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