HANDBOOK OF Pharmaceutical Manufacturing Formulations

Semisolid Products

VOLUME 4

Sarfaraz K. Niazi

CRC PRESS

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Handbook of Pharmaceutical Manufacturing Formulations

Volume Series

Sarfaraz K. Niazi

Volume 1
Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products

Volume 2
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Dedication

Dedicated to the memory of
John G. Wagner

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threats to patients' lives 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 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 in which 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 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 over-the-counter (OTC) products. The separation of OTC products, though they may easily fall into one of the other five categories, is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on current good manufacturing practice (CGMP) compliance specific to the dosage form and advice is offered on how to scale up the production batches.

It is expected that the formulation scientist would use this information to benchmark internal development protocols and to 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 closed paradigm when it comes to selecting formulations; "not invented here" perhaps subconsciously reigns in the minds of many seasoned formulations scientists when they prefer to choose only a certain platform for development. It is expected that with a 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, which has taken years to compile, and I am thankful to scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, though I hope these errors do not distract the reader from the utility of the book. I would sincerely appreciate readers pointing out these mistakes to me for corrections in future editions.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois

Preface to the Volume

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

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

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

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

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

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

Chapter 4 is a comprehensive review of the present thinking of the regulatory authorities on how the stability studies should be designed and conducted and how the data should be interpreted; the induction of ICH guidelines and an attempt to streamline the requirements of testing new drug products have resulted in much dispute when it comes to global marketing of products. Should the stability testing be done at all

environmental regional standards, or is it possible to extrapolate these data based on accelerated stability testing? These are some of the questions answered in this chapter, wherein the FDA and ICH guidelines are merged.

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

Chapter 6 introduces a topic of great importance in the development of semisolid, and particularly dermal, products: skin irritation and sensitization studies. Whereas the standard test protocols have almost become universal in their nature, it is always advised that these should be agreed on, most appropriately in a pre-Investigational New Drug Application (IND) filing. Established in 1988, the Office of Drug Evaluation IV (ODE IV) Pre-IND Consultation Program is designed to facilitate and foster informal early communications between the divisions of ODE IV and potential sponsors of new therapeutics for the treatment of bacterial infections, HIV, opportunistic infections, transplant rejection, and other diseases. The program is intended to serve sponsors of all drug products that may be submitted to any division within ODE IV, including but not limited to drugs for the treatment of life-threatening illnesses (21 CFR 312.82(a)). Pre-IND advice may be requested for issues related to drug development plans; data needed to support the rationale for testing a drug in humans; the design of nonclinical pharmacology, toxicology, and drug activity studies; data requirements for an IND application; and regulatory requirements for demonstrating safety and efficacy. Included among the ODE IV Pre-IND Program activities are coordination of all Pre-IND interactions with the FDA Topical Microbicide Working Group.

Chapter 7 deals with the topic of photosensitivity caused by drugs; photosafety is a serious issue in the development of topical products. It is worth noting here that certain classes of drugs such as quinolone antibiotics are generally regarded unsafe without thorough testing for photosensitivity. Does photosensitivity correlate with carcinogenicity? These are questions of importance to the regulatory authorities.

Chapter 8 includes a variety of topics related to formulation of semisolid drugs, from CGMP considerations to packaging and validation issues; these topics are collated for their particular importance, but the discussions provided are not comprehensive, and the reader is referred to standard texts on formulation theories, particularly where establishing a preservative system is required.

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

This volume is dedicated to John G. Wagner, the John G. Searle Professor Emeritus of Pharmaceutics in the College of Pharmacy and Professor Emeritus of Pharmacology in the Medical School, who passed away recently. Born in Weston, Ontario, Canada, in 1921, Wagner served in the Canada Air Force during World War II and then worked as a research scientist for the Upjohn Co. from 1953 to 1968, joining the University of Medicine in 1968. Wagner was the author of two books and coauthor of more than 340 articles. Throughout his life he received numerous awards, including the American Pharmaceutical Association (APhA) Ebert Prize, 1961; Academy Fellow of the AphA Academy of Pharmaceutical Sciences, 1969; the Centennial Achievement Award, Ohio State University, 1970; the Host-Madsen Medal, Federation Internationale Pharmaceutique, 1972; Outstanding Leadership and Research Award, Delta Chapter of Phi Lambda Epsilon, 1983; AAPS Fellow, American Association of Pharmaceutical Scientists, 1986; and Distinguished Professor, Michigan Association of Governing Boards, 1988. Following retirement, Wagner worked as a consultant to Upjohn, Schering Corp., Warner-Lambert/Parke-Davis, the Food and Drug Administration, and others.

John Wagner became famous with the publication of his book, *Biopharmaceutics and Relevant Pharmacokinetics*; he then followed with other books on the subject of pharmacokinetics. This was the time, in the early 1970s, when the discipline of mathematical pharmacokinetics was in its infancy, its creation spearheaded by such giants as Sid Riegelman, Milo Gibaldi, and Gerhard Levy. John took the lead in infusing complex mathematics to the resolution of pharmacokinetic modeling approach; his savvy of introducing Laplace transforms to all kinetics problems bears well in my mind. I never found it difficult to get lost somewhere in the long chain of mathematical transformations; John could easily make any model mathematically awesome. I met John several times when I had invited him to speak at the institutions where I was working to frequent meetings at the Academy of Pharmaceutical Science. John was a slim, trim man who spoke with a comparably lean choice of words. He was indeed a leader, a remarkable educator, and someone who left many indelible impressions on the students in his era—me included.

Sarfaraz K. Niazi, Ph.D.
Pharmaceutical Scientist, Inc.
20 Reverside Drive
Deerfield, Illinois, 60015

About the Author

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

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Part I

Regulatory and Manufacturing Guidance

1 Changes to Approved New Drug Applications or Abbreviated New Drug Applications

I. INTRODUCTION

The holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) can make postapproval changes in accordance with added Section 506A of the FDA Modernization Act. There are specific reporting requirements for postapproval changes in components and composition, manufacturing sites, manufacturing process, specifications, package labeling, miscellaneous changes, and multiple related changes. Reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by the Center for Drug Evaluation and Research (CDER) are found in the guidance for industry entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997). Information specific to products is developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories.

II. REPORTING CATEGORIES

Section 506A of the Act provides for four reporting categories that are distinguished in the following paragraphs.

A "major change" is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product (506A(c)(2)). A major change requires the submission of a supplement and approval by the Food and Drug Administration (FDA) before distribution of the product made using the change (506A(c)(1)). This type of supplement is called, and should be clearly labeled as, a Prior Approval Supplement. An applicant may ask the FDA to expedite its review of a Prior Approval Supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in the supplement would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled as, a Prior Approval Supplement—Expedited Review Requested. Requests for expedited review based on extraordinary hardship should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A "moderate change" is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to the FDA at least 30 days before the distribution of the product made using the change (506A(d)(3)(B)(i)). This type of supplement is called, and should be clearly labeled as, a Supplement—Changes Being Effected in 30 Days. The product made using a moderate change cannot be distributed if the FDA informs the applicant within 30 days of receipt of the supplement that a Prior Approval Supplement is required (506A(d)(3)(B)(i)). For each change, the supplement must contain information determined by the FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b)). If the FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended with the missing information. The FDA may identify certain moderate changes for which distribution can occur when the FDA receives the supplement (506A(d)(3)(B)(ii)). This type of supplement is called, and should be clearly labeled as, a Supplement—Changes Being Effected. If, after review, the FDA disapproves a Changes Being Effected in 30 Days supplement or a Changes Being Effected supplement, the FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change (506A(d)(3)(B)(iii)).

A "minor change" is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors

may relate to the safety or effectiveness of the product. The applicant must describe minor changes in its next annual report (506A(d)(1)(A) and (d)(2)).

An applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol should be submitted as a Prior Approval Supplement if not approved as part of the original application.

III. GENERAL REQUIREMENTS

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify the FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (506A(a)).

An applicant making a change to an approved application under Section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the Code of Federal Regulations (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant CGMP validation and record-keeping requirements and must ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection. A Changes Being Effected supplement for labeling changes must include 12 copies of the final printed labeling (21 CFR 314.50(e)(2)(ii)).

Except for a supplemental application providing for a change in labeling, an applicant should include a statement in a supplemental application or amendment certifying that the required field copy (21 CFR 314.50) of the supplement or amendment has been provided.

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Assessment of the Effects of the Change

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the holder validates (i.e., assesses) the effects of the change on the identity, strength, quality, purity, and potency of the product as these factors may relate to the safety or effectiveness of the product (506A(b)). For each change, the supplement or annual report must contain information determined by the FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (506A(b), (c)(1), (d)(2)(A), and (d)(3)(A)). Recommendations on the type of information that should be included in a supplemental application or annual report are available in guidance documents. If no guidance is available on the type of information that should be submitted to support a change, the applicant is encouraged to contact the appropriate chemistry or microbiology review staff.

1. Conformance to Specifications

An assessment of the effect of a change on the identity, strength, quality, purity, or potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, or drug product affected by the change conforms to the approved specifications. A "specification" is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems and their components and in-process materials. For the purpose of defining specifications, "acceptance criteria" are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirmation that the material affected by manufacturing changes continues to meet its specification, the applicant should perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance or drug product, and the effect of the change on the quality of the product. For example:

- Evaluation of changes in the impurity or degradation product profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests

to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.
- Evaluation of the hardness or friability of a tablet after changes in formulation or manufacturing procedure.
- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint or multimedia dissolution profiling or an *in vivo* bioequivalence study.
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product. Typically this is accomplished by comparing test results from prechange and postchange material and determining whether the test results are equivalent. Simply stated: Is the product made after the change equivalent to the product made before the change? An exception to this general approach is that when bioequivalence should be redocumented for certain ANDA postapproval changes, the comparator should be the reference-listed drug. Equivalence comparisons frequently require a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this reason, as well as for other reasons, "equivalent" does not necessarily mean "identical." Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these suboptimal manufacturing changes, but sometimes the applicant wishes to put them into practice. If an assessment concludes that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change should be filed in a Prior Approval Supplement, regardless of the recommended reporting category for the change. For example, a type of process change with a recommended filing category of a Supplement—Changes Being Effected in 30 Days could cause a new degradant to be formed that requires qualification or identification. However, the applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. The applicant should submit this change in a Prior Approval Supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the Prior Approval Supplement, the FDA will assess the impact of any adverse effect on the product as it may relate to the safety or effectiveness of the product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes and should be filed in a Prior Approval Supplement, unless exempted by regulation or guidance (506A(c)(2)(A)). The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report. Guidance on changes in components and composition that may be filed in a Changes Being Effected Supplement or annual report is not included in this document because of the complexity of these recommendations, but it may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. MANUFACTURING SITES

A. General Considerations

CDER should be notified about a change to a different manufacturing site used by an applicant to manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates; package drug products; label drug products; or test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered to be those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. The supplement or annual report should identify whether the proposed manufacturing site is an alternative or replacement to those provided for in the approved application.

A move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, should be filed as a Prior Approval Supplement if the site does not have a satisfactory CGMP inspection for the type of operation being moved. For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of

the product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or perform primary packaging operations, the potential for adverse effect and, consequently, the recommended reporting category depend on various factors such as the type of product and operation being performed. For this reason, recommended reporting categories may differ depending on the type of drug product and operations.

Except for those situations described in Sections VI.B.4, VI.C.1.b, and VI.D.5, moving production operations between buildings at the same manufacturing site or within a building, or having construction activities occur at a manufacturing site, do not have to be reported to CDER. A move to a different manufacturing site that involves other changes (e.g., process, equipment) should be evaluated as a multiple related change (see Section XII) to determine the appropriate reporting category.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by the FDA for the type of operation that is being moved, or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than 2 years
2. A move to a different manufacturing site, except one used to manufacture or process a drug; substance intermediate, when the new manufacturing site has not had a satisfactory CGMP inspection for the type of operation being moved
3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or when the formulation modifies the rate or extent of availability of the drug; or for (2) the manufacture or processing of in-process materials with modified-release characteristics; examples of these types of drug products include modified-release solid oral dosage forms, transdermal systems, liposomal products, depot products, oral and nasal metered-dose inhalers, dry powder inhalers, and nasal spray pumps
4. Transfer of manufacturing of an aseptically processed sterile drug substance or aseptically processed sterile drug product to a newly constructed or refurbished aseptic processing facility or area or to an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved products; for example, transferring the manufacture of a lyophilized product to an existing aseptic process area where no approved lyophilized products are manufactured or where the approved lyophilized products being manufactured have dissimilar container types or sizes to the product being transferred
5. Transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site: Once this change has been approved, subsequent site changes to the facility for similar product types and processes may be filed as a Supplement—Changes Being Effected in 30 Days

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a Prior Approval Supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see Sections VI.B.1 and 2).

1. Supplement—Changes Being Effected in 30 Days

a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance
b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site, except as provided for in Section VI.B.4

c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and of (2) modified-release solid oral dosage–form products
d. A move to a different manufacturing site for testing whether (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing

2. Supplement—Changes Being Effected

a. A move to a different manufacturing site for the manufacture or processing of the final intermediate

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a Prior Approval Supplement if the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see Sections VI.B.1 and 2).

1. A move to a different manufacturing site for secondary packaging
2. A move to a different manufacturing site for labeling
3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates, other than the final intermediate
4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application, and the facility has a satisfactory CGMP inspection for the type of operation being performed
5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site
6. A move to a different manufacturing site for the ink imprinting of solid oral dosage–form products

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases there may be a substantial potential for adverse effect, regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change should be filed in a Prior Approval Supplement.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Changes that may affect the controlled (or modified) release, metering, or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form
2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components, including

   Changes in the sterilization method (e.g., gas, dry heat, irradiation); these include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa

   Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation

   Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity-displacement steam process with a process using superheated water spray)

   Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel vs. glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line

   Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling: Once this change has been approved, subsequent

process changes for similar product types in the same barrier system or isolator may be filed as a Supplement—Changes Being Effected in 30 Days

Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time

Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa

Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50% beyond the validated limits in the approved application

Changes in sterilizer load configurations that are outside the range of previously validated loads

Changes in materials or pore-size rating of filters used in aseptic processing

3. The following changes for a natural product:

Changes in the virus or adventitious agent removal or inactivation methods; this is applicable to any material for which such procedures are necessary, including drug substance, drug product, reagents, and excipients

For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line

For drug substance and drug product, establishment of a new master cell bank or seed

4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant, for example:

a. Drug product

Dry to wet granulation, or vice versa

Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave)

b. Drug substance

Filtration to centrifugation, or vice versa

Change in the route of synthesis of a drug substance

5. The following changes for drug substance:

Any process change made after the final intermediate processing step in drug substance manufacture

Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile or the physical, chemical, or biological properties

6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage–form drug product when the ink as changed is not currently used on CDER-approved products

7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. For drug products, any change in the process, process parameters, or equipment, except as otherwise provided for in this guidance

b. For drug substances, any change in process or process parameters, except as otherwise provided for in this guidance

c. For natural protein drug substances and drug products:

Any change in the process, process parameters, or equipment, except as otherwise provided for in this guidance

An increase or decrease in production scale during finishing steps that involves new or different equipment

Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters

d. For sterile products, drug substances, and components, as appropriate:

Changes in dry heat depyrogenation processes for glass container systems for products that are produced by terminal sterilization processes or aseptic processing

Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume but not filter materials or pore size rating) that require additional validation studies for the new parameters

Filtration process changes that provide for a change from single to dual product sterilizing filters in series, or for repeated filtration of a bulk

Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters (time, temperature, F_0, and others)

Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by more than 50% beyond the validated limits in the approved application when bioburden limits are unchanged

e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material

2. Supplement—Changes Being Effected

a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports to or is represented to possess
b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. For drug products and protein drug substances, changes to equipment of the same design and operating principle or changes in scale, except as otherwise provided for in this guidance (e.g., Section VII.C.1.c; see FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* [November 1994])
2. A minor change in an existing code imprint for a dosage form; for example, changing from a numeric to alphanumeric code
3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage–form drug product when the ink is currently used on CDER-approved products
4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage–form drug product other than a modified-release dosage form
5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions)
6. Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50% beyond the validated limits in the approved application when bioburden limits are unchanged

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a Prior Approval Supplement unless otherwise exempted by regulation or guidance (506A(c)(2)(A)).

Specifications (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container and closure systems and in-process materials. For the purpose of defining specifications, acceptance criteria are numerical limits, ranges, or other criteria for the tests described. Examples of a test, an analytical procedure, and acceptance criteria are an assay, a specific fully described high-pressure liquid chromatography procedure, and 98.0%–102.0%. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions. A regulatory analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the U.S. Pharmacopeia/National Formulary (USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory analytical procedures for compendial items. The applicant may include in its application alternative analytical procedures to the approved regulatory procedure for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, the regulatory analytical procedure is used. In Sections B–D below, the use of the term "analytical procedure" without a qualifier such as "regulatory" or "alternative" refers to analytical procedures used to test materials other than the drug substance or drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes in specifications that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Relaxing an acceptance criterion, except as otherwise provided for in this guidance (e.g., Section VIII.C.1.b)
2. Deleting any part of a specification, except as otherwise provided for in this guidance (e.g., Section VIII.D.2)
3. Establishing a new regulatory analytical procedure
4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality,

purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application

5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as otherwise noted; for example, a change from a high-pressure liquid chromatography procedure that distinguishes impurities to one that does not, to another type of analytical procedure (e.g., titrimetric) that does not, or to one that distinguishes impurities but for which the limit of detection or limit of quantitation is higher
6. Relating to testing of raw materials for viruses or adventitious agents: (1) relaxing an acceptance criteria, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes in specifications that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. Any change in a regulatory analytical procedure other than editorial or those identified as major changes
b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials before the final intermediate, starting materials introduced before the final drug substance intermediate, or drug substance intermediates (excluding final intermediate), except as provided for in Section VIII.B.6
c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials before the intermediate, starting materials introduced before the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as provided for in Section VIII.B.6
d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions; for example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling

2. Supplement—Changes Being Effected

a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports to or is represented to possess; for example, adding a new test and associated analytical procedure and acceptance criterion
b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

D. Minor Changes (Annual Report)

The following are examples of changes in specifications that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Any change in a specification made to comply with an official compendium
2. For drug substance and drug product, the addition, deletion, or revision of an alternative analytical procedure that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application
3. Tightening of acceptance criteria
4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced before

the final drug substance intermediate, in-process materials before the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

IX. PACKAGE

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved product of the same dosage form and same route of administration; for example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for use with an ophthalmic ointment
2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change to an ink or adhesive used on the permeable or semipermeable packaging component to one that has never been used in a CDER-approved product of the same dosage form, same route of administration, and same type of permeable or semipermeable packaging component (e.g., low-density polyethylene, polyvinyl chloride)
3. A change in the primary packaging components for any product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler)
4. For sterile products, any other change that may affect product sterility assurance such as
   A change from a glass ampule to a glass vial with an elastomeric closure
   A change to a flexible container system (bag) from another container system
   A change to a prefilled syringe dosage form from another container system
   A change from a single-unit-dose container to a multiple-dose container system
   Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels)
   Changes in the size or shape of a container for a sterile drug product
5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases)
6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. A change to or in a container closure system, except as otherwise provided for in this guidance
b. Changes in the size or shape of a container for a sterile drug substance

2. Supplement—Changes Being Effected

a. A change in the size or shape of a container for a nonsterile drug product, except for solid dosage forms (see Section IX.D.2 regarding solid dosage forms)
b. A change in or addition or deletion of a desiccant

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium
2. A change in the size or shape of a container containing the same number of dose units, for a nonsterile solid dosage form
3. The following changes in the container closure system of solid oral dosage–form products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage–form products:
   Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap
   Changing from one plastic container to another of the same type of plastic (e.g., high-density polyethylene container to another high-density polyethylene container)
   Changes in packaging materials used to control odor (e.g., charcoal packets)
   Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon)
   Increasing the wall thickness of the container
   A change in or addition of a cap liner
   A change in or addition of a seal (e.g., heat induction seal)
   A change in an antioxidant, colorant, stabilizer, or mold-releasing agent for production of the container or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage–form products
   A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the product
4. The following changes in the container closure system of nonsterile liquid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical products):
   Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap
   Increasing the wall thickness of the container
   A change in or addition of a cap liner
   A change in or addition of a seal (e.g., heat induction seal)
5. A change in the container closure system of unit-dose packaging (e.g., blister packs) for nonsterile solid dosage form–products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved products of the same type (e.g., solid oral dosage form, rectal suppository)
6. The following changes in the container closure system of nonsterile semisolid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid products:
   Changes in the closure or cap
   Increasing the wall thickness of the container
   A change in or addition of a cap liner
   A change in or addition of a seal
   A change in the crimp sealant
7. A change in the flip seal cap color, as long as the cap color is consistent with any established color-coding system for that class of drug products

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations.

All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation or guidance, should be submitted as a Prior Approval Supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data
4. Changes based on data from preclinical studies
5. Revision (expansion or contraction) of population based on data
6. Claims of superiority to another product
7. Change in the labeled storage conditions, unless exempted by regulation or guidance

C. Moderate Changes (Supplement—Changes Being Effected)

A Changes Being Effected Supplement should be submitted for any labeling change that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage; adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product; deletes false, misleading, or unsupported indications for use or claims for effectiveness; or is specifically requested by the FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event because of information reported to the applicant or agency
2. Addition of a precaution arising out of a postmarketing study
3. Clarification of the administration statement to ensure proper administration of the product
4. Labeling changes, normally classified as major changes, that the FDA specifically requests be implemented using a Changes Being Effected Supplement

D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201) without a change in the content of the labeling
2. Editorial changes, such as adding a distributor's name
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included
4. Labeling changes made to comply with an official compendium

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug to the drug as manufactured without the change or to a reference-listed drug (506A(c)(2)(B))
2. Addition of a stability protocol or comparability protocol
3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2)
4. An extension of an expiration dating period based on data obtained under a new or revised stability testing protocol that has not been approved in the application or on full shelf-life data on pilot-scale batches using an approved protocol

B. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product

as these factors may relate to the safety or effectiveness of the product.

1. Supplement—Changes Being Effected in 30 Days

a. Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product; extension of an expiration date that has previously been reduced under this provision should be filed in a Supplement—Changes Being Effected in 30 Days even if it is based on data obtained under a protocol approved in the application

2. Supplement—Changes Being Effected

a. No changes have been identified.

C. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

1. An extension of an expiration dating period based on full shelf-life data on full production batches obtained under a protocol approved in the application
2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period
3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances
4. Non-USP reference standards:
   Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application
   Tightening of acceptance criteria for existing reference standards to provide greater assurance of product purity and potency

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes, or a components and composition change may necessitate a change in a specification. For multiple related changes for which the recommended reporting categories for the individual changes differ, CDER recommends that the filing be in accordance with the most restrictive of those reporting categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the filing be in accordance with the reporting category for the individual changes. For the purposes of determining the reporting category for moves between buildings, the terms "different manufacturing site" and "same manufacturing site" are defined as follows. Same manufacturing site: The new and old buildings are included under the same drug establishment registration number, and the same FDA district office is responsible for inspecting the operations in both the new and old buildings. Different manufacturing site: The new and old buildings have different drug establishment registration numbers, or different FDA district offices are responsible for inspecting operations in the new and old building.

The change to a different manufacturing site should be filed in a Prior Approval Supplement when the new manufacturing site has never been inspected by the FDA for the type of operation being moved, the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than 2 years, or the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.

Examples of postapproval manufacturing site changes and filing consequences include:

- An applicant wants to move the manufacture of an immediate-release tablet to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules and powders for oral solution. This manufacturing site change should be filed in a Prior Approval Supplement because the new manufacturing site does not have a satisfactory CGMP inspection for immediate-release tablets.
- An applicant wants to contract out his or her packaging operations for immediate-release tablets and capsules and modified-release capsules. The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet products should be filed in a Prior Approval Supplement. The packaging site change for the capsule products should be filed as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.
- An applicant wishes to consolidate his or her product testing to a single analytical laboratory at a manufacturing site. This manufacturing site

produces various solid oral dosage–form products, has an operational analytical laboratory currently at the site, and has satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories are not inspected on a dosage form/type of drug substance-specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form products, is considered to apply to all dosage forms, including those not actually produced at the site.

Different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. For example, certain changes in the container closure systems of solid oral dosage form products may be included in the annual report, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage–form products (see Section IX.D.3). If the primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage–form products, then submission of the change in an annual report is not recommended. CDER-approved products are considered those subject to an approved NDA or ANDA. When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, the applicant has the option of filing the change for a single NDA or ANDA, using the higher recommended reporting category and, after approval, filing similar subsequent changes for other NDAs and ANDAs, using the lower recommended reporting category.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other criteria for the tests described

Active Ingredient/Drug Substance—Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient, including 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 (21 CFR 210.3(b)(7) and 314.3)

Component—Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3))

Container Closure System—The sum of packaging components that together contain and protect the dosage form; this includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product

Drug Product—A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4))

Final Intermediate—The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance must involve covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. As a consequence, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate

Inactive Ingredients—Any intended component of the drug product other than an active ingredient

In-Process Material—Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical)

Intermediate—A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance

Package—The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap)

Packaging Component—Any single part of a container closure system

Primary Packaging Component—A packaging component that is or may be in direct contact with the dosage form

Reference-Listed Drug—The listed drug identified by the FDA as the drug product on which an applicant relies

in seeking approval of its abbreviated application (21 CFR 314.3)

Satisfactory CGMP Inspection—A satisfactory CGMP inspection is an FDA inspection during which no objectionable conditions or practices were found during (No Action Indicated), or an inspection during which objectionable conditions were found, but corrective action is left to the firm to take voluntarily, and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated). Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP reports information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing and should follow the instructions found in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at http://www.fda.gov/opacom/backgrounders/foiahand.html.

Secondary Packaging Component—A packaging component that is not and will not be in direct contact with the dosage form

Specifications—The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems and in-process materials

Validate the Effects of the Change—To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug

2 Postapproval Changes to Semisolid Drugs

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

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

It is important to define

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

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

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

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

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

Definition of level 2 changes are those that could have a significant effect on formulation quality and performance. Examples:

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

E. Change in the technical grade of structure-forming excipient
F. Change in particle size distribution of the drug substance if the drug is in suspension

Definition of level 3 changes are those that are likely to have a significant effect on formulation quality and performance. Examples:

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

I. PRESERVATIVE

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

II. MANUFACTURING CHANGES

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

III. PROCESS

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

Batch Size (Scale Up or Down)

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

IV. MANUFACTURING SITE

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

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

3 Scale-Up and Postapproval Changes for Nonsterile Semisolid Dosage Forms: Manufacturing Equipment

I. INTRODUCTION

Any equipment changes should be validated in accordance with current good manufacturing practices (CGMPs). The resulting data will be subject to examination by field investigators during routine GMP inspections. The information here is presented in broad categories of unit operation (particle size reduction or separation, mixing, emulsification, deaeration, transfer, and packaging).

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

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

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

II. PARTICLE SIZE REDUCTION AND SEPARATION

A. Definitions

1. Unit Operations

a. Particle Size Reduction

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

i. Particle

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

ii. Particle Size Reduction Mechanisms

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

b. Particle Separation

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

2. Operating Principles

a. Fluid Energy Milling

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

b. Impact Milling

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

c. Cutting

Cutting is particle size reduction by mechanical shearing.

d. Compression Milling

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

e. Screening

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

f. Tumble Milling

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

g. Separating

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

B. Equipment Classifications

1. Fluid Energy Mills

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

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

2. Impact Mills

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

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

3. Cutting Mills

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

4. Compression Mills

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

5. Screening Mills

Screening mill subclasses primarily differ in the rotating element.

- Oscillating bar
- Rotating impeller
- Rotating screen

6. Tumbling Mills

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

- Ball media
- Rod media
- Vibrating

7. Separators

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

- Centrifugal
- Vibratory or shaker

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

III. MIXING

A. Definitions

1. Unit Operation

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

2. Operating Principles

a. Convection Mixing, Low Shear

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

b. Convection Mixing, High Shear

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

c. Roller Mixing (Milling)

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

d. Static Mixing

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

B. Equipment Classification

1. Convection Mixers, Low Shear

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

- Anchor or sweepgate
- Impeller
- Planetary

2. Convection Mixers, High Shear

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

- Dispersator
- Rotor stator

3. Roller Mixers (Mills)

No roller mixer subclasses have been identified.

4. Static Mixers

No static mixer subclasses have been identified.

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

5. Low-Shear Emulsifiers

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

IV. TRANSFER

A. Definitions

1. Unit Operation

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

2. Operating Principles

a. Passive

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

b. Active

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

B. Equipment Classification

1. Low Shear

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

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

2. High Shear

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

- Centrifugal or turbine
- Piston
- Rotating gear

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

V. PACKAGING

A. Definitions

1. Unit Operation

a. Holding

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

b. Transfer

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

c. Filling

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

d. Sealing

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

2. Operating Principles

a. Holding

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

b. Transfer

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

c. Filling

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

d. Sealing

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

B. Equipment Classification

1. Holders

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

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

2. Fillers

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

- Auger
- Gear pump
- Orifice
- Peristaltic pump
- Piston

3. Sealers

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

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

4 Stability Testing of Drug Substances and Drug Products

I. INTRODUCTION

There are specific regulatory recommendations regarding the design, conduct, and use of stability studies that should be performed to support

- Investigational new drug applications (INDs) (21 CFR 312.23(a)(7))
- New drug applications (NDAs) for both new molecular entities and non–new molecular entities, new dosage forms (21 CFR 314.50(d)(1))
- Abbreviated new drug applications (ANDAs) (21 CFR 314.92–314.99)
- Supplements and annual reports (21 CFR 314.70, and 601.12)
- Biologics license application (BLAs) and product license applications (PLAs) (21 CFR 601.2)

Given below is a comprehensive description of the principle established in International Conference on Harmonisation (ICH) Q1A—that information on stability generated in any one of the three areas of the European Union, Japan, and the U.S. would be mutually acceptable in both of the other two areas. Also included here is a discussion of biological products and products submitted to the Center for Biologics Evaluation and Research (CBER). (Note that effective July 2003, the U.S. Food and Drug Administration has transferred several therapeutic proteins to the Center for Drug Evaluation and Research [CDER] from CBER.)

Given below are recommendations for the design of stability studies for drug substances and drug products that should result in a statistically acceptable level of confidence for the established retest or expiration dating period for each type of application. The applicant is responsible for confirming the originally established retest and expiration dating periods by continual assessment of stability properties (21 CFR 211.166). Continuing confirmation of these dating periods should be an important consideration in the applicant's stability program. The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the European Union, Japan, and the U.S. The mean kinetic temperature in any region of the world can be derived from climatic data (Grimm, W., *Drugs Made in Germany*, 28:196–202, 1985, and 29:39–47, 1986). [ICH Q1A]

II. STABILITY TESTING FOR NEW DRUG APPLICATIONS

A. Drug Substance

Information on the stability of a drug substance under defined storage conditions is an integral part of the systematic approach to stability evaluation. Stress testing helps to determine the intrinsic stability characteristics of a molecule by establishing degradation pathways to identify the likely degradation products and to validate the stability, indicating the power of the analytical procedures used.

Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the drug substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of the drug substance. These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual drug substance and type of drug product.

This testing is likely to be carried out on a single batch of a drug substance. Testing should include the effects of temperatures in 10°C increments above the accelerated temperature test condition (e.g., 50°, 60°C) and humidity, where appropriate (e.g., 75% or greater). In addition, oxidation and photolysis on the drug substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension should be evaluated. Results from these studies will form an integral part of the information provided to regulatory authorities. Light testing should be an integral part of stress testing. The standard test conditions for photostability are discussed in the ICH Q1B guidance.

It is recognized that some degradation pathways can be complex and that under forced conditions, decomposition products may be observed that are unlikely to be formed under accelerated or long-term testing. This information may be useful in developing and validating suitable analytical methods, but it may not always be necessary to examine specifically for all degradation products if it has been demonstrated that, in practice, these decomposition products are not formed.

Primary stability studies are intended to show that a drug substance will remain within specifications during the retest period if stored under recommended storage conditions. [ICH Q1A]

1. Selection of Batches

Stability information from accelerated and long-term testing should be provided on at least three batches. Long-term testing should cover a minimum of 12 months' duration on at least three batches at the time of submission. The batches manufactured to a minimum of pilot-plant scale should be formed by the same synthetic route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale. The overall quality of the batches of drug substance placed on stability should be representative of both the quality of the material used in preclinical and clinical studies and the quality of material to be made on a manufacturing scale. Supporting information may be provided using stability data on batches of drug substance made on a laboratory scale. [ICH Q1A]

The first three production batches of drug substance manufactured postapproval, if not submitted in the original drug application, should be placed on long-term stability studies postapproval, using the same stability protocol as in the approved drug application. [ICH Q1A]

2. Test Procedures and Test Criteria

The testing should cover those features that are susceptible to change during storage and that are likely to influence quality, safety, or efficacy. Stability information should cover, as necessary, the physical, chemical, biological, and microbiological test characteristics. Validated stability-indicating test methods should be applied. The extent of replication will depend on the results of validation studies. [ICH Q1A]

3. Specifications

Limits of acceptability should be derived from the quality profile of the material as used in the preclinical and clinical batches. Specifications will need to include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials. [ICH Q1A]

4. Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use. Application of the same storage conditions applied to the drug product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature-sensitive drug substances should be stored under an alternative lower-temperature condition, which will then become the designated long-term testing storage temperature. The 6-month accelerated testing should then be carried out at a temperature at least 15°C above this designated long-term storage temperature (together with the appropriate relative humidity conditions for that temperature). The designated long-term testing conditions will be reflected in the labeling and retest date. [ICH Q1A]

Where significant change occurs during 6 months of storage under conditions of accelerated testing at 40° ± 2°C/75% RH ± 5%, additional testing at an intermediate condition (such as 30° ± 2°C/60% RH ± 5%) should be conducted for a drug substance to be used in the manufacture of a dosage form tested for long-term at 25° ± 2°C/60% RH ± 5%, and this information should be included in the drug application. The initial drug application should include at the intermediate storage condition a minimum of 6 months of data from a 12-month study. [ICH Q1A]

Significant change at 40°C/75% RH or 30°C/60% RH is defined as failure to meet the specifications. [ICH Q1A] If any parameter fails significant change criteria during the accelerated stability study, testing of all parameters during the intermediate stability study should be performed.

If stability samples have been put into the intermediate condition but have not been tested, these samples may be tested as soon as the accelerated study shows significant change in the drug substance. Alternatively, studies in the intermediate condition would be started from the initial time point.

Where a significant change occurs during 12 months of storage at 30°C/60% RH, it may not be appropriate to label the drug substance for controlled room temperature (CRT) storage with the proposed retest period even if the stability data from the full long-term studies at 25°C/60% RH appear satisfactory. In such cases, alternate approaches, such as qualifying higher acceptance criteria for a degradant, shorter retest period, refrigerator temperature storage, or more protective container and closure, should be considered during drug development.

The long-term testing should be continued for a sufficient period of time beyond 12 months to cover all appropriate retest periods, and the further accumulated data can be submitted to the FDA during the assessment period of the drug application. [ICH Q1A]

The data (from accelerated testing or from testing at an intermediate storage condition) may be used to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. [ICH Q1A]

5. Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug substance. Testing under the defined long-term conditions will normally be

every 3 months over the first year, every 6 months over the second year, and then annually. [ICH Q1A]

6. Packaging and Containers

The containers to be used in the long-term, real-time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution. [ICH Q1A]

7. Evaluation

The design of the stability study is to establish a retest period applicable to all future batches of the bulk drug substance manufactured under similar circumstances, based on testing a minimum of three batches of the drug substance and evaluating the stability information (covering as necessary the physical, chemical, and microbiological test characteristics). The degree of variability of individual batches affects the confidence that a future production batch will remain within specifications until the retest date. [ICH Q1A]

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate, which can be done by first applying appropriate statistical tests (for example, *P* values for level of significance of rejection of more than .25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits. [ICH Q1A]

The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve. [ICH Q1A]

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under the circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a full justification for the omission is usually sufficient. [ICH Q1A]

Limited extrapolation may be undertaken of the real-time data beyond the observed range to extend the retest period at approval time, particularly where the accelerated data support this. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about such factors as the mechanism of degradation, the goodness of fit of any mathematical model, the batch size, and the existence of supportive data. Any evaluation should cover not only the assay but also the levels of degradation products and other appropriate attributes. [ICH Q1A]

8. Statements and Labeling

A storage temperature range may be used in accordance with relevant national and regional requirements. The range should be based on the stability evaluation of the drug substance. Where applicable, specific requirements should be stated, particularly for drug substances that cannot tolerate freezing. The use of terms such as "ambient conditions" or "room temperature" is unacceptable. [ICH Q1A]

A retest period should be derived from the stability information. [ICH Q1A]

B. Drug Product

1. General

The design of the stability protocol for the drug product should be based on the knowledge obtained on the behavior, properties, and stability of the drug substance and the experience gained from clinical formulation studies. The changes are likely to occur on storage, and the rationale for the selection of drug product parameters to be monitored should be stated. [ICH Q1A]

2. Selection of Batches

Stability information from accelerated and long-term testing is to be provided on three batches of the same formulation of the dosage form in the container and closure proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller (e.g., 25,000 to 50,000 tablets or capsules for solid oral dosage forms). The long-term testing should cover at least 12 months' duration at the time of submission. The manufacturing process to be used should meaningfully simulate that to be applied to large-scale production batches for marketing. The process should provide product of the same quality intended for marketing and should meet the same quality specification to be applied for release of material. Where possible, batches of the finished product should be manufactured using identifiably different batches of the drug substance. [ICH Q1A]

Data on laboratory-scale batches are not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supportive information. The first three production batches manufactured postapproval, if not submitted in the original application, should be placed on accelerated and long-term stability

studies using the same stability protocols as in the approved drug application. [ICH Q1A]

3. Test Procedures and Test Criteria

The test parameters should cover those features that are susceptible to change during storage and that are likely to influence quality, safety, or efficacy. Analytical test procedures should be fully validated, and the assays should be stability-indicating. The need for replication will depend on the results of validation studies. [ICH Q1A]

The range of testing should cover not only chemical and biological stability, but also loss of preservative efficacy, physical properties and characteristics, organoleptic properties, and, where required, microbiological attributes. Preservative efficacy testing and assays on stored samples should be carried out to determine the content and efficacy of antimicrobial preservatives. [ICH Q1A]

4. Specifications

Where applicable, limits of acceptance should relate to the release limits to be derived from consideration of all the available stability information. The shelf-life specifications could allow acceptable and justifiable deviations from the release specifications based on the stability evaluation and the changes observed on storage. They need to include specific upper limits for degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials. The justification for the limits proposed for certain other tests, such as particle size or dissolution rate, will require reference to the results observed for the batch or batches used in bioavailability or clinical studies. Any differences between the release and the shelf-life specifications for antimicrobial preservatives content should be supported by preservative efficacy testing. [ICH Q1A]

5. Storage Test Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use (e.g., reconstitution or dilution as recommended in the labeling). The recommended accelerated and long-term storage conditions and minimum times are

Long-term testing 25°C ± 2°C/60% RH ± 5% 12 Months;

Accelerated Testing 40°C ± 2°C/75% RH ± 5% 6 Months.

Assurance that long-term testing will continue to cover the expected shelf life should be provided. [ICH Q1A]

Other storage conditions are allowable if justified. Heat-sensitive drug products should be stored under an alternative lower temperature condition, which will eventually become the designated long-term storage temperature. Special consideration may need to be given to products that change physically or even chemically at lower storage temperatures (e.g., suspensions or emulsions that may sediment, or cream, oils, and semisolid preparations, which may show an increased viscosity). Where a lower temperature condition is used, the 6-month accelerated testing should be carried out at a temperature at least 15°C above its designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long-term under refrigerated conditions, accelerated testing should be conducted at 25° ± 2°C/60% RH ± 5%. The designated long-term testing conditions will be reflected in the labeling and expiration date. [ICH Q1A]

Storage under conditions of high relative humidity applies particularly to solid dosage forms. For drug products such as solutions and suspensions contained in packs designed to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary, but the same range of temperatures should be applied. Low relative humidity (e.g., 10%–20% RH) can adversely affect products packed in semipermeable containers (e.g., solutions in plastic bags, nose drops in small plastic containers), and consideration should be given to appropriate testing under such conditions. [ICH Q1A]

Where significant change occurs because of accelerated testing, additional testing at an intermediate condition (e.g., 30° ± 2°C/60% RH ± 5%) should be conducted. Significant change at the accelerated conditions is defined as

- A 5% potency loss from the initial assay value of a batch
- Any specified degradant exceeding its specification limit
- The product exceeding its pH limits
- Dissolution exceeding the specification limits for 12 capsules or tablets (USP [U.S. Pharmacopeia] Stage 2)
- Failure to meet specifications for appearance and physical properties (e.g., color, phase separation, ability to be resuspended, delivery per actuation, caking, hardness) [ICH Q1A]

Should significant change occur at 40°C/75% RH, the initial application should include a minimum of 6 months' data from an ongoing 1-year study at 30°C/60% RH; the same significant change criteria shall then apply. [ICH Q1A]

If any parameter fails significant change criteria during the accelerated stability study, testing of all parameters during the intermediate stability study should be performed.

If stability samples have been put into the intermediate condition but have not been tested, testing these samples may begin as soon as the accelerated study shows significant change in the drug product. Alternatively, the study at the

intermediate condition would be started from the initial time point.

Where a significant change occurs during 12 months of storage at 30°C/60% RH, it may not be appropriate to label the drug product for CRT storage with the proposed expiration dating period even if the stability data from the full long-term studies at 25°C/60%RH appear satisfactory. In such cases, alternate approaches, such as qualifying higher acceptance criteria for a degradant, shorter expiration dating period, refrigerator temperature storage, more protective container and closure, and modification to the formulation or manufacturing process, should be considered during drug development. If CRT storage is ultimately justified, it may be necessary to add to the product labeling a cautionary statement against prolonged exposure at or above 30°C.

The long-term testing will be continued for a sufficient period of time beyond 12 months to cover shelf life at appropriate test periods. The further accumulated data should be submitted to the FDA during the assessment period of the drug application. [ICH Q1A]

The first three production batches manufactured post-approval, if not submitted in the original application, should be placed on accelerated and long-term stability studies using the same stability protocol as in the approved drug application. [ICH Q1A] A minimum of four test stations (e.g., at 0, 2, 4, and 6 months) are recommended for the 6-month accelerated stability study.

6. Stability Storage Conditions not Defined in ICH Q1A

The stability sample storage conditions for most dosage forms (e.g., solid oral dosage forms, solids for reconstitution, dry and lyophilized powders in glass vials) are defined in Section V.E of the ICH Q1A Guidance and in Section II.B.5 of this guidance. However, the stability storage conditions are not indicated in ICH Q1A for certain other drug products including those packaged in semipermeable containers (except for accelerated studies), products intended to be stored under refrigerator or freezer temperatures, or certain studies on metered dose inhalations (MDIs) and dry powder inhalers (DPIs). Further information about these products and containers is provided in this section.

a. Stability Storage Conditions for Drug Products in Semipermeable and Permeable Containers

For large-volume parenterals (LVPs), small-volume parenterals (SVPs), ophthalmics, otics, and nasal sprays packaged in semipermeable containers, such as plastic bags, semirigid plastic containers, ampoules, vials and bottles with or without droppers or applicators, which may be susceptible to water loss, the recommended stability storage conditions are

- Accelerated condition: 40° ± 2°C/15% RH ± 5% (hereafter referred to as 40°C/15% 326 RH)[ICH Q1A]
- Intermediate condition: 30° ± 2°C/40% RH ± 5% (hereafter referred to as 30°C/40% RH)
- Long-term condition: 25C ± 2C/40% RH ± 5%

For liquids in glass bottles, vials, or sealed glass ampoules, which provide an impermeable barrier to water loss,

- Accelerated condition: 40°C/ambient humidity is an acceptable alternative to 40°C/75% RH
- Intermediate condition: 30°C/ambient humidity is an acceptable alternative to 30°C/60% RH
- Long-term condition: 25°C/ambient humidity is an acceptable alternative to 25°C/60% RH

b. Stability Storage Conditions for Drug Products Intended to be Stored at Refrigerator Temperature

- Accelerated conditions: 25°C/60% RH, with ambient humidity an acceptable alternative for aqueous products that would not be affected by humidity conditions
- Long-term conditions: 5° ± 3°C, with monitoring, but not control of, humidity

c. Stability Storage Conditions for Drug Products Intended to be Stored at Freezer Temperature

- Accelerated conditions: 5° ± 3°C/ambient humidity
- Long-term conditions: −15° ± 5°C

d. Stability Storage Conditions for Some Inhalation Products

Additional storage conditions may apply to inhalation powders and suspension inhalation aerosols when significant change in aerodynamic particle size distribution or in dose content uniformity occurs at accelerated conditions (40°C/75% RH). (At present, the agency is developing a draft guidance to address chemistry, manufacturing, and controls documentation for MDIs and DPIs.)

7. Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug product. Testing will normally be every 3 months over the first year, every 6 months over the second year, and then annually. Matrixing or bracketing can be used if justified. [ICH Q1A] A minimum of four test stations (e.g., at 0, 2, 4, and 6 months)

are recommended for the 6-month accelerated stability study.

8. Application of ICH Stability Study Storage Conditions to Approved Applications

Although the ICH Guidance for *Stability Testing of New Drug Substances and Products* applies only to new molecular entities and associated drug products, applicants may wish to voluntarily switch to the ICH-recommended storage conditions as defined in ICH Q1A or other FDA-recommended conditions as described in Section II.B.6, as appropriate, for previously approved drug or biologic products. Applicants are not required to make such a switch for either annual stability batches or batches intended to support supplemental changes. Although the following discussions refer only to the ICH conditions, the same recommendations can be applied when a switch to other FDA-recommended conditions is contemplated.

Two plans are presented to assist applicants who desire to switch their approved drug products to the ICH-recommended storage conditions. Under each plan, recommendations will be made on how to initiate a switch to the ICH storage testing conditions, select batches, collect data, report results, and proceed if products fail the approved specifications under the ICH conditions.

a. Plan A: Using the ICH Storage Testing Conditions for an Approved Stability

This plan may be most suitable for drug products that have been confirmed to be stable when exposed to the controlled level of humidity on a long-term basis. Only one set of conditions (i.e., the ICH conditions) and one set of testing for each of the three verification batches, as defined below, are necessary under this plan.

i. Drug Products with an Approved Stability Protocol

Applicants who have previously performed drug product stability studies under an approved protocol at 25°, 30°, or 25°–30°C without humidity controls may switch over to the ICH long-term conditions, as defined in V.E. of the ICH Q1A guidance and incorporated in Section II.B of this guidance, for all of their annual stability studies. A revised stability protocol may be submitted in the annual report, reflecting changes in temperature and humidity to conform to those recommended by the ICH. Any other changes to the stability protocol should be submitted as a Prior Approval Supplement. Once adopted through an annual report, the ICH conditions should be used to generate stability data for subsequent supplemental changes. Alternatively, the applicant may report the ICH switch in a supplement, which requires stability data, if the supplement occurs before the next scheduled annual report. Data from the first three consecutive annual batches after the switch can be used to verify the previously approved expiration dating period. However, if the applicant wishes to verify product stability under the ICH conditions over a shorter time span, three production batches within 1 year, instead of three consecutive annual batches, may be studied.

ii. Products without an Approved Stability Protocol

Applicants who have previously performed stability studies on a drug product without an approved protocol are required to submit an appropriate protocol under a Prior Approval Supplement under 21 CFR 314.70(b) or (g) or 601.12(b) (see Section V regarding an Approved Stability Protocol). On approval of the protocol, applicants may initiate stability studies on all annual batches under the ICH long-term conditions. Data from the first three consecutive annual batches after the switch can be used to verify the current—or establish a new—expiration dating period. However, if the applicant wishes to verify product stability under the ICH conditions over a shorter time span, three production batches within 1 year, instead of three consecutive annual batches, may be studied

iii. Stability Data for Supplemental Changes

Stability data submitted in support of supplemental changes for an existing drug product may be generated with samples stored at the ICH-recommended accelerated testing conditions, long-term testing conditions, and, if applicable, intermediate conditions, as described in V.E of the ICH Q1A guidance (Section II.B or Section III.B).

iv. Other Considerations

For a moisture-sensitive product, the applicant may wish to explore the possibility of improving the container and closure before embarking on the switch to the ICH condition.

Although 30°C/60% RH is an acceptable alternative to 25°C/60% RH for long-term studies, these conditions should not be used as the basis for a labeling statement such as "store at 30°C" or "store at 15°–30°C" to gain marketing advantage.

With respect to ongoing stability studies, applicants may carry them to completion under the previously approved conditions or may, for practical or economic reasons, choose to make an immediate switch to ICH conditions and report the change in the next annual report.

v. Data Submission to the FDA

Satisfactory Data If the stability data generated on the first three annual batches after the switch to the ICH-recommended long-term testing conditions using an approved protocol, as defined above, support the previously approved expiration dating period under the non-ICH conditions, the data can be submitted in the next annual report, and the current expiration dating period can be retained.

Unsatisfactory Data If the stability data under the ICH conditions fall outside the specifications established for the previously approved expiration dating period, the

applicant should perform an investigation to determine the probable cause of the failure in accordance with current good manufacturing practices (CGMPs) regulations under 21 CFR 211.192. In addition, the applicant should submit an NDA Field-Alert Report in accordance with 21 CFR 314.81(b)(1)(ii) or an error and accident report for a biological product under 21 CFR 600.14. A recall of the corresponding product in the marketplace may also be necessary. If it is determined that the ICH storage conditions, particularly the added humidity, are the cause for the stability failure, the applicant may shorten the expiration dating period in a Changes Being Effected Supplement while retaining the ICH storage condition. Subsequently, if justified, the applicant may request an approval for a revision of the product specifications and for reinstating the previously approved expiration dating period under the non-ICH conditions through a Prior Approval Supplement. Other measures (e.g., more protective container and closure, or product reformulation) may be considered through a Prior Approval Supplement.

Alternatively, the applicant may, after careful consideration of all aspects, request for a return to the previous storage conditions in a Changes Being Effected Supplement if justification, including all related data and investigational results, is provided.

b. Plan B: Using the ICH Conditions under an Alternate Protocol

An alternative to Plan A is to conduct two side-by-side studies by simultaneously placing samples from the same batch of drug product under the ICH conditions as well as the previously approved storage condition. The protocol containing the ICH storage conditions is considered an alternative to the approved protocol. This plan may prove to be particularly useful if the drug product is believed to be sensitive to moisture.

i. Products with an Approved Stability Protocol

Applicants may initiate stability studies under the ICH-recommended long-term testing conditions, in addition to the previously approved conditions at 25°, 30°, or 25°–30°C without humidity controls, for three consecutive annual batches. Data from these annual batches under the ICH conditions should be used to verify the current expiration dating period. However, if the applicant wishes to verify the ICH conditions over a shorter time span, three production batches within 1 year or less may be selected, instead of three consecutive annual batches.

ii. Products without an Approved Stability Protocol

Applicants who have previously performed stability studies on a drug product without an approved protocol should submit an appropriate protocol as a Prior Approval Supplement. This protocol should contain 25°C/ambient humidity as the primary long-term storage testing conditions, and the ICH long-term conditions as the alternative, as well as the ICH-recommended accelerated testing conditions. On approval of the protocol, applicants may initiate stability studies on three consecutive annual batches at both 25°C/ambient humidity and 25°C/60% RH or 25°C/40% RH. Data from these annual batches under the ICH conditions can be used to verify the current—or establish a new—expiration dating period.

iii. Other Considerations

Same as in Plan A.

iv. Protocol Revisions

Products with an Approved Stability Protocol Applicants who have an approved stability protocol may submit the alternate stability protocol in the annual report, reflecting the temperature and humidity as recommended by the ICH. Other changes to the stability protocol generally should be submitted in a Prior Approval Supplement, unless the changes are to comply with the current compendium.

Once adopted as an alternate protocol through an annual report, the ICH conditions can be used, in parallel with the previously approved conditions, to generate stability data for subsequent supplemental changes. Alternatively, the applicant may report the alternative ICH conditions in a supplement, which requires stability data, if the supplement occurs before the next scheduled annual report.

If the complete stability data generated on the first three annual batches under the ICH long-term conditions using an approved alternate protocol (as defined above) support the previously approved expiration dating period under the non-ICH conditions, the alternate stability protocol can be adopted as the primary stability protocol through an annual report.

Products without an Approved Stability Protocol For applications that do not contain an approved stability protocol as defined above, a new or revised stability protocol may be submitted in a Prior Approval Supplement marked "expedited review requested." This protocol should encompass 25°C/ambient humidity as the primary long-term storage conditions, and the ICH long-term conditions as the alternate, as well as accelerated stability storage conditions as defined by the ICH Guidance and above, in addition to other recommendations described in this guidance. On approval of the protocol, stability studies may be initiated on annual batches and on batches intended to support supplemental changes.

v. Stability Data for Supplemental Changes

Applicants may provide stability data in support of post-approval supplemental changes with samples stored at the ICH-recommended accelerated testing conditions and long-term testing conditions, both previously approved and ICH, as well as, if applicable, intermediate conditions. See Change in Stability Protocol (Section IX.J) for the recommended filing mechanism.

vi. Data Submission

Satisfactory Data If the complete stability data generated on the first three annual batches under the ICH long-term conditions using an approved alternate protocol support the previously approved expiration dating period under the non-ICH conditions, the data can be submitted in the annual report and the current expiration dating period can be retained.

Unsatisfactory Data If the stability data under the ICH conditions fall outside the acceptance criteria while data from the parallel study under the previously approved conditions or 25°C/ambient humidity, whichever applies, are satisfactory during the previously approved expiration dating period, and the added humidity is determined to be the cause for the stability failure, the product will still be considered to be in compliance with the regulatory specifications approved in the application. If the applicant decides to adopt the ICH conditions, a Changes Being Effected Supplement with a shortened expiration dating period or a Prior Approval Supplement with revised product specifications may be submitted where justified. Other measures (e.g., more protective container and closure or product reformulation) may be considered through a Prior Approval Supplement.

Alternatively, after careful consideration of all aspects, the applicant may decide not to pursue the switch to the ICH conditions for the product. The applicant may eliminate the alternate stability protocol in the next annual report if a full explanation, including all related data and investigational results, is provided.

In the case where the product fails to meet the specifications under the non-ICH conditions, irrespective of whether it also fails under the ICH conditions, a thorough investigation in accordance with CGMP should be performed and appropriate corrective actions should be taken, including a Field-Alert Report and recall of the affected product from the marketplace if warranted.

9. Packaging Materials [ICH Q1A]

The testing should be carried out in the final packaging proposed for marketing. Additional testing of the unprotected drug product can form a useful part of the stress testing and package evaluation, as can studies carried out in other related packaging materials in supporting the definitive pack or packs.

10. Evaluation [ICH Q1A]

A systematic approach should be adopted in the presentation of the evaluation of the stability information, which should cover, as necessary, physical, chemical, biological, and microbiological quality characteristics, including particular properties of the dosage form (e.g., dissolution rate for oral solid dose forms).

The design of the stability study is to establish a shelf life and to label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances based on testing a minimum of three batches of the drug product. The degree of variability of individual batches affects the confidence that a future production batch will remain within specifications until the expiration date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it may be advantageous to combine the data into one overall estimate by first applying appropriate statistical tests (e.g., *P* values for level of significance of rejection of more than .25) to the slopes of the regression lines and zero time intercepts for the individual batches. If combining data from several batches is inappropriate, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function of an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and, combined batches (where appropriate) to the assumed degradation line or curve.

Where the data show so little degradation and so little variability that it is apparent from looking at the them that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis, but a justification for the omission should be provided.

Limited extrapolation may be taken of the real-time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data support this. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and, hence, the use of extrapolation must be justified in each application in terms of what is known about such factors as the mechanism of degradation, goodness of fit of any mathematical model, batch size, and existence of supportive data.

Any evaluation should cover not only the assay but also the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance, different stability, and degradation performance.

The stability of the drug product after reconstituting or diluting according to labeling should be addressed to provide appropriate and supportive information. See Section VIII.N for additional information on drug products that are reconstituted or diluted.

11. Statements and Labeling

A storage temperature range may be used in accordance with FDA regulations. The range should be based on the stability evaluation of the drug product. Where applicable, specific requirements should be stated, particularly for drug products that cannot tolerate freezing.

The use of terms such as "ambient conditions" or "room temperature" is unacceptable. There should be a direct linkage between the label statement and the demonstrated stability characteristics of the drug product. A single set of uniform storage statements for NDAs, ANDAs, PLAs, and BLAs is recommended to avoid different labeling storage statements for products stored under controlled room-temperature conditions. The storage statements and storage conditions listed in this section are intended to be standardized and harmonized with the CRT definition in the USP and the recommendations in the ICH guidance.

a. Room Temperature Storage Statements

i. Liquid Dosage Forms in Semipermeable Containers

The recommended storage statement for LVPs, SVPs, ophthalmics, otics, and nasal sprays packaged in semipermeable containers, such as plastic bags, semirigid plastic containers, ampoules, vials, and bottles with or without droppers or applicators, that may be susceptible to water loss but that have been demonstrated to be stable at 25° ± 2°C/40% or 60% RH ± 5% (or 30° ± 2°C/40% or 60% RH ± 5%); at 25°C/NMT 40% or 30°C/NMT 40% RH; or at 30°, 25°–30°, or 25°C without humidity controls, is:

> Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

For sterile water for injection and LVP solutions of inorganic salts packaged in semipermeable containers (e.g., plastic bags), the following statement may be used on the immediate container labels:

> Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature] (see insert for further information),

and the following statement may be used in the "How Supplied" section of the package insert:

> Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

Brief exposure to temperatures up to 40°C/104°F may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F). However, such exposure should be minimized.

LVP solutions packaged in a semipermeable container (e.g., a plastic bag) and containing simple organic salts (e.g., acetate, citrate, gluconate, and lactate, and dextrose 10% or less) may be labeled as above, provided there are adequate stability data (at least 3 months at 40° ± 2°C/15% RH ± 5% or 40°C/NMT 20% RH) to support such labeling.

ii. All Other Dosage Forms

For all other dosage forms (e.g., solid oral dosage forms, dry powders, aqueous liquid, semisolid, and suspension dosage forms) that have been demonstrated to be stable at the ICH-recommended conditions (25° ± 2°C/60% RH ± 5%, or 30°C/60% RH ± 5%) or at non-ICH conditions, such as 30°, 25°–30°, or 25°C without humidity controls and intended to be stored at room temperature, the recommended labeling statement is

> Store at 25°C (77°EF); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

iii. Where Space on the Immediate Container is Limited

Where an abbreviated labeling statement is necessary because space on the immediate container is limited, either of the following statements is acceptable provided the full labeling statement, as shown above, appears on the outer carton and in the package insert:

> Store at 25°C (77°F); excursions 15°–30°C (59°–86°F);
>
> Store at 25°C (77°F) (see insert).

b. Refrigerator Storage Statement

For a drug product demonstrated to be stable at 5° ± 3°, 2°–5°, or 2°–8°C with or without humidity control and that is intended to be stored at refrigerator temperature, the recommended storage statement for labeling may be one of the following:

> Store in a refrigerator, 2°–8°C (36°–46°F);
>
> Store refrigerated, 2°–8°C (36°–46°F).

Where an abbreviated labeling statement is necessary because space on the immediate container is limited, the following statement is acceptable, provided one of the full labeling statements, as shown above, appears on the outer container and in the package insert:

> Refrigerate (see insert).

c. Room Temperature or Refrigerator Storage Statement

For a drug product demonstrated to be stable both at 25° ± 2°C/60% RH ± 5% and at refrigerator temperature, both of the room temperature and refrigerator labeling statements, as described above, are acceptable, depending on the storage conditions intended for the product. A statement such as "store at 2°–25°C" is not recommended.

d. Additional Cautionary Statements

If warranted, additional cautionary statements to protect a drug product from excessive heat, light, humidity, freezing, and other damaging conditions should be included on the container label and the package insert. If the space on the container label is too limited to display all the recommended statements in detail, a reference to the package insert for further information (e.g., "see insert") is recommended.

e. Other Considerations

The applicant may wish to include the definition of USP CRT in its entirety in the package insert to provide easy reference.

f. Implementation of the Uniform Storage Statements in Labeling for New Product Applications

The recommended storage statements in labeling should be adopted for new or pending NDA, ANDA, BLA, or PLA products. For applications approved before the publication of the guidance, the recommended storage statements should be adopted through the annual report mechanism at the next printing opportunity if desired, but within 3 years of the date of the final guidance. With respect to room temperature storage statements for already approved products, new stability studies under the ICH conditions are not required to adopt the recommended room temperature labeling statements, provided the products have been demonstrated to be stable through expiry under one of the following controlled temperatures: 30°, 25°–30°, and 25°C, and at ambient humidity.

C. New Dosage Forms [ICH Q1C]

A new dosage form is defined as a drug product that is a different pharmaceutical product type but that contains the same active substance as included in an existing drug product approved by the FDA.

New dosage forms include products of different administration route (e.g., oral, when the original new drug product was a parenteral), new specific functionality and delivery system (e.g., modified release tablet, when the original new drug product was an immediate release tablet), and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension).

Stability protocols for new dosage forms should follow the guidance in the ICH Q1A in principle. However, a reduced stability database at submission time (e.g., 6 months' accelerated and 6 months' long-term data from ongoing studies) may be acceptable in certain justified cases.

D. Other NDAs

Stability protocols for new combination products or new formulations (which require clinical data for approval) should follow the guidance in the ICH Q1A in principle. However, a reduced stability database at submission time (e.g., 6 months' accelerated and 6 months' data from ongoing studies at the long-term condition) may be acceptable in certain justified cases, such as when there is a significant body of information on the stability of the drug product and the dosage form.

III. STABILITY TESTING FOR ABBREVIATED NDAs

Much of the general information provided in this guidance is applicable to ANDAs. However, depending on the availability of significant information on, and the complexity of, these drug products and dosage forms, the amount of information necessary to support these applications may vary from that proposed for NDAs. This section is intended to provide specific recommendations on abbreviated applications.

A. Drug Substance Stability Data Submission

For drug products submitted under an ANDA, including antibiotics, supporting information may be provided directly to the drug product ANDA or by reference to an appropriately referenced drug master file. Publications may be provided or referenced as supportive information. For ANDA bulk drug substances, stability data should be generated on a minimum of one pilot-scale batch. All batches should be made using equipment of the same design and operating principle as the manufacturing-scale production equipment, with the exception of capacity. For ANDA bulk drug substances produced by fermentation, stability data should be provided on three production batches, at least two of which should be generated from different starter cultures.

B. Drug Substance Testing

A program for stability assessment may include storage at accelerated, long-term, and, if applicable, intermediate stability study storage conditions (refer to IV.G of the ICH Q1A Guidance and Section II.A). Stability samples should be stored in the bulk storage container equivalent (e.g., same composition and type of container, closure, and liner, but smaller in size).

If not previously generated or available by reference, stress-testing studies should be conducted to establish the inherent stability characteristics of the drug substance and support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual drug substance, type of drug product, and available supporting information. Any necessary testing may be carried out as described in Section II.A.

C. Drug Product

Original ANDAs should contain stability data generated under the long-term and accelerated stability storage conditions delineated in V.E of the ICH Q1A guidance (Section II.B of this chapter). The data package for ANDAs (e.g., the number of batches; the length of studies needed at submission and at approval; and the accelerated, intermediate, and long-term stability data) should be based on several factors, including the complexity of the dosage form, the existence of a significant body of information for the dosage form, and the existence of an approved application for a particular dosage form.

D. ANDA Data Package Recommendations

For simple dosage forms, the following stability data package is recommended:

- Accelerated stability data at 0, 1, 2, and 3 months: A tentative expiration dating period of up to 24 months will be granted based on satisfactory accelerated stability data unless not supported by the available long-term stability data
- Long-term stability data (available data at the time of original filing and subsequent amendments)
- A minimum of one batch; pilot scale
- Additional stability studies (12 months at the intermediate conditions or long-term data through the proposed expiration date) if significant change is seen after 3 months during the accelerated stability study; the tentative expiration dating period will be determined on the basis of the available data from the additional study

E. Exceptions to the ANDA Data Package Recommendations

The following may be considered exceptions to the general ANDA recommendations:

- Complex dosage forms, such as modified-release products, transdermal patches, and metered-dose inhalers
- Drug products without a significant body of information
- New dosage forms submitted through the ANDA suitability petition process (Q1C applications)
- Other exceptions may exist and should be discussed with the Office of Generic Drugs

An ANDA that is determined to be one of the above categories should contain a modified ICH Q1A stability data package, including

- 3-month accelerated stability studies
- Long-term stability studies (available data at the time of original filing and subsequent amendments): The expiration dating period for complex dosage forms will be determined on the basis of available long-term stability data submitted in the application
- A minimum of three batches manufactured in accordance with the ICH Q1A batch size recommendations (refer to V.B of the ICH Q1A guidance and Section II.B of this chapter)
- Additional stability studies (12 months at the intermediate conditions or long-term stability testing through the proposed expiration date) if significant change is seen after 3 months during the accelerated stability studies (the tentative expiration dating period will be determined based on the available data from the additional studies)

F. Data Package for Approval

Full-term stability testing of the primary stability batch or batches is suggested. However, in the absence of full-term stability data for the drug product, adequate accelerated stability data combined with available long-term data can be used as the basis for granting a tentative expiration dating period. The batch or batches used for stability testing should comply fully with the proposed specifications for the product and be packaged in the market package, and the release assay should be within reasonable variation (taking into account inherent assay variability) from the labeled strength or theoretical strength of the reference-listed drug. If formulated with an overage, the overage should be justified as necessary to match that of the reference-listed drug.

Other supportive stability data may be submitted on drug product batches that may or may not meet the above criteria. Data on relevant research batches, investigational formulations, or alternate container and closure systems, or from other related studies, may also be submitted to support the stability of the drug product. The supportive stability data should be clearly identified.

G. Stability Study Acceptance

If the results are satisfactory, a tentative expiration dating period of up to 24 months at the labeled storage conditions may be granted. Where data from accelerated studies are used to project a tentative expiration dating period that is beyond a date supported by actual long-term studies on production batches, the application should include a commitment to conduct long-term stability studies on the first three production batches and annual batches until the tentative expiration dating period is verified or the appropriate expiration dating period is determined. Extension of the

tentative expiration dating period should be based on data generated on at least three production batches tested according to the approved protocol outlined in the stability commitment. Reporting of the data should follow Section VI of this guidance.

ANDAs withdrawn before publication of this guidance should not normally have to include stability data in conformance with the guidance on resubmission if the original application was withdrawn because of non–stability-related issues. However, if new stability studies are conducted to support the submission, such studies should be conducted as recommended in the guidance.

IV. STABILITY TESTING FOR INVESTIGATIONAL NDAs

The regulation at 312.23(a)(7) emphasizes the graded nature of manufacturing and controls information. Although in each phase of the investigation, sufficient information should be submitted to ensure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to achieve that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. Therefore, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited.

It is recognized that modifications to the method of preparation of the new drug substance and dosage form, and even changes in the dosage form itself, are likely as the investigation progresses. In an initial phase 1 Chemistry, Manufacturing and Control section (CMC) submission, the emphasis should generally be placed on providing information that will allow evaluation of the safety of subjects in the proposed study. The identification of a safety concern or insufficient data to make an evaluation of safety are the only reasons for placing a trial on clinical hold based on the CMC section.

A. Phase 1

Information to support the stability of the drug substance during the toxicologic studies and the proposed clinical study or studies should include a brief description of the stability study and the test methods used to monitor the stability of the drug substance, and preliminary tabular data based on representative material. Neither detailed stability data nor the stability protocol need to be submitted.

Information to support the stability of the drug product during the toxicologic studies and the proposed clinical study or studies should include a brief description of the stability study and the test methods used to monitor the stability of the drug product packaged in the proposed container and closure system, and storage conditions and preliminary tabular data based on representative material. Neither detailed stability data nor the stability protocol need to be submitted.

When significant decomposition during storage cannot be prevented, the clinical trial batch of drug product should be retested before the initiation of the trial, and information should be submitted to show that it will remain stable during the course of the trial. This information should be based on the limited stability data available when the trial starts. Impurities that increase during storage may be qualified by reference to prior human or animal data.

B. Phase 2

Development of drug product formulations during phase 2 should be based in part on the accumulating stability information gained from studies of the drug substance and its formulations.

The objectives of stability testing during phases 1 and 2 are to evaluate the stability of the investigational formulations used in the initial clinical trials, to obtain the additional information needed to develop a final formulation, and to select the most appropriate container and closure (e.g., compatibility studies of potential interactive effects between the drug substance or substances and other components of the system). This information should be summarized and submitted to the IND during phase 2. Stability studies on these formulations should be well underway by the end of phase 2. At this point the stability protocol for study of both the drug substance and drug product should be defined, so that stability data generated during phase 3 studies will be appropriate for submission in the drug application.

C. Phase 3

In stability testing during phase 3 IND studies, the emphasis should be on testing final formulations in their proposed market packaging and manufacturing site based on the recommendations and objectives of this guidance. It is recommended that the final stability protocol be well defined before the initiation of phase 3 IND studies. In this regard, consideration should be given to establishing appropriate linkage between the preclinical and clinical batches of the drug substance and drug product and those of the primary stability batches in support of the proposed expiration dating period. Factors to be considered may include, for example, source, quality and purity of various components of the drug product, manufacturing process of and facility for the drug substance and the drug product, and use of same containers and closures.

V. APPROVED STABILITY PROTOCOL

A. Stability Protocol

An approved stability protocol is a detailed plan described in an approved application that is used to generate and analyze stability data to support the retest period for a drug substance or the expiration dating period for a drug product. It also may be used in developing similar data to support an extension of that retest or expiration dating period via annual reports under 21 CFR 314.70(d)(5). If needed, consultation with FDA is encouraged before the implementation of the stability protocol.

To ensure that the identity, strength, quality, and purity of a drug product are maintained throughout its expiration dating period, stability studies should include the drug product packaged in the proposed containers and closures for marketing as well as for physician or promotional samples. The stability protocol may also include an assessment of the drug product in bulk containers to support short-term storage before packaging in the market container.

The stability protocol should include methodology for each parameter assessed during the stability evaluation of the drug substance and the drug product. The protocol should also address analyses and approaches for the evaluation of results and the determination of the expiration dating period, or retest period. The stability-indicating methodology should be validated by the manufacturer and described in sufficient detail to permit validation or verification by FDA laboratories.

The stability protocol for both the drug substance and the drug product should be designed in a manner to allow storage under specifically defined conditions. For the drug product, the protocol should support a labeling storage statement at CRT, refrigerator temperature, or freezer temperature. See Sections II.B.5 and 6.

A properly designed stability protocol should include the following information:

- Technical grade and manufacturer of drug substance and excipients
- Type, size, and number of batches
- Type, size, and source of containers and closures
- Test parameters
- Test methods
- Acceptance criteria
- Test time points
- Test storage conditions
- Container storage orientations
- Sampling plan
- Statistical analysis approaches and evaluations
- Data presentation
- Retest or expiration dating period (proposed or approved)
- Stability commitment

The use of alternative designs, such as bracketing and matrixing, may be appropriate (see Sections VII.G and H).

At the time of a drug application approval, the applicant has probably not yet manufactured the subject drug product repeatedly on a production scale or accrued full long-term data. The expiration dating period granted in the original application is based on acceptable accelerated data, statistical analysis of available long-term data, and other supportive data for an NDA or is based on acceptable accelerated data for an ANDA. It is often derived from pilot-scale batches of a drug product or from less-than-full long-term stability data. An expiration dating period assigned in this manner is considered tentative until confirmed with full long-term stability data from at least three production batches reported through annual reports. The stability protocol approved in the application is then crucial for the confirmation purpose.

B. Stability Commitment

A stability commitment is acceptable when there are sufficient supporting data to predict a favorable outcome with a high degree of confidence, such as when an application is approved with stability data available from pilot-plant batches, when a supplement is approved with data that do not cover the full expiration dating period, or as a condition of approval. This commitment constitutes an agreement to

1. Conduct or complete the necessary studies on the first three production batches and annual batches thereafter of each drug product, container, and closure according to the approved stability protocol through the expiration dating period
2. Submit stability study results at the time intervals and in the format specified by the FDA, including the annual batches
3. Withdraw from the market any batches found to fall outside the approved specifications for the drug product. If the applicant has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, the applicant should immediately discuss it with the appropriate chemistry team and provide justification for the continued distribution of that batch; the change or deterioration in the distributed drug or biological product must be reported under 21 CFR 314.81(b)(1)(ii) or 21 CFR 601.14, respectively

For postapproval changes, items 2 and 3 remain the same and item 1 becomes

1. Conduct or complete the necessary studies on the appropriate number of batches

The amount of stability data supplied will depend on the nature of the change being made. Applicants may determine the appropriate data package by consulting the Postapproval Changes section of this guidance (Section IX) and in consultation with the appropriate chemistry review team.

The approved stability protocol should be revised as necessary to reflect updates to USP monographs or the current state of the art regarding the type of parameters monitored, the acceptance criteria of such parameters, and the test methodology used to assess such parameters. However, other modifications are discouraged until the expiration dating period granted at the time of approval has been confirmed by long-term data from production batches. Once a sufficient database is established from several production batches to confirm the originally approved expiration dating period, it may be appropriate to modify the stability protocol (see Section IX.J).

VI. REPORTING STABILITY DATA

A. General

Stability data should be included in the application (NDA, ANDA, BLA, PLA, IND, supplement) they are intended to support. The extent of stability data expected at the time of submission is discussed at length throughout this guidance. Additional data from ongoing studies and regular annual batches should be included in the application's annual report.

Annual reports should include new or updated stability data generated in accordance with the approved stability protocol. These data may include accelerated and long-term studies for each product to satisfy the standard stability commitment made in the original or supplemental application, including the annual batch or batches, and to support postapproval changes. The data should be presented in an organized, comprehensive, and cumulative format.

B. Content of Stability Reports

It is suggested that stability reports include the following information and data to facilitate decisions concerning drug product stability:

1. General product information
   - Name, source, manufacturing sites, and date of manufacture of drug substance and drug or biological product
   - Dosage form and strength, including formulation: The application should provide a table of specific formulations under study, and when more than one formulation has been studied, the formulation number is acceptable
   - Composition, type, source, size, and adequate description of container and closure; stuffers, seals, and desiccants should also be identified
2. Specifications and test methodology information
   - Physical, chemical, and microbiological attributes and regulatory specifications (or specific references to NDA, BLA, PLA, or USP)
   - Test methodology used (or specific reference to IND, ANDA, NDA, BLA, PLA prior submissions, or USP) for each sample tested
   - Information on accuracy, precision, and suitability of the methodology (cited by reference to appropriate sections)
   - Where applicable, a description of the potency test or tests for measuring biological activity, including specifications for potency determination
3. Study design and study conditions
   - Description of the sampling plan, including
     - Batches and number selected
     - Container and closures and number selected
     - Number of dosage units selected and whether tests were conducted on individual units or on composites of individual units
     - Sampling time points
     - Testing of drug or biological products for reconstitution at the time of reconstitution (as directed on the labeling) as well as through their recommended use periods
   - Expected duration of the study
   - Conditions of storage of the product under study (e.g., temperature, humidity, light, container orientation)
4. Stability data and information
   - Batch number (research, pilot, production) and associated manufacturing date
   - For antibiotic drug products, the age of the bulk active drug substance or substances used in manufacturing the batch
   - Analytical data, source of each data point, and date of analysis (e.g., batch, container, composite, etc); pooled estimates may be submitted if individual data points are provided
   - Individual data as well as mean and standard deviation should be reported
   - Tabulated data by storage condition
   - Summary of information on previous formulations during product development; this summary may be referenced (if previously submitted) and should include other containers and closures investigated
5. Data analysis: The following data analysis of quantitative parameters should be provided:
   - Evaluation of data, plots, or graphics

Documentation of appropriate statistical methods and formulas used
Results of statistical analysis and estimated expiration dating period
Results of statistical tests used in arriving at microbiological potency estimates

6. Conclusions
Proposed expiration dating period and its justification
Regulatory specifications (establishment of acceptable minimum potency at the time of initial release for full expiration dating period to be warranted)

C. Formatting Stability Reports

Submitted information should be cumulative and in tabular form.

VII. SPECIFIC STABILITY TOPICS

A. Mean Kinetic Temperature

1. Introduction

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act states that a drug shall be deemed to be adulterated if the facilities or controls used for holding drugs do not conform to or are not operated or administered in conformity with good manufacturing practice to ensure that such drugs meet the requirements of the Act as to safety and have the identity and strength, and meet the quality and purity characteristics, that they purport to or are represented to possess. This applies to all persons engaged in manufacture and holding, that is, storage, of drugs.

CGMP regulations applicable to drug manufacturers (21 CFR 211.142) state that written procedures describing the warehousing of drug products shall be established and followed. These regulations also state that such procedures shall include instructions for the storage of drug products under appropriate conditions of temperature, humidity, and light so the identity, strength, quality, and purity of the drug products are not affected.

The regulation governing state licensing of wholesale prescription drug distributors (21 CFR 205.50 (c)) states that all prescription drugs shall be stored at appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the USP/NF. The regulation also states that if no storage requirements are established for a prescription drug, the drug may be held at CRT, as defined in an official compendium, to help ensure that its identity, strength, quality, and purity are not adversely affected (21 CFR 205.50 (c)(1)).

Mean kinetic temperature (MKT) is defined as the isothermal temperature that corresponds to the kinetic effects of a time–temperature distribution. The Haynes formula can be used to calculate the MKT. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Haynes derived his formula. Thus, MKT is the single calculated temperature that simulates the nonisothermal effects of storage temperature variations. This section of the guidance explains how to calculate MKT. It also recommends a course of action should a facility containing products that are labeled for CRT storage fail to maintain the drugs at appropriate temperature conditions as defined in this guidance. Because MKT is intended to provide guidance on temperature control of drug storage facilities and is not correlated to any specific lot of drug product in the storage facility, an MKT in excess of 25°C does not, on its own, infer that CGMPs have been violated.

Any time the yearly MKT of a facility approaches 25°C, the occurrence should be documented, the cause for such an occurrence should be investigated, and corrective actions should be taken to ensure that the facility is maintained within the established conditions for drug product storage. The FDA recognizes that, when the yearly MKT of a facility begins to exceed 25°C, it may not necessarily have an effect on products that have been stored for less than 1 year at the time, but it should be a warning that the facility itself may not be under adequate control.

In addition, whenever the recorded temperature (as opposed to the calculated MKT) exceeds the allowable excursions of 15°–30°C in a facility that contains drugs labeled for storage at CRT, the occurrence should be documented. The cause for such an occurrence should be investigated and corrective actions taken to ensure that the facility is maintained within the established conditions for drug product storage. The FDA recognizes that brief spikes outside of 15°–30°C may, in fact, be expected from time to time in the real world and may not necessarily have an effect on product quality. However, depending on the duration and extent of such an exposure and the dosage form, it may be necessary to determine whether the product quality has been adversely affected.

B. Container and Closure

Stability data should be developed for the drug product in each type of immediate container and closure proposed for marketing, promotion, or bulk storage. The possibility of interaction between the drug and the container and closure and the potential introduction of extractables into the drug product formulations during storage should be assessed during container and closure qualification studies using sensitive and quantitative procedures. These studies are recommended even if the container and closure meet compendial suitability tests, such as those

outlined in the USP for plastic containers and elastomeric or plastic closures.

1. Container and Closure Size

Stability data for a given strength may be bracketed by obtaining data for the smallest and the largest container and closure to be commercially marketed, provided that the intermediate container and closure is of comparable composition and design (Section VII.G).

Physician or promotional samples that are in different containers and closures or sizes from the marketed package should be included in the stability studies. Samples in similar container closure systems may be included in bracketing or matrixing studies (Section VII.H). For solid oral dosage forms packaged in large containers (i.e., those not intended for direct distribution to the patient), full stability studies should be performed if further packaging by health institutions or contract packagers is anticipated. Samples for stability testing at different time points may be taken from the same container. Stability data also may be necessary when the finished dosage form is stored in interim bulk containers before filling the marketed package. If the dosage form is stored in bulk containers for over 30 days, real-time stability data under specified storage conditions should be generated to demonstrate comparable stability to the dosage form in the marketed package. Interim storage of the dosage form in bulk containers should generally not exceed 6 months. The computation of the expiration dating period of the final marketed product should begin within 30 days of the date of production (see Glossary) of the dosage form, as defined in the section on Computation of Expiration Date (Section VII.F.1), irrespective of the packaging date. If the dosage form is shipped in bulk containers before final packaging, a simulated study may be important to demonstrate that adverse shipping or climatic conditions do not affect its stability.

2. Container Orientations

Solutions (i.e., oral, SVPs, LVPs, oral and nasal inhalations, and topical preparations), dispersed systems (oral, MDIs, injectables), and semisolid drug products (topical, ophthalmics, and otics) should be stored in both the upright and either inverted or on-the-side positions until contact with the container and closure system has been shown not to affect drug product quality. The comparison between upright and inverted or on-the-side position is important to determine whether contact of the drug product (or solvent) with the closure results in extraction of chemical substances from the closure components or in adsorption and absorption of product components into the container and closure. The evaluation should include the set of test parameters that are listed in Considerations for Specific Dosage Forms (Section VIII). Upright vs. inverted or on-the-side stability studies should be performed during the preapproval and postapproval verification stages of the stability program. Once it has been demonstrated that the product in maximum contact with the primary pack does not have a significantly greater effect on drug product quality than the upright orientation, stability studies may be continued only in the most stressful orientation, which is generally the inverted or on-the-side position.

3. Extractables and Adsorption or Absorption of Drug Product Components

Specific extractables testing on a drug product is not recommended. Inverted vs. upright stability testing during preapproval and postapproval verification is usually adequate. Extensive testing for extractables should be performed as part of the qualification of the container and closure components, labels, adhesives, colorants, and ink (see previously cited packaging guidance for additional information). Such testing should demonstrate that the levels of extractables found during extraction studies, which are generally performed with various solvents, elevated temperatures, and prolonged extraction times, are at levels determined to be acceptable and that those levels will not be approached during the shelf life of the drug product. Loss of the active drug substance or critical excipients of the drug product by interaction with the container and closure components or components of the drug delivery device is generally evaluated as part of the stability protocol. This is usually accomplished by assaying those critical drug product components, as well as monitoring various critical parameters (e.g., pH, preservative effectiveness). Excessive loss of a component or change in a parameter will result in the failure of the drug product to meet applicable specifications.

C. Microbiological Control and Quality

1. Preservatives Effectiveness

Both sterile and nonsterile drug products may contain preservative systems to control bacteria and fungi that may be inadvertently introduced during manufacturing. Acceptance criteria should be provided as part of the drug product specifications for the chemical content of preservatives at the time of product release or through the product shelf life.

The minimum acceptable limit for the content of preservatives in a drug product should be demonstrated as microbiologically effective by performing a microbial challenge assay of the drug formulated with an amount of preservative less than the minimum amount specified as acceptable. This approach provides a margin of safety within the limit and a margin of error for the assays. In addition, compatibility of the preservative system with the container, closure, formulation, and devices (e.g., pumps,

injection pens) should be demonstrated over the contact period. Multiple-use container systems, for example, containers that are used after the closure is replaced with an applicator or dropper and large bottles containing syrups or suspensions, should be tested for the microbiological effectiveness of the preservatives system following simulated uses, including breaches of the container system as permitted in the labeling. USP "Antimicrobial Preservatives-Effectiveness"<51> provides a microbial challenge assay.

For the purpose of approval of drug applications, stability data on pilot-scale batches should include results from microbial challenge studies performed on the drug product at appropriate intervals. In general, microbial challenge studies conducted initially, annually, and at the end of the expiration dating period are adequate. Chemical assays of preservative contents should be performed at all test points.

For postapproval testing, the first three production batches should be tested with a microbial challenge assay at the start and the end of the stability period and at one point in the middle of the stability period if the test period equals or exceeds 2 years. The first three production batches should be assayed for the chemical content of the preservatives at all appropriate test points. On demonstration of chemical content commensurate with microbial effectiveness in the first three production batches, chemical assays may be adequate to demonstrate the maintenance of the specified concentrations of preservatives for subsequent annual batches placed into stability testing.

2. Microbiological Limits for Nonsterile Drug Products

Nonsterile drug products that have specified microbial limits for drug product release should be tested for conformance to the specified limits at appropriate, defined time points during stability studies. The USP provides microbiological test methods for microbial limits and guidance concerning microbiological attributes of nonsterile drug products.

3. Sterility Assurance for Sterile Drug Products

The stability studies for sterile drug products should include data from a sterility test of each batch at the beginning of the test period. Additional testing is recommended to demonstrate maintenance of the integrity of the microbial barrier provided by the container and closure system. These tests should be performed annually and at expiry.

Integrity of the microbial barrier should be assessed using an appropriately sensitive and adequately validated container and closure integrity test. The sensitivity of this test should be established and documented to show the amount of leakage necessary to detect a failed barrier in a container and closure system. The number of samples to be tested should be similar to the sampling requirement provided in current USP "Sterility Tests" <71>. The samples that pass container and closure integrity testing may be used for other stability testing for that specific time point but should not be returned to storage for future stability testing. Container and closure integrity tests do not replace the current USP "Sterility Tests" <71> or 21 CFR 610.12 for product release.

4. Pyrogens and Bacterial Endotoxins

Drug products with specified limits for pyrogens or bacterial endotoxins should be tested at the time of release and at appropriate intervals during the stability period. For most parenteral products, testing at the beginning and the end of the stability test period may be adequate. Sterile dosage forms containing dry materials (powder-filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional testing beyond the initial time point. Products containing liquids in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and the end of the stability test period.

D. Stability Sampling Considerations

The design of a stability study is intended to establish, based on testing a limited number of batches of a drug product, an expiration dating period applicable to all future batches of the drug product manufactured under similar circumstances. This approach assumes that inferences drawn from this small group of tested batches extend to all future batches. Therefore, tested batches should be representative in all respects such as formulation, manufacturing site, container and closure, manufacturing process, source, and quality of bulk material of the population of all production batches, and should conform to all quality specifications of the drug product.

The design of a stability study should take into consideration the variability of individual dosage units, of containers within a batch, and of batches, to ensure that the resulting data for each dosage unit or container are truly representative of the batch as a whole and to quantify the variability from batch to batch. The degree of variability affects the confidence that a future batch would remain within specifications until its expiration date.

1. Batch Sampling

Batches selected for stability studies should optimally constitute a random sample from the population of production batches. In practice, the batches tested to establish the expiration dating period are often made at a pilot plant that may only simulate full-scale production. Future changes in the production process may thus render the initial stability study conclusions obsolete.

At least three batches, and preferably more, should be tested to allow an estimate of batch-to-batch variability and to test the hypothesis that a single expiration dating period for all batches is justifiable. Testing of fewer than three batches does not permit a reliable estimate of batch-to-batch variability unless a significant body of information is available on the dosage form or drug product. Although data from more batches will result in a more precise estimate, practical considerations prevent collection of extensive amounts of data. When a significant body of information is not available, testing at least three batches represents a compromise between statistical and practical considerations.

2. Container, Closure, and Drug Product Sampling

Selection of containers, such as bottles, packages, and vials, from the batch chosen for inclusion in the stability study should ensure that the samples represent the batch as a whole. This can be accomplished by taking a random sample of containers from the finished batch, by using a stratification plan whereby at a random starting point every *n*th container is taken from the filling or packaging line (*n* is chosen such that the sample is spread over the whole batch), or by some other plan designed to ensure an unbiased selection.

In general, samples to be assayed at a given sampling time should be taken from previously unopened containers. For this reason, at least as many containers should be sampled as the number of sampling times in the stability study.

For products packaged in containers intended for dispensing by a pharmacy to multiple patients, or intended for repackaging or packaging in unit-of-use containers, samples may be taken from previously opened containers. More than one container should be sampled during the stability study. The sampling protocol should be submitted in the drug application.

Dosage units should be sampled from a given container randomly, with each dosage unit having an equal chance of being included in the sample. If the individual units entered the container randomly, then samples may be taken from units at the opening of the container. However, because dosage units near the caps of large containers may have different stability properties than do dosage units in other parts of the container, dosage units should be sampled from all parts of the container. For dosage units sampled in this fashion, the location within the container from which the samples were taken should be documented and this information included with the test results.

Unless the product is being tested for homogeneity, composites may be assayed, rather than individual units. If more than one container is sampled at a given sampling time, an equal number of units from each container may be combined into the composite. If composites are used, their makeup should be described in the stability study report. The same type of composite should be used throughout the stability study. For example, if 20-tablet composites are tested initially, then 20-tablet composites should be used throughout. If a larger sample at a later sampling time is desired, replicated 20-tablet composites should be assayed rather than a single assay of a composite made from more than 20 tablets. An average of these composite values may be used for the release assay. However, the individual assay values should be reported as well. Although other release and stability tests may be performed on these samples (e.g., impurities, preservatives' effectiveness), the results of these tests do not need to be subjected to top, middle, or bottom comparisons.

Semisolid drug products in sizes that are intended for multiple uses should be tested for homogeneity. Homogeneity testing may be bracketed by container or fill size, with testing done only on the smallest and largest marketed package sizes of each strength. Stability protocols should provide for increased testing in the event of homogeneity failures or following a change in packaging materials or procedures; for example, with a change to a new sealant, or a change in tube crimping procedures. Where the largest marketed size is more than 20 times the smallest, homogeneity testing of an intermediate size is recommended, but semisolid drug products in sizes that are intended for single use need not be tested for homogeneity.

3. Sampling Time

The sample time points should be chosen so that any degradation can be adequately profiled (i.e., at a sufficient frequency to determine with reasonable assurance the nature of the degradation curve). Usually the relationship can be adequately represented by a linear, quadratic, or cubic function on an arithmetic or a logarithmic scale.

Stability testing for long-term studies generally should be performed at 3-month intervals during the first year, 6-month intervals during the second, and yearly thereafter. For drug products predicted to degrade more rapidly, for example, certain radiopharmaceuticals, the intervals between sampling times should be shortened. Stability testing for accelerated studies generally should be performed at a minimum of four time points, including the initial sampling time.

Freezing samples after sampling for the convenience of scheduling analysis is not an acceptable practice because it may cause delay in finding and responding to out-of-specification test results or may adversely affect the stability of a product that does not withstand freezing.

The degradation curve is estimated most precisely, in terms of the width of the confidence limit about the mean curve (Section VII.E.2), around the average of the sampling times included in the study. Therefore, testing an increased number of replicates at the later sampling

times—particularly the latest sampling time—is encouraged because this will increase the average sampling time toward the desired expiration dating period.

4. Annual Stability Batches

After the expiration dating period has been verified with three production batches, a testing program for an approved drug product should be implemented to confirm ongoing stability. For every approved application, at least one batch of every strength in every approved container and closure system, such as bottles or blisters, should be added to the stability program annually in all subsequent years. If the manufacturing interval is greater than 1 year, the next batch of drug product released should be added to the stability program. Bracketing and matrixing can be used to optimize testing efficiency.

The recommendations in this section do not apply to compressed medical gases, blood, or blood products.

E. Statistical Considerations and Evaluation

1. Data Analysis and Interpretation for Long-term Studies

A stability protocol should describe not only how the stability study is to be designed and carried out but also the statistical method to be used in analyzing the data. This section describes an acceptable statistical approach to the analysis of stability data and the specific features of the stability study that are pertinent to the analysis. In general, an expiration dating or retest period should be determined on the basis of statistical analysis of observed long-term data. Limited extrapolation of the real-time data beyond the observed range to extend the expiration dating or retest period at approval time may be considered if it is supported by the statistical analysis of real-time data, satisfactory accelerated data, and other nonprimary stability data.

The methods described in this section are used to establish with a high degree of confidence an expiration dating period during which average drug product attributes such as assay and degradation products of the batch will remain within specifications. This expiration dating period should be applicable to all future batches produced by the same manufacturing process for the drug product.

If an applicant chooses an expiration dating period to ensure that the characteristics of a large proportion of the individual dosage units are within specifications, different statistical methods than those proposed below should be considered. In this setting, testing of individual units, rather than composites, may be important.

Applicants wishing to use a statistical procedure other than those discussed in this guidance should consult with the chemistry review team before the initiation of the stability study and data analysis.

2. Expiration Dating Period for an Individual Batch

The time during which a batch may be expected to remain within specifications depends not only on the rate of physical, chemical, or microbiological changes but also on the initial average value for the batch. Thus, information on the initial value for the batch is relevant to the determination of the allowable expiration dating period and should be included in the stability study report. Percentage of label claim, not percentage of initial average value, is the variable of interest.

The expiration dating period for an individual batch is based on the observed pattern of change in the quantitative attributes (e.g., assay, degradation products) under study and the precision by which change is estimated.

An acceptable approach for analyzing an attribute that is expected to decrease with time is to determine the time at which the 95% one-sided lower confidence limit, also known as the 95% lower confidence bound, for the estimated curve intersects the acceptable lower specification limit. Where the estimated curve is assumed to be linear based on 24 months of real-time data and the lower specification limit is assumed to be 90% of label claim, an expiration dating period of 24 months could be granted. When analyzing an attribute that is expected to increase with time, the 95% one-sided upper confidence limit for the mean is recommended.

When analyzing an attribute with both an upper and a lower specification limit, special cases may lead to application of a two-sided 95% confidence limit. For example, although chemical degradation of the active ingredient in a solution product would cause a decrease in the assayed concentration, evaporation of the solvent in the product (through the container and closure) would result in an increase in the concentration. Because both possibilities should be taken into account, two-sided confidence limits would be appropriate. If both mechanisms were acting, the concentration might decrease initially and then increase. In this case, the degradation pattern would not be linear, and more complicated statistical approaches should be considered. If the approach presented in this section is used, average parameters such as assay and degradation products of the dosage units in the batch can be expected to remain within specifications to the end of the expiration dating period at a confidence level of 95%. The expiration dating period should not be determined using the point at which the fitted least-squares line intersects the appropriate specification limit. This approach is as likely to overestimate the expiration dating period as it is to underestimate it, in which case the batch average can be expected to remain within specifications at expiration if the fitted least-squares line is used with a confidence level of only 50%.

The statistical assumptions underlying the procedures described above, such as the assumption that the variability of the individual units from the batch average remains constant over the several sampling times, are well known and have been discussed in numerous statistical texts. The above procedures will remain valid even when these assumptions are violated to some degree. If severe violation of the assumptions in the data is noted, an alternate approach may be necessary to accomplish the objective of determining an expiration dating period with a high degree of confidence.

3. Expiration Dating Period for All Batches

If batch-to-batch variability is small, that is, the relationship between the parameter of interest such as assay or degradation products and time is essentially the same from batch to batch, stability data should be combined into one overall estimate. Combining the data should be supported by preliminary testing of batch similarity. The similarity of the estimated curves among the batches tested should be assessed by applying statistical tests of the equality of slopes and of zero time intercepts. The level of significance of the tests, expressed in the *P* value, should be chosen so that the decision to combine the data is made only if there is strong evidence in favor of combining. A *P* value of .25 for preliminary statistical tests has been recommended. If the tests for equality of slopes and for equality of intercepts do not result in rejection at a level of significance of .25, the data from the batches could be pooled. If these tests resulted in *P* values less than .25, a judgment should be made as to whether pooling could be permitted. The appropriate FDA chemistry review team should be consulted regarding this determination.

If the preliminary statistical test rejects the hypothesis of batch similarity because of unequal initial intercept values, it may still be possible to establish that the lines are parallel (i.e., that the slopes are equal). If so, the data may be combined for the purpose of estimating the common slope. The individual expiration dating period for each batch in the stability study may then be determined by considering the initial values and the common slope using appropriate statistical methodology. If data from several batches are combined, as many batches as feasible should be combined because confidence limits about the estimated curve will become narrower as the number of batches increases, usually resulting in a longer expiration dating period. If it is inappropriate to combine data from several batches, the overall expiration dating period will depend on the minimum time a batch may be expected to remain within acceptable limits.

4. Precautions in Extrapolation beyond Actual Data

The statistical methods for determining an expiration dating period beyond the observed range of time points are the same as for determining an expiration dating period within the observed range. The *a priori* correctness of the assumed pattern of change as a function of time is crucial in the case of extrapolation beyond the observed range. When estimating a line or curve of change within the observed range of data, the data themselves provide a check on the correctness of the assumed relationship, and statistical methods may be applied to test the goodness of fit of the data to the line or curve. No such internal check is available beyond the range of observed data. For example, if it has been assumed that the relationship between log assay and time is a straight line when, in fact, it is a curve, it may be that within the range of the observed data, the true curve is close enough to a straight line that no serious error is made by approximating the relationship as a straight line. However, beyond the observed data points, the true curve may diverge from a straight line enough to have a significant effect on the estimated expiration dating period.

For extrapolation beyond the observed range to be valid, the assumed change must continue to apply through the estimated expiration dating period. Thus, an expiration dating period granted on the basis of extrapolation should always be verified by actual stability data as soon as these data become available.

F. Expiration Dating Period and Retest Period

1. Computation of Expiration Date

The computation of the expiration dating period of the drug product should begin no later than the time of quality control release of that batch, and the date of release should generally not exceed 30 days from the production date, regardless of the packaging date. The data generated in support of the assigned expiration dating period should be from long-term studies under the storage conditions recommended in the labeling. If the expiration date includes only a month and year, the product should meet specifications through the last day of the month.

In general, proper statistical analysis of long-term stability data collected, as recommended in Section VII.E, should support at least a 1-year expiration dating period. Exceptions do exist, for example, with short half-life radioactive drug products.

If the production batch contains reprocessed material, the expiration dating period should be computed from the date of manufacture of the oldest reprocessed material used.

a. Extension of Expiration Dating Period

An extension of the expiration dating period based on full long-term stability data obtained from at least three production batches in accordance with a protocol approved in the application may be described in an annual report (21 CFR 314.70(d)(5). The expiration dating period may be extended in an annual report only if the criteria set forth in the approved stability protocol are met in obtaining and analyzing data, including statistical analysis if appropriate.

Alternatively, if the stability study on at least three pilot-scale batches is continued after the NDA/BLA approval, it is feasible to extend the tentative expiration dating period based on full long-term data obtained from these batches in accordance with the approved protocol, including statistical analysis if appropriate, through a Prior Approval Supplement. However, the expiration dating period thus derived remains tentative until confirmed with full long-term data from at least three production batches.

Unless a new stability protocol has been adopted via a Prior Approval Supplement before the change is made, stability protocols included in drug applications before the 1985 revisions to the NDA regulations (50 FR 7452) may not support the extension of expiration dating periods through annual reports. If the data are obtained under a new or revised stability protocol, a Prior Approval Supplement under 21 CFR 314.70(b) or (g) or 21 CFR 601.12 should be submitted to extend the expiration dating period.

b. Shortening of Expiration Dating Period

When warranted, a previously approved expiration dating period may be shortened via a Changes Being Effected Supplement (21 CFR 314.70(c)(1) or 21 CFR 601.12). The supplemental application should provide pertinent information and the data that led to the shortening of the expiration dating period. The expiration dating period should be shortened to the nearest available real-time long-term test point where the product meets acceptance criteria. The expiration dating period thus derived should be applied to all subsequent production batches and may not be extended until the cause for the shortening is fully investigated, the problem is resolved, and satisfactory stability data become available on at least three new production batches to cover the desired expiration dating period and are submitted in a Changes Being Effected Supplement.

2. Retest Period for Drug Substance

A retest period for a drug substance may be established on the basis of the available data from long-term stability studies and, as such, can be longer than 24 months if supported by data. A retest date should be placed on the storage container and on the shipping container for a bulk drug substance. A drug substance batch may be used without retest during an approved retest period. However, beyond the approved retest period, any remaining portion of the batch should be retested immediately before use. Retest of different portions of the same batch for use at different times as needed is acceptable, provided that the batch has been stored under the defined conditions, the test methods are validated and stability indicating, and all stability-related attributes are tested with satisfactory test results.

Satisfactory retest results on a drug substance batch after the retest date do not mean that the retest period can be extended for that batch or any other batch. The purpose of retest is to qualify a specific batch of a drug substance for use in the manufacture of a drug product, rather than to recertify the drug substance with a new retest date. To extend the retest period, full long-term data from a formal stability study on three production batches using a protocol approved in an application or found acceptable in a drug master file should be provided.

Similar to the extension of an expiration dating period for a drug product, a retest period for a drug substance may be extended beyond what was approved in the original application. This can be achieved through an annual report based on full long-term stability data (i.e., covering the desired retest period on three production batches using an approved stability protocol).

In a case where testing reveals a limited shelf life for a drug substance, it may be inappropriate to use a retest date. An expiration dating period, rather than a retest period, should be established for a drug substance with a limited shelf life (e.g., some antibiotics, biological substances).

3. Holding Times for Drug Product Intermediates

Intermediates such as blends, triturates, cores, extended-release beads, or pellets may be held for up to 30 days from their date of production without being retested before use. An intermediate that is held for longer than 30 days should be monitored for stability under controlled, long-term storage conditions for the length of the holding period. In addition, the first production batch of the finished drug product manufactured with such an intermediate should be monitored on long-term stability. When previous testing of an intermediate or the related drug product batches indicates that an intermediate may not be stable for 30 days, the holding time should be kept to a minimum and qualified by appropriate stability testing.

The frequency of testing of an intermediate's stability is related to the length of the holding time. Where practical, testing should be done at a minimum of three time points after the initial testing of an intermediate. At a minimum, all critical parameters should be evaluated at release of an intermediate and immediately before its use in the manufacture of the finished drug product.

In the event that the holding time for an intermediate has not been qualified by appropriate stability evaluations, the expiration date assigned to the related finished drug product batch should be computed from the quality control release date of the intermediate if this date does not exceed 30 days from the date of production of the intermediate. If the holding time has been qualified by appropriate stability studies, the expiration date assigned to the related finished drug product can be computed from its quality control release date if this release date does not exceed 30 days from the date that the intermediate is introduced into the manufacture of the finished drug product.

G. Bracketing

1. General

The use of reduced stability testing, such as a bracketing design, may be a suitable alternative to a full testing program where the drug is available in multiple sizes or strengths. This section discusses the types of products and submissions to which a bracketing design is applicable and the types of factors that can be bracketed. Applicants are advised to consult with the FDA when questions arise.

2. Applicability

The factors that may be bracketed in a stability study are outlined in ICH Q1A and described in further detail below. The types of drug products and the types of submissions to which bracketing design can be applied are also discussed.

a. Types of Drug Product

Bracketing design is applicable to most types of drug products, including immediate- and modified-release oral solids, liquids, semisolids, and injectables. Certain types of drug products, such as MDIs, DPIs, and transdermal delivery systems, may not be amenable to, or may need additional justification for, bracketing design.

b. Factors

Where a range of container fill sizes for a drug product of the same strength is to be evaluated, bracketing design may be applicable if the material and composition of the container and the type of closure are the same throughout the range. In a case in which either the container size or the fill size varies but the other remains the same, bracketing design may be applicable without justification. In a case in which both container size and fill size vary, bracketing design is applicable if appropriate justification is provided. Such justification should demonstrate that the various aspects (surface area/volume ratio, dead space/volume ratio, container wall thickness, closure geometry) of the intermediate sizes will be adequately bracketed by the extreme sizes selected.

Where a range of dosage strengths for a drug product in the same container and closure (with identical material and size) is to be tested, bracketing design may be applicable if the formulation is identical or very closely related in components and composition. Examples for the former include a tablet range made with different compression weights of a common granulation, or a capsule range made by filling different plug fill weights of the same composition into different-size capsule shells. The phrase "very closely related formulation" means a range of strengths with a similar, but not identical, basic composition such that the ratio of active ingredient to excipients remains relatively constant throughout the range (e.g., addition or deletion of a colorant or flavoring).

In the case in which the amount of active ingredient changes but the amount of each excipient or the total weight of the dosage unit remains constant, bracketing may not be applicable unless justified. Such justification may include a demonstration of comparable stability profile among the different strengths based on data obtained from clinical and development batches, primary stability batches, or production batches in support of primary stability batches, commitment batches, or annual batches and batches for postapproval changes, respectively. With this approach, the formulations should be identical or very closely related, and the container and closure system should be the same between the supportive batches and the batches for which the bracketing design is intended.

If the formulation is significantly different among the different strengths (e.g., addition or deletion of an excipient, except colorant or flavoring), bracketing is generally not applicable.

Because of the complexity in product formulation, applicants are advised to consult the appropriate chemistry review team in advance when questions arise in the above situations or where justification is needed for bracketing design. In the case in which the strength and the container or fill size of a drug product both vary, bracketing design may be applicable if justified.

c. Types of Submissions

A bracketing design may be used for primary stability batches in an original application, postapproval commitment batches, annual batches, or batches intended to support supplemental changes. Bracketing design should not be applied to clinical batches during the IND stages when the product is still under development. Where additional justification is needed for applying a bracketing design, product stability should be demonstrated using supportive data obtained from clinical or development or NDA batches, commitment batches, or production batches. Before a bracketing protocol is applied to primary stability batches to support an application, the protocol should be endorsed by agency chemistry staff via an IND amendment, an end-of-phase 2 meeting, or before submission of an ANDA. Bracketing protocols to be applied to postapproval commitment batches and annual batches, if proposed, will be approved as part of the original application.

A bracketing design that is not contained in the approved protocol in the application is subject to supplemental approval (21 CFR 314.70(b)(2)(ix)) (601.12). If the new bracketing design is used to generate stability data to support two different chemistry, manufacturing, or controls changes, the two proposed changes could be combined into one Prior Approval Supplement even though the latter may otherwise qualify for a Changes Being Effected Supplement or annual report under 314.70 (c) or (d) or 601.12, or relevant SUPAC guidances. Alternatively, the applicant may consult the appropriate agency review staff through general

correspondence regarding the acceptability of the new bracketing design before the initiation of the stability studies, and subsequently submit the data to support the proposed change through the appropriate filing mechanism.

3. Design

A bracketing protocol should always include the extremes of the intended commercial sizes or strengths. Physician samples or bulk pharmacy packs intended to be repackaged should be excluded from the bracketing protocol for commercial sizes but could be studied under their own bracketing protocols, if applicable. Where a large number (for example, four or more) of sizes or strengths is involved, the inclusion of one batch each of the intermediates or three batches of the middle size or strength in the bracketing design is recommended. Where the ultimate commercial sizes or strengths differ from those bracketed in the original application, a commitment should be made to place the first production batches of the appropriate extremes on the stability study postapproval. Such differences should, however, be justified. Where additional justification for the bracketing design is needed in the original application, one or more of the first production batches of the intermediate or intermediates should be placed on the postapproval long-term stability study.

4. Data evaluation

The stability data obtained under a bracketing protocol should be subjected to the same type of statistical analysis described in Section VII.E. The same principle and procedure on poolability should be applied (i.e., testing data from different batches for similarity before combining them into one overall estimate). If the statistical assessments of the extremes are found to be dissimilar, the intermediate sizes or strengths should be considered to be no more stable than the least stable extreme.

H. Matrixing

1. General

The use of reduced stability testing, such as a matrixing design, may be a suitable alternative to a full testing program where multiple factors involved in the product are being evaluated. The principle behind matrixing is described in ICH Q1A. This section provides further guidance on when it is appropriate to use matrixing and how to design such a study. Consultation with the FDA is encouraged before the design is implemented.

2. Applicability

The types of drug products and the types of submissions to which matrixing design can be applied are the same as described for bracketing above. The factors that can be matrixed with or without justification and those that should not be matrixed are discussed below. In addition, data variability and product stability, as demonstrated through previous supportive batches, should be considered when determining whether matrixing can be applied to the batches of interest.

a. Types of Drug Product

Matrixing design is applicable to most types of drug products, including immediate- and modified-release oral solids, liquids, semisolids, and injectables. Certain types of drug products such as MDIs, DPIs, and transdermal delivery systems may not be amenable to, or may need additional justification for, matrixing design.

b. Factors

Some of the factors that can be matrixed include batches, strengths with identical formulation, container sizes, fill sizes, and intermediate time points. With justification, additional factors that can be matrixed include strengths with closely related formulation, container and closure suppliers, container and closure systems, orientations of container during storage, drug substance manufacturing sites, and drug product manufacturing sites. For example, to justify matrixing across HDPE bottles and blister packs, a tablet dosage form could be shown not to be sensitive to moisture, oxygen, or light (through stressed studies, including open-dish experiments) and to be so stable that the protective nature of the container and closure system made little or no difference in the product stability (through supportive data). Alternatively, it could be demonstrated, if appropriate, that there is no difference in the protective nature of the two distinctively different container and closure systems. The justification is needed to ensure that the matrixing protocol would lead to a successful prediction of the expiration dating period when two otherwise different container and closure systems are studied together.

Factors that should not be matrixed include initial and final time points, attributes (test parameters), dosage forms, strengths with different formulations (i.e., different excipients or different active and excipient ratios), and storage conditions.

c. Data Variability and Product Stability

The applicability of matrixing design to primary stability batches depends on the product stability and data variability demonstrated through clinical or developmental batches. Data variability refers to the variability of supportive stability data within a given factor (i.e., batch to batch, strength to strength, and size to size) and across different factors (e.g., batch vs. strength, strength vs. size). It is assumed that there is very little variability in the analytical methods used in the testing of stability samples. Matrixing design is applicable if these supportive data indicate that the product exhibits excellent stability with

very small variability. Where the product displays moderate stability with moderate variability in the supportive data, matrixing design is applicable with additional justification. Conversely, if supportive data indicate poor product stability with large variability, matrixing design is not applicable. Similarly, whether or not matrixing design can be applied to postapproval commitment batches or supplemental changes will depend on the cumulative stability data on developmental batches, primary batches, or production batches, as appropriate.

d. Types of Submission

Same as Section VII.G.1.c.

3. Design

a. General

For original applications, a matrixing design should always include the initial and final time points, as well as at least two additional time points through the first 12 months, that is, at least three time points including the initial and 12-month time points. This approach is especially important if the original application contains less than full long-term data at the time of submission.

Although matrixing should not be performed across attributes, different matrixing designs for different attributes may be suitable where different testing frequencies can be justified. Likewise, each storage condition should be treated separately under its own matrixing design, if applicable. Care must be taken to ensure that there are at least three time points, including initial and end points, for each combination of factors under an accelerated condition. If bracketing is justified, the matrixing design should be developed afterward.

All samples should be placed on stability including those that are not to be tested under the matrixing design. Once the study begins, the protocol should be followed without deviation. The only exception is that, if necessary, it is acceptable to revert back to full stability testing during the study. However, once reverted, the full testing should be carried out through expiry.

b. Size of Matrixing Design

The appropriate size of a matrix is generally related to the number of combinations of factors and the amount of supportive data available. The size of a matrixing design is expressed as a fraction of the total number of samples to be tested in the corresponding full stability protocol. For a product available in three batches, three strengths, and three container or fill sizes, the number of combinations of factors to be tested in a full design is $3 \times 3 \times 3$, or 27. Similarly, if there are three batches with one strength and no other factors, the number of combinations of factors is expressed as 3×1. The larger the number of combinations of factors to be tested and the greater the amount of available supportive data, the smaller the size of matrixing design that may be justified. The phrase "substantial amount of supportive data" means that a sufficient length of stability data are available on a considerable number of clinical or development batches, primary stability batches, or production batches to justify the use of matrixing design on primary stability batches, commitment batches, or annual batches and batches for postapproval changes. The formulations used in a matrixing design should be identical or very closely related, and the container and closure system should be the same between the supportive batches and the batches for which the matrixing design is intended.

c. Statistical Considerations

The design should be well balanced. An estimate of the probability that stability outcomes from the matrixed study would be the same for a given factor or across different factors should be provided if available.

4. Data Evaluation

The stability data obtained under a matrixing protocol should be subjected to the same type of statistical analysis with the same vigor and for the same aspects as outlined in Section VII.E. The same principle and procedure on poolability (i.e., testing data from different batches for similarity before combining them into one overall estimate, as described in Section VII.E.1) should be applied.

I. Site-Specific Stability Data for Drug and Biologic Applications

1. Purpose

At the time of NDA submission, at least 12 months of long-term data and 6 months of accelerated data should be available on three batches of the drug substance (all of which should be at least pilot scale) and three batches of the drug product (two of which should be at least pilot scale); reference is made to the drug substance and drug product sections of the ICH Q1A Guidance and to Sections II.A and II.B of this chapter, respectively. Because the ICH Guidance did not address where the stability batches should be made, this section provides recommendations on site-specific stability data: the number and size of drug substance and drug product stability batches made at the intended manufacturing-scale production sites, and the length of stability data on these batches, for an original NDA, ANDA, BLA, or PLA application. Applicants are advised to consult with the respective chemistry review team when questions arise.

2. Original NDAs, BLAs, or PLAs

In principle, primary stability batches should be made at the intended commercial site. If the primary stability batches are not made at the intended commercial site,

stability data from the drug substance product batches manufactured at that site (i.e., site-specific batches) should be included in the original submission to demonstrate that the product made at each site is equivalent. If at the time of application submission there are 12 months of long-term data and 6 months of accelerated data on three primary stability batches made at other than the intended commercial site, a reduced number of site-specific batches with shorter duration of data than the primary batches may be acceptable. In addition, these site-specific batches may be of pilot scale.

A drug substance should be adequately characterized (i.e., results of chemical, physical, and, when applicable, biological testing). Material produced at different sites should be of comparable quality. In general, 3 to 6 months of stability data on one to three site-specific drug substance batches, depending on the availability of sufficient primary stability data from another site, should be provided at the time of application submission.

The complexity of the drug product dosage form is a critical factor in determining the number of site-specific batches for an original application. The quality or stability of a simple dosage form is less likely to vary because of a different manufacturing site than is that of a complex dosage form. Three site-specific batches are needed for a complex dosage form to provide an independent and statistically meaningful stability profile for the product made at that site. One site-specific batch may be sufficient to verify the stability profile of a simple dosage form.

Other factors, such as lack of experience at the new site in a particular dosage form or difference in the environmental conditions between the sites, can potentially affect the quality or stability of a drug product. Therefore, one site-specific batch may not be sufficient in these cases. More than one site-specific batch may be needed for a drug substance or product that is intrinsically unstable.

Although one site-specific batch may be sufficient under certain situations, the data so generated, particularly if limited to accelerated studies, may not be amenable to statistical analysis for the establishment of a retest period or expiration dating period. Instead, the single site-specific batch may serve only to verify the stability profile of a drug substance or product that has been established based on primary stability batches at a pilot plant.

In general, site-specific drug product batches should be made with identifiable site-specific drug substance batches both for original applications, wherever possible, and for postapproval stability commitment.

Although pilot and commercial facilities may or may not be located on the same campus or within the same geographical area, they will generally employ similar processes and equipment of the same design and operating principles. If different processes or equipment are used, more site-specific batches or longer duration of data are recommended. If the pilot plant where the primary stability batches are made is located at the intended commercial site (i.e., on the same campus as the intended manufacturing-scale production facility), the site-specific stability recommendations are met (provided the processes and equipment are the same) and no additional data will be needed. A commitment should be made to place the first three production batches on accelerated and long-term stability studies. If more than one manufacturing-scale production site is proposed for an original NDA, BLA, or PLA, the recommendations above would be applicable to each site.

3. Site-Specific Data Package Recommendations for ANDAs

For ANDAs, the primary batch or batches to support the application are usually manufactured in the production facility. If the primary stability batch or batches are not made at the intended commercial site, stability data should be generated on the drug product manufactured at that site, that is, site-specific batches, and the data should be included in the original submission to demonstrate that the product made at each site is equivalent.

If the pilot plant where the primary stability batches are made is located at the intended commercial site (i.e., on the same campus as the intended commercial facility), the site-specific stability recommendations are met and no additional data will be needed. A commitment should be made to place the first three production batches and annual batches thereafter on long-term stability studies.

For complex dosage forms as described in the previous section, a reduced number of site-specific batches may be justified if accelerated and long-term data are available at the time of application submission on batches made at a different pilot or commercial site from the intended commercial facility.

J. Photostability

1. General

The *ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products* (hereafter referred to as the parent guidance) notes that light testing should be an integral part of stress testing.

The ICH Q1B guidance *Photostability Testing of New Drug Substances and Products* primarily addresses the generation of photostability information for new molecular entities and associated drug products and the use of the data in determining whether precautionary measures in manufacturing, labeling, or packaging are needed to mitigate exposure to light. Q1B does not specifically address other photostability studies that may be needed to support, for example, the photostability of a product under in-use conditions or the photostability of analytical samples. Because data are generated on a directly exposed

drug substance alone or in simple solutions and drug products when studies are conducted as described in the Q1B guidance, knowledge of photostability characteristics may be useful in determining when additional studies may be needed or in providing justification for not performing additional studies. For example, if a product has been determined to photodegrade on direct exposure but is adequately protected by packaging, an in-use study may be needed to support the use of the product (e.g., a parenteral drug that is infused over a period of time). The test conditions for in-use studies will vary depending on the product and use but should depend on and relate to the directions for use of the particular product.

Photostability studies are usually conducted only in conjunction with the first approval of a new molecular entity. Under some circumstances, photostability studies should be repeated if certain postapproval or supplemental changes, such as changes in formulation or packaging, are made to the product or if a new dosage form is proposed. Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of changes made. For example, if initial studies demonstrate that an active moiety in a simple solution degrades on exposure to light and the tablet drug product is stable, a subsequent filing requesting approval of a liquid dosage form may warrant additional studies to characterize the photostability characteristics of the new dosage form.

Photostability studies need not be conducted for products that duplicate a commercially available listed drug product provided that the packaging (immediate container and closure and market pack) and labeling storage statements regarding light duplicate those of the reference-listed drug. If deviations in packaging or labeling statements are made, additional studies may be recommended. The decision as to whether additional studies should be conducted will be made on a case-by-case basis by the chemistry review team.

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected, as described in the section Selection of Batches in the parent guidance. Under some circumstances, these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation or change made. [ICH Q1B]

A systematic approach to photostability testing is recommended, covering, as appropriate, studies such as

- Tests on the drug substance
- Tests on the exposed drug product outside the immediate pack
- If necessary, tests on the drug product in the immediate pack
- If necessary, tests on the drug product in the marketing pack [ICH Q1B]

The extent of drug product testing should be established by assessing whether acceptable change has occurred at the end of the light exposure testing. Acceptable change is change within limits justified by the applicant. [ICH Q1B]

The formal labeling requirements for photolabile drug substances and drug products are established by national/regional requirements. [ICH Q1B]

2. Light Sources

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified. For both options 1 and 2, a pharmaceutical manufacturer or applicant can rely on the spectral distribution specification of the light-source manufacturer. [ICH Q1B]

a. Option 1

Option 1 is any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter or filters may be fitted to eliminate such radiation. [ICHQ1B]

b. Option 2

For option 2 the same sample should be exposed to both the cool white fluorescent and the near-ultraviolet lamp.

- A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977 (1993)
- A near-UV fluorescent lamp having a spectral distribution from 320 to 400 nm with a maximum energy emission between 350 and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm [ICH Q1B]

3. Procedure [ICH Q1B]

For confirmatory studies, samples should be exposed to light providing an overall illumination of no less than 1.2 million lux hours and an integrated near-ultraviolet

energy of not less than 200 watt hours/square meter to allow direct comparisons to be made between the drug substance and the drug product.

Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters. An example of an actinometric procedure is provided in the Annex.

If protected samples (e.g., those wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, they should be placed alongside the authentic sample. [ICH Q1B]

4. Drug Substance [ICH Q1B]

For drug substances, photostability testing should consist of two parts: forced degradation testing and confirmatory testing.

The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes or degradation pathway elucidation. This testing may involve the drug substance alone or in simple solutions or suspensions to validate the analytical procedures. In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used. For development and validation purposes, it is appropriate to limit exposure and end the studies if extensive decomposition occurs. For photostable materials, studies may be terminated after an appropriate exposure level has been used. The design of these experiments is left to the applicant's discretion, although the exposure levels used should be justified.

Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If, in practice, it has been demonstrated they are not formed in the confirmatory studies, these degradation products need not be examined further.

Confirmatory studies should then be undertaken to provide the information necessary for handling, packaging, and labeling.

Normally, only one batch of drug substance is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guidance if the drug is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted. Samples should be selected as described in the parent guidance.

a. Presentation of Samples [ICH Q1B]

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account, and efforts should be made, such as cooling or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as sublimation, evaporation, or melting are minimized. All such precautions should be chosen to provide minimal interference with the exposure of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever they are not relevant to the test being carried out.

As a direct challenge for samples of solid drug substances, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent cover if considered necessary. Solid drug substances should be spread across the container to give a thickness of typically not more than 3 mm. Drug substances that are liquids should be exposed in chemically inert and transparent containers.

b. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

Where solid drug substance samples are involved, sampling should ensure that a representative portion is used in individual tests. Similar sampling considerations, such as homogenization of the entire sample, apply to other materials that may not be homogeneous after exposure. The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark control if they are used in the test.

c. Judgment of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

The confirmatory studies should identify precautionary measures needed in manufacturing or in formulation of the drug product and if light-resistant packaging is needed. When evaluating the results of confirmatory studies to determine whether change caused by exposure to light is acceptable, it is important to consider the results

from other formal stability studies to ensure that the drug will be within justified limits at time of use (see the relevant ICH stability and impurity guidance).

5. Drug Product [ICH Q1B]

Normally, the studies on drug products should be carried out in a sequential manner, starting with testing the fully exposed product and then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light. The drug product should be exposed to the light conditions described under the procedure in Section VII.J.3.

Normally, only one batch of drug product is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guidance if the product is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, testing should normally be conducted only on directly exposed drug product.

It may be appropriate to test certain products, such as infusion liquids or dermal creams, to support their photostability in use. The extent of this testing should depend on and relate to the directions for use and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

a. Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account, and efforts, such as cooling or placing the samples in sealed containers, should be made to ensure that the effects of the changes in physical states are minimized, such as sublimation, evaporation, or melting. All such precautions should be chosen to provide minimal interference with the irradiation of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

Where practicable, when testing samples of the drug product outside of the primary pack, these should be presented in a way similar to the conditions mentioned for the drug substance. The samples should be positioned to provide maximum area of exposure to the light source. For example, tablets and capsules should be spread in a single layer.

If direct exposure is not practical (e.g., because of oxidation of a product), the sample should be placed in a suitable protective inert transparent container (e.g., quartz).

If testing of the drug product in the immediate container or as marketed is needed, the samples should be placed horizontally or transversely with respect to the light source, whichever provides for the most uniform exposure of the samples. Some adjustment of testing conditions may have to be made when testing large-volume containers (e.g., dispensing packs).

b. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution; dissolution or disintegration for dosage forms such as capsules) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

When powder samples are involved, sampling should ensure that a representative portion is used in individual tests. For solid oral dosage–form products, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions). The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if they are used in the test.

c. Judgment of Results

Depending on the extent of change, special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change caused by exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies to ensure that the product will be within proposed specifications during the shelf life (see the relevant ICH stability and impurity guidance).

6. Quinine Chemical Actinometry [ICH Q1B]

The following text provides details of an actinometric procedure for monitoring exposure to a near-UV fluorescent lamp (based on work done by the FDA/National Institute of Standards and Technology study). For other light sources and actinometric systems, the same approach may be used, but each actinometric system should be calibrated for the light source used.

Prepare a sufficient quantity of a 2% weight/volume aqueous solution of quinine monohydrochloride dihydrate (if necessary, dissolve by heating).

a. Option 1

Put 10 mL of the solution into a 20-mL colorless ampoule (see drawing), seal it hermetically, and use this as the sample. Separately, put 10 mL of the solution into a 20-mL colorless ampoule (shape and dimensions; see Japanese

Industry Standard [JIS] R3512 [1974] for ampoule specifications), seal it hermetically, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure, determine the absorbances of the sample (AT) and the control (AO) at 400 nm using a 1-cm path length. Calculate the change in absorbance units (AU): A = AT − AO. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.9 AU.

b. Option 2

Fill a 1-cm quartz cell and use this as the sample. Separately fill a 1-cm quartz cell, wrap it in aluminum foil to protect it completely from light, and use it as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure, determine the AT and the AO at 400 nm. Calculate the change in absorbance, A = AT − AO. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.5.

Alternative packaging configurations may be used if appropriately validated, and alternative validated chemical actinometers may be used.

7. Acceptable/Unacceptable Photostability Change

The extent of the drug product photostability testing depends on the change that has occurred at the end of each test tier. Test results that are outside the proposed acceptance criteria for the product would not be considered acceptable change. This is a stress test designed to determine the intrinsic photostability characteristics of new drug substances and products, and no correlation has been developed to equate a within-specification result to an expiration dating period. The acceptability of any observed changes should be justified in the application. It may be important to consider other degradative processes (e.g., thermal) when justifying a photostability change as acceptable because the processes may be independent and additive. For example, a 5% loss in potency caused by photodegradation may be considered acceptable if that is the only type of degradation observed. If the product is also expected to degrade 5% over the shelf life because of thermal degradation, the photodegradation may then be considered unacceptable based on the potential additive effect of the changes. In this case, precautions should be taken to mitigate the product's exposure to light.

Under the intense light-exposure conditions included in the Q1B guidance, certain colors in solid dosage forms may fade. Quantitative analysis of the color change is not recommended, as these changes are not likely to occur under actual storage conditions. In the absence of change in other parameters such as assay, these color changes may be acceptable.

8. Photostability Labeling Considerations

The data generated using the procedure described in the ICH Q1A guidance are useful in determining when special handling or storage statements regarding exposure to light should be included in the product labeling (21 CFR 201.57(k)(4)). The labeling guidance provided below pertains only to products as packaged for distribution. Instructions and stability statements that may be needed to address in-use conditions pursuant to 21 CFR 201.57(j) are not covered.

a. Change after Direct Exposure

If changes that are observed when the product is directly exposed under the light conditions described in the Q1B guidance are acceptable, no labeling storage statement regarding light is needed.

b. Change after Exposure in the Immediate Container and Closure

If changes observed when the product is directly exposed are unacceptable but are acceptable when the product is tested in the immediate container and closure under the conditions described in the Q1B guidance, the inclusion of a labeling storage statement regarding light would depend on the likelihood of the product being removed from the immediate package during the distribution process. For those products that are unlikely to be removed from the immediate container, such as creams or ointments in tubes dispensed directly to the patient and ophthalmic products, the use of a labeling storage statement regarding light is optional. For products that may be removed from the immediate pack, such as pharmacy bulk packs, a light-storage statement should be included, such as "PROTECT FROM LIGHT. Dispense in a light-resistant container."

c. Change after Exposure in the Market Pack

If changes that are observed are acceptable only when the product in the market pack is exposed under the conditions described in the Q1B guidance, labeling storage statements regarding light should be included.

Examples of typical storage statements are, for single-dose and multiple-dose products, respectively, "PROTECT FROM LIGHT. Retain in carton until time of use." and "PROTECT FROM LIGHT. Retain in carton until contents are used."

K. Degradation Products

When degradation products are detected upon storage, the following information about them should be submitted:

- Procedure for isolation and purification
- Identity and chemical structures
- Degradation pathways
- Physical and chemical properties
- Detection and quantitation levels
- Acceptance criteria (individual and total)
- Test methods
- Validation data
- Biological effect and pharmacological actions, including toxicity studies, at the concentrations likely to be encountered (cross-reference to any available information is acceptable)

If racemization of the drug substance in the dosage form is possible, the information described above also should be provided.

L. Thermal Cycling

A study of the effects of temperature variation, particularly if appropriate for the shipping and storage conditions of certain drug products, should be considered. Drug products susceptible to phase separation, loss of viscosity, precipitation, and aggregation should be evaluated under such thermal conditions. As part of the stress testing, the packaged drug product should be cycled through temperature conditions that simulate the changes likely to be encountered once the drug product is in distribution.

- A temperature cycling study for drug products that may be exposed to temperature variations above freezing may consist of three cycles of 2 days at refrigerated temperature (2°–8°C) followed by 2 days under accelerated storage conditions (40°C).
- A temperature cycling study for drug products that may be exposed to subfreezing temperatures may consist of three cycles of 2 days at freezer temperature (−10° to −20°C) followed by 2 days under accelerated storage conditions (40°C).
- For inhalation aerosols, the recommended cycle study consists of three or four 6-hour cycles per day, between subfreezing temperature and 40°C (75%–85% RH) for a period of up to 6 weeks.
- For frozen drug products, the recommended cycle study should include an evaluation of effects caused by accelerated thawing in a microwave or a hot-water bath unless contraindicated in the labeling.
- Alternatives to these conditions may be acceptable with appropriate justification.

M. Stability Testing in Foreign Laboratory Facilities

Stability testing (as well as finished-product release testing) performed in any foreign or domestic facility may be used as the basis for approval of an application. This includes all NDAs, ANDAs, and related CMC supplements. A satisfactory inspection of the laboratory or laboratories that will perform the testing will be necessary.

Applicants should consider the effects of bulk packaging, shipping, and holding of dosage forms and subsequent market packaging, in addition to distribution of the finished drug product, and be aware of the effect of such operations on product quality. Time frames should be established to encompass the date of production, date of quality control release of the dosage form, bulk packaging, shipping, and market packaging, and initiation and performance of the stability studies on the drug product should be established, controlled, and strictly followed. Maximum time frames for each operation should be established and substantiated by the applicant.

N. Stability Testing of Biotechnology Drug Products

1. General [ICH Q5C]

The ICH harmonized tripartite guidance entitled Q1A *Stability Testing of New Drug Substances and Products* issued by ICH on October 27, 1993, applies in general to biotechnological and biological products. However, biotechnological and biological products have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. For such products in which the active components are typically proteins or polypeptides, maintenance of molecular conformation and, hence, of biological activity is dependent on noncovalent as well as covalent forces. The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. To ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary.

The evaluation of stability may necessitate complex analytical methodologies. Assays for biological activity, where applicable, should be part of the pivotal stability studies. Appropriate physicochemical, biochemical, and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program whenever purity and molecular characteristics of the product permit use of these methodologies.

With these concerns in mind, the applicant should develop the proper supporting stability data for a biotechnological or biological product and consider many

external conditions that can affect the product's potency, purity, and quality. Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications. It is understood that during the review and evaluation process, continuing updates of initial stability data may occur.

2. Scope [ICH Q5C]

The guidance in this section applies to well-characterized proteins and polypeptides, their derivatives, and products of which they are components and that are isolated from tissues, body fluids, or cell cultures or produced using recombinant deoxyribonucleic acid (r-DNA) technology. Thus, the section covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides. In addition, the guidance outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the product review office. The section does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components.

3. Terminology [ICH Q5C]

For the basic terms used in this section, the reader is referred to the Glossary. However, because manufacturers of biotechnological and biological products sometimes use traditional terminology, traditional terms are specified in parentheses to assist the reader.

4. Selection of Batches [ICH Q5C]

a. Drug Substance (Bulk Material)

Where bulk material is to be stored after manufacture, but before formulation and final manufacturing, stability data should be provided on at least three batches for which manufacture and storage are representative of the manufacturing scale of production. A minimum of 6 months' stability data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug substances with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Data from pilot-scale batches of drug substance produced at a reduced scale of fermentation and purification may be provided at the time the application is submitted to the agency, with a commitment to place the first three manufacturing-scale batches into the long-term stability program after approval.

The quality of the batches of drug substance placed into the stability program should be representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made at manufacturing scale. In addition, the drug substance (bulk material) made at pilot-scale should be produced by a process and stored under conditions representative of those used for the manufacturing scale. The drug substance entered into the stability program should be stored in containers that properly represent the actual holding containers used during manufacture. Containers of reduced size may be acceptable for drug substance stability testing provided that they are constructed of the same material and use the same type of container and closure system that is intended to be used during manufacture.

b. Intermediates

During manufacture of biotechnological and biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that ensure their stability within the bounds of the developed process. Although the use of pilot-scale data is permissible, the manufacturer should establish the suitability of such data using the manufacturing-scale process.

c. Drug Product (Final Container Product)

Stability information should be provided on at least three batches of final container product representative of that which will be used at manufacturing scale. Where possible, batches of final container product included in stability testing should be derived from different batches of bulk material. A minimum of 6 months' data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug products with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Product expiration dating should be based on the actual data submitted in support of the application. Because dating is based on the real-time/real-temperature data submitted for review, continuing updates of initial stability data should occur during the review and evaluation process. The quality of the final container product placed on stability studies should be representative of the quality of the material used in the preclinical and clinical studies. Data from pilot-scale batches of drug product may be provided at the time the application is submitted to the agency, with a commitment to place the first three manufacturing-scale batches into the long-term stability program after approval.

Where pilot-plant scale batches were submitted to establish the dating for a product, and in the event that the product produced at manufacturing scale does not meet those long-term stability specifications throughout the dating period or is not representative of the material used in preclinical and clinical studies, the applicant should notify the appropriate FDA reviewing office to determine a suitable course of action.

d. Sample Selection

Where one product is distributed in batches differing in fill volume (e.g., 1, 2, or 10 mL), unitage (e.g., 10, 20, or 50 units), or mass (e.g., 1, 2, or 5 mg), samples to be entered into the stability program may be selected on the basis of a matrix system or by bracketing.

Matrixing—the statistical design of a stability study in which different fractions of samples are tested at different sampling points—should be applied only when appropriate documentation is provided that confirms that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same closure, and possibly, in some cases, different container and closure systems. Matrixing should not be applied to samples with differences that may affect stability, such as different strengths and different containers and closures, where it cannot be confirmed that the products respond similarly under storage conditions.

Where the same strength and exact container and closure system is used for three or more fill contents, the manufacturer may elect to place only the smallest and largest container size into the stability program (i.e., bracketing). The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples are represented by those at the extremes. In certain cases, data may be needed to demonstrate that all samples are properly represented by data collected for the extremes.

5. Stability-Indicating Profile [ICH Q5C]

On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological or biological product. As a consequence, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity, and potency of the product will be detected.

At the time of submission, applicants should have validated the methods that comprise the stability-indicating profile, and the data should be available for review. The determination of which tests should be included will be product-specific. The items emphasized in the following subsections are not intended to be all-inclusive, but represent product characteristics that should typically be documented to demonstrate product stability adequately.

a. Protocol

The marketing application should include a detailed protocol for the assessment of the stability of both drug substance and drug product in support of the proposed storage conditions and expiration dating periods. The protocol should include all necessary information that demonstrates the stability of the biotechnological or biological product throughout the proposed expiration dating period including, for example, well-defined specifications and test intervals. The statistical methods that should be used are described in the ICH Q1A guidance on stability.

b. Potency

When the intended use of a product is linked to a definable and measurable biological activity, testing for potency should be part of the stability studies. For the purpose of stability testing of the products described in this guidance, potency is the specific ability or capacity of a product to achieve its intended effect. It is based on the measurement of some attribute of the product and is determined by a suitable *in vivo* or *in vitro* quantitative method. In general, potencies of biotechnological and biological products tested by different laboratories can be compared in a meaningful way only if they are expressed in relation to that of an appropriate reference material. For that purpose, a reference material calibrated directly or indirectly against the corresponding national or international reference material should be included in the assay.

Potency studies should be performed at appropriate intervals as defined in the stability protocol, and the results should be reported in units of biological activity calibrated, whenever possible, against nationally or internationally recognized standards. Where no national or international reference standards exist, the assay results may be reported in in-house derived units using a characterized reference material.

In some biotechnological and biological products, potency is dependent on the conjugation of the active ingredient or ingredients to a second moiety or binding to an adjuvant. Dissociation of the active ingredient or ingredients from the carrier used in conjugates or adjuvants should be examined in real-time/real-temperature studies (including conditions encountered during shipment). The assessment of the stability of such products may be difficult because, in some cases, *in vitro* tests for biological activity and physicochemical characterization are impractical or provide inaccurate results. Appropriate strategies (e.g., testing the product before conjugation or binding, assessing the release of the active compound from the second moiety, *in vivo* assays) or the use of an appropriate surrogate test should be considered to overcome the inadequacies of *in vitro* testing.

c. Purity and Molecular Characterization

For the purpose of stability testing the products described in this guidance, purity is a relative term. Because of the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a biotechnological or biological product is extremely difficult to determine. Thus, the purity of a biotechnological or biological product should be typically assessed by more than one method, and the purity value derived is method-dependent. For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products.

The degree of purity, as well as the individual and total amounts of degradation products of the biotechnological or biological product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies.

The use of relevant physicochemical, biochemical, and immunochemical analytical methodologies should permit a comprehensive characterization of the drug substance or drug product (e.g., molecular size, charge, hydrophobicity) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation, or fragmentation during storage. As examples, methods that may contribute to this include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (e.g., reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography), and peptide mapping.

Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated, or stress–stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products within the long-term stability program. Acceptable limits should be proposed and justified, taking into account the levels observed in material used in preclinical and clinical studies.

For substances that cannot be properly characterized or products for which an exact analysis of the purity cannot be determined through routine analytical methods, the applicant should propose and justify alternative testing procedures.

d. Other Product Characteristics

The following product characteristics, though not specifically relating to biotechnological/biological products, should be monitored and reported for the drug product in its final container:

- Visual appearance of the product (color and opacity for solutions and suspensions; color, texture, and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilized cakes, pH, and moisture level of powders and lyophilized products.
- Sterility testing or alternatives (e.g., container and closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf life.
- Additives (e.g., stabilizers, preservatives) or excipients may degrade during the dating period of the drug product. If there is any indication during preliminary stability studies that reaction or degradation of such materials adversely affects the quality of the drug product, these items may need to be monitored during the stability program.
- The container/closure has the potential to affect the product adversely and should be carefully evaluated (see following).

6. Storage Conditions [ICH Q5C]

a. Temperature

Because most finished biotechnological and biological products need precisely defined storage temperatures, the storage conditions for the real-time/real-temperature stability studies may be confined to the proposed storage temperature.

b. Humidity

Biotechnological and biological products are generally distributed in containers protecting them against humidity. Therefore, where it can be demonstrated that the proposed containers (and conditions of storage) afford sufficient protection against high and low humidity, stability tests at different relative humidities can usually be omitted. Where humidity-protecting containers are not used, appropriate stability data should be provided.

c. Accelerated and Stress Conditions

As previously noted, the expiration dating should be based on real-time/real-temperature data. However, it is strongly recommended that studies be conducted on the drug substance and drug product under accelerated and stress conditions. Studies under accelerated conditions may provide useful support data for establishing the expiration date, provide product stability information or future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation and scale-up), assist in validation of analytical methods for the stability program, or generate information that may help elucidate the degradation profile of the drug substance or drug product. Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of

the drug substance or drug product to extreme conditions may help reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions. Although the OCH Q1A guidance on stability describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological and biological products. Conditions should be carefully selected on a case-by-case basis.

d. Light

Applicants should consult the FDA on a case-by-case basis to determine guidance for testing.

e. Container and Closure

Changes in the quality of the product may occur as a result of the interactions between the formulated biotechnological or biological product and the container and closure. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality. Data should be supplied for all different container and closure combinations that will be marketed.

In addition to the standard data necessary for a conventional single-use vial, the applicant should demonstrate that the closure used with a multiple-dose vial is capable of withstanding the conditions of repeated insertions and withdrawals so that the product retains its full potency, purity, and quality for the maximum period specified in the instructions for use on containers, packages, or package inserts. Such labeling should be in accordance with FDA requirements.

f. Stability after Reconstitution of Freeze-Dried Product

The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, packages, or package inserts. Such labeling should be in accordance with FDA requirements.

7. Testing Frequency [ICH Q5C]

The shelf lives of biotechnological and biological products may vary from days to several years. Thus, it is difficult to draft uniform guidances regarding the stability study duration and testing frequency that would be applicable to all types of biotechnological and biological products. With only a few exceptions, however, the shelf lives for existing products and potential future products will be within the range of 0.5 to 5 years. Therefore, the guidance is based on expected shelf lives in that range. This takes into account that degradation of biotechnological and biological products may not be governed by the same factors during different intervals of a long storage period.

When shelf lives of 1 year or less are proposed, the real-time stability studies should be conducted monthly for the first 3 months and at 3-month intervals thereafter. For products with proposed shelf lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter.

Although the testing intervals listed above may be appropriate in the preapproval or prelicense stage, reduced testing may be appropriate after approval or licensing, where data are available that demonstrate adequate stability. Where data exist that indicate that the stability of a product is not compromised, the applicant is encouraged to submit a protocol that supports elimination of specific test intervals (e.g., 9-month testing) for postapproval or postlicensing long-term studies.

8. Specifications [ICH Q5C]

Although biotechnological and biological products may be subject to significant losses of activity, physicochemical changes, or degradation during storage, international and national regulations have provided little guidance with respect to distinct release and end-of-shelf-life specifications. Recommendations for maximum acceptable losses of activity, limits for physicochemical changes, or degradation during the proposed shelf life have not been developed for individual types or groups of biotechnological or biological products but are considered on a case-by-case basis. Each product should retain its specifications within established limits for safety, purity, and potency throughout its proposed shelf life. These specifications and limits should be derived from all available information, using the appropriate statistical methods. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that the clinical performance is not affected, as discussed in the OCH Q1A guidance on stability.

9. Labeling [ICH Q5C]

For most biotechnological and biological drug substances and drug products, precisely defined storage temperatures are recommended. Specific recommendations should be stated, particularly for drug substances and drug products that cannot tolerate freezing. These conditions and, where appropriate, recommendations for protection against light or humidity should appear on containers, packages, or package inserts. Such labeling should be in accordance with Section II.B.11.

VIII. CONSIDERATIONS FOR SPECIFIC DOSAGE FORMS

The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a stability study. In general, appearance, assay, and degradation products should be evaluated for all dosage forms.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every listed test be included in the design of a stability protocol for a particular drug product (e.g., a test for odor should be performed only when necessary and with consideration for analyst safety). Furthermore, it is not expected that every listed test be performed at each time point.

A. Tablets

Tablets should be evaluated for appearance, color, odor, assay, degradation products, dissolution, moisture, and friability.

B. Capsules

Hard gelatin capsules should be evaluated for appearance (including brittleness), color, odor of contents, assay, degradation products, dissolution, moisture, and microbial limits. Testing of soft gelatin capsules should include appearance, color, odor of contents, assay, degradation products, dissolution, microbial limits, pH, leakage, and pellicle formation. In addition, the fill medium should be examined for precipitation and cloudiness.

C. Emulsions

An evaluation should include appearance (including phase separation), color, odor, assay, degradation products, pH, viscosity, microbial limits, preservative content, and mean size and distribution of dispersed phase globules.

D. Oral Solutions and Suspensions

The evaluation should include appearance (including formation of precipitate, clarity for solutions), color, odor, assay, degradation products, pH, preservative content, and microbial limits.

In addition, for suspensions, redispersibility, rheological properties, and mean size and distribution of particles should be considered. After storage, samples of suspensions should be prepared for assay according to the recommended labeling (e.g., "shake well before using").

E. Oral Powders for Reconstitution

Oral powders should be evaluated for appearance, odor, color, moisture, and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described in Section VIII.D, after preparation according to the recommended labeling, through the maximum intended use period.

F. Metered-Dose Inhalations and Nasal Aerosols

Metered-dose inhalations and nasal aerosols should be evaluated for appearance (including content, container, and the valve and its components), color, taste, assay, degradation products, assay for cosolvent (if applicable), dose content uniformity, labeled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, microbial limits, valve delivery (shot weight), and extractables and leachables from plastic and elastomeric components. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, the appearance of the valve components and container's contents should be evaluated microscopically for large particles and changes in morphology of the drug surface particles, extent of agglomerates, crystal growth, and foreign particulate matter. These particles lead to clogged valves or nonreproducible delivery of a dose. Corrosion of the inside of the container or deterioration of the gaskets may adversely affect the performance of the drug product.

A stress temperature-cycling study should be performed under the extremes of high and low temperatures expected to be encountered during shipping and handling to evaluate the effects of temperature changes on the quality and performance of the drug product. Such a study may consist of three or four 6-hour cycles per day, between subfreezing temperature and 40°C (75–85% RH), for a period of up to 6 weeks.

Because the inhalant drug products are intended for use in the respiratory system, confirmation that initial release specifications are maintained should be provided to ensure both the absence of pathogenic organisms (e.g., *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli*, and *Salmonella* species) and that the total aerobic count and total mold and yeast count per canister are not exceeded.

G. Inhalation Solutions and Powders

The evaluation of inhalation solutions and solutions for inhalation should include appearance, color, assay, degradation products, pH, sterility, particulate matter, preservative and antioxidant content (if present), net contents (fill weight and volume), weight loss, and extractables or leachables from plastic, elastomeric, and other packaging components.

The evaluation of inhalation powders should include appearance, color, assay, degradation products, aerodynamic particle size distribution of the emitted dose, microscopic

evaluation, microbial limit, moisture content, foreign particulates, content uniformity of the emitted dose, and number of medication doses per device meeting content uniformity of the emitted dose (device metered products).

H. Nasal Sprays: Solutions and Suspensions

The stability evaluation of nasal solutions and suspensions equipped with a metering pump should include appearance, color, clarity, assay, degradation products, preservative and antioxidant content, microbial limits, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter, and extractables and leachables from plastic and elastomeric components of the container, closure, and pump.

I. Topical, Ophthalmic, and Otic Preparations

Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, and nonmetered aerosols for application to the skin.

Topical preparations should be evaluated for appearance, clarity, color, homogeneity, odor, pH, resuspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), assay, degradation products, preservative and antioxidant content (if present), microbial limits and sterility, and weight loss (when appropriate).

Appropriate stability data should be provided for products supplied in closed-end tubes to support the maximum anticipated use period—during patient use—once the tube seal is punctured, allowing product contact with the cap and cap liner. Ointments, pastes, gels, and creams in large containers, including tubes, should be assayed by sampling at the surface, top, middle, and bottom of the container. In addition, tubes should be sampled near the crimp (see also Section VII.D.2).

Evaluation of ophthalmic or otic products (e.g., creams, ointments, solutions, and suspensions) should include the following additional attributes: sterility, particulate matter, and extractables.

Evaluation of nonmetered topical aerosols should include appearance, assay, degradation products, pressure, weight loss, net weight dispensed, delivery rate, microbial limits, spray pattern, water content, and particle size distribution (for suspensions).

J. Transdermals

Stability studies for devices applied directly to the skin for the purpose of continuously infusing a drug substance into the dermis through the epidermis should be examined for appearance, assay, degradation products, leakage, microbial limit and sterility, peel and adhesive forces, and drug release rate.

K. Suppositories

Suppositories should be evaluated for appearance, color, assay, degradation products, particle size, softening range, appearance, dissolution (at 37°C), and microbial limits.

L. SVPs

SVPs include a wide range of injection products such as drug injection, drug for injection, drug injectable suspension, drug for injectable suspension, and drug injectable emulsion.

Evaluation of drug injection products should include appearance, color, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, and pyrogenicity.

Stability studies for drug for injection products should include monitoring for appearance, clarity, color, reconstitution time, and residual moisture content. The stability of drug for injection products should also be evaluated after reconstitution according to the recommended labeling. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under conditions recommended in labeling, should include appearance, clarity, odor, color, pH, assay (potency), preservative (if present), degradation products and aggregates, sterility, pyrogenicity, and particulate matter.

The stability studies for drug injectable suspension and drug for injectable suspension products should also include particle size distribution, redispersibility, and rheological properties in addition to the parameters cited above for drug injection and drug for injection products.

The stability studies for drug injectable emulsion products should include, in addition to the parameters cited above for drug injection, phase separation, viscosity, and mean size and distribution of dispersed phase globules. The functionality and integrity of parenterals in prefilled syringe delivery systems should be ensured through the expiration dating period with regard to factors such as the applied extrusion force, syringeability, pressure rating, and leakage.

Continued assurance of sterility for all sterile products can be assessed by a variety of means, including evaluation of the container and closure integrity by an appropriate challenge test or tests, or sterility testing as described in Section VII.C. Stability studies should evaluate product stability following exposure to at least the maximum specified process lethality (e.g., F, Mrads).

Inclusion of testing for extractables and leachables in the stability protocol may be appropriate in situations in which other qualification tests have not provided sufficient information or assurance concerning the levels of extractables and leachables from plastics and elastomeric components.

Interaction of administration sets and dispensing devices with parenteral drug products, where warranted, should also be considered through appropriate-use test protocols to assure that absorption and adsorption during dwell time do not occur.

M. LVPs

Evaluation of LVPs should include appearance, color, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, pyrogenicity, clarity, and volume.

Continued assurance of sterility for all sterile products may be assessed by a variety of means, including evaluation of the container and closure integrity by an appropriate challenge test or tests, or sterility testing as described in Section VII.C. Stability studies should include evaluation of product stability following exposure to at least the maximum specified process lethality (e.g., F, Mrads).

Interaction of administration sets and dispensing devices with this type of dosage form should also be considered through appropriate-use test protocols to ensure that absorption and adsorption during dwell time do not occur.

N. Drug Additives

For any drug product or diluent that is intended for use as an additive to another drug product, the potential for incompatibility exists. In such cases, the drug product labeled to be administered by addition to another drug product (e.g., parenterals, inhalation solutions) should be evaluated for stability and compatibility in admixture with the other drug products or with diluents both in upright and inverted/on-the-side orientations, if warranted.

A stability protocol should provide for appropriate tests to be conducted at 0-, 6 to 8-, and 24-hour time points, or as appropriate over the intended use period at the recommended storage and use temperature or temperatures. Tests should include appearance, color, clarity, assay, degradation products, pH, particulate matter, interaction with the container and closure and device, and sterility. Appropriate supporting data may be provided in lieu of an evaluation of photodegradation. The compatibility and the stability of the drug products should be confirmed in all diluents and containers and closures as well as in the presence of all other drug products indicated for admixture in the labeling. Compatibility studies should be conducted on at least the lowest and highest concentrations of the drug product in each diluent as specified in the labeling. The stability and compatibility studies should be performed on at least three batches of the drug product. Compatibility studies should be repeated if the drug product or any of the recommended diluents or other drug products for admixture are reformulated.

Testing for extractables and leachables on stability studies may be appropriate in situations where other qualification tests have not provided sufficient information or assurance concerning the levels of extractables and leachables from plastics and elastomeric components. Interaction of administration sets and dispensing devices with parenteral drug products, where warranted, should also be considered through appropriate use test protocols to ensure that absorption and adsorption during dwell time do not occur.

O. Implantable Subdermal, Vaginal, and Intrauterine Devices that Deliver Drug Products

A device containing a drug substance reservoir or matrix from which drug substance diffuses should be tested for total drug substance content, degradation products, extractables, *in vitro* drug release rate, and as appropriate, microbial burden or sterility. The stability protocol should include studies at 37° or 40°C over a sufficient period of time to simulate the *in vivo* use of the drug delivery device.

Stability testing for intrauterine devices (IUDs) should include the following tests: deflection of horizontal arms or other parts of the frame if it is not a T-shaped device (frame memory), tensile strength of the withdrawal string, integrity of the package (i.e., seal strength of the pouch), and sterility of the device.

IX. STABILITY TESTING FOR POSTAPPROVAL CHANGES

A. General

Because of the great variety of changes that may be encountered after a drug application is approved, it is impossible to address stability requirements for all changes in an exhaustive manner in this guidance. Some more common examples of changes to an approved drug application for which supportive stability data should be submitted are listed below. All changes should be accompanied by the standard stability commitment to conduct or complete long-term stability studies on the first one or three batches of the drug substance or drug product and annual batches thereafter, in accordance with the approved stability protocol. The accumulated stability data should be submitted in the subsequent annual reports. Unless otherwise noted, if the data give no reason to believe that the proposed change will alter the stability of the drug product, the previously approved expiration dating period can be used.

B. Change in Manufacturing Process of the Drug Substance

A change in the manufacturing process of the drug substance at the approved manufacturing site should be supported by the submission of sufficient data to show that such a change does not compromise the quality, purity, or stability of the drug substance and the resulting drug product. Because chemical stability of a substance is an intrinsic property, changes made in the preparation of that substance should not affect its stability, provided the isolated substance remains of comparable quality for attributes such as particle size distribution, polymorphic form, impurity profile, and other physiochemical properties. Special concerns for biological products may exist if changes are made in the manufacturing process of a drug substance that may not exist in a chemically synthesized drug substance.

Specific submission and stability issues will be addressed in detail in a separate forthcoming guidance dealing with postapproval changes for drug substances.

C. Change in Manufacturing Site

Site changes consist of changes in the location of the site of manufacture, packaging operations, or analytical testing laboratory both of company-owned as well as contract manufacturing facilities. The stability data package and filing mechanisms indicated below apply to site changes only. If other changes occur concurrently, the most extensive data package associated with the individual changes should be submitted.

When a change to a new manufacturer or manufacturing site for any portion of the manufacturing process of a drug substance or drug product is made, sufficient data to show that such a change does not alter the characteristics or compromise the quality, purity, or stability of the drug substance or drug product may be necessary. The data should include a side-by-side comparison of all attributes to demonstrate comparability and equivalency of the drug substance or drug product manufactured at the two facilities. New manufacturing locations should have a satisfactory CGMP inspection.

1. Site Change for the Drug Substance

For a change limited to an alternate manufacturing site for the drug substance using similar equipment and manufacturing process, stability data on the drug substance may not always be necessary because, for essentially pure drug substances, stability is an intrinsic property of the material. Biotechnology and biologic products may be an exception (see 21 CFR 601.12 and 314.70 (g)). In general, such a change can be made in a Changes Being Effected Supplement as allowed under 21 CFR 314.70(c)(3). The standard stability commitment should be made to conduct long-term stability studies in accordance with the approved stability protocol on the first production batch of drug product produced from a production batch of drug substance manufactured at the new site. Ordinarily, the approved expiration dating period for the drug product may be retained if the drug substance is shown to be of comparable quality (e.g., particle size distribution, polymorphic form, impurity profile, and other physiochemical properties). If the drug substance is not of comparable quality, then more extensive stability data on the drug product manufactured from the drug substance will be needed.

Specific submission and stability issues pertaining to manufacturing site changes for a drug substance or its intermediates in the drug substance manufacturing process will be addressed in a separate forthcoming guidance on postapproval changes for the drug substance.

2. Site Change for the Drug Product

For a move of the manufacturing site within an existing facility or a move to a new facility on the same campus using similar equipment and manufacturing processes, submission of stability data on the drug product in the new facility before implementation is generally not necessary.

For a move to a different campus using similar equipment and manufacturing processes, stability data on the drug product in the new facility should be submitted in a supplemental application. Three months of accelerated and available long-term stability data on one to three batches of drug product manufactured in the new site is recommended, depending on the complexity of the dosage form and the existence of a significant body of information. A commitment should be made to conduct long-term stability studies on the first or first three production batch or batches of the drug product, depending on the dosage form and the existence of a significant body of information, manufactured at the new site in accordance with the approved stability protocol. If the stability data are satisfactory, the existing expiration dating period may be used.

3. Change in Packaging Site for Solid Oral Dosage–Form Drug Products

A stand-alone packaging operation site change for solid oral dosage–form drug products using containers and closures in the approved application should be submitted as a Changes Being Effected Supplement. No up-front stability data are necessary. The facility should have a current and satisfactory CGMP compliance profile for the type of packaging operation under consideration before submitting the supplement. The supplement should also contain a commitment to place the first production batch and annual batches thereafter on long-term stability studies using the approved protocol in the application and to submit the resulting data in annual reports.

A packaging site change for other than solid oral dosage–form drug products is considered a manufacturing site change, and the data package that should be submitted for approval is indicated in Section IX.C.2.

4. Change in Testing Laboratory

An analytical testing laboratory site change may be submitted as a Changes Being Effected Supplement under certain circumstances. No stability data are required.

D. Change in Manufacturing Process or Equipment for the Drug Product

A change limited to the manufacturing process of the drug product, such as a change in the type of equipment used, can be supported by the submission of sufficient data to show that such a change does not alter the characteristics or compromise the stability of the drug product.

E. Change in Batch Size of the Drug Product

A key question in considering an increase in batch size beyond the production batch size approved in the application is whether the change involves a change in equipment or its mode of operation, or other manufacturing parameters described for the approved batch size. If no equipment change is planned, then the next concern is the size of the change relative to the approved batch size, with larger changes expected to present a greater risk of stability problems in the drug product. If an equipment change is part of the batch size change, please refer to Change in Manufacturing Process or Equipment of the Drug Product (Section IX.F).

F. Reprocessing of a Drug Product

Stability data submitted in support of reprocessing a specific batch of a drug product should take into account the nature of the reprocessing procedure and any specific effect it might have on the existing stability profile of the drug. The expiration dating period for a reprocessed batch should not exceed that of the parent batch, and the expiration date should be calculated from the original date of manufacture of the oldest batch.

The acceptability of reprocessing of a specific batch of a drug product will depend on the nature of the reprocessing procedure, which can range from repackaging a batch when packing equipment malfunctions to regrinding and recompressing tablets. The appropriate chemistry review team should be contacted to determine whether the reprocessing procedure is acceptable. Any batch of the drug product that is reprocessed should be placed on accelerated and long-term stability studies using the approved protocol to generate a Type 2 stability data package.

G. Change in Container and Closure of the Drug Product

The stability data packages for changes in container and closure of a drug product vary. The first factor used in determining the stability data package recommendation is whether the protective properties of the container and closure system are affected by the proposed change. Protective properties of the container and closure system include, but are not limited to, moisture permeability, oxygen permeability, and light transmission. Changes that may affect these properties should be supported by a greater amount of data to support the change. The second factor is the nature of the dosage form itself. A solid dosage form will generally be less affected by a container change than a liquid dosage form. Because considerably more information will be needed to document a container and closure change than just stability data, applicants are encouraged to consult with the appropriate chemistry review team to determine the appropriate filing mechanisms.

H. Changes in the Stability Protocol

In general, modification of the approved stability protocol is discouraged until the expiration dating period granted at the time of approval has been confirmed by long-term data from production batches. However, changes in analytical methods providing increased assurance in product identity, strength, quality, and purity, or to comply with USP monographs, may be appropriate before the confirmation of the expiration dating period.

Certain parameters may be reduced in test frequency or omitted from the stability protocol for annual batches on a case-by-case basis through a Prior Approval Supplement. A justification for such a reduction or omission should be adequately provided.

If justified, test frequency for all parameters may be reduced for annual batches based on accumulated stability data. Such a modification to the approved stability protocol should be submitted as a Prior Approval Supplement. The justification may include a demonstrated history of satisfactory product stability, which may in turn include, but not be limited to, full long-term stability data from at least three production batches. The reduced testing protocol should include a minimum of four data points, including the initial time point and the expiry, and two points in-between. For example, drug products with an expiration dating period of less than 18 months should be tested at quarterly intervals, products with an expiration dating period of 18 but not more than 30 months should be tested semiannually, and products with an expiration dating period of 36 months or longer should be tested annually. It should be noted, however, that the reduced testing protocol applies only to annual batches and does not apply to batches used to support a postapproval change that requires

long-term stability data at submission or as a commitment. Furthermore, whenever product stability failures occur, the original full protocol should be reinstated for annual batches until problems are corrected.

A bracketing or matrixing design, if proposed for annual batches or to support a supplemental change, should be submitted as a Prior Approval Supplement (see Sections VII.G and H). It is acceptable to submit these modifications to the protocol, along with data generated there to support a supplemental change, in one combined Prior Approval Supplement. However, the applicant is encouraged to consult with the appropriate FDA chemistry review team before initiating such studies.

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Note: All references citing FDA or ICH or U.S. Department of Health and Human Services are available at http://www.fda.gov.

GLOSSARY

Accelerated Testing [ICH Q1A] — Studies designed to increase the rate of chemical degradation or physical change of an active drug substance and drug product by using exaggerated storage conditions as part of the formal, definitive stability protocol. These data, in addition to long-term stability data, may also be used to assess longer term chemical effects at nonaccelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Acceptance Criteria [21 CFR 210.3] — Product specifications and acceptance or 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).

Active Substance; Active Ingredient; Drug Substance; Medicinal Substance [ICH Q1A] — Unformulated drug substance that may be subsequently formulated with excipients to produce the drug product.

Approved Stability Protocol — Detailed study plan described in an approved application to evaluate the physical, chemical, biological, and microbiological characteristics of a drug substance and a drug product as a function of time. The approved protocol is applied to generate and analyze acceptable stability data in support of the expiration dating period. It may also be used in developing similar data to support an extension of that expiration dating period and other changes to the application. It should be designed in accordance with the objectives of this guidance.

Batch [21 CFR 210.3(b)(2)] — Specific quantity of a drug 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.

Bracketing [ICH Q1A] — Design of a stability schedule so that at any time point only the samples on the extremes, for example, of container size or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples is represented by those at the extremes.

Climatic Zones [ICH Q1A] — Concept of dividing the world into four zones based on defining the prevalent annual climatic conditions.

Complex Dosage Form — A form in which quality or stability is more likely to be affected by changes because the release mechanism, delivery system, and manufacturing process are more complicated and thus more susceptible to variability. Examples of complex dosage forms include modified-release dosage forms, metered-dose inhalers, transdermal patches, and liposome preparations. Because of the diversity of currently marketed dosage forms and the ever-increasing complexity of new delivery systems, it is impossible to clearly identify simple vs. complex dosage forms in an exhaustive manner. Applicants are advised to consult with the appropriate FDA chemistry review team when questions arise.

Confirmatory Studies [ICH Q1B] — Studies undertaken to establish photostability characteristics under standardized conditions. These studies are used to identify precautionary measures needed in manufacturing or formulation and whether light-resistant packaging or special labeling is needed to mitigate exposure to light. For the confirmatory studies, the batch or batches should be selected according to batch selection for long-term and accelerated testing, described in the parent guidance.

Conjugated Product [ICH Q5C] — Made up of an active ingredient (e.g., peptide, carbohydrate) bound covalently or noncovalently to a carrier (e.g., protein, peptide, inorganic mineral) with the objective of improving the efficacy or stability of the product.

Controlled Room Temperature [USP] — Temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25°C (68°–77°F) and that results in a mean kinetic temperature calculated to be not more than 25°C and allows for excursions between 15° and 30°C (59°–86°F) that are experienced in pharmacies, hospitals, and warehouses.

Date of Production — Date that the first step of manufacture is performed that involves the combining of an active ingredient, antioxidant, or preservative with other ingredients in the production of a dosage form. For drug products consisting of a single ingredient filled into a container, the date of the production is the initial date of the filling operation. For a biological product subject to licensure, see the definition of date of manufacture in 21 CFR 610.50.

Degradation Product [ICH Q5C] — Molecule resulting from a change in the drug substance bulk material brought about over time. For the purpose of stability testing of the products described in this guidance, such changes could occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, and proteolysis). For biotechnological and biological products, some degradation products may be active.

Dosage Form; Preparation [ICH Q1A] — Pharmaceutical product type, for example, tablet, capsule, solution, ocream, that contains a drug substance, generally, but not necessarily, in association with excipients.

Drug Product; Finished Product [ICH Q1A] — Dosage form in the final immediate packaging intended for marketing.

Drug Substance; Active Substance [21 CFR 312.3(b)] — Active ingredient 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 human body.

Excipient [ICH Q1A] — Anything other than the drug substance in the dosage form.

Expiry or Expiration Date [ICH Q1A] **—** Date placed on the container or labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions and after which it must not be used.

Extractables and Leachables — Materials or components derived from the container and closure that have been transferred into the contained drug substance or drug product.

Forced Degradation Testing Studies [ICH Q1B] — Studies undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substances, are used to evaluate the overall photosensitivity of the material for method development purposes or degradation pathway elucidation.

Formal (Systematic) Studies [ICH Q1A] — Studies undertaken to a preapproval stability protocol that embraces the principles of these guidances.

Immediate (Primary) Pack [ICH Q1B] — Constituent of the packaging that is in direct contact with the drug substance or drug product and that includes any appropriate label.

Impurity — Any entity of the drug substance (bulk material) or drug product (final container product) that is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product.

Intermediate [ICH Q5C] — For biotechnological or biological products, a material produced during a manufacturing process that is not the drug substance or the drug product but for which manufacture is critical to the successful production of the drug substance or the drug product. Generally, an intermediate will be quantifiable and specifications

will be established to determine the successful completion of the manufacturing step before continuation of the manufacturing process. This includes material that may undergo further molecular modification or be held for an extended period before further processing.

Long-Term (Real-Time) Testing [ICH Q1A] — Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a drug product and a drug substance, covering the expected duration of the shelf life and retest period, which are claimed in the submission and will appear on the labeling.

Lot [21 CFR 210.3(b)(10)] — 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, specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specific limits.

Manufacturing-Scale Production [ICH Q5C] — Manufacture at the scale typically encountered in a facility intended for product production for marketing.

Marketing Pack [ICH Q1B] — Combination of immediate pack and other secondary packaging such as a carton.

Mass Balance (Material Balance) [ICH Q1A] — Process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical precision. This concept is a useful scientific guide for evaluating data but is not achievable in all circumstances. The focus may instead be on ensuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing [ICH Q1A] — Statistical design of a stability schedule so that only a fraction of the total number of samples are tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure, and possibly, in some cases, different containers and closure systems. Matrixing can cover reduced testing when more than one variable is being evaluated. Thus, the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the FDA chemistry review team where this is possible. In every case, it is essential that all batches are tested both initially and at the end of the long-term testing period.

Mean Kinetic Temperature [ICH Q1A] — Isothermal temperature that corresponds to the kinetic effects of a time–temperature distribution.

Modified-Release Dosage Forms [SUPAC-MR] — Dosage forms whose drug-release characteristics of time course or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

New Dosage Form [ICH Q1C] — Drug product that is a different pharmaceutical product type but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority.

New Molecular Entity; New Active Substance [ICH Q1A] — Substance that has not previously been registered as a new drug substance with the national or regional authority concerned.

Pilot-Plant Scale — Manufacture of either drug substance or drug product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale. For oral solid dosage forms this is generally taken to be at a minimum scale of one tenth that of full production or 100,000 tablets or capsules, whichever is the larger. [Q1A] For biotechnology products, the methods of cell expansion, harvest, and product purification should be identical except for the scale of production. [ICH Q5C]

Primary Stability Data [ICH Q1A] — Data on the drug substance stored in the proposed packaging under storage conditions that support the proposed retest date. Data on the drug product stored in the proposed container and closure for marketing under storage conditions that support the proposed shelf life.

Production Batch — Batch of a drug substance or drug product manufactured at the scale typically encountered in a facility intended for marketing production.

Random Sample — Selection of units chosen from a larger population of such units so that the probability of inclusion of any given unit in the sample is defined. In a simple random sample, each unit has an equal chance of being included. Random samples are usually chosen with the aid of tables of random numbers found in many statistical texts.

Reference-Listed Drug [21 CFR 314.3] — Listed drug identified by the FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application.

Retest Date [ICH Q1A] — Date when samples of the drug substance should be reexamined to ensure that the material is still suitable for use.

Retest Period [ICH Q1A] — Time interval during which the drug substance can be considered to remain within the specifications and therefore be acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions; after this period

the batch should be retested for compliance with specifications and then used immediately.

Semipermeable Container — Container that permits the passage of a solvent, such as water contained therein, but prevents the passage of the dissolved substance or solute, thus resulting in an increased concentration of the latter over time. It may also permit the ingress of foreign volatile materials. The transport of the solvent, its vapor, or other volatile material occurs through the container by dissolution into one surface, diffusion through the bulk of the material, and desorption from the other surface, all caused by a partial-pressure gradient. Examples of semipermeable containers include plastic bags or semirigid LDPE for LVPs, and LDPE ampoules, vials, or bottles for inhalation or ophthalmic solutions.

Semisolid Dosage Forms [SUPAC-SS] — Semisolid dosage forms include nonsterile and semisolid preparations, for example, creams, gels, and ointments, intended for all topical routes of administration.

Shelf Life; Expiration Dating Period [ICH Q1A] — Time interval that a drug product is expected to remain within the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed containers and closure.

Significant Body of Information [SUPAC-IR/MR] — Immediate Release Solid Oral Dosage Forms: A significant body of information on the stability of the drug product is likely to exist after 5 years of commercial experience for new molecular entities or 3 years of commercial experience for new dosage forms. Modified-Release Solid Oral Dosage Forms: A significant body of information should include, for modified-release solid oral dosage forms, a product-specific body of information. This product-specific body of information is likely to exist after 5 years of commercial experience for the original complex dosage form drug product or 3 years of commercial experience for any subsequent complex dosage form drug product.

Significant Change [ICH Q1A] — Significant change for a drug product at the accelerated stability condition and the intermediate stability condition is defined as

1. A 5% potency loss from the initial assay value of a batch
2. Any specified degradant exceeding its specification limit
3. The product exceeding its pH limits
4. Dissolution exceeding the specification limits for 12 capsules or tablets
5. Failure to meet specifications for appearance and physical properties; for example, color, phase separation, resuspendibility, delivery per actuation, caking, hardness

Simple Dosage Form — Dosage form whose quality or stability is less likely to be affected by the manufacturing site because the release mechanism, delivery system, and manufacturing process are less complicated and less susceptible to variability. Examples of simple dosage forms include immediate-release solid oral dosage forms; for example, tablets, capsules, semisolid dosage forms, and oral and parenteral solutions. Because of the diversity of currently marketed dosage forms and the ever-increasing complexity of new delivery systems, it is impossible to clearly identify simple vs. complex dosage forms in an exhaustive manner. Applicants are advised to consult with the appropriate FDA chemistry review team when questions arise.

Site-Specific Batches — Batches of drug substance or drug product made at the intended manufacturing-scale production site from which stability data are generated to support the approval of that site, as well as to support the proposed retest period or expiration dating period, respectively, in an application. The site-specific batch or batches of the drug product should be made from identifiable site-specific batch or batches of the drug substance whenever possible.

Specification-Check/Shelf Life [ICH Q1A] — Combination of physical, chemical, biological, and microbiological test requirements if a drug substance must meet up to its retest date or that a drug product must meet throughout its shelf life.

Specification-Release [ICH Q1A] — Combination of physical, chemical, biological, and microbiological test requirements that determine if a drug product is suitable for release at the time of its manufacture.

Stability — Capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest period or expiration dating period, as appropriate.

Stability Commitment — Statement by an applicant to conduct or complete prescribed studies on production batches of a drug product after approval of an application.

Stability-Indicating Methodology — Validated quantitative analytical methods that can detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference.

Stability Profile — Physical, chemical, biological, and microbiological behavior of a drug substance or drug product as a function of time when stored under the conditions of the Approved Stability Protocol.

Storage Conditions Tolerances [ICH Q1A] — Acceptable variation in temperature and relative humidity of stability storage.

Strength [21 CFR 210.3(b)(16)] — Concentration of the drug substance (e.g., weight/weight, weight/volume, or unit dose/volume basis) or the potency, that is, the therapeutic activity of the drug product as indicated by an appropriate laboratory test or by adequately developed and

controlled clinical data (e.g., expressed in terms of units by reference to a standard).

Stress Testing—Drug Product [ICH Q1A] — Light testing should be an integral part of stress testing. Special test conditions for specific products (e.g., metered dose inhalations and creams and emulsions) may require additional stress studies.

Stress Testing—Drug Substance [ICH Q1A] — Studies undertaken to elucidate intrinsic stability characteristics. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated tests.

Supporting Stability Data [ICH Q1A] — Data other than the primary stability data, such as stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers or closures other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support the analytical procedures, the proposed retest period, or shelf life and storage conditions.

Tentative Expiration Dating Period — Provisional expiration dating period that is based on acceptable accelerated data, statistical analysis of available long-term data, and other supportive data for an NDA product, or on acceptable accelerated data for an ANDA product but not on full long-term stability data from at least three production batches.

5 Guidelines for Evaluation of Stability Data in Retest Periods

I. INTRODUCTION

This chapter describes when and how limited extrapolation can be undertaken to propose a retest period for a drug substance or shelf life for a drug product beyond the observed range of data from the long-term storage condition.

A. Background

Although the parent guideline (see Chapter 4) states that regression analysis is an acceptable approach to analyzing quantitative stability data for retest period or shelf-life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25, it includes few details. In addition, the parent guideline does not cover situations in which multiple factors are involved in a full or reduced-design study.

B. Scope of the Guideline

This guideline, an annex to the parent guideline (Chapter 4), is intended to provide a clear explanation of expectations when proposing a retest period or shelf-life and storage conditions based on the evaluation of stability data for both quantitative and qualitative test attributes. This guideline outlines recommendations for establishing a retest period or shelf life based on stability data from single or multifactor and full or reduced-design studies. International Conference on Harmonisation (ICH) Guidelines Q6A and Q6B provide guidance on the setting and justification of acceptance criteria.

II. GUIDELINES

A. General Principles

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances.

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms). Where appropriate, attention should be paid to reviewing the adequacy of the mass balance. Factors that can cause an apparent lack of mass balance should be considered; for example, the mechanisms of degradation and the stability-indicating capability and inherent variability of the analytical procedures. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life.

The recommendations in this guideline on statistical approaches are not intended to imply that use of statistical evaluation is preferred when it can be justified as being unnecessary. However, statistical analysis can be useful in the extrapolation of retest periods or shelf lives in certain situations and may be called for to verify the retest periods or shelf lives in other cases.

The basic concepts of stability data evaluation are the same for single- vs. multifactor studies and for full- vs. reduced-design studies. Data evaluation from the formal stability studies and, as appropriate, supporting data should be used to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately and an overall assessment made of the findings for the purpose of proposing a retest period or shelf life. The retest period or shelf life proposed should not exceed that predicted for any single attribute.

A flow diagram on how to analyze and evaluate long-term stability data for appropriate quantitative test attributes from a study with a multifactor full or reduced design is provided in Appendix A. The statistical method used for data analysis should consider the stability study design to provide a valid statistical inference for the estimated retest period or shelf life.

In general, certain quantitative chemical attributes (e.g., assay, degradation products, and preservative content) for a drug substance or product can be assumed to follow zero-order kinetics during long-term storage. Data for these attributes are therefore amenable to linear regression and poolability testing. Qualitative attributes are not amenable to statistical analysis and microbiological attributes, and certain quantitative attributes (e.g., pH,

dissolution) are generally not amenable to the type of statistical analysis.

B. Data Presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative), and an evaluation of those data should be included in the application. If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis or graphical presentation of the long-term data should be included.

C. Extrapolation

Limited extrapolation to extend the retest period or shelf life beyond the observed range of available long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Any extrapolation should take into consideration the possible worst-case situation at the time of batch release.

Extrapolation is the practice of using a known data set to infer information about future data sets. An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the observed range of available long-term data. Hence, the use of extrapolation should be justified in terms of, for example, what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, and the existence of relevant supporting data.

The correctness of the assumed change pattern is crucial if extrapolation beyond the available long-term data is contemplated. For example, when estimating a regression line or curve within the available data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of fit of the data to the assumed line or curve. No such internal check is available beyond the length of observed data. Thus, a retest period or shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the extrapolated retest period or shelf life.

D. Data Evaluation for Retest Period or Shelf-Life Estimation for Drug Substances or Products Intended for "Room Temperature" Storage

A systematic evaluation of the data from formal stability studies should be performed as illustrated in this section. In general, stability data for each attribute should be assessed sequentially, beginning with significant change, if any, at the accelerated condition and, if appropriate, the intermediate condition, and progressing through the trends and variability of long-term data. The circumstances are delineated under which extrapolation of retest period or shelf life beyond the observed length of long-term data can be appropriate.

1. No Significant Change at Accelerated Condition

Where no significant change occurs at the accelerated condition, the retest period or shelf-life setting would depend on the nature of the long-term and accelerated data.

a. Long-Term and Accelerated Data Showing Little or No Change over Time and Little or No Variability

Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it may be apparent that the drug substance or product will remain well within its acceptance criterion for that attribute during the proposed retest period or shelf life. Under these circumstances, it is normally considered unnecessary to go through a statistical analysis, but justification for the omission should be provided. Justification can include a discussion of the mechanisms of degradation or lack of degradation, relevance of the accelerated data, mass balance, or other supporting data as defined in the parent guideline.

Extrapolation of the retest period or shelf life beyond the length of available long-term data can be proposed. A proposed retest period or shelf life up to twice the length of available long-term data can be proposed, but it should not exceed the length of available long-term data by more than 12 months.

b. Long-Term or Accelerated Data Showing Change over Time and Variability

If the long-term or accelerated data for an attribute show change over time or variability within a factor or among factors, statistical analysis of the long-term data can be useful in establishing a retest period or shelf life. Where there are considerable differences in stability observed among batches or other factors (e.g., container size or fill strength) or factor combinations (e.g., strength-by-container size or fill), the proposed retest period or shelf life should be based on the shortest period supported by the worst batch, factor, or factor combination. Alternatively, where the differences are readily attributed to a particular factor (e.g., strength), different shelf lives can be assigned to different levels within the factor (e.g., different strengths). A discussion should be provided to address the cause for the differences and the overall significance of such a difference on the product. Extrapolation beyond the length of available long-term data can be proposed; however, the

extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

i. Data Not Amenable to Statistical Analysis (for Qualitative Attributes or Certain Quantitative Attributes)

When relevant supporting data are provided, a retest period or shelf life up to one and one-half times the length of available long-term data can be proposed, but it should not exceed the length of available long-term data by more than 6 months. Relevant supporting data include satisfactory long-term data from development batches that are made with a closely related formulation to, manufactured on a smaller scale than, or packaged in a container closure system similar to that of the primary stability batches.

ii. Data Amenable to Statistical Analysis

If a statistical analysis is not performed, the extent of extrapolation should be the same as above (i.e., when relevant supporting data are provided, a retest period or shelf life up to one and one-half times the length of available long-term data can be proposed, but it should not exceed the length of available long-term data by more than 6 months). However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to twice the length of available long-term data when supported by the statistical analysis and supporting data, although this proposed retest period or shelf life should not exceed the length of available long-term data by more than 12 months.

2. Significant Change at Accelerated Condition

Where significant change (see below) occurs at the accelerated condition, the retest period or shelf life setting would depend on the outcome of stability testing at the intermediate condition, as well as long-term testing. The following physical changes can be expected to occur at the accelerated condition and would not be considered significant changes that call for intermediate testing if there is no other significant change (potential interaction effects should also be considered in establishing that there is no other significant change): softening of a suppository that is designed to melt at 37°C, if the melting point is clearly demonstrated, and failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if it can be unequivocally attributed to cross-linking. However, phase separation of semisolid dosage forms at the accelerated condition could call for testing at the intermediate condition.

a. No Significant Change at Intermediate Condition

If there is no significant change at the intermediate condition, extrapolation beyond the length of available long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

i. Data Not Amenable to Statistical Analysis

Based on an attribute that is not amenable to statistical analysis, a retest period or shelf life can be proposed when relevant supporting data are provided, but the proposed retest period or shelf life should not exceed the length of available long-term data by more than 3 months.

ii. Data Amenable to Statistical Analysis

If the long-term data for an attribute are amenable to statistical analysis but such an analysis is not performed, the extent of extrapolation would be the same as above. However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to one and one-half times the length of available long-term data when supported by the statistical analysis and relevant supporting data, but not exceeding the length of available long-term data by more than 6 months.

b. Significant Change at Intermediate Condition

Where significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the extent of available long-term data. In addition, a shorter retest period or shelf life could be called for. If the long-term data show variability, verification of the retest period or shelf life by statistical analysis can be appropriate.

E. Data Evaluation for Retest Period or Shelf-Life Estimation for Drug Substances or Products Intended for Storage Below "Room Temperature"

1. Drug Substances or Products Intended for Refrigerated Storage

Data from products intended to be stored in a refrigerator should be assessed according to the same principles described throughout this document for the general case pertaining to products intended for "room temperature" storage, except where explicitly noted in the section below. A decision tree is provided in Appendix A as an aid to the guidance below.

a. No Significant Change at Accelerated Condition for Products Intended for Refrigerated Storage

Where no significant change occurs at the accelerated condition, extrapolation of retest period or shelf life beyond the length of available long-term data can be proposed. The proposed retest period or shelf life can be up to one and one-half times the length of available long-term data, but should not exceed the length of available long-term data by more than 6 months.

b. Significant Change at Accelerated Condition for Products Intended for Refrigerated Storage

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the real-time data available at the long-term storage condition. No extrapolation can be considered.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the real-time data available at the long-term storage condition. No extrapolation should be performed. In addition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance or product for a period shorter than 3 months.

2. Drug Substances or Products Intended for Storage in a Freezer

For drug substances and products intended for storage in a freezer, the retest period or shelf life should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances or products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5° ± 3°C or 25° ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

3. Drug Substances or Products Intended for Storage Below −20°C

For drug substances and products intended for storage below −20°C, the retest period or shelf life should be based on the real-time data obtained at the proposed long-term storage condition and should be assessed on a case-by-case basis.

F. General Statistical Approaches

Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances. This same method could also be applied to commitment batches to verify or extend the originally approved retest period or shelf life.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear or nonlinear function on an arithmetic or logarithmic scale. Sometimes a nonlinear regression can be expected to better reflect the true relationship.

An appropriate approach to retest period or shelf-life estimation is to analyze a quantitative attribute by determining the earliest time at which the 95% confidence limit for the mean around the regression curve intersects the proposed acceptance criterion.

For an attribute known to decrease with time, the lower one-sided 95% confidence limit should be compared with the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95% confidence limit should be compared with the criterion. For an attribute that can either increase or decrease, or whose direction of change is not known, two-sided 95% confidence limits should be calculated and compared with the upper and lower acceptance criteria.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated retest period or shelf life. The approach described above can be used to estimate the retest period or shelf life for a single batch or for multiple batches when combined after an appropriate statistical test.

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APPENDIX A: DECISION TREE FOR DATA EVALUATION FOR RETEST PERIOD OR SHELF LIFE ESTIMATION FOR DRUG SUBSTANCES OR PRODUCTS (EXCLUDING FROZEN PRODUCTS)

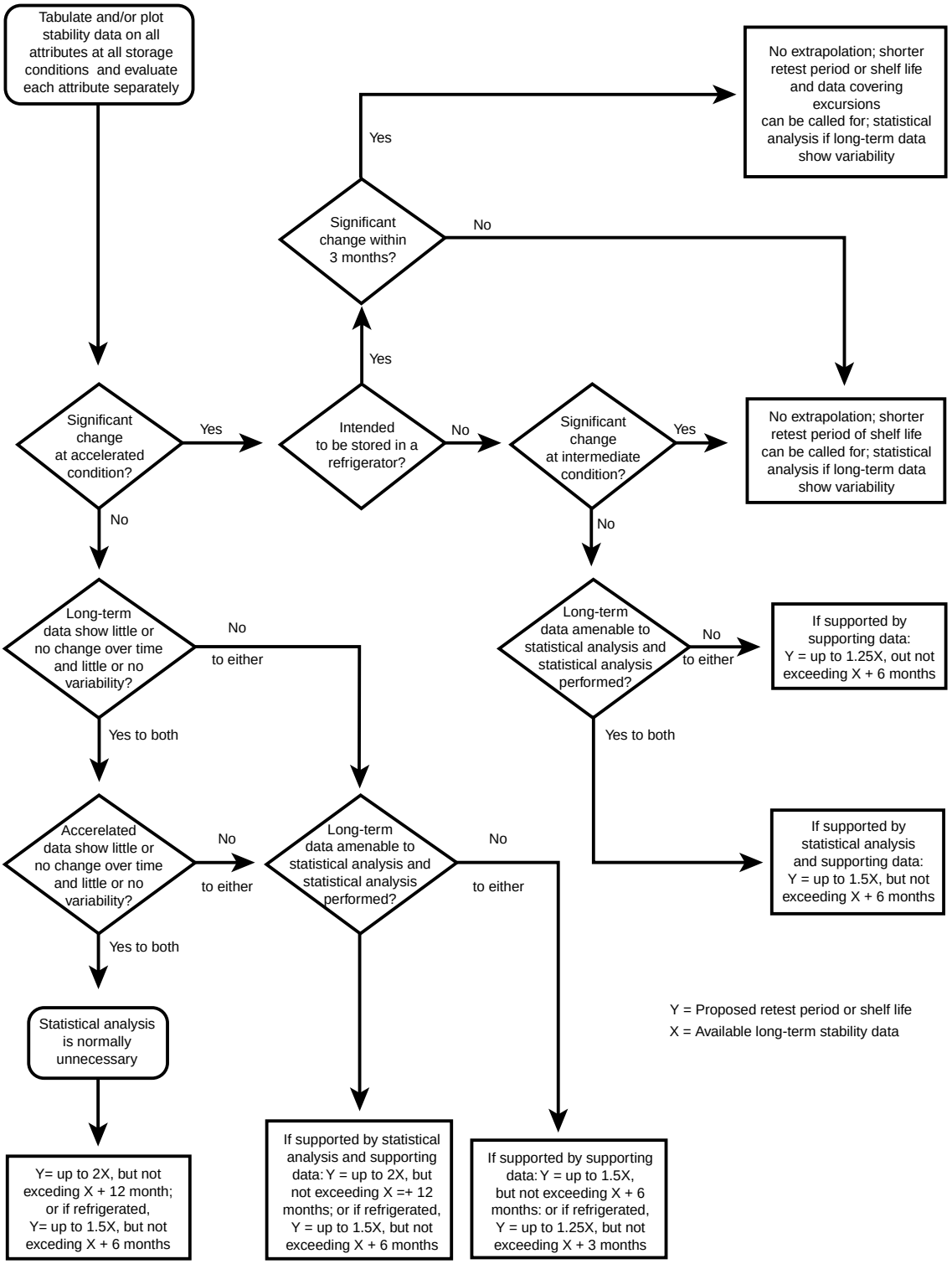

FIGURE 5.1

6 Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products

To fully evaluate the equivalence of a transdermal product for an abbreviated new drug application to a reference-listed drug, skin irritation and sensitization should be assessed because the condition of the skin may affect the absorption of a drug from a transdermal system. More severe skin irritation may affect the efficacy or safety of the product.

Transdermal products have properties that may lead to skin irritation or sensitization. The delivery system, or the system in conjunction with the drug substance, may cause these reactions. In the development of transdermal products, dermatologic adverse events are evaluated primarily with animal studies and safety evaluations in the context of large clinical trials generally associated with the submission of new drug applications. Separate skin irritation and skin sensitization studies also are used for this purpose. These latter studies are designed to detect irritation and sensitization under conditions of maximal stress and may be used during the assessment of transdermal drug products for abbreviated new drug applications.

I. STUDY DESIGNS

Recommended designs for skin irritation and skin sensitization studies for the comparative evaluation of transdermal drug products for an abbreviated new drug application are delineated below. Other proposals for studies may be suggested, but potential applicants are advised to consult the Office of Generic Drugs about alternative study designs before the initiation of such a study.

A. Recommendations for a Cumulative Skin Irritation Study

1. Sample Size

The sample size should be 30 subjects.

2. Exclusion Criteria

Dermatologic disease that might interfere with the evaluation of test site reaction should be grounds for exclusion.

3. Duration of Study

The study should last for 22 days.

4. Study Design

The study should be a randomized, controlled, repeat patch test study that compares the test patch with the innovator patch. Placebo patches (transdermal patch without active drug substance) or high- and low-irritancy controls (e.g., sodium lauryl sulfate 0.1% and 0.9% saline) can be included as additional test arms.

5. Patch Application

Each subject applies one of each of the patches to be tested. Test sites should be randomized among patients. Patches should be applied for 23 hours (±1 hour) daily for 21 days to the same skin site. At each patch removal, the site should be evaluated for reaction and the patch reapplied.

Application of a test patch should be discontinued at a site if predefined serious reactions occur at the site of repeated applications. Application at a different site may subsequently be initiated.

6. Evaluations

Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritations. (See Appendix A for an example of a scoring system that can be used.) The percentage adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

7. Data Presentation and Analysis

Individual daily observations should be provided, as well as a tabulation that presents the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score, the total cumulative irritation score, and the number of days until sufficient irritation occurred to preclude patch application for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed (see Appendix C).

B. Recommendations for a Skin Sensitization Study (Modified Draize Test)

1. Sample Size

Two hundred subjects should be sampled.

2. Exclusion Criteria

Exclusion criteria include

a. Dermatologic disease that might interfere with the evaluation of the test site reactions
b. Use of systemic or topical analgesics or antihistamines within 72 hours of study enrollment or systemic or topical corticosteroids within 3 weeks of study enrollment

3. Duration of Study

The study should last 6 weeks.

4. Study Design

The study should be a randomized, controlled study on three test products: the test transdermal patch, the innovator patch, and the placebo patch (transdermal patch without the active drug substance).

5. Patch Application

Test sites should be randomized among patients. The study is divided into three sequential periods.

a. Induction Phase

Applications of the test materials should be made to the same skin sites three times weekly for 3 weeks, for a total of nine applications. The patches should remain in place for 48 hours on weekdays and for 72 hours on weekends. Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. (See Appendix A for an example of a scoring system that can be used.) The percentage adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

b. Rest Phase

The induction phase is followed by a rest phase of 2 weeks, during which no applications are made.

c. Challenge Phase

The patches should be applied to new skin sites for 48 hours. Evaluation of skin reactions should be made by a trained blinded observer at 30 minutes and at 24, 48, and 72 hours after patch removal. (See Appendix A for an example of a scoring system that can be used.)

6. Data Presentation and Analysis

The individual daily observations should be provided, as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed.

A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of contact sensitization.

C. Combined Studies

Alternatively, the cumulative skin irritation study and the skin sensitization study can be combined into a single study. The study design would be identical to that described for the skin sensitization study (see Section I.B), except that patch application during the induction phase should be daily for 23 hours (±1 hour) each day over 21 days.

APPENDIX A

Skin Irritation Scoring Systems

The following scoring system for irritation or sensitization reactions is included as an example of a scoring system that can be used for these studies. Other validated scoring systems can be used in quantifying skin reactions. The inclusion of this system should not be interpreted as an endorsement of the system by the agency. It is provided as an example only.

1. Dermal response:
   0 = no evidence of irritation
   1 = minimal erythema, barely perceptible
   2 = definite erythema, readily visible; minimal edema or minimal papular response
   3 = erythema and papules
   4 = definite edema
   5 = erythema, edema, and papules
   6 = vesicular eruption
   7 = strong reaction spreading beyond test site
2. Other effects:
   A = slight glazed appearance
   B = marked glazing
   C = glazing with peeling and cracking
   D = glazing with fissures

E = film of dried serous exudate covering all or part of the patch site
F = small petechial erosions or scabs

APPENDIX B

Adhesion Score

The following scoring system is included as an example of a scoring system that can be used for this type of study. Other validated scoring systems may be equally effective in quantifying comparative adhesion of transdermal systems. The inclusion of this system is not to be interpreted as an endorsement of the system by the agency. It is provided as an example only.4

An estimate of the adherence of the transdermal system will be rated as follows:

0 ≥ 90% adhered (essentially no lift off of the skin)
1 ≥ 75% to <90% adhered (some edges only lifting off of the skin)
2 ≥ 50% to <75% adhered (less than half of the system lifting off of the skin)
3 ≤ 50% adhered but not detached (more than half the system lifting off of the skin without falling off)
4 = patch detached (patch completely off the skin)

APPENDIX C

To be considered equivalent for a particular response, the average response for the generic (μ_T) should be between 80% and 125% of the average response for the innovator (μ_R). It is recommended that the response of the generic be equivalent to or better than the innovator. This implies a one-sided test.

For a variable for which low scores are better, such as mean irritation score or total cumulative irritation score, the hypotheses would be

$$H_0: \mu_T/\mu_R > 1.25,$$

$$H_1: \mu_T/\mu_R \leq 1.25;$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 1.25\ \mu_R > 0,$$

$$H_1: \mu_T - 1.25\ \mu_R \leq 0.$$

The null hypothesis H_0 will be rejected when the upper limit of the 90% confidence interval (that is, the 95% upper confidence bound) for the quantity $\mu_T - 1.25\ \mu_R$ is less than or equal to zero.

For a variable for which high values are better, such as time to removal score, the hypotheses would be

$$H_0: \mu_T/\mu_R < 0.80,$$

$$H_1: \mu_T/\mu_R \geq 0.80;$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 0.80\ \mu_R < 0,$$

$$H_1: \mu_T - 0.80\ \mu_R \geq 0.$$

The null hypothesis H_0 will be rejected in this case when the lower limit of the 90% confidence interval (that is, the 95% lower confidence bound) for the quantity $\mu_T - 0.80\ \mu_R$ is greater than or equal to zero.

In either case, if the null hypothesis H_0 is rejected the generic should be considered equivalent or better than the innovator.

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7 Photosafety Testing

I. INTRODUCTION

This guidance is intended to help applicants decide whether they should test for photoirritation and assess the potential of their drug product to enhance ultraviolet (UV)-associated skin carcinogenesis, something the new applicants will find the U.S. Food and Drug Administration (FDA) is often keen to know. The guidance describes a consistent, science-based approach for photosafety evaluation of topically and systemically administered drug products. Basic concepts of photobiology and phototesting are described, along with a process that can be used to make testing decisions or communicate risks.

Use of the principles expressed in this guidance should reduce unnecessary testing while ensuring an appropriate assessment of photosafety. The document does not recommend specific tests but refers to some available testing methods. Sponsors may choose to use some of these tests to evaluate photoirritation, photochemical carcinogenicity potential, or potential to enhance UV-associated skin carcinogenesis. Sponsors also can propose other assays that are scientifically sound. Tests involving biomarkers in the skin of humans receiving the drug product may clarify mechanisms of direct or indirect photoeffects seen in nonclinical studies (see section IV.C, Mechanistically Based and Other Assays).

Photosafety testing (testing for adverse effects of drug products in the presence of light) is recommended only when it is felt that the results of such testing would yield important safety information or would be informative for the consumer and healthcare practitioner.

The glossary at the end of the document defines abbreviations and important terminology used to describe photobiologic concepts. The clinical definition of photosensitivity includes both phototoxicity (photoirritation) and photoallergy. This document uses the clinical definition but addresses nonclinical testing for photochemical irritation (photoirritation) only. At this time, nonclinical models of testing for photoallergy are not considered to be predictive of clinical effects and are not recommended.

II. BACKGROUND

A. Photoirritation and Photococarcinogenicity

Photobiology is the study of the effect of UVA or UVB, visible, and infrared radiation on living systems.[1,2] The first law of photochemistry (Grotthaus-Draper Law) states that light must be absorbed for a photochemical event to occur.[3] Chromophores in drug products and DNA in dermal tissue are targets for photochemical reactions. Photoirritation or photoallergy occur when a photoactive chemical enters the skin by dermal penetration or systemic circulation and becomes excited by appropriate UV or visible light photons. Fortunately, the skin is an optically heterogeneous medium that modifies the amount of radiation that can reach deeper dermal structures and functions as a protective barrier that minimizes damage from light exposure. Protective mechanisms include reflection, refraction, scattering, and absorption.[4] Excision-repair and other DNA repair mechanisms of UV-damaged DNA[5–7] provide further protection against gene mutation and skin cancer.

Photoirritation is a light-induced, nonimmunologic skin response to a photoreactive chemical. The route of exposure to the photoreactive chemical can be by direct application to the skin or by the circulatory system following systemic administration. Photoirritation reactions resemble primary irritation reactions in that they can be elicited following a single exposure, in contrast to photoallergic reactions, which have an induction period before elicitation of the response. A photoactive chemical can be the parent drug or an excipient in a drug product, or it can be a metabolite, impurity, or degradant. Many diverse classes of drugs (including antimicrobials, NSAIDs, antidepressants, anticonvulsants, diuretics, and antihypertensives) have been reported to cause photoirritation in humans.[8–10] Acute photoirritation reactions can resemble sunburn and may range from a mild erythema to blistered skin with sloughing. Although a relatively small percentage of the population may show clinical symptoms of photoirritation, a much larger percentage may have immediate subclinical effects. Nonclinical tests can identify some photoirritating drug products before widespread clinical exposure occurs, allowing appropriate precautions to be implemented.

Photoallergy is an acquired, immunologically mediated reaction to a chemical, activated by light. The occurrence of a photoallergic response to a chemical is idiosyncratic (highly dependent on the specific immune reactivity of the host). Compounds that elicit a photoirritation response also may be capable of initiating a photoallergic reaction. Examples of photoallergens in humans include promethazine, benzocaine, and *p*-aminobenzoic acid.[8,9] Photoallergy is

best assessed clinically; several approaches for evaluation of clinical photoallergy potential are available.

Data from animals and humans indicate that at least some photoirritants enhance UV-associated skin carcinogenesis. 8-Methoxypsoralen (8-MOP), used in psoralen plus UVA treatment therapy,[12] is considered to be a photococarcinogen in humans, whereas several fluoroquinolones have been demonstrated to be photoirritants and photochemical carcinogens in hairless mice.[11] However, data for many other classes of pharmaceuticals are unavailable.

Other drug products that are not photochemical irritants can enhance UV-induced skin carcinogenesis. Epidemiologic data[10,13,14] indicate that persons on chronic immunosuppressive therapy (e.g., cyclosporin following organ transplantation) are at greater risk for skin cancer than the general population. A compound can also enhance UV carcinogenicity indirectly by altering biologic processes or optical or structural features of the skin that function as protective mechanisms. Data from animals exposed to drug vehicles that decrease protective properties of the skin support this concept.[15]

Changes in the optical properties of the skin, such as those caused by a drug vehicle, can result in a greater UV dose to the viable layers of the skin. Data on correlation of latitude, UV exposure, and cancer risk in humans indicate that an increase in UV exposure as small as 20% could result in a fourfold increase in basal-cell carcinoma.[16]

B. Historical Approach to Photosafety Testing

Historically, the majority of systemically administered drugs have not undergone controlled testing for determining their potential for photoirritation, yet a number of these drugs were later identified as phototoxic to humans. Topically applied dermatologic drugs routinely have been tested for photoirritation in both animals and humans if they absorb light in the UVA, UVB, or visible spectrum. In the absence of data from photoirriation or photoallergy tests conducted in animals or humans, warnings about the potential for photoirritation or photoallergy generally have been added to labels after reports of adverse reactions resulting from widespread clinical use of the products.

Relatively few drug products have been tested to elucidate their potential for enhancing UV-mediated carcinogenic effects on the skin. By itself, UV light is a carcinogen in humans.[17] The regulatory issue is whether a drug enhances the carcinogenic effect of UV light to such an extent that it significantly increases the potential human carcinogenic risk, making it important that the patient and the physician be informed. However, testing for photococarcinogenicity in humans is unethical, so animal testing has been used as a surrogate. The method that has commonly been used for testing the potential photococarcinogenicity of a compound has been the Skh1-*hr* hairless mouse model. A positive response in this photococarcinogenicity assay is a decreased time to skin neoplasm development in animals exposed to the test material plus UV radiation (i.e., sunlight simulation), compared with exposure to the same dose of UV radiation alone. Information from this assay has been included in labels and may furnish a frame of reference for comparisons among drugs. Numerous researchers have conducted variants of this assay in several strains of haired mice that had been shaved. However, because of the uncertainties involved in extrapolation from such animal testing to humans and the apparent insensitivity of this assay to some topical immunosuppressants and topical photogenotoxicants, other scientifically valid methods providing relevant information for assessing the long-term adverse photoeffects of drug products on biomarkers in human skin are desirable.

III. TESTING CONSIDERATIONS

A. General Considerations for Testing a Drug Product or Drug Substance

For most drugs, it is generally adequate to test only the drug substance without the excipients for adverse photoeffects. For topical products that will be applied to sun-exposed skin, the FDA recommends that the drug product, not just the active ingredient, be evaluated under conditions of simulated sunlight. This is because many excipients in these types of products modify the skin, and dermal applications usually deliver relatively large amounts of both parent drug and vehicle to the skin. Many researchers have reported the effects of topically applied vehicles on the skin, some of which alter the optical properties of human skin. Some examples of these effects are as follows:

- Pharmaceutical vehicles (e.g., creams, gels, lotions, or solutions) can decrease the amount of light reflected, scattered, or absorbed in the skin[18,19] or increase the percutaneous absorption of drugs in the skin of humans and mice.[20,21]
- Vehicles can increase or decrease adverse photoproperties[22,23] or photostability of drug products.[24–26] Vehicles can enhance the effects of other components in the formulation and increase epidermal thickening in rodent skin,[27] change collagen gene expression in hairless mice,[28] or influence the solubility and general stability of the drugs.[29]
- Some cream-based vehicles have been found to be photosensitizers themselves (proprietary), whereas some oil-based emollients can increase UVB transmission and UV carcinogenicity in mice.[15]

B. Testing for Photochemical Irritation

1. Background

Nonclinical tests for photochemical irritation are considered predictive of human effects. The intent of the procedures discussed below is to ascertain the potential of pharmaceuticals to elicit a photochemical irritation reaction before widespread human use. The process attempts to address these safety concerns adequately while optimizing the use of resources. To accomplish this goal, a decision tree approach is recommended to assess whether testing should be conducted and what type of testing may be appropriate. Other approaches may also accomplish this goal. It is recognized that even short-term exposure to some nonphotoreactive drugs in the presence of ultraviolet light could result in adverse effects in the skin (e.g., those that can immediately change the optical properties of the skin).

2. Proposed Approaches to Identifying Photochemical Irritants

Short-term photoirritation testing in animals, perhaps followed by photoirritation and photoallergy studies in humans, should be considered for all drug substances and formulation components that absorb UVB, UVA, or visible radiation (290–700 nm) and that are directly applied to the skin or eyes, significantly partition to one of these areas when administered systemically, or are known to affect the condition of the skin or eyes. A drug product would not be considered for testing for photoirritation potential if the person receiving the drug would not be exposed to light in the sunlight spectrum while the drug or photoactive metabolites were in the body. In addition, it would not be appropriate to conduct photochemical irritation testing on a drug product that was applied only to skin not exposed to the sun if the drug did not undergo significant distribution to sun-exposed areas.

A description of the flowchart testing paradigm follows. Information regarding the UV/visible radiation absorption spectrum for the drug substance or drug formulation, as appropriate, is important in making a testing decision. A spectroscopic scan will determine whether a drug absorbs between 290 and 700 nm of the electromagnetic spectrum. The scan is an important component of the safety assessment. Presentation of only absorption maxima will not adequately address safety concerns. Drug products that do not absorb between 290 and 700 nm will not be photoactivated. Therefore, they cannot be direct photochemical photosensitizers. Some drugs elicit a photosensitivity reaction that is unrelated to the UV absorbance of the administered drug. These secondary mechanisms include perturbation of heme synthesis and increased formation of other light-absorbing endogenous molecules resulting from administration of non–light-absorbing drugs (e.g., aminolevulinic acid).[11] These effects may be identified from standard toxicologic testing. In addition to absorption of UV or visible radiation, the drug (or metabolites) should reach the skin or eye at levels sufficient to cause photoirritation reactions. Tissue distribution studies of systemically administered drug products, usually included in Investigational New Drug Application (IND) submissions, can be used to assess the extent of partitioning into the skin or eyes. In the absence of partitioning into light-exposed compartments, photoirritation testing is unlikely to be informative and need not be conducted. However, agents used for photodynamic therapy might be an exception, and valuable safety information (e.g., effects on internal organs after exposure to operating room lighting) can be generated even if partitioning into the skin or eyes does not occur.

When drugs are identified as photoirritants, the FDA recommends that the risk communication include a warning to avoid sun exposure. In the absence of human data, a drug shown to be a photoirritant in nonclinical studies could be indicated as potentially causing photosensitivity. When adequate human data addressing photoirritation are available, they would be included in the description of the product and would supplant animal data.

3. Testing of Reformulations

In general, reformulations intended for administration by routes other than topical application to the skin do not have to be tested, provided that any new excipients undergo appropriate evaluation. It is also not necessary to test most reformulations of a topical product for nonclinical photoeffects. If the drug substance or excipients have previously been shown to cause photoirritation, additional nonclinical photoirritation testing is generally not needed. However, the FDA recommends that excipient changes that could modify adverse photoeffects on the skin be tested. For example, the agency recommends that a switch to a cream formulation from an ethanolic solution generally be evaluated for photoeffects. Information on the photoirritant properties of excipients and their effects on the penetration of the drug substance into the skin would be useful in further defining whether new formulations should be studied. Studies of dermal absorption of the drug substance for one formulation do not necessarily supply relevant data on the absorption for all formulations. Inclusion of topical excipients not previously studied for adverse photoeffects in a new formulation may also warrant testing of the new formulation.

4. Tests for Evaluation of Photosensitivity

Testing should be conducted under conditions of simulated sunlight to be clinically relevant. Even though a particular substance has ground-state absorption in UVA

or UVB after it absorbs radiation, a transient or stable photoproduct may be produced that absorbs in a different absorption range.[30,31] A number of methods and approaches are used that test for photoirritation. Appropriate animal models (generally mice or guinea pigs, but also rabbits or swine) have been discussed by Marzulli and Maibach[32,33] and Lambert et al.[34] Several *in vitro* screens for photoirritation, such as the 3T3 neutral red uptake photocytotoxicity test, are available.[35] The 3T3 assay may be useful for products that absorb UVA, UVB, or visible radiation. This assay may not be appropriate for the evaluation of some water-insoluble substances or complete drug formulations. Data from *in vitro* studies may provide sufficient information when conditions of the study are appropriate for the evaluation of the drug product of interest and may be important in planning more efficient comprehensive *in vivo* assessments. For *in vivo* nonclinical studies, acute drug exposure followed by simulated sunlight exposure is generally considered adequate to identify potential risks. Assessments of photoirritation may be incorporated into ongoing general toxicity studies in some circumstances. Human studies are also often conducted to follow up on potential risks identified on the basis of animal or *in vitro* evaluations.

IV. TESTING FOR ENHANCEMENT OF UV-ASSOCIATED SKIN CARCINOGENESIS (DIRECT PHOTOCHEMICAL CARCINOGENICITY OR INDIRECT EFFECTS IN SKIN)

A. Considerations and Decision Tree for Testing Photosensitizing Drugs for Long-Term Photosafety

Long-term photosafety testing is generally conducted only when it can provide useful information. Long-term photosafety studies should be avoided when sufficient information has already been collected for a drug or a class of drugs to appropriately inform potential users regarding photoreactivity.

Once a systemically or dermally administered drug has been identified as a photoirritant in animal or human testing, one should consider the drug's potential to increase UV-associated skin cancer risk. Because patients are already cautioned against excessive sunlight exposure during use of photoirritating drugs, sponsors could choose to strengthen these warnings with regard to photocarcinogenic potential, rather than conduct testing to determine the photochemical carcinogenicity potential for photoirritating drugs. The option to strengthen the warning statements without conducting additional testing would be appropriate primarily in those circumstances in which photochemical carcinogenic activity would not affect approvability or significantly reduce the utility of a drug product. The warning statement should convey the basis of the warning and the conditions under which the potential carcinogenic effect is likely to be realized.

Warnings alone may be sufficient because drug products that are photoirritants can cause rapid erythema (sunburn) reactions in patients who expose themselves to sun without adequate protection. Unlike many drug side effects, sunburn is immediately apparent to affected patients, who become quickly aware of the reactions during use. However, not all patients receiving a photoirritating drug may experience overt photoirrritation effects. Some drugs can cause subthreshold photoeffects (e.g., DNA damage) that are not apparent to patients. Thus, these drugs can also pose a long-term risk for adverse skin effects. It is important for product warnings to address this situation. Other circumstances for which product warning statements, rather than long-term testing, may be appropriate include the following:

- Drugs having structures significantly similar to known photochemical carcinogens
- Drugs that are in a known pharmacologic class of photochemical carcinogens, where the pharmacology of the product is believed to be directly related to the carcinogenic potential
- Drugs for which several other tests for photoreactivity, such as *in vitro* photogenotoxicity, adduct formation, human photoirritation, or short-term *in vivo* nonclinical tests, are positive
- Drugs that have been identified as carcinogens with potential human relevance in other assays that do not include UV sunlight, such as traditional 2-year bioassays or transgenic assays
- Drugs for indications intended for populations in which the life expectancy is short (i.e., less than 5 years)

The warning should be informative, advising patients to avoid sun exposure, or if sunlight exposure cannot be avoided, to use protective clothing and broad-spectrum (UVA/UVB) sunscreens (when the wavelengths eliciting photoirritation are in the range covered by the sunscreen). However, it is important to recognize that subclinical photoirritation responses with prolonged use could also result in increased skin cancer risk. In general, for the above cases, warning statements are considered an adequate option, and phototesting, although potentially scientifically informative, may not be warranted. In those cases in which additional testing may be of value, it can often be conducted during phase 4 of the drug development process (i.e., postapproval). For drugs for which the approvability or utility would be an issue (e.g., sunscreens), testing beyond that noted above may be appropriate. Testing should be conducted using a model for which there is

evidence that relevant end points are assessed and considered scientifically valid. In some circumstances, a drug sponsor may want to demonstrate that, despite initial results indicating a potential for photocarcinogenicity, the drug does not pose a risk for UV-associated skin cancer. The results of appropriately conducted assays would be included in any communication of the overall risk.

Short-term assays that measure photoreactivity (such as photogenotoxicity) have been developed in the hope that they would provide information about the potential to enhance UV-induced skin carcinogenesis. However, the interpretation of such assays is not always straightforward, and their role in the evaluation of human risk should be carefully assessed. Although the most widely performed test for the potential to enhance UV-induced skin cancer is the hairless albino mouse model with solar simulation, other scientifically valid assays for evaluating the photochemical carcinogenicity potential can also be considered for regulatory purposes. When considering testing strategy, it is strongly encouraged that sponsors discuss issues with the appropriate Center for Drug Evaluation and Research review staff. One potential strategy is the use of biomarkers in human skin to evaluate the consequences of combined drug and UV exposure. Use of biomarkers should be considered and supported on the basis of a thorough evaluation of the scientific data (see Section IV.C, Mechanistically Based and Other Assays).

B. Decision Tree for Testing Nonphotoreactive Drugs for Long-Term Photosafety

The decision tree approach would apply to products used chronically or for chronic conditions as defined in the International Conference on Harmonization guidance for industry *S1B Testing for Carcinogenicity of Pharmaceuticals*.[41] As noted earlier, drug products that do not cause photoirritation reactions can enhance UV carcinogenicity. The decision tree used for nonphotoreactive products attempts to balance the risks associated with these potentially silent enhancers of UV-induced skin carcinogenesis while attempting to identify areas where testing is unnecessary. Pharmacologic activity (see Section IV.B.3) could provide information on such risks. It is anticipated that, even in the absence of information about such risks, most nonphotoreactive drugs would not be tested for their potential to enhance UV-induced skin carcinogenesis, even if they were administered chronically. This assumes that when administered chronically, drugs usually would be tested for carcinogenicity in traditional bioassays. Some secondary mechanisms of enhancement of UV carcinogenicity, such as immunosuppression or inhibition of DNA repair, would be detected by use of traditional carcinogenicity studies. The approach for nonphotoreactive drugs is described as follows.

1. Duration of Use

Nonphotoreacting drugs that are not used long term or that are not chronic conditions do not appear to present a significant risk of enhancing UV-induced skin carcinogenesis. Thus, it is unlikely that these drugs would be tested in any assay for potential to enhance UV-induced skin cancer. In addition, drug products intended solely for use in populations with a short life expectancy (less than 5 years) need not be tested. Chronic use may be continuous or substantial, repeated use, and it may justify such testing.

2. Route of Administration

In general, topically applied drugs for which the intended effect is localized only to the area of application to non–sun-exposed skin and that do not reach pharmacologically measurable systemic levels will not need to be tested for potential to enhance UV-induced skin cancer. This principle also applies to other drugs that do not reach measurable systemic levels (e.g., drugs with mainly local effects on the respiratory tract).

3. Reasons to Suspect Drug May Enhance UV-Induced Skin Carcinogenesis

The majority of drug products that are investigated and marketed are not photoreactive and are unlikely to be photococarcinogens. However, a major class of potent, known human photococarcinogens (e.g., immunosuppressants such as cyclosporine)[10,13] that cause skin neoplasms are nonphotoreactive. There are other examples of drug vehicles or nonphotoreactive drugs that enhance UV-induced skin carcinogenesis in mice.[36,37] The mechanisms of enhancement by these nonphotoreactive drugs or vehicles have not been studied and can only be surmised.[42] Some of the mechanisms by which nonphotoreactive vehicles or drugs can enhance UV-induced skin carcinogenesis include, but are not limited to, immunosuppression, neoplastic promotion, inhibition of apoptosis or DNA repair, and irritation, altering the protective layers of the epidermis or changing the optical properties of the skin. Such mechanisms are applicable to both rodent and human skin and are biologically plausible mechanisms of enhancement. Products, such as some emollients, that change the optical properties of the skin or alter the protective layers of the epidermis can greatly change UV penetration of the skin or the effective UV dose that the skin receives. The open literature contains ample references to the effects of vehicles on skin and on the overall performance of a drug product. These and other indirect effects (discussed in section IV.C, Mechanistically Based and Other Assays) can also occur in human skin and may be as important as direct photoreactive effects. For example, studies sponsored by the cosmetics industry indicated increased sensitivity to UVB by persons using alphahydroxy acid

preparations. As a consequence, the Cosmetic Ingredient Review Expert Panel[38] recommended that persons using these products avoid unprotected exposure to the sun. The alphahydroxy acids used in these studies do not absorb UV between 280 and 400 nm. Thus, a thoughtful approach is called for when deciding whether additional testing for potential to enhance UV-induced skin carcinogenesis is justified.

4. Warning or Test

If preliminary evaluations indicate that a drug or drug product may have the potential to enhance UV-induced skin carcinogenesis, the sponsor should warn of this potential effect or conduct studies to evaluate this potential. Such studies could be a panel of appropriately selected and scientifically valid biomarkers in human skin, referred to in Section IV.C, Mechanistically Based and Other Assays. Although some drug products that do not absorb light could lower the minimal erythema dose (MED) by changing the optical properties of the skin, resulting in increased UV effects, drugs that do not absorb light are not tested for photoirritation according to the current testing paradigm. If it were demonstrated that a nonphotoreactive drug product increased transmission of UV radiation through the skin, resulting in measurable increases in UV susceptibility, such as lowering the MED in animals or humans, then further photosafety studies in animals, such as a photococarcinogenesis study, may not be appropriate. A product that increases the dose of UV light penetrating the skin would likely shorten the time to skin neoplasms and could be labeled appropriately.

C. Mechanistically Based and Other Assays

Mouse and human skin share many of the same responses to sunlight and drugs. Exposure to sunlight clearly modifies DNA and causes nonmelanoma skin cancer in both animals and humans.[17] Although there are a number of differences, many of the proposed mechanisms by which drug substances or drug products can enhance UV-associated skin carcinogenesis are shared by mice and humans. Pyrimidine dimer formation and p53 protein induction have been demonstrated in human skin *in situ* after suberythemal doses of solar-simulated light.[39] Evaluation of the potential to indirectly enhance UV carcinogenicity using biomarkers in skin may be appropriate, provided that the biomarkers are scientifically supported. A testing strategy can be discussed with the appropriate Center for Drug Evaluation and Research review division. To improve testing procedures, it would be helpful to identify appropriate surrogate markers in human skin for increased UV exposure or UV damage.

Useful tests would be those that provide information on the relevance of, or sensitivity to, adverse photoeffects *in vitro* or in animals relative to humans. Tests could include, but would not be limited to, *in vitro* measures of photocytotoxicity, *in vitro* measures of photogenotoxicity (e.g., in Salmonella, yeast, or V79 cells), transgenic models, and biomarkers (molecular, biochemical, cellular, or structural) for enhancement of UV-induced skin carcinogenesis in human skin. Changes in the MED, sunburn cell number,[40] p53 alterations, dimer formation in DNA,[41] and other end points have been proposed as markers of increased UVB exposure or skin damage. Markers for increased UVA exposure, as well as for UVB exposure, would be desirable. Although the preferred radiation exposure in these assays would be sunlight simulation, at a minimum, the appropriate absorption spectrum for a photoreactive drug product should be covered. Assays assessing immunosuppression or inhibition of DNA repair, particularly in human skin, may be useful in testing some products. It is important to define the strengths and limitations of the assays. Correlation of the *in vitro* results for photoirritation with data from controlled clinical studies would add to the potential utility of such tests. Correlation of the biomarker response in animal skin with the biomarker response in human skin for the same UV dose could provide a basis for evaluation of the size of a response in a clinical surrogate that would translate into a clinically meaningful increase in skin cancer risk. Submission of a test or rationale including relevant data should accompany any proposal to use novel methods. The recommendations of this guidance recognize both the importance of adverse photoeffects and the difficulty in appropriately assessing human risks. This guidance allows a flexible approach to be used to address adverse photoeffects and does not require that a specific assay be used. Most important, it encourages the development of methods that can efficiently be used to evaluate human safety.

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GLOSSARY

ADR—Adverse drug reaction
Excipients—Ingredients that are intentionally added to therapeutic products but that do not directly exert pharmacologic effects at the intended dosage
Indirect Photoeffects—Effects of an agent, vehicle, or product on the optical, structural, molecular, or physiologic properties of the skin, such that the interaction of light and skin or effects of drug in skin are altered
IR—Infrared radiation 0.76–1000 μm
MED—Minimal erythema dose
8-MOP—8-methoxypsoralen
Nonphotoreactive—Drugs or chemicals that do not react with another molecule in the formulation or skin after exposure to UVA, UVB, or visible radiation
NSAID—Nonsteroidal anti-inflammatory drug
Photoallergy—An acquired, immunologically mediated reaction to a drug or chemical initiated by the formation of photoproducts when that drug or chemical is exposed to light
Photochemical carcinogenesis—Carcinogenesis resulting from a reaction with a photoactivated drug or chemical
Photococarcinogenicity—The direct (photochemical carcinogenesis) or indirect enhancement of UV-associated skin carcinogenesis (e.g., sunlight-associated carcinogenesis) by a drug or chemical
Photoirritation or Photochemical Irritation—A light-induced, nonimmunologic skin response to a photoreactive drug or chemical
Photoproducts—Compounds resulting from absorption of radiation by a drug or chemical
Photoreactive—Drugs or chemicals that react with another molecule in the formulation or skin after exposure to UVA, UVB, or visible radiation
Photosafety Testing—Testing for the potential of a drug product to cause photoirritation or photoallergy or to enhance UV-induced skin carcinogenesis
Photosensitivity—Photoirritation- or photoallergy-induced reaction
Photosensitizer—Drug or chemical that causes an adverse effect in the presence of UVA/UVB or visible light
Phototoxicity—Light-induced, nonimmunologic response to a photoreactive drug or chemical
PUVA—Psoralen plus UVA treatment
UV—Ultraviolet radiation (wavelengths between 10 and 400 nm)
UVA—Ultraviolet radiation A (wavelengths between 320 and 400 nm)
UVB—Ultraviolet radiation B (wavelengths between 290 and 320 nm)
UVC—Ultraviolet radiation C (wavelengths between 200 and 290 nm)

8 Guidance on Formulating Semisolid Drugs

The subjects covered here are generally applicable to all forms of topical drug products, including those that are intended to be sterile. The topics given below address several problem areas that may be encountered in the production of semisolid drug products (including transdermal products) including their potency, active ingredient uniformity, physical characteristics, microbial purity, and chemical purity.

I. POTENCY UNIFORMITY

Active ingredient solubility and particle size are generally important ingredient characteristics that need to be controlled to ensure potency uniformity in many topical drug products such as emulsions, creams, and ointments. Crystalline form is also important where the active ingredient is dispersed as a solid phase in either the oil or water phase of an emulsion, cream, or ointment.

It is important that active ingredient solubility in the carrier vehicle be known and quantified at the manufacturing step in which the ingredient is added to the liquid phase. The development data should adequately demonstrate such solubility and its validation.

Substances that are very soluble, as is frequently the case with ointments, would be expected to present less of a problem than if the drug substance were to be suspended, as is the case with creams. If the drug substance is soluble, then potency uniformity would be based largely on adequate distribution of the component throughout the mix.

If the active ingredient is insoluble in the vehicle, then in addition to ensuring uniformity of distribution in the mix, potency uniformity depends on control of particle size and use of a validated mixing process. Particle size can also affect the activity of the drug substance because the smaller the particle size, the greater its surface area, which may influence its activity. Particle size also affects the degree to which the product may be physically irritating when applied; in general, smaller particles are less irritating.

Production controls should be implemented that account for the solubility characteristics of the drug substance; inadequate controls can adversely affect product potency, efficacy, and safety. For example, in one instance, residual water remaining in the manufacturing vessel, used to produce an ophthalmic ointment, resulted in partial solubilization and subsequent recrystallization of the drug substance; the substance recrystallized in a larger particle size than expected and thereby raised questions about the product efficacy.

In addition to ingredient solubility and particle size, other physical characteristics and specifications for both ingredients and finished products are important.

II. EQUIPMENT AND PRODUCTION CONTROL

A. Mixers

There are many different kinds of mixers used in the manufacture of topical products. It is important that the design of a given mixer is appropriate for the type of topical product being mixed. One important aspect of mixer design is how well the internal walls of the mixer are scraped during the mixing process. This can present some problems with stainless steel mixers because scraper blades should be flexible enough to remove interior material, yet not rigid enough to damage the mixer itself. In general, good design of a stainless steel mixer includes blades that are made of some hard plastic, such as Teflon®, which facilitates scrapping of the mixer walls without damaging the mixer.

If the internal walls of the mixer are not adequately scraped during mixing and the residual material becomes part of the batch, the result may be nonuniformity. Such nonuniformity may occur, for example, if operators use handheld spatulas to scrape the walls of the mixer.

Another mixer design concern is the presence of "dead spots" where quantities of the formula are stationary and not subject to mixing. Where such dead spots exist, there should be adequate procedures for recirculation or nonuse of the cream or ointment removed from the dead spots in the tank.

B. Filling and Packaging

Suspension products often require constant mixing of the bulk suspension during filling to maintain uniformity. When validating a suspension manufacturing process, determine how to ensure that the product remains homogeneous during the filling process and establish the data that support the adequacy of the firm's process. When the batch size is large and the bulk suspension is in large tanks, determine how the low levels of bulk suspension near the end of the filling process are handled. If the bulk suspension drops

below a level, can this be adequately mixed? This question must be answered. If the residual material transferred to a smaller tank, how is the reliance made on handmixing of the residual material? The adequacy of the process for dealing with residual material should be demonstrated.

C. Process Temperature Control

Typically, heat is applied in the manufacture of topical products to facilitate mixing or filling operations. Heat may also be generated by the action of high-energy mixers. It is important to control the temperature within specified parameters, not only to facilitate those operations but also to ensure that product stability is not adversely affected. Excessive temperatures may cause physical or chemical degradation of the drug product, vehicle, active ingredient or ingredients, or preservatives. Furthermore, excessive temperatures may cause insoluble ingredients to dissolve, reprecipitate, or change particle size or crystalline form.

Temperature control is also important where microbial quality of the product is a concern. The processing of topical products at higher temperatures can destroy some of the objectionable microorganisms that may be present. However, elevated temperatures may also promote incubation of microorganisms.

Temperature uniformity within a mixer should be controlled. In addressing temperature uniformity, one should consider the complex interaction among vat size, mixer speed, blade design, viscosity of contents, and rate of heat transfer. Where temperature control is critical, use of recording thermometers to continuously monitor and document temperature measurements is preferred to frequent manual checks. Where temperature control is not critical, it may be adequate to manually monitor and document temperatures periodically by use of handheld thermometers.

III. CLEANING VALIDATION

It is current good manufacturing practice for a manufacturer to establish and follow written standard operating procedures to clean production equipment in a manner that precludes contamination of current and future batches. This is especially critical where contamination may present direct safety concerns, as with a potent drug such as a steroid (e.g., cortisone, and estrogen), antibiotic, or sulfa drug, where there are hypersensitivity concerns.

The insolubility of some excipients and active substances used in the manufacture of topical products makes some equipment, such as mixing vessels, pipes, and plastic hoses, difficult to clean. Often piping and transfer lines are inaccessible to direct physical cleaning. Some firms address this problem by dedicating lines and hoses to specific products or product classes.

It is therefore important that the following considerations be adequately addressed in a cleaning validation protocol and in the procedures that are established for production batches.

A. Detailed Cleaning Procedures

Cleaning procedures should be detailed and provide specific understandable instructions. The procedure should identify equipment, cleaning methods, solvents and detergents approved for use, inspection and release mechanisms, and documentation. For some of the more complex systems, such as clean-in-place systems, it is usually necessary both to provide a level of detail that includes drawings and to provide provision to label valves. The time that may elapse from completion of a manufacturing operation to initiation of equipment cleaning should also be stated where excessive delay may affect the adequacy of the established cleaning procedure. For example, residual product may dry and become more difficult to clean.

B. Sampling Plan for Contaminants

As part of the validation of the cleaning method, the cleaned surface is sampled for the presence of residues. Sampling should be made by an appropriate method, selected on the basis of factors such as equipment and solubility of residues. For example, representative swabbing of surfaces is often used, especially in areas that are hard to clean or where the residue is relatively insoluble. Analysis of rinse solutions for residues has also been shown to be of value where the residue is soluble or difficult to access for direct swabbing. Both methods are useful when there is a direct measurement of the residual substance. However, it is unacceptable to test rinse solutions (such as purified water) for conformance to the purity specifications for those solutions instead of testing directly for the presence of possible residues.

C. Equipment Residue Limits

Because of improved technology, analytical methods are becoming much more sensitive and capable of determining very low levels of residues. Thus, it is important to establish appropriate limits on levels of post–equipment-cleaning residues. Such limits must be safe, practical, achievable, and verifiable and must ensure that residues remaining in the equipment will not cause the quality of subsequent batches to be altered beyond established product specifications. The rationale for residue limits should be established. Because surface residues will not be uniform, it should be recognized that a detected residue level may not represent the maximum amount that may be present. This is particularly true when surface sampling by swabs is performed on equipment.

IV. MICROBIOLOGICAL

A. Controls (Nonsterile Topicals)

The extent of microbiological controls needed for a given topical product will depend on the nature of the product, the use of the product, and the potential hazard to users posed by microbial contamination. This concept is reflected in the current good manufacturing practice regulations at 21 Code of Federal Regulations (CFR) 211.113(a) (Control of microbiological contamination), and in the U.S. Pharmacopeia (USP). It is therefore vital that manufacturers assess the health hazard of all organisms isolated from the product.

1. Deionized Water Systems for Purified Water

The microbiological control of deionized water systems used to produce purified water is important. Deionizers are usually excellent breeding areas for microorganisms. The microbial population tends to increase as the length of time between deionizer service periods increases. Other factors that influence microbial growth include flow rates, temperature, surface area of resin beds, and, of course, the microbial quality of the feed water. These factors should be considered in assessing the suitability of deionizing systems where microbial integrity of the product incorporating the purified water is significant. There should be a suitable routine water monitoring program and a program of other controls as necessary.

It is not necessary to assess and monitor the suitability of a deionizer by relying solely on representations of the deionizer manufacturer. Specifically, product quality could be compromised if a deionizer is serviced at intervals based not on validation studies but, rather, on the "recharge" indicator built into the unit. Unfortunately, such indicators are not triggered by microbial population but, rather, are typically triggered by measures of electrical conductivity or resistance. If a unit is infrequently used, sufficient time could elapse between recharging and sanitizing to allow the microbial population to increase significantly.

Preuse validation of deionizing systems used to produce purified water should include consideration of such factors as microbial quality of feed water (and residual chlorine levels of feed water where applicable), surface area of ion-exchange resin beds, temperature range of water during processing, operational range of flow rates, recirculation systems to minimize intermittent use and low flow, frequency of use, quality of regenerant chemicals, and frequency and method of sanitization.

A monitoring program used to control deionizing systems should include established water quality and conductivity monitoring intervals, measurement of conditions and quality at significant stages through the deionizer (influent, postcation, postanion, post–mixed bed, etc.), microbial conditions of the bed, and specific methods of microbial testing. Frequency of monitoring should be based on the firm's experience with the systems.

Other methods of controlling deionizing systems include establishment of water-quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, documentation of regeneration, and a description of sanitization and sterilization procedures for piping, filters, and so forth.

2. Microbiological Specifications and Test Methods

Microbiological specifications and microbial test methods for each topical product should be well-established to ensure that they are consistent with any described in the relevant application or USP. In general, product specifications should cover the total number of organisms permitted, as well as specific organisms that must not be present. These specifications must be based on use of specified sampling and analytical procedures. Where appropriate, the specifications should describe action levels where additional sampling or speciation of organisms is necessary.

Manufacturers must demonstrate that the test methods and specifications are appropriate for their intended purpose. Where possible, firms should use methods that isolate and identify organisms that may present a hazard to the user under the intended use. It should be noted that the USP does not state methods that are specific for water-insoluble topical products.

One test deficiency to be aware of is inadequate dispersement of a cream or ointment on microbial test plates. Firms may claim to follow USP procedures, yet in actual practice they may not disperse product over the test plate, resulting in inhibited growth as a result of concentrated preservative in the nondispersed inoculate. The spread technique is critical, and the firm should document that the personnel performing the technique have been adequately trained and are capable of performing the task. Validation of the spread-plate technique is particularly important when the product has a potential antimicrobial affect.

In assessing the significance of microbial contamination of a topical product, both the identification of the isolated organisms and the number of organisms found are significant. For example, the presence of a high number of organisms may indicate that the manufacturing process, component quality, or container integrity may be deficient. Although high numbers of nonpathogenic organisms may not pose a health hazard, they may affect product efficacy and physical/chemical stability. Inconsistent batch-to-batch microbial levels may indicate some process or control failure in the batch. The batch release evaluation should extend to both organism identification and numbers and, if limits are exceeded, there should be an investigation into the cause.

B. Preservative Activity

Manufacturing controls necessary to maintain the antimicrobiological effectiveness of preservatives should be evaluated. For example, for those products that separate on standing, there should be data available that show the continued effectiveness of the preservative throughout the product's shelf life.

For preservative-containing products, finished product testing must ensure that the specified level of preservative is present before release. In addition, preservative effectiveness must be monitored as part of the final ongoing stability program. This can be accomplished through analysis for the level of preservative previously shown to be effective or through appropriate microbiological challenge at testing intervals.

For concepts relating to sterility assurance and bioburden controls on the manufacture of sterile topicals, see the Guideline on Sterile Drug Products Produced by Aseptic Processing.

V. CHANGE CONTROL

As with other dosage forms, it is important to carefully control how changes are made in the production of topical products. The procedures should be able to support changes that represent departures from approved and validated manufacturing processes. There should be written change control procedures that have been reviewed and approved by the quality-control unit. The procedures should provide for full description of the proposed change, the purpose of the change, and controls to ensure that the change will not adversely alter product safety and efficacy. Factors to consider include potency or bioactivity, uniformity, particle size (if the active ingredient is suspended), viscosity, chemical and physical stability, and microbiological quality.

Of particular concern are the effects that formulation and process changes may have on the therapeutic activity and uniformity of the product. For example, changes in vehicle can affect absorption, and processing changes can alter the solubility and microbiological quality of the product.

VI. TRANSDERMAL TOPICAL PRODUCTS

The manufacturing of topical transdermal products (patches) has many problems in scale-up and validation. Problems analogous to production of topical creams or ointments include uniformity of the drug substance and particle size in the bulk gel or ointment. Uniformity and particle size are particularly significant when the drug substance is suspended or partially suspended in the vehicle. Viscosity also needs control because it can affect the absorption of the drug; the dissolution test is important in this regard. Other areas that need special inspectional attention are assembly and packaging of the patch, including adhesion, package integrity (regarding pinholes), and controls to ensure that a dose is present in each unit.

Because of the many quality parameters that must be considered in the manufacture and control of a transdermal dosage form, scale-up may be considerably more difficult than for many other dosage forms. Therefore, special attention should be given to evaluating the adequacy of the process validation efforts. As with other dosage forms, process validation must be based on multiple lots, typically at least three consecutive successful batches. Summary data should be augmented by comparison with selected data contained in supporting batch records, particularly where the data appear unusually uniform or disparate. Given the complexities associated with this dosage form, the tolerances or variances may be broader than for other dosage forms. In addition, batches may not be entirely problem free. Nevertheless, there should be adequate rationale for the tolerances and production experiences, based on appropriate developmental efforts and investigation of problems.

A. Formulations of Semisolid Drugs

In general, semisolid dosage forms are complex formulations having complex structural elements. Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend on various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug as well as other characteristics, such as viscosity.

For a true solution, the order in which solutes are added to the solvent is usually unimportant. The same cannot be said for dispersed formulations, however, because depending on at which phase a particulate substance is added, dispersed matter can distribute differently. In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added. Because the solubility of each added ingredient is important for determining whether a mixture is visually a single homogeneous phase, such data, possibly supported by optical microscopy, should usually be available for review. This is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed. Variations in the manufacturing procedure that occur after either of these events are likely to be critical to

the characteristics of the finished product. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization). Aging of the finished bulk formulation before packaging is critical and should be specifically addressed in process validation studies.

B. The Role of *In Vitro* Release Testing

The key parameter for any drug product is its efficacy as demonstrated in controlled clinical trials. The time and expense associated with such trials make them unsuitable as routine quality control methods. Therefore, *in vitro* surrogate tests are often used to ensure that product quality and performance are maintained over time and in the presence of change. A variety of physical and chemical tests commonly performed on semisolid products and their components (e.g., solubility, particle size and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance. More recently, *in vitro* release testing has shown promise as a means to comprehensively ensure consistent delivery of the active component or components from semisolid products. An *in vitro* release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, *in vitro* release rate is a useful test to assess product sameness between prechange and postchange products. However, there may be instances in which it is not suitable for this purpose. In such cases, other physical and chemical tests to be used as measures of sameness should be proposed and discussed with the agency. With any test, the metrics and statistical approaches to documentation of "sameness" in quality attributes should be considered. The evidence available at this time for the *in vitro–in vivo* correlation of release tests for semisolid dosage forms is not as convincing as that for *in vitro* dissolution as a surrogate for *in vivo* bioavailability of solid oral dosage forms. Therefore, the FDA's current position concerning *in vitro* release testing is as follows:

a. *In vitro* release testing is a useful test to assess product sameness under certain scale-up and postapproval changes for semisolid products.
b. The development and validation of an *in vitro* release test are not required for approval of an NDA, ANDA, or AADA, nor is the *in vitro* release test required as a routine batch-to-batch quality control test.
c. *In vitro* release testing alone is not a surrogate test for *in vivo* bioavailability or bioequivalence.
d. The *in vitro* release rate should not be used for comparing different formulations across manufacturers.

In vitro release is one of several standard methods that can be used to characterize performance characteristics of a finished topical dosage form; that is, semisolids such as creams, gels, and 20 ointments. Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug or drugs it contains should show up as a difference in drug release. Release is theoretically proportional to the square root of time when the formulation in question is in control of the release process because the release is from a receding boundary. *In vitro* release method for topical dosage forms is based on an open chamber diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane. The test product is placed on the upper side of the membrane in the open donor chamber of the diffusion cell, and a sampling fluid is placed on the other side of the membrane in a receptor cell. Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples of the receptor fluid. The *in vitro* release methodology should be appropriately validated. Sample collection can be automated. Aliquots removed from the receptor phase can be analyzed for drug content by high-pressure liquid chromatography or other analytical methodology. A plot of the amount of drug released per unit area (mcg/cm) against the square root of time yields a straight line, the slope of which represents the release rate. This release rate measure is formulation specific and can be used to monitor product quality. The release rate of the biobatch or currently manufactured batch should be compared with the release rate of the product prepared after a change, as defined in this guidance.

C. *In Vivo* Bioequivalence Studies

The design of *in vivo* bioequivalence studies for semisolid dosage forms varies depending on the pharmacological activity of the drug and dosage form. A brief general discussion of such tests follows. The objective is to document the bioequivalence of the drug product for which the manufacture has been changed, as defined in this guidance, compared with the drug product manufactured before the change or with the reference-listed drug. The study design is dependent on the nature of the active drug. The bioequivalence study can be a comparative skin-blanching study as in glucocorticoids (FDA, 1995) or a comparative clinical trial or any other appropriate validated bioequivalence study (e.g., dermatopharmacokinetic study) for the topical dermatological drug product. The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method. (See Van Buskirk et al., 1994.)

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FDA, Topical Dermatological Corticosteroids: *In Vivo* Bioequivalence, June 2, 1995. Van Buskirk, G.A., Shah, V.P., Adair, D., et al., Workshop report: scale-up of liquid and semi-solids disperse systems, *Pharm. Res.*, 11, 1216–1220, 1994.

GLOSSARY

Approved Target Composition—Components and amount of each ingredient for a drug product used in an approved pivotal clinical study or bioequivalence study

Batch—Specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits (21 CFR 210.3(b)(2))

Contiguous Campus—Contiguous or unbroken site or a set of buildings in adjacent city blocks

Creams/Lotions—Semisolid emulsions that contain fully dissolved or suspended drug substances for external application. Lotions are generally of lower viscosity

Diluent—Vehicle in a pharmaceutical formulation commonly used for making up volume or weight (e.g., water, paraffin base)

Drug Product—Finished dosage form (e.g., cream, gel, or ointment) in its marketed package. It also can be a finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b))

Drug Release—Disassociation of a drug from its formulation, thereby allowing the drug to be distributed into the skin or be absorbed into the body, where it may exert its pharmacological effect

Drug Substance—Active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease or to affect the structure or any function of the human body, but that does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b))

Emulsion—Two-phase systems in which an immiscible liquid (dispersed phase) is dispersed throughout another liquid (continuous phase or external phase) as small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) do this by concentration in the interface between the droplet and external phase and by providing a physical barrier around the particle to coalesce. Surfactants also reduce the interfacial tension between the phases, thus increasing the ease of emulsification on mixing. Emulsifying agents substantially prevent or delay the time needed for 27 emulsion droplets to coalesce. Emulsification is the act of forming an emulsion. Emulsification can involve the incorporation of a liquid within another liquid to form an emulsion or a gas in a liquid to form a foam.

Formulation—Listing of the ingredients and quantitative composition of the dosage form

Gel—Semisolid system in which a liquid phase is constrained within a three-dimensional, cross-linked matrix. The drug substance may be either dissolved or suspended within the liquid phase.

Homogenization—Method of atomization and thereby emulsification of one liquid in another in which the liquids are pressed between a finely ground valve and seat under high pressure (e.g., up to 5,000 psi)

Internal Phase—Internal phase or dispersed phase of an emulsion that comprises the droplets that are found in the emulsion

***In Vitro* Release Rate**—Rate of release of the active drug from its formulation, generally expressed as amount/unit area/time

Ointment—Unctuous semisolid for topical application. Typical ointments are based on petrolatum. An ointment does not contain sufficient water to separate into a second phase at room temperature. Water-soluble ointments may be formulated with polyethylene glycol.

Pilot-Scale Batch—Manufacture of drug product by a procedure fully representative of and simulating that intended to be used for full manufacturing scale

Preservative—Agent that prevents or inhibits microbial growth in a formulation to which it has been added

Process—Series of operations, actions, and controls used to manufacture a drug product

Scale-down—Process of decreasing the batch size

Scale-up—Process of increasing the batch size

Shear—Strain resulting from applied forces that cause or tend to cause contiguous parts of a body to slide relative to one another in direction parallel to their plane of contact. In emulsification and suspensions, it is the strain produced on passing a system through a homogenizer or other milling device. Low shear: Processing in which the strain produced through mixing or emulsifying shear is modest. High shear: Forceful processes that, at point of mixing or emulsification, place a great strain on the product. Homogenization, by its very nature, is a high-shear process that leads to a small and relatively uniform emulsion droplet size. Depending on their operation, mills and mixers are categorized as either high-shear or low-shear devices.

S**ignificant Body of Information**—A significant body of information on the stability of the product is likely to exist after 5 years of commercial experience for new molecular

entities or 3 years of commercial experience for new dosage forms.

Strength—Strength is the concentration of the drug substance (e.g., weight/weight, weight/volume, or unit dose/volume basis) or 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 (e.g., expressed in terms of units by reference to a standard) (21 CFR 210.3(b)(16)). For semisolid dosage forms the strength is usually stated as a weight/weight or weight/volume percentage.

Structure-Forming Excipient—Excipient that participates in the formation of the structural matrix that gives an ointment, cream, gel, etc., its semisolid character. Examples are gel-forming polymers, petrolatum, certain colloidal inorganic solids (e.g., bentonite), waxy solids (e.g., cetyl alcohol, stearic acid), and emulsifiers used in creams.

Suspending Agent—Excipient added to a suspension to control the rate of sedimentation of the active ingredients

Technical Grade—Technical grades of excipients differ in their specifications and intended use. Technical grades may differ in specifications or functionality, impurities, and impurity profiles.

Validation—Procedure to establish documented evidence that provides a high degree of assurance that a specific process or test will consistently produce a product or test outcome meeting its predetermined specifications and quality attributes. A validated manufacturing process or test is one that has been proven to do what it purports to or is represented to do. The proof of process validation is obtained through collection and evaluation of data, preferably beginning with the process development phase and continuing through the production phase. Process validation necessarily includes process qualification (the qualification of materials, equipment, systems, building, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

Part II

Formulations of Semisolid Drugs

Aceclofenac Gel-Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg Tablets (g)
1.5	1	Aceclofenac	1.5
9.9	2	Miglyol 812 (Dynamit-Nobel)	9.9
4.9	3	Lutrol E 400	4.9
64.0	4	Deionized water	64.0
19.7	5	Lutrol F 127	19.7

MANUFACTURING DIRECTIONS

1. Mix item 1 with water and cool to about 5°C.
2. Add slowly Lutrol F 127 and continue stirring until it is dissolved.
3. Maintain cool until the air bubbles escape. A milky, firm gel is obtained.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
125.00	1	Acetaminophen micronized, 5% excess	131.25
785.54	2	Suppocire AM	785.54
3.21	3	Crill-3	3.21

MANUFACTURING DIRECTIONS

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer about one third of step 1 to a Becomix vessel through filter sieves; set the temperature to 60°C.
3. Add item 3 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 60°C under vacuum of 0.4–0.6 bar to dissolve.
4. Cool down to 50°–55°C.
5. Load item 1 in step 4 and mix at 10 rpm and homogenize at speed I for 10 minutes maintaining the temperature of 50°–55°C under vacuum as above to make a smooth slurry.
6. Transfer balance quantity of item 2 from step 1 into step 5 through filter sieve, set the temperature at 50°C and speed at 10 rpm, homogenize at speed II and under vacuum for 10 minutes.
7. Transfer into storage vessel and set temperature at 45°C.
8. Fill 920 mg in a suppository mold.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
250.00	1	Acetaminophen micronized, 5% excess	252.50
1137.50	2	Suppocire AM	1137.50

MANUFACTURING DIRECTIONS

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer step 1 to a Becomix vessel through filter sieves; set the temperature to 60°C.
3. Cool down to 50°–55°C and apply vacuum 0.4–0.6 bar.
4. Load item 1 and mix at 10 rpm and homogenize at speed I for 10 minutes, maintaining the temperature of 50°–55°C under vacuum as above to make a smooth slurry.
5. Transfer into storage vessel and set temperature at 45°C.
6. Fill 1390 mg in a suppository mold.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
500.00	1	Acetaminophen micronized, 5% excess	525.00
1137.50	2	Suppocire AM	1137.50

MANUFACTURING DIRECTIONS

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer step 1 to a Becomix vessel through filter sieves; set the temperature to 60°C.
3. Cool down to 50°–55°C and apply vacuum 0.4–0.6 bar.
4. Load item 1 and mix at 10 rpm and homogenize at speed I for 10 minutes maintaining the temperature of 50°–55°C under vacuum as above to make a smooth slurry.
5. Transfer into storage vessel and set temperature at 45°C.
6. Fill 1390 mg in a suppository mold.

Acetylsalicylic Acid Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
100.00	1	Acetylsalicylic acid	100.00
400.00	2	Suppocire AM	400.00

MANUFACTURING DIRECTIONS

1. Heat item 2 to 50°C.
2. Allow to cool to 40°C and add item 1 while stirring with a turbine mixer.
3. Continue mixing and cooling and pour into molds at 35°C that were previously chilled to 0° to –5°C; remove suppositories from molds after 7 minutes.
4. Fill to appropriate weight for strength desired.

Alclometasone Dipropionate Cream and Ointment

The cream and ointment contain alclometasone dipropionate [7(alpha)-chloro-11(beta),17,21-trihydroxy-16(alpha)-methylpregna-1,4-diene-3,20-dione17,21-dipropionate)], a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Each gram of cream contains 0.5 mg of alclometasone dipropionate in a hydrophilic, emollient cream base of propylene glycol, white petrolatum, cetearyl alcohol, glyceryl stearate, PEG 100 stearate, ceteth-20, monobasic sodium phosphate, chlorocresol, phosphoric acid, and purified water. Each gram of ointment contains 0.5 mg of alclometasone dipropionate in an ointment base of hexylene glycol, white wax, propylene glycol stearate, and white petrolatum.

Acyclovir Cream

Bill of Materials

Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
5.00	1	Acyclovir: Use acyclovir micronized	52.00
5.20	1	Acyclovir: Use acyclovir micronized	52.00
1.63	2	Poloxyl 20 cetostearyl ether (cetomacrogol 1000)	16.35
20.40	3	Propylene glycol	204.00
17.00	4	Propylene glycol	170.00
9.65	5	Petrolatum (white soft paraffin)	96.50
6.50	6	Cetostearyl alcohol	65.00
3.50	7	Mineral oil (liquid paraffin)	35.00
36.50	8	Purified water	365.00

MANUFACTURING DIRECTIONS

1. Oil phase
   Load items 5, 6, and 7 in fat-melting vessel and melt at 70°C. Maintain temperature at 70° ± 2°C.
2. Aqueous phase
   Heat item 8 in mixer at 90°C. Cool down to 70°C. Add item 2 in item 8 at 70°C and stir to dissolve. Add item 4 to mixer (step 2.2) and mix. Maintain temperature at 70° ± 2°C.
3. Cream phase
   a. Add oil phase through stainless steel filter to aqueous phase in mixer while mixing at 10–12 rpm, manual mode, and temperature 70° ± 2°C.
   b. Homogenize at low speed with mixing 10–12 rpm, vacuum 0.4–0.6 bar, temperature 70° ± 2°C for 10 minutes.
   c. Cool down to 50°C with mixing.
4. Drug phase
   a. Heat 169.0 g of item 3 at 50°C in water bath.
   b. Disperse item 1 in item 3 (step 4.1) with the help of homogenizer. Homogenize two times with homogenizer (gap setting 1) to make smooth dispersion. Dispersion should be smooth with no gritty particles.
   c. Add the drug phase from step 4.2 to cream base at step 3.3 in mixer.
   d. Rinse the homogenizer and the container with 35.0 g of item 3 (50°C) and add the rinsing to cream base in mixer.
5. Final mixing
   a. Homogenize at high speed for 15 minutes at a temperature of 45°C with continuous mixing at 10–12 rpm.
   b. Cool down to 25°–30°C with continuous mixing.
   c. Unload in stainless steel drum lined with Polythene bag.

Acyclovir Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.000	1	Acyclovir micronized (4% excess)	52.00
28.000	2	Polyethylene glycol 3350	280.00
41.800	3	Polyethylene glycol 400	418.00
25.000	4	Propylene glycol	250.00

MANUFACTURING DIRECTIONS

1. Oil phase
   a. Heat items 2 and 3 to 70°C ± 2°C in mixer to melt. Cool down to 45°C with mixing.
2. Drug dispersion
   a. Disperse item 1 in 200.0 g of item 4 at 50°C in a water bath with the help of homogenizer. The drug dispersion should be smooth with no gritty particles.
   b. Add the drug dispersion to mixer at step 1.
   c. Rinse the container with 50.0 g of item 4 at 50°C and add the rinsing to mixer.
3. Final mixing
   a. Homogenize at high speed with mixing under vacuum 0.4–0.6 bar at 45° ± 2°C for 30 minutes.
   b. Cool down to 25°–30°C with continuous mixing.
   c. Unload in stainless steel drum lined with Polythene bag.

Adapalene Cream

Adapalene cream, 0.1%, contains adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methylparaben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propylparaben, purified water, squalane, and trolamine. The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

Aloe Vera Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
4.0	1	Aloe vera extract 200X	4.0
50.0	2	Propylene glycol	50.0
q.s	3	Preservative	q.s
736.0	4	Water	736.0
11.0	5	Cremophor RH 40	11.0
q.s.	6	Perfume	q.s.
200.0	7	Lutrol F 127	200.0

MANUFACTURING DIRECTIONS

1. Prepare solutions items 1–4 and items 5 and 6 separately and add second to first mixture.
2. Cool this mixture to <10°C (or heat to 70°–80°C) and dissolve item 7. Maintain the temperature until the air bubbles escape and the appearance is clear. Viscosity should be about 60 Pascals, pH about 5.5 (20°–25°C) in the storage vessel.
3. Mix for 2 minutes. Store in a clean storage vessel.

Alum Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
4.00	1	Cetostearyl alcohol	40.00
5.00	2	Octyldodecanol	50.00
4.00	3	Lanolin alcohol	40.00
2.00	4	Ethoxylated castor oil	20.00
2.00	5	White petrolatum	20.00
6.50	6	Alum (aluminum potassium sulfate, 12 H_20)	65.00
2.50	7	Cetylpyridinium ammonium chloride	25.00
95.00	8	Water purified	740.00

MANUFACTURING DIRECTIONS

1. Cetostearyl alcohol, ethoxylated castor oil, lanolin alcohol, octyldodecanol, and white petrolatum weighed and mixed in the ratio defined above are heated to 60°C.
2. Alum and item 7 are dissolved in water at room temperature, and then the solution is heated to 62°C.
3. Both phases are combined in an ointment mixer and homogenized by stirring.
4. While stirring, the cream is cooled to about 30°C, and its weight is supplemented with purified water.
5. The cream is again homogenized by stirring and then filled into an electrolyte-resistant storage bottle.

Aminacrine Hydrochloride Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.10	1	Aminacrine hydrochloride	1.00
5.00 mg	2	Thymol	50.00 mg
9.50	3	Glyceryl monostearate	95.00
3.20	4	Cetostearyl alcohol	32.00
1.90	5	Polyoxyl 40 stearate	19.00
10.00	6	Liquid paraffin	100.00
0.45	7	Cetrimide	4.50
q.s.	8	Isopropyl alcohol	1.30 L
q.s.	9	Perfume	q.s.
q.s.	10	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Charge items 3–5 and half of item 6 into a suitable mixing vessel; heat to 60°C and mix well.
2. Prepare slurry of item 1 in the balance of item 6 and add to step 1 slowly at 60°C under constant stirring.
3. Heat item 10 to 60°C and add to step 2 with stirring to form an emulsion.
4. Cool down to 45°C and add perfume, continue to mix to cool down to room temperature.
5. Fill in appropriate containers.

Amoxacillin Lotion

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.00	1	Ethoxylated cetylstearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isoprpyl myristate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
71.80	6	Water purified	718.00
3.00	7	Propylene glycol	30.00
10.00	8	Acetone	100.00
0.10	9	Dioctyl sodium sulfosuccinate	1.00
2.00	10	Amoxacillin	20.00

Ampicillin Lotion

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.00	1	Ethoxylated cetylstearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isoprpyl myristate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
71.80	6	Water purified	718.00
3.00	7	Propylene glycol	30.00
10.00	8	Acetone	100.00
0.10	9	Dioctyl sodium sulfosuccinate	1.00
2.00	10	Ampicillin	20.00

Anthralin Cream

The anthralin cream 1.0% USP is a smooth, yellow cream containing 1% anthralin USP in an aqueous cream base of glyceryl monolaurate, glyceryl monomyristate, citric acid, sodium hydroxide, and purified water. For topical dermatological use only. The chemical name of anthralin is 1,8-dihydroxy-9-anthrone.

Antifungal Topical Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
39.00	1	Urea*	390.00
0.15	2	Carbopol 940	1.50
5.94	3	Petrolatum	59.40
12.06	4	Mineral oil	120.60
1.875	5	Glyceryl stearate	187.50
0.626	6	Cetyl alcohol	6.26
3.00	7	Propylene glycol	30.00
0.05	8	Xanthan gum	0.50
0.15	9	Trolamine	1.50
1.00–5.00	10	Antifungal compound*	10.00–50.00

*Adjust quantity of urea for the quantity of antifungal compound; this formula is for 1% level of antifungal added.

Arginine and Oleoresin Capsicum Cream

Active ingredients: L-arginine and oleoresin capsicum. Other ingredients: Water, choline chloride, sodium chloride, magnesium chloride, white oil, glyceryl stearate SE, squalane, cetyl alcohol, propylene glycol stearate SE, wheat germ oil, glyceryl stearate, isopropyl myristate, stearyl stearate, polysorbate-60, propylene glycol, oleic acid, tocopheryl acetate, collagen, sorbitan stearate, vitamin A and D, triethanolamine, aloe vera extract, imidazolidinyl urea, Oleoresin Capsicum, methylparaben, propylparaben, BHA.

Arginine Cream

Active ingredient: L-arginine. Other ingredients: Water, choline chloride, sodium chloride, magnesium chloride, white oil, glyceryl stearate SE, squalane, cetyl alcohol, propylene glycol stearate SE, wheat germ oil, glyceryl stearate, isopropyl myristate, stearyl stearate, polysorbate-60, propylene glycol, oleic acid, tocopheryl acetate, collagen, sorbitan stearate, vitamin A and D, triethanolamine, aloe vera extract, imidazolidinyl urea, methylparaben, propylparaben, BHA.

Arginine-Aspartate Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
3.50	1	Cetostearyl alcohol	35.00
40.00	2	Squalane	400.00
3.00	3	Beeswax	30.00
5.00	4	Reduced lanolin	50.00
0.30	5	Ethyl *p*-oxybenzoate	3.00
2.00	6	Polyoxyethylene (20 mol) sorbitan monopalmitate	20.00
2.00	7	Monoglyceride stearate	20.00
0.50	8	Sodium N-stearoyl glutamate	5.00
1.00	9	2-Hydroxy-4-methoxy benzophenone	10.00
2.00	10	Retinol acetate	20.00
0.05	11	Evening primrose oil	0.50
0.03	12	Perfume	0.30
0.01	13	L-Arginine-L-aspartate	0.10
5.00	14	1,3-butylene glycol	50.00
5.00	15	Polyethylene glycol 1500	50.00
q.s.	16	Water purified q.s. to	1 Kg

MANUFACTURING DIRECTIONS

1. Charge items 1–12 in a heating vessel and dissolve and mix.
2. In another vessel, prepare a solution of items 13–16 heated to 75°C with stirring.
3. Add step 2 into step 1 and homogenize to reduce the size of emulsified particles.
4. Cool rapidly to produce a cream.

Atropine Opthalmic Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Atropine sulfate	10.00
5.00	2	Liquid paraffin	50.00
5.00	3	Cetostearyl alcohol	50.00
5.00	4	Hard paraffin	50.00
84.00	5	Soft paraffin	840.00

MANUFACTURING DIRECTIONS

1. Load items 2–5 in a melting vessel. Heat to 145°C and keep it at this temperature for 45 minutes.
2. Allow to cool to room temperature.
3. In a separate vessel, dissolve item 1 in 200 mL of water for injection and add to step 1 under aseptic conditions.
4. Fill and sterilize in tubes (gamma radiation).

Azelaic Acid Cream and Gel

Azelaic acid cream 20% contains azelaic acid, a naturally occurring saturated dicarboxylic acid. Structural formula: $HOOC–(CH_2)_7–COOH$. Chemical name: 1,7-heptanedicarboxylic acid. Empirical formula: $C_9H_{16}O_4$. Each gram contains azelaic acid (0.2 g; 20% w/w). Inactive ingredients: cetearyl octanoate, glycerin, glyceryl stearate, cetearyl alcohol, cetyl palmitate, cocoglycerides, PEG-5 glyceryl stearate, propylene glycol, and purified water. Benzoic acid is present as a preservative.

Azelaic acid in a gel form is manufactured by the following method: Benzoic acid and EDTA are dissolved in usual concentrations in 60–70 parts of water. Then a mixture of 1 part midchain triglycerides and 1.5 parts polysorbate 80 is added and homogenized while being stirred (preemulsion). One part lecithin is introduced into 12 parts propylene glycol. The solution that is produced is stirred into the preemulsion and homogenized. After 1 part polyacrylic acid is added, 15 parts azelaic acid are added. Sodium hydroxide is used to neturalize the carbomer to form the gel.

Baby Lotion

Bill of Materials

Scale (mg/mL)	Item	Material Name	Quantity/L (g)
50.0	1	Alcohol	50.0
50.0	2	Propylene glycol	50.0
0.80	3	Ethoxylated nonyl phenol	0.80
0.57	4	Dye red FD&C N40	0.57
0.41	5	Dye blue FD&C N1	0.41
0.70	6	Dye yellow FD&C N5	0.70
0.40	7	Perfume essence nelandia	0.40
q.s.	8	Acid hydrochloric reagent grade bottles approx	0.012
q.s.	9	Water purified q.s. to	1 L

MANUFACTURING DIRECTIONS

1. Use 316 or more resistant-grade stainless steel tank.
2. Charge approximately 800 mL of purified water in main mixing tank.
3. Add alcohol and propylene glycol and mix for 5 minutes. Separately dissolve each dye in sufficient water to obtain 0.5% dye solutions.
4. Add color solutions to main tank and mix. Rinse containers with small portions of purified water and add rinsings.
5. Dissolve perfume essence nelandia in ethoxylated nonyl phenol.
6. Add solution from step above to main tank and mix for 5 minutes.
7. Determine pH of solution and adjust if necessary with 5% hydrochloric acid solution.
8. Mix well (pH 5.7–5.9). Q.s. to 1 L with purified water.

Bacitracin Zinc and Polymyxin B Sulfate Opthalmic Ointment

The bacitracin zinc and polymyxin B sulfate ophthalmic ointment USP is a sterile antimicrobial ointment formulated for ophthalmic use. Bacitracin zinc is the zinc salt of bacitracin, a mixture of related cyclic polypeptides (mainly bacitracin A) produced by the growth of an organism of the lichenlformis group of *Bacillus subtilis* var Tracy. It has a potency of not less than 40 bacitracin units per milligram. Polymyxin B sulfate is the sulfate salt of polymyxin B1 and B2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6000 polymyxin B units per milligram, calculated on an anhydrous basis. Each gram contains the following actives: Bacitracin zinc equal to 500 bacitracin units and polymyxin B sulfate equal to 10,000 polymyxin B units; inactives: white petrolatum and mineral oil.

Base Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.50	1	Propylene glycol	25.00
2.50	2	Triacetin	25.00
57.00	3	Mineral oil	570.00
35.00	4	Microcrystalline wax	350.00
3.00	5	Propylene glycol stearate	30.00
0.05	6	Citric acid	0.50

MANUFACTURING DIRECTIONS

1. The mineral oil, microcrystalline wax, and propylene glycol stearate are melted together by heating to 75°–85°C, and mixed, thus creating the oleaginous phase.
2. The citric acid, if used, is dissolved in the triacetin by stirring, and using heat is necessary.
3. If used optionally, the propylene glycol is added to the traiacetin and mixed.
4. After cooling the oleaginous phase to about 55°C, the triacetin solution is added to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
5. Mixing is continued while cooling the ointment to 30°C or lower.

Base Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
10.00	1	Triacetin	100.00
30.00	2	Lanolin alcohol and petrolatum (Americhol CAB)	300.00
1.00	3	Cholesterol	10.00
59.00	4	White petrolatum	590.00

MANUFACTURING DIRECTIONS

1. The Amerchol CAB, white petrolatum, and cholesterol are melted together by heating to 75°–85°C, and are mixed to form the oleaginous phase.
2. After cooling the oleaginous phase to about 45°C, the triacetin is added to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
3. Mixing is continued while cooling the ointment to 30°C or lower.

Base Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Triacetin	50.00
25.00	2	Dimethicone (1000 cSt)	250.00
61.50	3	White petrolatum	615.00
5.00	4	Microcrystalline wax	50.00
1.00	5	Cholesterol	10.00
2.50	6	Sucrose distearate	25.00

MANUFACTURING DIRECTIONS

1. To make the oleaginous phase, white petrolatum, sucrose distearate, cholesterol, and microcrystalline wax are melted at 75°–85°C.
2. Dimethicone is added and mixed. After cooing the oleaginous phase to about 55°C, the triacetin is added to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
3. Mixing is continued while cooling the ointment to 30°C or lower.

Base Cream for Extemporaneous Preparations

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.0	1	Cetylstearyl alcohol	70.00
1.5	2	Cremophor A 6	15.00
1.5	3	Cremophor A 25	15.00
12.0	4	Liquid paraffin	120.00
0.2	5	Paraben(s)	2.00
67.8–69.7	6	Water	678–697
8.0	7	Propylene glycol	80.00
0.1– 2.0	8	Active ingredient	1–2.00

MANUFACTURING DIRECTIONS

1. Heat a mixture of items 1–5 and the water separately to about 80°C.
2. With rigorous stirring, add the water to the obtained solution.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with aqueous solution, and continue to stir during cooling to room temperature.
4. This white basic cream can be readily used for active ingredients soluble in 1, 2-propylene glycol.

Base Ointment for Therapeutic Delivery

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methylparaben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
q.s.	8	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Preparation of water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation to a melting kettle.
   b. Heat the contents to 61°–65°C.
   c. Add methylparaben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase:
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix tontinuously while heating to 71°–75°C.
3. Mixing of phases:
   a. The mixture of step 2 is transferred to step 1 kettle with the water phase maintained under 300 mbar vacuum.
   b. With mixing, and keeping the temperature at 61°–65°C, draw the oil phase into the water phase.
   c. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°–65°C.
   d. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Becaplermin Gel 0.01%

The gel contains becaplermin, a recombinant human platelet-derived growth factor for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor into the yeast *Saccharomyces cerevisiae*. Becaplermin has a molecular weight of approximately 25 kDa and is a homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. The gel is a nonsterile, low-bioburden, preserved, sodium carboxymethylcellulose-based topical gel containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methylparaben, propylparaben, and m-cresol as preservatives and l-lysine hydrochloride as a stabilizer. Each gram of gel contains 100 μg of becaplermin.

Benzalkonium Chloride and Zinc Oxide Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.0023 mL	1	Benzalkonium chloride solution	2.3 mL
85.0	2	Zinc oxide USP powder	85.0
100.0	3	Wax emulsifying nonionic (Polawax®)	100.0
16.0	4	Alcohol cetostearyl	16.0
4.0	5	Lanolin acetylated/anhydrous USP regular	4.0
80.0	6	Glycerin USP (96%)	80.0
10.0	7	Oil-neutral vegetable triglycerides mixture miglyol	10.0
0.5	8	Propylparaben NF (aseptoform P)	0.5
1.0	9	Methylparaben NF (aseptoform M)	1.0
0.80 mL	10	Purified water, q.s.	800.0 mL
0.24	11	Perfume diabolo 110.388/B	0.24g

MANUFACTURING DIRECTIONS

1. Avoid mixing air into emulsion. Emulsify under vacuum to minimize air entrapment. Use jacketed tank with vacuum with high-speed agitator and an adjustable slow-speed anchor type with Teflon sweep blades.
2. If necessary, mill zinc oxide in a Fitz mill or similar impact-forward, maximum-speed mill, fitted with a 250-µm aperture screen. Repeat three times. Heat 800 mL of water to 75°C in a steam-jacketed mixing tank and dissolve methylparaben.
3. Maintain temperature at 75°C. Disperse milled zinc oxide in solution of stepabove. Maintain temperature at 75°C.
4. Dissolve benzalkonium chloride and glycerin in solution maintain temperature at 75°C.
5. In a separate steam jacketed tank, add Polawax, cetostearyl alcohol, acetylated lanolin, oil-neutral vegetable triglycerides mixture, and propylparaben, and carefully melt at 70°C.
6. Adjust the turbo-mixer of the steam-jacketed tank containing the aqueous phase to maximum speed, keeping the temperature at 75°C. Slowly add the oil phase into the aqueous phase. Generate as much vacuum as possible, and maintain it for the rest of the process.
7. Circulate cold water to allow for a very slow temperature decrease (down to 60°C). Stop turbo-mixer and put the anchor-type agitator at minimum speed until 40°–45°C is reached. The temperature decrease must be very slow.
8. Break the vacuum and add perfume to cream with anchor-type agitator at slow speed.
9. Continue to mix until the perfume is completely dispersed.

Benzalkonium Chloride Contraceptive Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	PEG-6 and PEG-32 and glycol stearate (Tefose 63)	50.00
30.00	2	Apricol kernel oil PEG-6 esters (Labrafil M 1944 CS)	30.00
816.00	3	Deionized water	816.00
80.00	4	Hydroxyethylcellulose	80.00
24.00	5	Benzalkonium chloride 50% weight% in water	24.00

MANUFACTURING DIRECTIONS

1. Mix items 3 and 4 at room temperature.
2. Heat to 75°C and add items 1 and 2 while stirring.
3. Cool with gentle stirring to 30°C and then add item 5 and stir.

Benzocaine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
180.00	1	Trilaneth-4 phosphate and glyceryl stearate and PEG-2 stearate	180.00
20.00	2	Hydrogenated palm/kernel oil PEG-6 esters	20.00
80.00	3	Mineral oil	80.00
0.30	4	Sodium methylparaben	0.30
0.70	5	Sorbic acid	0.70
646.70	6	Deionized water	646.70
10.00	7	Benzocaine	10.00
10.00	8	Butamben	10.00
2.00	9	Menthol	2.00
0.30	10	Resorcinol	0.30
50.00	11	Ethoxydiglycol	50.00

MANUFACTURING DIRECTIONS

1. Dissolve items 7–10 in item 11.
2. Mix and heat items 1–6 to 75°C; allow to cool slowly with constant stirring. At 35°C, add this to mixture above.
3. Homogenize if necessary.

Benzoyl Peroxide and Alpha-Bisabolol Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.00	1	Alpha-bisabolol, natural (BASF)	2.00
60.00	2	Propylene glycol	60.00
100.00	3	Triethanolamine	100.00
30.00	4	Cremophor RH 40	30.00
30.00	5	Kollidon 30	30.00
408.00	6	Water	408.00
10/00	7	Carbopol 940	10.00
400.00	8	Water	400.00
50.00	9	Benzoyl peroxide	50.00

MANUFACTURING DIRECTIONS

1. Prepare suspension of items 7 and 8, then let swell for 1 hour.
2. Add this suspension to the well-stirred solution of items 1–5.
3. Add item 9 to create a colorless transparent gel.

Benzoyl Peroxide Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
460.50	1	Deionized water	460.50
5.00	2	Carbomer 940	5.00
10.00	3	Hydroxypropyl methylcellulose, medium viscosity	10.00
137.50	4	Deionized water	137.50
70.00	5	Purified bentonite (Polargel NF)	70.00
2.00	6	Methylparaben	2.00
1.00	7	Propylparaben	1.00
20.00	8	Glyceryl stearate	20.00
60.00	9	Propylene glycol	60.00
20.00	10	Polyethylene glycol 600	20.00
20.00	11	Myristyl propionate	20.00
50.00	12	Dimethicone	50.00
70.00	13	Purified bentonite (Polargel NF)	70.00
10.00	14	Titanium dioxide	10.00
100.00	15	Benzoyl peroxide 70%	100.00

MANUFACTURING DIRECTIONS

1. Sift carbomer 940 into vortex in water; when completely dispersed, sift in item 3.
2. Add parabens with stirring and heat (to 80°C at least) until dissolved.
3. Add glyceryl stearate.
4. Blend items 10–13 in propylene glycol, in order, and mix well. With the addition of Polargel, allow 15 minutes of mixing to complete hydration.
5. Blend propylene glycol portion into the first part. Finally, add benzoyl peroxide and titanium dioxide to the mixture and mill.

Benzoyl Peroxide Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.50	1	Acrylates/C10-30 alklyl acrylate crosspolymer	2.50
4.00	2	Carbopol 980	4.00
q.s.	3	Deionized water q.s. to	1 kg
40.00	4	Isopropyl myristate	40.00
10.00	5	Cetyl alchol	10.00
20.00	6	Glyceryl stearate	20.00
50.00	7	Sodium hydroxide 0.5 *M*	50.00
15.00	8	Deionized water	15.00
50.00	9	Benzoyl peroxide	50.00
50.00	10	PEG 600	50.00
q.s.	11	Perfume, preservative	q.s.

MANUFACTURING DIRECTIONS

1. Hydrate carbopol and permulen in warm water, 60°C. When fully hydrated, heat to 70°C.
2. Heat oil phase to 70°C. Add water phase to oil phase while stirring.
3. Add sodium hydroxide and continue stirring. Combine benzoyl peroxide, PEG 600, and water (item 8) and add to the emulsion.
4. At 35°C, homogenize with caution, using suitable equipment.

Benzoyl Peroxide Lotion

The cleansing lotions contain benzoyl peroxide 4% and 8%, respectively, in a lathering vehicle containing purified water, cetyl alcohol, citric acid, dimethyl isosorbide, docusate sodium, hydroxypropyl methylcellulose, laureth-12, magnesium aluminum silicate, propylene glycol, sodium hydroxide, sodium lauryl sulfoacetate, and sodium octoxynol -2 ethane sulfonate.

Bill of Materials

Scale (mg/g)	Item	Material Name	Quantity/kg (g)
40.00	1	Purified bentonite (Polargel NF)	40.00
10.00	2	Hydroxy propyl methyl cellulon	10.00
522.20	3	Water	522.20
190.00	4	Water	190.00
2.00	5	Methylparaben	2.00
2.00	6	Propylparaben	2.00
20.00	7	Glyceryl stearate	20.00
60.00	8	Propylene glycol	60.00
20.00	9	Myristyl propionate	20.00
5.00	10	Dimethicone	5.00
q.s.	11	Iron oxides	q.s.
10.00	12	Titanium dioxide	10.00
100.00	13	Benzoyl peroxide 77%	100.00

MANUFACTURING DIRECTIONS

1. Sift the Polargel NF into water with rapid mixing. Allow to hydrate for 15 minutes.
2. Pass through coarse sieve, add item 2, and mix until all lumps are removed.
3. Add parabens to the water with stirring and heat to 90°C to dissolve parabens.
4. Add items 4–10 and mix well and then add these to the item 2 part. Mix well again. Finally, add items 11–13 and mix.
5. Mill it and fill.

Betamethasone and Cinchocaine Suppositories

Bill of Materials

Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
1.00	1	Betamethasone valerate	1.00
1.00	2	Cinchocaine hydrochloride	1.00
1,798.00	3	Witepsol W45	1,798.00

MANUFACTURING DIRECTIONS

1. Charge item 3 in the fat-melting vessel and heat to 55°C; transfer molten mass to Becomix through stainless steel sieve. Set the temperature at 50°C.
2. Add items 1 and 2, mix well at 50°C, and mix for 20 minutes.
3. Homogenize at 0.6 bar vacuum and 50°C.
4. Transfer to storage at 40°C.
5. Fill suppository mold.

Betamethasone and Neomycin Gel-Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.300	1	Betamethasone valerate	0.13
6.50	2	Neomycin sulfate	0.65
150.00	3	Lutrol E 400	15.00
100.00	4	Miglyol 812 (Dynamit-Nobel)	10.00
200.00	5	Lutrol F 127	20.00
q.s.	6	Water q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Dissolve betamethasone valerate in the mixture of Lutrol E 400 and Miglyol 812.
2. Dissolve Lutrol F 127 and neomycin sulfate in water at 5°–10°C.
3. Mix both solutions. Maintain cool temperature until the air bubbles disappear. A milky-white soft gel-cream is obtained.

Betamethasone and Salicylic Acid Lotion

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.10	1	Betamethasone dipropionate micronized, 5% excess*	1.05
1.90	2	Salicylic acid	19.00
0.032	3	Disodium edetate	0.32
0.55	4	Hydroxypropyl methylcellulose	5.50
0.55	5	Sodium hydroxide	5.50
40.00	6	Isopropyl alcohol	400.00
q.s.	7	Water purified q.s. to	1 kg

*Adjust quantity of the basis of assay.

MANUFACTURING DIRECTIONS

1. Charge about half of item 7 into a suitable vessel and slowly add item 4 with vigorous mixing; use item 7 to rinse the container for item 4, and add rinsings to the mixing vessel.
2. In 10% of the amount of item 6, add and dissolve item 1 in a separate vessel and then add an additional 20% of item 6 and mix well until completely dissolved.
3. Add 10% of item 7 in a separate vessel and add and dissolve item 5 into it.
4. Add 10% of item 7 in a separate vessel and add and dissolve item 3 into it.
5. Add 20% of item 7 in a separate vessel and add and dissolve item 2 into it.
6. Add 50% of item 6 to step 4 and mix slowly for 15 minutes. Add to this vessel step 3 and step 5 and mix vigorously. Use item 7 to rinse all vessels and add rinsings.
7. Check pH to 4.8–5.3 and adjust if necessary.
8. Add step 1 to this and mix.
9. Fill in appropriate containers.

Betamethasone Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	120.00
2.00	5	Paraben(s)	2.00
697.00	6	Water	697.00
80.00	7	Propylene glycol	80.00
1.00	8	Betamethasone	1.00

MANUFACTURING DIRECTIONS

1. Heat a mixture of items 1–5 and item 6 separately to about 80°C.
2. Add together with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with above mixture, and continue to stir to cool to room temperature. This creates a white cream.

Betamethasone Dipropionate Cream, Lotion, and Ointment

Betamethasone dipropionate USP is a synthetic adrenocorticosteroid for dermatologic use. Betamethasone, an analog of prednisolone, has high corticosteroid activity and slight mineralocorticoid activity. Betamethasone dipropionate is the 17,21-dipropionate ester of betamethasone. Each gram of cream 0.05% contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a hydrophilic emollient cream consisting of purified water USP, mineral oil USP, white petrolatum USP, ceteareth-30, cetearyl alcohol 70/30 (7.2%), sodium phosphate monobasic monohydrate R, and phosphoric acid NF, with chlorocresol and propylene glycol USP as preservatives. It may also contain sodium hydroxide R to adjust pH to approximately 5.0. Each gram of lotion 0.05% w/w contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a lotion base of isopropyl alcohol USP (39.25%) and purified water USP and is slightly thickened with carbomer 974P; the pH is adjusted to approximately 4.7 with sodium hydroxide R. Each gram of lotion 0.05% contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a lotion base of purified water USP, isopropyl alcohol USP (30%), hydroxypropyl cellulose NF, propylene glycol USP, and sodium phosphate monobasic monohydrate R, with phosphoric acid NF used to adjust the pH to 4.5. Each gram of ointment 0.05% contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil USP and white petrolatum USP.

Betamethasone Dipropionate Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.064	1	Betamethasone dipropionate	0.64
2.50	2	Propylene glycol stearate	25.00
3.50	3	Triacetin	35.00
0.05	4	Citric acid	0.50
35.00	5	Microcrystalline wax	350.00
58.88	6	Mineral oil	588.80

MANUFACTURING DIRECTIONS

1. The betamethasone dipropionate and citric acid are dissolved in the triacetin with mixing and heat to 35°C if needed.
2. The microcrystalline wax, propylene glycol stearate, and mineral oil are melted together by heating to 75°–85°C while stirring to make the oleaginous phase.
3. After cooling the oleaginous phase to about 55°C, the tiacetin solution is added while mixing to make a homogenous dispersion. Mixing should be of sufficient intensity to disperse the triacetin solution finely and uniformly.
4. Mixing is continued while cooling at room temperature.

Betamethasone Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Betamethasone valerate	1.00
100.00	2	Ethanol 96%	100.00
200.00	3	Propylene glycol	200.00
220.00	4	Lutrol F 127	220.00
q.s.	5	Water	470.00

MANUFACTURING DIRECTIONS

1. Prepare the solution of items 1–3 at room temperature and solution of items 4 and 5 at about 6°C (or at >70°C).
2. Mix both solutions. Maintain the temperature until the air bubbles disappeared.
3. A certain amount of propylene glycol could be substituted by water. The obtained gel is clear and colorless.

Betamethasone Opthalmic Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Betamethasone sulfate	10.00
5.00	2	Liquid paraffin	50.00
5.00	3	Cetostearyl alcohol	50.00
5.00	4	Hard paraffin	50.00
84.00	5	Soft paraffin	840.00

MANUFACTURING DIRECTIONS

1. Load items 2–5 in a melting vessel. Heat to 145°C and keep it at this temperature for 45 minutes.
2. Allow to cool to room temperature.
3. In a separate vessel, dissolve item 1 in 200 mL of water for injection and add to step 1 under aseptic condition.
4. Fill and sterilize in tubes.

Betamethasone Valerate and Cinchocaine Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Cinchocaine hydrochloride	5.00
1.00	2	Betamethasone valerate	1.00
75.00	3	Hydrogenated castro oil	75.00
400.00	4	Eutenol G (2-octyldodecanol)	400.00
75.00	5	PEG 400 monoricinoleate	75.00
0.08	6	Lavender oil	0.08
443.00	7	Castro oil	443.00

MANUFACTURING DIRECTIONS

1. Charge items 3, 4, 5, and 7 in a melting vessel and heat to 85°C. Melt to a clear solution and cool down to 65°C. Transfer to Becomix.
2. Mix in Becomix at 65°C under vacuum. Cool down to 50°C.
3. Add items 1 and 2 in a small portion of the melt from step 2 in a separate vessel and homogenize and then add to step 3.
4. Add item 6 at 30°C and mix for 10 minutes.
5. Transfer to storage vessel and fill.

Betamethasone Valerate Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.100	1	Betamethasone valerate (34% excess)	1.34
2.000	2	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
8.000	3	Cetostearyl alcohol	80.00
0.100	4	Methyl paraben	1.00
0.034	5	Propyl paraben	0.34
0.100	6	Chlorocresol	1.00
6.000	7	Mineral oil (liquid paraffin)	60.00
0.290	8	Monobasic sodium phosphate	2.90
17.800	9	Petrolatum (white soft paraffin)	178.00
66.000	10	Purified water	660.00

MANUFACTURING DIRECTIONS

1. Heat item 10 to 90°C in mixer. Dissolve items 4 and 5 (parabens) to a clear solution by stirring.
2. Dissolve 3.0 g of item 2 in parabens solution while stirring. Dissolve items 6 and 8 in Parabens solution while stirring.
3. Set the mixer at temperature 65°–70°C, mixer speed 8 rpm, manual mode. Load 17.0 g of items 2, 9, and 3 and 45.0 g of item 7 in fat-melting vessel.
4. Heat to 70°–75°C while stirring. Maintain temperature at 65°–75°C.
5. Mix item 1 in 10.0 g of item 7 in a stainless steel container.
6. Homogenize for 10 minutes under homogenizer to make a smooth slurry.
7. Check the temperature of aqueous phase in mixer 65°–70°C. Check the temperature of fatty phase in fat melting vessel at 65°–70°C.
8. Set the mixer speed 8 rpm, vacuum 0.4–0.6 bar. Transfer fatty phase to the aqueous phase in mixer vessel through filter under vacuum while mixing. Start the homogenizer at high speed. Homogenize for 10 minutes. Check and record the pH of cream. Limit 4.5–5.2 at 30°C.
9. Cool down the temperature to 50°C.
10. While mixing, release the vacuum.
11. Put 400 g of the cream into stainless steel vessel and keep aside.
12. Add slurry from step above to the remaining cream base in mixer. Rinse the container of slurry using 5.0 g of item 7 and transfer the rinsing to the mixer.
13. Homogenize for 10 minutes at high speed, mixer speed 8 rpm.
14. Load 400 g cream from step above to the mixer. Set the mixer speed 8 rpm, manual mode, vacuum 0.4–0.6 bar. Homogenizer at high speed with recirculation, temperature 25°C.
15. Homogenize for 10 minutes with recirculation, stop the homogenizer, and continue mixing. White homogeneous cream firms at pH 4.5–5.2 at 30°C.

Betamethasone Valerate Foam

Betamethasone valerate USP is a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory agents. Each gram of foam contains 1.2 mg betamethasone valerate USP in a hydroalcoholic, thermolabile foam. The foam also contains cetyl alcohol, citric acid, ethanol (60.4%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol and is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).

Betamethasone Valerate Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.100	1	Betamethasone, USE: betamethasone valerate	1.300
84.870	2	Petrolatum (white soft paraffin)	848.700
15.000	3	Mineral oil (liquid paraffin)	150.000

MANUFACTURING DIRECTIONS

1. Melt item 2 in a fat-melting vessel at 75°C while mixing—do not overheat.
2. Maintain temperature of the molten mass in the melting vessel at 60°–65°C.
3. Start the steam on the mixer vessel, and set the temperature at 60°C.
4. Transfer 160.0 g of the molten mass at 60°C to the mixer vessel. Retain the rest of the quantity in the fat-melting vessel.
5. Start mixing in the mixer vessel at medium speed with vacuum between 0.4 and 0.6 bar until obtaining an actual temperature of 40°–45°C.
6. Maintain the temperature of mixer vessel at 40°–45°C. Add item 1 to 80.0 g of item 3 and homogenize for 3 minutes, using homogenizer. Keep the slurry aside.
7. Rinse the homogenizer and container with 70.0 g of item 3. Transfer item 1 slurry from step above and the rinsing from previous step to the mixer vessel. Start mixing under vacuum 0.4–0.6 bar for 15 minutes. Temperature should be maintained at 40°–45°C.
8. Transfer the rest of the quantity of molten mass (temperature 60°C) into mixer vessel slowly, continuing to mix for 5 minutes after each addition. At the end of addition, mix a further 10 minutes under vacuum 0.4–0.6 bar.
9. Homogenize for 5 minutes at high speed under vacuum 0.4–0.6 bar.
10. Cool the ointment to 30°–35°C while stirring under a vacuum of 0.4–0.6 bar.

Betamethasone Valerate Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.100	1	Betamethasone USE betamethasone valerate with 10% excess	1.34
0.020	2	Vitamin E oily	0.20
79.34	3	White soft paraffin	793.40
3.00	4	Cetostearyl alcohol	20.00
2.50	5	Cetmacrogol 1000	25.00
15.00	6	Liquid paraffin	150.00

MANUFACTURING DIRECTIONS

1. Melt item 3 in a fat-melting vessel at 60°C, add items 4 and 5, and mix until clear.
2. Transfer to Becomix at 60°C. Mix at 9 rpm under vacuum of 0.4–0.6 bar. Cool to 40°–45°C.
3. Add items 1, 2, and 6 to a stainless steel container and homogenize for 3 minutes. Transfer slurry to step 2.
4. Mix under vacuum at 40°–45°C.
5. Transfer to storage vessel and fill.

Bisacodyl Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
5.000	1	Bisacodyl (micronized)* 2% excess	5.10
447.500	2	Hard fat (Witepsol E 76®)	447.50
447.500	3	Hard fat (Witepsol W 45®)	447.50

*100% particles should be less than 70 μm. Fill weight: 1800 mg per suppository

MANUFACTURING DIRECTIONS

1. The molten suppository mass must be kept stirred throughout the storage period, during manufacturing, and during filling to avoid the sedimentation of active drug. The active ingredient causes skin irritation, which vanishes after sometime without having aftereffects. Avoid dust formation during processing. In particular, protect eyes and mucous membranes.
2. Load items 2 and 3 in the fat-melting vessel and heat to 50° ± 3°C.
3. Transfer the molten mass to mixer through filter sieves. Set the temperature at 40° ± 2°C. Load item 1 to the mixer containing the molten mass. Carefully mix the powder with the molten mass.
4. Set the mixer at temperature 40° ± 2°C, speed 10 rpm (manual mode), and mix for 20 minutes. Set the mixer at temperature 40° ± 2°C, speed 10 rpm (manual mode), vacuum 0.6 bar.
5. Homogenize at low speed while mixing for 10 minutes. Homogenize at high speed while mixing for 3 minutes.
6. Continue mixing of the mass under vacuum in mixer.
7. Heat the storage vessel, set the temperature at 40° ± 2°C.
8. Transfer the molten mass from mixer to the storage vessel. Hold the mass at 40° ± 2°C while mixing continuously at low speed.
9. Fill weight is 900 mg/suppository, but use a fill weight of 1.8 g for 10-mg suppositories.

Bisacodyl Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
10.00	1	Bisacodyl (micronized) 2% excess	10.02
895.00	2	Witepsol E 76®	895.00
895.00	3	Witepsol W 45®	895.00

MANUFACTURING DIRECTIONS

1. Charge items 2 and 3 to a melting vessel, heat to 50°C, transfer to Becomix through filter sieve. Set temperature to 40°C.
2. Charge item 1 and mix carefully. Set temperature to 40°C, speed 10 rpm for 20 minutes.
3. Homogenize for 3 minutes, continue mixing under vacuum.
4. Transfer to storage vessel and fill.

Biscarboxychromonyloxy Propanol Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
4.00	1	Disodium 1,3-bis(2-carboxychromonyloxy)propan-2-ol (micronized)	40.00
76.80	2	Yellow soft paraffin	768.00
9.60	3	Liquid paraffin	96.00
9.60	4	Lanolin acetylated (Modulan R)	96.00

MANUFACTURING DIRECTIONS

1. The disodium salt of 1,3-bis(2-carboxychromon-5-yloxy) propan-2-ol is added slowly in small portions, with vigorous mixing, to a small portion of the preheated and sterilized components of the ointment base at 90°C.
2. When the addition is complete, mixing is continued for a further 15 minutes, and then the concentrated dispersion is sterilized by heating at 150°C for 1 hour.
3. The concentrated dispersion is then added to a homogenizer heated at 80°–100°C, and the remaining components of the ointment basis are added slowly with continuous blending.
4. When this addition is complete, the molten ointment is blended for a further 15 minutes and then cooled to a temperature of 58°–62°C.
5. The ointment is then filled in presterilized eye ointment tubes, which are crimped and allowed to cool to room temperature.

Breast Care Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
20.00	1	Polysorbate 60	20.00
70.00	2	Cetyl alcohol	70.00
60.00	3	Mineral oil 70cS	60.00
40.00	4	Glyceryl stearate	40.00
q.s.	5	Deionized water	q.s.
q.s.	6	Preservative	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately at 65°–70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 20°C. Only food-grade materials should be used in this preparation. Do not use unapproved preservatives.

Budesonide Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.25	1	Budesonide	0.25
30.00	2	Polyoxy 40 stearate	30.00
80.00	3	Stearyl alcohol	80.00
150.00	4	Liquid paraffin	150.00
30.00	5	White soft paraffin	30.00
0.10	6	Ethylene diamine tetraacetate	0.10
3.00	7	Carbopol 934	3.00
0.67	8	Sodium hydroxide	0.67
0.70	9	Sodium methylparaben	0.70
0.30	10	Sodium propylparaben	0.30
q.s.	11	Water purified	685.00

MANUFACTURING DIRECTIONS

1. Melt white soft paraffin, stearyl alcohol, and polyoxyl 40 stearate in the fat-melting vessel at 70°–75°C.
2. Heat the purified water in the manufacturing vessel to a temperature of 80°–90°C. Disperse carbopol 934 in the heated water. Homogenize the dispersion to obtain clear gel.
3. Dissolve item 6, sodium methylparaben, sodium propylparaben, and sodium hydroxide in purified water. Transfer this solution to the clear gel from step 2 in the manufacturing vessel and homogenize well.
4. Transfer the fat phase (70°–75°C) into the manufacturing vessel containing aqueous phase (70°–75°C) while mixing. Homogenize under vacuum for few minutes.
5. Disperse budesonide with liquid paraffin in a stainless steel container at 40°–45°C and transfer this dispersion to the manufacturing vessel from step 4 at temperature 40°–45°C; mix and homogenize under vacuum to obtain a smooth, homogeneous cream and the stated amount of budesonide per 100 g.
6. Cool the cream to 25°–30°C while stirring continuously.

Budesonide Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.25	1	Budesonide	0.25
369.75	2	Liquid paraffin	369.75
450.00	3	Hard paraffin	450.00
150.00	4	White wax	150.00
30.00	5	Hydrogenated castor oil	30.00

MANUFACTURING DIRECTIONS

1. Melt hard paraffin, white wax, and hydrogenated castor oil in the fat-melting vessel at 100°C and maintain this temperature for 20 minutes. Then transfer this melted mass to the manufacturing vessel preheated to 85°C through 0.150 mm. Cool to 33°C while stirring.
2. Disperse budesonide with liquid paraffin at 33°C; use homogenizer to get homogeneous suspension.
3. Transfer the dispersion from step 2 to the ointment base from step 1 in the manufacturing vessel while stirring. Homogenize well to obtain a homogeneous ointment containing the stated amount of budesonide per 100 g ointment.
4. Filling in the tube is performed in an aseptic area at 33°C.

Burn Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
120.00	1	Glyceryl stearate SE (monthybase)	120.00
80.00	2	Octyldodecyl myristate (MOD)	80.00
20.00	3	Apricol kernel oil PEG-6 esters (labrafil M1944CS)	20.00
0.50	4	Sodium methylparaben	0.50
0.50	5	Sodium propylparaben	0.50
0.50	6	Sorbic acid	0.50
767.50	7	Deionized water	767.50
10.00	8	Avocado oil	10.00
1.00	9	Fragrance	1.00

MANUFACTURING DIRECTIONS

1. Mix and heat items 1–7 to 75°C. Cool slowly with stirring.
2. At 30°C, add item 8 and then item 9.

Burn Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
15.00	1	Magnesium aluminum silicate (Veegum®)	15.00
568.00	2	Deionized water	568.00
30.00	3	Propylene glycol	30.00
2.00	4	Dimethecone emulsion	2.00
100.00	5	Mineral oil, light	100.00
170.00	6	Acetylated lanolin alcohol	170.00
50.00	7	Benzocaine USP	50.00
30.00	8	C-18-C36 acid	30.00
120.00	9	Glyceryl stearate and PEG-100 stearate	120.00
5.00	10	Polysorbate 60	5.00
q.s.	11	Preservatives	q.s.

MANUFACTURING DIRECTIONS

1. Add item 1 to water slowly, agitating with extensive shear force until smooth.
2. Add items 3 and 4 to the mixture and heat to 75°–80°C. Mix and heat items 5–11, keeping item 7 suspended to 75°–80°C; mix the two parts while cooling; pour and fill at 40°C.

Butenafine Hydrochloride Cream

Butenafine cream, 1%, contains the synthetic antifungal agent butenafine hydrochloride. Butenafine is a member of the class of antifungal compounds known as benzylamines, which are structurally related to the allylamines. Each gram of cream, 1%, contains 10 mg of butenafine HCl in a white cream base of purified water USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene cetyl ether, benzyl alcohol NF, diethanolamine NF, and sodium benzoate NF.

Butesin Picrate and Metaphen Ointment

Bill of Materials

Scale (mg/g)	Item	Material Name	Quantity/kg (g)
6.48	1	Lanolin anhydrous	6.48
0.219	2	Metaphen chloride powder	0.219
q.s.	3	Acetone	0.96
8.80	4	Sodium borate	8.80
2.48	5	Potassium chloride	2.48
q.s.	6	Water purified	253.70
115.00	7	Beeswax white	115.00
80.00	8	Wax ceresin white	80.00
510.00	9	Mineral oil	510.00
10.00	10	Butyl aminobenzoate (butsin) picrate powder	10.00
13.31	11	2-Ethoxyethanol (cellosolve)	13.31

MANUFACTURING DIRECTIONS

1. Melt lanolin in vacuum flask and heat to 60°–45°C. Use sufficient acetone to completely dissolve metaphen chloride. Add metaphen solution to melted lanolin and mix thoroughly. Use vacuum to remove all acetone.
2. Dissolve borax and potassium chloride in the purified water at 85°–90°C.
3. Melt beeswax, ceresin wax, and mineral oil and strain into ointment mixing tub at 95°C.
4. Add prepared base, step 1, to melted oil–wax mixture, step 4.
5. Add borax-potassium chloride solution, step 2, to oil–wax mixture with constant stirring.
6. Mix for 1 hour.
7. Dissolve butesin picrate in warm (50°C) cellosolve, and filter. Hold solution at 50°C for use in following step.
8. Adjust temperature of mass from step 5 to 50°C (this temperature is important).
9. Add butesin picrate solution (at 50°C) to mass (at 50°C), with constant stirring.
10. Mix for several hours. Circulate cold water in jacket overnight.
11. Mill to smooth ointment and fill suitable containers.

Butesin Picrate Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
249.40	1	Water purified	249.40
8.85	2	Sodium borate powder	8.85
2.47	3	Potassium chloride	2.47
1.00	4	Methylparaben	1.00
1.00	5	Propylparaben	1.00
6.65	6	Lanolin anhydrous	6.65
114.60	7	Beeswax white	114.60
79.82	8	Wax ceresin white	79.82
405.30	9	Oil mineral light	405.30
119.90	10	Oil-neutral vegetable triglycerides mixture: miglyol 812; neobee M-5	119.90
10.00	11	Butyl aminobenzoate picrate (butesi picrate), 11% excess	11.10

MANUFACTURING DIRECTIONS

1. Charge purified water into a suitable steam tank and begin heating to 85°–90°C.
2. Add borax and potassium chloride and mix until dissolved (at 85°–90°C).
3. Add parabens to above solution and mix for at least 15 minutes (at 85°–90°C) or until dissolution.
4. Melt lanolin, beeswax, ceresin wax, and mineral oil into a suitable equipment. Heat mixture to 90°–95°C, mix until uniform.
5. Filter the melted waxes from step 4 through a 74-µm-aperture SS screen into a suitable mixing tank.
6. Heat waxes to 90°–95°C while mixing slowly.
7. Filter approximately 6.3 mL of borax–potassium–paraben solution (at 85°–90°C) from step 2 slowly through a 74-µm-aperture SS screen into the wax–oil mixture from step 5. *Caution: Slow the addition of water solution should the product show tendency to bubble over the side of the equipment.*
8. While mixing, slowly pass the remaining borax–potassium–paraben solution (at 85°–90°C) from step 2 through a 74-µm-aperture SS screen into the wax–oil mixture from step 5. See caution above.
9. If necessary, adjust batch temperature to 85°–90°C and maintain temperature of batch at 85°–90°C while mixing for 60 minutes (range 60–75 minutes).
10. Add neobee M-5 oil to a clean suitable SS container and start heating to 72°C (70°–74°C). Add and dissolve the butyl aminobenzoate picrate while mixing and maintaining temperature at 72°C (70°–74°C).
11. Reduce main batch temperature to 70°C (68°–72°C) while continuing mixing slowly.
12. Filter neobee M-5 oil–butyl picrate solution at 72°C (70°–74°C) through a 74-µm-aperture SS screen, into the main batch, mixing and maintaining temperature at 70°C (68°–72°C).
13. Continue mixing and maintain main batch temperature at 70°C (68°–72°C) for 15–30 minutes.
14. While mixing slowly cool the main batch to 40°–45°C. Maintain 40°–45°C temperature and continue mixing for at least 10 minutes. Note: use 35°C (30°–40°C) water for cooling. Do not force cool with cold water.
15. Set cooling water to 20°C (range 18°–25°C) and continue cooling batch to 25°–30°C while mixing. When batch reaches 25°–30°C, stop mixing. The product is ready for milling. Note: The cooling water temperature must not drop below 18°C.
16. Pump product to roller mill, and mill at high speed to a smooth uniform consistency.
17. Collect product in suitable bulk containers.
18. Fill in suitable containers. Theoretical tube-fill weight: 30 g, minimum 28.35 g. If product does not flow freely, heat the water in hopper jacket to a maximum of 40°C.

Butoconazole Nitrate Vaginal Cream

The butoconazole nitrate vaginal cream, 2%, contains butoconazole nitrate 2%, an imidazole derivative with antifungal activity. Its chemical name is (±)-1-[4-(p-chlorophenyl)-2-[(2,6-dichlorophenyl)thio]butyl] imidazole mononitrate. It contains 2% butoconazole nitrate in a cream of edetate disodium, glyceryl monoisostearate, methylparaben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propylparaben, colloidal silicon dioxide, sorbitol solution, purified water, and microcrystalline wax. Another formulation contains inactive ingredients cetyl alcohol, glyceryl stearate and PEG-100 stearate, methylparaben and propylparaben (preservatives), mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol, and water (purified).

Calamine and Diphenhydramine Hydrochloride Lotion

Bill of Materials

Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
8.00	1	Calamine	80.00
1.00	2	Diphenhydramine hydrochloride	10.00
0.10	3	Camphor	1.00
2.40	4	Alcohol	24.00
70.00	5	Water purified	700.00
2.70	6	Carboxymethyl cellulose	27.00
7.00	7	Zinc oxide	70.00
2.00	8	Water purified	20.00
0.06	9	Ferric oxide yellow	0.60
1.00	10	Zinc oxide	10.00
1.00	11	Glycerin	10.00
1.50	12	Glycerin	15.00
0.12	13	Ferric oxide red	1.20
q.s.	14	Perfume	q.s.
q.s.	15	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Hydrate item 6 in item 5 and disperse item 7 in the suspension.
2. Mix the ferric oxides in items 10 and 11; homogenize and add to step 1.
3. Dissolve item 2 in item 15 at 75°C; dissolve camphor and perfume in alcohol and add to step 2.
4. Add item 12 and blend well.
5. q.s. to volume with item 15.

Calamine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
80.00	1	Polawax GP200	80.00
10.00	2	Polysorbate 60	10.00
50.00	3	Caprylic/capric triglyceride	50.00
q.s.	4	Deionized water q.s. to	1 kg
100.00	5	Witch hazel distillate	100.00
50.00	6	Glycerin	50.00
20.00	7	Zinc oxide	20.00
20.00	8	Calamine	20.00
q.s.	9	Preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately to 65°–70°C.
2. Add water phase to oil phase while stirring.
3. Add zinc oxide and calamine under high shear. Stir to cool.

Calamine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
20.00	1	Microcrystalline cellulose (Avicel RC-591)	20.00
100.00	2	Glycerin	100.00
1.80	3	Methylparaben	1.80
0.20	4	Propylparaben	0.20
100.00	5	Glyceryl stearate and PEG-100 stearate	100.00
25.00	6	Cetyl alcohol	25.00
50.00	7	Zinc oxide	50.00
50.00	8	Calamine	50.00
653.00	9	Distilled water	653.00

MANUFACTURING DIRECTIONS

1. Mix item 2 with item 9 and heat to 75°C.
2. Add items 3 and 4; mix until dissolved using a shearing mixer.
3. Maintain temperature at 75°C and gradually add item 1; continue mixing at 75°C for 15 minutes or until item 1 is homogenously dispersed. Mix well.
4. When temperature drops to 60°–65°C, gradually add items 7 and 8; mix well until powders are homogenously dispersed.
5. Pass through homogenizer if necessary; adjust theoretical weight with warm distilled water and continue mixing until the cream congeals.

Calamine and Pramoxine Hydrochloride Lotion

Active ingredients are calamine 8% and pramoxine hydrochloride 1%. Inactive ingredients include caladryl lotion: alcohol USP, camphor, diazolidinyl urea, fragrance, hydroxypropyl methylcellulose, methylparaben, oil of lavender, oil of rosemary, polysorbate 80, propylene glycol, propylparaben, purified water, and xanthan gum.

Calamine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
80.00	1	Polawax GP200	80.00
10.00	2	Polysorbate 60	10.00
50.00	3	Caprylic/capric triglyceride	50.00
q.s.	4	Deionized water q.s. to	1 kg
100.00	5	Witch hazel distillate	100.00
50.00	6	Glycerin	50.00
20.00	7	Zinc oxide	20.00
20.00	8	Calamine	20.00
q.s.	9	Preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately to 65°–70°C.
2. Add water phase to oil phase while stirring.
3. Add zinc oxide and calamine under high shear. Stir to cool.

Calamine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
20.00	1	Microcrystalline cellulose (Avicel RC-591)	20.00
100.00	2	Glycerin	100.00
1.80	3	Methylparaben	1.80
0.20	4	Propylparaben	0.20
100.00	5	Glyceryl stearate and PEG-100 stearate	100.00
25.00	6	Cetyl alcohol	25.00
50.00	7	Zinc oxide	50.00
50.00	8	Calamine	50.00
653.00	9	Distilled water	653.00

MANUFACTURING DIRECTIONS

1. Mix item 2 with item 9 and heat to 75°C.
2. Add items 3 and 4; mix until dissolved using a shearing mixer.
3. Maintain temperature at 75°C and gradually add item 1, continue mixing at 75°C for 15 minutes or until item 1 is homogenously dispersed. Mix well.
4. When temperature drops to 60°–65°C, gradually add items 7 and 8; mix well until powders are homogenously dispersed.
5. Pass through homogenizer if necessary; adjust theoretical weight with warm distilled water and continue mixing until the cream congeals.

Calamine Lotion

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
78.30	1	Calamine	78.30
78.30	2	Zinc oxide	78.30
19.60	3	Glycerin	19.60
230.80	4	Deionized water	230.80
558.00	5	Calcium hydroxide solution	558.00
34.40	6	Purfied bentonite (Polargel NF)	34.40
0.60	7	Carboxymethyl cellulose	0.60

MANUFACTURING DIRECTIONS

1. Prepare a saturated item 5 solution using 3 g of item 5 in 1000 mL purified water, mixing vigorously for 1 hour.
2. Decant the clear, supernatant liquid for use in the formula.
3. Add the balance of water. Add item 6 and item 7 to the above solution with rapid mixing for 15 minutes.
4. In a separate vessel, blend items 1 and 2.
5. Add item 3 and mix until uniform. Begin adding the aqueous solution with mixing until it is blended into a lotion.

Calcipotriene Cream

Calcipotriene cream, 0.005%, contains calcipotriene monohydrate, a synthetic vitamin D 3 derivative, for topical dermatological use. Chemically, calcipotriene monohydrate is (5Z,7E,22E,24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1(alpha),3(beta),24-triol monohydrate, with the empirical formula C_{27} H_{40} O_3 • H_2O. Cream contains calcipotriene monohydrate equivalent to 50 µg/g anhydrous calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, glycerin, mineral oil, petrolatum, and water.

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00 mg	1	Calcipotriene	10.00 mg
1.00	2	Almond oil	10.00
40.00	3	Mineral oil	400.00
20.00	4	Self-emylsifying beeswax	200.00
q.s.	5	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Add and dissolve item 1 in item 2.
2. Add to this solution item 3 and item 4.
3. Heat the mixture to liquefy at 70°C.
4. In a separate vessel, heat item 5 to 80°C and add to step 3.
5. Mix well and then homogenize.
6. Cool and fill.

Camphor, Eucalyptus Oil, and Menthol Ointment

Camphor, eucalyptus oil, and menthol ointment contains camphor 5.2%, eucalpytus oil 1.2%, and menthol 2.8%. Inactive ingredients are carbomer 954, cedar leaf oil, cetyl alcohol, cetyl palmitate, cyclomethicone copolyol, dimethicone copolyol, dimethicone, ethylene diamine tetraacetate, glycerin, imidazolidinyl urea, isopropyl palmitate, methylparaben, nutmeg oil, PEG-100 stearate, propylparaben, purified water, sodium hydroxide, stearic acid, stearyl alcohol, thymol, titanium dioxide, turpentine oil.

Carbamazepine Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Carbamazepine	50.00
93.00	2	Propylene glycol	930.00
2.00	3	Carbopol 934	20.00
q.s.	4	Sodium hydroxide (to neutralize item 3)	q.s.

Carbamazepine Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Carbamazepine	10.00
50.00	2	Propylene glycol	500.00
5.00	3	Cetostearyl alcohol	50.00
1.00	4	Sodium lauryl sulfate	10.00
43.00	5	Water purified	430.00

MANUFACTURING DIRECTIONS

1. Oil-in-water emulsion is prepared to form an elegant cream. Carbamazepine in pure powder form is dissolved in propylene glycol (e.g., up to about 95%). Alternatives for the aqueous phase include an alcohol, such as ethanol or isopropanol, with a thickener added; for example, carbomer 934 or 940.
2. The oil phase preferably includes mineral oil, petrolatum, cetyl alcohol, or stearyl alcohol. Emulsifiers such as polysorbate 80, sorbitan monostearate, or others known in the art may be used. Buffering agents, antioxidants, and chelating agents may be added to improve the characteristics of the formulation.

Carbamazepine Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
3.00	1	Carbamazepine	30.00
5.00	2	Mineral oil	50.00
92.00	3	Petrolatum	920.00

MANUFACTURING DIRECTIONS

1. Micronize carbamazepine to provide particles with a size distribution primarily below 10 μm.
2. Add item 1 to mineral oil to form a finely dispersed suspension; homogenize.
3. Add and mix item 3 and homogenize again.

Castor Oil Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
68.80	1	Castor oil	688.00
10.00	2	Hydrogenated castor oil	100.00
8.70	3	Balsam peru oil	87.00
0.018	4	Trypsin	0.180
q.s.	5	Safflower oil q.s. to	1 kg

MANUFACTURING DIRECTIONS

This is an enzymatic wound debrider.

1. The aluminum/magnesium hydroxide stearate is dispersed in the castor oil.
2. The hydrogenated castor oil is added while mixing with a high-shear mixer.
3. Mixing is continued until a semisolid forms.
4. The remaining ingredients are then blended to the semisolid until homogeneous mixing appears.

Cefaclor and Benzoyl Peroxide Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
3.00	1	Cefaclor	30.00
5.00	2	Benzoyl peroxide	50.00
92.00	3	Gel carrier or vehicle	920.00
q.s.	4	Alcohol 70%	q.s.
q.s.	5	Citric acid for pH adjustment	q.s.

MANUFACTURING DIRECTIONS

1. To a first container, add the benzoyl peroxide and the gel carrier or vehicle ingredients (approximately 5 g of benzoyl peroxide and approximately 89 g of gel carrier or vehicle).
2. To a second container, add powdered cefaclor (approximately 3 g of cefaclor) and dissolve in item 4 and add to step 1.
3. Adjust pH using citric acid.

Cefaclor and Benzoyl Peroxide Lotion

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.00	1	Ethoxylated cetylstearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isostearyl neopentanoate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
66.80	6	Water purified	668.00
3.00	7	Propylene glycol	30.00
5.00	8	Benzoyl peroxide micronized	50.00
10.00	9	Acetone	100.00
0.10	10	Dioctyl sodium sulfosuccinate	1.00
2.00	11	Cefaclor	20.00

Cetrimonium Bromide Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	Cetearyl alchol and cetrimonium bromide	50.00
75.00	2	White petroleum jelly	75.00
60.00	3	Mineral oil 70cS	60.00
q.s.	4	Deionized water q.s. to	1 kg
q.s.	5	Perfume, preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately to 60°–65°C.
2. Add water phase to oil phase while stirring. Stir to cool.

Chlorhexidine and Cetrimonium Bromide Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	Polawax GP200	50.00
10.00	2	Lanolin	10.00
150.00	3	Mineral oil 70cS	150.00
70.00	4	Cetearyl alcohol	70.00
30.00	5	Dimethicone	30.00
q.s.	6	Deionized water q.s. to	1 kg
5.00	7	Cetrimonium bromide	5.00
0.50	8	Chlorhexidine gluconate	0.50
q.s.	9	Perfume, preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil (items 1–5) and water (items 6–9) phases to 65°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool. Fill.

Chlorhexidine Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
20.00	1	Chlorhexidin diacetate	20.00
300.00	2	1,2-Propylene glycol pharma	300.00
220.00	3	Lutrol F 127	220.00
460.00	4	Water	460.00

MANUFACTURING DIRECTIONS

1. Dissolve chlorhexidin diacetate in propylene glycol at >70°C, stir well, and slowly add Lutrol F 127 and water.
2. Maintain the temperature until the air bubbles escape. A clear colorless gel is obtained.

Chloramphenicol Opthalmic Ointment

Each gram of ophthalmic ointment, 1%, contains 10 mg chloramphenicol in a special base of liquid petrolatum and polyethylene. It contains no preservatives. Another formulation contains active ingredients chloramphenicol 11% (10 mg/g) and preservative chlorobutanol (chloral derivative) 0.5% (5 mg/g) and inactives white petrolatum, mineral oil, polyoxyl 40 stearate, polyethylene glycol 300, and petrolatum and lanolin alcohol.

Chlorpromazine Suppositories

Each suppository contains chlorpromazine (25 or 100 mg), glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated coconut oil fatty acids, and hydrogenated palm kernel oil fatty acids.

Ciclopirox Cream, Lotion, and Gel

Cream 0.77% and lotion 0.77% are for topical use. Each gram of cream contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water-miscible vanishing-cream base consisting of purified water USP, cetyl alcohol NF, mineral oil USP, octyldodecanol NF, stearyl alcohol NF, cocamide DEA, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative. Each gram of lotion contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water-miscible lotion base consisting of purified water USP, cocamide DEA, octyldodecanol NF, mineral oil USP, stearyl alcohol NF, cetyl alcohol NF, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative. Cream and lotion contain a synthetic, broad-spectrum, antifungal agent ciclopirox (as ciclopirox olamine). The chemical name is 6-cyclohexyl-1-hydroxy-4-methyl-2(1 H)-pyridone, 2-aminoethanol salt. Each gram of gel contains 7.70 mg ciclopirox in a gel consisting of purified water USP, isopropyl alcohol USP, octyldodecanol NF, dimethicone copolyol 190, carbomer 980, sodium hydroxide NF, and docusate sodium USP.

Ciclopirox Nail Varnish

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
57.50	1	Isopropyl alcohol	575.00
33.00	2	Ethyl acetate	330.00
3.80	3	Polyvinyl butyral	38.00
3.10	4	Cellulose nitrate	31.00
0.60	5	Dibuty phthalate	6.00
2.00	6	Ciclopirox	20.00

MANUFACTURING DIRECTIONS

1. All items are mixed to a uniform mixture; pigments may be added to color the varnish.
2. A thixotropic paste is prepared by slowly stirring 10 parts of an organically modified montmorillonite (e.g., bentone 27) into 80 parts toluene and subsequently adding 8 parts wetting agent (e.g., anti-terra-U) and 2 parts methanol. A clear varnish is also prepared by dissolving 22 parts butanol-moist collodion cotton (e.g., type E 510) and 8 parts toluene sulfonamide resin (e.g., santolite MS 80) in a mixture of 3 parts dibutyl phthalate, 20 parts ethyl acetate, 10 parts butyl acetate, 7 parts ethyl alcohol, and 30 parts toluene. Forty parts DC ROT No. 7 calcium varnish (e.g., color pigment C 19021) and 60 parts dibutyl phthalate are also processed to give a color paste with a particle size of less than 1 μm.
3. To prepare the pigmented nail varnish, 12 parts thixotropic paste and 0.8 parts antisettling agent (e.g., MPA 2000 X) are dispersed in 83.7 parts clear varnish, during which operation a temperature of at least 38°C is to be reached. One part 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone is then dissolved in the thixotropic clear varnish, and 2.5 parts color paste was stirred in. The finished nail varnish is filtered through a 70-μm sieve.

Ciprofloxacin Hydrochloride Opthalmic Ointment

The ciprofloxacin hydrochloride ophthalmic ointment consists of synthetic, sterile, multiple-dose, antimicrobials for topical ophthalmic use. Ciprofloxacin is a fluoroquinolone antibacterial that is active against a broad spectrum of gram-positive and gram-negative ocular pathogens. It is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid. It is a faint to light-yellow crystalline powder with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$. Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6– position, a piperazine moiety at the 7– position, and a cyclopropyl ring at the 1– position. Each gram of ophthalmic ointment contains active ingredients ciprofloxacin HCl 3.33 mg equivalent to 3-mg base. Inactive ingredients are mineral oil and white petrolatum.

Clindamycin Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Clindamycin USE clindamycin phosphate	11.90
0.15	2	Methylparaben	1.50
0.20	3	Carbopol 941	2.00
15.00	4	Propylene glycol 400	50.00
5.00	5	Polyethylene glycol	50.00
q.s.	6	Sodium hydroxide 10% solution for pH adjustment	q.s.
q.s.	7	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

The viscosity of this composition is about 1000 cP.

1. Weigh approximately 90% of the purified water into a stainless steel kettle.
2. Add the propylene glycol 400 and polyethylene glycol. Stir with a propeller mixer.
3. At room temperature, add methylparaben to step 1 with continued stirring. Mix until dissolved.
4. While continuing to mix, add clindamycin phosphate to step 2. Mix until dissolved.
5. While continuing to mix, add carbopol 941 slowly to step above, avoiding clumping.
6. Mix vigorously at room temperature until a uniform and lump-free dispersion is achieved.
7. While mixing, add sufficient sodium hydroxide, 10% solution, to achieve a pH of 5.3–5.7. Mix until uniform.
8. Add the remaining water to make 100% and mix until uniform. Please note that a commercial preparation contains an additional component: allantoin.

Clindamycin Lotion and Gel

The topical lotion contains clindamycin phosphate USP at a concentration equivalent to 10 mg clindamycin per milliliter. The lotion contains cetostearyl alcohol (2.5%), glycerin, glyceryl stearate SE (with potassium monostearate), isostearyl alcohol (2.5%), methylparaben (0.3%), sodium lauroyl sarcosinate, stearic acid, and purified water. Topical gel contains clindamycin phosphate USP at a concentration equivalent to 10 mg clindamycin per gram. The gel contains allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water.

Clindamycin Phosphate Topical Gel

Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro- substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. Chemically, clindamycin phosphate is ($C_{18}H_{34}CIN_2O_8PS$). The topical gel also contains benzoyl peroxide for topical use. Each gram of topical gel contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

Clindamycin Phosphate Vaginal Cream

Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro- substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-(alpha)-D-galacto-octopyranoside 2-(dihydrogen phosphate). It has a molecular weight of 504.96, and the molecular formula is $C_{18}H_{34}CIN_2O_8$. Vaginal cream, 2%, is a semisolid white cream that contains 2% clindamycin phosphate USP at a concentration equivalent to 20 g clindamycin per gram. The pH of the cream is between 3.0 and 6.0. The cream also contains benzyl alcohol, cetostearyl alcohol, cetyl palmitate, mineral oil, polysorbate 60, propylene glycol, purified water, sorbitan monostearate, and stearic acid. Each applicatorful of 5 g of vaginal cream contains approximately 100 mg of clindamycin phosphate.

Clindamycin Phosphate Vaginal Suppository

Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro- substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. Vaginal ovules are semisolid, white to off-white suppositories for intravaginal administration. Each 2.5-g suppository contains clindamycin phosphate equivalent to 100 mg clindamycin in a base consisting of a mixture of glycerides of saturated fatty acids.

Clobetasol Propionate Cream

Bill of Material

Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
0.050	1	Clobetasol propionate (5% excess)	0.525
44.500	2	Propylene glycol	445.000
0.050	3	Sodium citrate	0.500
0.050	4	Citric acid	0.500
5.000	5	Glyceryl monostearate A/S	50.000
4.000	6	Cetostearyl alcohol	40.000
0.600	7	White wax (beeswax bleached)	6.000
0.075	8	Chlorocresol	0.750
1.000	9	Glyceryl monostearate SE	10.000
7.000	10	Propylene glycol	70.000
2.675	11	Propylene glycol	26.750
35.000	12	Purified water	350.000

MANUFACTURING DIRECTIONS

1. Aqueous phase:
   a. Heat item 12 to 90°C in mixer. Bring down the temperature to 60°C. Dissolve all ingredients to a clear solution. Maintain temperature at 60°C.
   b. Filter through a polyester cloth. Check the weight. Clean the manufacturing vessel with item 12. Adjust the weight with item 12, if required. Record the quantity of extra item 12.
   c. Transfer again to manufacturing vessel. Maintain temperature at 60°C.
2. Oil phase:
   a. Melt items 5, 9, 6, 7, and 8 in melting vessel at 70°–75°C while stirring. Cool to 60°C. Maintain temperature at 60°C.
3. Dispersed phase:
   a. Transfer the oil phase to aqueous phase in the manufacturing vessel through mesh by vacuum while stirring at manual mode 10 rpm, temperature 60°C. Mix at 10 rpm for 10 minutes at 60°C. Homogenize at high speed under vacuum 0.4 bar for 5 minutes at temperature 60°C. Cool down the temperature to 50°C while mixing at 10 rpm.

4. Drug phase:
   a. Mix item 1 in item 10 in a water bath at 50°C until a clear solution is obtained. A homogenizer may be used. Add to dispersed phase at step 3.2. Rinse with item 11 and add to dispersed phase at step 3a. Mix and homogenize under vacuum 0.4 bar for 5 minutes, high speed, 10 rpm, temperature 50°C.
   b. Cool to 30°C while mixing at 10 rpm, auto mode under vacuum 0.4 bar, mixing time 20 minutes.
   c. Unload the cream in stainless steel drum and fill.

Clobetasol Propionate Cream, Ointment, and Gel

Clobetasol propionate cream and ointment contain the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. Cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water. Ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum. Gel contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.

Clobetasol Propionate Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.050	1	Clobetasol propionate (5% excess)	0.525
94.460	2	Petrolatum (white soft paraffin)	944.600
0.500	3	Sorbitan sesquioleate (arlacel 83)	5.000
4.000	4	Propylene glycol	40.000
0.500	5	Propylene glycol	5.000

MANUFACTURING DIRECTIONS

1. Melt items 2 and 3 in a fat-melting vessel at temperature 75°C while mixing.
2. Start heating mixer vessel to 75°C. Transfer molten items 2 and 3 to mixer through stainless steel mesh under vacuum 0.4–0.6 bar. Start mixer at 10 rpm manual mode.
3. Cool down to 50°C.
4. In a water bath (temperature 60°C), dissolve item 1 in item 4 using homogenizer for 5 minutes. Add this to mixer with stirring.
5. Rinse with item 5 and add to mixer at temperature 50°C.
6. Start homogenizer under vacuum 0.4–0.6 bar while stirring at 10 rpm high speed for 10 minutes.
7. Cool down the temperature to 30°C, 10 rpm, auto mode, vacuum 0.4–0.6 bar.
8. Transfer the ointment to a stainless steel container. Fill.

Clotrimazole and Betamethasone Cream and Lotion

Clotrimazone cream and lotion contain combinations of clotrimazole, a synthetic antifungal agent, and betamethasone dipropionate, a synthetic corticosteroid, for dermatologic use. Chemically, clotrimazole is 1-(o-chloro-(alpha),(alpha)-diphenylbenzyl) imidazole, with the empirical formula $C_{22}H_{17}ClN_2$. Each gram of cream contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic cream consisting of purified water, mineral oil, white petrolatum, cetearyl alcohol 70/30, ceteareth-30,

propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid, with benzyl alcohol as preservative. Each gram of lotion contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic base of purified water, mineral oil, white petrolatum, cetearyl alcohol 70/30, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid, with benzyl alcohol as a preservative. Lotion may also contain sodium hydroxide.

Clotrimazole Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.00	1	Cetyl stearyl alcohol	70.00
1.50	2	Cremophor A6	15.00
1.50	3	Cremophor A25	15.00
12.00	4	Liquid paraffin	120.00
0.20	5	Methyl and propyl parabens	2.00
68.80	6	Water purified	688.00
8.00	7	Propylene glycol	80.00
1.00	8	Clotrimazole	1.00

MANUFACTURING DIRECTIONS

1. Heat the mixture of items 1–5 and item 6 separately to about 80°C.
2. Add item 6 to the obtained solution step 1 mixture of items 1–5 with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with step 2 and continue to stir during cooling to room temperature.

Clotrimazole Lotion

Each gram of lotion contains 10 mg clotrimazole USP dispersed in an emulsion vehicle composed of benzyl alcohol NF (1%), cetearyl alcohol 70/30 (3.7%), cetyl esters wax NF, octyldodecanol NF, polysorbate 60 NF, sodium phosphate dibasic anhydrous R, sodium phosphate monobasic monohydrate USP, sorbitan monostearate NF, and purified water USP.

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
40.00	1	Clotrimazole	40.00
50.00	2	White petrolatum	50.00
20.00	3	Mineral oil	60.00
24.00	4	Cetearyl alcohol	72.00
22.50	5	Ceteth 20	22.50
10.00	6	Benzyl alcohol	10.00
100.00	7	Propylene glycol	100.00
0.35	8	Sodium phosphate dibasic anhydrous	0.35
5.00	9	Sodium phosphate monobasic monohydrate	5.00
q.s.	10	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Heat 75% of the water to 70°C in a suitable vessel. Add the monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, propylene glycol, and benzyl alcohol to the vessel with agitation, maintaining the temperature at 70°C.
2. In a separate vessel, melt the petrolatum and heat to 70°C.
3. Add the mineral oil and mix. Add the cetearyl alcohol and 95% of the ceteth 20; mix and maintain at 70°C.
4. Combine the contents of the two vessels with agitation, maintaining at 70°C.
5. Cool to 38°C with agitation.
6. In a separate vessel dissolve the remaining ceteth 20 in the remaining water at 65°C with agitation.
7. Cool to room temperature and slurry the clotrimazole with vigorous agitation until smooth uniform slurry is obtained.
8. Add the slurry to the previous emulsion mixture and agitate while cooling to room temperature.

Clotrimazone Vaginal Cream Inserts

Clotrimazone vaginal inserts each contain 100 mg clotrimazole with inactive ingredients benzyl alcohol, cetostearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate. The inserts are made of corn starch, lactose, magnesium stearate, and povidone.

Clotrimazone Vaginal Cream

The vaginal cream's active ingredient is clotrimazole 2% (100 mg per applicator). The inactive ingredients are benzyl alcohol, cetearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate.

Bill of Materials

Scale (mg/g)	Item	Material Name	Quantity/kg (g)
40.00	1	Clotrimazole	40.00
150.00	2	White petrolatum	150.00
60.00	3	Mineral oil	60.00
72.00	4	Cetearyl alcohol	72.00
22.50	5	Ceteth 20	22.50
10.00	6	Benzyl alcohol	10.00
100.00	7	Propylene glycol	100.00
0.35	8	Sodium phosphate dibasic anhydrous	0.35
5.00	9	Sodium phosphate monobasic monohydrate	5.00
q.s.	10	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Heat 75% of the water to 70°C in a suitable vessel. Add the monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, propylene glycol, and benzyl alcohol to the vessel with agitation, maintaining the temperature at 70°C.
2. In a separate vessel, melt the petrolatum and heat to 70°C.
3. Add the mineral oil and mix. Add the cetearyl alcohol and 95% of the ceteth 20; mix and maintain at 70°C.
4. Combine the contents of the two vessels with agitation, maintaining at 70°C.
5. Cool to 38°C with agitation.
6. In a separate vessel dissolve the remaining ceteth 20 in the remaining water at 65°C with agitation.
7. Cool to room temperature and slurry the clotrimazole with vigorous agitation until smooth uniform slurry is obtained.
8. Add the slurry to the previous emulsion mixture and agitate while cooling to room temperature.

Clotrimazole and Clindamycin Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
20.00	1	Clotrimazole	20.00
4.00	2	Clindamycin base USE clindamycin hydrochloride	4.54
20.00	3	Sorbitan monostearate	20.00
30.00	4	Tween 60	30.00
130.46	5	Paraffin viscous	130.46
100.00	6	Cetylstearyl alcohol	100.00
10.00	7	Benzyl alcohol	10.00
670.00	8	Water purified	670.00

MANUFACTURING DIRECTIONS

One application unit is equivalent to 5 g. This comprises 100 mg clotrimazole and 20 mg clindamycin.

1. Add and dissolve items 1 and 2 in items 7 and 8 in a blender.
2. Add and dissolve remaining items in a separate blender and heat to 40°C.
3. Add into step 2 with vigorous mixing to form a cream base.

Clotrimazole and Clindamycin Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
100.00	1	Clotrimazole	100.00
20.00	2	Clindamycin base USE clindamycin hydrochloride	22.70
77.30	3	Calclium lactate pentahydrate	77.30
250.00	4	Gelatin	250.00
250.00	5	Water purified	250.00
1250.00	6	Glycerol	1250.00

MANUFACTURING DIRECTIONS

1. Dissolve items 1 and 2 in item 5.
2. Heat item 4 in item 6 in a separate vessel and add item 3.
3. Mix well and add to step 1.
4. Fill suppository 2.0 g each.

Clotrimazole and Clindamycin Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 suppositories (g)**
100.00	1	Clotrimazole	100.00
20.00	2	Clindamycin Base USE clindamycin hydrochloride	22.70
77.30	3	Calclium lactate pentahydrate	77.30
1000.00	4	Macrogol 400	1000.00
800.00	5	Macrogol 6000	800.00
200.00	6	Lactic acid	200.00

MANUFACTURING DIRECTIONS

1. Add and mix all ingredients.
2. Heat to 70°C and mix well.
3. Cool to 40°C and fill.

Coal Tar and Allantoin Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
40.00	1	Lanolin alcohol	40.00
50.00	2	White petroleum jelly	50.00
120.00	3	Parafiin wax 140F	120.00
300.00	4	Mineral oil 70cS	300.00
20.00	5	Coal tar	20.00
2.50	6	Allantoin	2.50
q.s.	7	Deionized water q.s. to	1 kg
q.s.	8	Preservative	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately to 70°C.
2. Slowly add water phase in increments to the oil phase.
3. Allow each addition time to be fully incorporated.
4. Stir to cool. Fill just above melting point. Further homogenization may improve stability before filling.

Coal Tar and Allantoin Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
160.00	1	Stearic acid	16.00
60.00	2	Oleyl alcohol	6.00
20.00	3	Lanolin	2.00
20.00	4	Coal tar	2.00
6.00	5	Triethanolamine 99%	0.60
2.50	6	Allantoin	0.25
q.s.	7	Deionized water q.s. to	1 kg
q.s.	8	Preservative	q.s.

MANUFACTURING DIRECTIONS

1. Heat water (items 7 and 8) and oil phases (all other items) separately to 80°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 40°C. May homogenize.

Coal Tar Cream

The active ingredient in coal tar cream is 5% coal tar solution USP, equivalent to 0.8% coal tar. Inactive ingredients include acetylated lanolin alcohol, alcohol (4.7%), carbomer-934P, ceteth-2, ceteth-16, cetyl acetate, cetyl alcohol, D&C; red no. 28, fragrance, glyceryl tribehenate, laneth-16, lanolin alcohol, laureth-23, methyl gluceth-20, methylchloroisothiazolinone, methylisothiazolinone, mineral oil, octyldodecanol, oleth-16, petrolatum, potassium hydroxide, purified water, steareth-16, stearyl alcohol, titanium dioxide.

Collagenase Ointment

Collagenase ointment is a sterile enzymatic debriding ointment that contains 250 collagenase units per gram of white petrolatum USP. The enzyme collagenase is derived from the fermentation by *Clostridium histolyticum*. It possesses the unique ability to digest collagen in necrotic tissue.

Conjugated Estrogens Vaginal Cream

Each gram of conjugated estrogens vaginal cream contains 0.625 mg conjugated estrogens USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. It is is applied intravaginally. Conjugated estrogens is a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blend to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17 (alpha)-dihydroequilin, together with smaller amounts of 17 (alpha)-estradiol, equilenin, and 17 (alpha)-dihydroequilenin as salts of their sulfate esters.

Cyanocobalamin Gel

Cyanocobalamin is a synthetic form of vitamin B_{12} with equivalent vitamin B_{12} activity. The chemical name is 5,6-dimethyl-benzimidazolyl cyanocobamide. The cobalt content is 4.35%. Cyanocobalamin occurs as dark-red crystals or orthorhombic needles or crystalline red powder. It is very hygroscopic in the anhydrous form and sparingly to moderately soluble in water (1:80). Its pharmacologic activity is destroyed by heavy metals (iron) and strong oxidizing or reducing agents (vitamin C), but not by autoclaving for short periods of time (15–20 minutes) at 121°C. The vitamin B_{12} coenzymes are very unstable in light. Cyanocobalamin gel for intranasal administration is a solution of cyanocobalamin USP (vitamin B_{12}) for administration as a metered gel to the nasal mucosa. Each bottle of gel contains 2.3 mL of a 500 mcg/0.1 mL gel solution of cyanocobalamin with methylcellulose, sodium citrate, citric acid, glycerin, and benzalkonium chloride in purified water. The gel solution has a pH between 4.5 and 5.5. After initial priming, each metered gel delivers an average of 500 mcg of cyanocobalamin, and the 2.3 mL of gel contained in the bottle will deliver 8 doses.

DBcAMP Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
3.00	1	DBcAMP	35.10
68.49	2	Polyethylene glycol 400	684.90
28.00	3	Polyethylene glycol 4000	280.00

MANUFACTURING DIRECTIONS

1. In a glass-lined melting vessel, charge 90% of item 3 and item 2 and melt at 70°–80°C.
2. Transfer to a homogenizer and cool to 50°C.
3. Prepare a dispersion of item 1 in balance of item 3 in a separate vessel and add to step 2.
4. Rinse the container with item 2 and add rinsings.
5. Mix at 50°C. Cool and fill.

Desonide Cream, Ointment, and Lotion

Cream 0.05%, ointment 0.05%, and lotion 0.05% contain desonide (Pregna-1,4-diene-3,20-dione,11,21-dihydroxy-16, 17-[(1-methylethylidene)bis(oxy)]-,[11(beta),16(alpha)-]), a synthetic nonfluorinated corticosteroid, for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Each gram of cream contains 0.5 mg of desonide in a base of purified water, emulsifying wax, propylene glycol, stearic acid, isopropyl palmitate, synthetic beeswax, polysorbate 60, potassium sorbate, sorbic acid, propyl gallate, citric acid, and sodium hydroxide. Each gram of ointment contains 0.5 mg of desonide in a base of mineral oil and polyethylene. Each gram of lotion contains 0.5 mg of desonide in a base of sodium lauryl sulfate, light mineral oil, cetyl alcohol, stearyl alcohol, propylene glycol, methylparaben, propylparaben, sorbitan monostearate, glyceryl stearate SE, edetate sodium, and purified water and may contain citric acid or sodium hydroxide for pH adjustment.

Desoximetasone Emollient Cream, Gel, and Ointment

Desoximetasone emollient cream 0.25%, desoximetasone gel 0.05%, desoximetasone ointment 0.25%, and desoximetasone emollient cream 0.05% contain the active synthetic corticosteroid desoximetasone. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Each gram of emollient cream 0.25% contains 2.5 mg desoximetasone in an emollient cream consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, and magnesium stearate. Each gram of gel 0.05% contains 0.5 mg desoximetasone in a gel consisting of purified water USP, SD alcohol 40 (20% w/w), isopropyl myristate NF, carbomer 940, trolamine NF, edetate disodium USP, and docusate sodium USP. Each gram of ointment 0.25% contains 2.5 mg of desoximetasone in a base consisting of white petrolatum USP, propylene glycol USP, sorbitan sesquioleate, beeswax, fatty alcohol citrate, fatty acid pentaerythritol ester, aluminum stearate, citric acid, and butylated hydroxyanisole. Each gram of emollient cream 0.05% contains 0.5 mg desoximetasone in an emollient cream consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, edetate disodium USP, lactic acid USP, and magnesium stearate.

Dexamethasone Sodium Phosphate Ointment

Dexamethasone sodium phosphate is 9-fluoro-11(beta), 17-dihydroxy-16(alpha)-methyl-21-(phosphonooxy)pregna-1,4-diene-3,20-dione disodium salt. Sterile ophthalmic ointment dexamethasone sodium phosphate is a topical steroid ointment containing dexamethasone sodium phosphate equivalent to 0.5 mg (0.05%) dexamethasone phosphate in each gram. Inactive ingredients are white petrolatum and mineral oil.

Dexpanthenol Cream

Bill of Materials

Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
5.00	1	Dexpanthenol	50.00
10.00	2	White soft paraffin	100.00
5.00	3	Cetostearyl alcohol	50.00
2.00	4	Lanolin anhydrous	20.00
10.00	5	Liquid paraffin	100.00
11.00	6	Propylene glycol	110.00
0.15	7	Methyl paraben	1.50
0.05	8	Propyl paraben	0.50
1.00	9	Tween 60	10.00
1.00	10	Simethicone M30	10.00
0.072	11	Lavender oil	0.072
0.028	12	Rose oil perfume	0.28
64.70	13	Water purified	647.00

MANUFACTURING DIRECTIONS

1. Charge items 2–5 in a melting vessel and heat to 70°C.
2. Charge portion of item 13 (at 70°C), item 1, and item 9 and heat to 70°C and mix for 10 minutes.
3. In a separate container add and dissolve items 7 and 8 in item 6 at 70°C and add to step 2.
4. Add step 1 into step 3. Mix under vacuum and at 70°C for 20 minutes.
5. Cool to 35°–40°C and add item 10; mix again under vacuum.
6. Add items 11 and 12 and mix (without vacuum) and cool down to 25°C.
7. Transfer to storage vessel and fill.

Dexpanthenol Gel-Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	Dexpanthenol (BASF)	50.00
100.00	2	Liquid paraffin	100.00
150.00	3	Lutrol E 400	150.00
180.00	4	Lutrol F 127	180.00
q.s.	5	Water q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Dissolve dexpanthenol and Lutrol E 400 in water, add liquid paraffin, and stir, heating to 60°–70°C.
2. Slowly add Lutrol F 127 and stir until it is dissolved.
3. Cool to room temperature, stirring continuously until the air bubbles disappear.

Diclofenac Diethylamine Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Diclofenac diethylamine, 10% excess	11.00
1.20	2	Carbopol 934P	12.00
23.00	3	Isopropyl alcohol	230.00
5.00	4	Propylene glycol	50.00
2.50	5	Liquid paraffin	25.00
2.50	6	Cetiol LC	25.00
2.00	7	Cetomacrogol 1000	20.00
0.90	8	Diethylamine	9.00
0.028	9	Perfume	0.28
0.072	10	Perfume	0.72
68.00	11	Water purified	680.00

MANUFACTURING DIRECTIONS

1. Charge 90% of item 11 in a mixing vessel, heat to 80°C; stir to produce vortex and add item 2 to disperse after passing through 1-mm sieve; mix for 5 minutes, avoiding foam.
2. Transfer step 1 into Becomix and maintain temperature at 70°C.
3. Charge items 5–7 in a separate vessel, melt at 70°C, transfer to step 2.
4. Mix at speed II under vacuum of 0.4–0.6 bar for 5 minutes at 10 rpm.
5. Cool down to 30°C.
6. Add and dissolve item 8 in item 11 separately and then add to step 5 and mix for 10 minutes,
7. Dissolve item 1 in items 3 and 4 separately and transfer to step 6 through a cloth filter; mix for 20 minutes.
8. Homogenize at speed I for 5 minutes under vacuum at 10 rpm.
9. Add perfumes and mix for 5 minutes.
10. Fill in appropriate containers.

Diclofenac Diethylammonium Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
q.s.	1	Water purified	465.53
500.00	2	Alcohol 190 proof	500.00
2.00	3	Menthol	2.00
10.00	4	Diclofenac USE diclofenac diethylammonium	12.47
8.00	5	Carbopol 940	8.00
12.00	6	Trolamine	12.00

MANUFACTURING DIRECTIONS

1. Place water purified and alcohol in a 316 grade stainless steel mixing tank.
2. Add menthol crystals to the alcohol–water mixture. Mix for 5 minutes or until completely dissolved.
3. Add diclofenac diethylammonium to the mixing tank. Mix for 10 minutes or until completely dissolved.
4. While mixing, sprinkle in carbomer. Continue mixing slowly at intervals for 1–2 hours or until carbomer swells completely in the hydroalcoholic solution.
5. Add trolamine and mix for 10 minutes or until gel forms.
6. Fill into suitable lined, collapsible aluminum tube.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
12.50	1	Diclofenac sodium micronized, 1% excess	12.62
530.32	2	Suppocire CM	530.32
353.00	3	Suppocire AS2X	353.00
2.90	4	Crill 3	2.90
1.15	5	Aerosil 200	1.15

MANUFACTURING DIRECTIONS

1. Load items 2–4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves; set the temperature to 50°C.
3. Add item 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°–55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 900 mg in a suppository mold.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
25.00	1	Diclofenac sodium micronized, 1% excess	25.25
522.70	2	Suppocire CM	522.70
348.00	3	Suppocire AS2X	348.00
2.90	4	Crill 3	2.90
1.15	5	Aerosil 200	1.15

MANUFACTURING DIRECTIONS

1. Load items 2–4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a Becomix vessel through filter sieves; set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°–55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 900 mg in a suppository mold.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
50.00	1	Diclofenac sodium micronized, 1% excess	50.50
1045.40	2	Suppocire CM	1045.40
696.00	3	Suppocire AS2X	696.00
5.80	4	Crill 3	5.80
2.30	5	Aerosil 200	2.30

MANUFACTURING DIRECTIONS

1. Load items 2–4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves; set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°–55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 1800 mg in a suppository mold.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
100.00	1	Diclofenac sodium micronized, 1% excess	101.00
1015.00	2	Suppocire CM	1015.00
675.00	3	Suppocire AS2X	675.00
6.00	4	Crill 3	6.00
2.50	5	Aerosil 200	2.50

MANUFACTURING DIRECTIONS

1. Load items 2–4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves; set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°–55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 1800 mg in a suppository mold.

Dichlorobenzyl Alcohol Tooth Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	2,4-dichlorobenzyl alcohol (myacid)	10.00
2.00	2	Sodium carboxymethylcellulose*	20.00
q.s.	3	Water purified q.s. to	1 kg

*To obtain thicker gel, the quantity can be increased to 4.00.

MANUFACTURING DIRECTIONS

1. Disperse item 2 in item 3 heated to 70°C.
2. Cool and add item and mix well.
3. Cool to 40°C and fill.

Dienestrol Vaginal Cream

The active ingredient in dienestrol vaginal cream is dienestrol 0.01%. Dienestrol is a synthetic, nonsteroidal estrogen. It is compounded in a cream base suitable for intravaginal use only. The cream base is composed of glyceryl monostearate, peanut oil, glycerin, benzoic acid, glutamic acid, butylated hydroxyanisole, citric acid, sodium hydroxide, and water. The pH is approximately 4.3. Available in 2.75-oz (78 g) tubes with or without a measured dose applicator.

Diethylamine Salicylate Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
22.50	1	White soft paraffin	225.00
12.50	2	Glyceryl monostearate	125.00
5.00	3	Criss-3 (span 60)	50.00
0.10	4	Vitamin E oily	1.00
45.24	5	Water purified	452.40
0.71	6	Sodium phosphate monobasic	7.10
0.13	7	Sodium hydroxide pellets	1.30
0.10	8	Sodium disulfide pure	1.00
0.166	9	Sodium ethylene diamine tetraacetate	1.66
12.00	10	Diethylamine salicylate	120.00
0.12	11	Menthol	1.20
0.50	12	Chlorbutol	5.00
0.30	13	Lavender oil	3.00
0.40	14	Glycerin	4.00
0.20	15	Methylparaben	2.00
0.12	16	Propylparaben	1.20

MANUFACTURING DIRECTIONS

1. Charge, one by one, items 1–4 to a melting vessel at 79°–75°C; hold molten fat at 70°C with continuous stirring at low speed.
2. In a separate vessel, heat 90% of item 5 to 90°C, add and dissolve parabens by stirring. Cool to 65°–70°C.
3. In a separate vessel, take the balance of item 5 and sodium hydroxide pellets and sodium phosphate monobasic and dissolve.
4. Transfer step 3 to the paraben solution and mix for 5–10 minutes at slow speed and at 65°–70°C.
5. Cool to 25°C; check and adjust pH 6.8–7.2. Add items 8–10 and mix to dissolve at 50°C.
6. Filter solution through polyester cloth and keep aside at 50°C.
7. Set Becomix temperature to 70°C, 10 rpm, and vacuum 0.6 bar.
8. Transfer molten fat at 70°C after passing through a stainless steel filter to step above while mixing.
9. Homogenize at slow speed for 10 minutes; temperature 65°–70°C.
10. Set Becomix to 50°C and transfer diethylamine salicylate solution to the cream at 50°C while stirring.
11. Continue mixing and add chlorbutol, menthol, lavender oil, and glycerin at 40°C. (Menthol and chlorbutol first dissolve in a separate container.)
12. Homogenize for 10 minutes under vacuum.
13. Cool to 25°C, transfer to storage vessel. Fill.

Diflorasone Diacetate Cream and Ointment

Each gram of cream contains 0.5 mg diflorasone diacetate in a cream base. Chemically, diflorasone diacetate is 6(alpha),9-difluoro-11(beta),17,21-trihydroxy-16(beta)-methyl-pregna1,4-diene-3,20-dione17,21-diacetate. Each gram of cream contains 0.5 mg diflorasone diacetate in a hydrophilic vanishing-cream base of propylene glycol, stearyl alcohol, cetyl alcohol, sorbitan monostearate, polysorbate 60, mineral oil, and purified water. Each gram of ointment contains 0.5 mg diflorasone diacetate in an ointment base. Emollient ointment contains diflorasone diacetate in an emollient, occlusive base consisting of polyoxypropylene 15-stearyl ether, stearic acid, lanolin alcohol, and white petrolatum.

Dimethicone and Zinc Oxide Ointment

Active ingredients in dimethicone and zinc oxide ointment are dimethicone 1% and zinc oxide 10%. Inactive ingredients include aloe extract, benzyl alcohol, cod liver oil (contains vitamins A and D), fragrance, glyceryl oleate, light mineral oil, ozokerite, paraffin, propylene glycol, sorbitol, synthetic beeswax, and water.

Dinoprostone Cervical Gel

Dinoprostone is the naturally occurring form of prostaglandin E_2 (PGE_2) and is designated chemically as (5Z, 11a, 13E, 15S)-11,15-dihydroxy-9-oxo-prosta-5,13-dien-1-oic acid. The molecular formula is $C_{20}\,H_{32}\,O_5$, and the molecular weight is 352.5. The active constituent of gel is dinoprostone 0.5 mg/3 g (2.5 mL gel); other constituents are colloidal silicon dioxide NF (240 mg/3 g) and triacetin USP (2760 mg/3 g).

Dinoprostone Vaginal Insert and Suppositories

Dinoprostone vaginal insert is a thin, flat, polymeric slab that is rectangular with rounded corners, contained within the pouch of a knitted polyester retrieval system, an integral part of which is a long tape. Each slab is buff colored and semitransparent and contains 10 mg of dinoprostone. The hydrogel insert is contained within the pouch of an off-white knitted polyester retrieval system designed to aid retrieval at the end of the dosing interval. The finished product is a controlled release formulation that has been found to release dinoprostone *in vivo* at a rate of approximately 0.3 mg/h. The chemical name for dinoprostone (commonly known as prostaglandin E_2 or PGE_2) is 11(alpha),15S-dihydroxy-9-oxo-prosta-5Z,13E-dien-1-oic acid. Dinoprostone occurs as a white to off-white crystalline powder. It has a melting point within the range of 65°–69°C. Dinoprostone is soluble in ethanol and in 25% ethanol in water. Each insert contains 10 mg of dinoprostone in 241 mg of a cross-linked polyethylene oxide/urethane polymer that is a semiopaque, beige-colored, flat rectangular slab measuring 29 mm by 9.5 mm and 0.8 mm in thickness. The insert and its retrieval system, made of polyester yarn, are nontoxic, and when placed in a moist environment, they absorb water, swell, and release dinoprostone. The insert contains 10 mg dinoprostone. The product is wound and enclosed in an aluminum sleeve that is contained in an aluminum/polyethylene pack. Vaginal suppositories are available. Each suppository contains 20 mg of dinoprostone in a mixture of glycerides of fatty acids.

Diphenhydramine Hydrochloride and Zinc Acetate Ointment

Diphenhydramine hydrochloride and zinc acetate ointment contain diphenhydramine hydrochloride 1% and zinc acetate 0.1%. The extra-strength formulation is diphenhydramine hydrochloride 2% and zinc acetate 0.1%. Inactive ingredients include cetyl alcohol, diazolidinyl urea, methylparaben, polyethylene glycol monostearate 1000, propylene glycol, propylparaben, and purified water.

Docosanol Lotion

Docosanol 10% is a cold sore/fever blister treatment. Inactive ingredients include benzyl alcohol, light mineral oil, propylene glycol, purified water, sucrose distearate, and sucrose stearate.

Econazole Nitrate and Benzoyl Peroxide Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
200.00	1	PEG-6 and PEG-32 and glyceryl stearate (TEFOSE 63)	200.00
30.00	2	Mineral oil	30.00
30.00	3	Apricol kernel oil PEG-6 esters (LABRIFIL M 1944)	30.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methylparaben	0.50
724.00	6	Deionized water	724.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

MANUFACTURING DIRECTIONS

1. Mix and heat items 1–6 together and bring temperature to 75°C.
2. Allow to cool while stirring. Add items 7 and 8 at 30°C and mix well until uniform.

Econazole Nitrate and Benzoyl Peroxide Lotion

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	PEG-6 stearate and cetech-20 and steareth-20 (TEFOSE 2000)	50.00
30.00	2	Mineral oil	30.00
20.00	3	Cetyl alcohol	20.00
0.70	4	Sodium methylaraben	0.70
0.30	5	Sorbic acid	0.30
884.00	6	Deionized water	884.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

MANUFACTURING DIRECTIONS

1. Mix and heat items 1–3 together and bring temperature to 75°C.
2. Allow to cool while stirring. Mix items 4–6 and add to above while stirring.
3. Cool with stirring. Add items 7 and 8 at 30°C while stirring.

Eflornithine Hydrochloride Cream

The cream contains 13.9% (139 mg/g) anhydrous eflornithine hydrochloride as eflornithine hydrochloride monohydrate (150 mg/g). Chemically, eflornithine hydrochloride is (±)-2-(difluoromethyl)ornithine monohydrochloride monohydrate, with the empirical formula $C_6H_{12}F_2N_2O_2 \cdot HCl \cdot H_2O$ and a molecular weight of 236.65. Other ingredients include ceteareth-20, cetearyl alcohol, dimethicone, glyceryl stearate, methylparaben, mineral oil, PEG-100 stearate, phenoxyethanol, propylparaben, stearyl alcohol, and water.

Enzyme Extract Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	Fumed silica	500.00
18.50	2	Enzyme extract*	185.00
0.20	3	Methylparaben	2.00
0.50	4	Propylparaben	5.00
0.03	5	Bromopal	0.30
0.02	6	Fragrance	0.20
q.s.	7	Water purified q.s. to	1 kg

*This is a generic formula to incorporate proteins, tissue components, or enzyme extracts (in powder form).

Erythromycin Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
10.00	1	Erythromycin powder 850 mcg/mg, 10% excess*	12.94
100.00	2	Mineral oil light	100.00
q.s.	3	Petrolatum white q.s. to	1 kg

*Adjust petrolatum weight to compensate for change in weight of erythromycin base calculated from its potency.

MANUFACTURING DIRECTIONS

1. Heat petrolatum and mineral oil in a steam kettle to 115°C and maintain temperature for at least 3 hours.
2. Strain into mixing tank and cool to 40°–45°C.
3. Reserve portion of petrolatum–oil mixture for step 6.
4. Mix erythromycin with 78 g of base and stir until thoroughly dispersed.
5. Run through 200 mesh (74-μm aperture) screen on Homoloid mill directly into main portion of petrolatum–oil mixture.
6. Rinse mill with reserved petrolatum–oil mixture from step 3.
7. Mix 2 hours before cooling. Cool slowly to avoid condensation.
8. Fill into suitable approved containers.

Erythromycin Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
23.75	1	Isostearyl benzoate	237.50
23.85	2	Bis (2-ethylhexyl) maleate	238.50
10.00	3	Cyclomethicone	100.00
5.00	4	Stearyl alcohol	50.00
10.00	5	Starch	100.00
10.00	6	Microcrystalline cellulose	100.00
15.00	7	Ethylene/vinyl copolymer	150.00
0.10	8	Propylparaben	1.00
0.10	9	Butylparaben	1.00
0.10	10	Fragrance	1.00
2.00	11	Erythromycin	21.00

MANUFACTURING DIRECTIONS

1. Blend items 1–4 in a high-shear mixer.
2. Add balance ingredients and mix well.
3. Fill.

Erythromycin and Neomycin Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
10.00	1	Erythromycin-base fine powder 10% excess (900 mcg/mg potency)*	12.22
3.50	2	Neomycin-base USE neomycin sulfate (200 Waksman units/mg potency)*	5.00
100.00	3	Mineral oil light	100.00
q.s.	4	Petrolatum white q.s. to	1 kg

*Adjust petrolatum weight to compensate for change in weight of erythromycin base and neomycin.

MANUFACTURING DIRECTIONS

1. Heat petrolatum and mineral oil in a steam kettle to 115°C and maintain temperature for at least 3 hours.
2. Strain into mixing tank and cool to 40°–45°C.
3. Reserve portion of petrolatum–oil mixture for step 5.
4. Mix erythromycin and neomycin with 95 g of base and stir until thoroughly dispersed.
5. Run through 200 mesh (74-μm aperture) screen on Homoloid mill directly into main portion of petrolatum–oil mixture.
6. Rinse mill with reserved petrolatum– oil mixture from step 3.
7. Mix 2 hours before cooling. Cool slowly to avoid condensation.
8. Fill into suitable approved containers.

Erythromycin Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Erythromycin base	10.00
20.00	2	Lutrol E 400	200.00
20.00	3	Propylene glycol	200.00
20.00	4	Lutrol F 127	200.00
39.00	5	Water purified	390.00

MANUFACTURING DIRECTIONS

1. Heat solution of items 1–3 to about 70°C.
2. Dissolve item 4, mix with item 5, and cool when the air bubbles escape.

Estradiol and Norethindrone Acetate Transdermal System

The estradiol/norethindrone acetate transdermal system is an adhesive-based matrix transdermal patch designed to release both estradiol and norethindrone acetate, a progestational agent, continuously on application to intact skin. The patch is an alcohol-free, adhesive-based matrix transdermal drug delivery system comprising three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing, an adhesive layer, and a protective liner. The adhesive matrix containing estradiol and norethindrone acetate is applied to a adhesive backing of polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer-coated release liner. The transparent release liner must be removed before the system can be used. Each system is enclosed in a heat-sealed pouch. The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive: a silicone and acrylic-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

Estradiol Transdermal System

Estradiol transdermal system is designed to deliver 17(beta)-estradiol continuously and consistently over a 3- or 4-day interval on application to intact skin. Three strengths of Alora systems are available, having nominal *in vivo* delivery of 0.05, 0.075, and 0.1 mg estradiol per day through skin of average permeability (interindividual variation in skin permeability is approximately 20%). Alora systems have contact surface areas of 18, 27, and 36 cm^2 and contain 1.5, 2.3, and 3.0 mg of estradiol USP, respectively. The composition of the systems per unit active surface area is identical. Estradiol USP [17(beta)-estradiol] is a white, crystalline powder that is chemically described as estra-1,3,5(10)-triene-3,17(beta)-diol, has an empirical formula of $C_{18}H_{24}O_2$, and has a molecular weight of 272.37. The delivery system consists of three layers. Proceeding from the polyethylene backing film, the adhesive matrix drug reservoir that is in contact with the skin consists of estradiol USP and sorbitan monooleate dissolved in an acrylic adhesive matrix. The polyester overlapped release liner protects the adhesive matrix during storage and is removed before application of the system to the skin.

MANUFACTURING DIRECTIONS

Estradiol-containing matrices are prepared by mixing acrylic adhesive (National Starch Durotac 1194), sorbitan monooleate (Arlacel 80), and estradiol at a ratio of 80-*X*/(20/*X*), where *X* is the proportion (wt%) of estradiol. The matrix contains 25 estradiol (8% estradiol was saturated) for optimal permeation.

Estradiol Vaginal Cream

Each gram of estradiol vaginal cream USP 0.01% contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and diglycerides, hydroxypropyl methylcellulose, 2208 (4000 CPS; CPS refers to centipoise, a designation of viscosity) sodium lauryl sulfate, methylparaben, edetate disodium, and tertiary-butylhydroquinone. Estradiol is chemically described as estra-1,3,5(10)-triene-3,17(beta)-diol. Tubes contain 1.5 oz (42.5 g), with a calibrated plastic applicator for delivery of 1, 2, 3, or 4 g.

Each gram of estradiol vaginal cream USP 0.01% contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and diglycerides, hydroxypropyl methylcellulose, 2208 (4000 CPS) sodium lauryl sulfate, methylparaben, edetate disodium, and tertiary-butylhydroquinone. Estradiol is chemically described as estra-1,3,5(10)-triene-3,17(beta)- diol. It has an empirical formula of $C_{18}H_{24}O_2$ and a molecular weight of 272.37.

Bill of Materials

Scale (g/100 g)	Item	Material Name	Quantity/10 kg (g)
7.00	1	Stearyl alcohol	700.00
4.00	2	Glyceryl monostearate (nonemulsifying)	400.00
7.00	3	Ceresin wax 160	700.00
0.02	4	Monotertiary butyl hydroquinone	2.00
0.01	5	17-beta estradiol	1.00
10.00	6	Propylene glycol	1000.00
0.15	7	Methylparaben	15.00
0.30	8	Hydroxypropyl methylcellulose 4000 CPS	30.00
0.05	9	Disodium edetate	5.00
0.30	10	Sodium lauryl sulfate	30.00
71.77	11	Water purified	7177.00

MANUFACTURING DIRECTIONS

1. A nonaqueous phase premix is prepared by thoroughly mixing stearyl alcohol (700 g), glyceryl monostearate, non–self-emulsifying (400 g), white ceresin wax 160 (160 signifies the approximate melting point in degrees Fahrenheit; 700 g), and mono-tertiary-butylhydroquinone (2.0 g) while heating to 75°C.
2. Mixing with heating is continued until all solids are dissolved, and then 17-beta-estradiol (1.0 g dry weight) is added. The mixing is then continued until this phase is in the form of a clear solution, at which point it is held at 75°C for later use.
3. Propylene glycol (1000 g) and methylparaben (15 g) are mixed together until all solids are dissolved. Hydroxypropyl methylcellulose 4000 CPS (CPS refers to centipoise, a designation of viscosity; 30 g) is added to and dispersed in the propylene glycol solution, and this resulting mixture is then added to an aqueous solution of disodium edetate (5.0 g) and sodium lauryl sulfate (30 g) in 7117 g purified water. This mixture is heated and held at 75°C while being stirred to facilitate the formation of an oil-in-water emulsion.
4. The hot nonaqueous phase premix, prepared earlier, is then added to this hot aqueous phase slowly while mixing with an appropriate mixer. If the equipment used permits moisture loss, water may be added during this step to compensate for the loss.
5. The resultant hot emulsion is allowed to cool to 60°C, at which point it is thoroughly homogenized using a recirculating homogenizer, homomixer, or other suitable equipment to provide a particle size reduction to a range of 5–20 μm for most particles.
6. The fluid emulsion, still at 60°C, is passed through a #100 to #200 stainless steel or nylon screen into a vessel equipped for slow stirring.
7. The emulsion is then cooled under vacuum while using slow sweep stirring until the temperature reaches 25°C.

Ethylenediamine Tetracetate Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methylparaben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
q.s.	8	Water purified q.s. to	1 kg
1.00	9	Ethylene diamine tetraacetate	10.00

MANUFACTURING DIRECTIONS

1. Water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation in a melting kettle.
   b. Heat the contents to 61°–65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Oil phase:
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°–75°C.
3. Mixing of phases:
   a. The mixture of step 2 is transferred to the step 1 kettle, with the water phase maintained under 300 mbar vacuum.
   b. Add EDTA and dissolve.
   c. With mixing, and keeping the temperature at 61°–65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°–65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Fluocinonide Cream, Ointment, and Gel

The active component is the corticosteroid fluocinonide, which is the 21-acetate ester of fluocinolone acetonide.

The cream contains fluocinonide 0.5 mg/g in a specially formulated cream base consisting of citric acid, 1,2,6-hexanetriol, polyethylene glycol 8000, propylene glycol, and stearyl alcohol. This white cream vehicle is greaseless, nonstaining, anhydrous, and completely water miscible. The base provides emollient and hydrophilic properties. In this formulation, the active ingredient is totally in solution.

The cream contains fluocinonide 0.5 mg/g in a water-washable aqueous emollient base of cetyl alcohol, citric acid, mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol, and water (purified).

Another strength of cream contains fluocinolone acetonide 0.25 mg/g in a water-washable aqueous base of butylated hydroxytoluene, cetyl alcohol, citric acid, edetate disodium, methylparaben and propylparaben (preservatives), mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, simethicone, stearyl alcohol, water (purified), and white wax.

The gel contains fluocinonide 0.5 mg/g in a specially formulated gel base consisting of carbomer 940, edetate disodium, propyl gallate, propylene glycol, sodium hydroxide or hydrochloric acid (to adjust the pH), and water (purified). This clear, colorless, thixotropic vehicle is greaseless, nonstaining, and completely water miscible. In this formulation, the active ingredient is totally in solution.

The ointment contains fluocinonide 0.5 mg/g in a specially formulated ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol, and white wax. It provides the occlusive and emollient effects desirable in an ointment. In this formulation, the active ingredient is totally in solution. In another formulation, the ointment contains fluocinolone acetonide 0.25 mg/g in a white petroleum USP vehicle.

Fluocinonide Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.05	1	Flucinonide	0.50
7.00	2	Crotamiton	70.00
10.00	3	Liquid paraffin	100.00
1.00	4	Polyoxyethylene lauryl ether	10.00
20.00	5	Carboxyvinyl polymer	200.00
1.20	6	Disodium edetate	12.00
4.68	7	Triethanolamine	46.80
q.s.	8	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Fluocinonide (50 mg) is dissolved in crotamiton (7 g) with warming, and thereto is added liquid paraffin (10 g), propylene glycol (10 g), polyoxyethylene lauryl ether (1 g), a 4% aqueous solution of carboxyvinyl polymer (20 g), purified water (47 g), and a 1% aqueous solution of disodium edetate (1.2 g).
2. The mixture is heated until about 70°–80°C, and then a 2% aqueous solution of triethanolamine (4.68 g) is added to it with stirring, and further purified water is then added until the amount becomes 100 g.
3. The mixture is stirred well and then cooled to give a creamy preparation having a viscosity of 65,000 centipoises and a pH of 4.47.

Fluorometholone Opthalmic Ointment

The fluorometholone ophthalmic ointment 0.1% is a topical anti-inflammatory agent for ophthalmic use. Its chemical name is fluorometholone [9-Fluoro-11(beta),17-dihydroxy-6(alpha)-methylpregna-1,4-diene-3,20-dione]. It contains active ingredients fluorometholone 0.1% and the preservative phenylmercuric acetate (0.0008%). Inactives are white petrolatum, mineral oil, and petrolatum and lanolin alcohol.

Fluorouracil Cream

Fluorouracil cream, 0.5%, contains fluorouracil for topical dermatologic use. Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge®) composed of methyl methacrylate/glycol dimethacrylate crosspolymer and dimethicone. The cream formulation contains the following other inactive ingredients: carbomer 940, dimethicone, glycerin, methyl gluceth-20, methyl methacrylate/glycol dimethacrylate crosspolymer, methylparaben, octyl hydroxy stearate, polyethylene glycol 400, polysorbate 80, propylene glycol, propylparaben, purified water, sorbitan monooleate, stearic acid, and trolamine.

The 5% cream contains fluorouracil in a vanishing-cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and parabens (methyl and propyl).

The 1% topical cream contains inactive ingredients benzyl alcohol, emulsifying wax, mineral oil, isopropyl myristate, sodium hydroxide, and purified water.

Flurandrenolide Lotion

Flurandrenolide USP is a potent corticosteroid intended for topical use. The chemical name of flurandrenolide is Pregn-4-ene-3,20-dione,6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-,(6(alpha),11(beta),16(alpha))-; its empirical formula is $C_{24}H_{33}FO_6$. Each milliliter of lotion contains 0.5 mg (1.145 μmol) (0.05%) flurandrenolide in an oil-in-water emulsion base composed of glycerin, cetyl alcohol, stearic acid, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, menthol, benzyl alcohol, and purified water.

Flurandrenolide Topical Film

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.10	1	Flurandrenolide	1.00
9.00	2	Polyvinyl alcohol	90.00
11.00	3	Polyvinyl pyrrolidone	110.00
9.00	4	Glycerin	90.00
10.00	5	Alcohol	100.00
2.00	6	Benzyl alcohol	20.00
3.00	7	Propylene glycol	30.00
0.02	8	Disodium edetate	0.20
0.10	9	Citric acid	1.00
q.s.	10	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Add and dissolve flurandrenolide in propylene glycol, glycerine, and ethyl alcohol.
2. Dissolve all the remaining items (including some water) separately and add to step 1.
3. Mix thoroughly and make up the volume.
4. The formulation is spread manually or with an applicator. On evaporation of the solvents including water over a period of 20–30 minutes, a continuous medicated adherent film of about 0.05- to 0.15-mm (average 0.08 mm) thickness is formed. After 18–24 hours or another desirable time span, the film is removed with water or is peeled.

Fluticasone Propionate Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.05	1	Fluticasone propionate	0.05
87.00	2	Propylene glycol	87.00
21.00	3	Sorbitan sesquioleate	21.00
200.00	4	Liquid paraffin	200.00
180.00	5	Microcrystalline wax	180.00
481.95	6	White soft paraffin	481.95
30.00	7	Hard paraffin	30.00

MANUFACTURING DIRECTIONS

1. Melt microcrystalline wax, hard paraffin, and sorbitan sesquioleate in a fat-melting vessel at 70°–75°C while mixing. Add liquid paraffin and mix well.
2. Transfer the mixture in step 1 to the manufacturing vessel through stainless steel filter. Mix and homogenize for 10 minutes under vacuum at 0.5 bar. Cool the mixture to 40°–45°C.
3. Disperse fluticasone propionate in propylene glycol, mix, and homogenize at a temperature of 40°–45°C.
4. Transfer the drug mixture from step 3 into the manufacturing vessel from step 2 while mixing. Mix and homogenize for 10 minutes under vacuum at 0.5 bar to obtain uniform homogeneous ointment to contain label amount of fluticasone propionate per gram.
5. Cool to a temperature of 25°–30°C with continuous stirring.
6. Fill the ointment into the tube.

Fluticasone Ointment

Fluticasone ointment 0.005% contains fluticasone propionate [(6(alpha),11(beta),16(alpha),17(alpha))-6,9,-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Each gram of ointment contains fluticasone propionate 0.05 mg in a base of propylene glycol, sorbitan sesquioleate, microcrystalline wax, and liquid paraffin.

Fluticasone Propionate Cream

Fluticasone propionate cream 0.05% contains fluticasone propionate [(6(alpha),11(beta),16(alpha),17(alpha))-6,9,-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester], a synthetic fluorinated corticosteroid for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Each gram of cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.

Fluticasone Propionate Cream

Bill of Materials

Scale (mg/g)	Item	Material Name	Quantity/kg (g)
0.50	1	Fluticasone propionate	0.50
40.00	2	Propylene glycol	40.00
100.00	3	Liquid paraffin	100.00
70.70	4	Cetostearyl alcohol	70.70
40.00	5	Cetomacrogol 1000	40.00
50.00	6	Isopropyl myristate	50.00
4.80	7	Dibasic sodium phosphate	4.80
1.50	8	Citric acid monohydrate	1.50
2.50	9	Imidurea	2.50
690.00	10	Purified water	690.00

MANUFACTURING DIRECTIONS

1. Melt cetostearyl alcohol and cetomacrogol 1000 in a fat-melting vessel at 70°C. Add liquid paraffin and isopropyl myristate and mix well. Hold the temperature between 60° and 70°C.
2. Add purified water to the manufacturing vessel and heat to 70°–80°C.
3. Dissolve dibasic sodium phosphate, citric acid, and imidurea in purified water. Hold the temperature between 60° and 70°C.
4. Transfer the fat phase of step 1 through a stainless steel filter to the manufacturing vessel while stirring at a temperature of 60°–70°C. Mix and homogenize for 10 minutes under vacuum at 0.5 bar. Cool the mixture to 40°–45°C.
5. Disperse fluticasone propionate in propylene glycol at a temperature of 40°–45°C.
6. Transfer the drug mixture of step 5 into step 4 to the manufacturing vessel while mixing. Mix and homogenize for 10 minutes under vacuum at 0.5 bar to obtain a uniform homogenous cream to contain labeled amount of drug per gram.
7. Cool the cream to a temperature of 25°–30°C with continuous stirring.
8. Transfer into stainless steel storage container with product identification label.
9. Fill the cream into the tube.

Foscarnet Cream

Bill of Materials			
Scale (mg/100 g)	**Item**	**Material Name**	**Quantity/kg (mg)**
3.00	1	Trisodium phosphonoformate hexahydrate (foscarnet sodium)	30.00
4.40	2	Polyoxyethylene fatty acid ester	44.00
2.00	3	Cetyl alcohol	20.00
2.00	4	Stearic acid	20.00
2.00	5	Liquid paraffin	20.00
2.00	6	Propylene glycol	20.00
1.50	7	Glycerin	15.00
0.07	8	Methylparaben	0.70
0.03	9	Propylparaben	0.30
q.s.	10	Water purified q.s. to	1 kg

Gamma Benzene Hexachloride Lotion

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Gamma benzene hexachloride, 1% excess	10.10
2.00	2	Emulsifying wax	20.00
5.00	3	Xylene	50.00
0.50	4	Cetomacrogol 1000	5.00
10.00	5	Liquid paraffin	100.00
72.00	6	Water purified	720.00

MANUFACTURING DIRECTIONS

1. Heat items 2, 4, and 5 to 95°C and pass through a stainless steel sieve.
2. Heat water to 65°C and add to step 1.
3. Dissolve item 1 in item 3 with stirring and add to step 2 at 35°C.
4. Adjust pH to 7.5–8.0 if necessary and mix for 2 hours.

Gentamicin Sulfate Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.100	1	Gentamycin sulfate (100% excess)	2.00
0.400	2	Cetostearyl alcohol	4.00
0.100	3	Poloxyl 20 cetostearyl ether (cetomacrogol 1000)	1.00
1.500	4	Mineral oil (liquid paraffin)	15.00
1.000	5	Mineral oil (liquid paraffin)	10.00
96.600	6	Petrolatum (white soft paraffin)	966.00
0.200	7	Purified water	2.00

MANUFACTURING DIRECTIONS

1. Melt items 2, 3, and 5 at 70°C in a small container using water bath. Put the melt under homogenizer (keep homogenizer warm to avoid losses caused by sticking).
2. Dissolve item 1 in item 7 and heat to 50°C in water bath. Add step 2 to step 1 and homogenize for 2–3 minutes using homogenizer. Maintain the temperature around 50°C.
3. Load item 6 in a fat-melting vessel while stirring at 70°C. Transfer the molten mass through filter to mixer and cool it down to 50°C. Note that the mixer should be warmed before the transfer starts to avoid sticking on the wall. Add step 2 to the step 3 while stirring. Maintain temperature at around 50°C.
4. Rinse the homogenizer with warm item 4 and transfer the rinsing to the mixer.
5. Mix and homogenize for 10 minutes at low speed, mixer speed 10–12 rpm, vacuum 0.4–0.6 bar, and temperature 50°C.
6. Cool the ointment to 30°–35°C with stirring under vacuum 0.4–0.6 bar.
7. Transfer the ointment to stainless steel drum and fill.

Gentamicin Sulfate Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.100	1	Gentamycin USE gentamycin sulfate*	1.82
15.000	2	Petrolatum (white soft paraffin)	150.00
1.800	3	Poloxyl 20 cetostearyl ether (cetomacrogol 1000)	18.00
7.200	4	Cetostearyl alcohol	72.00
0.100	5	Chlorocresol	1.00
6.000	6	Mineral oil (liquid paraffin)	60.00
0.300	7	Monobasic sodium phosphate	3.00
69.417	8	Purified water	694.17

*Considering the potency of the gentamicin sulfate is 700 mcg/mg (anhydrous basis) with 15.0% water content. Quantity of gentamicin sulfate per batch will vary according to the actual potency. Required quantity should be calculated as below. Quantity of gentamicin sulfate required per batch is based on potency.

MANUFACTURING DIRECTIONS

1. Fat phase: Load items 2–6 in a fat-melting vessel. Heat to 70°C. Stir to melt. Hold the molten fat at 70°C while stirring at low speed in the fat-melting vessel.
2. Aqueous phase: Set the mixer at temperature 70°C. Heat 608.00 g of item 8 to 70°C in mixer.
3. Cream preparation: Transfer the molten fat at 70°C from step 1 into mixer through a stainless steel filter while mixing at speed 10 rpm, vacuum 0.6 bar.
4. When the transfer is over, start the homogenizer at low speed. Homogenize for 10 minutes with recirculation. Temperature 65°–70°C.
5. Stop the homogenizer, set the mixer at temperature 50°C, speed 10 rpm (manual mode), and vacuum 0.6 bar. Cool the cream to 50°C.
6. Drug phase: Dissolve items 7 and 1 in 86.17 g of item 8 in a stainless steel container while mixing with a stirrer. Hold the temperature at 50°C.
7. Transfer the drug solution from step 4 to the cream phase in mixer at 50°C while mixing.
8. Start the homogenizer at high speed, mixer speed 10 rpm. Mix and homogenize for 10 minutes under vacuum 0.6 bar.
9. While homogenization is in progress, set the temperature at 25°C so that the cream temperature shall not increase. Continue mixing at 10 rpm under vacuum 0.6 bar until the temperature reaches 25°C.
10. When the cream is cooled to 25°C, unload the cream in stainless steel container and fill.

Gentamicin Sulfate Ointment

Gentamicin sulfate ointment is a sterile, topical anti-infective agent for ophthalmic use. The active ingredient, gentamicin sulfate, is a water-soluble antibiotic of the aminoglycoside group. Gentamicin sulfate is the sulfate salt of gentamicin C_1, gentamicin C_2, and gentamicin C_{1A}, which are produced by the growth of *Micromonospora purpurea*. Each gram of ointment contains gentamicin sulfate USP (equivalent to 3.0 mg gentamicin) in a base of white petrolatum, with methylparaben (0.5 mg) and propylparaben (0.1 mg) as preservatives. Active ingredients are gentamicin sulfate equivalent to 0.3% gentamicin base, prednisolone acetate 0.6%, and the preservative (chloral derivative) 0.5%. Inactives are white petrolatum, mineral oil, petrolatum and lanolin alcohol, and purified water.

Glycerin Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
1800.00	1	Glycerin (glycerol)	1800.00
178.00	2	Sodium stearate	178.00
99.00	3	Purified water	99.00

MANUFACTURING DIRECTIONS

The suppository mass is manufactured at a temperature of 120°C. Care must be taken to see that molten suppository mass does not accidentally spill on the person. The inside of the vessel should not be touched with a bare hand, as it is at a temperature of 120°C. Sodium stearate powder is light and fluffy—avoid inhaling the dust.

1. Load item 1 into the mixer and heat to 120° ± 2°C while stirring at low speed.
2. Load item 2 to the mixer containing item 1. Mix until complete solubilization occurs. Cool to 105° ± 2°C.
3. Add item 3 slowly to the mixer containing mass while stirring. Mix for 20 minutes. Immediately transfer the hot mass to the heated storage vessel or heated vessel of suppository filling machine.
4. Check the temperature; it should be 105° ± 2°C. Fill weight: 2077 mg per suppository.

Glycerin Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
900.00	1	Glycerin (glycerol) excess 0.06%	900.50
89.00	2	Sodium stearate	89.00
49.50	3	Purified water	49.50

MANUFACTURING DIRECTIONS

1. See above, fill weight: 1039 mg per suppository.

Glycolic Acid Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
3.00	1	Polyoxyethylene (40) stearate	30.00
2.00	2	Polyoxyethylene (200 sorbitan monooleate	20.00
8.00	3	Glycerol monostearate	80.00
2.00	4	Lanolin	20.00
1.00	5	Mineral oil	10.00
49.00	6	Water purified	490.00
5.00	7	Propylene glycol	50.00
3.00	8	Sorbitol	30.00
1.00	9	Carbopol 940	10.00
10.00	10	Glycolic acid	100.00
16.00	11	Triisopropanolamine	160.00

MANUFACTURING DIRECTIONS

1. Heat items 1–5 in a stainless steel container to 80°C.
2. In a separate container, heat items 6–9 to 80°C.
3. Add step to step 1 with agitation.
4. After the mixture is congealed, add glycolic acid and triisopropanolamine.
5. Continue agitation until a uniform consistency is obtained. The pH of the cream is 3.8.

Gramicidin, Neomycin, Nystatin, and Triamcinolone Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.025	1	Gramicidin	0.025
10.00	2	Liquid paraffin	10.00
0.48	3	Neomycin sulfate	0.48
2.72	4	Nystatin micronized	2.72
1.00	5	Syncrowax	1.00
0.105	6	Triamcinolone acetonide micronized	0.105
86.72	7	White soft paraffin	86.72

MANUFACTURING DIRECTIONS

1. Charge items 5 and 7 in a melting vessel and heat to 70°C to melt; transfer to Becomix through stainless steel filters and cool to 40°C while mixing.
2. Add items 2 (half quantity) and 4 to a separate vessel and disperse using a spatula; homogenize twice with fine-gap setting to make smooth dispersion, and add this dispersion to step 1.
3. Charge items 1, 2 (balance quantity), 3, and 6 in a separate stainless steel vessel and homogenize to a smooth dispersion until here are no lumps. Transfer to step 2.
4. Rinse homogenizer with liquid paraffin and add rinsings.
5. Homogenize the final mixture under a vacuum of 0.4–0.6 at 10 rpm and set temperature to 28°–30°C.
6. Mix till ointment is smooth, transfer to a stainless steel vessel, and fill.

Halobetasol Propionate Cream and Ointment

The cream contains halobetasol propionate, a synthetic corticosteroid for topical dermatological use. The corticosteroids constitute a class of primarily synthetic steroids used topically as an anti-inflammatory and antipruritic agent. Chemically, halobetasol propionate is 21-chloro-6(alpha),9-difluoro-11(beta),17-dihydroxy-16(beta)-methylpregna-1,4-diene-3-20-dione,17-propionate, $C_{25}H_{31}CIF_2O_5$. Each gram of cream contains 0.5 mg/g of halobetasol propionate in a cream base of cetyl alcohol, glycerin, isopropyl isostearate, isopropyl palmitate, steareth-21, diazolidinyl urea, methylchloroisothiazolinone, methylisothiazolinone, and water. Each gram of ointment contains 0.5 mg/g of halobetasol propionate in a base of aluminum stearate, beeswax, pentaerythritol cocoate, petrolatum, propylene glycol, sorbitan sesquioleate, and stearyl citrate.

Heparin Gel-Cream

Bill of Materials

Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
0.186	1	Heparin sodium	1.86
15.00	2	Lutrol E 400	150.00
10.00	3	Liquid paraffin	100.00
23.00	4	Lutrol F 127	230.00
q.s.	5	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Dissolve heparin sodium in water, add Lutrol E 400 and liquid paraffin.
2. Stir and cool to 6°C. Add Lutrol F 127 slowly, and stir until it is dissolved.
3. Heat to room temperature when the air bubbles escape.

Hexachlorophen Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
45.80	1	Olive oil, low acidity	45.80
45.00	2	Diglycol stearate S	45.00
5.00	3	Cetyl alcohol	5.00
5.00	4	Lanolin anhydrous	5.00
5.00	5	Petrolatum white	5.00
1.03	6	Polysorbate 40	1.03
5.00	7	Hexachlorophene	5.00
0.10	8	Simethicone	0.10
50.00	9	Glycerin	50.00
1.00	10	Methyl paraben	1.00
10.00	11	Sodium borate	10.00
1.30	12	Sodium lauryl sulfate	1.30
1.76	13	Perfume	1.76
2.00	14	Menthol	2.00
14.02	15	Alcohol	14.02
q.s.	16	Water purified	779.0 mL

MANUFACTURING DIRECTIONS

1. Strain olive oil through voile cloth or equivalent into a suitable stainless steel-jacketed tank.
2. Add diglycol stearate. While heating oil–stearate mix, add cetyl alcohol, lanolin, petrolatum, and polysorbate 40 with mixing. Mix until all are dissolved and temperature of mixture reaches 65°–70°C.
3. Add and dissolve hexachlorophene in the oil mix, then add and disperse the simethicone.
4. Start heating another jacketed tank as 820 mL of purified water is added to it. Add and dissolve glycerin, methylparaben, and borax as purified water is added and as solution is heated to 65°–70°C.
5. Stop mixer, add sodium lauryl sulfate, and continue mixing under vacuum.
6. Reserve 4 mL of solution from step 5 in a separate container to rinse equipment in step 2.
7. While both solutions are at 65°–70°C, form the primary emulsion by pumping the aqueous solution from step 5 into the oil mixture from step 3 and q.s. to 200 mL with vigorous agitation.
8. Homogenize primary emulsion through a Troy Mill, or similar device, into the balance of aqueous solution, mixing continually under vacuum. Rinse pump, mill, tank, and lines with reserved solution from step 6. Note that the primary emulsion should strained through voile cloth or equivalent before being run through the Troy Mill.
9. Cool emulsion to 40°–50°C with agitation under vacuum.
10. Dissolve perfume and menthol in the alcohol and add.
11. Using purified water, q.s. to 1 liter.
12. Continue mixing and cooling to 25°C. Fill.

Hydrocortisone Acetate and Pramoxine Hydrochloride Cream and Lotion

The cream contains hydrocortisone acetate 1% or 2.5% and pramoxine HCl 1% in a hydrophilic cream base containing stearic acid, cetyl alcohol, aquaphor, isopropylpalmitate, polyoxyl-40 stearate, propylene glycol, potassium sorbate, sorbic acid, triethanolamine lauryl sulfate, and water. The lotion 2.5% contains hydrocortisone acetate 2.5% and pramoxine hydrochloride 1% in a hydrophilic lotion base containing stearic acid, cetyl alcohol, forlan-L, glycerin, triethanolamine, polyoxyl 40 stearate, diisopropyl adipate, povidone, silicone, potassium sorbate, sorbic acid, and purified water. Topical corticosteroids are anti-inflammatory and antipruritic agents. Other formulations include cream, which contains hydrocortisone acetate 1% or 2.5% and pramoxine HCl 1% in a hydrophilic base containing stearic acid, cetyl alcohol, aquaphor, isopropyl palmitate, polyoxyl 40 stearate, propylene glycol, potassium sorbate, sorbic acid, triethanolamine lauryl sulfate, and water; lotion, which contains hydrocortisone acetate 1% or 2.5% and pramoxine HCl 1% in a base containing forlan-L, cetyl alcohol, stearic acid, diisopropyl adipate, polyoxyl 40 stearate, silicone, triethanolamine, glycerine, polyvinylpyrolidone, potassium sorbate, sorbic acid, and water; ointment, which contains hydrocortisone acetate 1% or 2.5%; and pramoxine HC1 1% in an emollient ointment base containing sorbitan sesquioleate, water, aquaphor, and white petrolatum.

Hydrocortisone Ointment

Bill of Materials			
Scale (mg/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Hydrocortisone micronized 6% excess	10.60
91.50	2	White soft paraffin	915.00
7.00	3	Liquid paraffin	70.00
0.50	4	Sorbitan sesquioleate (arlacel 83)	5.0

MANUFACTURING DIRECTIONS

1. Charge items 2 and 4 in a melting vessel and melt at 75°C.
2. Transfer to preheated Becomix at 75°C through stainless steel mesh under 0.4–0.6 bar vacuum.
3. Start mixing at 10 rpm manual mode. Cool to 50°C.
4. In a separate vessel, disperse item 1 in item 3, using a spatula, in a water bath maintained at 60°C. Homogenize for 6 minutes using Ultra-Turrax homogenizer.
5. Add to step 3 while mixing.
6. Rinse with item 3 and add and mix.
7. Homogenize dispersion under vacuum at 0.4–0.6 bar at 10 rpm.
8. Cool down to 30°C while mixing.
9. Transfer to storage vessel.
10. Fill appropriate quantity at a suitable temperature.

Hydrocortisone Acetate Suppositories

Hydrocortisone acetate is a corticosteroid designated chemically as pregn-4-ene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-(11(beta)). Each rectal suppository contains hydrocortisone acetate USP 30 mg in a specially blended hydrogenated vegetable oil base. Each Anusol-HC 25-mg suppository contains 25 mg hydrocortisone acetate in a hydrogenated cocoglyceride base.

Hydrocortisone and Nitrofurazone Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.20	1	Nitrofurazone, 4% excess	2.08
1.00	2	Hydrocortisone acetate, 5% excess	10.50
7.20	3	Cetostearyl alcohol	72.00
1.80	4	Cetomacrogol 1000	18.00
6.00	5	Liquid paraffin	60.00
15.00	6	White soft paraffin	150.00
1.00	7	Propylene glycol	10.00
0.020	8	Chlorocresol	0.20
69.00	9	Water purified	690.00

MANUFACTURING DIRECTIONS

1. Charge items 3, 4, 5 (90%), and 6 in a melting vessel after passing through stainless steel sieve and heat to melt.
2. In a separate vessel, heat two thirds of item 9 to 50°C and dissolve item 8 in it. Add to step 1.
3. Add and mix item 1 with item 5 (balance) and add to step 2.
4. Dissolve item 2 in balance of item 9 and a portion of item 5 in a separate vessel and homogenize; add to step 3 with stirring. Mix for several hours.
5. Fill.

Hydrocortisone Butyrate Cream and Ointment

The cream, ointment, and topical solution contain the topical corticosteroid hydrocortisone butyrate, a nonfluorinated hydrocortisone ester. It has the chemical name pregn-4-ene-3,20-dione,11,21-dihydroxy-17-[(1-oxobutyl)oxy-,(11(beta))-; the molecular formula is $C_{25}H_{36}O_6$; and the molecular weight is 432.54. Each gram of cream contains 1 mg hydrocortisone butyrate in a hydrophilic base consisting of cetostearyl alcohol, ceteth-20, mineral oil, white petrolatum, citric acid, sodium citrate, propylparaben and butylparaben (preservatives), and purified water. Each gram of ointment contains 1 mg of hydrocortisone butyrate in a base consisting of mineral oil and polyethylene.

Hydrocortisone Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.000	1	Hydrocortisone, micronized (3% excess)	10.30
6.000	2	Propylene glycol	60.00
0.100	3	Chlorocresol	1.00
5.000	4	Mineral oil (liquid paraffin)	50.00
2.000	5	Poloxyl 20 cetostearyl ether (cetomacrogol 1000)	20.00
8.000	6	Cetostearyl alcohol	80.00
18.000	7	Petrolatum (white soft paraffin)	180.00
0.290	8	Monobasic sodium phosphate	2.90
0.035	9	Propylparaben	0.35
0.100	10	Methylparaben	1.00
59.600	11	Purified water	596.00

MANUFACTURING DIRECTIONS

1. Load 10.0 g of item 5 and items 4, 6, and 7 in a fat-melting vessel.
2. Heat to 70°–75°C while stirring. Cool down the temperature to 65°C.
3. Maintain temperature at 65°–70°C.
4. Heat item 11 to 90°C in mixer. Dissolve items 9 and 10 to a clear solution by stirring. Cool down the temperature to 65°C. Maintain temperature at 65°–70°C.
5. Add 10.0 g of item 5 and items 3 and 8 to the parabens solution to dissolve.
6. Mix for 0–15 minutes. Maintain temperature at 65°–70°C.
7. Transfer the oil phase to the aqueous phase in a mixer vessel through mesh by vacuum while stirring at manual mode, 10 rpm, temperature 60°C.
8. Homogenize at high speed, temperature 60°C, vacuum 0.4 bar, 10 minutes.
9. Cool down temperature to 45°C. Mix item 1 in 48.0 g of item 2 in a separate container at 45°C using homogenizer to make slurry.
10. Add to the dispersed phase while mixing at 10 rpm and temperature 45°C.
11. Rinse the container with 12.0 g of item 2 and add to the dispersed phase.
12. Mix and homogenize under vacuum 0.4 bar for 10 minutes, low speed, 10 rpm, temperature 45°C.
13. Cool down the temperature to 30°C while mixing at 10 rpm. Auto mode, under vacuum 0.4 bar.

Hydrocortisone Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
120.00	4	Liquid paraffin	120.00
2.00	5	Paraben	2.00
688.00	6	Water	688.00
80.00	7	Propylene glycol	80.00
10.00	8	Hydrocortisone	10.00

MANUFACTURING DIRECTIONS

1. Heat the mixture of items 1–5 and the water separately to about 80°C.
2. Add the water to the obtained solution of items 1–5 with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with 1/2, and continue to stir during cooling to room temperature. White cream.

Hydrocortisone Cream

Bill of Materials			
Scale (mg/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Hydrocortisone, micronized	10.00
6.00	2	Propylene glycol	60.00
0.10	3	Chlorocresol	1.00
5.00	4	Liquid paraffin	5.00
2.00	5	Cetomacrogol 1000	20.00
8.00	6	Cetostearyl alcohol	80.00
18.00	7	Soft white paraffin	180.00
0.29	8	Sodium phosphate monobasic	2.90
0.035	9	Propylparaben	0.35
0.10	10	Methylparaben	1.00
59.60	11	Deionized water	596.00

MANUFACTURING DIRECTIONS

1. Load items 4–7 in a fat-melting vessel (the oily phase; use only half of item 5) and heat to 70°–75°C while stirring.
2. Cool down temperature to 65°C and maintain within the range of 65°–70°C.
3. In a Becomix vessel, heat item 11 to 90°C.
4. Add and dissolve items 9 and 10 in step 3. Cool down to 65°C and maintain temperature between 65° and 70°C.
5. Add item 3, balance of item 5, and item 8 and dissolve by mixing for 10–15 minutes at 65°–70°C.
6. Transfer the oil phase from step 2 into step 5 through vacuum transfer while stirring at manual 10 rpm and temperature of 60°C.
7. Homogenize at speed 2 at 60°C and vacuum of 0.4 bar for 10 minutes. Cool down to 45°C.
8. In a separate vessel, charge items 1 and 2 at 45°C using ultra Turrax homogenizer to make a slurry.
9. Add step 8 into step 7 at 10 rpm and 45°C. Rinse container with item 2 and add to mix for 10 minutes at speed 2.
10. Cool down to 30°C while mixing at 10 rpm auto mode and under vacuum of 0.4 bar.
11. Fill appropriate quantity into collapsible tubes.

Hydrocortisone Cream and Ointment

Hydrocortisone provides safe, effective relief of many different types of itches and rashes; it is available in 1% and 0.5% strength. For 1% cream, the inactive ingredients are aloe vera, benzyl alcohol, ceteareth-20, cetearyl alcohol, cetyl palmitate, glycerin, isopropyl myristate, isostearyl neopentanoate, methylparaben, and purified water. For the 1% ointment, they are butylparaben, cholesterol, methylparaben, microcrystalline wax, mineral oil, and white petrolatum. The 0.5% cream includes aloe vera, butylparaben, cetyl palmitate, glyceryl stearate, methylparaben, polyethylene glycol, stearamidoethyl diethylamine, and purified water. The intensive therapy cream includes cetyl alcohol, citric acid, glyceryl stearate, isopropyl myristate, methylparaben, polyoxyl 40 stearate, polysorbate 60, propylene glycol, propylparaben, purified water, sodium citrate, sorbic acid, sorbitan monostearate, stearyl alcohol, and white wax. Another formulation of cream with aloe contains the active ingredient hydrocortisone 1%, and the inactive ingredients aloe barbadensis gel, aluminum sulfate, calcium acetate, cetearyl alcohol, glycerin, light mineral oil, maltodextrin, methylparaben, potato dextrin, propylparaben, purified water, sodium cetearyl sulfate, sodium lauryl sulfate, white petrolatum, and white wax. Hydrocortisone 0.5% ointment comprises active ingredient hydrocortisone 0.5% and inactive ingredients aloe barbadensis extract and white petrolatum. Hydrocortisone 0.5% cream includes aloe barbadensis gel, aluminum sulfate, calcium acetate, cetearyl alcohol, glycerin, light mineral oil, maltodextrin, methylparaben, potato dextrin, propylparaben, purified water, sodium cetearyl sulfate, sodium lauryl sulfate, white petrolatum, and white wax.

Hydrocortisone Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
10.00	1	Hydrocortisone acetate	10.00
100.00	2	Lutrol E 400	100.00
50.00	3	Cremophor RH 40	50.00
5.00	4	Carpopol 940 (Goodrich)	5.00
495.00	5	Water	495.00
q.s.	6	Preservative	q.s.
260.00	7	Water	260.00
8.00	8	Triethanolamine	8.00
q.s.	9	Water	7.2

MANUFACTURING DIRECTIONS

1. Suspend item 1 in a mixture of items 2 and 3 at 70°C that contains item 6.
2. Add item 8 and continue to stir until the gel is cool.

Hydrocortisone Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
10.00	1	Hydrocortisone acetate	10.00
150.00	2	Cremophor A 25	150.00
20.00	3	Cremophor RH 40	20.00
q.s.	4	Preservative	q.s.
640.00	5	Water	640.00

MANUFACTURING DIRECTIONS

1. Suspend item 1 in the mixture of items 2 and 3 at 70°C.
2. Prepare solution of item 4, heat item 5 to 70°C and add slowly to the hot-mixture item 4.
3. Continue to stir until the gel is cool. Clear colorless gels.

Hydrocortisone Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Hydrocortisone acetate	5.00
60.00	2	Cremophor RH 40	60.00
9.00	3	Triethanolamine	9.00
76.00	4	Water	76.00
600.00	5	Ethanol 96%	600.00
5.00	6	Carbopol 940 (Goodrich)	5.00
245.00	7	Water	245.00

MANUFACTURING DIRECTIONS

1. Prepare solution of items 6 and 7 and mix slowly with solution of items 1–5.
2. Form a clear, colorless gel.

Hydrocortisone Ointment

Bill of Materials			
Scale (mg/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Hydrocortisone micronized 6% excess	10.60
91.50	2	White soft paraffin	915.00
7.00	3	Liquid paraffin	70.00
0.50	4	Sorbitan sesquioleate (arlacel 83)	5.0

MANUFACTURING DIRECTIONS

1. Charge items 2 and 4 in a melting vessel and melt at 75°C.
2. Transfer to preheated Becomix at 75°C through stainless steel mesh under 0.4–0.6 bar vacuum.
3. Start mixing at 10 rpm manual mode. Cool to 50°C.
4. In a separate vessel, disperse item 1 in item 3 using spatula in a water bath maintained at 60°C. Homogenize for 6 minutes using Ultra-Turrax homogenizer.
5. Add to step 3 while mixing.
6. Rinse with item 3 and add and mix.
7. Homogenize dispersion under vacuum at 0.4–0.6 bar at 10 rpm.
8. Cool down to 30°C while mixing.
9. Transfer to storage vessel.
10. Fill appropriate quantity at a suitable temperature.

Hydrogen Peroxide Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methylparaben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
q.s.	8	Water purified q.s. to	1 kg
8.00	9	Hydrogen perioxide*	80.00

*Hydrogen peroxide, at different strengths, is used as an anti-infective for use in the oral cavity or topically for minor wounds.

MANUFACTURING DIRECTIONS

1. Preparation of water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation in a melting kettle.
   b. Heat the contents to 61°–65°C.
   c. Add methylparaben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase:
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°–75°C.
3. Mixing of phases:
   a. Transfer the mixture of step 2 to the step 1 kettle, with the water phase maintained under 300-mbar vacuum.
   b. Add hydrogen perioxide and dissolve.
   c. With mixing, and keeping the temperature at 61°–65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°–65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Hydrophilic Ointment USP

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.0250	1	Methylparaben	0.250
0.015	2	Propylparaben	0.15
1.00	3	Sodium lauryl sulfate	10.00
12.00	4	Propylene glycol	120.00
25.00	5	Stearyl alcohol	250.00
25.00	6	White petrolarum	250.00
37.00	7	Water purified	370.00

MANUFACTURING DIRECTIONS

1. Melt the stearyl alcohol and the white petrolatum on a steam bath and warm to about 75°C.
2. Dissolve the other ingredients in the purified water and warm to about 75°C.
3. Mix all ingredients together and stir until the mixture congeals.

Hydroquinone Cream and Gel

Hydroquinone is 1,4-benzenediol. Hydroquinone is structurally related to monobenzone. Hydroquinone occurs as fine, white needles. The drug is freely soluble in water and in alcohol and has a pK_a of 9.96. Chemically, hydroquinone is designated as p-dihydroxybenzene; the empirical formula is $C_6H_6O_2$.

Each gram of 4% cream contains 40 mg of hydroquinone USP in a vanishing-cream base of purified water USP, stearic acid NF, propylene glycol USP, polyoxyl 40 stearate NF, polyoxyethylene (25) propylene glycol stearate, glycerol monostearate, light mineral oil NF, squalane NF, propylparaben NF, and sodium metabisulfite NF.

The sunblocking 4% cream contains 40 mg hydroquinone USP in a tinted sunblocking-cream base of purified water USP, stearic acid NF, talc USP, polyoxyl 40 stearate NF, polyoxyethylene (25) propylene glycol stearate, propylene glycol USP, glycerol monostearate, iron oxides, light mineral oil NF, squalane NF, edetate disodium USP, sodium metabisulfite NF, and potassium sorbate NF.

In another formulation, the each gram of 4% cream contains 40 mg hydroquinone USP, 80 mg padimate O USP, 30 mg dioxybenzone USP, and 20 mg oxybenzone USP in a vanishing-cream base of purified water USP, glycerol monostearate and polyoxyethylene stearate, ootyldodecyl stearoyl stearate, glyceryl dilaurate, quaternium-26, cetearyl alcohol and ceteareth-20, stearyl alcohol NF, propylene glycol USP, diethylaminoethyl stearate, polydimethylsiloxane, polysorbate 80 NF, lactic acid USP, ascorbic acid USP, hydroxyethyl cellulose, quaternium-14 and myristalkonium chloride, edetate disodium USP, and sodium metabisulfite NF.

Each gram of 4% gel contains 40 mg hydroquinone USP, 50 mg padimate O USP, and 30 mg dioxybenzone USP in a hydro-alcoholic base of alcohol USP, purified water USP, propylene glycol USP, entprol, carbomer 940, edetate disodium USP, and sodium metabisulfite NF.

Hydroquinone Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.50	1	Ascobyl palmitate	15.00
1.00	2	Tocopherol acetate	10.00
4.00	3	Linoleic acid	40.00
17.75	4	Safflower oil	177.50
12.00	5	Oleyl alcohol	120.00
12.00	6	SDA 40 anhydrous alcohol	120.00
0.50	7	Benzyl alcohol	5.00
0.50	8	Butylated hydroxyanisole	5.00
16.60	9	Cyclomethicone	166.00
0.15	10	Sodium bisulfite	1.50
2.00	11	Sorbital laurate	20.00
5.00	12	C18-C36 acid glyco ester	50.00
5.00	13	Tribehenin	50.00
7.50	14	Petrolatum	75.00
15.00	15	Behenyl erucate	150.00
4.00	16	Hydroquinone	40.00
q.s.	17	Fragrance	q.s.

MANUFACTURING DIRECTIONS

1. Charge ascorbyl palmitate and butylated hydroxy anisole in a suitable vessel and dissolve in oleyl alcohol, SDA anhydrous alcohol, and benzyl alcohol; heat to 45°C.
2. Add sodium bisulfite and mix while keeping it covered. Keep it aside.
3. In a separate vessel, charge items 11–16 and heat to 70°C.
4. Cool to 55°C and then add tocopherol acetate, linoleic acid, and safflower oil.
5. Add step 4 into step 2 while mixing to minimize air entrapment.
6. Add item 16 and mix well; add item 17 and mix well.
7. Cool to 30°C and fill.

Hydroquinone Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.50	1	Ascobyl palmitate	15.00
1.00	2	Tocopherol acetate	10.00
2.00	3	Linoleic acid	20.00
3.00	4	Safflower oil	30.00
4.00	5	Oleyl alcohol	40.00
1.00	6	Jojoba oil	10.00
8.00	7	SDA 40 anhydrous alcohol	80.00
0.50	8	Benzyl alcohol	5.00
0.50	9	Butylated hydroxyanisole	5.00
0.15	10	Sodium bisulfite	1.50
3.00	11	Petrolatum	30.00
5.00	12	PEG-4 diheptanoate	50.00
4.00	13	Glyceryl stearate SE	40.00
1.80	14	Cetyl alcohol	18.00
2.00	15	Polyacrylamide and C13-14 isoparaffin and laureth-7	20.00
0.20	16	Hydroxy ethylcellulose	2.00
q.s.	17	Water purified	q.s.
4.00	18	Hydroquinone	40.00
q.s.	19	Fragrance	q.s.

MANUFACTURING DIRECTIONS

1. Charge linoleic acid, safflower oil, jojoba oil, petrolatum, behenyl erucate, and cetyl alcohol and heat to 70°C.
2. Add tocopherol to above just before adding the rest of the ingredients (see below).
3. Heat item 15 to 70°C and add and dissolve item 18. Add and disperse item 16.
4. In a separate vessel, add item 1 and BHA and heat to 45°C; dissolve items 5, 7, and 8, and heat to 45°C. Add sodium bisulfite. Stir to dissolve.
5. Add step 2 to step 1 in a homogenizer, and then during homogenization add step 4 and also add tocopherol. Homogenize well.
6. Add items 18 and 19 and mix well. Cool to 35°C and fill.

Ibuprofen Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Ibuprofen	50.00
24.00	2	Glyceryl stearate and PEG 75 stearate (gelot 64)	240.00
5.00	3	Labrafil M 1944	50.00
3.00	4	Octyldodecyl myristate	30.00
0.07	5	Sodium methyl paraben	0.70
0.03	6	Sorbic acid	0.30
1.00	7	Stearic acid	10.00
15.00	8	Ethoxydiglycol (transcutol)	150.00
0.150	9	Lavender oil	1.50
46.75	10	Water purified	467.50

MANUFACTURING DIRECTIONS

1. Charge item 9 in Beocmix and heat to 80°C. Charge items 2–7 one by one and mix for 20 minutes.
2. Homogenize at speed I under vacuum. Cool to 25°C.
3. In a separate container, charge items 1, 8, and 9; dissolve and filter through polyester filter.
4. Add step 3 into step 2. Mix well and fill.

Ibuprofen Gel-Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Ibuprofen	50.00
12.00	2	Propylene glycol	120.00
12.00	3	Isopropyl alcohol	120.00
12.00	4	Lutrol F 127	120.00
44.00	5	Water purified	440.00
15.00	6	Nonionic hydrophilic cream: DAB 1996	150.00

Ibuprofen Gel-Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Polysorbate 60	50.00
10.00	2	Cetylstearyl alchol	100.00
10.00	3	Glycerin	100.00
25.00	4	White petrolatum	250.00
50.00	5	Water purified	500.00

MANUFACTURING DIRECTIONS

1. Prepare solution of items 1–3 and cool to about 8°C. Dissolve item 4 in items 5 and 6.
2. Maintain cool until the air bubbles escape.

Ibuprofen Gel-Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Ibuprofen	50.00
24.00	2	Glyceryl stearate and PEG 75 stearate (Gelot 64)	240.00
5.00	3	Labrafil M 1944	50.00
3.00	4	Octyldodecyl myristate	30.00
0.07	5	Sodium methyl paraben	0.70
0.03	6	Sorbic acid	0.30
1.00	7	Stearic acid	10.00
15.00	8	Ethoxydiglycol (transcutol)	150.00
0.150	9	Lavender oil	1.50
46.75	10	Water purified	467.50

MANUFACTURING DIRECTIONS

1. Charge item 9 in Beocmix and heat to 80°C. Charge items 2–7 one by one and mix for 20 minutes.
2. Homogenize at speed I under vacuum. Cool to 25°C.
3. In a separate container, charge items 1, 8, and 9; dissolve and filter through polyester filter.
4. Add step 3 into step 2. Mix well and fill.

Ibuprofen Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Ibuprofen	50.00
10.00	2	Alcohol	100.00
20.00	3	Propylene glycol	200.00
22.00	4	Lutrol F 127	220.00
q.s.	5	Preservatives	q.s.
43.00	6	Water purified	430.00

MANUFACTURING DIRECTIONS

1. Heat solution of items 1–3 to 70°–80°C.
2. Dissolve item 4 and cool.
3. Add solution of item 5.
4. Fill.

Ibuprofen Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Ibuprofen	50.00
10.00	2	Alcohol	100.00
10.00	3	Propylene glycol	100.00
15.00	4	Lutrol F 127	150.00
1.00	5	Isopropyl myristate	10.00
q.s.	6	Preservatives	q.s.
59.00	7	Water purified	590.00

MANUFACTURING DIRECTIONS

The addition of item 5 to the formulation makes the product less sticky and is preferred.

1. Heat solution of items 1–3 to 70°–80°C.
2. Dissolve items 4 and 5 and cool. Add solution of item 6.
3. Fill.

Ibuprofen Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Ibuprofen	51.00
27.35	2	Propylene glycol	273.50
10.00	3	Isopropyl alcohol	100.00
5.00	4	Isopropyl alcohol	50.00
0.10	5	Potassium sorbate	1.00
2.50	6	Carbopol 940	25.00
0.20	7	Sodium methyl paraben	2.00
0.0025	8	FD & C red 40	0.025
22.50	9	Ethoxydiglycol (transcutol)	225.00
0.150	10	Lavender oil	1.50
27.09	11	Water purified	270.90

MANUFACTURING DIRECTIONS

1. Charge and mix items 11, 2, and 3 in a stainless steel vessel.
2. Add and dissolve item 5 in step 1 by stirring.
3. Add and dissolve item 6 in step 1 after passing through a stainless steel sieve.
4. Mix and homogenize suspension.
5. Dissolve item 7 in item 11 and add to step 4.
6. Add and dissolve item 8 in item 11 separately and add to step 5.
7. Charge item 2 and in a separate vessel, dissolve, and add to step 7.
8. Charge items 9 and 10 in a separate container, mix, and transfer to step 8.
9. Mix thoroughly, transfer to storage vessel, and fill.

Imiquimod Cream

Imiquimod is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing-cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben. Chemically, imiquimod is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3.

Indomethacin Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Indomethacin	10.00
10.00	2	Cremophor RH 40	100.00
15.00	3	Lutrol F 127	150.00
74.00	4	Water purified	740.00

MANUFACTURING DIRECTIONS

1. Dissolve indomethacin in Cremophor RH 40 at 60°–70°C.
2. Add the water slowly (60°–70°C), stir the mixture well, and dissolve Lutrol F 127.
3. Cool to room temperature. Fill.

Indomethacin Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Indomethacin	10.00
20.00	2	Propylene glycol	200.00
20.00	3	Lutrol E 400	200.00
21.00	4	Lutrol F 127	210.00
38.00	5	Water purified	380.00

MANUFACTURING DIRECTIONS

1. Heat solution of items 1–3 to about 70°C.
2. Dissolve item 4 with stirring for about 30 minutes.
3. Add and mix item 5 and cool to form a yellow gel.
4. Fill.

Indomethacin Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Indomethacin	10.00
15.00	2	Alcohol	150.00
22.00	3	Lutrol E 400	220.00
23.00	4	Lutrol F 127	230.00
39.00	5	Water purified	390.00

MANUFACTURING DIRECTIONS

Addition of item 5 enhances chemical stability of item 1.

1. Heat solution of items 1–3 to about 70°C.
2. Dissolve item 4 with stirring for about 30 minutes.
3. Add and mix item 5 and cool to form a yellow gel.
4. Fill.

Indomethacin Suppositories

The suppositories for rectal use contain 50 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000, and sodium chloride. Indomethacin is a nonsteroidal anti-inflammatory indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy- 2- methyl-1H-indole-3-acetic acid.

Indomethacin Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
100.00	1	Indomethacin	100.00
0.082	2	Butylated hydroxyanisole	0.082
0.082	3	Butylated hyroxytolune	0.082
0.163	4	Edetic acid	0.163
128.00	5	Glycerin	128.00
128.00	6	Polyethylene glycol 6000	128.00
1630.00	7	Polyethylene glycol 4000	1630.00

MANUFACTURING DIRECTIONS

1. Charge the polyethylene glycol 6000, polyethylene glycol 4000 (16.3 kg), and glycerol to the Becomix machine.
2. Heat to 70°C to melt, stir until homogenous, and cool to 60°–65°C.
3. Maintain temperature at 60°–65°C. Apply a head of nitrogen gas to hopper, then charge to the hopper the parabens.
4. Stir until dissolved.
5. Charge indomethacin slowly to hopper while stirring. Stir until completely dissolved. A clear yellow melt is produced.
6. Charge edetic acid to the hopper and stir for 15 minutes to disperse it (material does not dissolve), then cool to 55°–60°C.
7. Stir the mixture for 30 minutes, maintaining the temperature at 55°–60°C, then commence filling into molds at filling limits 1.581–1.679 g.

Indomethacin Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
50.00	1	Indomethacin	50.00
8.30 mcg	2	Butylhydroxy toluene	8.30 mg
141.00	3	Lutrol E 4000	141.00
14.00	4	Lutrol E 6000	14.00
16.30 mcg	5	EDTA	16.30 mg
3.00	6	Water purified	3.00

MANUFACTURING DIRECTIONS

1. Prepare solution of items 5 and 6.
2. Mix with the melted mixture of items 1–4 and fill into the molds of suppositories. Fill 1.6 g per suppository.

Kojic Dipalmitate Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.20	1	Kojic dipalmitate	2.00
6.00	2	Finetex TN	60.00
3.00	3	Bernel FAO	30.00
2.00	4	Carbosil M-5 (fumed silica)	20.00
0.30	5	Microtitanium dioxide	3.00
0.50	6	Lecithin Z-3	5.00
5.00	7	Bentone TN (hectorite compound)	50.00
2.00	8	Mineral oil	20.00
8.00	9	Isopropyl myristate	80.00
0.08	10	Fragrance	0.80

MANUFACTURING DIRECTIONS

1. Heat the Kojic dipalmitate, Finetex, FAO, Bentone, and isopropyl myristate to 70°C in a jacketed kettle.
2. Transfer to a homogenizer mill.
3. Slowly add, with high-shear agitation, the Carbosil and the microtitanium dioxide.
4. Mill and cool to 45°–50°C.
5. Add, with milling, the remaining ingredients except the fragrance and SD alcohol. Cool with milling (and cooling jacket if needed) to 25°–30°C.
6. Add, with mixing, the fragrance and alcohol. Package immediately.

Ketoconazole Cream

The ketoconazole 2% cream contains the broad-spectrum synthetic antifungal agent ketoconazole 2%, formulated in an aqueous cream vehicle consisting of propylene glycol, stearyl and cetyl alcohols, sorbitan monostearate, polysorbate 60, isopropyl myristate, sodium sulfite anhydrous, polysorbate 80, and purified water. Ketoconazole is cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3- dioxolan-4- yl]methoxy]phenyl]piperazine.

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.00	1	Ketoconazole micronized	20.00
20.00	2	Propylene glycol	200.00
8.00	3	Stearyl alcohol	80.00
2.00	4	Cetyl alcohol	20.00
2.00	5	Span 60	20.00
1.50	6	Tween 60	15.00
1.00	7	Isoprpyl myristate	10.00
0.20	8	Sodium sulfite anhydrous	2.00
0.10	9	Tween 80	1.00
q.s.	10	Water purified to	1 kg

MANUFACTURING DIRECTIONS

1. Charge items 3–5 in a steam-jacketed kettle. Heat to 75°C and then begin stirring to ensure complete melting; maintain temperature, keep stirring.
2. Charge items 2 and 10 in a separate heating vessel and heat to 75°C; add item 6 and stir, preferably under vacuum of 0.5 bar to avoid frothing and add to step 1, passing through a 100-mesh screen by a pump. Rinse with item 10 and add rinsings.
3. Stir for 1 hour. Cool to 40°C while stirring.
4. In a separate vessel, add 10% of item 10 and item 1 to make a slurry, heat to 40°C, and pass through colloid mill after adding another 10% of item 10.
5. Separately dissolve in 5% of item 10, item 8, and add to step above. Mix for 30 minutes.
6. Pass again through colloid mill and add to step 3, mix, and pass again through colloid mill.
7. Fill in appropriate containers.

Lactic Acid Cream

The cream is a formulation of 12% lactic acid neutralized with ammonium hydroxide, as ammonium lactate, with a pH of 4.4–5.4. The cream also contains cetyl alcohol, glycerin, glyceryl stearate, laureth-4, light mineral oil, magnesium aluminum silicate, methylcellulose, methyl and propyl parabens, PEG-100 stearate, polyoxyl 40 stearate, propylene glycol, and water. Lactic acid is a racemic mixture of 2-hydroxypropanoic acid.

Lanolin Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
60.00	1	Stearic acid	60.00
145.00	2	White petrolatum jelly	145.00
116.00	3	Mineral oil 25cS	116.00
10.00	4	Lanolin	10.00
20.00	5	Cetearyl alcohol	20.00
q.s.	6	Deionized water q.s. to	1 kg
14.00	7	Triethanolamine 99%	14.00
q.s.	8	Perfume, preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool, adding triethanolamine at 60°C and perfuming at 40°–50°C.
3. This cream serves as a base for drugs as well. Tirethanolamine may be omitted, as it gives a higher pH.

Lidocaine and Prilocaine Topical Adhesive System Cream

Lidocaine 2.5% and prilocaine 2.5% is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature; therefore, both local anesthetics exist as liquid oil rather than as crystals. It is also packaged in the anesthetic disc, which is a single-dose unit contained within an occlusive dressing. The anesthetic disc is composed of a laminate backing, an absorbent cellulose disc, and an adhesive tape ring. The disc contains 1 g of emulsion, the active contact surface being approximately 10 cm^2. The surface area of the entire anesthetic disc is approximately 40 cm^2. Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), and has an octanol:water partition ratio of 43 at pH 7.4. Prilocaine is chemically designated as propanamide, N-(2-methylphenyl)-2-(propylamino), and has an octanol:water partition ratio of 25 at pH 7.4. Each gram contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters (as emulsifiers), carboxypolymethylene (as a thickening agent), sodium hydroxide to adjust to a pH approximating 9, and purified water to 1 g. It contains no preservative; however, it passes the USP antimicrobial effectiveness test because of the pH. The specific gravity of the cream is 1.00.

Lidocaine Adhesive System Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
8.00	1	Lidocaine base	80.00
5.00	2	Dipropylene glycol	50.00
8.00	3	Lecithin 60% in propylene glycol	80.00
10.00	4	Karaya gum	100.00
2.00	5	Bentonite (polargel)*	20.00
0.10	6	Zinc oxide	1.00
6.00	7	Glycerin	60.00

*Optional ingredients

MANUFACTURING DIRECTIONS

1. Blend the lidocaine base, the propylene glycol, lecithin, and glycerin at about 70°–90°C until the entire drug is dissolved.
2. Cool the solution to 20°–35°C before adding the karaya gum and clay.
3. Once the karaya gum and clay are added, the final composition is applied to a suitable backing material such as a nonwoven, polyester film (e.g., the film sold under the trademark Sontara 8100, manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed to about 100°C to accelerate the formation of the gel into its final, finite form.

Lidocaine and Tribenoside Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Tribenoside	50.00
2.00	2	Lidocaine hydrochloride	20.00
5.00	3	Cetyl alcohol	50.00
9.00	4	Stearic acid	90.00
10.00	5	Liquid paraffin	100.00
2.00	6	Isopropyl palmitate	20.00
4.45	7	Cetomacrogol 1000	44.50
1.55	8	Crill 3	15.50
0.180	9	Methylparaben	1.80
0.05	10	Propylparaben	0.50
6.00	11	Sorbitol 70% solution	60.00
54.80	12	Water purified	548.00

MANUFACTURING DIRECTIONS

1. Charge and dissolve items 9 and 10 in portion of item 12 at 90°C.
2. Charge item 11 into Becomix and heat to 60°C.
3. Add item 2 to step 3 and dissolve, maintaining temperature at 60°C.
4. Charge in a melting vessel items 3, 4, 7, and 8 and melt at 70°C; cool to 55°C.
5. Add items 5, 6, and 1 to a fat-melting vessel and melt at 60°C.
6. Transfer step 5 to step 4 and mix well. Cool down to 25°C.
7. Transfer to storage vessel and fill.

Lidocaine and Tribenoside Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Tribenoside	5.00
2.00	2	Lidocaine	2.00
79.20	3	White soft paraffin	79.20
0.30	4	Hard paraffin	0.30
3.50	5	Microcrystalline wax	3.50

MANUFACTURING DIRECTIONS

1. Charge items 3–5 in a melting vessel and heat to 70°C to melt, transfer to Becomix, and maintain 40°–45°C.
2. In a portion of the melt above, add items 1 and 2 in a separate vessel and homogenize for 5 minutes. Transfer to step 1 using the melt to rinse and adding rinsings.
3. Allow to cool to 40°C; transfer to storage vessel and fill.

Lidocaine and Tribenoside Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
40.00	1	Lidocaine	40.00
400.00	2	Tribenoside	400.00
281.00	3	Witepsol E85	281.00
1124.60	4	Witepsol W 35	1124.60
4.40	5	Miglyol 812 N	4.40

MANUFACTURING DIRECTIONS

1. Load items 3 and 4 in a fat-melting vessel and heat to 50°C. Transfer molten material to Becomix through filter sieves, keeping a small portion on the side.
2. Charge items 1, 2, and 4 in step 1, rinsing the container of item 2 with the molten portions kept aside in step 1.
3. Mix for 20 minutes at 10 rpm (manual), temperature 50°C, homogenize at speed II for 4 minutes under 0.6 bar vacuum. Check for clarity; if not clear, homogenize again.
4. Set the temperature to 39°C and mix at 10 rpm.
5. Fill 1850 mg in suppository molds.

Lidocaine Anorectal Cream

Anorectal cream (lidocaine 5%) is a topical anesthetic cream. Each gram of anorectal cream contains lidocaine 50 mg, benzyl alcohol, carbomer 940, cholesterol, hydrogenated lecithin, isopropyl myristate, polysorbate 80, propylene glycol, triethanolamine, vitamin E acetate, and water.

Lidocaine Gels

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
20.00	1	Lidocaine hydrochloride	2
560.00	2	Water	56
200.00	3	Propylene glycol pharma	20
220.00	4	Lutrol F 127	22

MANUFACTURING DIRECTIONS

1. Prepare solution of items 1–3 at room temperature, heat to 70°C or cool to 6°C, and slowly add item 4 to the well-stirred solution until it is dissolved.
2. Maintain the temperature until the air bubbles escape. A clear, colorless gel is obtained.

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
50.00	1	Lidocaine hydrochloride	5
500.00	2	Water	50
150.00	3	Propylene glycol pharma	15
100.00	4	Liquid paraffin	10
200.00	5	Lutrol F 127	20

MANUFACTURING DIRECTIONS

1. Prepare solution of items 1–3 at room temperature and mix with item 4.
2. Heat to 70°C or cool to 6°C and slowly add item 5 to the well-stirred solution until it is dissolved. Maintain cool until the air bubbles escape. A gel-cream is obtained.

Lidocaine Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Lidocaine base	50.00
28.00	2	Polyethylene glycol (PEG 3350)	280.00
40.00	3	Polyethylene glycol (PEG 400)	400.00
25.00	4	Propylene glycol	250.00
2.00	5	Purified water	20.00

MANUFACTURING DIRECTIONS

1. Load items 2 and 3 into a fat-melting vessel and heat to 70°C.
2. Cool to 40°C while stirring at slow speed (10–12 rpm).
3. Maintain the temperature between 40° and 45°C under continuous stirring.
4. Heat 200.0 g of item 4 to 40°–45°C in a stainless steel container.
5. Dissolve item 1 by stirring with stirrer. Add item 5 with continuous stirring.
6. Maintain the temperature between 40° and 45°C with continuous stirring.
7. Filter through cloth filter. Transfer the drug solution in to mixer previously set with temperature at 40°–45°C.
8. Rinse the stainless steel container with 50.0 g of item 4.
9. Add the rinsing into mixer. Transfer the molten mass from the fat-melting vessel at 40°C through a stainless steel filter to the mixer containing the drug solution while mixing at 10–12 rpm.
10. When the transfer is over, start the homogenizer at low speed, vacuum 0.6 bar, with stirrer speed at 10 rpm (manual mode).
11. Mix and homogenize for 10 minutes with recirculation at temperature 40°–45°C.
12. Stop the homogenizer, set the mixer at temperature 25°C, with stirrer speed at 10 rpm (manual mode).
13. Cool the cream to 25°C. When the ointment is cooled to 25°C, unload the ointment in stainless steel container.

Lidocaine, Eugenol, and Menthol Dental Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
55.2	1	Beeswax white	55.2
150.0	2	Lanolin anhydrous	150.0
723.7	3	Petrolatum	723.7
40.0	4	Lidocaine base	40.0
1.2	5	Saccharin sodium powder	1.2
q.s.	6	Water purified	3.0 mL
1.0	7	Eugenol	1.0
5.0	8	Menthol	5.0
0.8	9	Oil peppermint	0.8
20.16	10	Metaphen ointment base	20.16

MANUFACTURING DIRECTIONS

1. Melt beeswax white, lanolin, and petrolatum white together at 70°–80°C and strain into a suitable container.
2. Do not heat above 70°–80°C.
3. Melt Lidocaine base and strain into the container while mixing.
4. Dissolve the sodium saccharin in purified water heated to 70°C. Add to the container while mixing. Cool down to 45°–50°C while mixing.
5. Liquefy eugenol, menthol, and peppermint oil together by mixing all three items.
6. Warm gently to 35°–40°C if necessary. Strain into the container while mixing. Gently melt metaphen ointment base and strain into the container while mixing.
7. Mix thoroughly until congealed.

Lindane Lotion

Lindane lotion USP 1% is an ectoparasiticide and ovicide effective against *Sarcoptes scabiei* (scabies). In addition to the active ingredient, lindane, it contains glycerol monostearate, cetyl alcohol, stearic acid, trolamine, carrageenan, 2-amino-2-methyl-1-propanol, methylparaben, butylparaben, perfume, and water to form a nongreasy lotion, which is the highly purified gamma isomer of 1, 2, 3, 4, 5, 6, hexachlorocyclohexane.

Mafenide Acetate Cream

The cream is a soft, white, nonstaining, water-miscible, anti-infective cream for topical administration to burn wounds. Cream spreads easily and can be washed off readily with water. It has a slight acetic odor. Each gram of cream contains mafenide acetate equivalent to 85 mg of the base. The cream vehicle consists of cetyl alcohol, stearyl alcohol, cetyl esters wax, polyoxyl 40 stearate, polyoxyl 8 stearate, glycerin, and water, with methylparaben, propylparaben, sodium metabisulfite, and edetate disodium as preservatives. Chemically, mafenide acetate is (alpha)-Amino-(rho)-toluenesulfonamide monoacetate.

Malathion Lotion

The lotion contains 0.005 g of malathion per milliliter in a vehicle of isopropyl alcohol (78%), terpineol, dipentene, and pine needle oil. The chemical name of malathion is (±)-[(dimethoxyphosphinothioyl)-thio]butanedioic acid diethyl ester. Malathion has a molecular weight of 330.36, represented by $C_{10}H_{19}O_6PS_2$.

Mandelic Acid Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.00	1	Polyoxyethylene (40) stearate	20.00
1.00	2	Polyoxyethylene (20) sorbitan monooleate	10.00
5.00	3	Glycerol monostearate	50.00
3.00	4	Beeswax	30.00
2.00	5	Mineral oil	20.00
71.00	6	Water purified	710.00
5.00	7	Propylene glycol	50.00
0.50	8	Carbopol 934	5.00
5.00	9	DL-mandelic acid	50.00
1.7 mL	10	Ammonium hydroxide concentrated	17.00 mL

MANUFACTURING DIRECTIONS

1. Heat items 1–5 in a stainless steel container to 80°C.
2. In a separate container, heat items 6–8 to 80°C.
3. Add step to into step 1 with agitation.
4. After the mixture is congealed, add mandelic acid and ammonium hydroxide.
5. Continue agitation until a uniform consistency is obtained. The pH of the cream is 4.0.

Menthol, Methyl Salicylate, and Menthol Cream and Ointment

This cream and ointment contain menthol in an alcohol base gel, combinations of methyl salicylate, and menthol in cream and ointment bases, as well as a combination of methyl salicylate, menthol, and camphor in a nongreasy cream base; all are suitable for topical application. The varieties include the ointment (methyl salicylate, 18.3%; menthol, 16%), the cream (methyl salicylate, 15%; menthol, 10%), an arthritis formula cream (methyl salicylate, 30%; menthol, 8%), an ultra-strength pain-relieving cream (methyl salicylate, 30%; menthol, 10%; camphor, 4%), vanishing gel (2.5% menthol), and cream (10% menthol) with a fresh scent.

Mesalamine Suppository

The active ingredient is mesalamine, also known as 5-aminosalicylic acid (5-ASA). Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid and is classified as an anti-inflammatory drug. The rectal suppository contains 500 mg of mesalamine in a base of hard fat NF.

Methotrexate Cataplasms

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Diisopropanolamine	50.00
3.00	2	Methotrexate	30.00
10.00	3	Poly sodium acrylate	100.00
10.00	4	Gelatin	100.00
30.00	5	Glycerin	300.00
q.s.	6	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture with an aqueous solution of the corresponding base components [poly(sodiumacrylate), gelatin, and glycerin] in the remaining portion of the purified water.
3. Cast the mass in step 2 on a release sheet; apply a nonwoven fabric backing to a surface of the mass.

Methotrexate Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
92.00	1	Hydrocarbon gel	920.00
5.00	2	Diisopropanolamine	50.00
3.00	3	Methotrexate	30.00

MANUFACTURING DIRECTIONS

1. Mix diisopropanolamine and methotrexate and stir with gelated hydrocarbon gel, whereby the ointment is obtained. Item 2 can be omitted.

Methotrexate Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.00	1	Stearic acid	70.00
0.50	2	Behenyl alcohol	5.00
7.00	3	Squalene	70.00
2.00	4	Polyethylene glycol monostearate	20.00
5.00	5	Glyceryl monostearate (self-emulsifying type)	50.00
0.10	6	Butyl hydroxybenzoate	1.00
0.10	7	Methyl hydroxybenzoate	2.00
5.00	8	1,3-butylene glycol	50.00
3.00	9	Methotrexate	30.00
5.00	10	Diisopropanolamine*	50.00
q.s.	11	Water purified q.s. to	1 kg

*May be omitted.

MANUFACTURING DIRECTIONS

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture under heat with a liquid mixture of stearic acid, behenyl alcohol, squalane, polyethylene glycol stearate glyceryl monostearate acid, and butyl parahydroxybenzoate and also with an aqueous mixture of methyl parahydroxybenzoate, 1,3-butylene glycol and the remaining portion of the purified water.
3. Cool the resulting mass whereby the cream is obtained.

Methotrexate Lotion

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Stearic acid	10.00
0.50	2	Behenyl alcohol	5.00
1.00	3	Polyoxyethylene sorbitan monooleate	10.00
1.00	4	Glyceryl monostearate (self-emulsifying type)	10.00
0.10	6	Butyl hydroxybenzoate	1.00
0.10	7	Methyl hydroxybenzoate	2.00
5.00	8	1,3-butylene glycol	50.00
1.00	9	Carboxyvinyl polymer	10.00
3.00	10	Methotrexate	30.00
5.00	11	Diisopropanolamine*	50.00
q.s.	12	Water purified q.s. to	1 kg

*May be omitted.

MANUFACTURING DIRECTIONS

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture under heat with a liquid mixture of stearic acid, behenyl alcohol, polyoxyethylene sorbitan monostearate, glyceryl monostearate, and butyl parahydroxybenzoate and also with an aqueous mixture of methyl parahydroxybenzoate, 1,3-butylene glycol, and another portion of the purified water.
3. Cool the resulting mixture to room temperature and mix with a water-base dispersion of carboxyvinyl polymer in the remaining water, whereby the lotion is obtained.

Methoxsalen Lotion

Each milliliter of lotion contains 10 mg methoxsalen in an inert vehicle containing alcohol (71% v/v), propylene glycol, acetone, and purified water.

Methyl Salicylate and Menthol Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
110.00	1	Methyl salicylate	110.00
50.00	2	Menthol	50.00
200.00	3	Lutrol E 400	200.00
60.00	4	Cremophor RH 40	60.00
70.00	5	Propylene glycol pharma	70.00
320.00	6	Lutrol F 127	320.00
190.00	7	Water	190.00

MANUFACTURING DIRECTIONS

1. Dissolve item 6 in solution of items 1–5 and mix with item 7.
2. The clear gel can be diluted with water. Because of the high concentration of the active ingredients and of Lutrol F 127, the consistency of the colorless clear gel is extremely hard. By reducing the concentration of the active ingredients, the amount of Lutrol F 127 could be reduced, too, and the consistency of the gel will be normal.

Methyl Salicylate and Menthol Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
150.00	1	Polawax	150.00
100.00	2	Methyl salicylate	100.00
50.00	3	Menthol	50.00
100.00	4	Mineral oil 70cS	100.00
q.s.	5	Deionized water q.s. to	1 kg
q.s.	6	Preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately to 70°C.
2. Add water to oil phase while stirring; stir to cool. Fill at 30°C.

Methyl Salicylate Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
30.00	1	Tromethamine magnesium aluminum silicate (veegum PRO)	30.00
30.00	2	Hydroxypropylcellulose	30.00
350.00	3	Deionized water	350.00
350.00	4	Ethanol	350.00
40.00	5	Cocoyl sarcosine (vanseal CS)	40.00
25.00	6	Oleath-10	25.00
25.00	7	PEG-25 hydrogenated castor oil	25.00
50.00	8	Isopropyl myristate	50.00
20.00	9	Triethanolamine	20.00
5.00	10	Camphor	5.00
5.00	11	Menthol	5.00
2.00	12	Eucalyptus oil	2.00
65.00	13	Methyl salicylate	65.00
q.s.	14	Preservatives	q.s.

MANUFACTURING DIRECTIONS

1. Dry blend items 1 and 2 and slowly add them to items 2 and 4, agitating to ensure homogenous dispersion.
2. Combine items 5–9 separately and items 10–14 separately and mix them together; add this mixture to the first mix and then mix until uniform.

Methyl Salicylate Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
15.00	1	Magnesium aluminum silicate (veegum)	1.50
547.00	2	Deionized water	54.70
2.00	3	Simethicone emulsion	0.20
30.00	4	Propylene glycol	3.00
150.00	5	Methyl salicylate	15.00
50.00	6	Menthol	5.00
6.00	7	Polysorbate	0.60
50.00	8	C18-C36 acid	5.00
150.00	9	Glycerl stearate and PEG-100 stearate	15.00
q.s.	10	Preservatives	q.s.

MANUFACTURING DIRECTIONS

1. Add item 1 slowly to water and mix vigorously to smooth dispersion.
2. Add items 3 and 4, mixing one at a time; heat to 75°–80°C.
3. Separately mix and heat items 5–9 to 75°–80°C and add the two parts while mixing. Cool while mixing and add item 10 at 40°C.

Methyl Salicylate Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
30.00	1	Tromethamine magnesium aluminum silicate (veegum PRO)	30.00
30.00	2	Hydroxypropylcellulose	30.00
350.00	3	Deionized water	350.00
350.00	4	Ethanol	350.00
40.00	5	Cocoyl sarcosine (vanseal CS)	40.00
25.00	6	Oleath-10	25.00
25.00	7	PEG-25 hydrogenated castor oil	25.00
50.00	8	Isopropyl myristate	50.00
20.00	9	Triethanolamine	20.00
5.00	10	Camphor	5.00
5.00	11	Menthol	5.00
2.00	12	Eucalyptus oil	2.00
65.00	13	Methyl salicylate	65.00
q.s.	14	Preservatives	q.s.

MANUFACTURING DIRECTIONS

1. Dry blend items 1 and 2 and slowly add them to items 2 and 4, agitating to ensure homogenous dispersion.
2. Combine items 5–9 separately and items 10–14 separately and mix them together; add this mixture to the first mix and then mix until uniform.

Methyl Salicylate Lotion

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
25.00	1	PPG-5-cetech-10-phosphate (Crodafos SG)	25.00
40.00	2	Emulsifying wax NF (Polawax)	40.00
45.00	3	PPG-1 cetyl ether (Procetyl 10)	45.00
10.00	4	Menthol	10.00
10.00	5	Camphor	10.00
75.00	6	Methyl salicylate	75.00
30.00	7	Glycerin	30.00
10.00	8	Gelatin (Crodyne BY-19)	10.00
3.00	9	Diethanolamine	3.00
742.00	10	Deionized water	742.00
10.00	11	Propylene glycol, diazolidinyl urea, methylparaben, and propylparaben	10.00

MANUFACTURING DIRECTIONS

1. Premix items 4, 5, and 6 with item 3.
2. When completely dissolved, add items 1 and 2 and heat to 75°–80°C.
3. Dissolve item 8 in water and add items 7 and 9.
4. Heat to 80°C; add this part to previous part slowly, using good mechanical mixing.
5. Allow to cool while mixing to 40°C and then add item 11; cool to 30°C and fill.

Methyl Salicylate, Thyme, Pine, and Menthol Foot Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Lanolin	5.00
90.00	2	Stearic acid	90.00
5.00	3	Cetyl alcohol	5.00
40.00	4	Isopropyl palmitate	40.00
10.00	5	Oleyl alcohol	10.00
20.00	6	Mineral oil and lanolin alcohol (liquid base CB3929)	20.00
7.50	7	Oil of wintergreen	7.50
3.00	8	Oil of thyme	3.00
5.00	9	Oil of pine	5.00
5.00	10	Menthol	5.00
5.00	11	Camphor	5.00
q.s.	12	Deionized water q.s. to	1 kg
80.00	13	Glycerin	8.00
18.00	14	Triethanolamine 99%	1.80
q.s.	15	Preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately at 65°–70°C.
2. Add water phase to oil phase while stirring. Add the triethanolamine dropwise.
3. Stir to cool. This product can be used as disinfecting and soothing cream for the feet.

Methyl Salicylate and Menthol Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
130.00	1	Methyl salicylate	130.00
60.00	2	Menthol	60.00
20.00	3	Eucalyptus oil	20.00
5.00	4	Lanolin	5.00
1.00	5	Chloroxylenol	1.00
150.00	6	Glyceryl stearate and PEG-100 stearate	150.00
73.00	7	Cetearyl alcohol	73.00
70.00	8	Glyceryl stearate	70.00
q.s.	9	Deionized water q.s. to	1 kg
q.s.	10	Preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring; stir to cool.
3. Fill at 30°C.

Methyl Salicylate and Menthol Lotion

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
150.00	1	Methyl salicylate	150.00
70.00	2	Menthol	70.00
10.00	3	Lanolin oil	10.00
30.00	4	PEG-40 stearate	30.00
20.00	5	Glyceryl stearate	20.00
q.s.	6	Deionized water	q.s.
1.50	7	Carbopol 980	1.50
10.00	8	Potassium hydroxide (10% aqueous solution)	10.00
q.s.	9	Preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Heat oil and water phases (except potassium hydroxide) separately to 65°–70°C.
2. Add water phase to oil phase while stirring. Add potassium hydroxide solution to neutralize.
3. Stir to cool. Fill at 30°C.

Methyl Salicylate Clear Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
25.00	1	Hydroxypropyl cellulose	25.00
q.s.	2	Deionized water q.s. to	1 kg
400.00	3	Ethanol DEB 100	400.00
100.00	4	Menthol	100.00
150.00	5	Methyl salicylate	150.00
25.00	6	DEA-oleth-3-phosphate	25.00

MANUFACTURING DIRECTIONS

1. Hydrate hydroxypropoyl cellulose in water at 60°–65°C.
2. Stir to cool; add ethanol.
3. Add remaining ingredients and stir until homogenous.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
005.00	1	Metoclopramide (5.0% excess)	5.25
894.75	2	Hard fat (Suppocire AM®)	894.75
q.s.	3	Ethanol 95%*	35.00

*To be evaporated during manufacturing process.

MANUFACTURING DIRECTIONS

1. Load item 2 in the fat-melting vessel and heat to 65° ± 2°C.
2. Transfer the molten mass in a stainless steel container through clean polyester cloths.
3. Wash the mixer with purified water (65° ± 2°C). Set the temperature to 65° ± 2°C. Transfer the molten mass to the mixer.
4. Heat 32.5 g of item 3 in a stainless steel container using a water bath at 65° ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in mixer at 65° ± 2°C while mixing.
7. Wash the drug container with 2.5 g of hot item 3 (65° ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50° ± 2°C, Mixing 10 rpm manual mode, homogenize under vacuum with air circulation at temperature 50° ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4–0.6 bar while cooling it to 40° ± 2°C.
10. Heat the storage vessel, set temperature at 40° ± 2°C.
11. Transfer the molten mass from the mixer to the storage vessel.
12. Hold the molten mass 40° ± 2°C while mixing continuously at low speed.
13. Fill 900 mg/suppository.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
10.00	1	Metoclopramide (5.0% excess)	10.50
1339.50	2	Hard fat (Suppocire AM®)	1339.50
q.s.	3	Ethanol 95%*	62.00

*To be evaporated during manufacturing process.

MANUFACTURING DIRECTIONS

1. Load item 2 in the fat-melting vessel and heat to 65° ± 2°C.
2. Transfer the molten mass in a stainless steel container through clean polyester cloths.
3. Wash the mixer with purified water (65° ± 2°C). Set the temperature to 65° ± 2°C. Transfer the molten mass to the mixer.
4. Heat 57.0 g of item 3 in a stainless steel container using a water bath at 65° ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in the mixer at 65° ± 2°C while mixing.
7. Wash the drug container with 5.0 g of hot item 3 (65° ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50° ± 2°C, mix, homogenize under vacuum with air circulation at temperature 50° ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4–0.6 bar while cooling to 40° ± 2°C.
10. Heat the storage vessel, set temperature at 40° ± 2°C.
11. Transfer the molten mass from mixer to the storage vessel.
12. Hold the molten mass at 40° ± 2°C while mixing continuously at low speed.
13. Fill 1350 mg/suppository.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
20.00	1	Metoclopramide (5.0% excess)	21.00
1779.00	2	Hard fat (suppocire AM)	1779.00
q.s.	3	Ethanol 95%*	90.00

*To be evaporated during manufacturing process.

MANUFACTURING DIRECTIONS

Fill weight: 1800 mg/suppository.
Precautions: The molten suppository mass must be kept under stirring throughout the storage period, during manufacturing, and during filling to avoid the sedimentation of the active drug.

1. Load item 2 in the fat-melting vessel and heat to 65° ± 2°C.
2. Transfer the molten mass in a stainless steel container through clean polyester cloths.
3. Wash the mixer with purified water (65° ± 2°C). Set the temperature to 65° ± 2°C. Transfer the molten mass to the mixer.
4. Heat 82.5 g of item 3 in a stainless steel container using a water bath at 65° ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in the mixer at 65° ± 2°C while mixing.
7. Wash the drug container with 7.5 g of hot item 3 (65° ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50° ± 2°C, homogenize under vacuum with air circulation at temperature 50° ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4–0.6 bar while cooling to 40° ± 2°C.
10. Heat the storage vessel, set temperature at 40° ± 2°C.
11. Transfer the molten mass from mixer to the storage vessel.
12. Hold the molten mass at 40° ± 2°C while mixing continuously at low speed.
13. Fill 1,800 mg/suppository.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
10.00	1	Metoclopramide base 5% excess	10.50
1339.00	2	Suppocire AM	1339.00
q.s.	3	Alcohol	q.s.

MANUFACTURING DIRECTIONS

1. Add and melt item 2 in a melting vessel at 65°C; transfer to mixing vessel through filter sieve at 65°C.
2. Heat item 3 to 65°C in a separate vessel and add item 1 to dissolve; add to step 1.
3. Set mixing vessel under vacuum with air circulation and at 50°C; homogenize at speed II.
4. Completely evaporate alcohol and continue to mix at 0.4–0.6 bar and cool down to 40°C.
5. Fill suppository mold.

Metronidazol Vaginal Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.20	1	Metronidazole	1.20
21.00	2	Lutrol F 127	21.00
40.00	3	Lutrol E 400	40.00
37.80	4	Water purified	37.80

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1–3 to 70°–80°C and slowly add the water heated to about 70°C.
2. Maintain the temperature until the air bubbles disappear.

Metronidazole Cream

The topical cream contains metronidazole USP at a concentration of 7.5 mg per gram (0.75%) in an emollient cream consisting of emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid or sodium hydroxide to adjust pH, and purified water. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is 2-methyl-5-nitro-1H-imidazole-1-ethanol. The molecular formula is $C_6H_9N_3O_3$, and molecular weight is 171.16. For metronidazole cream 1%, each gram contains 10 mg micronized metronidazole USP in a base of purified water USP, stearic acid NF, glyceryl monostearate NF, glycerin USP, methylparaben NF, trolamine NF, and propylparaben NF.

Metronidazole Lotion

Metronidazole lotion contains metronidazole USP at a concentration of 7.5 mg per gram (0.75% w/w) in a lotion consisting of benzyl alcohol, carbomer 941, cyclomethicone, glycerin, glyceryl stearate, light mineral oil, PEG-100 stearate, polyethylene glycol 400, potassium sorbate, purified water, steareth-21, stearyl alcohol, and sodium hydroxide or lactic acid to adjust pH. Metronidazole is an imidazole and is classified therapeutically as an antiprotozoal and antibacterial agent.

Metronidazole Gel Solution

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Metronidazole	10.00
5.00	2	Hydroxy-beta-cyclodextrin	50.00
0.15	3	Methylparaben	1.50
0.03	4	Propylparaben	0.30
5.00	5	Glycerin	50.00
1.50	6	Hydroxyethyl cellulose	15.00
0.05	7	Disodium edetate	0.50
q.s.	8	Water purified q.s. to	1 kg

Miconazole Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.00	1	Cetostearyl alcohol	70.00
1.50	2	Cremophor A6	15.00
1.50	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	120.00
0.10	5	Parabens mixture	1.00
67.80	6	Water purified	678.00
8.00	7	Propylene glycol	80.00
2.00	8	Miconazole nitrate	20.00

MANUFACTURING DIRECTIONS

1. Heat the mixture of items 1–5 and the water separately to about 80°C.
2. Add the water to the obtained solution with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with step 2, and continue to stir during cooling to room temperature.

Miconazole Mouth Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.00	1	Miconazole nitrate	20.00
0.10	2	Orange flavor	1.00
20.00	3	Lutrol F 127	200.00
10.00	4	Cremophor RH 40	100.00
10.00	5	Propylene glycol	100.00
5.00	6	Kollidon 90F	50.00
0.30	7	Saccharin sodoium	3.00
52.60	8	Water purified	526.00

MANUFACTURING DIRECTIONS

1. Dissolve items 1 and 2 in the molten mixture of items 3 and 4.
2. Heat solution of items 6–8 to 90°C and mix slowly with step 1.
3. Let cool to room temperature when the air bubbles have escaped.

Miconazole Nitrate Vaginal Suppositories

Bill of Materials			
Scale (mg/ovule)	**Item**	**Material Name**	**Quantity/1000 Ovules (g)**
200.00	1	Miconazole nitrate micronized	200.00
1250.00	2	Hard fat (Witepsol H37®)	1250.00
1250.00	3	Hard fat (Witepsol H35®)	1250.00

MANUFACTURING DIRECTIONS

Fill weight: 2700 mg per ovule. The following are additional requirements: All particle sizes must be below 30 μm, and 60%–80% must be below 20 μm.

Precaution: The molten suppository mass must be kept under stirring throughout the storage period, during the manufacturing, and during filling to avoid the sedimentation of the active drug. Check the molten witepsols for phase separation by draining about 18.0 to 37.0 mL of molten witepsols in a glass beaker.

1. Load items 2 and 3 in the fat-melting vessel and heat to 50° ± 3°C.
2. Check the molten mass for phase separation.
3. Transfer the molten mass to the mixer through filter sieves. Set the temperature at 40° ± 2°C.
4. Load item 1 to the mixer containing molten witepsol (items 2 and 3).
5. Carefully mix the powder with the witepsol melt.
6. Set the mixer at temperature 40° ± 2°C, speed 10 rpm (manual mode), and mix for 10 minutes.
7. Set the mixer at temperature 40° ± 2°C, speed 10 rpm (manual mode), vacuum 0.6 bar.
8. Homogenise at low speed while mixing for 5 minutes.
9. Homogenise at high speed while mixing for 3 minutes.
10. Continue mixing of the mass under vacuum in mixer.
11. Heat the storage vessel, set the temperature at 40° ± 2°C.
12. Transfer the molten mass from the mixer to the storage vessel.
13. Hold the mass at 40° ± 2°C, while mixing continuously at low speed. Fill.

Miconazole Nitrate Vaginal Suppositories 400 mg

Bill of Materials			
Scale (mg/ovule)	**Item**	**Material Name**	**Quantity/1000 Ovules (g)**
400.00	1	Miconazole nitrate micronized	200.00
1150.00	2	Hard fat (witepsol H37)	1250.00
1150.00	3	Hard fat (witepsol H35)	1250.00

MANUFACTURING DIRECTIONS

1. Load items 2 and 3 in the fat-melting vessel and heat to 50° ± 3°C.
2. Check the molten mass for phase separation.
3. Transfer the molten mass to the mixer through filter sieves. Set the temperature at 40° ± 2°C.
4. Load item 1 to the mixer containing molten witepsol (items 2 and 3).
5. Carefully mix the powder with the witepsol melt.
6. Set the mixer at temperature 40° ± 2°C, speed 10 rpm (manual mode), and mix for 10 minutes.
7. Set the mixer at temperature 40° ± 2°C, mix under vacuum 0.6 bar.
8. Homogenize at low speed while mixing for 5 minutes.
9. Homogenize at high speed while mixing for 3 minutes.
10. Continue mixing of the mass under vacuum in mixer.
11. Heat the storage vessel, set the temperature at 40° ± 2°C.
12. Transfer the molten mass from the mixer to the storage vessel.
13. Hold the mass at 40° ± 2°C while mixing continuously at low speed. Fill.
14. Fill 2,700 mg.

Mometasone Furoate Lotion

Mometasone furoate is a synthetic corticosteroid with anti-inflammatory activity. Chemically, mometasone furoate is 9α, 21-dichloro-11β,17-dihydroxy-16α-methyl-pregna-1,4-diene-3,20-dione-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$ and a molecular weight of 521.4. Mometasone furoate is a white to off-white powder practically insoluble in water, slightly soluble in octanol, and moderately soluble in ethyl alcohol.

Each gram of cream 0.1% contains 1 mg mometasone furoate in a cream base of hexylene glycol, phosphoric acid, propylene glycol stearate, stearyl alcohol and ceteareth-20, titanium dioxide, aluminum starch ocetenylsuccinate, white wax, white petrolatum, and purified water.

Each gram of ointment 0.1% contains 1 mg mometasone furoate in an ointment base of hexylene glycol, phosphoric acid, propylene glycol stearate, white wax, white petrolatum, and purified water.

Each gram of lotion 0.1% contains 1 mg of mometasone furoate in a lotion base of isopropyl alcohol (40%), propylene glycol, hydroxypropylcellulose, sodium phosphate, and water. It may also contain phosphoric acid and sodium hydroxide, used to adjust the pH to approximately 4.5.

Mometasone Furoate Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.20	1	Mometasone furoate mironized	2.00
40.00	2	Isopropyl alcohol	400.00
0.15	3	Hydroxypropyl cellulose	1.50
0.226	4	Sodium acid phosphate	0.226
30.00	5	Propylene glycol	300.00
q.s.	6	Water purified q.s. to	1 kg
q.s.	7	Phosphoric acid to adjust pH (10% w/v solution)	q.s.

MANUFACTURING DIRECTIONS

1. Charge item 2 to a suitable vessel, add item 1, and mix for 25 minutes to dissolve completely.
2. Add item 3 slowly to step 1 and mix for 15 minutes to disperse evenly.
3. In a separate vessel, dissolve item 4 in a suitable quantity of item 6 and add to step above and mix for 10 minutes. Circulate cold water in the jacket to aid in gel formation.
4. Add item 5 to step above and mix until uniform.
5. Check and adjust the pH to 4.5 ± 0.2 with 10% w/v phosphoric acid solution. Mix the batch for at least 2 hours for pH adjustment and check the final pH.
6. Adjust the volume, pass through 100 mesh screen.
7. Fill in a suitable container.

Monobenzone Cream

Monobenzone is the monobenzyl ether of hydroquinone. Chemically, monobenzone is designated as p-(benzyloxy)phenol; the empirical formula is $C_{13}H_{12}O_2$, molecular weight 200.24. Each gram of benoquin cream contains 200 mg monobenzone USP in a water-washable base consisting of purified water USP, cetyl alcohol NF, propylene glycol USP, sodium lauryl sulfate NF, and white wax NF.

Multivitamin Oral Gel Veterinary

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
18,700 IU	1	Vitamin A palmitate1.7 million IU/g (BASF)	1.10
1.06	2	Vitamin E acetate (BASF)	10.60
0.50	3	Butylhydroxytoluene	500.00
20.00	4	Cremophor RH 40	20.00
725.00	5	Water	725.00
0.35	6	Thiamine hydrochloride (BASF)	3.55
0.03	7	Riboflavin (BASF)	0.35
0.17	8	Pyridoxin hydrochloride (BASF)	1.77
0.03	9	Cyanocobalamin gelatin coated 1%	0.35
0.35	10	Nicotinamide	3.53
0.03	11	Folic acid	0.35
0.35	12	Dexpanthenol (BASF)	3.53
0.30	13	EDTA sodium	3.00
0.43	14	Ferrous sulfate (7 H2 O)	4.38
0.63	15	Manganese chloride (4 H2 O)	6.38
0.11	16	Potassium iodide	1.15
50.00	17	Kollidon 90 F	50.00
100.00	18	Lutrol F 127	100.00
100.00	19	Lutrol F 127	100.00

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1–4 to about 60°C to obtain a clear solution, and slowly add the water (item 5) to the well-stirred solution.
2. Dissolve items 6–16 and item 17 separately in this mixed solution at room temperature, cool to about 6°C, add item 19, and stir until all Lutrol F 127 is dissolved.
3. Maintain the cool temperature until the air bubbles have escaped.

Multivitamin Oral Gel with Linoleic and Linolenic Acid

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/100 mL (g)**
0.050	1	Evening primrose oil (epopure, Prima Rosa/SA)	5.0 mL
0.30	2	Vitamin A palmitate 1.7 million IU/g (BASF)	0.30
0.190	3	Vitamin E acetate (BASF)	0.19
0.00150	4	Vitamin D3 40 MM IU/g	150 μg
200.00	5	Cremophor RH 40	20.0
550.00	6	Water	55.0
0.030	7	Thiamine hydrochloride (BASF)	0.03
0.030	8	Riboflavin (BASF)	0.03
0.150	9	Pyridoxin hydrochloride (BASF)	0.15
0.001	10	Cyanocobalamin, crystalline	10 μg
0.001	11	Calcium D-pantothenate (BASF)	0.10
0.005	12	Nicotinamide	0.50
10.00	13	Ascorbic acid, crystalline (BASF)	1.0
140.00	14	Lutrol F 127	14.0
50.00	15	Lutrol F 127	5.0

MANUFACTURING DIRECTIONS

1. Prepare mixture of items 1–5 and heat to about 65°C.
2. Add the warm water (item 6 at 65°C) slowly to the well-stirred mixture, as before.
3. Dissolve the items 7–14 at 20°–25°C in this clear solution. Cool the obtained solution to about 5°C and dissolve the rest of Lutrol F 127 item 15. Maintain the cool temperature until the air bubbles have escaped.
4. A clear yellow gel was obtained. Five milliliters of evening primrose oil epopure contains 3.5 g linoleic acid and 0.45 g gamma-linolenic acid.

Mupirocin Calcium Cream

Mupirocin calcium cream 2% contains the dihydrate crystalline calcium hemisalt of the antibiotic mupirocin. Chemically, it is ((alpha) *E*,2 *S*,3 *R*,4 *R*,5 *S*)-5-[(2 *S*,3 *S*,4 *S*,5 *S*)-2,3-epoxy-5-hydroxy-4-methylhexyl]tetra-hydro-3, 4-dihydroxy-(beta)-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2:1), dihydrate. Cream is a white cream that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% mupirocin free acid) in an oil-and-water-based emulsion. The inactive ingredients are benzyl alcohol, cetomacrogol 1000, cetyl alcohol, mineral oil, phenoxyethanol, purified water, stearyl alcohol, and xanthan gum.

Mupirocin Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.00	1	Mupirocin crystalline USE mupircon calcium dihydrate equivalent	20.00
1.00	2	Hydrocortisone	10.00
87.30	3	White soft paraffin	873.00
4.85	4	Softisan 649	48.50

MANUFACTURING DIRECTIONS

1. Heat appropriate proportions of white soft paraffin and Softisan 649 together to meet at 60°–70°C.
2. Mix thoroughly.
3. Allow to cool with stirring to room temperature.
4. Add items 2 and 3 with stirring.
5. Pass ointment through a mill (such as triple roller mill).

Mupirocin Ointment

Each gram of mupirocin ointment 2% contains 20 mg mupirocin in a bland water-miscible ointment base (polyethylene glycol ointment NF) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The nasal ointment 2% contains the dihydrate crystalline calcium hemisalt of the antibiotic mupirocin. It is a white to off-white ointment that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% pure mupirocin free acid) in a soft, white ointment base. The inactive ingredients are paraffin and a mixture of glycerin esters (Softisan®).

Naftifine Hydrochloride Cream

The cream 1% contains the synthetic, broad-spectrum, antifungal agent naftifine hydrochloride. It is for topical use only. The chemical name is (E)-N-Cinnamyl-N-methyl-1-naphthalenemethyl-amine hydrochloride. Naftifine hydrochloride has an empirical formula of $C_{21}H_{21}N \bullet HCl$ and a molecular weight of 323.86. The active ingredient is naftifine hydrochloride 1%; the inactive ingredients are benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol. Hydrochloric acid may be added to adjust pH.

Bill of Materials

Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
39.00	1	Urea	390.00
0.15	2	Carbopol 940	1.50
5.94	3	Petrolatum	59.40
12.06	4	Mineral oil	120.60
1.875	5	Glyceryl stearate	187.50
0.626	6	Cetyl alcohol	6.26
3.00	7	Propylene glycol	30.00
0.05	8	Xanthan gum	0.50
0.15	9	Trolamine	1.50
1.00	10	Naftifine hydrochloride*	10.00

*This formulation can serve as a generic formula for topical antifungals.

Nanoxynol Suppository with Bacterial Culture

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
125.00	1	Benzalkonium chloride or methyl benzythonium chloride	125.00
110.00	2	Imidiazolidinyl urea	110.00
11.00	3	Diazolidinyl urea	11.00
400.00	4	Hydroxypropyl methyl cellulose	400.00
200.00	5	Microcrystalline cellulose	200.00
100.00	6	Ascorbic acid	100.00
110.00	7	Nanoxynol 9	110.00
q.s.	8	Lactic acid for pH adjustment	q.s.
1 million	9	Encapsulated lactobacilli (bacteria)*	1billion
30.00	10	Magnesium stearate	30.00
30.00	11	Silicon dioxide	30.00
30.00	12	Lactose	30.00
q.s.	13	Sterile normal saline	q.s.

*Encapsulation methods: Viable, lyophilized lactobacilli bacteria that have been lyophilized after the removal of the media are used for encapsulation. The organisms are grown to log phase in nutrient media. The removal of the nutrient media is done by centrifugation at 14,000 *g* at 0°–4°C and then washing with sterile, balanced salts and 5% glucose solution at least three times after the initial centrifugation. The bacteria are then "snap frozen" with liquid nitrogen and lyophilized under high vacuum. The freshly obtained, washed, and lyophilized bacteria are suspended in 10 mL of 5% glucose saline solution in such volume so as to obtain a heavy suspension of bacteria that contains between 1 and 10 billion organisms per milliliter at 0°–4°C. The suspension of bacteria is rapidly, but gently, stirred while 0.2–0.4 mL of sodium alginate solution (1.5% weight by volume) is added. The above mixture is then transferred into a 4-L round-bottom flask by using a nitrogen stream through a sheathed 14-gauge needle. The 4-L round-bottom flask was previously washed with a 5% albumin solution and, thereafter, heated for at least 10 hours at 65°C, and the needle and the tubing used in the process have also been treated this way. Thereafter, the above mixture is forced through a 30-gauge multibeveled needle under pressure, using a large syringe and nitrogen stream. Very small droplets are generated at the end of the needle, which are dried by the nitrogen and airstream around the 30-gauge needle, and the droplets are collected in an aqueous solution of 1.3%–2% calcium chloride, where they gel. Thereafter, they are washed at least three times with 0.08%–0.13% 2-(N-cyclohexyl-amino) ethanesulfonic acid (CHES) solution and 1.0%–1.5% calcium chloride solution. The gelled droplets or little spheres are further washed with at least a fivefold excess of the 0.1% CHES 1.1% calcium chloride and normal saline solution. The resultant spheres are then "snap frozen" in liquid nitrogen and then lyophilized. After these steps, the encapsulated organisms can be used in the formulation below.

MANUFACTURING DIRECTIONS

1. The benzalkonium chloride or methylbenzethonium chloride, imidiazolidinyl urea, and diazolidinyl urea are added slowly, while thoroughly stirring, to a suspension of hydroxypropyl methyl cellulose and microcrystalline cellulose in a sterile normal saline solution (quantity sufficient to a make a thick paste) at 35°–37°C.
2. The pH is slowly lowered to about 6.0–6.3 with reagent grade lactic acid. (This step binds the antimicrobials to the "cellulose" excipients.)
3. The suspension is stirred for 2 hours, and then ascorbic acid that was dissolved in about 10–15 mL sterile saline is slowly added with gentle stirring.
4. The material is, at this point, a very thick paste. Spermicide (Nonoxynol 9) is now added and thoroughly mixed. After this step, the process is performed at 0°–4°C.
5. The pH of the mixture is then lowered to 4.3–4.5 with reagent-grade lactic acid.
6. Then freshly obtained encapsulated lactobacilli bacteria are added to achieve a final concentration of at least 1 million viable bacteria per suppository. (Inasmuch as the goal is to achieve a final concentration of at least 1 million viable bacteria per suppository, a four- to sixfold excess of bacteria are usually added because some loss of the viability occurs during the various mixing processes. This means that about 500 mg of the encapsulated bacteria are usually added.) It is important to mix these organisms not only thoroughly to ensure uniformity but also quickly because moisture adversely affects the viability of the organisms.

Rapid and thorough mixing can be done, for example, by spreading the paste in a thin layer on a sterile glass plate and then using a replicator to spread the bacteria evenly over the paste.

7. Magnesium stearate and silicon dioxide are added, with or without lactose.
8. After the materials are thoroughly mixed at 0°–4°C, they are pressed into a mold and dried in a desiccating jar under vacuum at 0°–4°C. (Drying at room temperature [25°C] or at higher temperatures decreases the number of viable bacteria.)
9. The suppositories are then sealed in air- and moisture-proof containers until used. During storage they should be protected from moisture and extreme temperatures to ensure the viability of the lactobacilli.

Neomycin and Bacitracin Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
50,000 IU	1	Bacitracin zinc, 8% excess (69 IU/mg)	7.80
0.50	2	Neomycin sulfate, 8% excess	5.40
85.00	3	White soft paraffin	850.00
5.00	4	Hard paraffin	50.00
10.00	5	Liquid paraffin	100.00
0.10	6	Edetate disodium	1.00

MANUFACTURING DIRECTIONS

1. Charge items 3 and 4 and half of item 5 in a melting vessel and heat to 100°C; bubble nitrogen gas to remove moisture and reduce oxygen load.
2. In a separate vessel, charge balance of item 5 and mix items 1 and 2 to make a paste.
3. Add step 2 to step 1 and mix at 30°C for 2 hours.

Neomycin Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.50	1	Neomycin sulfate	0.50
50.00	2	Propylene glycol	50.00
5.00	3	Parabens	5.00
200.00	4	Lutrol F 127	200.00
745.00	5	Water	745.00

MANUFACTURING DIRECTIONS

1. Dissolve the parabens and Lutrol F 127 in water heated to about 80 C.
2. Add the propylene glycol and dissolve neomycin sulfate.
3. Either cool to room temperature when the air bubbles escape or dissolve parabens in hot water, cool to 5°–10°C, dissolve Lutrol F 127, add propylene glycol, and dissolve neomycin sulfate.
4. Maintain the cool temperature until the air bubbles have escaped.

Neomycin, Polymyxin B Sulfate, and Bacitracin Zinc Opthalmic Ointment

The neomycin and polymyxin B sulfates and bacitracin zinc ophthalmic ointment is a sterile antimicrobial ointment for ophthalmic use. Each gram contains neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, bacitracin zinc equivalent to 400 bacitracin units, and white petrolatum, q.s.

Nicotine Polymer Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
66.70	1	N-30 polyvinyl pyrrolidone	667.00
28.60	2	Lauryl methylacrylate	286.00
5.00	3	Sodium stearate	50.00
1.25	4	Hydrogen peroxide (30%)	12.50
q.s.	5	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. The emulsion copolymerization of 66.7 parts N-30 vinylpyrrolidone and 28.6 parts lauryl methacrylate is carried out in 200 parts water containing 5 parts sodium stearate and 1.25 parts 30% hydrogen peroxide as catalyst.
2. The mixture is heated with stirring and the polymerization is carried out at 75°C for about 10 hours. The conversion is approximately 92%.
3. The emulsion is spray dried at about 210°C to yield a fine, off-white powder.
4. The nitrogen content of the copolymer is 8.6%, indicating an item 1 content of 68%.
5. A gel base is prepared by vigorously mixing the following ingredients (in parts by weight): copolymer prepared above, 6.75; propylene glycol, hydroxypropyl cellulose, isopropyl myristate, stearic acid, cetyl alcohol, fumed silica, 12.45; and ethanol, 80.80. The resultant gel has a viscosity of 12,000 CPS and a specific gravity of 0.8.
6. To 40 g of the gel above is added 140 mg nicotine; mix thoroughly to obtain a composition containing 3.5 mg/g (2.8 mg/ml).

Nitrofurazone Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.20	1	Nitrofurazone, 4% excess	2.08
7.20	2	Cetostearyl alcohol	72.00
1.80	3	Cetomacrogol 1000	18.00
6.00	4	Liquid paraffin	60.00
15.00	5	White soft paraffin	150.00
1.00	6	Propylene glycol	10.00
0.020	7	Chlorocresol	0.20
69.00	8	Water purified	690.00

MANUFACTURING DIRECTIONS

1. Charge items 3, 4, 5 (90%), and 6 in a melting vessel after passing it through a stainless steel sieve, and heat to melt.
2. In a separate vessel, heat two thirds of item 9 to 50°C and dissolve item 8 in it. Add to step 1.
3. Add and mix item 1 with item 5 (balance) and add to step 2.
4. Fill.

Nystatin Ointment

Bill of Materials			
Scale mg/g	**Item**	**Material Name**	**Quantity/kg (g)**
21.05	1	Nystatin microfine*	21.05
22.00	2	Cetostearyl alcohol	22.00
8.00	3	Paraffin (hard paraffin)	8.00
100.00	4	Mineral oil (liquid paraffin)	100.00
848.95	5	Petrolatum (white soft paraffin)	848.95

*Actual quantity to be calculated as per the actual potency; adjust with soft paraffin. Meets the current USP requirements with following additional requirement: particle size not less than 90% below 45 μm, 100% below 80 μm.

MANUFACTURING DIRECTIONS

1. Melt items 5, 3, and 2 at 70°C in a fat-melting vessel.
2. Disperse item 1 in 80.0 g of item 4 in a separate stainless steel container by using a spatula.
3. Pass the dispersion through homogenizer twice, then transfer the dispersion to mixer.
4. Rinse the homogenizer and container with 20.0 g of item 4 and transfer the rinsings to the mixer.
5. Homogenize the dispersion at high speed for 15 minutes. Set the mixer at 40°–45°C.
6. Transfer the molten mass from the fat-melting vessel to the mixer at 45°–50°C.
7. Mix for 10 minutes at manual mode and 10 minutes at auto mode at 12 rpm and vacuum 0.4–0.6 bar.
8. Homogenize at high speed for 10 minutes with recirculation. Mix until the temperature of the ointment reaches 28°–30°C.
9. Transfer the ointment to a stainless steel drum. Keep tightly closed.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
22.96	1	Nystatin microfine*	22.96
4.43	2	Neomycin sulfate**	4.43
0.28	3	Gramicidin***	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
80.00	5	Cetostearyl alcohol	80.00
20.00	6	Poloxyl 20 cetostearyl ether (cetomacrogol 1000)	20.00
80.00	7	Mineral oil (liquid paraffin)	80.00
2.00	8	Methylparaben	2.00
1.00	9	Propylparaben	1.00
60.00	10	Propylene glycol	60.00
4.86	11	Dibasic sodium phosphate	4.86
2.36	12	Monobasic sodium phosphate	2.36
180.00	13	Petrolatum (white soft paraffin)	180.00
531.86	14	Purified water	531.86

*Actual quantity to be calculated as per the actual potency. Difference in quantity to be adjusted by purified water.
*Meets current USP requirements with the following additional requirement: paticles size NLT 90% below 45 μm, 100% below 80 μm.
**Meets the current USP requirements with the following additional requirement: particle size 99% below 20 μm, 75% below 10 μm.
***Meets the current USP requirements with the following additional requirement: paticles size 98% below 50 μm.

MANUFACTURING DIRECTIONS

1. Load items 13, 5, 6, and 7 in a fat-melting vessel, and heat to 70°C. Stir to melt. Maintain temperature 70°–75°C. Heat 420.0 g of item 14 to 90°C in mixer.
2. Dissolve items 8 and 9 by stirring. Mix for 15 minutes at 10–12 rpm.
3. Cool to 65°–70°C. Dissolve items 11 and 12 in 71.86 g of item 14 at 40°–45°C in a stainless steel drum.
4. Check the pH limit 6.3–7.0 (at 25°C).
5. Dissolve item 2 into 79.08 g phosphate solution. The solution should be clear.
6. Disperse item 1 in the neomycin–phosphate solution above.
7. Homogenize twice to make a smooth dispersion. Dispersion should be smooth with no lumps.
8. Add 50.0 g of item 10 in a separate stainless steel container and heat to 40°–45°C, then dissolve item 3 by using homogenizer. The solution should be clear. Disperse item 4 in the clear solution of gramicidin–propylene glycol by using the homogenizer. Homogenize until there are no lumps.
9. Maintain temperature at 40°–45°C.
10. Transfer the melt from the step above to the mixer through a stainless steel sieve while mixing at temperature 65°C.
11. Homogenize at high speed for 10–12 minutes at 60°–65°C, vacuum 0.6 bar. Scrap the sides and blade. Cool down to 50°C. Transfer the homogenized dispersion from to the mixer.
12. Rinse the container with 10.0 g item 10. Add to the mixer and mix for 10 minutes. Transfer the dispersion to the mixer.
13. Rinse the container with 40.0 g item 14. Add to the mixer and mix for 10 minutes.
14. Homogenize at high speed for 20 minutes at temperature 45°C, mixer speed 10–12 rpm, and vacuum 0.6 bar.
15. Cool down to 25°–30°C while mixing. Transfer the cream to stainless steel drum.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
22.96	1	Nystatin microfine*	22.96
4.43	2	Neomycin sulfate*	4.43
0.28	3	Gramicidin*	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
100.00	5	Mineral oil (liquid paraffin)	100.00
10.00	6	Syncrowax	10.00
861.33	7	Petrolatum (white soft paraffin)	861.33

*Actual quantity to be calculated as per the actual potency. Difference in quantity to be adjusted by white soft paraffin.

MANUFACTURING DIRECTIONS

1. Melt item 7 at 70°C in a fat-melting vessel.
2. Add item 6 to the melt while mixing. Transfer the melt to the mixer through filters and cool to 40°C while mixing.
3. Add 60.0 g of item 5 in stainless steel container and disperse item 1 manually by using a spatula. Homogenize two times with homogenizer (gap setting 1) to make smooth dispersion and then transfer to the mixer.
4. Add 20.0 g of item 5 in a stainless steel container and disperse items 2, 4, and 3 by using homogenizer to make a smooth dispersion. Homogenize until no lumps.
5. Transfer the dispersion to the mixer. Rinse the homogenizer and stainless steel container with 20.0 g of item 5 and transfer the rinsing to the mixer.
6. Mix for 10 minutes, mixer speed 10 rpm, vacuum 0.4–0.6 bar, and set thermostat at 28°–30°C. Homogenize at high speed for 20 minutes with recirculation.
7. Mix until the temperature of the ointment reaches 28°–30°C.
8. Transfer the ointment to a stainless steel drum. Keep tightly closed.

Octyl Methoxycinnamate, Octyl Salicylate, and Oxybenzone Gel

The active ingredients in octyl methoxycinnamate, octyl salicylate, and oxybenzone gel are octyl methoxycinnamate 7.5%, octyl salicylate 4%, and oxybenzone 3%. The inactive ingredients are purified water, C12-15 alkyl benzoate, cetearyl alcohol and ceteareth-20, cetyl alcohol, glyceryl monostearate, propylene glycol, petrolatum, diazolidinyl urea, triethanolamine, disodium ethylene diamine tetraacetate, xanthan gum, acrylates/C10-30 alkyl acrylate crosspolymer, tocopheryl acetate, iodopropynyl butylcarbamate, fragrance, carbomer.

Olibanum Gum Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Gum olibanum powder	50.00
26.00	2	Emulsifying ointment	260.00
0.15	3	Methylparaben	1.50
0.15	4	Propylparaben	1.50
q.s.	5	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. The naturally occurring gum olibanum exudate in dry state is taken as it is.
2. The lumps (1 kg) are powdered in an edge runner mill for 30 minutes.
3. The powdered raw gum olibanum is passed through a 100-mesh sieve.
4. Weighed quantity of the powder is dispersed in appropriate quantity of water, along with methylparaben (0.15%).
5. Weighed quantity of emulsifying ointment is melted in another vessel, and propylparaben (0.15%) in dispersed in it (oily phase).
6. The dispersion containing gum olibanum powder and methylparaben is also heated to the same temperature as that of emulsifying ointment.
7. The aqueous dispersion containing gum olibanum powder is added to the molten emulsifying ointment, and the mixture is stirred continuously at 10,000 rpm for 1 hour using a homogenizer to obtain cream consistency.

Oxiconazole Cream and Lotion

The cream and lotion formulations contain the antifungal active compound oxiconazole nitrate. Both formulations are for topical dermatologic use only. The cream contains 10 mg oxiconazole per gram of cream in a white to off-white, opaque cream base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, and cetyl alcohol NF, with benzoic acid USP 0.2% as a preservative. The lotion contains 10 mg oxiconazole per gram of lotion in a white to off-white, opaque lotion base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, and cetyl alcohol NF, with benzoic acid USP 0.2% as a preservative.

Oxymorphone Hydrochloride Suppositories

The rectal suppository is available in a concentration of 5 mg of oxymorphone hydrochloride in a base consisting of polyethylene glycol 1000 and polyethylene glycol 3350.

Oxytetracycline Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
3.00	1	Oxytetracycline hydrochloride micronized	3.00
93.00	2	White soft paraffin	93.00
3.70	3	Liquid paraffin	3.70
0.02	4	Vitamin E oily	0.02

MANUFACTURING DIRECTIONS

1. Charge item 2 in a fat-melting vessel and heat to 75°C.
2. In a separate vessel, add and mix items 1, 3, and 4 and mix manually using a spatula.
3. Transfer step 1 to Becomix through a stainless steel mesh. Cool down to 50°C.
4. Add step 2 to step 3 and mix for 20 minutes; check for smoothness of dispersion.
5. Homogenize under 0.4–0.6 bar vacuum and cool down to 30°C.
6. Fill.

Panthenol and Chlorhexidine Lotion

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
25.00	1	D-panthenol (adjusted for potency)	26.25
2.50	2	DL-lactone pure	2.50
1.00	3	Sequestrene disodium	1.00
3.00	4	Chlorthexidine hydrochloride micropowder	3.00
5.00	5	POEG 300-stearate*	5.00
50.00	6	Paraffin oil low viscosity	50.00
5.00	7	Polydimethylsiloxane M 350	5.00
3.00	8	Perfume PCV 1155/8	3.00
—	9	Purified water q.s. to	1 L

*POEG 300 is a mixture of monoesters and diesters of polyoxyethylene glycol 300, with palmitic and stearic acids and free polyoxyethylene glycol 300.

MANUFACTURING DIRECTIONS

1. Aqueous phase: Prepare a solution of DL-lactone (previously liquefied at approximately 100°C) in water.
2. Add the DL-lactone solution to the main part of water at 70°C.
3. Incorporate the D-panthenol (previously liquefied at approximately 45°C).
4. Admix and dissolve sequestrene disodium.
5. Fatty phase: Melt at approximately 65°C under stirring POEG 300-stearate, paraffin oil, and polydimethylsiloxane M 350.
6. Emulsion: Add the fatty phase at 65°C to the aqueous phase at approximately 45°C. Cool to approximately 36°C while stirring and homogenizing.
7. Chlorhexidine suspension: Suspend chlorhexidine in water. Lotion: Add the chlorhexidine suspension to the emulsion at approximately 36°C. Stir, homogenize, and deaerate.
8. Finally, add the perfume, homogenize again, and filter.

Panthenol Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	Protegin X	50.00
18.00	2	Cetyl alcohol	18.00
12.00	3	Stearyl alcohol	12.00
40.00	4	Wax white	40.00
250.00	5	Wool fat deodorized	250.00
130.00	6	Vaseline white	130.00
50.00	7	Almond oil	50.00
150.00	8	Paraffin oil	150.00
50.00	9	D-panthenol	50.00
250.00	10	Deionized water	250.00

MANUFACTURING DIRECTIONS

1. Place wool fat, vaseline, almond oil, and paraffin in a heating vessel; heat and melt the fats together at 80°C with stirring to keep the fatty phase at this temperature until further processing.
2. In a separate container, add protegin X, cetyl alchol, stearyl alcohol, and wax white; melt these fats with stirring at 80°C. Add to above. The final temperature in the melt should be about 70°C. Keep this temperature until further processing.
3. Transfer D-panthenol into a suitable container by pouring and then rinsing it with hot deionized water 1.67 kg, continue to mix another 5 minutes, check the final weight, and make up for evaporated water.
4. Place into kettle and heat to 70°C while stirring; transfer the melted fatty mass under vacuum (−0.3 mm) through the inline sieve (mesh size 0.150 mm). After the addition, evacuate again to −0.3 atm, then stir for another 15 minutes and homogenize for 5 minutes under the same condition.
5. Cool to 30°C. (The cooling should be within 4 hours.) When this temperature is reached, continue stirring until the ointent has reached 24°–26°C; stop cooling. Then evacuate to −0.3 atm and stir for 5 minutes.
6. Transfer the ointment in a mixer and mix for 5 minutes with electric mixture. Fill the ointment.

Papain Ointment

The ointment is an enzymatic debriding-healing ointment that contains standardized papain USP (not less than 521,700 USP units per gram of ointment), urea USP 10%, and chlorophyllin copper complex sodium 0.5% in a hydrophilic base composed of purified water USP, propylene glycol USP, white petrolatum USP, stearyl alcohol NF, polyoxyl 40 stearate NF, sorbitan monostearate NF, boric acid NF, chlorobutanol (anhydrous) NF (as a preservative), and sodium borate NF. In another formulation, each gram of enzymatic debriding ointment contains papain (8.3×10^5 USP units of activity) and 100 mg urea in a hydrophilic ointment base composed of purified water, emulsifying wax, glycerin, isopropyl palmitate, potassium phosphate monobasic, fragrance, methylparaben, and propylparaben.

Penciclovir Cream

The cream contains penciclovir, an antiviral agent active against herpes viruses for topical administration as a 1% white cream. Each gram of cream contains 10 mg penciclovir and the following inactive ingredients: cetomacrogol 1000 BP cetostearyl alcohol, mineral oil, propylene glycol, purified water, and white petrolatum.

Peppermint Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
25.00	1	Sorbital stearate	25.00
15.00	2	Polysorbate 60	15.00
300.00	3	Peppermint oil	300.00
20.00	4	Cetyl alcohol	20.00
40.00	5	Stearic acid	40.00
10.00	6	Triethanolamine 99%	10.00
2.00	7	Carbopol 980	2.00
q.s.	8	Deionized water	q.s.
q.s.	9	Preservative, color	q.s.

MANUFACTURING DIRECTIONS

1. Hydrate carbopol in water 60°–65°C.
2. Add remaining water-phase ingredients.
3. Heat oil and water phases separately to 70°–75°C.
4. Add water phase to oil phase while stirring. Stir to cool, neutralizing at 65°C with triethanolamine.

Permethrin Cream and Lotion

Permethrin cream 5% is a topical scabicidal agent for the treatment of infestation with *Sarcoptes scabiei* (scabies). It is available in an off-white, vanishing cream base. The permethrin used is an approximate 1:3 mixture of the cis and trans isomers of the pyrethroid (±)-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. Permethrin has a molecular formula of $C_{21}H_{20}Cl_2O_3$. Each gram of cream 5% contains permethrin 50 mg (5%) and the inactive ingredients butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isopropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.

Each fluid ounce of lotion contains permethrin 280 mg (1%) as its active ingredient and balsam fir canada, cetyl alcohol, citric acid, FD&C yellow No. 6, fragrance, hydrolyzed animal protein, hydroxyethyl cellulose, polyoxyethylene 10 cetyl ether, propylene glycol, stearalkonium chloride, water, isopropyl alcohol 5.6 g (20%), methylparaben 56 mg (0.2%), and propylparaben 22 mg (0.08%) as its inactive ingredients.

Petrolatum and Lanolin Ointment

Active ingredients in petrolatum and lanolin ointment are petrolatum 53.4% and lanolin 15.5%. Inactive ingredients are cod liver oil (contains vitamin A and vitamin D), fragrance, light mineral oil, microcrystalline wax, and paraffin.

Phenylephrine Ointment, Cream, Suppositories, and Gel

The ointment contains petrolatum 71.9%, mineral oil 14%, shark liver oil 3%, and phenylephrine HCl 0.25%. The cream contains petrolatum 18%, glycerin 12%, shark liver oil 3%, and phenylephrine HCl 0.25%. The suppositories contain cocoa butter 85.5%, shark liver oil 3%, and phenylephrine HCl 0.25%. The cooling gel contains phenylephrine HCl 0.25% and witch hazel 50%.

Piroxicam Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Piroxican	10.00
1.00	2	Carbopol 940	10.00
30.00	3	Alcohol	300.00
30.00	4	Propylene glycol	300.00
1.50	5	Diethanolamine	15.00
0.50	6	Hydroxyethyl cellulose	5.00
0.50	7	Polyvinyl pyrrolidone K-30	5.00
q.s.	8	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. All items are blended uniformly together to produce an ointment formulation having a pH of 7.9. The carbopol is neutralized using item 5.

Piroxicam and Dexpanthenol Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.50	1	Piroxicam	5.00
25.00	2	1, 2 propylene glycol	250.00
5.00	3	Alcohol	50.00
0.40	4	Triethanolamine (approx.)	4.00
23.00	5	Lutrol F 127	230.00
46.00	6	Water purified	460.00

MANUFACTURING DIRECTIONS

1. Prepare the solution of piroxicam in propylene glycol and dexpanthenol at 70–80°C.
   a. Add ethanol and Lutrol F 127.
   b. Stir the highly viscous mixture, add 50% of the hot water (70°C).
   c. Adjust the pH with triethanolamine to about 7.
   d. Add the rest of the water, cool to room temperature when the air bubbles escape, and adjust the pH to about 8.

or 1. Dissolve piroxicam in propylene glycol, dexpanthenol, and triethanolamine.
   a. Cool the mixture of Lutrol F 127 and water to about 5°C and mix with the piroxicam solution.
   b. Add the ethanol.
   c. Maintain the cool temperature until the air bubbles escape.

Polymyxin, Bacitracin, Hydrocortisone, and Zinc Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
18.00	1	Wax	180.00
69.80	2	Petrolatum	698.00
7.50	3	Polymyxin B sulfate	75.00
0.60	4	Bacitracin	6.00
4.00	5	Zinc oxide	40.00
0.50	6	Hydrocortisone acetate	5.00

MANUFACTURING DIRECTIONS

1. Add items 1 and 2 to a melting vessel; heat to 75°C.
2. Add items 3–5 one by one and mix to dissolve.
3. Cool to 40°C and fill.

Povidone-Iodine and Lidocain Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	PVP-iodine 30/06	100.00
10.00	2	Lidocain hydrochloride	10.00
10.00	3	Sodium chloride	10.00
200.00	4	Lutrol F 127	200.00
79.00	5	Sodium hydroxide solution, 1 *M*	79.00
61.10	6	Water	61.10

MANUFACTURING DIRECTIONS

1. Dissolve items 1–3 in item 6, cool to about 6°C, dissolve item 4, and adjust the pH value (4.5–5.0) with item 5.
2. Maintain the cool temperature until the air bubbles escape. Viscosity (Brookfield, 23°C) 54,000 mPas.

Povidone-Iodine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	PVP-iodine 30/06	100.00
241.00	2	Citric acid solution 0.1 *M*	241.00
369.00	3	Na2HPO4 solution 0.2 *M*	369.00
20.00	4	Cremophor A 6	20.00
20.00	5	Cremophor A 25	20.00
100.00	6	Cetylstearyl alcohol	100.00
100.00	7	Liquid paraffin	100.00
50.00	8	Glycerol	50.00

MANUFACTURING DIRECTIONS

1. Prepare a basic cream from the emulsifying agents and the fatty substances, items 4–8.
2. Stir in the PVP-iodine dissolved in the buffer solutions made from items 2 and 3.
3. Brown cream having a pH of 4.5 is obtained.

Povidone-Iodine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	PVP-iodine 30/06	100.00
100.00	2	Liquid paraffin	100.00
100.00	3	Vaseline	100.00
50–80	4	Cetylstearyl alcohol	50–80
20.00	5	Cremophor A 6	20.00
20.00	6	Cremophor A 25	20.00
50.00	7	Propylene glycol pharma	50.00
530–560	8	Water	530–560

MANUFACTURING DIRECTIONS

This cream is suitable for veterinary mastitis treatment.

1. Dissolve PVP-iodine in the solvents, items 7 and 8.
2. Mix items 2–6 by heating, stir the solution in the previous mixture, and cool by stirring.

Povidone-Iodine Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	PVP-iodine 30/06	100.00
359.00	2	Citric acid solution, 0.1 *M*	359.00
181.00	3	$NA_2HPO_4 \cdot 12H_2O$ solution, 0.2 *M*	181.00
50.00	4	Lutrol E 400	50.00
100.00	5	Liquid paraffin	100.00
150.00	6	Lutrol F 127	150.00
70.00	7	Lutrol F 127	70.00

MANUFACTURING DIRECTIONS

1. Dissolve item 1 in a solution of items 2–4, mix with item 5, and dissolve item 6 at about 20°C.
2. Cool to 5°–8°C and dissolve item 7. Maintain cool until all air bubbles have disappeared.
3. Brown turbid gel.

Povidone-Iodine Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	PVP-iodine 30/06	100.00
10.00	2	Sodium chloride	10.00
200.00	3	Lutrol F 127	200.00
79.00	4	Sodium hydroxide solution, 1 *M*	79.00
610.00	5	Water	610.00

MANUFACTURING DIRECTIONS

1. Dissolve items 1 and 2 in item 5 and cool to about 6°C.
2. Dissolve Lutrol F 127 and item 2 and adjust the pH value with item 4.
3. Maintain cool until all air bubbles have escaped. Viscosity 61,000 mPa to· s 54,000 mPas (brookfield, 23°C). pH value (20% in water) 2.2–4.6.

Povidone-Iodine Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	PVP-iodine 30/06	100.00
600.00	2	Lutrol E 400	600.00
46.00	3	Sodium hydroxide, 1 *M* solution	46.00
4.00	4	Water	4.00
250.00	5	Lutrol E 4000	250.00

MANUFACTURING DIRECTIONS

1. Prepare solution of items 1–4, heat to about 60°C, incorporate item 6, stir very well, and cool to room temperature.
2. Transparent ointment like a gel having a pH of 4. Miscible and washable with water.

Povidone-Iodine Glucose Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
20.00	1	PVP-iodine 30/06, with excess	26.00
45.00	2	Ethanol 96%	45.00
849.00	3	Glucose	849.00
34.00	4	Lutrol E 4000	34.00
6.00	5	Glycerol	6.00
6.00	6	Water	6.00

MANUFACTURING DIRECTIONS

1. Dissolve Lutrol E 4000 in the hot mixture of glycerol and water and add the glucose warmed to 60°–80°C.
2. Incorporate solution in the obtained paste. Brown viscous and turbid paste.

Povidone-Iodine Vaginal Ovules

Bill of Materials			
Scale (mg/ovule)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	PVP-iodine 30/06 M 10	5
200.00	2	Lutrol E 400	10
170.00	3	Lutrol E 4000	85

MANUFACTURING DIRECTIONS

1. Melt the Lutrol E grades by gentle heating. Stir the micronized PVP-iodine product in small portions into the melt.
2. After a uniform suspension has been obtained, pour it into polyethylene molds. The result is a homogeneous brown-colored ovule having a weight of 2.0 g.

Bill of Materials			
Scale (mg/ovule)	**Item**	**Material Name**	**Quantity/kg (g)**
200.00	1	PVP-iodine 30/06 M 10	200.00
100.00	2	Lutrol E 400	100.00
100.00	3	Lutrol E 1500	100.00
700.00	4	Lutrol E 4000	700.00

MANUFACTURING DIRECTIONS

1. Melt the Lutrol E grades by gentle heating. Stir the micronized PVP-iodine product in small portions into the melt.
2. After a uniform suspension has been obtained, pour it into polyethylene mold. The result is a homogeneous brown-colored ovula having a weight of 2.0 g.

Pramoxine Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
150.00	1	Cetyl alcohol*	150.00
50.00	2	Cetyl esters wax*	50.00
0.72 mL	3	Water purified	720 mL
1.80	4	Methylparaben	1.80
0.20	5	Propylparaben	0.20
20.00	6	Sodium lauryl sulfate	20.00
50.00	7	Glycerin	50.00
10.00	8	Pramoxine hydrochloride	10.00

*Beeswax 75.00 mg/g can be added and adjusted with items 1 and 2.

MANUFACTURING DIRECTIONS

1. Phase A: Add the cetyl alcohol (item 1) and the cetyl esters wax (item 2) to a suitable jacketed stainless steel tank fitted with efficient agitation. Heat to 60°–65°C and mix until materials are melted and phase is uniform.
2. Preheat a suitable jacketed stainless steel batch tank to 60°–65°C. Strain phase A (step 1) into the batch tank, maintaining temperature at 60°–65°C and gentle agitation.
3. Phase B: Charge 530 mL of purified water (item 3) into a suitable jacketed stainless steel tank fitted with a high-speed mixer. Adjust the water temperature to 80°–90°C and add methylparaben (item 4) and propylparaben (item 5). Stir until dissolved, ensuring that no solids are entrained in the bottom valve. Commence cooling to 60°–65°C.
4. Add the sodium lauryl sulfate (item 6) with care and stir to dissolve.
5. Add the glycerin (item 7) and mix until uniform. *Caution: Do not create excessive foam.*
6. Cool to 60°–65°C.
7. Strain phase A and sweep mix. Rinse through with 12 mL of purified water.
8. Phase C: To a suitable jacketed stainless steel tank fitted with high-speed agitation, charge 166 mL of purified water and raise the temperature to 60°–65°C. Add the pramoxine hydrochloride (item 8) and mix until dissolved. Strain the solution via a 100 to 150-μm aperture mesh into the mass from step above. Rinse through with 12 mL of purified water. Reduce agitation rate to prevent air entrainment and commence cooling to 32°–36°C. Please note that you should maintain cooling water at 10°C below batch temperature until 45°C, switching then to full cooling.
9. Fill.

Pramoxine Hydrochloride and Zinc Acetate Lotion and Ointment

The lotion contains pramoxine hydrochloride 1% and zinc acetate 0.1% and inactive ingredients alcohol USP, camphor, citric acid, diazolidinyl urea, fragrance, glycerin, hydroxypropyl methylcellulose, methylparaben, oil of lavender, oil of rosemary, polysorbate 40, propylene glycol, propylparaben, purified water, and sodium citrate. The ointment contains active ingredients pramoxine HCl 1%, zinc oxide 12.5%, and mineral oil as well as benzyl benzoate, calcium phosphate dibasic, cocoa butter, glyceryl monooleate, glyceryl monostearate, kaolin, peruvian balsam, and polyethylene wax.

Pramoxine Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
1782.00	1	Witepsol H-15®	1782.00
18.00	2	Pramoxine hydrochloride	18.00

MANUFACTURING DIRECTIONS

1. Conventional method:
   a. In a suitable jacketed, stainless steel tank, premelt the witepsol H-15 at 35°–45°C.
   b. Transfer 200 g of premelted witepsol H-15 from step 1 into a suitable premix tank fitted with an efficient agitator. Slowly add the pramoxine and mix for 15 minutes.
   c. Run the premix through a suitable colloid mill into a jacketed stainless steel batching tank fitted with a suitable homogenizer. Maintain the temperature at 40°C.
   d. Flush the premix tank, lines, and colloid mill with 50.0 g of premelted Witepsol H-15 from step 1 into the batching tank. Homogenize the contents of the batch tank at high speed for 15 minutes.
   e. Add the balance of the premelted Witepsol H-15 from step 1 to the contents of the batching tank. Homogenize for 15 minutes, then cool with mixing to 27°–38°C.
   f. Commence batch recirculation through a 150-µm-aperture screen. Maintain until the batch is filled. Fill 1.8 g per suppository.
2. Turbo-mixer/emulsifier method:
   a. In a suitable jacketed stainless steel tank fitted with a turno mixer/emulsifier, premelt the Witepsol H-15 at 35°–45°C.
   b. After melting, adjust the mixer/emulsifier in a batching tank containing the premelted mass to maximum speed and slowly add the pramoxine and mix.
   c. Homogenize the contents of the batching tank at 38°C with mixer at high speed. Then cool to 35°–36°C, always maintaining the whole mass under agitation.
   d. Filter the mass through a 150-µm screen and maintain the blending until the batch is filled.
3. Fill 1.8 g per suppository.

Pramoxine Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
1781.00	1	Witepsol W-32®	1781.00
17.1	2	Pramoxine base	17.10
1.01	3	Pramoxine hydrochloride	1.01

MANUFACTURING DIRECTIONS

This formula is less irritating and preferred.

1. In a suitable stainless steel tank fitted with an efficient agitator, melt Witepsol W-32® (#3) at about 45°C.
2. Activate mixer and maintain temperature of 40°–50°C.
3. Weigh pramoxine base into a separate suitable stainless steel container.
4. Slowly add pramoxine hydrochloride to step 3 and premix using homomixer or similar. Take precaution to minimize spread of powder to adjacent areas.
5. Continue to mix for 15 minutes. Make certain that pramoxine hydrochloride is completely dispersed and the mixture is free of lumps.
6. Verify that witepsol W-32 from step 2 is completely melted and is below 50°C, then add the premix to it from step 5.
7. Continue mixing at least 15 minutes while maintaining temperature below 50°C.
8. Commence batch recirculation through a 150-µm-aperture stainless steel screen. Maintain until batch is filled.
9. Cool batch slowly, about 3°C per hour, until it reaches 31°C.
10. Maintain product temperature at 31°–33.5°C with constant recirculation or mixing throughout filling operation. Adjust mixing as necessary to prevent aeration of the product.

Pranoprofen Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Pranoprofen	10.00
2.00	2	Triisopropanolamine	20.00
5.00	3	Carboxyvinyl polymer solution (HIVISWAKO 104)	50.00
52.00	4	Alcohol	520.00
q.s.	5	Water purified q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. To 52 g of ethanol are added 1 g of pranoprofen and 2 g of triisopropanolamine. To the mixture are added 30 g of a 5% carboxyvinyl polymer solution and 15 g of purified water.
2. The pH of ointment thus obtained is 6.6, and the viscosity, which is measured at 20°C and 20 rpm, is 460 poises.

Prednicarbate Emollient Cream

Prednicarbate emollient cream 0.1% contains prednicarbate, a synthetic corticosteroid for topical dermatologic use. The chemical name of prednicarbate is 11(beta),17,21-trihydroxypregna-1,4-diene-3,20-dione 17-(ethyl carbonate) 21-propionate. Prednicarbate has the empirical formula $C_{27}H_{36}O_8$ and a molecular weight of 488.58. Topical corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Each gram of emollient cream 0.1% contains 1.0 mg of prednicarbate in a base consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, edetate disodium USP, lactic acid USP, and magnesium stearate DAB 9.

Prochlorperazine Suppositories

Prochlorperazine suppositories contain prochlorperazine base. Empirical formulas (and molecular weights) are prochlorperazine base—$C_{20}H_{24}ClN_3S$ (molecular weight, 373.95). Each suppository contains 2.5, 5, or 25 mg of prochlorperazine with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated coconut oil fatty acids, and hydrogenated palm kernel oil fatty acids.

Progesterone Gel

Progesterone gel is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single-use, one-piece polyethylene vaginal applicators. The carrier vehicle is an oil-in-water emulsion containing the water-swellable, but insoluble polymer, polycarbophil. The progesterone is partially soluble in both the oil and the water phases of the vehicle, with the majority of the progesterone existing as a suspension. The active ingredient, progesterone, is present in either a 4% or an 8% concentration (w/w). The chemical name for progesterone is pregn-4-ene-3,20-dione. It has an empirical formula of $C_{21}H_{30}O_2$ and a molecular weight of 314.5. Progesterone exists in two polymorphic forms. Form 1, which is the form used, exists as white orthorhombic prisms with a melting point of 127°–131°C. Each applicator delivers 1.125 grams of gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide, and purified water.

Promethazine Hydrochloride Suppositories

Each rectal suppository contains 12.5, 25, or 50 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter. Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \bullet HCl$, and its molecular weight is 320.88. Promethazine hydrochloride, a phenothiazine derivative, is designated chemically as 10 H-phenothiazine-10-ethanamine,N,N,(alpha)-trimethyl-,monohydrochloride, (±)-.

Promethazine Suppository

Each rectal suppository contains 12.5, 25, or 50 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter. Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S \bullet HCl$, and its molecular weight is 320.88. Phenergan suppositories are for rectal administration only.

Resorcinol Acne Cream

Bill of Materials

Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Polychol 10 [Laneth-10]	20.00
5.00	2	Lanolin alcohols [Super Hartolan]	5.00
55.00	3	Cetyl alcohol C90	55.00
60.00	4	Polawax	60.00
14.00	5	Sulfur	14.00
q.s.	6	Deionized water	q.s.
40.00	7	Veegum regular	40.00
20.00	8	Propylene glycol	20.00
20.00	9	Resorcinol	20.00
q.s.	10	Perfume, preservative	q.s.

MANUFACTURING DIRECTIONS

1. Hydrate Veegum in water. Add rest of water-phase ingredients and heat to 70°C.
2. Heat oil phase to 70°C. Disperse sulfur in oil phase.
3. Add oil phase to water phase while stirring. Stir to cool. Fill.

Salicylic Acid Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/100 g (g)**
150.00	1	Polawax (self-emulsifying wax)	15.00
150.00	2	PPG-2 myristyl ether propionate (CRODAMOL PMP)	15.00
50.00	3	Sorbital isostearate	5.00
35.00	4	Safflower oil, super refined	3.50
20.00	5	Avocado oil, super refined	2.00
20.00	6	Cetyl palmitate	2.00
50.00	7	Salicylic acid	5.00
1.50	8	Propylparaben	0.15
1.00	9	Butylated hydroxyl anisole	0.10
487.50	10	Deionized water	48.75
10.00	11	Sodium borate	1.00
3.00	12	Methylparaben	0.30
2.00	13	Imidazolidinyl urea	0.20
20.00	14	Hydrolyzed collagen + hyaluronic acid (CROMOIST HTA)	2.00

MANUFACTURING DIRECTIONS

1. Dissolve item 7 in item 2 with mixing and heating to 70°C.
2. Add balance of items 1–9 and mix with heat to 80°C.
3. Mix together items 10–13 separately and heat to 80°C.
4. Add this mixture to earlier mixture with mixing and cool to 40°C.
5. Add item 14 with mixing and cool to desired fill temperature.
6. Adjust pH if necessary to 3.0–4.0 with 10% triethanolamine solution.

Salicylic Acid Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
5.00	2	Stearic acid	5.00
80.00	3	Mineral oil	80.00
665.00	4	Deionized water	665.00
100.00	5	Salicylic acid	100.00

MANUFACTURING DIRECTIONS

1. Mix and heat items 1–4 to 75°C.
2. Allow to cool with gentle stirring. At 30°C add item 5; homogenize if necessary.

Salicylic Acid Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
422.00	1	Witch hazel distilled, 14% alcohol	422.00
5.00	2	Salicylic acid	5.00
5.00	3	Aloe vera gel	5.00
10.00	4	Sorbitol	10.00
500.00	5	Polyglycerylmethylacrylate	500.00
10.00	6	Propylene glycol	10.00
0.80	7	Methylparaben	0.80
0.20	8	Propylparaben	0.20

MANUFACTURING DIRECTIONS

1. Premix items 1–4. Add item 5 with low-shear mixing until homogenous.
2. Mix items 6–8 together and then add them to the formulation.

Scopolamine Transdermal Therapeutic System

The transdermal scopolamine system is a circular flat patch designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Each system contains 1.5 mg of scopolamine base. Scopolamine is (alpha)-(hydroxymethyl)benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo [3.3.1.0 2,4] non-7-yl ester. Scopolamine is a viscous liquid that has a molecular weight of 303.35 and a pKa of 7.55–7.81. The transdermal system is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing layer of tan-colored, aluminized, polyester film; a drug reservoir of scopolamine, light mineral oil, and polyisobutylene; a microporous polypropylene membrane that controls the rate of delivery of scopolamine from the system to the skin surface; and an adhesive formulation of mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, light mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not released from the system.

Selenium Sulfide Detergent Lotion

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.0	1	Selenium sulfide	10.0
2.0	2	Methyl paraben	2.0
10.0	3	Magnesium aluminum silicate type IIA	10.0
20.0	4	Titanium	20.0
0.170	5	Dye	0.170
230.0	6	Sodium alkyl ether sulfate/sulfonate	230.0
30.0	7	Surfactant cocamide DEA	30.0
40.0	8	Cocoamphocarboxyglycinate	40.0
10.0	9	Protein hydrolyzed	10.0
4.0	10	Perfume	4.0
q.s.	11	Acid citric	q.s.
q.s.	12	Sodium chloride	q.s.
q.s.	13	Water purified	q.s. to 1 L

Notes: Item 11 used for pH adjustment, if necessary. Item 12 used for viscosity adjustment, if necessary.

MANUFACTURING DIRECTIONS

1. Selenium sulfide is toxic—handle carefully and use approved respiratory protection.
2. Add selenium sulfide. Seal the mill and agitate for approximately 10 minutes to wet down the powdered material.
3. Recycle for approximately 5 minutes. Stop agitation. If necessary, add purified water (25°–30°C) to nearly cover the grinding media.
4. Seal the mill and recirculate the slurry for 1–2 hours to the required particle size specifications for the selenium sulfide.
5. Load 250 mL of purified water into a suitable jacketed mixing tank and heat to 60°–70°C. With good stirring, add and dissolve methyl paraben. Slowly add and disperse magnesium aluminum silicate. Continue mixing until fairly smooth. Stop mixing and allow hydrating for 1 hour.
6. Add and disperse titanium dioxide. Mix for 30 minutes. With good stirring, add selenium sulfide slurry and rinse the mill with purified water. Mix for 30 minutes.
7. Stop mixing and add sodium lauryl ether sulfate/sulfonate. Mix slowly for 5 minutes. Add cocamide DEA. Mix slowly for approximately 3 minutes.
8. Add cocoamphocarboxyglycinate. Mix slowly for 30 minutes.
9. Separately dissolve hydrolyzed protein (Hydro gel) in 4 mL of purified water and mix until uniform. Add solution from above to the tank and mix until uniform.
10. Add perfume and mix for 1 minute. Dissolve dye in 2 mL warm purified water (50°–60°C) and add to mixing tank. Mix until uniform. Check and record pH and adjust it to 4.5–5.0, if necessary, using citric acid.
11. Add purified water q.s. to 980 mL, mix for 30 minutes. Check and record viscosity. If necessary, adjust by adding sodium chloride.
12. Deaerate by slow stirring under vacuum or use of a suitable deaerator. Mix for 1 hour.

Selenium Sulfide Lotion

The active ingredient for selenium sulfide lotion is selenium sulfide 2.5% w/v in aqueous suspension; it also contains bentonite, lauric diethanolamide, ethylene glycol monostearate, titanium dioxide, amphoteric-2, sodium lauryl sulfate, sodium phosphate (monobasic), glyceryl monoricinoleate, citric acid, captan, and perfume.

Silicone Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
150.00	1	Polawax NF	150.00
40.00	2	Oleyl alcohol	40.00
50.00	3	PEG-75 lanolin	50.00
150.00	4	Minerat oil 70cS	150.00
50.00–100.00	5	Dimethicone	50.00–100.00
q.s.	6	Deionized water q.s. to	1 kg

MANUFACTURING DIRECTIONS

1. Heat water and oil phase separately to 60°–65°C.
2. Add water phase to oil phase while stirring. Stir to cool to 30°C. May add perfume or color as desired.

Silver Sulfadiazine Cream

Silver sulfadiazine cream 1% is a soft, white, water-miscible cream containing the antimicrobial agent silver sulfadiazine in micronized form. Each gram of cream 1% contains 10 mg micronized silver sulfadiazine. The cream vehicle consists of white petrolatum, stearyl alcohol, isopropyl myristate, sorbitan monooleate, polyoxyl 40 stearate, propylene glycol, and water, with methylparaben 0.3% as a preservative.

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
1.00	1	Silver sulfadiazine	10.00
5.00	2	Cetyl alcohol	50.00
8.00	3	Glyceryl monostearate A/S	80.00
8.00	4	Liquid paraffin	80.00
3.00	5	Tween 80	30.00
2.00	6	Tween 60	20.00
15.00	7	Propylene glycol	150.00
58.00	8	Water purified	580.00

MANUFACTURING DIRECTIONS

1. Charge items 2–6 in a fat-melting vessel, heat to 75°C, and then cool down to 60°C.
2. Charge item 8 to Becomix and heat to 90°C, cool down to 65°C.
3. Transfer step 1 into step 2, mix under vacuum; cool to 40°C.
4. In a separate vessel, add items 7 and 1 and homogenize.
5. Add to step 3 and mix. Cool to 25°C.
6. Transfer to storage vessel and fill.

Sodium Chloride Ointment

The sodium chloride ointment is a sterile ophthalmic ointment used to draw water out of the cornea of the eye. Each gram contains active ingredient sodium chloride 5% and inactives lanolin, mineral oil, white petrolatum, and purified water. Sodium chloride (e.g., about 0.9%) is used for treating cold sores and fever blisters and lesions associated with herpesvirus.

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methylparaben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
q.s.	8	Water purified q.s. to	1 kg
0.90	9	Sodium chloride	9.00

MANUFACTURING DIRECTIONS

1. Preparation of water phase:
   a. Charge purified water, Polysorbate 60, and glycerin with agitation to a melting kettle.
   b. Heat the contents to 61°–65°C.
   c. Add methylparaben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase:
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°–75°C.
3. Mixing of phases:
   a. The mixture of step 2 is transferred to step 1's kettle, with the water phase maintained under 300 mbar vacuum.
   b. Add sodium chloride and dissolve.
   c. With mixing, and keeping the temperature at 61°–65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°–65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Sodium Sulfacetamide Lotion

Each milliliter of sodium sulfacetamide lotion 10% contains 100 mg of sodium sulfacetamide in a vehicle consisting of purified water, propylene glycol, lauramide DEA and diethanolamine, polyethylene glycol 400 monolaurate, hydroxyethyl cellulose, sodium chloride, sodium metabisulfite, methylparaben, xanthan gum, EDTA, and simethicone. Sodium sulfacetamide is a sulfonamide with antibacterial activity. Chemically, sodium sulfacetamide is N′-[(4-aminophenyl)sulfonyl] -acetamide, monosodium salt, monohydrate.

Squalene Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Polyoxyethylene sorbitan monooleate	50.00
23.00	2	Cetyl alcohol	230.00
0.40	3	Cholesterol	4.00
0.20	4	Squalene	2.00
56.00	5	Water purified	560.00
10.00	6	Propylene glycol	100.00
5.00	7	L-cysteic acid	50.00
1.00 mL	8	Ethanolamine	10.00 mL

MANUFACTURING DIRECTIONS

1. Heat items 1–4 in a jacketed kettle to 70°C.
2. In a separate kettle, heat items 5–8 to 70°C.
3. Add step 1 to step 2 at 72°C slowly, with agitation.
4. Continue agitation until the mixture is congealed. The water-washable cream thus prepared consists of 5% active ingredient.

Starch Ointment

The active ingredient in starch ointment is topical starch 51%. It also contains benzyl alcohol, hydrogenated vegetable oil, and tocopheryl acetate.

Sucralafate Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
30.00	1	Sucralafate (2–10 micron)	300.00
10.00	2	Pectin	100.00
10.00	3	Gelatin	100.00
10.00	4	Carboxymethyl cellulose	100.00
60.00	5	Fractionated coconut oil	600.00

MANUFACTURING DIRECTIONS

1. Mix finely divided sucralfate thoroughly with the other ingredients also in finely divided form.
2. Add fractionated coconut oil to the resulting powder to a suitable consistency and homogenize.

Sucralafate and Hyaluronic Acid Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
30.00	1	Sucralafate (2–10 μm)	300.00
0.60	2	Hyaluronic acid	6.00
10.00	3	Pectin	100.00
10.00	4	Gelatin	100.00
4.00	5	Carboxymethyl cellulose	40.00
60.00	6	Fractionated coconut oil	600.00

MANUFACTURING DIRECTIONS

1. Mix finely divided sucralfate with the other ingredients also in finely divided form.
2. Add fractionated coconut oil to the resulting powder and homogenize.

Sucralafate Opthalmic Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.00	1	Sucralafate (micronized less than 10 μm)	20.00
0.50	2	Carbopol 934	5.00
5.00	3	Mannitol	50.00
0.01	4	Benzalkonium chloride	0.10
0.05	5	Sodium EDTA	0.50
q.s.	6	Sodium hydroxide	q.s.
q.s.	7	Water purified q.s. to	1 kg

Sulfacetamide Ointment

Sulfacetamide sodium ophthalmic solution and ointment USP 10% are sterile topical antibacterial agents for ophthalmic use. They contain sulfacetamide sodium 10% (100 mg/g). The preservative is phenylmercuric acetate (0.0008%). Inactive ingredients are white petrolatum, mineral oil, and petrolatum and lanolin alcohol.

Sulfacetamide Sodium and Prednisolone Aetate Opthalmic Ointment

The sulfacetamide sodium and prednisolone acetate ophthalmic ointment USP is a sterile topical ophthalmic ointment combining an antibacterial and a corticosteroid. Active ingredients are sulfacetamide sodium 10% and prednisolone acetate 0.2%. Inactives are phenylmercuric acetate (0.0008%), mineral oil, white petrolatum, and petrolatum and lanolin alcohol.

Sulfanilamide Suppositories

The suppositories contain sulfanilamide 15.0% in a water-miscible, nonstaining base made from lactose, propylene glycol, stearic acid, diglycol stearate, methylparaben, propylparaben, trolamine, and water, buffered with lactic acid to an acid pH of approximately 4.3. Each suppository contains sulfanilamide 1.05 g with lactose in a base made from polyethylene glycol 400, polysorbate 80, polyethylene glycol 3350, and glycerin, buffered with lactic acid to an acid pH of approximately 4.5. The suppositories have an inert, white, nonstaining covering that dissolves promptly in the vagina. The covering is composed of gelatin, glycerin, water, methylparaben, propylparaben, and coloring. Sulfanilamide is an anti-infective agent. It is p-aminobenzenesulfonamide.

Sulfathiazole Cream

The cream contains sulfathiazole (benzenesulfonamide,4-amino-N-2-thiazolyl-N1-2-thiazolylsulfanilamide) 3.42%, sulfacetamide (acetamide,N-[(4-aminophenyl)sulfonyl]-N-sulfanilylacetamide) 2.86%, and sulfabenzamide (benzamide,N-[(4-aminophenyl)sulfonyl]-N-sulfanilylbenzamide) 3.7%, compounded with cetyl alcohol 2%, cholesterol, diethylaminoethyl stearamide, glyceryl monostearate, lanolin, lecithin, methylparaben, peanut oil, phosphoric acid, propylene glycol, propylparaben, purified water, stearic acid, and urea.

Sulfur Ointment

Bill of Materials

Scale (mg/g)	Item	Material Name	Quantity/kg (g)
15.00	1	Sulfur precipitated	15.00
85.00	2	Kaolin	85.00
q.s.	3	White petroleum jelly q.s. to	1 kg
60.00	4	Isopropyl palmitate	60.00
13.00	5	Camphor	13.00
13.00	6	Methyl salicylate	13.00
20.00	7	Lanolin	20.00
50.00	8	Tribehenin	50.00
50.00	9	Ozokerite wad	50.00
35.00	10	Sorbitan oleate	35.00
15.00	11	Deionized water	15.00
4.00	12	Salicylic acid	4.00
24.00	13	Glycerin	24.00
q.s.	14	Preservative	q.s.

MANUFACTURING DIRECTIONS

1. Heat oils except sulfur and lanolin to 70°C. Disperse sulfur and kaolin in oil phase.
2. Heat water, glycerin, and salicylic acid gently. Add to oil phase while stirring. Stir to 55°C.
3. Mill to disperse sulfur.

Tacrolimus Ointment

Tacrolimus ointment contains tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Each gram of ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum, and white wax.

Terconazole Vaginal Cream

Terconazole vaginal cream 0.4% is a white to off-white, water-washable cream for intravaginal administration containing 0.4% of the antifungal agent terconazole, cis-1-[p-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water. Terconazole vaginal cream 0.8% is a white to off-white, water-washable cream for intravaginal administration containing 0.8% of the antifungal agent terconazole, cis-1-[p-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.

Terconazole Vaginal Suppositories

Terconazole vaginal suppositories are white to off-white suppositories for intravaginal administration containing 80 mg of the antifungal agent terconazole, cis-1-[p-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-isopropylpiperazine in triglycerides derived from coconut or palm kernel oil (a base of hydrogenated vegetable oils) and butylated hydroxyanisole.

Testosterone Gel

Testosterone gel is a clear, colorless hydroalcoholic gel containing 1% testosterone. It provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean, dry skin of the shoulders, upper arms, or abdomen. A daily application of 5, 7.5, or 10 g contains 50, 75, or 100 mg of testosterone, respectively, to be applied daily to the skin surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period. The active pharmacologic ingredient is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. Inactive ingredients are ethanol 68.9%, purified water, sodium hydroxide, Carbomer 940, and isopropyl myristate; these ingredients are not pharmacologically active.

Testosterone Transdermal System

The testosterone transdermal system provides continuous delivery of testosterone (the primary endogenous androgen) for 24 hours following application to intact, nonscrotal skin (e.g., back, abdomen, thighs, and upper arms). Two strengths are available that deliver *in vivo* either 2.5 or 5 mg of testosterone per day across skin of average permeability. It has a central drug delivery reservoir surrounded by a peripheral adhesive area. The 2.5-mg system has a total contact surface area of 37 cm^2 with a 7.5-cm^2 central drug delivery reservoir containing 12.2 mg testosterone USP dissolved in an alcohol-based gel. The 5-mg system has a total contact surface area of 44 cm^2 with a 15-cm^2 central drug delivery reservoir containing 24.3 mg testosterone USP dissolved in an alcohol-based gel. The delivery systems have six components. Proceeding from the top toward the surface attached to the skin, the system is composed of (1) metallized polyester/Surlyn (E.I. DuPont de Nemours Co.; ethylene-methacrylic acid copolymer)/ethylene vinyl acetate backing film with alcohol resistant ink; (2) a drug reservoir of testosterone USP, alcohol USP, glycerin USP, glycerol monooleate, methyl laurate, and purified water USP, gelled with an acrylic acid copolymer; (3) a permeable polyethylene microporous membrane; and (4) a peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system. Before opening of the system and application to the skin, the central delivery surface of the system is sealed with a peelable laminate disc (5) composed of a five-layer laminate containing polyester/polyesterurethane adhesive/aluminum foil/polyesterurethane adhesive/polyethylene. The disc is attached to and removed with the release liner (6), a silicone-coated polyester film, which is removed before the system can be used.

Testosterone Transdermal System Controlled Delivery

Testosterone transdermal system provides continuous delivery of testosterone (the primary endogenous androgen) for 24 hours following application to intact, nonscrotal skin (e.g., back, abdomen, thighs, and upper arms). Two strengths are available that deliver *in vivo* either 2.5 or 5 mg of testosterone per day across skin of average permeability. It has a central drug delivery reservoir surrounded by a peripheral adhesive area. The 2.5-mg system has a total contact surface area of 37 cm^2 with a 7.5-cm^2 central drug delivery reservoir containing 12.2 mg testosterone USP dissolved in an alcohol-based gel. The 5-mg system has a total contact surface area of 44 cm^2 with a 15-cm^2 central drug delivery reservoir containing 24.3 mg testosterone USP dissolved in an alcohol-based gel. Testosterone USP is a white or creamy white crystalline powder or crystals chemically described as 17(beta)-hydroxyandrost-4-en-3-one. The transdermal systems have six components. Proceeding from the top toward the surface attached to the skin, the system is composed of (1) metallized polyester/Surlyn (E.I. DuPont de Nemours and Co.; ethylene-methacrylic acid copolymer)/ethylene vinyl acetate backing film with alcohol resistant ink; (2) a drug reservoir of testosterone USP, alcohol USP, glycerin USP, glycerol monooleate, methyl laurate, and purified water USP, gelled with an acrylic acid copolymer; (3) a permeable polyethylene microporous membrane; and (4) a peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system. Before opening of the system and application to the skin, the central delivery surface of the system is sealed with a peelable laminate disc (5) composed of a five-layer laminate containing polyester/polyesterurethane adhesive/aluminum foil/polyesterurethane adhesive/polyethylene. The disc is attached to and removed with the release liner (6), a silicone-coated polyester film, which is removed before the system can be used.

Tetracaine Gel and Cream

Tetracaine gel's active ingredient is tetracaine HCl 2%, and it also contains ethoxydiglycol, eucalyptus oil, hydroxyethyl cellulose, maleated soybean oil, methylparaben, propylparaben, sodium lauryl sulfate, and water. The cream contains active ingredient tetracaine 2% as well as chloroxylenol, eucalyptus oil, hydrochloric acid, lauramide DEA, methylparaben, sodium borate, sodium lauryl sulfate, steareth-2, steareth-21, stearic acid, water, and white wax.

Tetracycline Hydrochloride Ointment

Bill of Materials

Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
3.00	1	Tetracycline hydrochloride micronized (10% excess)	33.00
93.00	2	Petrolatum (white soft paraffin)	930.00
3.70	3	Mineral oil (liquid paraffin)	37.00
0.02	4	Vitamin E (oily)	0.20

MANUFACTURING DIRECTIONS

1. Melt item 2 at 75°C in a fat-melting vessel.
2. In a suitable stainless steel container, disperse item 1 in items 3 and 4 manually by using a spatula.
3. Transfer 89.0–111.0 g of molten item 2 from step 1 to the mixer through stainless steel mesh. Cool down to 50°C.
4. Load tetracycline dispersion from step 2 to the mixer. Start mixer at speed 10 rpm, homogenizer high speed for 20 minutes. Check evenness and smoothness of the dispersion.
5. Transfer the remaining quantity of molten item 2 from step 1 at 50°–55°C to the mixer through stainless steel mesh while mixing and cooling at mixer speed 10 rpm, homogenizer high speed, under vacuum 0.4–0.6 bar for 30 minutes.
6. Stop homogenizer, continue mixing at 10 rpm, under vacuum 0.4–0.6 bar. Cool down to 28°C. Fill.

TGF-α Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
35.00	1	Polyethylene glycol 8000	350.00
36.70	2	Mineral oil	367.00
0.70	3	Tween 80	7.00
q.s.	4	Water purified q.s. to	1 kg
29.30	5	Hydroxypropyl methylcellulose	293.00
2.50 mg	6	TGF-α	25.00 mg

MANUFACTURING DIRECTIONS

1. Dissolve item 1 and add item 4 and heat to 80°C.
2. Add item 2 to step 1 and pass the mixture through a homogenizer until a fine emulsion is obtained.
3. Add item 5 to the emulsion in step 2 with vigorous mixing.
4. Homogenize again.
5. Sterilize the ointment at 121°C for 15 minutes in an autoclave.
6. Under sterile condition and at 4°C, transfer item 6 and mix thoroughly.
7. Sterile fill 5 g in capped ointment tube.

Therapeutic Skin Lotion

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
73.44	1	Water purified	734.40
2.50	2	Aloe vera gel	25.00
2.00	3	Walnut oil	20.00
2.00	4	Tocopherol acetate (vitamin E)	20.00
2.00	5	Glycerin	20.00
2.00	6	Stearic acid	20.00
2.00	7	1-Hexadecanol	20.00
2.00	8	Polysorbate 60	20.00
2.00	9	Apricol kernel oil	20.00
2.00	10	Jojoba oil	20.00
2.00	11	Glyceryl stearate	20.00
1.00	12	PEG-100 stearate	10.00
1.00	13	Dimethicone	10.00
1.00	14	Polyvinyl pyrrolidone	10.00
0.50	15	Hyaluronic acid	5.00
0.50	16	Fibronectin	5.00
0.50	17	Allantoin	5.00
0.50	18	Triethanolamine	5.00
0.20	19	Carbopol 934	2.00
0.20	20	Potassium chloride	2.00
0.06	21	Urea	0.60
0.03	22	Calcium phosphate	0.30

Tolnafate and Undecylanate Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
20.00	2	Hydrogenated palm/palm kernel oil PEG-6 esters	20.00
60.00	3	Mineral oil	60.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methylaraben	0.50
509.00	6	Deionized water	509.00
50.00	7	Undecylenic acid	50.00
200.00	8	Zinc undecylanate	200.00
10.00	9	Tolnafate	10.00

MANUFACTURING DIRECTIONS

1. Mix and heat items 1–7 to 75°C.
2. Allow to cool and with gentle stirring. At 30°C add items 8 and 9.
3. Homogenize if necessary.

Tretinoin and Alpha Bisabolol Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.05	1	Tretinoin	0.50
5.00	2	Lutrol E400	50.00
6.00	3	Cremophor RH400	60.00
0.04	4	Butylated hydroxytoluene	0.40
0.10	5	(-)Alpha-bisabolol natural (BASF)	1.00
70.30	6	Water purified	703.00
q.s.	7	Preservatives	q.s.
18.50	8	Lutrol F127	185.00

MANUFACTURING DIRECTIONS

1. Add solution of items 7 and 6 slowly to the clear solution of items 1–5 at about 40°C.
2. Heat to about 50°C and dissolve about 14 g of item 8 in the combined solution of step 1.
3. Cool to about 6°C and dissolve the rest of the items. Maintain cool until the air bubbles have escaped.

Tretinoin and Dexpanthenol Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00 mg	1	Tretinoin (BASF)	0.50
5.00	2	Lutrol E400	50.00
6.00	3	Cremophor RH40	60.00
40.00 mg	4	Butyl hydroxytoluene	0.40
68.40	5	Water purified	684.00
2.50	6	Dexpanthenol (BASF)	25.00
18.00	7	Lutrol F127	180.00

MANUFACTURING DIRECTIONS

1. Add items 5 and 6 slowly to the clear solution of items 1–4 at about 40°C.
2. Heat to about 50°C and dissolve about 40.00 g of item 7 in step 1.
3. Cool to about 6°C and dissolve the rest of item 7.
4. Maintain cool until the air bubbles have escaped.

Tretinoin Cream

Tretonin cream, a topical retinoid, contains tretinoin 0.025% by weight in a hydrophilic cream vehicle of stearic acid, polyolprepolymer-2, isopropyl myristate, polyoxyl 40 stearate, propylene glycol, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water. The tretinoin cream 0.02% contains the active ingredient tretinoin in a cream base. It is available at a concentration of 0.02% w/w in an oil-in-water emulsion formulation consisting of benzyl alcohol, butylated hydroxytoluene, caprylic/capric triglyceride, cetyl alcohol, edetate disodium, fragrance, methylparaben, propylparaben, purified water, stearic acid, stearyl alcohol, steareth 2, steareth 20, and xanthan gum.

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.05	1	Tretinoin (BASF)	0.50
8.00	2	Luvitol EHO	80.00
3.00	3	Cremophor A6	30.00
1.50	4	Cremophor A25	15.00
3.00	5	Glyeryl monostearate	30.00
3.00	6	Cetyl alcohol	30.00
0.50	7	Tegiloxane 100 (Goldschmidt)	5.00
0.04	8	Butyl hydroxytoluene	0.40
4.00	9	Propylene glycol	40.00
0.50	10	Preservatives	5.00
0.20	11	Perfumes	2.00
76.20	12	Water purified	762.00

MANUFACTURING DIRECTIONS

1. Separately prepare solution of items 1 and 2 and a mixture of items 3–7 by heating to about 75°C.
2. Heat mixture of items 8–12 until a clear solution is formed.
3. To the warm mixture of step 2 mix step 1 and cool by stirring.

Tretinoin Gel

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.05	1	Tretinoin (BASF)	0.50
15.00	2	Alcohol	150.00
1.00	3	Cremophor RH40	10.00
q.s.	4	Perfume	q.s.
0.04	5	Butyl hydroxytoluene	0.40
0.50	6	Carbopol 940	5.00
76.00	7	Water purified	760.00
0.70	8	Triethanolamine	7.00
6.60	9	Water purified	66.00

MANUFACTURING DIRECTIONS

1. Prepare suspension of items 6 and 7 and add solution of items 8 and 9 to the well-stirred suspension.
2. When a clear mixture is formed, add solution of items 1–5.

Tretinoin Gel Microsphere

Tretinoin gel microsphere, 0.1%, is a formulation containing 0.1% by weight tretinoin for the topical treatment of acne vulgaris. This formulation uses patented methy methacrylate/glycol dimethacrylate crosspolymer porous microspheres (Microsponge System®) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel. Other components of this formulation are purified water, carbomer 934P, glycerin, disodium EDTA, propylene glycol, sorbic acid, PPG-20 methyl glucose ether distearate, cyclomethicone and dimethicone copolyol, benzyl alcohol, trolamine, and butylated hydroxytoluene. Chemically, tretinoin is all-trans-retinoic acid, also known as (all-E)3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a member of the retinoid family of compounds and an endogenous metabolite of naturally occurring vitamin A.

Triacontanol Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.0250	1	Methylparaben	0.250
0.015	2	Propylparaben	0.15
1.00	3	Sodium lauryl sulfate	10.00
12.00	4	Propylene glycol	120.00
25.00	5	Stearyl alcohol	250.00
25.00	6	White petrolarum	250.00
37.00	7	Water purified	370.00
0.01	8	Triacontanol	0.10

MANUFACTURING DIRECTIONS

1. The stearyl alcohol and the white petrolatum are melted on a steam bath and warmed to about 75°C.
2. The other ingredients are dissolved in the purified water and are also warmed to about 75°C.
3. All ingredients are then mixed together and stirred until the mixture congeals.

Triclosan Foot Cream

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/L (g)**
30.00	1	Alcohol and ceteareth-20 [COSMOWAX EM5483]	30.00
30.00	2	Isopropyl myristate [CRODAOL IPM]	30.00
5.00	3	Cetyl esters [CRODAMOL SS]	5.00
20.00	4	Oleyl alcohol	20.00
5.00	5	Propylene glycol	5.00
5.00	6	Carbopol 980	5.00
q.s.	7	Deionized water q.s. to	1 L
300.00	8	Ethanol DEB100	300.00
2.00	9	Triclosan [Irgasan DP300]	2.00
0.50	10	Menthol	0.50
4.00	11	Triethanolamine 99 approximately to give pH 6.0–7.0	4.00

MANUFACTURING DIRECTIONS

1. Preblend ethanol, Irgasan, and menthol and warm to 50°C.
2. Heat water and oil phases separately to 70°C.
3. Add water phase to oil phase while stirring. Stir to cool, adding the preblend at 60°C; adjust pH.

Tridax Procumbens Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	*Tridax procumbens* leaf extract	50.00
3.00	2	Carbopol 934	30.00
0.15	3	Methylparaben	1.50
0.15	4	Propylparaben	1.50
q.s.	5	Monoethanol amine	q.s.
q.s.	6	Propylene glycol: water purified (50:50) to	1 kg

MANUFACTURING DIRECTIONS

1. The leaves of *Tridax procumbens* are shade dried for 48 hours at room temperature.
2. The crushed leaves (500 g) are then soaked with water (1 L) for 72 hours at room temperature.
3. Water is decanted and then concentrated to 100 mL by evaporating under vacuum at room temperature.
4. This concentrated solution is then lyophilized to obtain powder (item 1).
5. *Tridax procumbens* leaf extract is dispersed in pure propylene glycol along with propylparaben (0.15%).
6. The mixture is thoroughly agitated to get a clear solution. Carbopol 934 is dispersed in a propylene glycol and water (50:50) mixture along with methylparaben in another vessel.
7. The mixture is stirred continuously at 300 rpm for 2–3 hours.
8. *Tridax procumbens* solution is then added and stirring is continued for about 1 hour until a gel preparation is obtained.
9. The pH of this gel is adjusted to 6 using monoethanolamine.

Trolamine Salicylate Cream

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/kg (g)**
50.00	1	Glyceryl stearate	5.00
25.00	2	Cetyl alcohol	2.50
30.00	3	Cetyl phosphate and DEA cetyl phosphate	3.00
40.00	4	Stearyl stearoyl stearate	4.00
40.00	5	Coco-caprylate/caprate	4.00
40.00	6	Cetyl palmitate	4.00
5.00	7	Dimethicone	0.50
502.00	8	Deionized water	50.20
10.00	9	Propylene glycol, diazolidinyl urea, methylparaben, and propylparaben	1.00
5.50	10	Magnesium aluminum silicate	0.55
2.50	11	Xanthan gum	0.25
100.00	12	Deionized water	10.00
100.00	13	Trolamine salicylate (TEA salicylate)	10.00
50.00	14	Propylene glycol	5.00

MANUFACTURING DIRECTIONS

1. Heat items 8 and 9 to 85°C, add items 10 and 11, and mix until well dispersed.
2. Add items 1–7 and mix well at 80°–85°C; continue mixing; while cooling to 65°C, add items 12–14 and continue mixing and cooling to 35°C; pH should be 5.5–5.6.

Ultrasonic Adhesive Gel

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	Preservative (e.g., parabens)	5.00
754.00	2	Water	754.00
6.00	3	Carbopol 940 (Goodrich)	6.00
20.00	4	Sodium hydroxide solution 10%	20.00
15.00	5	Kollidon 30	15.00
200.00	6	Water	200.00

MANUFACTURING DIRECTIONS

1. Prepare solution of item 1 in item 2 by heating to 70°C, and add item 3 slowly to obtain a homogeneous suspension.
2. Add items 4–6. A clear colorless adhesive gel is obtained. Addition of sodium chloride changes consistency.

Vitamin A Suppositories

Bill of Materials			
Scale (mg/suppository)	**Item**	**Material Name**	**Quantity/1000 Suppositories (g)**
150,000 IU	1	Vitamin A palmitate 1.7 MMM IU/g	88.23 g
1.00	2	Butylhydroxytoluene	10
400.00	3	Cremophor RH 40	400
800.00	4	Lutrol E 1500	800
500.00	5	Lutrol E 4000	505

MANUFACTURING DIRECTIONS

1. Dissolve butylhydroxytoluene in the warm vitamin A, add cremophor, and mix with the molten Lutrol E grades.
2. Fill into molds of suppositories to obtain the weight of 2 g.

Vitamin A Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.20	1	Vitamin A propionate	22.00
70.00	2	Alcohol SD40-A	700.00
5.00	3	Glycolic acid	50.00
20.00	4	Propylene glycol	200.00
4.00	5	Hydroxypropyl cellulose	40.00
5.00	6	Aloe vera extract	50.00
0.10	7	Lactil	1.00

MANUFACTURING DIRECTIONS

1. Add 2.2 g vitamin A propionate to 70.0 g alcohol (SD40-A) and mix.
2. Add 5 g of glycolic acid to 20.0 g of propylene glycol and mix.
3. Add step 1 to step 2 at room temperature until the solution is homogeneous.
4. Sift in 4 g hydroxypropyl cellulose slowly over approximately 15 minutes while blending to avoid clumping.
5. While stirring, add 5.0 g extract of the aloe vera plant and 0.1 g Lactil.
6. Stir gently until cellulose is dissolved.

Vitamin C Vaginal Ointment

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
12.50	1	Vitamin C	125.00
21.80	2	White vaseline	218.00
23.00	3	Cetylstearyl aclohol	230.00
39.50	4	Liquid paraffin	395.00

MANUFACTURING DIRECTIONS

1. Charge items 2–4 in a melting tank and melt at 80°C.
2. Stir and homogenize for 20 minutes and cool.
3. At 30°C, add item 1 under vacuum and homogenize.

Vitamin E Gel-Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	Vitamin E acetate	100.00
150.00	2	Propylene glycol pharma	150.00
200.00	3	Lutrol F 127	200.00
550.00	4	Water	550.00

MANUFACTURING DIRECTIONS

1. Mix vitamin E acetate with propylene glycol and add the water. After cooling to about 6°C, dissolve Lutrol F 127 slowly in the well-stirred mixture.
2. Maintain cool until the air bubbles escape. A turbid white gel forms at temperatures between 20° and 50°C. Viscosity at 25°C is about 120,000 mPas.

Zinc Oxide and Vitamin E Cream

Bill of Materials			
Scale (g/100 g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.50	1	Zinc oxide	75.00
5.00	2	White soft paraffin	50.00
6.50	3	Cetostearyl alcohol	65.00
11.00	4	Lanolin anhydrous	110.00
2.00	5	Castor oil	20.00
12.00	6	Liquid paraffin	120.00
0.50	7	Vitamin E oily	5.00
1.04	8	Sodium lauryl sulfate	10.40
10.00	9	Propylene glycol	100.00
1.00	10	Simethicone M30	10.00
0.04	11	Lavender oil	0.40
43.20	12	Water purified	432.00

MANUFACTURING DIRECTIONS

1. Charge item 12 (two thirds) to Becomix, heat to 80°–85°C, and transfer to a stainless steel covered container.
2. Charge in a melting vessel items 2–7, one at a time, and heat to 70°C; stir to meet and maintain temperature at 70°–75°C.
3. Transfer step 2 to Becomix after passing through a stainless steel sieve while mixing.
4. Load item 12, set aside in a separate vessel, and stir to dissolve item 8, at 70°–75°C. Transfer this solution to Becomix through a stainless steel sieve.
5. Homogenize for 10 minutes under vacuum, 0.4–0.6 bar at 70°–75°C.
6. Cool down to 40°–45°C while mixing.
7. Charge balance of item 12 at 70°–75°C and items 9 and 1 in a separate vessel; mix using a stirrer, then cool down to 40°–45°C. Disperse zinc oxide in the solution while stirring and then pass dispersion twice through a homogenizer.
8. Transfer dispersion to Becomix and mix at slow speed.
9. Use item 12 to rinse vessel and add rinsings.
10. Homogenize at 35°–45°C under vacuum.
11. Add items 11 and 12 and mix again, homogenize again, and cool down to 25°–30°C.
12. Transfer to storage container and fill.

Zinc Oxide Lotion

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.00	1	Magnesium aluminum silicate	7.00
641.00	2	Water	641.00
7.00	3	Unimulse C	7.00
30.00	4	Propylene glycol	30.00
30.00	5	Eucalyptus oil	30.00
30.00	6	Lanollin oil	30.00
50.00	7	Dimethicone 350 cs	50.00
50.00	8	C12-C15 alcohols benzoate	50.00
100.00	9	Polysorbate 80	100.00
50.00	10	Zinc oixde	50.00
10.00	11	Corn starch	10.00
q.s.	12	Preservatives	q.s.

MANUFACTURING DIRECTIONS

1. Add item 1 to the water slowly, agitating with maximum shear until smooth.
2. Add item 3 and 4, mixing each time, until uniform.
3. Mix items 5–10 until uniform and mix with other portions until uniform.
4. Add item 11 and 12 and mix until smooth.

Zinc Oxide Ointment

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
120.00	1	Cetearyl alcohol, PEG-40 castor oil, and sodium cetearyl sulfate	120.00
180.00	2	Petrolatum	180.00
60.00	3	Oleayl oleate	60.00
60.00	4	Mineral oil, light	60.00
100.00	5	Zinc oxide	100.00
q.s.	6	Water q.s. to	1 kg
10.00	7	Propylene glycol, diazolidinyl urea, methylparaben, and propylparaben	10.00

MANUFACTURING DIRECTIONS

1. Mix and heat item 1–5 to 70°–75°C.
2. Mix and heat items 6 and 7 to 70°–75°C. While stirring, add this to the mixture made earlier.
3. Begin cooling, continue stirring until batch reaches 30°C and then homogenize.

Zinc Oxide Ointment with Vitamin E and Aloe

Zinc oxide ointment with vitamin E and aloe's active ingredient is zinc oxide (11.3%). Its inactive ingredients are aloe vera gel, balsan (specially purified balsam peru), beeswax, benzoic acid, dimethicone, methylparaben, mineral oil, propylparaben, purified water, sodium borate, and tocopheryl (vitamin E acetate).

Zinc Pyrithione Detergent Lotion

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
547.50	1	Deionized water	547.50
7.50	2	Hydroxyethylcellulose	7.50
347.00	3	TEA-lauryl sulfate	347.00
43.00	4	PEG-20 lanolin alcohol ether	43.00
20.00	5	Glycol stearate	20.00
15.00	6	Cocamide MEA	15.00
10.00	7	Zinc pyrithione 48%	20.00
q.s.	8	Fragrance, preservative	q.s.

MANUFACTURING DIRECTIONS

1. Add item 2 to the water and mix. In a separate vessel, combine items 3–5, heat to 80°C, and mix.
2. Cool to 50°C. Add items 6 and 7 and mix. Add this mixture to mixture of item 2.
3. Cool to 40°C and add item 8.

Zinc Undecylenate Cream

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
7.50	1	Magnesium aluminum silicate	7.50
487.50	2	Deionized water	487.50
100.00	3	Sorbitol 70%	100.00
10.00	4	Polysorbate 80	10.00
200.00	5	Zinc undecylenate	200.00
50.00	6	Caprylic acid	50.00
30.00	7	C12-C15 alcohols benzoate	30.00
15.00	8	Polysorbate 80	15.00
20.00	9	C18-C36 acid	20.00
80.00	10	Glyceryl stearate and PEG-100 stearate	80.00
q.s.	11	Preservatives	q.s.

MANUFACTURING DIRECTIONS

1. Slowly add item 1 in the water, mixing with maximum available shear until smooth.
2. Add items 2–5 in order, mixing each until uniform. Avoid incorporating air; heat while stirring to 70°–75°C.
3. Heat items 6–10 separately to 70°–75°C and add to the above mixture, mixing while cooling; fill at 45°–50°C.

Zirconium Oxide Lotion

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
15.00	1	Magnesium aluminum silicate	15.00
3.00	2	Carboxymethylcellulose sodium medium viscosity	3.00
796.50	3	Water	796.50
40.00	4	Zirconium oxide	40.00
50.00	5	Propylene glycol	50.00
80.00	6	Isopropyl alcohol	80.00
15.00	7	Benzocaine	15.00
0.50	8	Menthol	0.50
q.s.	9	Preservative	q.s.

MANUFACTURING DIRECTIONS

1. Dry blend items 1 and 2 and add them to water slowly while agitating with maximum shear until smooth.
2. Add items 4 and 5 and then items 6–9; mix.

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