HANDBOOK OF
Pharmaceutical Manufacturing Formulations

Uncompressed Solid Products

VOLUME 2

Handbook of Pharmaceutical Manufacturing Formulations

Volume Series

Sarfaraz K. Niazi

Volume 1
Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products

Volume 2
Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products

Volume 3
Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products

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Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products

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Dedication

Dedicated to the memory of
Takeru Higuchi

Preface to the Series

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

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

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

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

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

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

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

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

Preface to the Volume

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

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

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

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

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

Part II provides formulations for more than 400 pharmaceutical products. Included in part are not only the currently approved products, but also several innovative products such as small proteins, instantly liquefiable powders, and nanoparticles. Formulators are strongly urged to review the methodologies described here to serve as a reference point for their own formulations. Some combination products or dosage forms are described that are not currently approved by the FDA (i.e., not included in the *Orange Book*), and they may be in the development phase or in experimental phases. As is always the case, it is the responsibility of the manufacturer to ensure that the formulations used in the production do not violate any intellectual property or proprietary practice laws. The most effective means of establishing this is through a study of the *Orange Book*, which lists the exclusivities and unexpired patents. The patent numbers provided in the *Orange Book* should then be searched for collateral patents, the FDA Freedom of Information (FOI) database, and other literature to ensure that the intellectual or proprietary property rights are not violated.

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

The subject of powder technology is vast, with applications in many fields. The serious reader is referred to the journal *Advanced Powder Technology* (http://www.vsppub.com/journals/jn-AdvPowTec.html). Such advances as inhalation insulin in a powder form and the new science of nanoparticles opens a new phase of pharmaceutical research and development. Nanotechnology describes the ability to create new materials from building blocks the size of an atom cluster. Nanomaterials are powders and materials optimized at the nanoscale

(10^{-9} m or a billionth of a meter in size). Nanopowders consist of particles with dimensions that can be measured by x-ray crystallography to be a few hundred atoms in diameter.

The formulations are presented in this volume with a scale for each unit: per capsule or per unit dose of powder. Quantities are expressed for 1000 units. Sometimes, however, a different presentation is chosen for simplicity and clarity. It is often customary for manufacturers to scale formulae for a specific weight, such as 100 or 1000 kg to match the mixing vessel requirements. This can be done roughly by multiplying the weight of each capsule or unit powder by the quantity desired to calculate the size of the batch. The reader should be aware that the actual yield may be different because of differences in the scale and quantity due to differences in the chemical form of drugs used, excesses added, and loss of moisture during manufacturing. Further, adjustment of quantity based on potency of raw material, where pertinent, changes the quantity requirements. Most of these products are identified in this volume by a brief description before the listing of the Bill of Materials, which may not necessarily represent the commercially available dosage form; the description includes details of the commercial product.

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

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

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

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

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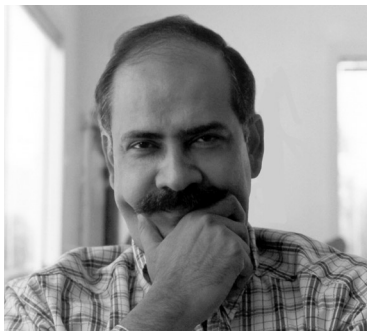

Dr. Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 30 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor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

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Regulatory and Manufacturing Guidelines

1 Global Good Manufacturing Practices Compliance

I. INTRODUCTION

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

1. 21 Code of Federal Regulations, Parts 210 and 211 (Part 210 — Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General Part 211 — Current Good Manufacturing Practice for Finished Pharmaceuticals) (http://www.fda.gov/cder/dmpq/cgmpregs.htm)
2. The World Health Organization (WHO): Quality Assurance of Pharmaceuticals: A compendium of guidelines and related materials, Volume 2, Good Manufacturing Practices and Inspection (http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html)
3. The Rules Governing Medicinal Products in the European Union: Volume 4, Good Manufacturing Practices (http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm)
4. The European Agency for the Evaluation of Medicinal Products — International Conference on Harmonisation (ICH) Guidelines (http://www.emea.eu.int/index/indexh1.htm)
5. Health Products and Food Branch Inspectorate of Canada. Good Manufacturing Practices Guidelines — (http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/gmp_guidelines_2002_tc_e.html)
6. Therapeutic Goods Administration, Government of Australia — Australian Code for Good Manufacturing Practices (http://www.health.gov.au/tga/docs/html/gmpcodau.htm)

The U.S. Food and Drug Administration (FDA) oversees the quality of drug products using a two-pronged approach including a review of information submitted in applications as well as an inspection of manufacturing facilities for conformance to requirements for current Good Manufacturing Practices (CGMPs). These two programs have served the United States well by helping to ensure the quality of drug products available. Now, as we approach the 25th anniversary of the last major revision to the drug CGMP regulations, the U.S. FDA has undertaken a program to overhaul the entire process of CGMP compliance so that:

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

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

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

- Application of biotechnology in drug discovery and manufacturing
- Advances in the science and management of quality
- Globalization of the pharmaceutical industry

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

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

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

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

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

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

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

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

The following immediate steps are planned:

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

Intermediate steps are:

- Use emerging science and data analysis to enhance compliance programs to target the highest risk areas
- Evaluate the feasibility of establishing dedicated cadres of pharmaceutical inspectors

Long-term steps are:

- Enhanced training of agency staff on new scientific approaches and innovative pharmaceutical manufacturing technology
- Develop and publish policies and procedures reflecting a science-based, risk management approach
- Educate industry on new regulatory approaches that encourage innovation

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

A. General Provisions

Section 211.1, "Scope," states that: "The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

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

B. Organization and Personnel

Section 211.22, "Responsibilities of Quality Control Unit," states that: "(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. (b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit. (c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product. (d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed."

Section 211.25, "Personnel Qualifications," states that: "(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them. (b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess. (c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product."

Section 211.28, "Personnel Responsibilities," states that: "(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination. (b) Personnel shall practice good sanitation and health habits. (c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas. (d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality

of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products."

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

C. Buildings and Facilities

Section 211.42, "Design and Construction Features," states that: "(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations. (b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination. (c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mixups as follows:

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

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use." (43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995.)

Section 211.44, "Lighting," states that: "Adequate lighting shall be provided in all areas."

Section 211.46, "Ventilation, Air Filtration, Air Heating, and Cooling," states that: "(a) Adequate ventilation shall be provided. (b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product. (c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants. (d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use."

Section 211.48, "Plumbing," states that: "(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's (EPA) Primary Drinking Water Regulations set forth in 40 CFR Part 141. Water not meeting such standards shall not be permitted in the potable water system. (b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage." (43 FR 45077, Sept. 29, 1978, as amended at 48 FR 11426, Mar. 18, 1983.)

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

Section 211.52, "Washing and Toilet Facilities," states that: "Adequate washing facilities shall be provided,

including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas."

Section 211.56, "Sanitation," states that: "(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner. (b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed. (c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135). (d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations."

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

D. Equipment

Section 211.63, "Equipment Design, Size, and Location," states that: "Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance."

Section 211.65, "Equipment Construction," states that: "(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Section 211.67, "Equipment Cleaning and Maintenance," states that: "(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

1. Assignment of responsibility for cleaning and maintaining equipment;
2. Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
3. A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
4. Removal or obliteration of previous batch identification;
5. Protection of clean equipment from contamination prior to use;
6. Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in Sections 211.180 and 211.182.

Section 211.68, "Automatic, Mechanical, and Electronic Equipment," states that: "(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained. (b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with

appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained." (43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995.)

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

E. Control of Components and Drug Product Containers and Closures

Section 211.80, "General Requirements," states that: "(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed. (b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination. (c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection. (d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected)."

Section 211.82, "Receipt and Storage of Untested Components, Drug Product Containers, and Closures," states that: "(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination. (b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of Section 211.80."

Section 211.84, "Testing and Approval or Rejection of Components, Drug Product Containers, and Closures," states that: "(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit. (b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by Section 211.170. (c) Samples shall be collected in accordance with the following procedures:

1. The containers of components selected shall be cleaned where necessary, by appropriate means.
2. The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.
3. Sterile equipment and aseptic sampling techniques shall be used when necessary.
4. If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.
5. Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.
6. Containers from which samples have been taken shall be marked to show that samples have been removed from them.

(d) Samples shall be examined and tested as follows:

1. At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.
2. Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the

manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

3. Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.
4. When appropriate, components shall be microscopically examined.
5. Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.
6. Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

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

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

Section 211.87, "Retesting of Approved Components, Drug Product Containers, and Closures," states that: "Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with Section 211.84 as necessary (e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure)."

Section 211.89, "Rejected Components, Drug Product Containers, and Closures," states that: "Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable."

Section 211.94, "Drug Product Containers and Closures," states that: "(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements. (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product. (c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. (d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures."

F. Production and Process Controls

Section 211.100, "Written Procedures; Deviations," states that: "(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit. (b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified."

Section 211.101, "Charge-In of Components," states that: "Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess: (a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient. (b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

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

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

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

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

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

Section 211.105, "Equipment Identification," states that: "(a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch. (b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code."

Section 211.110, "Sampling and Testing of In-Process Materials and Drug Products," states that: "(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

1. Tablet or capsule weight variation;
2. Disintegration time;
3. Adequacy of mixing to assure uniformity and homogeneity;
4. Dissolution time and rate;
5. Clarity, completeness, or pH of solutions.

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

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

Section 211.113, "Control of Microbiological Contamination," states that: "(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed. (b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

Section 211.115, "Reprocessing," states that: "(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics. (b) Reprocessing shall not be performed without the review and approval of the quality control unit."

G. Packaging and Labeling Controls

Section 211.122, "Materials Examination and Usage Criteria," states that: "(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product. (b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be

rejected to prevent their use in operations for which they are unsuitable. (c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected. (d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel. (e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed. (f) Use of gang printing of labeling for different drug products or different strengths, or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color. (g) If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:

1. Dedication of labeling and packaging lines to each different strength of each different drug product;
2. Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations; or
3. Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

(h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record." (43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41353, Aug. 3, 1993.)

Section 211.125, "Labeling Issuance," states that: "(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations. (b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records. (c) Procedures shall be utilized to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with Section 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with Section 211.122(g)(2). (d) All excess labeling bearing lot or control numbers shall be destroyed. (e) Returned labeling shall be maintained and stored in a manner to prevent mixups and provide proper identification. (f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed." (43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41345, Aug. 3, 1993.)

Section 211.130, "Packaging and Labeling Operations," states that: "There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features: (a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products. (b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container. (c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch. (d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record. (e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records." (43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993.)

Section 211.132, "Tamper-Resistant Packaging Requirements for Over-the-Counter (OTC) Human Drug Products," states that: "(a) *General.* The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act (the Act) to establish a uniform national requirement for tamper-resistant packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or throat lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the Act or misbranded under Section 502 of the Act, or both. (b) *Requirement for tamper-resistant package.* Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or throat lozenge product) for retail sale shall package the product in a tamper-resistant package, if this product is accessible to

the public while held for sale. A tamper-resistant package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design (e.g., an aerosol product container) or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes. For purposes of this section, the term "aerosol product" means a product which depends upon the power of a liquified or compressed gas to expel the contents from the container. A tamper-resistant package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-resistant feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.

1. For two-piece, hard gelatin capsule products subject to this requirement, a minimum of two tamper-resistant packaging features is required, unless the capsules are sealed by a tamper-resistant technology.
2. For all other products subject to this requirement, including two-piece, hard gelatin capsules that are sealed by a tamper-resistant technology, a minimum of one tamper-resistant feature is required.

(c) *Labeling.* Each retail package of an OTC drug product covered by this section, except ammonia inhalant in crushable glass ampules, aerosol products as defined in paragraph (b) of this section, or containers of compressed medical oxygen, is required to bear a statement that is prominently placed so that consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement is also required to be so placed that it will be unaffected if the tamper-resistant feature of the package is breached or missing. If the tamper-resistant feature chosen to meet the requirement in paragraph (b) of this section is one that uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say, "For your protection, this bottle has an imprinted seal around the neck." (d) *Request for exemptions from packaging and labeling requirements.* A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under Section 10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from Tamper-Resistant Rule." The petition is required to contain the following:

1. The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.
2. The reasons that the drug product's compliance with the tamper-resistant packaging or labeling requirements of this section is unnecessary or cannot be achieved.
3. A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.
4. Other information justifying an exemption.

(e) *OTC drug products subject to approved new drug applications.* Holders of approved new drug applications for OTC drug products are required under Section 314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under Section 314.70(c) of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under Section 314.70(b) of this chapter. (f) *Poison Prevention Packaging Act of 1970.* This section does not affect any requirements for "special packaging" as defined under Section 310.3(l) of this chapter and required under the Poison Prevention Packaging Act of 1970. (Approved by the Office of Management and Budget [OMB] under OMB control number 0910-0149) (54 FR 5228, Feb. 2, 1989.)

Section 211.134, "Drug Product Inspection," states that: "(a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label. (b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling. (c) Results of these examinations shall be recorded in the batch production or control records."

Section 211.137, "Expiration Dating," states that: "(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in Section 211.166.

(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in Section 211.166. (c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products. (d) Expiration dates shall appear on labeling in accordance with the requirements of Section 201.17 of this chapter. (e) Homeopathic drug products shall be exempt from the requirements of this section. (f) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section. (g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product. (h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data." (43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981; 60 FR 4091, Jan. 20, 1995.)

H. Holding and Distribution

Section 211.142, "Warehousing Procedures," states that: "Written procedures describing the warehousing of drug products shall be established and followed. They shall include: (a) Quarantine of drug products before release by the quality control unit. (b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected."

Section 211.150, "Distribution Procedures," states that: "Written procedures shall be established, and followed, describing the distribution of drug products. They shall include: (a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate. (b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary. Written procedures shall be established, and followed, describing the distribution of drug products. They shall include: (a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate. (b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary."

I. Laboratory Controls

Section 211.160, "General Requirements," states that: "(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified. (b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

1. Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
2. Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.
3. Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
4. The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

Section 211.165, "Testing and Release for Distribution," states that: "(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible. (b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms. (c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed. (d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels. (e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with Section 211.194(a)(2). (f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria."

Section 211.166, "Stability Testing," states that: "(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

1. Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;
2. Storage conditions for samples retained for testing;
3. Reliable, meaningful, and specific test methods;
4. Testing of the drug product in the same container-closure system as that in which the drug product is marketed;
5. Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined. (c) For homeopathic drug products, the requirements of this section are as follows:

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

(d) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section." (43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981.)

Section 211.167, "Special Testing Requirements," states that: "(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed. (b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed. (c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed."

Section 211.170, "Reserve Samples," states that: "(a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:

1. For an active ingredient in a drug product other than those described in paragraphs (a) (2) and

(3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

2. For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:
   i. Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or
   ii. Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.

3. For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under Section 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

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

1. For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.
2. For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:
   i. Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or
   ii. Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.
3. For an OTC drug product that is exempt for bearing an expiration date under Section 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed." (48 FR 13025, Mar. 29, 1983, as amended at 60 FR 4091, Jan. 20, 1995.)

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

Section 211.176, "Penicillin Contamination," states that: "If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in "Procedures for Detecting and Measuring Penicillin Contamination in Drugs," which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD-470), Center for Drug Evaluation and Research, Food and Drug Administration, 200 C Street S.W., Washington, D.C. 20204, or available for inspection at the Office of the Federal Register, 800 North Capitol Street N.W., Suite 700, Washington, D.C. 20408." (43 FR 45077, Sept. 29, 1978, as amended at 47 FR 9396, Mar. 5, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11577, Mar. 29, 1990.)

J. Records and Reports

Section 211.180, "General Requirements," states that: "(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under Section 211.137, 3 years after distribution of the batch. (b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under Section 211.137, 3 years after distribution of the last lot

of drug product incorporating the component or using the container, closure, or labeling. (c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph. (d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available. (e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

1. A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.
2. A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under Section 211.192 for each drug product.

(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under Sections 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration." (43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4901, Jan. 20, 1995.)

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

Section 211.184, "Component, Drug Product Container, Closure, and Labeling Records," states that: "These records shall include the following: (a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in Section 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known. (b) The results of any test or examination performed (including those performed as required by Sections 211.82(a), 211.84(d), or 211.122(a)) and the conclusions derived therefrom. (c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure. (d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with Sections 211.122(c) and 211.130(c). (e) The disposition of rejected components, drug product containers, closure, and labeling."

Section 211.186, "Master Production and Control Records," states that: "(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed. (b) Master production and control records shall include:

1. The name and strength of the product and a description of the dosage form;
2. The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;
3. A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;
4. An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be

permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;
5. A statement concerning any calculated excess of component;
6. A statement of theoretical weight or measure at appropriate phases of processing;
7. A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to Section 211.192 is required;
8. A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;
9. Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed."

Section 211.188, "Batch Production and Control Records," states that: "Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include: (a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed; (b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

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

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

Section 211.194, "Laboratory Records," states that: "(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

1. A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.
2. A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice.) The suitability of all testing methods used shall be verified under actual conditions of use. Copies may be obtained from: Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201-3301.
3. A statement of the weight or measure of sample used for each test, where appropriate.

4. A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.
5. A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
6. A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.
7. The initials or signature of the person who performs each test and the date(s) the tests were performed.
8. The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method. (c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions. (d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by Section 211.160(b)(4). (e) Complete records shall be maintained of all stability testing performed in accordance with Section 211.166. (43 FR 45077, Sept. 29, 1978, as amended at 55 FR 11577, Mar. 29, 1990.)

Section 211.196, "Distribution Records," "Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers." (Approved by the Office of Management and Budget [OMB] under control number 0910-0139) (49 FR 9865, Mar. 16, 1984)

Section 211.198, "Complaint Files," states that: "(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with Section 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with Section 310.305 of this chapter. (b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under Section 211.137, such written records shall be maintained for 3 years after distribution of the drug product.

1. The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.
2. Where an investigation under Section 211.192 is conducted, the written record shall include the findings of the investigation and followup. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with Section 211.180(c).
3. Where an investigation under Section 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination." (43 FR 45077, Sept. 29, 1978, as amended at 51 FR 24479, July 3, 1986.)

K. Returned and Salvaged Drug Products

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

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

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

2 Compliance Program Guidance Manual for FDA Staff: Drug Manufacturing Inspections

I. BACKGROUND

A primary mission of the Food and Drug Administration (FDA) is to conduct comprehensive regulatory coverage of all aspects of production and distribution of drugs and drug products to assure that such products meet the 501(a)(2)(B) requirements of the Food, Drugs and Cosmetics Act. The FDA has developed two basic strategies:

1. Evaluating through factory inspections, including the collection and analysis of associated samples, the conditions and practices under which drugs and drug products are manufactured, packed, tested, and held
2. Monitoring the quality of drugs and drug products through surveillance activities such as sampling and analyzing products in distribution

This compliance program is designed to provide guidance for implementing the first strategy. Products from production and distribution facilities covered under this program are consistently of acceptable quality if the firm is operating in a state of control. The Drug Product Surveillance Program (CP 7356.008) provides guidance for the latter strategy.

II. IMPLEMENTATION

A. Objectives

The goal of this program's activities is to minimize consumers exposure to adulterated drug products. Under this program, inspections and investigations, sample collections and analyses, and regulatory or administrative follow-up are made:

- To determine whether inspected firms are operating in compliance with applicable current Good Manufacturing Practices (CGMPs) requirements and, if not, to provide the evidence for actions to prevent adulterated products from entering the market; and, as appropriate, to remove adulterated products from the market and to take action against persons responsible as appropriate
- To provide CGMP assessment, which may be used in efficient determination of acceptability of the firm in the preapproval review of a facility for new drug applications
- To provide input to firms during inspections to improve their compliance with regulations
- To continue the FDA's unique expertise in drug manufacturing in determining the adequacy of CGMP requirements, FDA CGMP regulatory policy, and guidance documents.

B. Strategy

1. Biennial Inspection of Manufacturing Sites

Drugs and drug products are manufactured using many physical operations to bring together components, containers, and closures into a product that is released for distribution. Activities found in drug firms can be organized into systems that are sets of operations and related activities. Control of all systems helps to ensure that the firm will produce drugs that are safe, have the identity and strength, and meet the quality and purity characteristics as intended.

Biennial inspections (every 2 years) of manufacturing sites, which include repackaging, contract labs, etc., help to:

- Reduce the risk that adulterated products are reaching the marketplace
- Increase communication between the industry and the Agency
- Provide for timely evaluation of new manufacturing operations in the firm
- Provide for regular feedback from the Agency to individual firms on the continuing status of the firm's GMP compliance

This program applies to all drug manufacturing operations.

Currently, not enough FDA resources are available to audit every aspect of CGMP in every manufacturing facility during every inspection visit. Profile classes generalize inspection coverage from a small number of specific products to all the products in that class. This program

establishes a systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the firm. Reporting coverage for every profile class as defined in Field Accomplishment and Compliance Tracking System (FACTS), in each biennial inspection, provides the most broadly resource-efficient approach. Biennial updating of all profile classes will allow for CGMP acceptability determinations to be made without delays resulting from revisiting the firm. This will speed the review process, in response to compressed timeframes for application decisions and in response to provisions of the FDA Modernization Act of 1997 (FDAMA). This will allow for Preapproval Inspections/Investigations Program inspections and Postapproval Audit Inspections to focus on the specific issues related to a given application or the firm's ability to keep applications current.

The inspection is defined as audit coverage of two or more systems, with mandatory coverage of the Quality System (see the system definitions in Section II.B.3.). Inspection options include different numbers of systems to be covered depending on the purpose of the inspection. Inspecting the minimum number of systems, or more systems as deemed necessary by the regional District of the FDA, will provide the basis for an overall CGMP decision.

2. Inspection of Systems

Inspections of drug manufacturers should be made and reported using the system definitions and organization in this compliance program. Focusing on systems instead of on profile classes will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. One biennial inspection visit will result in a determination of acceptability/nonacceptability for all profile classes. Inspection coverage should be representative of all the profile classes manufactured by the firm. The efficiency will be realized because multiple visits to a firm will not be needed to cover all profile classes; delays in approval decisions will be avoided because up-to-date profile class information will be available at all times.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular system is adequate, it should be adequate for all profile classes manufactured by the firm. For example, the way a firm handles “materials” (i.e., receipt, sampling, testing, acceptance, etc.) should be the same for all profile classes. The investigator should not have to inspect the Material System for each profile class. Likewise, the Production System includes general requirements such as standard operating procedure (SOP) use, charge-in of components, equipment identification, and in-process sampling and testing, which can be evaluated through selection of example products in various profile classes. Under each system, there may be something unique for a particular profile class (e.g., under the Materials System, the production of Water for Injection USP (*U.S. Pharmacopeia*) for use in manufacturing. Selecting unique functions within a system will be at the discretion of the lead investigator). Any given inspection need not cover every system (see Section III).

Complete inspection of one system may necessitate further followup of some items within the activities of another/other system(s) to fully document the findings. However, this coverage does not constitute nor require complete coverage of these other systems.

3. A Scheme of Systems for the Manufacture of Drugs and Drug Products

A general scheme of systems for auditing the manufacture of drugs and drug products consists of the following:

1. *Quality System* — This system assures overall compliance with CGMPs and internal procedures and specifications. The system includes the quality control unit and all its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports). It includes all product defect evaluations and evaluation of returned and salvaged drug products. (See the CGMP regulation, 21 CFR 211 Subparts B, E, F, G, I, J, and K.)
2. *Facilities and Equipment System* — This system includes the measures and activities that provide an appropriate physical environment and the resources used in the production of the drugs or drug products. It includes:
   a. Buildings and facilities along with maintenance
   b. Equipment qualifications (installation and operation); equipment calibration and preventative maintenance; and cleaning and validation of cleaning processes as appropriate; process performance qualification will be evaluated as part of the inspection of the overall process validation that is done within the system where the process is employed
   c. Utilities not intended for incorporation into the product such as heating, ventilating, and air conditioning (HVAC), compressed gases, steam, and water systems. (See the CGMP regulation, 21 CFR 211 Subparts B, C, D, and J.)
3. *Materials System* — This system includes measures and activities to control finished products, components, including water or gases that are incorporated into the product, containers, and closures. It includes validation of computerized inventory control processes, drug storage,

distribution controls, and records. (See the CGMP regulation, 21 CFR 211 Subparts B, E, H, and J.)

4. *Production System* — This system includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures. (See the CGMP regulation, 21 CFR 211 Subparts B, F, and J.)
5. *Packaging and Labeling System* — This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations. (See the CGMP regulation, 21 CFR 211 Subparts B, G, and J.)
6. *Laboratory Control System* — This system includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program. (See the CGMP regulation, 21 CFR 211 Subparts B, I, J, and K.)

The overall theme in devising this scheme of systems was the subchapter structure of the CGMP regulation. Every effort was made to group whole subchapters together in a rational set of six systems that incorporates the general scheme of pharmaceutical manufacturing operations.

The organization and personnel, including appropriate qualifications and training, employed in any given system, is evaluated as part of that system's operation. Production, control, or distribution records required to be maintained by the CGMP regulation and selected for review should be included for inspection audit within the context of each of the previously described systems. Inspections of contract companies should be within the systems for which the products or services are contracted as well as their quality systems.

As this program approach is implemented, the experience gained will be reviewed to make modifications to the system definitions and organization as needed.

III. PROGRAM MANAGEMENT INSTRUCTIONS

A. Definitions

1. Surveillance Inspections

a. The Full Inspection Option

The Full Inspection Option is a surveillance or compliance inspection that is meant to provide a broad and deep evaluation of the firm's CGMP. This is done when little or no information is known about a firm's CGMP compliance (e.g., for new firms); or for firms where doubt exists about the CGMP compliance in the firm (e.g., a firm with a history of documented short-lived compliance and recidivism); or follow-up to previous regulatory actions. Based on findings of objectionable conditions (as listed in Section V) in one or more systems — a minimum of two systems must be completed — a Full Inspection may revert to the Abbreviated Inspection Option, with District concurrence (see Section III.B.1.). During the course of a Full Inspection, verification of Quality System activities may require limited coverage in other systems. The Full Inspection Option normally includes an inspection audit of at least four of the systems, one of which must be the Quality System (the system that includes the responsibility for the annual product reviews).

b. The Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance or compliance inspection that is meant to provide an efficient update evaluation of a firm's CGMP. The abbreviated inspection provides documentation for continuing a firm in a satisfactory CGMP compliance status. Generally, this is done when a firm has a record of satisfactory CGMP compliance, with no significant recall or product defect or alert incidents, or with little shift in the manufacturing profiles of the firm within the previous 2 years (see Section III.B.2.). A full inspection may revert to an abbreviated inspection based on findings of objectionable conditions as listed in Section V in one or more systems. The Abbreviated Inspection Option normally includes an inspection audit of at least two of the systems, one of which must be the Quality System (the system which includes the responsibility for the annual product reviews). The District drug program managers should ensure that the optional systems are rotated in successive abbreviated inspections. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems. Some firms participate in a limited part of the production of a drug or drug product (e.g., a contract laboratory). Such firms may employ only two of the systems defined. In these cases, the inspection of the two systems comprises inspection of the entire firm; this is considered as the Full Inspection Option.

c. Selecting Systems for Coverage

The selection of the system(s) for coverage will be made by the FDA's Regional District Office based on such factors as a given firm's specific operation, history of previous coverage, history of compliance, or other priorities determined by the District Office.

2. Compliance Inspections

Compliance inspections are inspections conducted to evaluate or verify compliance corrective actions after a regulatory action has been taken. First, the coverage given in compliance inspections must be related to the deficient areas and subjected to corrective actions.

In addition, coverage must be given to systems because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The firm is expected to address all its operations in its corrective action plan after a previously violative inspection, not just the deficiencies noted in the FDA-483 (inspectional observations). The Full Inspection Option should be used for a compliance inspection, especially if the Abbreviated Inspection Option was used during the violative inspection.

Compliance Inspections include "For Cause Inspections." For Cause Inspections are compliance inspections that are conducted to investigate a specific problem that has come to the attention of some level of the agency. The problems may be indicated in Field Alert Reports (FARs), industry complaints, recalls, indicators of defective products, etc. Coverage of these areas may be assigned under other compliance programs; however, expansion of the coverage to a GMP inspection must be reported under this program. For Cause Inspections may be assigned under this program as the need arises.

3. State of Control

A drug firm is considered to be operating in a "state of control" when it employs conditions and practices that assure compliance with the intent of Sections 501(a)(2)(B) of the Act and portions of the CGMP regulations that pertain to their systems. A firm in a state of control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity, and purity.

A firm is "out of control" if any one system is out of control. A system is out of control if the quality, identity, strength, and purity of the products resulting from that(those) system(s) cannot be adequately assured. Documented CGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See Section V, "Regulatory/Administrative Strategy," for a discussion of compliance actions based on inspection findings demonstrating out of control systems/firm.

4. Drug Process

A drug process is a related series of operations that result in the preparation of a drug or drug product. Major operations or steps in a drug process may include mixing, granulation, encapsulation, tabletting, chemical synthesis, fermentation, aseptic filling, sterilization, packing, labeling, and testing.

5. Drug Manufacturing Inspection

A Drug Manufacturing Inspection is a factory inspection in which evaluation of two or more systems, including the Quality System, is done to determine if manufacturing is occurring in a state of control.

B. Inspection Planning

The Field will conduct drug-manufacturing inspections and maintain profiles or other monitoring systems, which ensures that each drug firm receives biennial inspectional coverage, as provided for in the strategy.

The District Office is responsible for determining the depth of coverage given to each drug firm. CGMP inspectional coverage shall be sufficient to assess the state of compliance for each firm.

The frequency and depth of inspection should be determined by the statutory obligation, the firm's compliance history, the technology employed, and the characteristics of the products. When a system is inspected, the inspection of that system may be considered applicable to all products that use it. Investigators should select an adequate number and type of products to accomplish coverage of the system. Selection of products should be made so that coverage is representative of the firm's overall abilities to manufacture within CGMP requirements.

Review of new drug application/anticipated new drug application (NDA/ANDA) files may assist in selecting significant drug processes for coverage in the various systems. Significant drug processes are those that utilize all the systems in the firm very broadly and contain steps with unique or difficult manipulation in the performance of a step. Products posing special manufacturing features (e.g., low-dose products, narrow therapeutic range drugs, combination drugs, modified release products, etc.) and new products made under an approved drug application should be considered first in selecting products for coverage.

The health significance of certain CGMP deviations may be lower when the drug product involved has no major systemic effect or no dosage limitations, such as in products like calamine lotion or over-the-counter (OTC) medicated shampoos. Such products should be given inspection coverage with appropriate priority.

Inspections for this compliance program may be performed during visits to a firm when operations are being performed for other compliance programs or other investigations.

C. Profiles

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. Normally, an inspection under this

systems approach will result in the update of all profile classes.

IV. INSPECTIONAL OBSERVATIONS

A. Investigational Operations

1. General

Review and use the CGMPs for Finished Pharmaceuticals (21 CFR 210 and 211) to evaluate manufacturing processes. Use the Guides to Inspection published by the Office of Regional Operations for information on technical applications in various manufacturing systems.

The investigator should conduct inspections according to the "Strategy" section in Part II of this compliance program. Recognizing that drug firms vary greatly in size and scope, and manufacturing systems are more or less sophisticated, the approach to inspecting each firm should be carefully planned. For example, it may be more appropriate to review the Quality System thoroughly before entering production areas in some firms; in others, the Quality System review should take place concurrently with inspection of another system or systems selected for coverage. The complexity and variability necessitate a flexible inspection approach — one that not only allows the investigator to choose the inspection focus and depth appropriate for a specific firm, but also directs the performance and reporting on the inspection within a framework that will provide for a uniform level of CGMP assessment. Furthermore, this inspection approach provides for fast communication and evaluation of findings.

Inspectional Observations noting CGMP deficiencies should be related to a requirement. Requirements for the manufacture of drug products (dosage forms) are in the CGMP regulation and are amplified by policy in the Compliance Policy Guides, or case precedents. CGMP requirements apply to the manufacture of distributed prescription drug products, OTC drug products, approved products, and products not requiring approval, as well as drug products used in clinical trials. The CGMP regulations are not direct requirements for manufacture of active pharmaceutical ingredients (APIs); the regulations should not be referenced as the basis for a GMP deficiency in the manufacture of APIs, but they are guidance for CGMP in API manufacture.

Guidance documents do not establish requirements; they state examples of ways to meet requirements. Guidance documents are not to be referred to as the justification for an inspectional observation. The justification comes from the CGMPs. Current Guides to Inspection and Guidance to Industry documents provide interpretations of requirements, which may assist in the evaluation of the adequacy of CGMP systems.

Current inspectional observation policy as stated in the inspection operations manual (IOM) says that the FDA-483, when issued, should be specific and contain only significant items. For this program, inspection observations should be organized under separate captions by the systems defined in this program. List observations in order of importance within each system. Where repeated or similar observations are made, they should be consolidated under a unified observation. For those Districts utilizing Turbo EIR, a limited number of observations can be common to more than one system (e.g., organization and personnel including appropriate qualifications and training). In these instances, put the observation in the first system reported on the FDA-483 and in the text of the EIR, reference the applicability to other systems where appropriate. This should be done to accommodate the structure of Turbo EIR, which allows individual citation once per FDA-483. Refrain from using unsubstantiated conclusions. Do not use the term "inadequate" without explaining why and how. Refer to the policy in the IOM, Chapter 5, Section 512 and Field Management Directive 120 for further guidance on the content of Inspectional Observations.

Specific specialized inspectional guidance may be provided as attachments to this program, or in requests for inspection, assignments, etc.

2. Inspection Approaches

This program provides two surveillance inspectional options: Abbreviated Inspection Option and Full Inspection Option (see the definitions of the inspection options in Part II of this compliance program).

1. *Selecting the Full Inspection Option* — The Full Inspection Option will include inspection of at least four of the systems as listed in Part II "Strategy," one of which must be the Quality System.
   a. Select the Full Inspection Option for an initial FDA inspection of a facility. A full inspection may revert to the Abbreviated Inspection Option, *with District concurrence,* based on the finding of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).
   b. Select the Full Inspection Option when the firm has a history of fluctuating into and out of compliance. To determine if the firm meets this criterion, the District should utilize all information at its disposal, such as, inspection results, results of sample analyses, complaints, drug quality reporting system (DQRS) reports, recalls, etc., and the compliance actions resulting from them or from past inspections. A Full Inspection may

revert to the Abbreviated Inspection Option, *with District concurrence,* based on findings of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).

c. Evaluate if important changes have occurred by comparing current operations against the EIR for the previous full inspection. The following types of changes are typical of those that warrant the Full Inspection Option:
   - New potential for cross-contamination arising through change in process or product line
   - Use of new technology requiring new expertise, significant new equipment, or new facilities

d. A Full Inspection may also be conducted on a surveillance basis at the District's discretion.

e. The Full Inspection Option will satisfy the biennial inspection requirement.

f. Follow-up to a Warning Letter or other significant regulatory actions should require a Full Inspection Option.

2. *Selecting the Abbreviated Inspection Option* — The Abbreviated Inspection Option normally will include inspection audit of at least two systems, one of which must be the Quality System. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems.
   a. This option involves an inspection of the manufacturer to maintain surveillance over the firm's activities and to provide input to the firm on maintaining and improving the GMP level of assurance of quality of its products.
   b. A full inspection may revert to the Abbreviated Inspection Option, *with District concurrence,* based on findings of objectionable conditions as listed in Part V in one or more systems (a minimum of two systems must be completed).
   c. An abbreviated inspection is adequate for routine coverage and will satisfy the biennial inspectional requirement.

a. Comprehensive Inspection Coverage

It is not anticipated that full inspections will be conducted every 2 years. They may be conducted at less frequent intervals, perhaps at every third or fourth inspection cycle. Districts should consider selecting different optional systems for inspection coverage as a cycle of Abbreviated inspections are carried out to build comprehensive information on the firm's total manufacturing activities.

3. System Inspection Coverage

a. Quality System

Assessment of the Quality System is two-phased:

1. The first phase evaluates whether the Quality Control Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated record-keeping systems.
2. The second phase assesses the data collected to identify quality problems and may link to other major systems for inspectional coverage.

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other major systems that would warrant expansion of coverage. All areas under this system should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- *Product reviews* — at least annually; should include information from areas listed below as appropriate; batches reviewed for each product are representative of all batches manufactured; trends are identified (refer to 21 CFR 211.180(e))
- *Complaint reviews (quality and medical)* — documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- *Discrepancy and failure investigations related to manufacturing and testing* — documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- *Change control* — documented; evaluated; approved; need for revalidation assessed
- *Product improvement projects* — for marketed products
- *Reprocess/rework* — evaluation, review, and approval; impact on validation and stability
- *Returns/salvages* — assessment; investigation expanded where warranted; disposition
- *Rejects* — investigation expanded where warranted; corrective action where appropriate

- *Stability failures* — investigation expanded where warranted; need for field alerts evaluated; disposition
- Quarantine products
- *Validation* — status of required validation/revalidation (e.g., computer, manufacturing process, laboratory methods)
- Training/qualification of employees in quality control unit functions

b. Facilities and Equipment System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

1. Facilities

- Cleaning and maintenance
- Facility layout and air handling systems for prevention of cross-contamination (e.g., penicillin, beta-lactams, steroids, hormones, cytotoxics, etc.)
- Specifically designed areas for the manufacturing operations performed by the firm to prevent contamination or mix-ups
- General air handling systems
- Control system for implementing changes in the building
- Lighting, potable water, washing and toilet facilities, sewage and refuse disposal
- Sanitation of the building, use of rodenticides, fungicides, insecticides, and cleaning and sanitizing agents

2. Equipment

- Equipment installation and operational qualification where appropriate
- Adequacy of equipment design, size, and location
- Equipment surfaces should not be reactive, additive, or absorptive
- Appropriate use of equipment operations substances (lubricants, coolants, refrigerants, etc.), contacting products, containers, etc.
- Cleaning procedures and cleaning validation
- Controls to prevent contamination, particularly with any pesticides or any other toxic materials, or other drug or nondrug chemicals
- Qualification, calibration, and maintenance of storage equipment, such as refrigerators and freezers for ensuring that standards, raw materials, and reagents are stored at the proper temperatures
- Equipment qualification, calibration, and maintenance, including computer qualification/validation and security
- Control system for implementing changes in the equipment
- Equipment identification practices (where appropriate)
- Documented investigation into any unexpected discrepancy

c. Materials System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Identification of components, containers, and closures
- Inventory of components, containers, and closures
- Storage conditions
- Storage under quarantine until tested or examined and released
- Representative samples collected, tested, or examined using appropriate means
- At least one specific identity test is conducted on each lot of each component
- A visual identification is conducted on each lot of containers and closures
- Testing or validation of supplier's test results for components, containers, and closures
- Rejection of any component, container, or closure not meeting acceptance requirements

Investigate fully the firm's procedures for verification of the source of components.

- Appropriate retesting/reexamination of components, containers, and closures
- First in–first out use of components, containers, and closures

- Quarantine of rejected materials
- Water and process gas supply, design, maintenance, validation, and operation
- Containers and closures should not be additive, reactive, or absorptive to the drug product
- Control system for implementing changes in the materials handling operations
- Qualification/validation and security of computerized or automated processes
- Finished product distribution records by lot
- Documented investigation into any unexpected discrepancy

d. Production System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Control system for implementing changes in processes
- Adequate procedure and practice for charge-in of components
- Formulation/manufacturing at not less than 100%
- Identification of equipment with contents, and, where appropriate, phase of manufacturing or status
- Validation and verification of cleaning/sterilization/depyrogenation of containers and closures
- Calculation and documentation of actual yields and percentage of theoretical yields
- Contemporaneous and complete batch production documentation
- Establishing time limits for completion of phases of production
- Implementation and documentation of in-process controls, tests, and examinations (e.g., pH, adequacy of mix, weight variation, clarity)
- Justification and consistency of in-process specifications and drug product final specifications
- Prevention of objectionable microorganisms in unsterile drug products
- Adherence to preprocessing procedures (e.g., setup, line clearance, etc.)
- Equipment cleaning and use logs
- Master production and control records
- Batch production and control records
- Process validation, including validation and security of computerized or automated processes
- Change control; the need for revalidation evaluated
- Documented investigation into any unexpected discrepancy

e. Packaging and Labeling System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Acceptance operations for packaging and labeling materials
- Control system for implementing changes in packaging and labeling operations
- Adequate storage for labels and labeling, both approved and returned after issued
- Control of labels that are similar in size, shape, and color for different products
- Finished product cut labels for immediate containers that are similar in appearance without some type of 100% electronic or visual verification system or the use of dedicated lines
- Labels are not gang printed unless they are differentiated by size, shape, or color
- Control of filled unlabeled containers that are later labeled under multiple private labels
- Adequate packaging records that will include specimens of all labels used
- Control of issuance of labeling, examination of issued labels, and reconciliation of used labels
- Examination of the labeled finished product
- Adequate inspection (proofing) of incoming labeling
- Use of lot numbers and the destruction of excess labeling bearing lot/control numbers
- Physical/spatial separation between different labeling and packaging lines
- Monitoring of printing devices associated with manufacturing lines

- Line clearance, inspection, and documentation
- Adequate expiration dates on the label
- Conformance to tamper-evident packaging (TEP) requirements (see 21CFR 211.132 and Compliance Policy Guide, 7132a.17)
- Validation of packaging and labeling operations, including validation and security of computerized processes
- Documented investigation into any unexpected discrepancy

f. Laboratory Control System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Adequacy of staffing for laboratory operations
- Adequacy of equipment and facility for intended use
- Calibration and maintenance programs for analytical instruments and equipment
- Validation and security of computerized or automated processes
- Reference standards: source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate
- System suitability checks on chromatographic systems [e.g., gas chromatography (GC) or high pressure liquid chromatography (HPLC)]
- Specifications, standards, and representative sampling plans
- Adherence to the written methods of analysis
- Validation/verification of analytical methods
- Control system for implementing changes in laboratory operations
- Required testing is performed on the correct samples
- Documented investigation into any unexpected discrepancy
- Complete analytical records from all tests and summaries of results
- Quality and retention of raw data (e.g., chromatograms and spectra)
- Correlation of result summaries to raw data; presence of unused data
- Adherence to an adequate Out of Specification (OOS) procedure that includes timely completion of the investigation
- Adequate reserve samples; documentation of reserve sample examination
- Stability testing program, including demonstration of stability indicating capability of the test methods

4. Sampling

Samples of defective product constitute persuasive evidence that significant CGMP problems exist. Physical samples may be an integral part of a CGMP inspection where control deficiencies are observed. Physical samples should be correlated with observed control deficiencies. Consider consulting your servicing laboratory for guidance on quantity and type of samples (in-process or finished) to be collected. Documentary samples may be submitted when the documentation illustrates the deficiencies better than a physical sample. Districts may elect to collect, but not analyze, physical samples or to collect documentary samples to document CGMP deficiencies. Physical sample analysis is not necessary to document CGMP deficiencies.

When a large number of products have been produced under deficient controls, collect physical or documentary samples of products that have the greatest therapeutic significance, narrow range of toxicity, or low dosage strength. Include samples of products of minimal therapeutic significance only when they illustrate highly significant CGMP deficiencies.

5. Inspection Teams

An inspection team (see IOM 502.4) composed of experts from within the District, other Districts, or Headquarters is encouraged when it provides needed expertise and experience. Contact the ORO/Division of Field Investigations if technical assistance is needed (see also FMD 142). Participation of an analyst (chemist or microbiologist) on an inspection team is also encouraged, especially where laboratory issues are extensive or complex. Contact your Drug Servicing Laboratory or ORO/Division of Field Science.

6. Reporting

The investigator utilizes Subchapter 590 of the IOM for guidance in reporting of inspectional findings. The Summary of Findings should identify systems covered. The body of the report should identify and explain the rationale for inspecting the profile classes covered. Any adverse findings by systems under separate captions should be reported and discussed in full. Additional information should be provided as needed or desired, for example, a

description of any significant changes that have occurred since previous inspections.

Reports with specific, specialized information required should be prepared as instructed within the individual assignment/attachment.

V. ANALYTICAL OBSERVATIONS

A. Analyzing Laboratories

1. Routine chemical analyses — all Servicing Laboratories except WEAC.
2. Sterility testing:
   Region Examining Laboratory
3. Other microbiological examinations — NRL (for the CE Region), SRL, SAN, and DEN; Salmonella Serotyping Lab — ARL.
4. Chemical cross-contamination analyses by mass spectrometry (MS) — NRL, SRL, DEN, PRL/NW, and PHI. Non-mass-spectrometry laboratories should call one of their own regional MS-capable laboratories or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.
5. Chemical cross-contamination analyses by nuclear magnetic resonance (NMR) spectroscopy — NRL. Non-NMR laboratories should call one of their own regional labs equipped with NMR or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.
6. Dissolution testing — NRL, KAN, SRL, SJN, DET, PHI, DEN, PRL/SW, and PRL-NW. Districts without dissolution testing capability should use one of their own regional labs for dissolution testing. Otherwise, call DFS.
7. Antibiotic analyses:
   ORA Examining Laboratory
   Denver District Lab (HFR-SW260)
   Tetracyclines
   Erythromycins
   Northeast Regional Lab (HFR-NE500)
   Penicillins
   Cephalosporins
   CDER Examining Laboratory
   Office of Testing and Research
   Division of Pharmaceutical Analysis (HFD-473)
   All other antibiotics
8. Bioassays — Division of Testing and Applied Analytical Research, Drug Bioanalysis Branch (HFN-471).
9. Particulate Matter in Injectables — NRL, SRL.
10. Pyrogen/LAL Testing — SRL.

B. Analysis

1. Samples must be examined for compliance with applicable specifications as they relate to deficiencies noted during the inspection. The official method should be used for check analyses or, when no official method exists, by other validated procedures.
2. The presence of cross-contamination must be confirmed by a second method. Spectroscopic methods, such as MS, NMR, ultraviolet (UV)-Visible, or infrared (IR) are preferred. A second confirmatory method should be employed by different mechanisms than the initial analysis (i.e., ion-pairing vs. conventional reverse phase HPLC).
3. Check Analysis for dissolution rate must be performed by a second dissolution-testing laboratory.
4. Sterility testing methods should be based on current editions of USP and the *Sterility Analytical Manual*. Other microbiological examinations should be based on appropriate sections of USP and BAM.

VI. REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative, or judicial actions.

When the management of the firm is unwilling or unable to provide adequate corrective actions in an appropriate time frame, formal agency regulatory actions will be recommended that are designed to meet the situation encountered.

When deciding the type of action to recommend, the initial decision should be based on the seriousness of the problem and the most effective way to protect consumers. Outstanding instructions in the *Regulatory Procedures Manual* (*RPM*) should be followed.

The endorsement to the inspection report should point out the actions that have been taken or will be taken and when. All deficiencies noted in inspections/audits under this program must be addressed by stating the firm's corrective actions, accomplished or projected, for each as established in the discussion with management at the close of the inspection.

All corrective action approaches in domestic firms are monitored and managed by the District Offices. The approaches may range from shutdown of operations, recall of products, conducting testing programs, development of new procedures, modifications of plants and equipment,

to simple immediate corrections of conditions. CDER/DMPQ/CMGB/HFD-325 will assist District Offices as requested.

An inspection report that documents that one or more systems is/are out of control should be classified as OAI. District Offices may issue Warning Letters per RPM to warn firms of violations, to solicit voluntary corrections, and to provide for the initial phase of formal agency regulatory actions.

Issuance of a Warning Letter or taking other regulatory actions pursuant to a surveillance inspection (other than a For Cause Inspection) should result in the classification of all profile classes as unacceptable. Also, the inspection findings will be used as the basis for updating profile classes in FACTS.

The FDA laboratory tests that demonstrate the effects of absent or inadequate CGMPs are strong evidence for supporting regulatory actions. Such evidence development should be considered as an inspection progresses and deficiencies are found; however, the lack of violative physical samples is *not* a barrier to pursuing regulatory or administrative action, provided that CGMP deficiencies have been well documented. Likewise, physical samples found to be in compliance are *not* a barrier to pursuing action under CGMP charges.

Evidence to support significant deficiencies or a trend of deficiencies within a system covered could demonstrate the failure of a system and should result in consideration of the issuance of a Warning Letter or other regulatory action by the District. When deciding the type of action to recommend, the initial decision should be based on the seriousness or the frequency of the problem. Examples include the following:

Quality System

1. Pattern of failure to review/approve procedures
2. Pattern of failure to document execution of operations as required
3. Pattern of failure to review documentation
4. Pattern of failure to conduct investigations and resolve discrepancies/failures/deviations/complaints
5. Pattern of failure to assess other systems to assure compliance with GMP and SOPs

Facilities and Equipment

1. Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals, or a reasonable potential for contamination, with demonstrated avenues of contamination, such as airborne or through unclean equipment
2. Pattern of failure to validate cleaning procedures for non-dedicated equipment; lack of demonstration of effectiveness of cleaning for dedicated equipment
3. Pattern of failure to document investigation of discrepancies
4. Pattern of failure to establish/follow a control system for implementing changes in the equipment
5. Pattern of failure to qualify equipment, including computers

Materials System

1. Release of materials for use or distribution that do not conform to established specifications
2. Pattern of failure to conduct one specific identity test for components
3. Pattern of failure to document investigation of discrepancies
4. Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations
5. Lack of validation of water systems as required depending upon the intended use of the water
6. Lack of validation of computerized processes

Production System

1. Pattern of failure to establish/follow a control system for implementing changes in the production system operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of process validation
4. Lack of validation of computerized processes
5. Pattern of incomplete or missing batch production records
6. Pattern of nonconformance to established in-process controls, tests, and specifications

Packaging and Labeling

1. Pattern of failure to establish/follow a control system for implementing changes in the packaging or labeling operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of validation of computerized processes
4. Lack of control of packaging and labeling operations that may introduce a potential for mislabeling
5. Lack of packaging validation

Laboratory Control System

1. Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of validation of computerized and/or automated processes
4. Pattern of inadequate sampling practices
5. Lack of validated analytical methods
6. Pattern of failure to follow approved analytical procedures
7. Pattern of failure to follow an adequate OOS procedure
8. Pattern of failure to retain raw data
9. Lack of stability indicating methods
10. Pattern of failure to follow stability programs

Follow-up to a Warning Letter or other significant regulatory action because of an abbreviated inspection should warrant full inspection coverage as defined in this program.

3 Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification

I. INTRODUCTION

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

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

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

II. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability (http://www.fda.gov/cder/guidance/P116_4107#P116_4107). According to the BCS, drug substances are classified as follows:

Class 1: High Solubility — High Permeability
Class 2: Low Solubility — High Permeability
Class 3: High Solubility — Low Permeability
Class 4: Low Solubility — Low Permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers.

Observed *in vivo* differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution *in vivo*.[2] When the *in vivo* dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, however, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution or gastrointestinal transit time. Under such circumstances, demonstration of *in vivo* BA or BE may not be necessary for drug products containing Class 1 drug substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods (21 CFR 320.22(e)). The recommended methods for determining solubility, permeability, and *in vitro* dissolution are discussed next.

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1–7.5. The volume estimate of 250 ml is derived from typical BE study

protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

B. Permeability

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

C. Dissolution

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

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

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

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

A. Determining Drug Substance Solubility Class

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

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

B. Determining Drug Substance Permeability Class

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

1. Pharmacokinetic Studies in Humans

a. Mass Balance Studies

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

b. Absolute Bioavailability Studies

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

2. Intestinal Permeability Methods

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

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

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

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

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

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

For demonstration of suitability of a method, model drugs should represent a range of low (e.g., <50%),

moderate (e.g., 50–89%), and high (>90%) absorption. Sponsors may select compounds from the list of drugs and chemicals provided in Attachment A of this chapter, or they may choose to select other drugs for which there is information available on mechanism of absorption and reliable estimates of the extent of drug absorption in humans.

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

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

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the gastrointestinal fluid before intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human or animal gastrointestinal tract either *in vivo* or *in situ*. Documenting the fact that drug loss from the gastrointestinal tract arises from intestinal membrane permeation, instead of a degradation process, will help establish permeability. Stability in the gastrointestinal tract may be documented using gastric and intestinal fluids obtained from human subjects. Drug solutions in these fluids should be incubated at 37°C for a period that is representative of *in vivo* drug contact with these fluids (e.g., 1 hour in gastric fluid and 3 hours in intestinal fluid). Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (>5%) of a drug in this protocol could suggest potential instability. Obtaining gastrointestinal fluids from human subjects requires intubation and may be difficult in some cases. Use of gastrointestinal fluids from suitable animal models or simulated fluids such as Gastric and Intestinal Fluids USP can be substituted when properly justified.

C. Determining Drug Product Dissolution Characteristics and Dissolution Profile Similarity

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

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

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

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

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

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

$$f_2 = 50 \times \log \{[1+(1/n)_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

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

IV. ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

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

A. Excipients

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

B. Prodrugs

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

C. Exceptions

BCS-based biowaivers are not applicable for the following.

1. Narrow Therapeutic Range Drugs

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

2. Products Designed to Be Absorbed in the Oral Cavity

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

V. REGULATORY APPLICATIONS OF THE BCS

A. INDs/NDAs

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

Once the *in vivo* BA of a formulation is established during the IND period, waivers of subsequent *in vivo* BE studies, following major changes in components, composition, or method of manufacture (e.g., similar to SUPAC-IR Level 3 changes [http://www.fda.gov/cder/guid-

ance/P239_26745#P239_26745]), may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar *in vitro* dissolution profiles (see Sections II and III). This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and postchange are *pharmaceutical equivalents* (under the definition at 21 CFR 320.1 (c)). BCS-based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or other pharmacokinetic studies.

B. ANDAs

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

C. Postapproval Changes

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

VI. DATA TO SUPPORT A REQUEST FOR BIOWAIVERS

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

A. Data Supporting High Solubility

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

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

B. Data Supporting High Permeability

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

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

C. Data Supporting Rapid and Similar Dissolution

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

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

D. Additional Information

The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation vs. direct compression). A list of excipients used, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms.

REFERENCES

1. This guidance has been prepared by the Biopharmaceutics Classification System Working Group of the Biopharmaceutics Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the FDA (http://www.fda.gov/cder/guidance/P103_1926#P103_1926). This guidance represents the Agency's current thinking on the topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes, regulations, or both.
2. Amidon, G. L., H. Lennernäs, V. P. Shah, and J. R. Crison, A Theoretical Basis for a Biopharmaceutics Drug Classification: The Correlation of *in vitro* Drug Product Dissolution and *in vivo* Bioavailability, *Pharmaceutical Research*, 12: 413–420 (1995).
3. See the FDA guidance for industry on *Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987), posted at http://www.fda.gov/guidance/index.htm or http://www.fda.gov/cder/guidance/P147_9605#P147_9605.
4. See the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997), http://www.fda.gov/cder/guidance/P192_20128#P192_20128.
5. This guidance uses the term *narrow therapeutic range* instead of *narrow therapeutic index*, although the latter is more commonly used, http://www.fda.gov/cder/guidance/P223_24902#P223_24902.
6. See the FDA guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes* (November 1995), http://www.fda.gov/cder/guidance/P239_26746#P239_26746.

APPENDIX A

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

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

4 Guidelines on Formulating Uncompressed Solids

I. RELATIVE HUMIDITY

Relative humidity in the filling and storage areas is more important for powders than for other dosage forms because of the large specific surface area (area/weight), which can result in significant moisture uptake. The gelatin capsule shells are also susceptible to moisture and degradation at high moisture. In addition, at very low moisture, gelatin in capsules can become very brittle; therefore, an appropriate humidity level must be maintained.

II. SURFACE AREA

The large surface area of powders provides greater opportunity for the production of static electricity during the friction of flow and handling. Make sure all equipment is well grounded or else significant segregation and impeded flow of powder can result. Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be described completely by a single parameter; however, when either nonuniform size distribution or anisometric shapes exist, any single parameter is incapable of totally defining the powder. In addition to a value for the average particle size, often we use frequency histograms to help describe the powder. We also use other measures of powder characteristics such as angle of repose and bulk or tap density. Lastly, we use compressibility and the powder's ability to undergo plastic deformation.

III. SIEVE ANALYSIS

Dry sieving allows the fractionation of relatively coarse powders and granules. Sieves are stacked (*nested*) with the largest apertures at the top and the smallest at the bottom. A sample of powder is placed on the top sieve and shaken for a fixed time period at a given amplitude and pulse frequency.

The weight of powder on each sieve can then be calculated and the particle size distribution obtained. Particles must have a two-dimensional profile smaller than the sieve aperture in order to pass through a particular sieve. A *mean sieved diameter* is calculated. Because the weight of particles on each sieve is determined, the mean sieved diameter represents a *mass distribution.*

A mesh number denotes the size of the apertures in each sieve. The mesh number is the number of wire strands (of constant diameter) per inch used to weave the square mesh pattern. The side length of the aperture in microns is inversely related to the mesh number.

Whereas the specifications of starting materials are specified, the powders often form aggregates during storage; a point of use check of aggregation is needed. It is a good idea to sift all ingredients through specified sieves prior to adding them to mixing of blending vessels. For most raw materials, sifting through a No. 60 sieve (250 μm) is desirable; however, passing materials through finer sieves can generate electrostatic charges. Wet mass is passed through a No. 8 (2.38 mm) sieve and dried granules are passed through a No. 16 (1.19 mm) mesh sieve. Lubricants should be sieved through No. 60 mesh, except for magnesium stearate, which should not be shifted through an opening smaller than the opening in a No. 35 mesh. This is necessary to avoid building up electrical charges. A conversion chart for sieve sizes from U.S. Mesh to inches and microns (or millimeters) is presented next.

U.S. Mesh	Inches	Microns	Millimeters
3	0.2650	6730	6.730
4	0.1870	4760	4.760
5	0.1570	4000	4.000
6	0.1320	3360	3.360
7	0.1110	2830	2.830
8	0.0937	2380	2.380
10	0.0787	2000	2.000
12	0.0661	1680	1.680
14	0.0555	1410	1.410
16	0.0469	1190	1.190
18	0.0394	1000	1.000
20	0.0331	841	0.841
25	0.0280	707	0.707
30	0.0232	595	0.595
35	0.0197	500	0.500
40	0.0165	400	0.400
45	0.0138	354	0.354
50	0.0117	297	0.297
60	0.0098	250	0.250
70	0.0083	210	0.210
80	0.0070	177	0.177
100	0.0059	149	0.149
120	0.0049	125	0.125
140	0.0041	105	0.105
170	0.0035	88	0.088
200	0.0029	74	0.074
230	0.0024	63	0.063
270	0.0021	53	0.053
325	0.0017	44	0.044
400	0.0015	37	0.037

IV. PARTICLE SIZE DISTRIBUTION

Sieving is a common method for establishing the distribution of particle size in a powder sample. It is a simple method that works well for powders in the size ranges used most often in the pharmaceutical industry. Sieves are limited in that they cannot be made with very small openings. The current lower limit is 43 μm, which corresponds to a No. 325 sieve. The sieve number or mesh number refers to the number of openings per linear inch. You can easily calculate the opening size in millimeters. For example, a No. 2 sieve has an opening of 9.52 mm, while a No. 200 sieve has an opening of 0.074 mm.

A frequency histogram is a useful tool in understanding the nature of a sample of powder. It is a bar graph with the size range on the x-axis and the number or weight of each segment of the powder on the y-axis. The particle size distribution can be determined by a sample of coarse powder using a nest of sieves shaken in a sonic sifter:

1. Using at least a three-decimal-place electronic balance, record the weight of each empty sieve and the collection pan. Also record the sieve size.
2. Arrange the sieves in a sequential nest: smallest mesh number (largest aperture) at the top, largest mesh number (smallest aperture) at the bottom. Add the collection pan to the bottom of the nest.
3. Add approximately 5 g of accurately weighed coarse powder to the top sieve, and cover with the rubber cap.
4. Shake the sample for 5 min with a sieve "amplitude" greater than 3.
5. Reweigh each sieve and the collection pan. Calculate the weight and percentage of powder on each sieve and in the collection pan. Then calculate the cumulative weight percentage of powder that is finer than the aperture.
6. Use the probability paper to calculate the mean diameter and standard deviation; alternately, calculate the geometric mean and standard deviation for the coarse and fine powder particles.

V. POWDER FLOW PROPERTIES

During many pharmaceutical production processes, it is necessary to transfer large quantities of powder from one location to another in a controlled manner, for example, in powder blending, powder filling into containers (e.g., dusting powders), powder flow into capsules, and powder filling into the dies of a tablet press.

One method of assessing flow properties is the *Angle of repose*, which is another measure of the nature of the powder. It estimates the adhesive force between the particles. Uniform glass beads, which will show good flow properties, have an angle of repose of 23°. As the adhesive force between the particles increases, the angle increases. In rare cases, it can exceed 90°.

Powder is allowed to flow freely through a funnel onto the center of an upturned petri dish of known radius. When the powder reaches the side of the petri dish, the height of the cylindrical cone is determined. From the petri dish radius (r, cm) and cone height (h, cm), the angle of repose (between the petri dish and base of the powder cone) can be calculated. *Flow rate* can also be determined by measuring how fast a powder flows through an aperture. Free-flowing powders exhibit a high flow rate and a smaller angle of repose. Angle of repose and flow rate depend on particle size, shape, and surface roughness. Flow properties are frequently enhanced by the use of *glidants.*

Several commercial instruments are available to evaluate angle of repose. Follow the instructions from the supplier of instrument and test methods. A simple method is given here:

1. Measure the external diameter of a petri dish; position the bottom of a funnel or paper cone about 5 to 15 cm above the center of the upturned petri dish using a ring stand. Be sure a piece of paper is under the petri dish so you can pick up the powder and reuse the powder for all your replicates.
2. Slowly pour the *coarse powder* sample into the funnel, tapping the funnel as necessary to ensure that powder flows through the hole.
3. Continue this process until the bottom of the powder pile just begins to fall over the edge of the petri dish.
4. Measure the height of the pile using a ruler.
5. If the powder is lumpy, sieve it before beginning the experiment.
6. Repeat Step 2 until you consistently obtain the same answer.
7. Calculate the mean height of the coarse powder pile and the mean angle of repose (ϕ).

Note: Remember that Tan ϕ = Opposite/Adjacent, therefore, Tan ϕ = 2 h/D.

8. Repeat Steps 2 and 3 using both *fine powder* and *fine powder with glidant,* if the purpose is to select an appropriate glidant.
9. Plot angle of repose (x-axis) against Carr's index (y-axis).

VI. REAL, TAPPED, AND BULK DENSITY

Bulk or *tapped density* is a measure of the degree of packing or, conversely, the amount of space between the particles in the powder. Bulk density is determined by placing a sample of powder of known weight in a graduated cylinder. Tap density is determined by tapping the powder in the graduate until it no longer settles.

Many methods are also used to determine the true density of the powder (e.g., helium pycnometer or gas adsorption). Dividing the true density by the bulk or tap density yields a number that is related to the amount of space in the powder. If the particles are a sphere, the value is about 0.53, while irregular shaped particles can have values of 0.74 or more.

The *real density* of a powder sample is the weight per unit volume of the material with no air spaces between particles. Therefore, if a material has a true density of 1 g/cm^3, 100 g of material will occupy 100 ml, assuming individual particles fit together exactly. In practice, most powders do not fit together very well. Therefore, if one fills a graduated cylinder to 100 ml with a powder, the weight of powder required may only be 70 g. This apparent density is known as the *bulk* or *expanded density* (0.7 g/cm^3). If the100 ml cylinder is subsequently tapped, the particles slide past each other and become consolidated. The 70 g of particles that once occupied 100 ml may now only occupy 80 ml. They have an apparent *packed* or *tapped* density (g/cm^3) of 0.875 g/cm^3. Carr's index is a measure of interparticulate forces. If the interparticulate forces are high, powders will have a low bulk density because bridging will occur between particles. This results in a large Carr's index and a large change in volume caused by tapping. If the interparticulate forces are low, particles will have little affinity for one another and will compact spontaneously. Under these circumstances, Carr's index is small and little change in apparent density is induced by tapping. Porosity is the volume ratio occupied by air spaces (voids) between particles of a powder sample.

VII. SOLID HANDLING

A sample of powder is the most complex physical system. No two particles are identical. The properties of the powder are dependent on both the chemical and physical nature of the component and the nature of the interactions between the particles in the powder.

The ability of a powder to pack is dependent on the shape, size, and porosity of the particle.

VIII. MIXING OF POWDERS

Three primary mechanisms are responsible for mixing:

1. Convective movement of relatively large portions of the powder
2. Shear failure, which primarily reduces the scale of segregation
3. Diffusive movement of individual particles

Large-scale mixers
- Rotating shell
- Fixed shell
- Vertical impeller
- Fluid bed

Small-scale mixing
- Mortar and pestle
- Spatula and surface
- Paper bag

Extemporaneous techniques for mixing
- Geometric dilution
- Uniform particle size
- Trituration
- Sieving
- Pulverization by intervention
- Levigation

IX. ORAL POWDERS

Oral powders include headache powders, dusting powders (such as antifungal powders), powders to be reconstituted (such as antibiotics), and insufflations, which are powders intended to be blown into a body cavity such as in the ear or nose. Powder mixtures as a means of measuring small quantities of powders are called triturations.

X. CAPSULES

Capsules are solid dosage forms in which one or more medicinal ingredients and/or inert substances are enclosed within a small shell or container generally prepared from a suitable form of gelatin. Some of the best sources of information about capsules are the companies that manufacture capsule shells. For example, CAPSUGEL® (http://www.capsugel.com/contact.html) provides a lot of very useful information.

What goes into the capsule plays a role in proper capsule selection. Although the industry-leading Coni-Snap (http://www.capsugel.com/products/conisnap.html) capsule is extremely versatile for many formulations, other capsule types are used specifically with liquids or with materials with unique moisture retention properties.

The amount of active ingredient per dose has a direct bearing on the proper size capsule to use. Because capsules usually require less excipients and additives, it is easier to get a more potent dosage without having to use a large-size capsule.

For broad-based appeal, the Coni-Snap® capsule is a proven winner; however, for targeting select consumer

segments, such as vegetarians, Vcaps (http://www.capsugel.com/products/vcaps.html) capsules, which are of plant origin, may better meet customer needs.

Very often, strict governmental regulations are placed on products that are being consumed by the public for health reasons. In most cases, pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) face different regulatory constraints than do dietary supplements (http://www.capsugel.com/services/ds_dpstdy. html). Capsule shell manufacturers are well acquainted with Regulatory Information and Certification (http://www.capsugel.com/services/regulatory.html) and can alert you to important areas of consideration.

Adding to the complexity to the aforementioned regulatory issue, different countries have varying regulations that need to be considered. For example, regarding the issue of color selection (http://www.capsugel.com/services/color.html), countries have their own specific lists of colorants that can be legally used for capsules.

The appearance of the capsule itself is an important consideration. Colors are known to impact user perception, and the printing of logos on the capsule can increase brand recognition. Because capsules have a long and successful history as the dosage form of choice for pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) as well as for dietary supplement applications (http://www.capsugel.com/services/dsproduct.html), many options are available for locating capsule-filling-machinery (http://www.capsugel.com/equipment/index.html).

XI. FDA CLASSIFICATION OF CAPSULE TYPES

CAPSULE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin.	CAP	600
CAPSULE, COATED	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; additionally, the capsule is covered in a designated coating.	CAP COATED	602
CAPSULE, COATED, EXTENDED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.	CAP COATED ER	611
CAPSULE, COATED PELLETS	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which varying amounts of coating have been applied.	CAP COATED PELLETS	603
CAPSULE, DELAYED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms.	CAP DR	620
CAPSULE, DELAYED-RELEASE PELLETS	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which enteric coating has been applied, thus delaying release of the drug until its passage into the intestines.	CAP DR PELLETS	621
CAPSULE, EXTENDED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) in such a manner to allow a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.	CAP ER	610
CAPSULE, FILM COATED, EXTENDED RELEASE	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated film coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.	CAP FILM COATED ER	612
CAPSULE, GELATIN COATED	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin; through a banding process, the capsule is coated with additional layers of gelatin so as to form a complete seal.	CAP GELATIN COATED	605
CAPSULE, LIQUID FILLED	A solid dosage form in which the drug is enclosed within a soluble, gelatin shell that is plasticized by the addition of a polyol, such as sorbitol or glycerin, and is therefore of a somewhat thicker consistency than that of a hard shell capsule; typically, the active ingredients are dissolved or suspended in a liquid vehicle.	CAP LIQ FILLED	606

XII. FDA CLASSIFICATION OF POWDERS

POWDER	An intimate mixture of dry, finely divided drugs or chemicals that may be intended for internal or external use.	PWD	110
POWDER, DENTIFRICE	A powder formulation intended to clean and polish the teeth, and may contain certain additional agents.	PWD DENT	115
POWDER, FOR SOLUTION	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yields a solution.	PWD F/SOL	833
POWDER, FOR SUSPENSION	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yields a suspension (a liquid preparation containing the solid particles dispersed in the liquid vehicle).	PWD F/SUSP	834
POWDER, METERED	A powder dosage form that is situated inside a container, which has a mechanism to deliver a specified quantity.	PWD MET	841

XIII. INHALERS AND LUNG DELIVERY

Key factors that contribute to the aerodynamic properties of aerosol particles are found in Stokes' law. These factors may be monitored or controlled to optimize drug delivery to the lungs. Predictions of the aerodynamic behavior of therapeutic aerosols can be derived in terms of the physical implications of particle slip, shape, and density. The manner in which each of these properties has been used or studied by pharmaceutical scientists to improve lung delivery of drugs is readily understood in the context of aerosol physics. Additional improvement upon current aerosol delivery of particulates may be predicted by further theoretical scrutiny (*Fundamental Effects of Particle Morphology on Lung Delivery: Predictions of Stokes' Law and the Particular Relevance to Dry Powder Inhaler Formulation and Development.* Timothy M. Crowder, Jacky A. Rosati, Jeffrey D. Schroeter, Anthony J. Hickey, and Ted B. Martonen, *Pharmaceutical Research* 19 (2002) 239–245).

The history of inhaler development in modern times can be traced to the metering valve and propellants (metered dose inhalers, pMDI) used in the treatment of asthma in the 1950s. This was followed closely by somewhat primitive dry powder inhalers (DPIs) in the 1970s. Throughout this period, nebulizers were employed to deliver drugs in aqueous solution. In the past decade, research and development in the field has broadened. This may be explained, in part, by the demise of the Kyoto Treaty on Global Warming (1997), which has refocused activities in the area of alternative propellant formulation. More significantly, there has been an increase in research into alternative approaches to powder and solution formulation and stability. This review is intended to reflect the interest and growth that has occurred in the field of pharmaceutical inhalation aerosol technology in the last 4 years (T.M. Crowder, M.D. Louey, V.V. Sethuraman, H.D.C. Smyth, and A.J. Hickey, 2001: An Odyssey in Inhaler Formulations and Design, *Pharmaceutical Technology* 25(7) (2001) 99–113).

The field of inhalation science is expanding rapidly as scientists are designing delivery systems for proteins and peptides using nanoparticle inhalation systems; the quick absorption through lung surface offers an excellent administration route.

XIV. PROBLEMS IN POWDER HANDLING

Powder materials exhibit a number of technological challenges with their manufacture, storage, transportation, mixing, dusting, characterization, packing, crushing, and milling.

Symptoms of a non-optimized product system utilizing a powder include: unacceptable rehydration, dissolution and solubility rate/reproducibility of the powder mixture; degradation, loss of drug activity, and reduction of product shelf life; drug mixture heterogeneity both before and during use; clogging of spray nozzle; and loss of delivered drug. The following can have a significant impact on the performance of a product using a powder:

- Utilization of the appropriate binders and adhesives
- Disintegrating agents
- Fillers
- Lubricants
- Wetting agents/surfactants
- Glidants
- Flavoring and sweetening agents

Typical powder dispersion problems include:

- Chemical and morphological heterogenity of the surface
- Dissolution or isomorphous substitution of constituent components (metals)
- Dependency of the surface and solution (dissolved or added) ion species

A number of interrelated physicochemical properties, such as pH (acidity), pI (ionic strength), pe (redox), and pc (concentration) influence the properties of the dispersion beside of the pressure and temperature.

XV. CAPSULATION EQUIPMENT

Significant advances have been made within the recent years in automating and validating capsule filling equipment. For example, the German packaging company Bosch Packaging Technology recently introduced a new generation of capsule filling machines. A main feature of the models GKF 701, GKF 1400, and GKF 2500 ASB 100% is the dosing station on the slide-gate principle, which, according to the company, ensures low-loss processing, even for difficult powders. The machine is controlled by an industrial personal computer (PC), using software that complies with the Food and Drug Administration (FDA) 21 CFR part 11 federal regulations. In response to harmful dust that occurs in all areas of pharmaceutical production, Bosch has developed a containment system for its standard blister machine TLT 1400. The system, which produces 400 blisters per minute, protects the operator while processing toxic contents, according to the company. (No endorsement of any manufacturer or product is intended here.) Major suppliers of capsule filling equipment include: Farmatic, Hofliger and Karg, macofar, mGw, and Zanasi.

XVI. CAPSULE FINISHING

Capsules coming off the filling line require dedusting and polishing. These can be done by pan polishing, cloth dusting, and brushing. Commercial equipment to do this includes Rotosort™, Erwek deduser™, and the equipment from Seidenader™. Imprinting on capsules serves many purposes including ready identification. The choice of ink is important.

XVII. MODIFIED-RELEASE PRODUCTS

The capsulation process offers many advantages for designing modified-release products. The simple process of loading the drug onto non-pareil sugar beads and then coating them with a variety of release profiles offers the opportunity of not only separating the incompatible components, but also mixing granules that provide different release profiles, from instant release to step release to prolonged release. Equipment is available to fill several beads simultaneously into capsules, thus assuring dosing accuracies. (If granules with different coatings are mixed, segregation is likely because of the differences in their density.) Coated granules, if compressed, lose their release profiles.

XVIII. CLINICAL TEST SUPPLIES AND PLACEBOS

Encapsulation is the preferred form of drug delivery in preparing placebos and clinical test supplies wherein small runs are planned.

XIX. COATED PARTICLES

Use of hard gelatin capsules allows for the preparation of coated particles to provide modified release or stability; these particles are prepared generally by the method described in Section XVII; however, the possibilities of creating innovative dosage forms using different size of particles makes this dosage form highly desirable for many unstable drugs.

XX. MIXING MECHANISMS

Mixing solids involves a combination of one or more mechanisms of convection, shear, and diffusive mixing. Convection mixing is achieved by the transport of solids such as by blades or screws. Shear mixing results from the forces within the particulate mass; slip planes are set up. This can take place singularly or as a laminar flow. When shear occurs between regions of different composition and parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers. Shear occurring in a direction normal to the interface of such layers is also effective because it reduces segregation. The diffusive mixing is the random motion of particles.

XXI. SEGREGATION MECHANISMS

Particulate solids tend to segregate by virtue of differences in the size, density, shape, and other properties; it can happen during mixing or subsequent storage handling as well. It is important to note that powders that are difficult to flow do not segregate easily because of high interparticulate adhesion; however, because powders must be rendered flowable for the purpose of filling capsules or in bottles or sachet, the segregation phenomenon because very important. Note that often after the addition of magnesium stearate, it is advisable to mix the product only for a limited time because electrical charges on the particles may cause segregation. Often, additives are included in formulations to reduce the tendency of segregation; these components have polarity similar to the components of the formulation. A variety of mixers are designed to counter the segregation during mixing. Regardless of the formulation or equipment used, however, the formulator must conduct a validation study to assure that the product before filling is not segregated and that detailed Manufacturing Directions consequently include such conditions as humidity, mixing speeds, mixing times, and grounding of equipment. It is often said that longer mixing causes

unmixing; this occurs because of segregation as well as abrasion of particles, which alters the particle size distribution profile.

XXII. MIXING EQUIPMENT

Batch mixing is the most common practice using twin-shell, cubic, and cylindrical tumbling mixers on a common shaft. The speed of rotation (generally 30–100 rpm) for these mixers is crucial to good mixing. Other mixers of the same type take the shape of cylinders, cubes, or hexagonal cylinders. The stationary container mixers do not depend on gravity for tumbling as for the preceding mixers; these are useful for mixing sticky, wetted, or plastic mass where shear force is needed to impart mixing. Stationary container mixers include the ribbon blender and the helical flight mixer.

Large mixers produce continuous mixing; large mixers are less consistent in producing uniform mixing and are more useful in the stages where such consistency is not critical.

Selection of equipment depends on the measure of mixing degree required. Manufacturing process validation should include a definition of segregation where large-scale segregation is not present. A large volume of data on the statistics of "degree of mixing" is available where samples are drawn from the mix at various times, and the samples must be of a sufficiently large size to contain enough particles. Perfect mixtures, in statistical terms, are random mixtures. In capsules where pellets of different types are included, these considerations become critical. Let us take the example of a binary mixture where n is the number of particles in the sample and p is the fraction of particles of interest. For example, if a capsule contains 30% of type A pellets, then the average number is 150 in a 500-pellet capsule with standard deviation of:

$$\sigma = \tilde{A}(\text{average})(1 - p)$$

Thus, for the preceding composition, a deviation of 10.2 counts for 150 pellets occurs in each capsule when there is perfect mixing; in this instance, each capsule must be individually sampled because large bulk samples would not reveal the variations.

XXIII. MILLING

Mixing of powders is easier if all components are of the same dimension in particle size. Granulation of powders is done to provide a more uniform particle size; this is a common practice in tablet, capsule, and powder suspension formulations. Milling of granulated mass produces uniform particle size; where dyes are used, milling provides a more uniform mixing and spread of dyes. Lubricants act by coating the particles and require the presence of a certain amount of fines. Size distribution profiles are routinely prepared as part of the development pharmaceutics process, especially where high-speed filling machines are used. Frequency and cumulative plots are made to validate the process. Probability function values found in statistics books should be consulted when designing a robust evaluation program. Particles are measured either microscopically or by weight fractions through a stack of sieves. A sedimentation method is also used for particles in the range of 1–200 μm to obtain a size–weight distribution. Other methods include adsorption, electrical conductivity, light and x-ray scattering, permeametry, and particle trajectory.

During the process of milling or comminution, the particles undergo transformation based on the strain applied, which produces stress, and size reduction begins with the opening of new cracks. If the force applied is not sufficient, then the particle returns to its original state from a stressed state and does not yield. The type of mill used is important, such as a cutter, fluid-energy, hammer, or roller because each provides a special pattern of comminution. For example, is useful for fibrous material, but not for friable material; it produces a product size of 20–80 mesh. The fluid energy mill can produce 1–30 μm particles, and is more suitable for soft and sticky materials. The most common mill is the hammer mill, which is useful for abrasive materials and produces 4–325 mesh particles. In a hammer mill, it matters whether the blades are forward or reversed.

Part II

Uncompressed Solids Formulations

Uncompressed Solids Formulations

Acebutolol Hydrochloride Capsules

Acebutolol hydrochloride is a selective, hydrophilic beta β-adrenoreceptor blocking agent with mild intrinsic sympathomimetic activity. It is used to treat patients with hypertension and ventricular arrhythmias, and is marketed in capsule form for oral administration. The capsules are provided in two dosage strengths, which contain 200 or 400 mg of acebutolol as the hydrochloride salt. The inactive ingredients present are: D&C Red 22, FD&C Blue 1, FD&C Yellow 6, gelatin, povidone, starch, stearic acid, and titanium dioxide. The 200-mg dosage strength also contains D&C Red 28; the 400-mg dosage strength also contains FD&C Red 40.

Aceclofenac Instant Granules

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
50.00	1	Aceclofenac	50.00
165.83	2	Orange Flavor	165.83
3292.30	3	Sorbital	3292.30
169.23	4	Lutrol F 68	169.23
169.23	5	Cremophor RH 40	169.23
QS	6	Deionized Water	about 2 kg

MANUFACTURING DIRECTIONS

1. Granulate Items 1–3 with a solution of Items 4–6, pass through a 0.8-mm screen, dry, and sieve again.
2. Fill 3.9 g in sachets corresponding to 50 mg aceclofenac.

Acetaminophen and Diphenhydramine Hydrochloride Hot Therapy Sachet

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
1650.0000	1	Acetaminophen Micronized	1650.0000
250.0000	2	Diphenhydramine Hydrochloride	250.0000
0.9000	3	FD&C Yellow No. 10 Lake	0.9000
0.0005	4	FD&C Red No. 40	0.0005
18081.1000	5	Castor Sugar	18081.1000
200.0000	6	Aspartame	200.0000
250.0000	7	Cornstarch Dried	250.0000
180.0000	8	Citric Acid	180.0000
38.0000	9	Sodium Citrate	38.0000
200.0000	10	Sodium Chloride	200.0000
240.0000	11	Honey Dry Flavor	240.0000
100.0000	12	Lemon Dry Flavor	100.0000
QS	13	Purified Water	QS

MANUFACTURING DIRECTIONS

1. Items 1 and 2 are mixed well, followed by passing through sieves. Items 3, 5, and 13 are mixed and made into a clear solution.
2. Step 1 is added to Step 2 and mixed well.
3. This is added to Item 4 and mixed. Take care to avoid lump formation.
4. Dry in an oven. Sieve and add Items 6–12. Mix well.
5. Make sure all the solids added are in fine powder form. Fill 20 g powder into sachets and seal.

Acetaminophen Capsules 500 mg

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
500.00	1	Acetaminophen Powder	500.00
30.00	2	Sodium Starch Glycolate	30.00
1.00	3	Aerosil 200	1.00
2.00	4	Magnesium Stearate	2.00
17.00	5	Starch Dried	15.00

MANUFACTURING DIRECTIONS

1. Charge all items after passing through No. 60 screen mesh and mix for 1 h.
2. Fill 550 mg in size 0 capsule.

Acetaminophen, Doxylamine, and Caffeine Effervescent

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
500.00	1	Acetaminophen Powder	500.00
5.00	2	Doxylamine Succinate	5.00
33.00	3	Caffeine (Knoll)	33.00
391.00	4	Tartaric Acid	391.00
417.00	5	Sodium Hydrogen Carbonate	417.00
6.00	6	Kollidon 30	6.00
—	7	Isopropanol (or Ethanol)	QS
30.00	8	Sodium Citrate	30.00
707.00	9	Sugar	707.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1–5 with a solution of Items 6 and 7. Dry at 60°C under vacuum conditions, sieve, and mix with Items 8 and 9.
2. Fill 2.1 g in sachets at a maximum 30% of relative atmospheric humidity. If the solvent isopropanol is replaced by water, the granulation should be done in a fluidized bed.

Acetaminophen Instant Granules

1.

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
166.66	1	Acetaminophen Fine Powder	166.66
426.64	2	Sucrose Fine Powder	426.64
300.00	3	Kollidon CL-M	300.00
23.33	4	Aspartame	23.33
16.66	5	Orange Flavor	16.66
16.66	6	Strawberry Flavor	16.66
40.00	7	Kollidon 30	40.00
250.00	8	Ethanol 96%	250.00

MANUFACTURING DIRECTIONS

1. Granulate Items 1–6 with solution made from Items 7 and 8 and pass through a 0.8-mm sieve.
2. Fill 1.5 g or 3.0 g in sachets (for 250 or 500 mg strength, respectively). The free-flowing granules are very well dispersible in cold water. Suspend 1.5 g or 3.0 g of the granules (= 250 mg or 500 mg acetaminophen, respectively) in a glass of water.

2.

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
192.30	1	Acetaminophen Fine Powder	192.30
500.00	2	Sorbitol Instant (Merck)	500.00
192.30	3	Kollidon CL-M	192.30
27.00	4	Aspartame	27.00
19.23	5	Orange Flavor	19.23
19.23	6	Strawberry Flavor	19.23
11.53	7	Sodium Citrate	11.53
11.53	8	Citric Acid	11.53
30.76	9	Kollidon 90 F	30.76
192.30	10	Ethanol 96%	192.30

MANUFACTURING DIRECTIONS

1. Granulate Items 1–8 with a solution made from Items 9 and 10 and pass through a 0.8-mm sieve.
2. Fill 1.3 g or 2.6 g in sachets (for 250 or 500 mg strength, respectively).
3. The free-flowing granules are very well dispersible in cold water. Suspend 1.2 g or 2.6 g of the granules (= 250 mg or 500 mg acetaminophen, respectively) in a glass of water.

3.

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
500.00	1	Acetaminophen Fine Powder	500.00
1300.00	2	Sorbitol Instant (Merck)	1300.00
500.00	3	Lutrol F 127	500.00
30.00	4	Citric Acid Powder	30.00
30.00	5	Sodium Citrate	30.00
80.00	6	Kollidon 90 F	80.00
500.00	7	Ethanol 96%	500.00

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1–5 in a solution of Item 6 in Item 7. Fill 2.44 g in sachets (= 500 mg acetaminophen).
2. The free-flowing granules are very well dispersible in cold water.
3. The taste of the suspension is only slightly bitter (2.44 g in a glass of water).

Acetaminophen, Pseudoephedrine Hydrochloride, Chlorpheniramine Hot Therapy Sachet

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachets (g)**
650.00	1	Acetaminophen Micronized	650.00
60.00	2	Pseudoephedrine Hydrochloride	60.00
4.00	3	Chlorpheniramine Maleate	4.00
1.20	4	Dispersed Orange	1.20
18,081.10	5	Castor Sugar	18,081.10
200.00	6	Aspartame	200.00
250.00	7	Cornstarch Dried	250.00
180.00	8	Citric Acid	180.00
38.00	9	Sodium Citrate	38.00
200.00	10	Sodium Chloride	200.00
400.00	11	Blood Orange Dry Flavor	400.00
QS	12	Purified Water	QS

MANUFACTURING DIRECTIONS

1. Items 1 and 2 are mixed well, followed by passing through sieves and adding to Items 3 and 12 premixed and made into a clear solution.
2. Take care to avoid lump formation.
3. Dry in an oven.
4. Sieve and add Items 6–11. Mix well.
5. Make sure all the solids added are in fine powder form. Fill 20 g powder into sachets and seal.

Acetaminophen, Pseudoephedrine Hydrochloride Hot Therapy Sachet

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
650.00	1	Acetaminophen Micronized	650.00
260.00	2	Pseudoephedrine Hydrochloride	260.00
0.90	3	FD&C Yellow No. 10 Lake	0.90
18,081.10	4	Castor Sugar	18,081.10
200.00	5	Aspartame	200.00
250.00	6	Cornstarch Dried	250.00
180.00	7	Citric Acid	180.00
38.00	8	Sodium Citrate	38.00
200.00	9	Sodium Chloride	200.00
240.00	10	Apple Dry Flavor	240.00
100.00	11	Cinnamon Dry Flavor	100.00
QS	12	Purified Water	QS

MANUFACTURING DIRECTIONS

1. Items 1 and 2 are mixed well, followed by passing through sieves and added to Items 3 and 12 premixed and made into a clear solution.
2. Take care to avoid lump formation.
3. Dry in an oven.
4. Sieve and add Items 6–11. Mix well.
5. Make sure all the solids added are in fine powder form. Fill 20 g powder into sachets and seal.

Acetaminophen Swallow Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
325.00	1	Acetaminophen Fine Powder	325.00
409.50	2	Sodium Carbonate Fine Powder	409.50
13.91	3	Cornstarch	13.91
32.50	4	Starch Pregelatinized	32.50
1.30	5	Polyvinylpyrrolidone K25	1.30
0.39	6	Potassium Sorbate	0.39
9.75	7	Talc	9.75
3.25	8	Stearic Acid	3.25
23.86	9	Ac-Di-Sol®	23.86
QS	10	Water Purified	QS

MANUFACTURING DIRECTIONS

1. Sift Items 1–6 through 16-mesh sieve into a suitable mixer and granulate with a suitable quantity of Item 10 to form a medium/heavy granule.
2. Dry the granules in a suitable oven at 45°C until the water content is <1%.
3. Pass the dried granule through a 12-mesh sieve to produce a white granule (yield 20.250 kg).
4. Fill 819.46 mg in a suitable capsule size.

Acetazolamide Sustained-Release Capsules

Acetazolamide is *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl) acetamide. The sustained-release capsules, for oral administration, each contains 500 mg of acetazolamide and the following inactive ingredients: ethyl vanillin, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, glycerin, microcrystalline cellulose, methylparaben, propylene glycol, propylparaben, silicon dioxide, and sodium lauryl sulfate.

Acetylcysteine Sachets

1.

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
66.66	1	Acetylcysteine[a]	66.66
914.16	2	Sugar, 18 to 60 Mesh	914.16
3.33	3	Saccharin Sodium	3.33
0.66	4	Silicon Dioxide Colloidal	0.66
0.16	5	Dye FD&C Yellow No. 6	0.16
—	6	Mandarin Flavor (e.g., Naarden)	Approx. 13 ml

[a] 200 mg/sachet.

MANUFACTURING DIRECTIONS

1. Load the acetylcysteine, half the amount of sugar, and saccharin sodium into a suitable blender and premix for 30 min.
2. Sift the premix from Step 1 through an 850 µm aperture screen.
3. Load again into the blender. Add the remaining amount of sugar and colloidal silicon dioxide and blend until uniform (typically, this is achieved on the PK Processor® by heating the envelope to 40°C and mixing until the product cools to 30–35°C).
4. Dissolve the dye in 13 ml of distilled water. Continue mixing the blended powders from Step 3. When addition of the solution is complete, continue massing until the granulation is evenly wetted and colored. If necessary, complete massing with additional quantities of distilled water (approximately 1 ml increments).
5. Verify that massing is adequate. Do not overmass.
6. Spread the wet granules on trays and dry at 50°C until LOD is NMT 1% (3 h at 60°C at 5 mmHg).
7. Allow the granules to cool, then sift on an oscillating granulator fitted with a 1.18-mm aperture screen.
8. Load the granules from step above into a suitable blender, add the flavor, and blend until uniform (15 min) passing it through a 1.18-mm screen if necessary.
9. Fill into suitable sachets at a theoretical fill weight of 3.0 g per sachet.

2.

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
66.66	1	Acetylcysteine BP (200 mg/sachet)	66.66
914.16	2	Sugar 18 to 60 Mesh	914.16
3.33	3	Saccharin Sodium	3.33
0.66	4	Silicon Dioxide Colloidal	0.66
0.16	5	Dye FD&C Yellow No. 6	0.16
—	6	Mandarin Flavor (e.g., Naarden)	Approx. 13 ml

MANUFACTURING DIRECTIONS

1. Load the acetylcysteine, half the amount of sugar, and saccharin sodium into a suitable blender and premix for 30 min.
2. Sift the premix from Step 1 through an 850-µm aperture screen. Load again into the blender.
3. Add the remaining amount of sugar and colloidal silicon dioxide and blend until uniform (typically, this is achieved on the PK Processor® by heating the envelope to 40°C and mixing until the product cools to 30–35°C).
4. Dissolve the dye in 13 ml of distilled water. Continue mixing the blended powders from Step 3. When addition is complete, continue massing until the granulation is evenly wetted and colored. If necessary, complete massing by additional quantities of distilled water (approximately 1 ml increments). Verify that the massing is adequate, and note the total quantity of added water. Record total quantity of water added.
5. Do not overmass. Spread the wet granules on trays and dry at 50°C until LOD is NMT 1% (3 h at 60°C at 5 mmHg).
6. Allow the granules to cool, then sift on an oscillating granulator fitted with a 1.18-mm aperture screen.
7. Load the granules from Step 6 into a suitable blender, add the flavor, and blend until uniform (15 min), passing it through a 1.18-mm screen mesh if necessary.
8. Fill into suitable approved sachets at a theoretical fill weight of 3.0 g per sachet.

Acitretin Capsules

Acitretin, a retinoid, is available in 10-mg and 25-mg gelatin capsules for oral administration. Chemically, acitretin is all-*trans*-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid. It is a metabolite of etretinate and is related to both retinoic acid and retinol (vitamin A). Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink, and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, and edetate calcium disodium.

Acrivastine and Pseudoephedrine Hydrochloride Capsules

Acrivastine and pseudoephedrine hydrochloride is a fixed combination product formulated for oral administration. Acrivastine is an antihistamine and pseudoephedrine is a decongestant. Each capsule contains 8 mg of acrivastine and 60 mg of pseudoephedrine hydrochloride, and the following inactive ingredients: lactose, magnesium stearate, and sodium starch glycolate. The green and white capsule shell consists of gelatin, D&C Yellow No. 10, FD&C Green No. 3, and titanium dioxide. The yellow band around the capsule consists of gelatin and D&C Yellow No. 10. The capsules may contain one or more parabens and are printed with edible black and white inks.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
8.00	1	Acrivastine	8.00
60.00	2	Pseudoephedrine	60.00
440.00	3	Lactose	440.00
5.00	4	Magnesium Stearate	5.00

MANUFACTURING DIRECTIONS

1. Blend Items 1–3 after sifting through an 80-mesh screen.
2. Pass Item 4 through a 100-mesh screen and add to Step 1; blend for 2 min.
3. Fill 513 mg in size 0 capsules.

Acyclovir Capsules

Acyclovir is a synthetic nucleoside analog that is active against herpes viruses. The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6 *H*-purin-6-one. Each capsule contains 200 mg of acyclovir and the inactive ingredients cornstarch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. It may contain one or more parabens and is printed with edible black ink.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
200.00	1	Acyclovir, USE Acyclovir Micronized	212.00
3.00	2	Sodium Lauryl Sulfate	3.00
20.00	3	Cornstarch	20.00
52.00	4	Lactose Monohydrate	52.00
2.00	5	Magnesium Stearate	2.00
—	6	Ethanol	60 ml

MANUFACTURING DIRECTIONS

1. Charge Items 1–4 in a suitable mixer and mix for 5 min with slow chopper speed.
2. Add Item 6 slowly with mixing at slow speed; mix and chop for 2–3 min.
3. Check for satisfactory massing; use additional Item 6 if necessary.
4. Spread granules to 1/4-inch thick layer on paper trays and dry at 50°C for 4 h to a moisture of not more than 1%; dry further if required after testing.
5. Pass the dried granules through a granulator equipped with a 0-mm sieve.
6. Pass Item 5 through 250-µm sieve and add to Step 5, mix for 3 min.
7. Use size 1 capsules to fill 289 mg.

Adenosine Monophosphate Topical Powder

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
30.00	1	DBcAMP[a]	30.00
920.00	2	Polyethylene Glycol 6000	920.00
30.00	3	Talc	30.00
20.00	4	Colloidal Silica Aerosil 200	20.00

[a] Sodium N^6, 2′-O-dibutyryladenosine-3′,5′-cyclic phosphate.

MANUFACTURING DIRECTIONS

1. Pass all items through a 100-mesh sieve and blend.
2. Pack in a bottle. Topical powder for treatment of dermatosis.

Aluminum Acetate Powder

Each powder packet, when dissolved in water and ready for use, provides the active ingredient aluminum acetate, resulting from the reaction of calcium acetate (938 mg), and aluminum sulfate (1191 mg). The resulting astringent solution is buffered to an acid pH.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
200.00	1	Aluminum Hydroxide Dry Gel (Giulini)	200.00
200.00	2	Basic Magnesium Carbonate	200.00
240.00	3	Kollidon CL-M	240.00
211.50	4	Sorbitol, Crystalline	211.50
41.30	5	Orange Flavor	41.30
82.60	6	Kollidon 30	82.60
3.30	7	Coconut Flavor	3.30
4.13	8	Banana Flavor	4.13
4.13	9	Saccharin Sodium	4.13
8.26	10	Water	8.26

MANUFACTURING DIRECTIONS

1. Granulate mixture of Items 1–5 with solution of Items 6–10, pass through a sieve, and dry. Shake 58 g of the granules with 100 ml of water.

Aminosalicylic Acid Granules

Delayed release granule preparation of aminosalicylic acid (p-aminosalicylic acid:4-aminosalicylic acid) for use with other anti-tuberculosis drugs for the treatment of all forms of active tuberculosis due to susceptible strains of tubercle bacilli. The granules are designed for gradual release to avoid high peak levels that are not useful (and perhaps toxic) with bacteriostatic drugs. Aminosalicylic acid is rapidly degraded in acid media; the protective acid-resistant outer coating is rapidly dissolved in neutral media so a mildly acidic food, such as orange, apple, or tomato juice, or yogurt or applesauce, should be consumed. Aminosalicylic acid (p-aminosalicylic acid) is 4-amino-2-hydroxybenzoic acid. PASER granules are the free base of aminosalicylic acid and do NOT contain sodium or sugar. With heat p-aminosalicylic acid is decarboxylated to produce CO_2 and m-aminophenol. If the airtight packets are swollen, storage has been improper. Supply warning: DO NOT USE if packets are swollen or the granules have lost their tan color and are dark brown or purple. The granules are supplied as off-white, tan-colored granules with an average diameter of 1.5 mm and an average content of 60% aminosalicylic acid by weight. The acid-resistant outer coating will be completely removed after a few minutes at a neutral pH. The inert ingredients are: colloidal silicon dioxide, dibutyl sebacate, hydroxypropyl methylcellulose, methacrylic acid copolymer, microcrystalline cellulose, and talc.

Amlodipine Besylate and Benazepril Hydrochloride Capsules

The capsules are formulated for oral administration with a combination of amlodipine besylate equivalent to 2.5 mg or 5 mg of amlodipine and 10 mg or 20 mg of benazepril hydrochloride. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate, starch, talc, and titanium dioxide.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Benazepril Hydrochloride	20.00
32.92	2	Lactose Monohydrate	32.92
5.00	3	Pregelatinized Starch	5.00
1.00	4	Colloidal Silica	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline Cellulose	10.00
4.00	7	Hydrogenated Castor Oil	4.00
—	8	Water Purified	QS
4.88	9	Hydroxypropyl Methylcellulose 2910, 3 cps	4.88
0.12	10	Polysorbate 80	0.12
—	11	Water Purified	QS
QS	12	Talc	QS
5.00	13	Amlodipine, USE Amlodipine Besylate	6.94
124.05	14	Microcrystalline Cellulose, Avicel PH102	124.05
63.00	15	Dibasic Calcium Phosphate	63.00
4.00	16	Sodium Starch Glycolate	4.00
2.00	17	Magnesium Stearate	2.00

MANUFACTURING DIRECTIONS

1. Mill Items 1–3 and blend together.
2. Add water (Item 8) to granulate the blend.
3. Screen the wet granules and dry them in oven.
4. Mill the dried granules and then mill together with Items 5–7.
5. Screen Item 4 and mix in Step 4.
6. Compress into a core.
7. Dissolve Item 10 in Item 11 and add Item 9 to it.
8. Coat the core prepared in Step 6 using Item 12 to dust the cores.
9. Mix Items 13–16, then blend and screen; blend again in a separate vessel.
10. Screen Item 17 separately and add to Step 9.
11. Fill in size 1 hard gelatin capsules the coated cores with 200 mg of the powder in Step 10.

Amlodipine Besylate Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
5.00	1	Amlodipine, USE Amolodipine Besylate	7.00
93.00	2	Microcrystalline Cellulose, Avicel PH102	93.00
65.00	3	Dibasic Calcium Phosphate	65.00
8.00	4	Sodium Starch Glycolate	8.00
0.50	5	Colloidal Silicon Dioxide Aerosil 200	0.50
1.50	6	Magnesium Stearate	1.50
1	7	Empty Hard Gelatin Shell, Size 3	1000

MANUFACTURING DIRECTIONS

1. Sift amlodipine besylate, Avicel PH102, Dibasic calcium phosphate and Primojel® through a 0.500-mm sieve, and mix well in a mixer.
2. Lubricate the powder mixture in Step 1 with magnesium stearate and aerosil 200 that has been previously sieved. Mix for 2 min to get a homogeneous powder.
3. Fill the capsule in the capsule-filling machine to a weight adjusted to provide 5 mg amlodipine per capsule.

Amoxicillin and Bromhexine Hydrochloride Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Amoxicillin, USE Amoxicillin Trihydrate	290.00
8.00	2	Bromhexine, USE Bromhexine Hydrochloride	8.80
34.00	3	Starch Dried	34.00
3.00	4	Magnesium Stearate	3.00
3.50	5	Aerosil 200	3.50
40.00	6	Talc	40.00
1	7	Hard Gelatin Capsule, Size 1	1000.00

MANUFACTURING DIRECTIONS

1. Charge Items 1 and 3–6 in a suitable blender and mix for 10 min.
2. In a separate mixer, add small portion of Step 1 and add by geometric dilution Item 2 and mix well.
3. Sift through No. 60 mesh screen.
4. Fill 398 mg in each capsule.

Amoxicillin and Clavulanic Acid Powder for Suspension, 125 mg and 31.25 mg per 5 ml

Amoxicillin is a semisynthetic antibiotic and an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Chemically, it is (2 *S,*5 *R,*6 *R*)-6-[(*R*)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. Each capsule, with a royal blue opaque cap and pink opaque body, contains 250 mg or 500 mg of amoxicillin as the trihydrate. The cap and body of the 250-mg capsule are imprinted with the product name and 250; the cap and body of the 500-mg capsule are imprinted with AMOXIL and 500. The inactive ingredients are: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, and titanium dioxide.

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
19.00	1	Amoxicillin Trihydrate	19.00
10.60	2	Potassium Clavulanate (eq. Clavulanic Acid) 1:1 in Sylloid	10.60
15.00	3	Aerosil 200	15.00
48.80	4	Mannitol	48.80
0.50	5	Citric Acid Monohydrate	0.50
1.90	6	Sodium Citrate	1.90
1.20	7	Xanthan Gum	1.20
2.00	8	Powdered Flavor	2.00
0.45	9	Sweetener	0.45

MANUFACTURING DIRECTIONS

1. Charge Items 1–9 after passing through a No. 60 screen mesh at a temperature of 25°C and relative humidity of not more than 30% in a suitable blender-mixer.
2. Fill 5 g in a 30-ml bottle. Reconstitution with water gives 125 mg of Item 1 and 31.25 mg of Item 2 per 5 ml.

Amoxicillin and Clavulanate Potassium for Suspension

This is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the (beta)-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analog of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. Chemically, amoxicillin is (2S,5R,6R)-6-[(R)-(-)-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate. Clavulanic acid is produced by the fermentation of *Streptomyces clavuligerus*. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of (beta)-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated (beta)-lactamases that are frequently responsible for transferred drug resistance to penicillins and cephalosporins. Chemically clavulanate potassium is potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo [3.2.0]-heptane-2-carboxylate. The inactive ingredients are: powder for oral suspension (i.e., colloidal silicon dioxide, flavorings, succinic acid, xanthan gum, and aspartame) hydroxypropyl methylcellulose, mannitol, silica gel, silicon dioxide, and sodium saccharin.

Bill of Materials

Scale (mg/Bottle) (7 g/60 ml)	Item	Material Name	Qty/1000 Bottle (g)
1500.00	1	Amoxicillin Trihydrate (equivalent to 1,250 g of Amoxicillin)	1500.00
393.60	2	Potassium Clavulanate	393.60
150.00	3	Xanthan Gum	150.00
1800.00	4	Hydroxypropyl Methylcellulose Dried	1800.00
150.00	5	Saccharin Sodium	150.00
300.00	6	Silicon Dioxide Colloidal	300.00
10.00	7	Succinic Acid	10.00
1500.00	8	Silica Gel	1500.00
183.60	9	Peach Dry Flavor	183.60
236.40	10	Strawberry Dry Flavor	236.40
731.14	11	Lemon Dry Flavor	731.14

Note: 156 mg/5 ml syrup 60 ml (125 mg amoxicillin and 31.25 mg clavulanic acid.) 6.95 g/60 ml: Each 5 ml of reconstituted syrup contains 156.25 mg of amoxicillin and clavulanic acid.

MANUFACTURING DIRECTIONS

Note: Throughout the process of manufacturing and filling maintain RH of NMT 40%.

I. Preparation of Powder Mix
   A. Mill 50% of Amoxicillin Trihydrate, Saccharin Sodium (dried to NMT 2% moisture by Karl Fischer method), Succinic Acid through a 250-µm sieve or using a Fitz mill or equivalent with blades forward. Transfer to a blending mixer and mix for 15 min.
   B. Mill remaining Amoxicillin Trihydrate through a #100 mesh using a Fitz mill or equivalent and mix with above screened powders, mix for 15 min.
   C. Mill Xanthan Gum, Hydroxypropyl methylcellulose (dried to NMT 2% moisture dried at 105EC for 2 h), Colloidal Silica, and Silica Gel through a No. 250-µm sieve or using Fitz mill or equivalent with knives forward. Add to above mixture in Step B and mix for 15 min at medium speed.
   D. Screen all dry flavors through a 250-µm mesh screen and add to above mixture from Step C.

II. Finishing
   A. Fill dry powder about 7 g in dry 60-ml glass bottles at a fill weight based on the assay of the active constituent.

Amoxicillin Powder for Suspension 125 and 250 mg

Bill of Materials			
Scale (mg/5 ml)[a]	**Item**	**Material Name**	**Qty/5 l (g)**
125.00	1	Amoxicillin, USE Amoxicillin Trihydrate with 8% Excess	143.50
1.04	2	Simethicone A	1.04
111.11	3	Castor Sugar	111.11
444.44	4	Castor Sugar	444.44
2479.86	5	Castor Sugar	2479.86
23.33	6	Sodium Citrate	23.33
1.67	7	Xanthan Gum	1.67
13.33	8	Blood Orange Dry Flavor	13.33
0.74	9	Vanilla Dry Flavor	0.74
4.44	10	Orange Banana Dry Flavor	4.44
14.44	11	Aerosil 200	14.44

[a] After reconstitution.

MANUFACTURING DIRECTIONS

1. Charge Item 3 and Item 2 in a mixer and mix for 2 min.
2. Add Item 4 and Items 6–11 and mix for 5 min.
3. Pass through Fitz mill; impact forward at high speed using sieve 24228.
4. In a separate mixer, charge Item 5 and Item 1 and mix well, passing through a sifter.
5. Add to Step 3 and mix for 20 min.
6. Fill 65 g for 100-ml and 39 g for 60-ml pack size.

Amoxicillin Trihydrate Capsules 250 and 500 mg

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
500.00	1	Amoxicillin, USE Amoxicillin Trihydrate	576.00
1.20	2	Aerosil 200	1.20
7.72	3	Magnesium Stearate	7.72
8.91	4	Sodium Lauryl Sulfate	8.91

MANUFACTURING DIRECTIONS

1. All operations are to be completed at relative humidity 40–45% and temperature 20–25°C.
2. Pass Item 1 through 1.0-mm sieve in a mixing vessel.
3. Pass Items 2–4 after passing through 250-μm sieve; add one-third portion of Item 1 from Step 2 and mix for 10 min; add another one-third Item 1 and mix and, finally, add balance and mix.
4. Fill 594 mg in size 0 capsules.

Ampicillin Powder for Suspension

Bill of Materials			
Scale (mg/5 ml)	**Item**	**Material Name**	**Qty/5 l (g)**
125.00	1	Ampicillin, USE Ampicillin Trihydrate 8% excess	144.25
1.00	2	Simethicone A	1.00
138.90	3	Castor Sugar	138.90
27.44	4	Sodium Citrate	27.44
7.00	5	Xanthan Gum	7.00
15.00	6	Blood Orange Dry Flavor	15.00
0.78	7	Vanilla Dry Flavor	0.78
7.55	8	Strawberry Dry Flavor	7.55
10.00	9	Aerosil 200	10.00
138.90	10	Castor Sugar	138.90
2747.90	11	Castor Sugar	2747.90

MANUFACTURING DIRECTIONS

1. All operations should be completed in a relative humidity of 45–55% and a temperature of 23–25°C.
2. Charge Items 2 and 3 in a suitable blender, and mix for 5 min.
3. Charge Items 1 and 4–10 in a separate mixer, and mix for 5 min.
4. Add Step 2 into Step 3, and mix for 10 min.
5. Add Item 11, and mix for 10 min.
6. Fill 65 g for a 100-ml pack and 39 g for a 60-ml pack. For 250 mg strength, adjust active ingredient, and adjust with Item 11.

Ampicillin Trihydrate Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
500.00	1	Ampicillin, USE Ampicillin Trihydrate compacted	582.13
1.17	2	Aerosil 200	1.17
11.69	3	Magnesium Stearate	11.69

MANUFACTURING DIRECTIONS

1. Pass Item 1 through a 1-mm sieve into a double-cone blender, except about 5% of the quantity.
2. In a separate container, pass and collect Items 2 and 3 through a 250-μm sieve.
3. Add the balance of Item 1 retained in Step 1 into Step 2, and blend for 10 min; pass through a 900-μm sieve if necessary.
4. Add to Step 2, and blend for 10 min.
5. Fill 223.125 mg in size 0 capsules.

Ampicillin Trihydrate Capsules for Suspension

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Ampicillin, USE Ampicillin Trihydrate	250.00
2.50	2	Magnesium Stearate	2.50
—	3	Gelatin Capsule, Size 2	1000.00

MANUFACTURING DIRECTIONS

1. Dry blend ampicillin trihydrate and magnesium stearate in Baker Perkins mixer; bag off into polyethylene-lined drums.
2. Fill on Zanasi AZ20 capsule filling machine. The average fill weight is 295 ± 9 mg; the average total weight is 360 mg. For a 500-mg capsule (size 0 capsules), the average fill weight is 593 ± 15 mg; the average total weight is 690 mg.

Ampicillin Trihydrate Powder for Suspension

Bill of Materials			
Scale (mg/Bottle) (15 ml)	**Item**	**Material Name**	**Qty/1000 Bottles (g)**
1500.00	1	Ampicillin, USE Ampicillin Trihydrate (assuming potency 871; adjust amount accordingly)	1722.22
3072.10	2	Sucrose (adjust amount based on Item 1 potency)	3072.10
372.53	3	Sodium Citrate Dihydrate	372.53
31.93	4	Saccharin Sodium	31.93
2.12	5	Acid Citric Anhydrous	2.12
45.23	6	Sodium Carboxymethyl Cellulose	45.23
22.61	7	Magnesium Aluminum Silicate Veegum F	22.61
7.98	8	Dye	7.98
26.60	9	Flavor	26.60
18.00	10	Sodium Benzoate	18.00
QS	11	Water Purified	400.00
Note: Simethicone 0.15% can be added to reduce foaming during reconstitution. Adjust fill volume for the final size of reconstitution container, such as 60 ml or different strength desired, e.g., 250 mg/5 ml upon reconstitution.			

MANUFACTURING DIRECTIONS

CAUTION: Handle with extreme care. Protect face and hands from amoxicillin because some individuals may be sensitive and reactions may occur.

I. Mixing
   A. Pass sugar through a 2.38-mm aperture screen using an oscillating granulator.
   B. Pass the following ingredients through a 595-µm aperture screen in a Fitz mill (high speed, impact forward): sodium citrate, acid citric, saccharin sodium, carboxymethylcellulose, amoxicillin, and magnesium aluminum silicate.
   C. Charge ingredients from Steps A and B into a suitable mixer and mix for 10 min until uniform.
   D. Dissolve yellow dye in approximately 60 g of purified water.
   E. Mass mixture from Step C with dye solution from Step D. If necessary, pass wet mass through a 4.76-mm aperture screen. *CAUTION: Do not over wet or over mass. Product must remain as wet granules.*
   F. Spread evenly on stainless steel trays. If necessary, pass wet mass through a 4.76-mm aperture screen.
   G. Oven dry granules at 45°C until loss on drying is not more than 0.6% (vacuum 60°C, 2 h).

II. Finishing
   A. Fill product into suitable containers. Theoretical fill weight is 5.32 g (+3% fill excess) per 15-ml container, requiring approximately 12 ml of water for reconstitution.

Antibacterial and Bacterial Culture Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
125.00–500 mg	1	Penicillin, Cephalosporin or Macrolide	125.00–500.00
10–100 Million	2	Lactobacillus Acidophilus[a]	10–100 B

[a] Substitute with: Lactobacillus Spores, 300–600 million; streptococcus thermophillus 10 million, Lactobacillus Lactis, 10–500 million, streptococcus lactis 10 million, saccharomyces cerevisiae 10 million, Lactobacilli GG 10^{10} units. This formulation includes both the anti-infective agent which can be penicillin, a cephalosporin or a macrolide in doses ranging from 125 to 500 mg per capsule. Also included in the same capsule is a granulation of the bacteria which are known to be eradicated during the therapy with these antibiotics. The bacterial are coated to protect them from the effect of co-administered antibiotic and last in the intestine for over 3 months replenishing the lost flora and reduce many side effects related to use of antibiotics.

MANUFACTURING DIRECTIONS

1. Granules of one of the active ingredients (e.g., microorganisms) are first prepared by the following process:

INGREDIENTS PARTS BY WEIGHT

Microorganism: 42.86%
Microcrystalline cellulose: 53.93%
Magnesium stearate: 1.07%
Colloidal silicone dioxide: 0.71%
Cross carmellose sodium: 1.43%

The granules formed are compressed into a tablet-by-tablet compression machine heaving a laying facility at a temperature below 25°C and relative humidity not more than 50%.

Tablets are transferred to a coating pan for coating using the following formulation:

INGREDIENTS PARTS BY WEIGHT

Hydroxypropyl methylcellulose phthalate: 4.37%
Titanium dioxide: 0.96%
Purified talc: 0.19%
Polyethylene glycol: 0.99%
Isopropyl alcohol: 34.95%
Dichloromethane: 58.54%

2. The remaining active ingredient (antibacterial agent) is mixed with excipients and filled into gelatin capsules. Before sealing of capsules the coated tablet containing active ingredients is introduced into capsules. The relative proportion of anti-infective agent and excipients for filling in capsule:

INGREDIENTS PARTS BY WEIGHT

Anti-infective agent: 91.94%
Pregelatinized starch: 6.24%
Magnesium stearate: 1.44%
Sodium lauryl sulfate: 0.38%

Antifungal Foot Powder

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
5.00	1	Dichlorobenzyl Alcohol (Myacide SF)	5.00
5.00	2	Allantoin	5.00
200.00	3	Cornstarch	200.00
790.00	4	Talc	790.00

MANUFACTURING DIRECTIONS

Mix all ingredients using the geometric dilution technique and fill.

Aspartame Granules in Sachet

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
30.00	1	Aspartame	30.00
2.00	2	Silicon Dioxide Colloidal	2.00
968.00	3	Cerelose Powder No. 60[a]	1052.00

[a] Std. Qty. of Cerelose Powder allows for Loss on Drying.

MANUFACTURING DIRECTIONS

1. Protect from moisture; 40% relative humidity (RH) at 25°C.
2. Oven dry cerelose powder at 50°C overnight until loss on drying is no more than 3% (3 h, vacuum at 60°C). Pass dried cerelose powder through 595-µm aperture screen in oscillating granulator.
3. Charge the following ingredients into suitable blender: aspartame, half the amount dried of cerelose powder (milled) and silicon dioxide colloidal. Add balance of dried cerelose powder (total amount of dried powder is 968 g/kg), and blend for 15 min.
4. Pass blended powders through 840-µm aperture screen using an oscillating granulator, and discharge into polyethylene-lined drums. Fill weight of 1 g/sachet.

Aspartame Powder in Sachet

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
47.50	1	Aspartame	47.50
2.50	2	Silicon Dioxide Colloidal	2.50
950.00	3	Mannitol Granules	950.00

MANUFACTURING DIRECTIONS

1. Protect from high humidity; 40% RH at 25°C.
2. Pass mannitol granules and silicon dioxide colloidal through 840-µm aperture screen in oscillating granulator.
3. Charge the following ingredients into suitable blender: aspartame, half the amount of mannitol granules, and silicon dioxide colloidal.
4. Add balance of mannitol granules and blend for 15 min.
5. Pass blended powders through 840-µm aperture screen using an oscillating granulator and discharge into polyethylene-lined drums. Fill 0.8 g/sachet.

Aspirin and Chlorpheniramine Powder

The active ingredients are: aspirin (650 mg) and chlorpheniramine maleate (4 mg) per powder. The inactive ingredients are: fumaric acid, glycine, lactose, potassium chloride, silica, and sodium lauryl sulfate.

Aspirin and Phenylpropanolamine Powder

The active ingredients are: aspirin (650 mg), phenylpropanolamine hydrochloride (25 mg) per powder, and pseudoephedrine hydrochloride (60 mg) per powder sachet. The inactive ingredients are: fumaric acid, glycine, lactose, potassium chloride, silica, and sodium lauryl sulfate.

Aspirin Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
320.00	1	Aspirin	320.00
480.00	2	Gelatin	480.00
QS	3	Water Purified	QS
QS	4	Corn Oil	QS
QS	5	Petroleum Ether	QS
QS	6	Isopropyl Alcohol	QS
QS	7	Glutaraldehyde 1%	QS

MANUFACTURING DIRECTIONS

1. Item 2 is added to 0.8 l of Item 3 and the mixture is allowed to stand at 25°C for 1 h while the gelatin hydrates and swells.
2. This preparation is then heated to 60°C while it is stirred at 300 rpm for 30 min; 0.5 l of distilled water, previously heated to 60°C, is then added, and the solution is stirred at 500 rpm for an additional 5 min.
3. Item 1, as finely powdered aspirin, is then added to the solution while stirring is continued to give a uniform suspension.
4. After 1 min, the warm suspension is poured without delay into 5 l of a rapidly stirred (500 rpm) solution of 20% corn oil in petroleum ether, which has been previously brought to 25°C, and the resulting emulsion is rapidly (i.e., over a period of no more than 5 min) cooled to 5°C while the stirring is continued.
5. 3.2 l of cold (5°C) isopropyl alcohol is then added to dehydrate the gelatin microspheres while the preparation is stirred for another 10 min.
6. The microspheres are then collected by filtration and washed three times with cold (5°C) isopropyl alcohol.
7. They are then immersed in 0.8 l of a 1% solution of glutaraldehyde in cold (5°C) isopropyl alcohol for 8 h and then washed three times with isopropyl alcohol, collected by filtration, and vacuum dried for 24 h.
8. The microspheres, which average 300–400 μm in diameter, are filled into gelatin capsules for administration as a safer, long-acting, analgesic product (800 mg of the microsphere mix, which contains 320 mg of aspirin, is filled into each size 0 capsule). The capsules, when released into the stomach following ingestion, provide for sustained release of the drug for from 1–4 h and also assure that the drug reaches the gastrointestinal mucosa while in the solution state, instead of the more deleterious solid state that is characteristic of conventional dosage forms of this drug. Physical integrity of the matrix is maintained for 1–4 h after the release of its drug content, after which time the matrix dissolves.

Aspirin, Salicylamide, and Caffeine Powder

Each powder contains aspirin (650 mg), salicylamide (195 mg), and caffeine (33.3 mg). The inactive ingredients are: dioctyl sodium sulfosuccinate, fumaric acid, lactose, and potassium chloride. For arthritis strength powder, the active ingredients in each powder are: aspirin (742 mg), salicylamide (222 mg), and caffeine (38 mg). The inactive ingredients are: dioctyl sodium sulfosuccinate, fumaric acid, lactose, and potassium chloride.

Azithromycin Capsules

Each capsule contains azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard gelatin capsules (containing FD&C Red No. 40). They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate.

1.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Azithromycin, USE Azithromycin Dihydrate[a]	263.00
196.00	2	Anhydrous Lactose	196.00
50.00	3	Starch (Cornstarch Dried)	50.00
9.00	4	Magnesium Stearate	9.00
2.00	5	Sodium Lauryl Sulfate	2.00
—	6	Empty Hard Gelatin Capsules, Size 0	1000

Note: Weight of one capsule = 520 mg + shell.

[a] Considering the potency of the active ingredient is 1000 mcg/mg (anhydrous basis) with water content 5.0%, the required quantity of azithromycin dihydrate depends on the provided potency.

MANUFACTURING DIRECTIONS

Note: Processing should be done under a controlled room temperature and humidity area. The limits are: room temperature: 20–25°C; RH: 40–45%.

1. Mix Items 1 and 2 in a polyethylene bag. Pass through a 500-µm stainless steel sieve. Collect in a stainless steel drum lined with a polyethylene bag.
2. Mix Items 3–5 in a polyethylene bag. Pass through a 250-µm stainless steel sieve. Collect in a polyethylene bag.
3. Take a polyethylene bag. Check if there is any leakage. Add the powder mix from Steps 1 and 2. Mix manually for 1 min.
4. Unload the powder in a stainless steel drum.
5. Check the temperature and relative humidity of the room before beginning encapsulation. The limits are: RH: 40–45%; temperature: 20–25°C.
6. Load the empty capsule shells, size 0, in the hopper.
7. Switch the power to "ON." Check the locking of the capsules without powder. The locking length is 21.1–21.7 mm.
8. Load the powder in the hopper by scoop. Switch the power to "ON." Adjust the fill net weight to 520 mg per capsule. Nominal weight of one capsule: 520 mg + weight of one empty shell (95 mg). Target weight: 520 mg ± 2% + weight of one empty shell (95 mg).

2.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Azithromycin Base, USE Azithromycin Monohydrate	263.72
149.88	2	Lactose Anhydrous	149.88
9.40	3	Magnesium Stearate/Sodium Lauryl Sulfate (90/10)	9.40

Note: Based on bulk potency of 94.8%; adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Sift Items 1 and 2 through an 80-mesh screen and blend.
2. Add Item 3, and mix for 3 min.
3. Fill 470 mg in size 0 capsules.

Azithromycin Capsules and Oral Suspension

Azithromycin has the chemical name (*2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)*-13-[(2,6-dideoxy-3-*C*-methyl -3-*O*-methyl-(alpha)-*L-ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-(beta)-*D-xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-1. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red No. 40). They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate. It is also supplied as a powder for oral suspension in bottles containing azithromycin dihydrate powder equivalent to 300 mg, 600 mg, 900 mg, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate tribasic anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C Red No. 40; and spray-dried artificial cherry, creme de vanilla, and banana flavors. After constitution, each 5 ml of suspension contains 100 mg or 200 mg of azithromycin.

Azithromycin for Oral Suspension

1.

Bill of Materials

Scale (mg/5 ml)	Item	Material Name	Qty/Bottles (g)
200.00	1	Azithromycin, USE Azithromycin Dihydrate[a]	1.263
3861.50	2	Castor Sugar	23.169
18.00	3	Tribasic Sodium Phosphate	0.108
15.00	4	Sodium Benzoate	0.090
2.50	5	Hydroxypropyl Cellulose (Klucel EF)	0.015
2.50	6	Xanthan Gum	0.015
15.00	7	Cherry Dry Flavor	0.090
33.33	8	Vanilla Dry Flavor	0.200
25.00	9	Banana Dry Flavor	0.150

[a] Considering the potency of the active ingredient is 1000 mcg/mg (anhydrous basis) with water content 5.0%, the required quantity of azithromycin dihydrate depends on the provided potency.

MANUFACTURING DIRECTIONS

Note: Processing should be done under controlled room temperature and humidity conditions. The limits are: Room temperature: 20–25°C; RH: 40–45%.

1. Dry Item 3 at 90°C for 2 h.
2. Sift Item 2 through a Fitz mill, impact forward, medium speed using sieve No. 24228.
3. Collect in a stainless steel drum.
4. Sift 12.0 g of Item 2 (From Step 2) and Item 1 through 630-µm s.s. sieve in sifter. Load into a Drum Blender. Mix for 3 min.
5. Mix 5.0 g of Item 2 (From Step 2), Item 3 from Step 1, and Items 4–9 in a polyethylene bag. Sift through 630-µm s.s sieve in sifter. Collect in a polyethylene bag.
6. Load the powder mix from Step 4 into Step 3 in a Drum Blender. Mix for 3 min.
7. Load 6.17 g of Item 2 (From Step 2) into Step 5 in a Drum Blender. Mix for 3 min.
8. The fill weight for a 30-ml pack is 25.10 g.

2.

Bill of Materials			
Scale (mg/Bottle)	**Item**	**Material Name**	**Qty/1000 Bottles (g)**
838.57	1	Azithromycin Dihydrate	838.57
15,487.74	2	Sucrose	15,487.74
70.01	3	Sodium Phosphate Tribasic Anhydrous	70.01
26.62	4	Hydroxypropyl Cellulose (Klucel EF)	26.62
26.62	5	Xanthan Gum (Keltrol)	26.62
0.67	6	FD&C Red No. 40	0.67
59.94	7	Cherry Flavor Spray-Dried Artificial No. 11929	59.94
133.28	8	Vanilla Flavor Artificial No. 11489	133.28
99.96	9	Banana Flavor Spray-Dried Artificial No. 15223	99.96

Note: Based on bulk potency of 95.4%; adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Sift all ingredients through an 80-mesh screen, and mix well.
2. Fill 16.743 g per bottle.
3. To reconstitute, add 0.52 ml for each g of dry suspension.

Azithromycin Sachet for Oral Suspension

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachet (g)**
1.000	1	Azithromycin Base, USE Azithromycin Dihydrate	1.048
9.707	2	Sucrose	9.707
0.088	3	Sodium Phosphate Tribasic Anhydrous	0.088
0.055	4	Colloidal Silicon Dioxide	0.055
0.038	5	Cherry Flavor Spray-Dried Artificial	0.038
0.064	6	Banana Flavor Spray-Dried Artificial	0.064

Note: Based on bulk potency of 95.4% of azithromycin; adjust for potency using Item 2.

MANUFACTURING DIRECTIONS

1. Sift Items 1–4 through an 80-mesh screen into a blender; blend.
2. Sift Items 5 and 6, and add to Step 1. Blend.
3. Fill 11 g in one sachet, approximately 3.25×4 inch, polyethylene-lined. To reconstitute, add contents to 60 ml water, and stir well.

Balsalazide Disodium Capsules

Each capsule contains 750 mg of balsalazide disodium, a prodrug that is enzymatically cleaved in the colon to produce mesalamine (5-aminosalicylic acid), an anti-inflammatory drug. Each daily dose of 6.75 g is equivalent to 2.4 g of mesalamine. Balsalazide disodium has the chemical name (E)-5-[[-4-[[(2-carboxyethyl)amino] carbonyl]phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate. The inactive ingredients are colloidal silicon dioxide and magnesium stearate. The sodium content of each capsule is approximately 86 mg.

Benazepril Hydrochloride and Amlodipine Besylate Capsules

These capsules are a combination of amlodipine besylate and benazepril hydrochloride. Benazepril hydrochloride's chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride. Benazeprilat, the active metabolite of benazepril, is a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group. Amlodipine besylate is a white to pale yellow crystalline powder that is slightly soluble in water and sparingly soluble in ethanol. Its chemical name is (R,S)3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate. The capsules are formulated for oral administration with a combination of amlodipine besylate equivalent to 2.5 or 5 mg of amlodipine and 10 or 20 mg of benazepril hydrochloride. The inactive ingredients of the capsules are: calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Benazepril Hydrochloride	20.00
32.90	2	Lactose Monohydrate	32.90
5.00	3	Pregelatinized Starch	5.00
1.00	4	Colloidal Silicon Dioxide	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline Cellulose	10.00
4.00	7	Hydrogenated Castor Oil	4.00
QS	8	Water Purified	QS
4.88	9	Hydroxypropyl Methylcellulose 2910, 3 cps	4.88
0.19	10	Polysorbate 80	0.19
QS	11	Purified Water	QS
QS	12	Talc	QS
5.00	13	Amlodipine, USE Amlodipine Besylate	6.94
124.05	14	Microcrystalline Cellulose	124.05
63.00	15	Calcium Phosphate Dibasic	63.00
4.00	16	Sodium Starch Glycolate	4.00
2.00	17	Magenesium Stearate	2.00

MANUFACTURING DIRECTIONS

1. Benazepril hydrochloride cores are prepared using the following:
   a. Items 1–3 are milled and blended together and water is added to granulate the blend.
   b. The wet granules are screened and oven dried. The dried granules are then milled together with Items 5–7.
   c. Item 4 is screened and then mixed with the other ingredients. The resulting mixture is then compressed into a core.
2. The resulting cores are coated with a coating solution prepared as follows: Item 10 is dissolved in the water and Item 9 is added thereto.
   a. The previously made cores are then coated with this solution and the wet coated tablets are dried.
   b. The dried tablets are then dusted with Item 12.
3. Amlodipine besylate for incorporation into the formulation is prepared as follows:
   a. Items 13–16 are mixed together, and the blended mixture is screened and reblended.
   b. Item 17 is separately screened and then blended with the reblended mixture containing the amlodipine.
4. No. 1 hard gelatin capsules are used to encapsulate one benazepril hydrochloride containing coated core along with 200 mg of the amlodipine besylate containing powder per capsule.

Bisacodyl Colonic Delivery Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
210.00	1	Sugar Sphere	210.00
5.00	2	Hydroxypropyl Methylcellulose	5.00
3.00	3	Bisacodyl Micronized	3.00
1.00	4	Hydroxypropyl Methylcellulose	1.00
18.00	5	Eudragit L100-55	18.00
5.00	6	Eudragit S	5.00
4.00	7	Dibutyl Phthalate	4.00
8.00	8	Talc	8.00
1.00	9	Red Ferric Oxide	1.00
2.00	10	Talc	2.00

MANUFACTURING DIRECTIONS

1. Bisacodyl is micronized in a fluid energy mill using a grinding pressure of 50 psi to produce a powder with 90% of the particles below 10 μm.
2. It is dispersed in water at a level of 2.7% by weight, with 0.9% by weight of hydroxypropyl methylcellulose (HPMC) as a binding polymer sprayed onto sugar spheres (6.53–6.63 mm diameter) in a perforated pan coater maintaining an outlet airbed temperature of about 40°C.
3. Barrier Coat: HMPC is dissolved in water to produce a 4% by weight solution, which is coated on the substrates described above in a perforated pan coater maintaining an outlet air/bed temperature of about 40°C.
4. Inner Enteric Coat: Eudragit L100-55 and dibutyl phthalate are dissolved in a solution of isopropanol, acetone, and water (37:9:1) at levels of 8.0% and 1.6% (total weight percent), respectively. Talc is then suspended in the solution at a level of 3.3% by weight. The resulting mixture is coated onto the barrier-coated substrates in Step 4 in a perforated pan coater maintaining an outlet air/bed temperature of about 30°C.
5. Outermost Enteric Coat: Eudragit S and dibutyl phthalate are dissolved in a solution of isopropanol, acetone, and water (37:9:1) at levels of 8.0% and 1.6% (total weight percent), respectively. Red ferric oxide and talc are then suspended in the solution at levels of 1.2% and 2.1% by weight, respectively. The resulting mixture is coated onto the barrier-coated substrates above in a perforated pan coater maintaining an outlet air/bed temperature of about 30°C.
6. Appropriate theoretical quantity is filled in hard capsules.

Brompheniramine and Pseudoephedrine Capsules

These capsules are light green and clear, and contain white beads. The extended-release capsule contains: brompheniramine maleate (12 mg) and pseudoephedrine hydrochloride (120 mg) in a specially prepared base to provide prolonged action. Alternate strength is 6 mg and 60 mg, respectively. The capsules also contain the following inactive ingredients: calcium stearate, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, pharmaceutical glaze, starch, sucrose, and talc.

Budesonide Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
1.00	1	Budesonide Micronized	1.00
321.00	2	Sugar Spheres	321.00
6.60	3	Aquacoat ECD30	6.60
0.50	4	Acetyltributyl Citrate	0.50
0.10	5	Polysorbate 80	0.10
17.50	6	Eudragit L100-55	17.50
1.80	7	Triethylcitrate	1.80
8.80	8	Talc	8.80
0.01	9	Antifoam MMS	0.01

MANUFACTURING DIRECTIONS

1. Budesonide (32.2 g) is suspended in the Aquacoat ECD30 dispersion (0.70 kg) with the aid of the polysorbate 80 (0.42 g) together with acetyltributyl citrate (15.8 g).
2. The mixture is sprayed on to sugar spheres (10.2 kg) in a fluid bed apparatus.
3. The enteric coating, consisting of the Eudragit L100-55 dispersion (Eudragit L100-55 [0.558 kg], triethylcitrate [55.8 g], talc [0.279 kg], antifoam MMS [0.44 g], and polysorbate 80 [2.79 g]) is then sprayed on the spheres.
4. The pellets are dried in the fluid bed apparatus, sieved, and filled in hard gelatin capsules.

Budesonide Inhalation Powder

Budesonide is a corticosteroid designated chemically as (RS)-11(beta),16(alpha),17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The inhalation-driven, multi-dose dry powder inhaler contains only micronized budesonide. Each actuation of container provides 200 mcg budesonide per metered dose, which delivers approximately 160 mcg budesonide from the mouthpiece (based on *in vitro* testing at 60 l/min for 2 sec).

Butalbital and Acetaminophen Capsules

Each capsule contains butalbital (50 mg) and acetaminophen (325 mg). In addition, each capsule may also contain the following inactive ingredients: benzyl alcohol, butylparaben, D&C;Red No. 28, D&C Red No. 33, edetate calcium disodium, FD&C Blue No. 1, FD&C Red No. 40, gelatin, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, sodium propionate, and titanium dioxide.

Calcitonin (Salmon) Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
500 IU	1	Salmon Calcitonin	500,000 IU
0.048	2	Dimyristoyl Phosphatidic Acid	0.048
3.44	3	Aprotinin[a]	3.44
3.78	4	Hydroxypropyl Cellulose-LF	3.78
3.78	5	Polyoxy-40 Stearate	3.78
140.97	6	Polyethylene Glycol 400	140.97
15.55	7	Propylene Glycol	15.55
8.83	8	Citrate Buffer	8.83
31.49	9	Cholesterol	31.49
17.40	10	Tween 80	17.40
63.69	11	Egg Yolk Lecithin	63.69
19.79	12	d-alpha Tocopherol	19.79
28.15	13	Glyceryl Monooleate	28.15
251.45	14	Isostearic Acid	251.45

Note: Human Growth Hormone: 2.6 IU = 1 mg.

[a] Aprotinin: 7500 KIU = 1 mg.

MANUFACTURING DIRECTIONS

GENERAL:

1. Polyoxy-40 stearate is dispersed in the solvent mixture of polyethylene glycol 400 and propylene glycol.
2. Sodium cholate is also separately dispersed in the mixture.
3. A water solution containing recombinant human growth hormone, phospholipid, and aprotinin is then added to the solvent mixture from Step 1, and the pH is adjusted to 2.5 with the help of buffer.
4. The lipid solution is made separately in another vessel.
5. To the oil solution, the polyol solution is added dropwise while mixing continuously. While mixing, it is suggested that the vessel be ice jacketed to prevent the denaturation of the protein in the formulation.
6. Clear transparent liquid, which is called the preemulsion solution, is obtained after approximately 5 min of mixing at low speed. An *in situ* emulsion can be made by mixing any ratio of the preemulsion solution with the simulated intestinal fluid.
7. The preemulsion solution is filled in a size 0 hard gelatin capsule, and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
8. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, a 3.5–4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
9. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose pthalate, cellulose acetate pthalate, etc., are used.
10. Anionic copolymers, which are based on methacrylic acid and methyl methycrate and are commercially available as Eudragit, are also very suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, or isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5–6% of the weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows:

Methacrylic acid and methyl, 10% w/w
Methycrate copolymer (polymer)
Diethyl butyl pthalate (plasticizer), 2% w/w
Acetone, 22% w/w
Isopropanol, 66% w/w

PROCEDURE:

1. Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
2. For a size 0 capsule the above mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid bed sprayer/dryer is operated with the following parameters:

   Flow Rate: 1.5 ml/min
   Inlet Air Temp: 25°C
   Outlet Air Temp: 25°C
   Air Flap: 35
   Atomizer: 2.0 bar

3. A size 0 capsule after the enteric coating will typically have the following composition:

   Preemulsion Solution: 0.589 g
   Undercoat Polymer: 0.027 g
   Enteric Coat Polymer: 0.032 g, 0.648 g

Calcitriol Capsules

Calcitriol is a synthetic vitamin D analog that is active in the regulation of the absorption of calcium from the gastrointestinal tract and its utilization in the body. Chemically, calcitriol is 9,10-seco(5Z,7E)-5,7,10(19)-cholestatriene-1(alpha),3(beta),25-triol. The other names frequently used for calcitriol are 1(alpha),25-dihydroxycholecalciferol; 1,25-dihydroxyvitamin D3; 1,25-DHCC; 1,25(OH) 2 D 3; and 1,25-diOHC. It is available as capsules containing 0.25 mcg or 0.5 mcg calcitriol and as an oral solution containing 1 mcg/ml of calcitriol. All dosage forms contain butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) as antioxidants. The capsules contain a fractionated triglyceride of coconut oil, and the oral solution contains a fractionated triglyceride of palm seed oil. Gelatin capsule shells contain glycerin, parabens (methyl and propyl), and sorbitol, with the following dye systems: 0.25 mcg of FD&C Yellow No. 6 and titanium dioxide; 0.5 mcg FD&C Red No. 3, FD&C Yellow No. 6, and titanium dioxide. The oral solution contains no additional adjuvants or coloring principles.

Calcium Carbonate Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
600.00	1	Calcium Carbonate	600.00
900.00	2	Gelatin	900.00
QS	3	Water Purified	1.5 l
QS	4	Corn Oil	QS
QS	5	Petroleum Ether	QS
QS	6	Isopropyl Alcohol	QS
QS	7	Glutaraldehyde 1%	QS

MANUFACTURING DIRECTIONS

1. Item 2 is added to 1.5 l of Item 3, and the mixture is allowed to stand at 25°C for 1 h while the gelatin hydrates and swells.
2. To this mixture is added Item 1, and the preparation is heated to 60°C while it is stirred at 300 rpm for 30 min to effect dissolution of the gelatin and to ensure even suspension of the calcium carbonate. Additional distilled water, previously heated to 60°C, is then added to bring the total volume to 100°C while the stirring is continued.
3. This preparation is slowly poured into 12 l of a mixture consisting of 20% by volume of corn oil in petroleum ether, which has previously been heated to 60°C while the petroleum ether solution is stirred at 500 rpm. This preparation is then cooled to 5°C with continued stirring, and the stirring is continued at 500 rpm for 1 h after the lower temperature is reached.
4. While stirring of the preparation at 5°C is continued, 6 l of isopropanol are then added. The solid microspheres are then collected by filtration and washed three times with isopropyl alcohol. The capsules are then immersed in 1.5 L of a 1% solution of glutaraldehyde in isopropyl alcohol for 8 h at 5°C; the capsules are then washed again, three times, with isopropyl alcohol, filtered, and vacuum dried for 24 h.
5. The microspheres, which average between 200 and 300 μm in diameter, are filled into gelatin capsules for administration as a long-acting antacid product (1.5 g of the microsphere mix, which contains 600 mg calcium carbonate, are filled into each size 0 capsule). The microcapsules, when released into the stomach following ingestion, delay the reaction of the calcium carbonate with the acid of the stomach for a useful period of time (between 3 and 6 h), which provides for sustained antacid protection for the patient. Physical integrity of the matrix is maintained from 1 to 4 h after the release of its drug contents, after which the matrix dissolves through hydrolytic cleavage of its bonds and proteolytic digestion.

Camptothecin Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	CPT-11	100.00
470.00	2	Polyethylene Glycol 13000	470.00
50.00	3	Triacetin	50.00
5.00	4	Polysorbate 80	5.00
QS	5	Capsule Shell HPMC	1000.00

MANUFACTURING DIRECTIONS

1. Items 2–4 are melted, and Item 1 is added and admixed thoroughly; the mixture is allowed to cool and solidify.
2. Mill the Step 1 mixture into a suitable size, and fill in an HPMC shell capsule.

Carbamazepine Extended-Release Capsules

Carbamazepine is an anticonvulsant and a specific analgesic for trigeminal neuralgia, available for oral administration as 200 mg and 300 mg extended-release capsules of carbamazepine, USP. Carbamazepine is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide. The capsule is a multi-component capsule formulation consisting of three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice daily dosing of carbamazepine. The inactive ingredients are: citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate, and other ingredients. The 200-mg capsule shells contain gelatin, FD&C Red No. 3, FD&C Yellow No. 6, yellow iron oxide, FD&C Blue No. 2, and titanium dioxide, and are imprinted with white ink. The 300-mg capsule shells contain gelatin, FD&C Blue No. 2, FD&C Yellow No. 6, red iron oxide, yellow iron oxide, and titanium dioxide, and are imprinted with white ink.

MANUFACTURING DIRECTIONS

This product is made from three types of pellets, one with instant-release profile and two with sustained-release profile; generally, an equal component of each pellet is used but other variations may be used as well.

	Percent	Kilograms
Pellet A: Immediate-Release Component		
Microcrystalline Cellulose, N.F. (MCC) (Avicel PH-101/102, Emcocel, etc.)	40.0	0.400
Hydroxypropyl Methylcellulose (HPMC) (Methocel E5/E50/K5/K50)	2.5	0.025
Croscarmellose, Type A, N.F. (Ac-Di-Sol)	2.0	0.020
Sodium Lauryl Sulfate (SLS)	0.1	0.001
Carbamazepine	55.4	0.554
Total	100.0	1.000
Pellet B: Sustained-Release Component		
Microcrystalline Cellulose	30.0	0.300
Hydroxypropyl Methylcellulose	5.0	0.050
Sodium Monoglycerate	8.0	0.080
Tartaric Acid	5.0	0.050
Sodium Lauryl Sulfate	0.2	0.002
Carbamazepine	51.8	0.518
Total	100.0	1.000
Coating		
Ethacrylic/Methacrylic Acid Esters (Eudragit RS100)	45.0	0.450
Ethacrylic/Methacrylic Acid Esters (Eudragit RL100)	45.0	0.450
Propylene Glycol	9.0	0.090
Talc	1.0	0.010
Total	100.0	1.000
Pellet C: Delayed-Release Component		
Microcrystalline Cellulose	25.0	0.250
Hydroxypropyl Methylcellulose Phthalate	10.0	0.100
Tartaric Acid	10.0	0.100
Sodium Monoglycerate	7.5	0.075
Dioctyl Sodium Sulfosuccinate	0.5	0.005
Carbamazepine	47.0	0.470
Total	100.0	1.000
Coating		
Cellulose Acetate Phthalate (CAP)	60.0	0.600
Ethylcellulose	25.0	0.250
PEG400	15.0	0.150
Total	100.0	1.000

Cefaclor Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Cefaclor	250.00
15.00	2	Starch	15.00
5.00	3	Silicon Fluid 350 cs	5.00
4.00	4	Magnesium Stearate	4.00

Note: For 500-mg strength, fill proportionally higher quantity.

MANUFACTURING DIRECTIONS

1. Mix cefaclor with silicon fluid and magnesium stearate.
2. Slug and granulate if necessary for flow.
3. Mix with starch powder.
4. Fill in appropriate size 2 capsules. Finish capsules with polishing methods.

Cefdinir Capsules and Oral Suspension

Cefdinir capsules and cefdinir for oral suspension contain the active ingredient cefdinir, an extended-spectrum, semisynthetic cephalosporin, for oral administration. Chemically, cefdinir is [6R-[6(alpha),7(beta) (Z)]]-7-[[(2-amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, polyoxyl 40 stearate, magnesium stearate, and silicon dioxide. The capsule shells contain FD&C Blue No. 1; FD&C Red No. 40; D&C Red No. 28; titanium dioxide, gelatin, and sodium lauryl sulfate. Powder for oral suspension, after reconstitution, contains 125 mg cefdinir per 5 ml and the following inactive ingredients: sucrose, citric acid, sodium citrate, sodium benzoate, xanthan gum, guar gum, artificial strawberry and cream flavors, silicon dioxide, and magnesium stearate. Powder for oral suspension, after reconstitution, contains 125 mg cefdinir per 5 ml and the following inactive ingredients: sucrose, citric acid, sodium citrate, sodium benzoate, xanthan gum, guar gum, artificial strawberry and cream flavors, silicon dioxide, and magnesium stearate.

Cefixime for Oral Suspension

Cefixime is a semisynthetic, cephalosporin antibiotic for oral administration. Chemically, it is (6 *R,*7 *R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7 2-(*Z*)- [*O*-(carboxymethyl)oxime]trihydrate. Its molecular weight is 507.50 as the trihydrate.

Powder for oral suspension, when reconstituted, provides 100 mg/5 ml. The powder for oral suspension is strawberry flavored and contains sodium benzoate, sucrose, and xanthan gum.

Cefpodoxime Proxetil for Oral Suspension

Each 5 ml of oral suspension contains cefpodoxime proxetil equivalent to 50 mg or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: artificial flavorings, butylated hydroxy anisole (BHA), carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

Cefprozil for Oral Suspension

Cefprozil is a semisynthetic, broad-spectrum cephalosporin antibiotic. Cefprozil is a cis and trans isomeric mixture (≥90% cis). The chemical name for the monohydrate is (6*R*,7*R*)-7-[(R)-2-amino-2-(p-hydroxyphenyl)acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate. Cefprozil for oral suspension contains a cefprozil equivalent to 125 mg or 250 mg of anhydrous cefprozil per 5 ml of constituted suspension. In addition, the oral suspension contains the following inactive ingredients: aspartame, cellulose, citric acid, colloidal silicone dioxide, FD&C Red No. 3, flavors (natural and artificial), glycine, polysorbate 80, simethicone, sodium benzoate, sodium carboxymethylcellulose, sodium chloride, and sucrose.

Ceftibuten Capsules and Oral Suspension

Ceftibuten capsules and ceftibuten for oral suspension contain the active ingredient ceftibuten as ceftibuten dihydrate. Ceftibuten dihydrate is a semisynthetic cephalosporin antibiotic for oral administration. Chemically, it is (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-4-carboxycro-tonamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, dihydrate. Its molecular weight is 446.43 as the dihydrate. Capsules contain ceftibuten dihydrate equivalent to 400 mg of ceftibuten. Inactive ingredients contained in the capsule formulation include: magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell and band contain gelatin, sodium lauryl sulfate, titanium dioxide, and polysorbate 80. The capsule shell may also contain benzyl alcohol, sodium propionate, edetate calcium disodium, butylparaben, propylparaben, and methylparaben. Oral suspension after reconstitution contains ceftibuten dihydrate equivalent to 90 mg of ceftibuten per 5 ml. Oral suspension is cherry flavored and contains the following inactive ingredients: cherry flavoring, polysorbate 80, silicon dioxide, simethicone, sodium benzoate, sucrose (approximately 1 g/5 ml), titanium dioxide, and xanthan gum.

Ceftibutin for Oral Suspension

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
72.00	1	Ceftibutin Trihydrate	72.00
0.40	2	Polysorbate 80	0.40
0.80	3	Simethicone	0.80
16.00	4	Xanthan Gum	16.00
10.00	5	Silicone Dioxide	10.00
18.00	6	Titanium Dioxide	18.00
8.00	7	Sodium Benzoate	8.00
3.66	8	Cherry Flavor, Natural and Artificial (Microencapsulated)	3.66
QS	9	Sucrose QS to 1 kg	QS

MANUFACTURING DIRECTIONS

Note: This formulation, upon reconstitution, gives a final concentration of 19 mg/ml. For 36 mg/ml, use 144.00 g of Item 1 and 4.0 g of Item 7. Adjust quantity of Item 1 based on moisture content. The quantity given here is for anhydrous form; adjust with Item 9.

1. Pass all items through an 80-mesh screen and blend.
2. Fill into 60-ml bottles at either 5, 7.5, or 15 g, or 120-ml bottles at 25 or 30 g aliquots.

Cefuroxime for Oral Suspension

Cefuroxime oral suspension contains cefuroxime as cefuroxime axetil, which is a semisynthetic, broad-spectrum cephalosporin antibiotic for oral administration. Chemically, cefuroxime axetil, the 1-(acetyloxy) ethyl ester of cefuroxime, is (*RS*)-1-hydroxyethyl (6 *R,*7 *R*)-7-[2-(2-furyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7 2-(*Z*)-(*O*-methyl-oxime), 1-acetate 3-carbamate. The oral suspension, when reconstituted with water, provides the equivalent of 125 mg or 250 mg of cefuroxime (as cefuroxime axetil) per 5 ml of suspension. It contains the following inactive ingredients: povidone K30, stearic acid, sucrose, and tutti-frutti flavoring.

Celecoxib Capsules

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
200.00	1	Celecoxib	200.00
204.00	2	Lactose	204.00
12.00	3	Sodium Lauryl Sulfate	12.00
7.00	4	Polyvinyl Pyrrolidone Potassium 30	7.00
—	5	Isopropyl Alcohol	45.00 l
6.00	6	Polyvinyl Pyrrolidone Potassium 30	6.00
6.00	7	Magnesium Stearate	6.00
15.00	8	Talc	15.00
50.00	9	Croscarmellose Sodium	50.00

MANUFACTURING DIRECTIONS

1. Charge Items 1–3 in suitable vessel after passing through a No. 60 mesh and mix for 15 min.
2. In a separate container, mix and prepare a solution of Items 4 and 5.
3. Add Step 2 into Step 1 and mix; pass the granules through a 2.5-mm sieve; dry the granules at 40°C in open room or fluid-bed dryer to moisture of not more than 1%.
4. Pass the dried granules through a No. 30 sieve, and recycle through 1.5-mm sieve to size all granules through No. 30 mesh.
5. Pass Items 7–9 through No. 40 mesh, and add to Step 4; mix for 5–10 min.
6. Tap density is not more than 0.80 g/cc; fines are not more than 10%.
7. Fill 600 mg in size 0 capsules.

Cellulose Triacetate Liquefiable Topical Powder

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
120.00	1	Cellulose Triacetate	120.00
880.00	2	Dow Corning® 345	880.00

MANUFACTURING DIRECTIONS

1. A liquefiable powder was prepared by evaporative spray drying. Dow Corning 345, a slightly volatile cyclic silicone liquid, was used as the porogen.
2. Cellulose triacetate (40 g) was dissolved in 3000 g of methylene chloride by moderate stirring for 4 h. To that solution was added 270 g of the porogen dissolved in 1000 g of methylene chloride.
3. The resulting homogeneous solution was sprayed at 1000 PSI from a 0.0135-in. nozzle, downward into a tower 100 cm in diameter and 300 cm tall, through which 1250 l/min of solvent-free air was passing from top to bottom.
4. The evaporatively formed powder was collected on a fabric filter spanning the bottom of the tower, and the solvent-laden air was passed through carbon beds to collect and recover solvent.
5. The product was transferred to a steel tray and exposed as a 1-cm deep layer in a ventilated hood for 25 min to remove residual solvent.
6. An analysis showed 12% cellulose triacetate, 88% DC 345, and less than 4 ppm of residual methylene chloride.
7. The white powder readily could be dusted onto the feet and made to liquefy and vanish by gentle rubbing.

Cephalexin Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
500.00	1	Cephalexin, USE Cephalexin Monohydrate (0–2% excess)	526.31
2.50	2	Magnesium Stearate	2.50
QS	3	Cornstarch	600.00

MANUFACTURING DIRECTIONS

1. Charge magnesium stearate, cornstarch, and $^1/_{10}$ part of cephalexin into a suitable mixer. Mix well.
2. Pass blend from Step 1 and balance of cephalexin through an 840-µm aperture screen by hand or with a mechanical shaker.
3. Charge into a suitable mixer and mix well. Discharge into polyethylene-lined drums.
   Note: For slugging, first use 624 mg of magnesium stearate; balance after milling slugs through a 1.2-mm aperture screen in an oscillating granulator.
4. Machine fill using either size 00 or size 0 capsules; the theoretical weight of 10 caps is 6.0 g. Sort and final clean with sodium chloride.

Cephalexin Powder for Oral Suspension

Bill of Materials			
Scale (mg/5 ml)[a]	**Item**	**Material Name**	**Qty/5 l (g)**
125.00	1	Cephalexin, USE Cephalexin Monohydrate, 1.5% excess	131.50
0.50	2	FD&C No. 6	0.50
10.00	3	Orange Flavor	10.00
5.00	4	Vanilla Dry Flavor	5.00
5.00	5	Raspberry Dry Flavor	5.00
277.54	6	Castor Sugar	277.54
2844.80	7	Castor Sugar	2844.80

[a] Upon reconstitution as recommended. For 250-mg strength, adjust with Items 6 and 7.

MANUFACTURING DIRECTIONS

1. Charge Items 2–6 in a suitable mixer, and mix for 5 min.
2. Add Item 1 in portions, and mix well.
3. Pass through a Fitz mill, impact forward at high speed using sieve 24338.
4. Collect milled powder in Step 3 in a suitable mixer and mix for 10 min.
5. Pass Item 7 through 900-µm sieve; add 15% of quantity to Step 4, and mix for 10 min.
6. Load in a double-cone blender. Add the balance of Item 7 from Step 5, and mix for 20 min.
7. Fill appropriate quantity in bottles.

Cephradine Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
500.00	1	Cephradine, USE Cephradine Compacted (1000 mcg/mg with 5% moisture)[a]	526.00
7.00	2	Magnesium Stearate	7.00
8.40	3	Talc	8.40
18.60	4	Lactose Monohydrate[b]	18.60

[a] Adjust according to potency; taken as 105.2% of label.
[b] Adjust according to quantity of Item 1.

MANUFACTURING DIRECTIONS

1. Process limits are: relative humidity: 40–45%; temperature: 20–25°C.
2. Pass Item 1 through 630-µm sieve; crush larger particles in a Frewitt mill using a 1-mm sieve.
3. Load approximately half of Item 1 from Step 1 and 2 into a mixer.
4. Sift Items 2–4 through a 250-µm sieve in a suitable blender; blend for 5 min at slow speed.
5. Charge balance of Item 1 to Step 4, and blend for 5 min at slow speed.
6. Fill 560 mg per capsule.

Cephradine Powder for Suspension

Bill of Materials			
Scale (mg/5 ml)	**Item**	**Material Name**	**Qty/5 l (g)**
125.00	1	Cephradine, USE Cephradine Monohydrate with 10.8% excess[a]	131.50
8.00	2	Sodium Citrate	8.00
4.00	3	Citric Acid Anhydrous	4.00
10.00	4	Guar Gum	10.00
5.00	5	Methylcellulose, 15 cps	5.00
2.00	6	Yellow FD&C No. 6	2.00
20.00	7	Blood Orange Flavor	20.00
10.00	8	Orange Banana Flavor	10.00
3095.28	9	Castor Sugar	3095.28

[a] For 250 mg/5 ml, adjust active ingredient and adjust with Item 9.

MANUFACTURING DIRECTIONS

1. Pass Item 9 through a 500-μm sieve for use in later steps.
2. Charge Items 1–6 in a mixing vessel, and add about 10% of Item 9 from Step 1; mix for 5 min.
3. Pass the powder mixture in Step 2 through a Fitz mill.
4. Charge 10% of Item 9 from Step 1 in a separate mixing vessel, and add Items 7 and 8; blend for 5 min.
5. Add to Step 3, and blend for 5 min.
6. Pass Step 5 through a 500-μm sieve.
7. Add Item 9 (about 15%), and mix for 5 min; transfer to a double-cone blender.
8. Add 40% of Item 9, and mix for 10 min.
9. Add the balance of Item 9, and mix for another 15 min.
10. Fill. Fill weight for 100 ml = 66 g; fill weight for 60 ml = 39.60 g.

Cevimeline Capsules

Cevimeline is cis-2′-methylspiro (1-azabicyclo [2.2.2] octane-3, 5′-[1,3] oxathiolane) hydrochloride, hydrate (2:1). Each capsule contains 30 mg of active ingredient. The inactive ingredients are: lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
30.00	1	Cevimeline	30.00
60.00	2	Hydroxypropyl Cellulose	50.00
15.00	3	Sodium Carboxymethyl Cellulose Cross-Linked	15.00
189.00	4	Lactose	189.00
6.00	5	Magnesium Stearate	6.00

MANUFACTURING DIRECTIONS

1. Sift Items 1–3 through an 80-mesh screen and blend.
2. Pass Item 5 through a 100-mesh screen, and add to Step 1 and blend for 3 min.
3. Fill 300 mg in size 0 capsules.

Chlordiazepoxide Hydrochloride Capsules

Chlordiazepoxide hydrochloride (HCl) and the prototype for the benzodiazepine compounds provide a versatile therapeutic agent of proven value for the relief of anxiety. It is available as capsules containing 5 mg, 10 mg, or 25 mg chlordiazepoxide HCl. Each capsule also contains cornstarch, lactose, and talc. Gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, with the following dye systems: for 5-mg capsules — FD&C Yellow No. 6, plus D&C Yellow No. 10, and either FD&C Blue No. 1 or FD&C Green No. 3; for 10-mg capsules — FD&C Yellow No. 6, plus D&C Yellow No. 10, and either FD&C Blue No. 1 plus FD&C Red No. 3 or FD&C Green No. 3 plus FD&C Red No. 40; for 25-mg capsules — D&C Yellow No. 10 and either FD&C Green No. 3 or FD&C Blue No. 1.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Chlordiazepoxide Hydrochloride	5.10
114.00	2	Starch Dried	114.00
26.00	3	Dicalcium Phosphate	26.00
40.00	4	Talc	40.00

MANUFACTURING DIRECTIONS

1. Charge all ingredients in a suitable mixer after passing through a No. 60 mesh, and mix for 30 min.
2. Fill 185 mg in size 4 capsules.

Chloroxylenol and Chlorhexidine Topical Powder

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/Kg (g)
10.00	1	Chloroxylenol	10.00
10.00	2	Chlorhexidine Diacetate	10.00
30.00	3	Magnesium-L-Lactate	30.00
10.00	4	Allantoin	10.00
100.00	5	Zinc Stearate	10.00
840.00	6	Cornstarch	840.00

MANUFACTURING DIRECTIONS

1. Pass all Items through a 100-mesh screen and blend.
2. Fill; for use as a topical anti-infective formulation.

Chlorpromazine Sustained-Release Capsules

Chlorpromazine is 10-(3-dimethylaminopropyl)-2-chlorphenothiazine, a dimethylamine derivative of phenothiazine. Each sustained release capsule is so prepared that an initial dose is released promptly, and the remaining medication is released gradually over a prolonged period. Each capsule, with opaque orange cap and natural body, contains chlorpromazine hydrochloride as follows: 30 mg or 75 mg or 150 mg. Inactive ingredients consist of benzyl alcohol, calcium sulfate, cetylpyridinium chloride, FD&C Yellow No. 6, gelatin, glyceryl distearate, glyceryl monostearate, iron oxide, povidone, silicon dioxide, sodium lauryl sulfate, starch, sucrose, titanium dioxide, wax, and trace amounts of other inactive ingredients.

Cimetidine Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
275.00	1	Cimetidine	275.00
525.00	2	Sodium Alginate	525.00
QS	3	Calcium Chloride 2%	QS
QS	4	Poly-L-Glycine 0.05%	QS

MANUFACTURING DIRECTIONS

1. Item 2 is dissolved in 17.5 l of distilled water at 25°C, and Item 1 is added to this solution with constant mixing.
2. This preparation is added dropwise to a 2% calcium chloride solution through a small orifice that delivers droplets that are 1.0 mm in diameter. The spherical beads of cimetidine-containing calcium alginate thus formed are collected by filtration and washed three times with distilled water.
3. The beads are then immersed in a 0.05% aqueous solution of poly-L-lysine (molecular weight 14,000) for 4 h, then washed again three times with distilled water, collected by filtration, and dried under vacuum for 24 h. The beads thus produced are filled into gelatin capsules (800 mg per capsule, providing a dose of 275 mg of cimetidine).
4. This dosage form for the delivery of cimetidine over an extended time period allows for through-the-night protection for patients who suffer from excess gastric acidity without the high bedtime dose that conventional dosage forms require for this duration of protection. The high bedtime dose otherwise required for such protection is associated with untoward side effects, which are reduced through use of the dosage form described in this example.

Citrate Effervescent Powder

Bill of Materials			
Scale (mg/Tab)	**Item**	**Material Name**	**Qty/kg (g)**
0.50	1	Oil Lemon Terpeneless	0.50
10.00	2	Flavor, Lemon Natural Microseal	10.00
QS	3	Alcohol Dehydrated	6.50
440.33	4	Sodium Bicarbonate	440.33
0.35	5	Saccharin Sodium	0.35
157.50	6	Sodium Citrate Anhydrous	157.50
178.82	7	Acid Citric	178.82
222.50	8	Acid Tartaric	222.50

MANUFACTURING DIRECTIONS

Note: All processing is in controlled humidity; maximum RH 40% at 25°C. Sodium citrate and citric acid are anhydrous.

1. Dissolve lemon oil in dehydrated alcohol with stirring in a suitable container. Delete this step if using lemon flavored powder.
2. Sift sodium bicarbonate, if necessary, through a 595-µm aperture screen, and charge into a suitable mixer or charge material into mixer and mix for 10 min.
3. Add solution from Step 1 in the mixer very slowly while mixing; continue mixing at least 10 min and up to a total of 30 min, depending on equipment.
4. Screen the massed granulation mixture through a 595-µm aperture screen.
5. Divide approx. into two halves. Premix saccharin sodium into sodium citrate (and lemon powder if used) and sift through a 595-µm aperture screen or mill with a 595-µm aperture screen, knives forward at medium speed.
6. Sift both citric acid and tartaric acid separately through a 595-µm aperture screen or mill separately using a comminuting mill with a 595-µm aperture, knives forward at medium speed.
7. Load materials into a suitable blender, preferably in the following order: milled tartaric acid, milled citric acid, half of the granulation mixture, milled saccharin sodium and sodium citrate, and the remaining granulation mixture.
8. Blend for 20 min and pack into double plastic bags inside fiber drums. Provide silica gel protection to assure low humidity in drums. If blended material is lumpy, screen through a 1.2-mm aperture screen before bagging.

Clindamycin Capsules 150 mg

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
150.00	1	Clindamycin, USE Clindamycin Hydrochloride	163.00
12.00	2	Lactose	12.00
3.00	3	Magnesium Stearate	3.00
24.00	4	Talc	24.00
2.00	5	Aerosil 200	2.00
65.00	6	Starch Dried	65.00

MANUFACTURING DIRECTIONS

1. Pass all Items through a No. 60 mesh, and mix well for 30 min.
2. Fill 270 mg in size 2 capsules.

Clofibrate Capsules

A clofibrate capsule contains ethyl 2-(*p*-chlorophenoxy)-2-methyl-propionate, an antilipidemic agent. Each Capsule contains 500 mg of clofibrate for oral administration. Capsules also contain the following inactive ingredients: D&C Red No. 28, D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 28, FD&C Red No. 40, FD&C Yellow No. 6, and gelatin.

Clonidine Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
0.10	1	Clonidine Hydrochloride (equivalent to 0.087 mg Clonidine base) 100 μm or finer	0.10
70.00	2	Methocel® E4M[a]	70.00
129.90	3	Lactulose[b]	129.90

[a] This formulation is intended to provide an 8-h release pattern; for an extended release pattern of 12 h, use Methocel® K100M.
[b] Cornstarch can be used in place of lactulose.

MANUFACTURING DIRECTIONS

1. This is a low-dose product that requires a careful geometric dilution of Item 1 with portions of Item 3.
2. Add the triturate in Step 1 in one-half of Item 3, and mix well.
3. Add Item 2, and mix well; add balance of Item 3.
4. Fill 200 mg in an appropriate capsule size.

Clorazepate Dipotassium Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
7.50	1	Clorazepate Dipotassium	7.50
10.00	2	Potassium Carbonate Dried	10.00
0.45	3	Silicon Dioxide Colloidal	0.45
168.00	4	Talc	168.00
QS	5	Sodium Chloride Granules (for cleaning)	QS

MANUFACTURING DIRECTIONS

Note: Avoid exposing clorazepate to light and moisture; process in low-humidity area (46 grains, 35% RH at 76°F).

I. Blending
   A. Determine loss on drying (1 h Brabender or equivalent at 105°C) of potassium carbonate dried (NMT 0.5%), silicon dioxide (NMT 2.5%), and talc (NMT 0.3%).
   B. Mill, while mixing the potassium carbonate and silicon dioxide through a 60-mesh (250-µm aperture) screen using a Fitz mill or a similar mill, impact forward high speed.
   C. Premix screened clorazepate with the milled mixture of potassium carbonate and silicon dioxide in a suitable container. Pass the mix through a 40-mesh (420-µm) screen by hand. Clean the screen with a small portion of talc (about 0.63 g). Use rubber gloves when handling clorazepate.
   D. Charge about half of the remaining talc into a V-blender or a similar blender. Add the preblend from Step C and, finally, the remaining talc. Blend for 30 min. Discharge into polyethylene-lined drums, tightly tie, and seal.

II. Filling
   A. Fill blended material into hard gelatin capsules; fill weight for 10 caps is 1.85 g (± 0.06 g). Sort capsules on sort vibrator, clean with sodium chloride, and store in polyethylene-lined drums.

III. Printing
   A. Print capsules using edible ink.

Cyclosporin A Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	Cyclosporin A	100.00
300.00	2	Cremophor RH (or Tween)	300.00

MANUFACTURING DIRECTIONS

Mix ingredients and fill in hard gelatin capsule of a type that will not interact with ingredients. Optionally, the composition may contain ethanol 8%, propylene glycol 8%, or polyethylene glycol 300, 30% by weight.

Dantrolene Sodium Capsules

The chemical formula of dantrolene sodium is hydrated 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2, 4-imidazolidinedione sodium salt. It is supplied in capsules of 25 mg, 50 mg, and 100 mg. Each capsule contains the following inactive ingredients: edible black ink, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, starch, synthetic iron oxide red, synthetic iron oxide yellow, talc, and titanium dioxide.

Dextroamphetamine Sulfate Capsules

Dextroamphetamine is the dextro isomer of the compound *d,l*-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is *d*-alpha-methylphenethylamine and is present in all forms of dexedrine as the neutral sulfate. Each spansule sustained release capsule is so prepared that an initial dose is released promptly, and the remaining medication is released gradually over a prolonged period. Each capsule containing 5–15 mg of active and inactive ingredients consists of: cetyl alcohol, D&C Yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C Blue No. 1, FD&C Blue No. 1 aluminum lake, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres, and trace amounts of other inactive ingredients.

Diclofenac and Misoprostol Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	Diclofenac Delayed-Release Beads (47% Diclofenac)	214.00
0.20	2	Misoprostol (dilute 1:100 on HPMC)	20.00
150.00	3	Microcrystalline Cellulose	150.00
4.00	4	Stearic Acid	4.00
9.00	5	Talc	9.00

MANUFACTURING DIRECTIONS

1. Item 1 beads are prepared by spray coating a suspension or solution of diclofenac sodium onto a nonpareil sugar core, together with a binder (e.g., polyvinylpyrollidone or hydroxypropyl methylcellulose). The beads are subsequently coated with a delayed release coating (e.g., methylmethacrylate, for example Eudragit). Mixtures of beads with various levels of coating are used to give the required therapeutic release pattern.
   a. In a fluidized-bed apparatus, uniform spherical inert sugar sphere cores are coated with a first layer consisting of the compounds, an inert water soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, and talc. The second layer consists of an inert water soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, talc, and a pigment, such as titanium dioxide. The third and enteric coating layer consists of an enteric coating polymer, such as co-polymerized methacrylic acid/methacrylic acid methyl esters, a plasticizer, such as triethy acetate or similar plasticizers, and talc. The layers are applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions. Pseudo zero release is obtained by the use of a mixture of beads.
2. The beads in Item 1 contain 47% diclofenac, giving a dose per capsule of 75 mg.
3. The mixture of Items 1–4 is filled into suitable, hard gelatin capsules.

Diclofenac Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	Diclofenac, USE Diclofenac Sodium Pellets (520 mg/g)	192.50

MANUFACTURING DIRECTIONS

1. Fill at relative humidity that does not exceed 45% and a temperature of 20–25°C.
2. Calculate exact amount based on quantity of active ingredient in uncoated beads.
3. Fill 192.5 mg based on 100% potency basis.
4. Preparation of uncoated granules:
   a. 800 g of diclofenac sodium, 200 g of citric acid, and 200 g of cornstarch are mixed and pulverized.
   b. The fine powders thus prepared are processed to produce spherical granules, using 600 g of purified sucrose that was obtained by shifting through 20–28 mesh as a core, while spraying a solution of 25 g of hydroxypropyl cellulose in 475 g of ethyl alcohol.
   c. The granules are then dried for 3 h at 55°C.
   d. These dried granules are then passed through a 14 mesh, followed by passage through a 28 mesh. The granules that do not go through the 28 mesh are taken as uncoated granules A. The formulation of uncoated granules A is as follows:

Component	% by weight
Diclofenac sodium	43.7
Citric acid	11.0
Cornstarch	11.0
Purified sucrose	32.9
Hydroxypropyl cellulose	1.4
Total	100.0

   e. Alternate method of preparing uncoated granules:
      i. 1000 g of diclofenac sodium, 30 g of fumaric acid, and 170 g of cornstarch are mixed and pulverized.
      ii. The fine powders thus produced are processed to produce spherical granules, using 600 g of purified sucrose that is obtained by shifting through a 20–28 mesh as a core, while spraying a solution of 25 g of hydroxypropyl cellulose in 475 g of ethyl alcohol.
      iii. The granules are then dried for 3 h at 55°C.
      iv. These dried granules are then passed through a 14 mesh followed by passage through a 28 mesh. The granules that do not go through the 28 mesh are taken as uncoated granules. The formulation of this uncoated granules B was as follows:

Component	% by weight
Diclofenac sodium	54.8
Fumaric acid	1.6
Cornstarch	9.3
Purified sucrose	32.9
Hydroxypropyl cellulose	1.4
Total	100.0

5. Preparation of long-acting granules:
   a. 600 g of uncoated granules A are placed into a coating apparatus with a fluidized bed.
   b. The granules are spray-coated with 1263 g of a coating liquid having the following composition according to a conventional method to produce long-acting granules. The weight of the coat was about 8% of the weight of the uncoated granules.

Component	% by weight
Ethylcellulose	2.7
Polyvinyl pyrrolidone K30	0.9
Talc	0.2
Ethyl alcohol	96.2
Total	100.0

6. Preparation of long-acting granules, alternate method:
   a. 600 g of uncoated granules B are placed into a coating apparatus with fluidized bed.
   b. The granules are spray-coated with 1667 g of a coating liquid having the following composition according to a conventional method to produce long-acting granules.

The amount of the coat is about 20% based on the weight of the uncoated granules.

Component	% by weight
Methacrylic acid copolymer S	6.5
Glycerine fatty acid ester	0.5
Talc	0.2
Ethyl alcohol	92.8
Total	100.0

7. Preparation of long-acting granules having an exterior rapid-releasing layer:
   a. 50.7 g of diclofenac sodium and 149.3 g of cornstarch are mixed and pulverized.
   b. The fine powders thus produced are processed to produce spherical granules, using 500 g of the long-acting granules (Step 6) as a core, while spraying a solution of 4 g of hydroxypropyl cellulose in 76 g of ethyl alcohol.
   c. The granules are then dried for 2 h at 55°C to produce long-acting granules. These granules have an exterior rapid-releasing layer.

Didanosine Delayed-Release Capsules

Didanosine is given in an enteric-coated formulation of didanosine (ddl), a synthetic purine nucleoside analog active against the Human Immunodeficiency Virus (HIV). The delayed-release capsules, which contain enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include: carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine Delayed-Release Capsules Enteric-Coated Beadlets

Didanosine is the brand name for an enteric-coated formulation of didanosine (ddl), a synthetic purine nucleoside analog active against the Human Immunodeficiency Virus (HIV). Delayed-release capsules, containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine for Oral Suspension

Didanosine (ddl) is a synthetic purine nucleoside analog active against the Human Immunodeficiency Virus (HIV). The powder for oral solution is supplied for oral administration in single-dose packets containing 100, 167, or 250 mg of didanosine. Packets for each product strength also contain a citrate-phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose. Pediatric powder for oral solution is supplied for oral administration in 4- or 8-ounce glass bottles containing 2 or 4 grams of didanosine, respectively. The chemical name for didanosine is 2′,3′-dideoxyinosine.

Diethyl Toluamide Topical Powder

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
552.00	1	*N*,*N*-Diethyl-*m*-Toluamide (DEET)	600.00
368.00	2	2-Octyldodecanol	400.00
QS	3	Methylene Chloride	QS
80.00	4	Cellulose Triacetate	400.00

MANUFACTURING DIRECTIONS

1. A liquefiable powder was prepared by spray evaporative drying. A liquid porogen was prepared from 60 parts by weight of *N*,*N*-diethyl-*m*-toluamide (DEET) and 40 parts by weight of 2-octyldodecanol, a heavy secondary alcohol commonly used in cosmetic formulations.
2. Cellulose triacetate (40 g) was dissolved in 3000 gm of methylene chloride by moderate stirring for 4 h. To that solution was added 460 g of the previously prepared porogen diluted with 1000 g of methylene chloride.
3. The resulting homogeneous solution was sprayed at 1000 PSI from a 0.0135-in. nozzle, downward into a tower (100 cm in diameter × 300 cm tall), through which 1250 l/min of solvent-free air was passing from top to bottom.
4. The evaporatively formed powder was collected on a fabric filter spanning the bottom of the tower, and the solvent-laden air was passed through carbon beds to collect and recover solvent.
5. The product was transferred to a steel tray and exposed as a 1-cm deep layer in a ventilated hood for 25 min to remove residual solvent. Analysis showed 8% cellulose triacetate, 36.8% octyldodecanol, and 55.2% DEET, with less than 5 ppm or residual methylene chloride.
6. The resulting white powder could be readily dusted onto the skin and made to liquefy and vanish by gentle rubbing without any perceptible grit or gumminess.

Difluoromethylornithine-Alpha Capsules

Bill of Materials		
Item	**Material Name**	**Qty/2000 Caps (g)**
	Rapid-Release Granules	
1	Difluoromethylornithine-Alpha (DFMO)	100.00
2	Microcrystalline Cellulose (MCC) Avicel PH101	100.00
3	Water Purified	QS
	Slow-Release Granules	
4	Difluoromethylornithine-Alpha	500.00
5	Microcrystalline Cellulose PH101	500.00
6	Eudragit RS 30D	30-50
7	Triethyl Citrate	QS
8	Water Purified	QS

MANUFACTURING DIRECTIONS

1. Rapid-Release Granules: DFMO (100 g) and microcrystalline cellulose (MCC, Avicel PH101, 100 g) are mixed thoroughly. A sufficient amount of water to make a wet mass is added to the mixture, which is subsequently extruded and spheronized. The pellets are screened (size 14 to 20 mesh) and dried at 40°C for 24 h. Polyvinyl pyrrolidone (PVP, 2% by weight of total mass) can optionally be included in the formulation. Increasing PVP will generally lengthen the release profile of the formulation.
2. Slow-Release Granules: DFMO (500 g), MCC (500 g) and Eudragit (35–50 g) are mixed. To this mixture is added sufficient water to yield a 30% weight suspension. To the suspension is added triethylcitrate (10% weight based on dry polymer weight of Eudragit) to yield a dispersion that is wet granulated and dried to remove as much water as possible. The particles are then ground into a fine powder.
3. Fill the rapid-release granules (500 g prepared according) and slow release granules (750 g prepared) after thoroughly mixing.
4. Gastric-Release Granules: A slow gastric-release granule can be prepared as follows. DFMO (600 g), MCC (350 g), and HPC (50 g) are mixed thoroughly. To the mixture is added sufficient water to make a wet mass that is extruded and then spheronized using procedures well known in the art. The particles are then dried and ground.
5. Enteric-Release Granules: A latex dispersion is prepared as follows. To Eudragit L 30D-55 (1000 g, 15% weight in water) is added a plasticizer (15% weight of dry polymer weight in the Eudragit) while mixing for 1–24 h. Plasticizers, such as triethylcitrate, tributylcitrate, acetyltributylcitrate, or dibutylsebacate, can be used. To this mixture is added talc (50% weight of dry polymer in the Eudragit) or glycerylmonostearate (10% weight of dry polymer in the Eudragit) to form a dispersion. The rapid-release granules are coated in a fluidized bed with the latex dispersion until a 10–15% weight increase in granule weight is achieved. The fluidized bed inlet air temperature is adjusted to about 40–45°C. and the outlet air temperature is adjusted to about 30–35°C with a spray rate of about 2 g/min.
6. Slow-Release Granules: Granules previously prepared are coated with Eudragit L 30D (10–12% weight) or Aquateric (CAP, 10% weight, plasticized with TEC) until a 25–30% weight increase in granule weight is achieved.
7. Colorectal-Release Granules: A dispersion is prepared as follows. To Eudragit S100 (1000 g, 10% weight in water) is added a plasticizer (10% weight of dry polymer weight in the Eudragit) while mixing for 1–24 h. Plasticizers, such as triethylcitrate, tributylcitrate, acetyltributylcitrate, or dibutylsebacate, can be used. To this mixture is added talc (50% weight of dry polymer in the Eudragit) to form a dispersion. The rapid release granules previously prepared are coated in a fluidized bed with this dispersion until a 15% weight increase in granule weight is achieved.
8. Slow-Release Granules: A mixture is prepared as follows. Eudragit RS 30D (1000 g, 15% weight aqueous dispersion, AQUACOAT® or SURELEASE®) is plasticized with triethylcitrate (TEC, 20% wt of dry polymer in the Eudragit) for 1–24 h. Talc (50% weight of dry polymer in the Eudragit) is added with mixing

to form the mixture. The rapid-release granules are coated with this mixture until a 10–15% weight increase in granule weight is achieved. The coated granules are then coated with a Eudragit S100 dispersion as done immediately above until a 10–15% weight increase in granule weight is achieved.

9. Sustained-Release Granules: This procedure employs a double granulation. Thus, DFMO (500 g), MCC (500 g), and Eudragit RS 30D (75–100 g) are mixed. To this mixture is added sufficient water to yield a 30% weight suspension. To the suspension is added TEC (10% weight based on dry polymer weight of Eudragit) to yield a dispersion that is wet granulated and dried to remove as much water as possible. The granules are then ground into a fine powder. To the powder is added sufficient water to make a wet mass that is extruded, spheronized, dried, ground, and screened (size 14–20 mesh).
10. Gastric-, Enteric-, and Colorectal-Release Granules: The following procedure details the preparation of the dosage form. Rapid gastric-release granules (450 g, prepared previously), rapid enteric-release granules (100 g, prepared previously), and slow colorectal-release granules (450 g, prepared previously) are mixed thoroughly. Hard gelatin capsules are then filled with the mixture.

Diltiazem Hydrochloride Extended-Release Capsules

Diltiazem hydrochloride is a calcium ion cellular influx inhibitor (slow channel blocker). The extended-release capsules contain diltiazem hydrochloride in extended-release beads at doses of 120, 180, 240, 300, 360, and 420 mg. They also contains: microcrystalline cellulose, sucrose stearate, Eudragit, povidone, talc, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polysorbate, simethicone, gelatin, FD&C Blue No. 1, FD&C Red No. 40, D&C Red No. 28, FD&C Green No, 3, black iron oxide, and other solids.

In another formulation, the 120 mg, 180 mg, 240 mg, and 300 mg capsules also contain: black iron oxide, ethylcellulose, FD&C Blue No. 1, fumaric acid, gelatin, sucrose, starch, talc, titanium dioxide, white wax, and other ingredients. The 360 mg capsule also contains: black iron oxide, diethyl phthalate, FD&C Blue No. 1, gelatin, povidone K17, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other ingredients.

The rapid-release pellets of diltiazem can be manufactured by the following procedure: 2.00 kg of microgranules composed of sucrose and starch, with a particle size of 0.500–0.710 mm, are rotated in a trough with a stainless steel basket that is 450 mm in diameter. The rotating mass is sprayed, by means of a membrane-type proportioning pump, with 26 g of a 40% strength solution of shellac in ethanol and sprinkled with 80 g of diltiazem with a particle size of 40–80 μm.

MANUFACTURING DIRECTIONS

The sustained release pellets can be manufactured by following procedure: 2.00 kg of saccharose/starch pellets having a particle size between 0.500 and 0.710 mm are put in rotation in a suitable coating pan. The rotating mass is sprayed with 27.2 g of an ethanolic solution containing 9.79 g of shellac and 1.09 g of polyvinylpyrrolidone; and 80 g of diltiazem HCl are added. This operation is repeated 50 times. These pellets are then coated with the same amount of solution of ethylcellulose N100 and talc, respectively, 80 g of 0.5% solution of ethylcellulose N100, and 54 g of talc. This operation is repeated 25 times. The proportion of soluble vs. insoluble coating materials can be altered to obtain the best release profile. All the formulations are tested for *in vitro* dissolution, in the range of pH between 1 and 7.5, using the method described in the USP, paddle apparatus.

Alternate methods of preparing coated beads include first preparing beads and then coating them; the plain beads are prepared by:

FORMULA 1

Diltiazem hydrochloride	1120.00 g
Lactose	119.00 g
Microcrystalline cellulose (Avicel pH101)	140.00 g
Povidone K30	21.00 g

After introducing the powders into a planetary mixer and granulating same through the obtained plastic, mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60°C for 12 h, the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

FORMULA 2

Diltiazem HCl	560.00 g
Crodesta F 160	59.50 g
Microcrystalline cellulose (Avicel pH101)	70.00 g
Povidone K30	10.50 g

The ingredients are introduced in a planetary mixer and dry mixed for approximately 15 min. Thereafter, 100 ml purified water is added, and the mixing is pursued for 10 min more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal® extruder equipped with a 1-mm screen to obtain "spaghetti." A spheronizer-type caleva is used to transform the extruded product into beads. After drying for 12 h on trays in an oven at 60°C, the beads are sieved to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with sizes between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

The beads prepared previously are then coated in a STREA-1 (Aeromatic®) fluidized bed using the "top spraying" technique, and 440 g of coating suspension from the following composition is applied on 500 g of beads. Thereafter, the coated beads are dried at 50°C for 16 h.

COATING SUSPENSION COMPOSITION

Magnesium stearate	12.50 g
Titanium dioxide	5.00 g
Povidone K30	5.00 g
Eudragit NE30D	620.00 g
Talc	17.50 g
Water	338.00 g
Simethicone	1.00 g
Tween 80	0.80 g

Diphenhydramine Hydrochloride Capsules

Each capsule contains diphenhydramine hydrochloride 25 mg. Each capsule contains: lactose and magnesium stearate. The banded capsule shell contains: D&C Red No. 28, FD&C Red No. 3, FD&C Red No. 40, FD&C Blue No. 1, gelatin, glyceryl monooleate, and titanium dioxide.

Dipyridamole and Aspirin Extended-Release Capsules

This is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg of dipyridamole in an extended-release form and 25 mg of aspirin as an immediate-release sugar-coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, aluminum stearate, colloidal silicon dioxide, cornstarch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin. Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide, and water. Dipyridamole is an antiplatelet agent chemically described as 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido(5,4-d) pyrimidine (= dipyridamole). The antiplatelet agent aspirin (acetylsalicylic acid) is chemically known as benzoic acid, 2-(acetyloxy).

Divalproex Sodium Capsules

Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically, it is designated as sodium hydrogen *bis* (2-propylpentanoate). The sprinkle capsules are for oral administration and contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in a hard gelatin capsule. The inactive ingredients in the 125-mg sprinkle capsules are: cellulosic polymers, D&C Red No. 28, FD&C Blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

Divalproex Sodium Coated Particle Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
125.00	1	Valproic Acid, USE Divalproex Sodium Coated Particles	134.50
0.53	2	Magnesium Stearate	0.53
1.00	3	Silica Gel (Syloid 244)	1.00

MANUFACTURING DIRECTIONS

1. Prepare coated particles of divalproex sodium by coating with ethylcellulose (34.34 mg), triethyl citrate (5.8 mg), and magnesium citrate (35 mg), using a mixture of alcohol and acetone in an air suspension system; screen particles using 20- and 40-mesh screens; particles larger than 20 and smaller than 40 must be reworked.
2. Make the granules by wet granulation of divalproex sodium and silica gel, using alcohol.
3. Collect 20–40 mesh granules after drying not more than 50°C to loss on drying of not more than 0.5%.

Dofetilide Capsules

Dofetilide is an antiarrhythmic drug with Class III (cardiac action potential duration prolonging) properties. Each capsule contains the following inactive ingredients: microcrystalline cellulose, cornstarch, colloidal silicon dioxide, and magnesium stearate. It is supplied for oral administration in three dosage strengths: 125 mcg (0.125 mg) orange and white capsules; 250 mcg (0.25 mg) peach capsules; and 500 mcg (0.5 mg) peach and white capsules.

Doxepin Hydrochloride Capsules

Doxepin hydrochloride is one of a class of psychotherapeutic agents known as dibenzoxepin tricyclic compounds. It is a white crystalline solid that is readily soluble in water, lower alcohols, and chloroform. Inert ingredients for the capsule formulations are: hard gelatin capsules (which may contain Blue 1, Red 3, Red 40, Yellow 10, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; and starch.

Doxycycline Capsules

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. Available as 100 mg and 50 mg capsules, they contain doxycycline monohydrate equivalent to 100 mg or 50 mg of doxycycline for oral administration. The inert ingredients are: colloidal silicon dioxide; magnesium stearate; microcrystalline cellulose; and sodium starch glycolate.

Doxycycline Hyclate Capsules

These capsules contain specially coated pellets of doxycycline hyclate for oral administration. They also contain lactose, microcrystalline cellulose, and povidone. The capsule shell and band contain FD&C Blue No. 1, FD&C Yellow No. 6, D&C Yellow No. 10, gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. Doxycycline is a broad-spectrum antibiotic that is synthetically derived from oxytetracycline and is available as doxycycline hyclate. The chemical designation of this light-yellow crystalline powder is alpha-6-desoxy-5-oxytetracycline. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
122.00	1	Doxycycline Hyclate (22% excess)	122.00
26.00	2	Microcrystalline Cellulose (Avicel PH 102)	26.00
4.00	3	Starch (Cornstarch Dried)	4.00
0.60	4	Sodium Lauryl Sulfate	0.60
0.60	5	Colloidal Silicon Dioxide (Aerosil 200)	0.60
2.00	6	Magnesium Stearate	2.00
—	7	Hard Gelatin Capsules, Size 3	1000.00

MANUFACTURING DIRECTIONS

Note: Processing should be conducted in a controlled room temperature and humidity area. The limits are: room temperature 20–27°C; RH 40–45%.

1. Mix Items 1, 2, and 4 in a stainless steel drum. Pass the mixed material through a 500-µm sieve using a sifter. Collect in stainless steel drum.
2. Mix Items 3, 5, and 6 in a polyethylene bag. Pass the mixed material through a 250-µm sieve using a sifter. Pass two times. Collect in the polyethylene bag, and transfer to Step 1 in a stainless steel drum.
3. Mix the material in a drum mixer for 3 min.
4. Take a sample for assay and moisture content.
5. Load the empty capsule shells (size 3) in the hopper; cap is ivory opaque, and body is ivory opaque.
6. Run the machine, and check the locking of shells. Run the machine. Check the fill weight (155 mg) and locking of the capsules. Collect the filled capsules, from polyethylene-lined stainless steel container, in silica bags and close tightly.
7. Store the containers in a controlled room temperature and humidity area. The limits are: RH 45–50% at a temperature of 25–27°C.

Doxycycline Hydrochloride Capsules and Oral Suspension

It is a broad-spectrum antibiotic that is synthetically derived from oxytetracycline. The chemical designation for doxycycline is 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate. Inert ingredients in the capsule formulations are: hard gelatin capsules (which may contain Blue 1 and other inert ingredients); magnesium stearate; microcrystalline cellulose; and sodium lauryl sulfate. Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; Blue 1; methylparaben; microcrystalline cellulose; propylparaben; raspberry flavor; Red 28; and simethicone.

Efavirenz Capsules

Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. It is available as capsules for oral administration containing either 50 mg, 100 mg, or 200 mg of efavirenz as well as the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue, FD&C Blue No. 2, and titanium dioxide.

Enalapril Maleate Capsules

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
10.00	1	Enalapril Maleate	10.00
235.00	2	Lactose Anhydrous	235.00
1.25	3	Magnesium Stearate	1.25

MANUFACTURING DIRECTIONS

1. Pass all items through No. 60 mesh into blender; mix for 10 min.
2. Fill 250 mg.

Erythromycin and Bromhexine Powder for Suspension

Bill of Materials			
Scale (mg/5 ml)	**Item**	**Material Name**	**Qty/l (g)**
21.00	1	Sodium Carboxymethylcellulose	0.42
6.55	2	Dye Red	0.131
4735.00	3	Sugar Granular 39075 Mesh	94.70
2650.00	4	Sodium Citrate Dihydrate	53.00
659.00	5	Sodium Carboxymethylcellulose High Viscosity	13.18
393.50	6	Magnesium Aluminum Silicate Veegum F	7.87
78.50	7	Saccharin Sodium Dihydrate	1.57
200.00	8	Erythromycin, USE Erythromycin Ethylsuccinate[a] Citrate Washed	123.58
0.80	9	Bromhexine, USE Bromhexine Hydrochloride	2.10
QS	10	Flavor	3.95
QS	11	Water Purified, ca	67 ml

[a] Erythromycin Ethylsuccinate is factored = (123.58 × 850)/potency, mcg/g.

MANUFACTURING DIRECTIONS

I. Granulation
   A. Dissolve the sodium carboxymethylcellulose (Item 1) and the dye in approximately 67 ml of purified water with heat while stirring. Allow to cool. Ensure that the sodium carboxymethylcellulose is completely in solution.
   B. Pass sugar cane through a 2.38-mm aperture screen using an oscillating granulator.
   C. Pass the following through a 1.27-mm aperture or similar screen: sodium CMC (Item 5), veegum F, sodium saccharin, bromhexine HCl, and erythromycin ethylsuccinate. Use a Fitz mill or a similar mill, high speed, impact forward.
   D. Load the ingredients from Steps B and C into the mixer, and blend for 30 min.
   E. Mass with the solution from Step A. If necessary, add purified water to form a cohesive granule with even color dispersion.
   F. If necessary, pass the wet mass through a 4.76-mm aperture screen, and spread on stainless steel trays.
   G. Load trays of granulation into the oven, and dry at 49°C to loss on drying (LOD) of less than 0.5% (60°C/5 mm).
      Note: Stir granulation during drying.
   H. Allow granulation to cool in low-humidity area before passing through a 1.7-mm aperture screen.
      Note: Pre-cooling in a low-humidity area prevents condensation when later packed in polyethylene-lined bags.
   I. Request samples.
   J. Charge part of dry granulation and sodium citrate into a mixer. Slowly add flavor while mixing. Mix for a few minutes. Hand screen through a 1.2-mm aperture screen.
   K. Charge the screened granulation into a suitable blender, and add flavor mixture from Step J. Mix well (approximately 30 min).
   L. Take samples.
   M. Discharge blended granulation into tared polyethylene-lined drums; seal and weigh. Store until needed for filling.

II. Finishing
   A. At filling, weight for a 60-ml bottle should be 22.85 g; weight for a 100-ml bottle should be 39.08 g.

Erythromycin and Sulfisoxazole Granules for Suspension

Bill of Materials			
Scale (mg/5 ml)	**Item**	**Material Name**	**Qty/kg (g)**
180.63	1	Sodium Citrate Dihydrate	66.90
600.00	2	Sulfisoxazole, USE Sulfisoxazole Acetyl	222.30
13.50	3	Sodium Carboxymethylcellulose High Viscosity	5.00
10.80	4	Magnesium Aluminum Silicate Veegum F	4.00
5.40	5	Citric Acid	2.00
0.54	6	Polaxamer 188 (Pluronic F68)	0.20
200.00	7	Erythromycin, USE Erythromycin Ethylsuccinate Citrate Washed[a] (850 mcg/mg) 5% Excess	75.29
1661.28	8	Sucrose	615.29
QS	9	Water Purified	55 ml
7.56	10	Flavor	2.80
3.24	11	Flavor	1.20
10.80	12	Flavor	4.00
2.70	13	Ammonium Glycyrrhizinate	1.00

[a] Factored according to potency. Adjust with sugar.

MANUFACTURING DIRECTIONS

I. Premixing
Note: This milling step is hazardous.
CAUTION: EQUIPMENT MUST BE GROUNDED OR BONDED.
   A. Mill sodium citrate, sodium carboxymethylcellulose, magnesium aluminum silicate, citric acid. poloxamer and erythromycin ethylsuccinate through a no. 2 band (1.59-mm aperture) using a Fitz mill or similar mill, at high speed, impact forward.
   B. Load milled materials from Step A into a suitable blender. Mix for 15 min.
   C. Screen the sulfisoxazole acetyl through a 4.76-mm aperture screen, and add to the blender. Blend for 15 min.
   D. Discharge blender into polyethylene-lined drums.

II. Granulation
   A. Load mass mixer with the premix blend. Add the sucrose to mixer by hand screening through a 2.00-mm aperture screen. Dry mix for not less than 5 min.
   B. QS to mass using approximately 51 ml of purified water.
   C. Granulate the wet mass through a 5/8-in. band (15.88-mm aperture or similar) on a rotary granulator or similar granulator. Spread on paper-lined trays, no more than one scoopful per tray. Place granulation in oven set at 49°C.
   D. Dry to not more than a 0.7% loss on drying.
   E. Sift dried granulation through a 1.19-mm aperture screen, and grind coarse granulation through a no. 2AA band (1.98-mm aperture or similar) in a Fitz mill or a similar mill, medium speed, knives forward into polyethylene-lined drums.

III. Blending
   A. Load approximately one-half of the granulation from Step II-E into a suitable blender.
   B. Screen flavors and ammonium glycyrrhizinate through a 600-µm aperture screen into a portion of the granulation; mix and add to the blender.
   C. Add the remaining granulation into the blender. Blend for 20 min.
   D. Discharge mixture into polyethylene-lined drums.

IV. Finishing
   A. Fill into suitable approved bottles at a theoretical weight of 62.5 g per 100 ml, requiring approximately 50 ml of water for reconstitution.

Erythromycin Delayed-Release Capsules

Erythromycin delayed-release capsules contain enteric-coated pellets of erythromycin base for oral administration. Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids, but it is the base that is microbiologically active. Each erythromycin delayed-release capsule contains 250 mg of erythromycin base. The inactive ingredients are: cellulosic polymers, citrate ester, D&C Red No. 30, D&C Yellow No. 10, magnesium stearate, and povidone. The capsule shell contains FD&C Blue No. 1, FD&C Red No. 3, gelatin, and titanium dioxide.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Erythromycin, USE Erythromycin 66.7% Pellets (label claim is 667 mg/gm)	375.00[a]
—	2	Empty Hard Gelatin Capsule, Size 0	1000

[a] Quantity of pellets for 1000 capsules will be adjusted based on the pellets assay results.

MANUFACTURING DIRECTIONS

Note: Processing should be done under controlled room temperature and relative humidity. The limits are: room temperature 20–25°C; RH 40–45%.

1. Load the empty capsule shells (size 0), in the hopper.
2. Fill.

Erythromycin Ethylsuccinate for Oral Suspension

Bill of Materials			
Scale (mg/5 ml)	**Item**	**Material Name**	**Qty/1 kg (19 units) (g)**
125.00	1	Erythromycin Ethylsuccinate[a]	55.860
2168.00	2	Sucrose[b]	823.840
250.25	3	Sodium Citrate	95.095
2.97	4	Saccharin Sodium	1.128
0.27	5	FD&C Red No. 40	0.104
1.43	6	Carmellose Sodium (Sodium CMC 7 MFD)	0.543
21.45	7	Simethicone Emulsion 30% (Simethicone M30)	8.151
12.98	8	Xanthan Gum	4.932
6.27	9	Cherry Dry Flavor	2.382
—	10	Purified Water	15.200

[a] Potency: 850 mcg/mg, as is.
[b] Sucrose quantity to be adjusted accordingly. The weight of sucrose may be adjusted to compensate for potency variation of erythromycin ethylsuccinate to maintain the standard batch size (1 kg). Fill weight: 52.5 gm for 100-ml pack.

MANUFACTURING DIRECTIONS

Precautions: Handle erythromycin ethylsuccinate carefully to avoid any cross contamination. The processing area must be under controlled room temperature and humidity. The limits are: RH: 45–55%; temperature: 23–25°C.

1. Preparation of Solution: Dissolve Item 5 in Item 10 (25–30°C). Add Item 6 slowly while stirring with stirrer at medium speed until gel is formed. Check the weight; theoretical weight is 15.84 g. If required, adjust with Item 10.
2. Dry Mixing: Pass Item 2 (calculated quantity) through sifter using a 900-µm sieve. Crush the larger crystals of Item 2 using a Fitz mill, impact forward, high speed.
3. Load Item 2 from Step 2 into the mixer, and start mixing at high speed. Add Item 7 while mixing. Mix for 10 min with the mixer and chopper at high speed.
4. Mix Items 3, 4, 8, 1, and the mixture from Step 3 in a clean, dry stainless steel container using a clean, dry stainless steel scoop.
5. Pass the material through a Fitz mill, impact forward, high speed.
6. Add the milled material to the mixer; mix for 5 min with the mixer and chopper at high speed.
7. Scrap down the sides and blades and again mix for 2 min with the mixer and chopper at high speed.
8. Wet Granulation: Very slowly add the solution from Step 1 to Step 5 in mixer. Mix at low speed, until a satisfactory mass is obtained. Mix and chop for 1 min only. Do not over wet the mass.
9. Drying: Dry the wet granules in the fluid-bed dryer at 55°C to reach a loss on drying of no more than 0.4%.
10. Grinding: Pass the dried granules through a 1.0-mm sieve using Frewitt® granulator. Collect in a stainless steel drum.
11. Final Mixing: Pass Item 9 through 250-µm sieve using a sifter. Collect in a polyethylene-lined bag.
12 Load sieved material from Step 8 into the blender.
13. Add sieved flavor (Item 9) from Step 11 to the blender.
14. Blend the powders for 5 min.
15. Unload the blended powder in stainless steel drums.

Erythromycin Ethylsuccinate for Oral Suspension 200 mg/5 ml

Bill of Materials			
Scale (mg/5 ml)	**Item**	**Material Name**	**Qty/1 kg (18 Units) (g)**
200.00	1	Erythromycin, USE Erythromycin Ethylsuccinate[a]	89.3700
1342.00	2	Sucrose	483.1200
880.00	3	Sucrose[b]	316.8000
250.25	4	Sodium Citrate	90.0900
2.97	5	Saccharin Sodium	1.0692
0.27	6	FD&C Red No. 40	0.0990
1.43	7	Carmellose Sodium (Sodium CMC 7 MFD)	0.5148
21.45	8	Simethicone Emulsion 30% (Simethicone M30)	7.7220
12.98	9	Xanthan Gum	4.6728
6.27	10	Cherry Dry Flavor	2.2572
—	11	Purified Water	15.8400

[a] Potency: 850 mcg/mg, as is.
[b] The weight of sucrose may be adjusted to compensate for potency variation of erythromycin ethylsuccinate to maintain the standard batch size (1 kg). Fill Weight: 55 gm for 100-ml pack.

Erythromycin Stearate for Oral Suspension

1.

Bill of Materials			
Scale (mg/ml)	**Item**	**Material Name**	**Qty/l (g)**
25.00	1	Erythromycin Stearate 600 mcg/mg, 5% excess	43.75
1.00	2	Methyl Paraben	1.00
0.20	3	Propyl Paraben	0.20
10.00	4	Magnesium Aluminum Silicate	10.00
1.15	5	Sodium Carboxymethylcellulose (CMC), low viscosity	1.15
4.00	6	Alcohol 190 Proof	4.00
120.00	7	Sodium Citrate Dihydrate	120.00
0.20	8	Saccharin Sodium	0.20
700.00	9	Sugar Granular	700.00
0.07	10	Yellow Dye	0.07
2.76	11	Chocolate Flavor	2.76
0.54	12	Orange Flavor	0.54
1.25	13	Sodium Lauryl Sulfate	1.25
QS	14	Water Purified	QS

MANUFACTURING DIRECTIONS

I. Mixing
   A. Place sodium CMC and 40 g of sugar in a mixing drum. (If using alcohol, add it to the drum to wet the mixture, and indicate use on the work order.) Roll for 2 h to blend.
   B. Measure 350 ml of purified water into a jacketed mixing tank, and heat the water to 95°C. Maintain at this temperature.
   C. Add methyl paraben to the water at 95°C. Stir until completely dissolved.
   D. Add propyl paraben to the solution at 95°C. Stir until completely dissolved.
   E. Cool to 60°C and maintain temperature. Stir the solution and slowly sprinkle in Veegum®. Stir until veegum is completely dispersed. Check by passing quantity of the batch through a 350-µm aperture or similar screen, and watch for any undissolved residue.
   F. While stirring, add the blended powders from Step A slowly to the solution. Stir until completely dissolved. Screen a quantity through a 350-µm aperture or similar screen to check for undissolved sodium CMC.
   G. Maintain the batch at 50–55°C, and gradually add the remaining sugar (Item 9) with stirring. Stir until completely dissolved. Check for any undissolved sugar by passing a quantity of the bulk through a 350-µm aperture or similar screen.
   H. Dissolve the saccharin sodium in approximately 5 ml of purified water, and add the solution to the batch.
   I. While stirring, add the sodium citrate to the batch. Stir under maximum vacuum until completely dissolved. Check by passing a quantity of the bulk through a 350-µm aperture or similar screen.
   J. Dissolve FD&C Yellow No. 6 in approximately 5 ml of purified water, and add the solution to the batch. Cool the batch to 30°C (chilled water may be used).
   K. In a separate tank, stir approximately 85 ml of purified water and slowly, taking care to avoid a vortex, add and dissolve sodium lauryl sulfate. When dissolved, gradually sprinkle in the erythromycin stearate, and mix into a smooth slurry. Mix for 1/2 h.
   L. While stirring the batch from Step J, slowly add the slurry from Step K. Take care not to aerate the batch. Wash thoroughly into the batch with approximately 10 ml of purified water.
   M. With continual stirring, add the flavors (Items 11 and 12) to the batch.
   N. Pass the whole batch through a homogenizing mill, using a suitable setting such that crystal fracture is minimized. Rinse the mill with purified water, and add the rinsings to the batch.
   O. Return the milled batch back into the mixing tank. Gradually increase the application of

vacuum as allowed by the level in the tank. Stir under a 28-in. Hg vacuum for 1 h. Adjust the batch volume to 1 l, using purified water.

P. Repeat Step O until the volume is constant and specific gravity meets specifications.

2.

Bill of Materials			
Scale (mg/ml)	**Item**	**Material Name**	**Qty/l (g)**
25.00	1	Erythromycin Stearate 600 mcg/mg, 5% excess	43.75
1.00	2	Methyl Paraben	1.00
0.20	3	Propyl Paraben	0.20
2.00	4	Xanthan Gum	2.00
120.00	5	Sodium Citrate Dihydrate	120.00
0.20	6	Saccharin Sodium	0.20
100.00	7	Sorbitol Solution	100.00
4.50	8	Antifoam Emulsion Dow Corning	4.50
0.07	9	Dye Yellow	0.07
2.76	10	Flavor Chocolate	2.76
700.00	11	Sugar Granular	700.00
0.54	12	Flavor Orange	0.54
1.25	13	Sodium Lauryl Sulfate	1.25
QS	14	Water Purified	QS

MANUFACTURING DIRECTIONS

I. Mixing
   A. Heat 600 ml of purified water in a jacketed mixing tank to 95–100°C.
   B. Add the methyl paraben and propyl paraben and mix to dissolve.
   C. Withdraw the following preserved purified water:
      1. 200 ml and dissolve the sodium citrate.
      2. 150 ml and dissolve the sodium lauryl sulfate.
      3. 5 ml and dissolve the sodium saccharin and the dye yellow.
   D. In a plastic bag, mix together the xanthan gum and 20 g of sucrose (Item 11) for 10 min.
   E. Maintaining the batch at 50–60°C while mixing, slowly add the dry mixture from Step D, until a clear gel is obtained.
   F. Add the sorbitol and mix.
   G. While mixing, slowly add the solution obtained from Step C-1.
   H. Add the disperse 380 g of sucrose (Item 11) while mixing. Make sure that the temperature will not go over 60°C. Stop heating when all dissolved.
   I. Without producing the vortex, add erythromycin stearate to the solution from Step C-2, and continue mixing until smooth slurry is formed. Continue mixing for 15–30 min, and then pass slurry through a homogenizer. Add the Antifoam C to the slurry and mix; rinse the homogenizer with purified water, and add the rinsings to the slurry. Mix.
   J. While mixing, add the slurry obtained from Step I to the batch; rinse the vessel with 5 ml of purified water, and add the rinsings to the batch.
   K. Add and disperse the solution from Step C-3, and continue mixing.
   L. Mix under vacuum for 1 h. Release the vacuum and record the volume.
      CAUTION: DO NOT ADJUST VOLUME AT THIS STAGE.
   M. Repeat Step L until no further volume change is noticed.
   N. Add the flavors (Items 10 and 11) and bring to volume with purified water.

Erythropoietin Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
14,000 IU	1	Erythropoietin[a]	140,000,000 IU
0.047	2	Dimyristoyl Phosphatidyl Choline	0.047
3.42	3	Aprotinin[b]	3.42
3.78	4	Hydroxypropyl Cellulose-LF	3.78
3.78	5	Polyoxy-40 Stearate Myrj-52®	3.78
141.1	6	Polyethylene Glycol 400	141.1
15.72	7	Propylene Glycol	15.72
8.83	8	Phosphate Buffer	8.83
31.49	9	Cholesterol	31.49
17.72	10	Tween 80	17.72
63.68	11	Egg Yolk Lecithin	63.68
28.15	12	Glyceryl Amino Oleate	28.15
19.78	13	d-alpha Tocopherol	19.78
251.42	14	Oleic Acid	251.42

[a] Erythropoietin: 1000 IU = 8 μg.
[b] Aprotinin: 7500 KIU = 1.0 mg.

MANUFACTURING DIRECTIONS

1. Erythropoietin is a 165 amino acid glycoprotein of approximately 34,000 daltons. It is an endogenous protein, which is involved in the production of red blood cells. It is indicated for the treatment of anemia associated with chronic renal failure, in AIDS patients, and also to maintain or elevate the red blood cell level in the human body. In its preparations, there can be no use of heat or alcohol that can denature it.
2. The overall method is as follows: The high HLB surfactant polyoxy-40 stearate is slowly dispersed into the mixture of polyethylene glycol 400 and propylene glycol. Once it dissolves, hydroxypropyl cellulose as a stabilizer is also added which is dispersed slowly into the above mixture. A separate solution of the proteinaceous material along with the phospholipid and the protease inhibitor is made in a portion of the above solvent mixture. The solution can then be added to the PEG/PG mixture at room temperature. The amount of any water is limited to 5% of the polyol solvent. When the water solution is used, citrate buffer is used to maintain the pH at a point where the protein is most stable. For erythropoietin, pH can be adjusted to 7.0–7.5 with a phosphate buffer. The amount of aqueous buffer solution would still be 5% of the hydrophilic phase. At a pH of 7.0–7.5, erythropoietin has its maximum stability. It is known that in formulating proteins, the pH of the formulation should be distant from the isoelectric point of the protein which would not precipitate the protein from the solution. Separately, the ingredients of the lipid solvent are mixed together. Under gentle and constant stirring, the polyol solution is dispersed with the lipid solution.
3. The surfactant (polyoxy-40 stearate) is slowly dispersed into a mixture of polyethylene glycol and propylene glycol. Once it is dissolved, small amounts of hydroxypropyl cellulose are then added and dispersed into the same mixture. Erythropoietin is dissolved in the phosphate buffer/water/saline, along with aprotinin and dimyristoyl phosphatidyl choline. The aqueous solution is then added to the polyethylene glycol mixture at room temperature. The pH of the solution should be adjusted at 7.5 for maximum stability.
4. In a separate vessel, dissolve all the lipid-liking ingredients in oleic acid. Cholesterol is added slowly to achieve faster dissolution. Once both the phases are ready, the lipid solution is added slowly to polyol solution while mixing at low speed. Preferably, the vessel should be ice jacketed because mixing produces heat. Once the mixing is achieved, a transparent yellowish-brown preemulsion solution is obtained.
5. The preemulsion solution is filled in a size 0 hard gelatin capsule, and the capsule is sealed

with a band of gelatin solution. The banding helps to coat the capsule uniformly.

6. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, a 3.5–4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
7. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers, such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate, are used.
8. Anionic copolymers that are based on methacrylic acid and methyl methycrate, commercially available as Eudragit, are also very suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5–6% of the weight gain of the capsules from the original weight of the capsules before applying an enteric coat.

A typical enteric coating solution is made as follows:

Methacrylic acid and Methycrate copolymer 10% w/w
Diethyl butyl phthalate (plasticizer) 2% w/w
Acetone 22% w/w
Isopropanol 66% w/w

Procedure: Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.

For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid bed sprayer/dryer is operated with the following parameters:

Flow rate: 1.5 ml/minute
Inlet air temperature: 25°C
Outlet air temperature: 25°C
Air flap: 35
Atomizer: 2.0 bar
A size 0 capsule after the enteric coating will typically have the following composition:
Preemulsion solution: 0.589 g
Undercoat polymer: 0.027 g
Enteric coat polymer: 0.032 g, 0.648 g

Esomeprazole Magnesium Capsules

The active ingredient, esomeprazole magnesium, in delayed-release capsules is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 *H*-benzimidazole-1-yl) magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R-isomers. Each delayed-release capsule contains 20 mg or 40 mg of esomeprazole (present as 22.3 mg or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40-50, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C Blue No. 1, FD&C Red No. 40, D&C Red No. 28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow No. 10.

Estramustine Phosphate Capsules

Estramustine phosphate sodium is an antineoplastic agent. The capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate that is equivalent to 140 mg estramustine phosphate, for oral administration. Each capsule also contains magnesium stearate, silicon dioxide, sodium lauryl sulfate, and talc. Gelatin capsule shells contain titanium dioxide.

Ethosuximide Capsules

Ethosuximide is an anticonvulsant succinimide that is chemically designated as alpha-ethyl-alpha-methyl-succinimide. Each capsule contains 250 mg ethosuximide, and the inactive ingredient polyethylene glycol. The capsule contains D&C Yellow No. 10; FD&C Red No. 3; gelatin, glycerin, and sorbitol.

Etodolac Capsules

Etodolac is a pyranocarboxylic acid. The inactive ingredients in the capsules are: cellulose, gelatin, iron oxides, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide.

Eye Nutrition Supplement Capsules

This is an antioxidant supplement formulated to provide nutritional support for the eye. It contains essential antioxidant vitamins, minerals, and 6 mg of lutein. Each capsule contains: ascorbic acid, 60 mg; dl-alpha tocopheryl acetate, 30 IU; zinc oxide, 15 mg (elemental); cupric oxide, 2 mg (elemental). The inactive ingredients are: lactose monohydrate, crospovidone, magnesium stearate, and silicone dioxide.

Felbamate for Oral Suspension

Felbamate is an antiepileptic available as a 600 mg/5 ml suspension for oral administration. Its chemical name is 2-phenyl-1,3-propanediol dicarbamate. The inactive ingredients for a felbamate suspension (600 mg/5 ml) are: sorbitol, glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, simethicone, polysorbate 80, methylparaben, saccharin sodium, propylparaben, FD&C Yellow No. 6, FD&C Red No. 40, flavorings, and purified water.

Fenofibrate Capsules

Micronized fenofibrate is a lipid-regulating agent available in capsule form for oral administration. Each capsule contains 67 mg, 134 mg, or 200 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid,1-methylethyl ester. Each capsule also contains the following inactive ingredients: crospovidone, iron oxide, lactose, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide.

Bill of Materials

Scale(mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Fenofibrate Micronized (5 µm)	100.00
2.00	2	Sodium Lauryl Sulfate	2.00
100.00	3	Polyvinylpyrrolidone K 25, 100–400 µm	100.00
QS	4	Water Purified	1750.00
114.28	5	Lactose Monohydrate, 100–400 µm	114.28

Note: This formulation is expected to provide enhanced bioavailability of Item 1, thus the dose may be reduced by 33% for all strengths.

MANUFACTURING DIRECTIONS

1. Examine Item 1 using a Coulter® Counter to make sure 90% of particles are within the 5-µm range.
2. Add and dissolve Item 2 in Item 4; Item 1 is then added to make a smooth suspension using a high-speed stirrer and then passing it through a high-speed mill.
3. Add Item 3 while agitating until it is dissolved, and assure that no agglomerates are present.
4. Pass Step 3 through a 350-µm sieve.
5. Separately, Item 5 is charged in a fluid-bed granulator and brought into suspension, and the temperature is raised to 40°C.
6. Add Step 3 into Step 5 gradually at a spraying pressure of 2.1 bar; air throughput of 70 m^3/h; air inlet temperature of 45°C; air outlet temperature of 33°C; product temperature of 34°C; and a spraying duration of 3 h.
7. The granulate thus obtained is filled in a suitable size capsule.

Fexofenadine Hydrochloride Capsules

Fexofenadine hydrochloride is a histamine H1-receptor antagonist with the chemical name (±)-4-[1 hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-(alpha), (alpha)-dimethyl benzeneacetic acid hydrochloride. It is formulated as a capsule or tablet for oral administration. Each capsule contains 60 mg of fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
60.00	1	Fexofenadine Hydrochloride[a]	60.00
141.00	2	Microcrystalline Cellulose	141.00
141.00	3	Lactose	141.00
40.00	4	Pregelatinized Starch	40.00
20.00	5	Croscarmellose Sodium	20.00
14.70	6	Gelatin capsules	14.70

[a] Particle surface area of 2–4 m^2/g.

MANUFACTURING DIRECTIONS

1. Combine fexofenadine hydrochloride (Item 1), microcrystalline cellulose (Item 2), lactose (Item 3), and pregelatinized starch (Item 4), and blend in a mixer for 5 min.
2. To this mixture, add a solution of gelatin (Item 6) in purified water (prepared by adding the gelatin to the water and heating the dispersion with mixing until solution of the gelatin is attained), and continue mixing until a good granulation is formed.
3. Pass the granulation through a 0.375-in. screen, and dry at 60°C until a moisture content of less than 3.0% is achieved as determined by a Computrac moisture balance at 125°C.
4. Mill the dried granulation through a 0.065-in. screen.
5. To the granulation, add croscarmellose sodium, and mix for about 10 min.
6. Fill the granulation into size 0 hard gelatin capsules to a total fill weight of 416.7 mg granulation per capsule.

Fluconazole for Oral Suspension

Fluconazole is the first of a new subclass of synthetic triazole antifungal agents. Fluconazole is designated chemically as 2,4-difluoro-(α), 1-bis(1H-1,2,4-triazol-l-ylmethyl) benzyl alcohol. The oral suspension contains 350 mg or 1400 mg of fluconazole and the following inactive ingredients: sucrose, sodium citrate dihydrate, citric acid anhydrous, sodium benzoate, titanium dioxide, colloidal silicon dioxide, xanthan gum, and natural orange flavor. After reconstitution with 24 ml of distilled water or purified water, each ml of reconstituted suspension contains 10 mg or 40 mg of fluconazole.

Flucytosine Capsules

Flucytosine, an antifungal agent, is available as 250-mg and 500-mg capsules for oral administration. Chemically, flucytosine is 5-fluorocytosine, a fluorinated pyrimidine that is related to fluorouracil and floxuridine. Each capsule also contains cornstarch, lactose, and talc. Gelatin capsule shells contain parabens (butyl, methyl, propyl) and sodium propionate, with the following dye systems: 250-mg capsules contain black iron oxide, FD&C Blue No. 1, FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide; 500-mg capsules contain black iron oxide and titanium dioxide.

Fluoxetine Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
20.00	1	Fluoxetine, USE Fluoxetine Hydrochloride	22.36
80.14	2	Starch (Cornstarch)	80.14
10.00	3	Simethicone, USE Simethicone M30	35.00
42.00	4	Starch (Cornstarch Dried)	42.00
0.50	5	Colloidal Silicon Dioxide (Aerosil 200)	0.50
1.00	6	Empty Hard Gelatin Capsule, Shell Size 3	1000.00

MANUFACTURING DIRECTIONS

Note: The processing area must be under controlled room temperature and humidity. The limits are: RH 40–50%; temperature not more than 27°C.

I. Dry powder mixing
   A. Sift Items 1 and 2 through stainless steel sieve (630 μm) in a sifter.
   B. Load the powder mix in the mixer. Mix for 5 min at low speed.

II. Wet massing
   A. Add Item 3 suspension into the powder mix while mixing at low speed for 3 min. Scrape sides and blades. Mix for another 3 min at low speed.

III. Drying and grinding
   A. Spread the moist mass thinly on stainless steel trays. Break the big lumps if any.
   B. Dry the mass in oven at 55°C for 10 h.
   C. Check LOD (limit between 1.5% and 2.0%). If required, dry further for 1 h.
   D. Grind the dried granules through a granulator using a stainless steel sieve (1.00 mm). Collect in a stainless steel drum.

IV. Lubrication
   A. Sift Items 4 and 5 through a stainless steel sieve (500-μm) using a sifter. Collect in a stainless steel drum. Add into the drum blender (Step III-D). Mix for 5 min.
   B. Unload the final blend.

V. Take sample for analyzing fluoxetine hydrochloride content in the granules to fill.
   Note: Encapsulation is recommended within 7 days after lubrication.

Fluoxetine Hydrochloride Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
20.00	1	Fluoxetine, USE Fluoxetine Hydrochloride	22.40
160.00	2	Talc	160.00
100.00	3	Starch Dried	100.00
4.00	4	Magnesium Stearate	4.00
1.00	5	Aerosil 200	1.00

MANUFACTURING DIRECTIONS

1. Charge Items 1–5 in a suitable blender after passing through a No. 60 mesh.
2. Mix for 30 min.
3. Fill 350 mg in size 2 capsules.

Fluoxetine Hydrochloride Instant and Weekly Capsules

Fluoxetine hydrochloride is an antidepressant for oral administration; it is also marketed for the treatment of premenstrual dysphoric disorder. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated N-methyl-3-phenyl-3-[((alpha),(alpha),(alpha)-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride. Each capsule contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and optionally other inactive ingredients. The 10-mg and 20-mg Pulvules also contain FD&C Blue No. 1, and the 40-mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6. The capsules intended for weekly administration, a delayed release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain FD&C Yellow No. 10, FD&C Blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and optionally other inactive ingredients.

Flutamide Capsules

Flutamide, an acetanilid, nonsteroidal, orally active antiandrogen, has the chemical name, 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide. Each capsule contains 125 mg of flutamide. The inactive ingredients include: cornstarch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may also contain benzyl alcohol, butylparaben, colloidal silicon dioxide, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate, as well as the following dye systems: FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, titanium dioxide, and black ink.

Fluticasone Propionate and Salmeterol Xinafolate Inhalation Powder

This is a combination of fluticasone propionate and salmeterol xinafolate. One active component, fluticasone propionate, is a corticosteroid that has the chemical name S-(fluoromethyl)6(α),9-difluoro-11(β), 17-dihydroxy-16(α)-methyl-3-oxoandrosta-1, 4-diene-17(β)-carbothioate, 17-propionate. The other active component is salmeterol xinafolate, a highly selective beta 2-adrenergic bronchodilator. Salmeterol xinafolate is the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The chemical name of salmeterol xinafolate is 4-hydroxy-(α)1-[[[6-(4-phenylbutoxy)-hexyl]amino] methyl]-1,3-benzenedimethanol,1-hydroxy-2-naphthalenecarboxylate. These are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafolate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate and 72.5 mcg of microfine salmeterol xinafolate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose. Each blister contains one complete dose of both medications. After a blister containing the medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece. Under standardized *in vitro* test conditions, it delivers 93, 233, and 465 mcg of fluticasone propionate and 45 mcg of salmeterol base per blister, respectively, when tested at a flow rate of 60 l/min for 2 sec.

Fluvastatin Sodium Capsules

Fluvastatin sodium is a water-soluble cholesterol-lowering agent, which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. It is supplied in capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration. The inactive ingredients in the capsules are: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, and yellow iron oxide. Capsules may also include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Fluvastatin	20.00
62.84	2	Calcium Carbonate Heavy Precipitated	62.84
2.00	3	Sodium Bicarbonate	2.00
23.35	4	Microcrystalline Cellulose Avicel PH102	23.35
20.95	5	Pregelatinized Starch (Starch 1500)	20.95
QS	6	Water Purified	QS
33.88	7	Microcrystalline Cellulose	33.38
20.95	8	Pregelatinized Starch	20.95
9.43	9	Talc	9.43
1.05	10	Magnesium Stearate	1.05

MANUFACTURING DIRECTIONS

1. The fluvastatin (Item 1), sodium bicarbonate (Item 3), calcium carbonate (Item 2), microcrystalline cellulose (Item 4), and pregelatinized starch (Item 5) are mixed for 5 min, and the mixture is passed through a 40-mesh screen and blended for another 3 min.
2. Water is added to the mixture, while blending for about 4 min to form a wet granulation.
3. The wet granulation is dried in a fluid bed dryer at 50°C inlet temperature to a loss on drying of 1.59%.
4. The dried granules are passed through a 20-mesh screen and blended with the microcrystalline cellulose and pregelatinized starch set-asides (Items 7 and 8) for about 10 min.
5. Talc and magnesium stearate (each prescreened on a 60-mesh bolting cloth) are added to the mixture while blending for about 5 min. The resulting composition has a loss on drying of 2.65%.
6. A blue opaque capsule is filled with the composition and polished manually with salt.

Formoterol Fumarate Inhalation Powder

This consists of a capsule dosage form containing a dry powder formulation of formoterol fumarate intended for oral inhalation only with the AerolizerJ® inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 mcg of formoterol fumarate and 25 mg of lactose as a carrier. The active component is formoterol fumarate — a racemate.

Formoterol Fumarate Inhaler Capsules

The inhaler consists of a capsule dosage form containing a dry powder formulation of formoterol fumarate intended for oral inhalation only with the AerolizerJ inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 mcg of formoterol fumarate and 25 mg of lactose as a carrier.

Fosfomycin Tromethamine Sachets

Fosfomycin tromethamine sachet contains fosfomycin tromethamine, a synthetic, broad-spectrum, bactericidal antibiotic for oral administration. It is available as a single-dose sachet, which contains white granules consisting of 5.631 g of fosfomycin tromethamine (equivalent to 3 g of fosfomycin) and the following inactive ingredients: mandarin flavor, orange flavor, saccharin, and sucrose.

Gabapentin Capsules

Gabapentin capsules are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, The inactive ingredients for the capsules are: lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400-mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C Blue No. 2 and titanium dioxide.

Ganciclovir Capsules

Ganciclovir is a synthetic guanine derivative that is active against cytomegalovirus. It is available as 250 mg and 500 mg capsules. Each capsule contains 250 mg or 500 mg ganciclovir, respectively, and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and povidone. Both hard gelatin shells consist of gelatin, titanium dioxide, yellow iron oxide, and FD&C Blue No. 2.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Ganciclovir	250.00
3.00	2	Magnesium Stearate	3.00
30.00	3	Cornstarch	30.00
116.00	4	Lactose	116.00
4.00	5	Polyvinylpyrrolidone	3.00
QS	6	Methanol	QS

MANUFACTURING DIRECTIONS

1. Items 1, 3, and 4 are granulated in a solution of Item 5 in Item 6.
2. Granules are dried, lubricated with Item 2, and filled in capsules or tableted.

Gemfibrozil Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	Gemfibrozil	100.00
248.80	2	Lactose Anhydrous[a]	248.80
100.00	3	Cornstarch	100.00
25.00	4	Sodium Starch Glycolate	25.00
5.00	5	Povidone	5.00
15.00	6	Polysorbate 80	15.00
1.25	7	Colloidal Silicon Dioxide	1.25
5.00	8	Magnesium Stearate	5.00
QS	9	Water Purified	QS

[a] The quantity of lactose can be reduced to compensate if additional quantities of glycine 12.5 mg and citric acid 2.5 mg are used.

MANUFACTURING DIRECTIONS

1. An aqueous wet granulation process is used whereby the respective active ingredients of lactose, cornstarch, sodium starch glycolate, colloidal silicon dioxide, and povidone are mixed and subsequently granulated with polysorbate dissolved in purified water.
2. Additional purified water is then added until granules form and no dry powder remains.
3. Wet granules are dried at 60°C until the loss on drying is not more than 2%.
4. The dried granules are milled with the sodium starch glycolate, blended, and lubricated with screened magnesium stearate in a twinshell blender.
5. Size 0 capsules are used to fill 500 mg of granules.

Glycoprotein IIa/IIb Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
0.23	1	Glycoprotein IIa/IIb	0.23
53.77	2	Lactose Anhydrous	53.77
2.70	3	Crospovidone	2.70
1.20	4	Povidone	1.20
1.50	5	Disodium Citrate	1.50
0.60	6	Magnesium Stearate	0.60
QS	7	Water Purified	QS

MANUFACTURING DIRECTIONS

1. Triturate Item 1 with Item 2 (portion) in a small mixing vessel or mortar.
2. Charge the balance of Item 2 and two-thirds of the quantity of Item 3 in a shear granulator, and add Step 1 into it with fast mixing.
3. Granulate Step 2 using aqueous solution of balance of Item 4 and Item 5 (9.3% solids in Item 7 and pH adjusted to 4 using 1 N hydrochloric acid).
4. Screen the granulation through a No. 8 mesh and dry in vacuum at 40°C to a moisture content of 0.7%.
5. Blend the granulation with remaining amount of Items 3 and 6.
6. Fill 60 mg in size 3 capsules.

Guaifenesin Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
150.00	1	Guaifenesin	150.00
26.60	2	Carbopol 934P (B.F. Goodrich)	26.60
172.10	3	PVP C-15 (GAF Corporation)	172.10
3.50	4	Talc	3.50
1.80	5	Zinc Stearate	1.80

MANUFACTURING DIRECTIONS

1. The Carbopol 934P, PVP C-15, talc, and zinc stearate are combined in a mortar and triturated well.
2. The guaifenesin is added to this mixture in the mortar and triturated well until a substantially uniform particulate mixture is achieved.
3. The resulting particulate mixture is filled 354 mg into size 1 hard gelatin capsule shells.

Herbal AIDS Treatment Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
32.00	1	*Combretum quadrangulare*	32.00
20.00	2	*Houttuynia cordata*	20.00
20.00	3	*Mimusops elengi*	20.00
20.00	4	*Randia siemensis*	20.00
308.00	5	*Borassus flabellifer*	308.00

MANUFACTURING DIRECTIONS

1. Items 1–5 are prepared by first making a powdered form of herbs, extracting them in water or hydroalcoholic solution, and drying the extract.
2. Powdered extracts 1–5 are admixed and filled in a gelatin capsule. Add magnesium stearate 1%, if necessary, to improve flow.

Histadine Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Histadine	240.00
QS	2	Lactose	QS

MANUFACTURING DIRECTIONS

1. Mix Items 1 and 2 (using desired quantity of Item 2 to fit the capsule size chosen) by process of trituration.
2. Fill in appropriate capsule.

Human Growth Hormone Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
28.00 IU	1	Human Growth Hormone[a]	28,000 IU
0.047	2	Dimyristoyl Phosphatidic Acid	0.047
3.38	3	Aprotinin[b]	3.38
3.47	4	Sodium Cholate	3.47
3.70	5	Polyoxy-23 Lauryl Ether	3.70
138.60	6	Polyethylene Glycol 400	138.60
13.71	7	Propylene Glycol	13.71
8.67	8	Water/pH Adjuster	8.67
30.92	9	Cholesterol	30.92
17.40	10	Tween 80	17.40
62.53	11	Egg Yolk Lecithin	62.53
19.43	12	d-alpha Tocopherol	19.43
27.64	13	Sorbitan Monooleate	27.64
246.90	14	Isostearic Acid	246.90

[a] Human growth hormone 2.6 IU = 1 mg.
[b] Aprotinin: 7,500 KIU = 1 mg.

MANUFACTURING DIRECTIONS

1. Polyoxy-23 lauryl ether (commercially available as Brij™ 35) is dispersed in the solvent mixture of polyethylene glycol 400 and propylene glycol.
2. Sodium cholate is also separately dispersed in the mixture.
3. A water solution containing recombinant human growth hormone, phospholipid, and aprotinin is then added to the solvent mixture in Step 1 and the pH is adjusted to 7.5–7.8 with the help of a phosphate buffer.
4. The lipid solution is made separately in another beaker.
5. To the oil solution, the polyol solution is added dropwise while mixing continuously. While mixing, it is suggested that the vessel be ice jacketed to prevent the denaturation of the protein in the formulation.
6. A clear transparent liquid, which is called the preemulsion solution, is obtained after approximately 5 min of mixing at low speed. An *in situ* emulsion can be made by mixing any ratio of the preemulsion solution with the simulated intestinal fluid.
7. The preemulsion solution is filled in a size 0 hard gelatin capsule and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
8. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, 3.5–4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
9. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers, such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate are used.
10. Anionic copolymers which are based on methacrylic acid and methyl methacrylate, commercially available as Eudragit, are also very suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, and isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5–6% weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows:

Methacrylic acid and methyl methacrylate copolymer 10% w/w
Diethyl butyl phthalate (plasticizer) 2% w/w
Acetone 22% w/w
Isopropanol 66% w/w

Procedure:

Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.

For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid-bed sprayer/dryer is operated with the following parameters:

Flow rate: 1.5 ml/min
Inlet air temperature: 25°C
Outlet air temperature: 25°C
Air flap: 35
Atomizer: 2.0 bar

A size 0 capsule, after the enteric coating, will typically have the following composition:

Preemulsion solution: 0.589 g
Undercoat polymer: 0.027 g
Enteric coat polymer: 0.032 g, 0.648 g

Hydrochlorothiazide and Triamterene Capsules

This is a combination capsule with an opaque red cap and an opaque white body. It contains hydrochlorothiazide (25 mg) and triamterene (37.5 mg). Hydrochlorothiazide is a diuretic/antihypertensive agent, and triamterene is an antikaliuretic agent. Triamterene is 2,4,7-triamino-6-phenylpteridine. Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C Red No. 33, FD&C Yellow No. 6, gelatin, glycine, lactose, magnesium stearate, microcrystalline cellulose, povidone, polysorbate 80, sodium starch glycolate, titanium dioxide, and trace amounts of other inactive ingredients. These capsules meet Drug Release Test 3 as published in the USP monograph for Triamterene and Hydrochlorothiazide Capsules.

Hydrochlorothiazide Capsules

Hydrochlorothiazide is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2 *H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. It is supplied as 12.5 mg capsules for oral use. Each capsule contains the following inactive ingredients: colloidal silicon dioxide, cornstarch, D&C Red No. 28, D&C Yellow No. 10, FD&C Blue No. 1, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, and other optional ingredients.

Hydroxyzine Pamoate Capsules and Oral Suspension

Hydroxyzine pamoate is designated chemically as 1-(p-chlorobenzhydryl) 4-[2-(2-hydroxyethoxy) ethyl] diethylenediamine salt of 1,1'-methylene bis (2-hydroxy-3-naphthalene carboxylic acid). The inert ingredients for the capsule formulations are: hard gelatin capsules (which may contain FD&C Yellow No. 10, FD&C Green No. 3, FD&C Yellow No. 6, FD&C Red No. 33, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch; and sucrose. The inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; lemon flavor; propylene glycol; sorbic acid; sorbitol solution; and water.

Hyoscyamine Sulfate Capsules

Hyoscyamine sulfate is one of the principal anticholinergic/antispasmodic components of belladonna alkaloids. Chemically, it is benzeneacetic acid, (alpha)-(hydroxymethyl)-,8-methyl-8-azabicyclo[3.2.1.]oct-3-ylester,[3(S)-endo]-,sulfate (2:1), dihydrate. The sustained release capsules contain 0.375 mg hyoscyamine sulfate in an extended-release formulation designed for oral b.i.d. dosage. Each capsule also contains the following inactive ingredients: FD&C Blue No. 1, D&C Red No. 28, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, lactose monohydrate, sodium lauryl sulfate, magnesium stearate, silicon dioxide, titanium dioxide, and other optional ingredients.

Ibuprofen Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
450.00	1	Ibuprofen	450.00
450.00	2	Sodium Alginate	450.00
4.50 ml	3	Zinc Chloride Solution 2%	451.00
QS	4	Hydrochloric Acid	QS
0.22 ml	5	Glycerin	225.00 ml
—	6	Water Purified	22.5 l

MANUFACTURING DIRECTIONS

1. A mixture consisting of Item 1, previously triturated in 225 ml of glycerin, is added with rapid stirring to an aqueous solution consisting of 450 g (w/v) of sodium alginate in 22.5 l of purified water.
2. This solution is then added to 45 l of a 2% (w/v) zinc chloride solution, which has previously been adjusted to pH 3 by the addition of HCl while the rapid stirring is continued for 10 min.
3. The preparation is then allowed to stand at room temperature for 4 h, after which the drug-entrapped zinc alginate precipitate is collected by filtration, washed three times with distilled water, and dried under vacuum for 24 h.
4. After drying, the residue is granulated using minimal amounts of glycerin/water and processed into 0.5-mm diameter microspheres by mechanical extrusion and spheronization (Nica Extruder®; Aeromatic Ltd., Bubendorf, Switzerland), into which the slightly flexible mass represented by the above residue is fed, and which produces therefrom a continuous flow of cylindrical extrudate that is 0.5 mm in diameter.
5. This extrudate falls onto the spinning plate of a Nica Spheronizer® (Aeromatic Ltd.), where it is broken into cylinders of approximately 1:1 length:diameter ratio. Interaction then between the spinning disc and the wall of the spheronizer causes the cylinders to be worked into spheres of 0.5 mm diameter.
6. The spheres are then filled into gelatin capsules (1 g of spheres per size 0 capsule, which represents a total dose of 450 mg of ibuprofen). The capsules of spheres thus produced represent a sustained-release dosage form for analgesic–antipyretic activity with less propensity for gastrointestinal side effects than the conventional tablet form of ibuprofen. Upon ingestion, the spheres begin to release the incorporate drug almost immediately, but begin erosion in 3 to 5 h. Total erosion time is approximately 8 h.

Ibuprofen Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
800.00	1	Ibuprofen	800.00
8.00	2	Aerosil R972	8.00
8.00	3	Beeswax	8.00

MANUFACTURING DIRECTIONS

1. Charge Items 1 and 3 in a jacketed kettle, and heat to melt; stir until uniformly melted.
2. Add Item 2, with stirring, to form a homogeneous suspension. Allow to cool.
3. Pass through sieve. If needed, a lubricant may be added to facilitate flow (1% magensium stearate).
4. Fill size 00 capsules.
5. The 50% dissolution time is approximately 15 h.

Given below are guidelines on controlling release rates of ibuprofen using different compositions of excipients. In all instances, ibuprofen is melted with the ingredient, allowed to congeal, sized, and filled in appropriate size capsules. T_{50} represents time for 50% dissolution. A combination of these granules can be used to provide a wide range of ibuprofen release patterns that are particularly useful in arthritis therapy.

	Amount of		
	Ibuprofen (% w/w)	**Excipient (% w/w)**	**T_{50} (hours)**
None	100	—	2.9
Arachis oil	90	10	4.1
Beeswax	90	10	>24.0
Beeswax	90[a]	10	9.5
Colloidal silicon dioxide (Aerosil 200)	99	1	4.7
	97	3	6.6
	95	5	10.0
Colloidal silicon dioxide (Aerosil R972)	99	1	5.9
	95	5	20.5
Croscarmellose sodium (AcDiSol®)	99	1	0.4
	97.5	2.5	0.13
Glycerides	95	5	3.0
(Gelucire 50/13)	90	10	7.4
(Gelucire 50/13)	90[a]	10	2.9
Liquid paraffin	90	10	4.8
Cornstarch	99	1	3.5
	95	5	1.6
	90	10	0.16
Copolymer (Pluronic F68)	95	5	3.0
PEG 400	90	10	3.5
PEG 4000	90	10	3.3
PEG 6000	90	10	4.2
Polyvinylpyrrolidone (Crospovidone)	90	10	4.0
Sodium starch glycolate (Explotab®)	99	1	1.8
	95	5	0.3
Stearic acid	99	1	4.2
	95	5	7.8
	90	10	>24.0
Stearyl alcohol	99	1	10.0
	95	5	14.0
	90	10	>24.0

[a] Indicates S(+)ibuprofen.

Ifosfamide Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Ifosfamide	250.00
83.50	2	Microcrystalline Cellulose, Avicel PH105	83.50
1.50	3	Colloidal Silicon Dioxide	1.50
0.50	4	Magnesium Stearate	0.50

MANUFACTURING DIRECTIONS

1. Pass Items 1–3 through a 0.8-mm sieve into a blender.
2. Blend for 4 min.
3. Add Item 4, which has been sieved through a 0.8-mm sieve, to Step 2; mix for another 1 min.
4. Fill in size 1 capsule, 340 mg each. For a 500-mg capsule, fill 680 mg in size 00 capsules.
5. To impart enteric resistance to capsules, coat using a coating suspension. For example, to coat 2500 size 1 capsules containing 250 mg ifosfamide, use 3 kg of suspension containing 1440 g anionic polymerizate of methacrylic acid and methacrylic acid esters with a mean molecular weight of, for example, 150,000, to which a conventional softener has been added, 18 g of 1,2-propandiol, 36 g of magnesium stearate, and 1506 g of isopropanol. The copolymerizate of methacrylic acid and methylmethacrylate that may, for example, be considered is Eudragit® L, particularly in the form of a 12.5% solution in isopropanol (Eudragit® L RTM /12.5%). Copolymerizates for this type are soluble in neutral to weakly alkaline medium through salt formation with alkalis.

Imatinib Mesylate Capsules

The capsules contain imatinib mesylate equivalent to 100 mg of imatinib freebase. Imatinib mesylate is designated chemically as 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-henyl]benzamide methanesulfonate. The inactive ingredients are: colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The capsule shell contains gelatin; iron oxide; red (E172); iron oxide, yellow (E172); and titanium dioxide (E171).

Indinavir Sulfate Capsules

Indinavir sulfate is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name for indinavir sulfate is [1(1*S,2R),*5(*S)*]-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinyl-methyl)-1-piperazinyl]-2-(phenylmethyl)-D-*erythro*-pentonamide sulfate (1:1) salt. Capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide, and sodium lauryl sulfate.

Scale (mg/Caps)	Item	Material Name	Qty/1000 Caps (g)
400.00	1	Indinavir Sulfate, USE Invinavir Sulphate	400.00
7.00	2	Sodium Lauryl Sulphate	7.00
1.50	3	Colloidal Silicon Dioxide (Aerosil-200)	1.50
6.50	4	Magnesium Stearate	6.50
650.00	5	Lactose Monohydrate Dense QS to	650.00
1	6	Empty Hard Gelatin Capsule, size 00	1000

MANUFACTURING DIRECTIONS

1. Sift indinavir sulphate, lactose anhydrous, and Aerosil-200 through a specified sieve.
2. Load the sifted powder into a blender, and blend well.
3. Sift magnesium stearate and sodium lauryl sulphate through a specified sifter.
4. Mix Step 3 with Step 2, and blend well.
5. Encapsulate the powder to get the stated amount of indinavir per capsule.

Indomethacin Capsules

Indomethacin cannot be considered a simple analgesic and should not be used in conditions other than those recommended. Capsules for oral administration contain either 25 mg or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD&C Blue No. 1, FD&C Red No. 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide. Suspension for oral use contains 25 mg of indomethacin per 5 ml, alcohol 1%, and sorbic acid 0.1% added as a preservative. The suspension also contains the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, and tragacanth.

1.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
25.00	1	Indomethacin Micronized	26.25
1.00	2	Lecithin (Liquid)	1.00
—	3	Trichloro Trifluoro Ethane	17.00
218.25	4	Lactose Monohydrate (Dense)	218.25
1.50	5	Colloidal Silicon Dioxide (Aerosil 200)	1.50
2.00	6	Sodium Lauryl Sulfate	2.00
1.00	7	Magnesium Stearate	1.00
1	8	Empty Hard Gelatin Capsule, Size 3	1000

MANUFACTURING DIRECTIONS

I. Precautions
   A. The processing area must be under controlled room temperature and humidity. The limits are: RH: 40–50%; temperature: 21–27°C.
   B. Trichloro trifluoro ethane is a volatile substance when kept in open air. Always keep in covered containers.
   C. Do not expose the granules for a long time to light as discoloration will occur.
   D. Mix Item 2 with Item 3 in a clean stainless steel container. Firmly cover to avoid any vaporization.

II. Blending
   A. Mix Item 1 and 0.25 g of Item 5 in a drum mixer.
   B. Sift the "mix" through 1250-µm sieve using sifter. Collect in stainless steel drum and transfer to the mixer.
   C. Add Item 2 solution from Step 1 to the Item 1 powder in mixer while mixing at high speed. When the addition is over, mix the moist mass at highest speed for 5 min.
   D. Scrape the sides of mixer and mix at highest speed for 5 min.
   E. Again, scrape the sides of mixer and mix at highest speed for 10 min.

III. Drying
   A. Spread the moist mass thinly on stainless steel trays. Break the big lumps if any.
   B. Dry the mass in oven using only cold air (without temperature) for 6 h.

IV. Sifting
   A. Sift 168.25 g of Item 4 through 630-µm sieve, using a sifter. Collect in stainless steel drum. Keep aside.

V. Mixing
   A. Mix 50.0 g of Item 4, the indomethacin–lecithin mixture (dried), and 1.25 g of Item 5 in a drum mixer, for 10 min.
   B. Sift the mixture twice through 630-µm stainless steel sieve, using a sifter.
   C. Use Item 4 (about 2–4 g) to prevent the clogging of the sifter sieve, if required.
   D. Load sieved Item 4 from Step 4 into the blender.
   E. Add lactose–indomethacin–aerosil mixture from Step V-B to the blender. Mix for 10 min.

VI. Lubrication
   A. Sift Items 6 and 7 through a 630-µm sieve, using a sifter.
   B. Add to the powder in blender. Mix for 2 min.
   C. Unload the granules in stainless steel drums.

VII. Loading of Empty Shells
   A. Load the empty capsule shells (size 3) in the hopper.
   B. Run the machine and check the locking of shells.

VIII. Filling of Powder
   A. Calculation: A fill weight of one capsule = 250 mg.

2.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
25.00	1	Indomethacin	25.00
0.50	2	Lecithin Swiss	0.50
1.25	3	Colloidal Silicon Dioxide	1.25
1.67	4	Magnesium Stearate	1.67
200.00	5	Lactose	200.00
—	6	Chloroform	QS

3.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
50.00	1	Indomethacin	50.00
1.00	2	Lecithin Swiss	1.00
3.00	3	Colloidal Silicon Dioxide	3.00
4.00	4	Magnesium Stearate	4.00
325.00	5	Lactose	325.00
—	6	Chloroform	QS

MANUFACTURING DIRECTIONS

1. Mix indomethacin with about one-half of the quantity of lactose, and micronize.
2. Dissolve lecithin in chloroform, and wet this solution with the remaining half of the lactose.
3. Dry the chloroform mixture in a drying oven at 4°C for 4 h.
4. Pass the dried granulate through a Fitz mill sieve No. 24228 at a low speed; add the mixture of indomethacin and lactose from Step 1; add colloidal silicon dioxide and magnesium stearate, and mix for 15 min.
5. Fill into size 3 capsules as 200 mg ± 5%. For 50 mg capsules, fill into capsules as 325 mg ± 5%.

Indomethacin Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
45.00	1	Indomethacin	45.00
45.00	2	Sodium Alginate	45.00
4.50 ml	3	Zinc Chloride Solution 2%	45 l
QS	4	Hydrochloric Acid	QS
0.22	5	Glycerin	22.5 ml
—	6	Water Purified	2.25

MANUFACTURING DIRECTIONS

1. A mixture consisting of Item 1 previously triturated in 22.5 ml glycerin is added with rapid stirring to an aqueous solution consisting of 45.00 g (w/v) of sodium alginate in 2.25 l of purified water.
2. This solution is then added to 4.5 l of a 2% (w/v) zinc chloride solution, which has previously been adjusted to pH 3 by the addition of HCl, while the rapid stirring is continued for 10 min.
3. The preparation is then allowed to stand at room temperature for 4 h, after which the drug-entrapped zinc alginate precipitate is collected by filtration, washed three times with distilled water, and dried under vacuum for 24 h.
4. After drying, the residue is granulated using minimal amounts of glycerin/water and processed into 0.5-mm diameter microspheres by mechanical extrusion and spheronization (Nica Extruder®; Aeromatic Ltd., Bubendorf, Switzerland), into which the slightly flexible mass represented by the above residue is fed, and which produces therefrom a continuous flow of cylindrical extrudate that is 0.5 mm in diameter.
5. This extrudate falls onto the spinning plate of a Nica Spheronizer® (Aeromatic Ltd.), where it is broken into cylinders of approximately 1:1 length:diameter ratio. Interaction between the spinning disc and the wall of the spheronizer then causes the cylinders to be worked into spheres of 0.5 mm in diameter.
6. The spheres are then filled into gelatin capsules (100 mg of spheres per size 1 capsule, which represents a total dose of 45.0 mg indomethacin). The capsules of the spheres thus produced represent a sustained-release dosage form for analgesic–antipyretic activity with less propensity for gastrointestinal side effects than the conventional tablet form of indomethacin. Upon ingestion the spheres begin to release the incorporate drug almost immediately, but begin to erode in 3–5 h. Total erosion time is approximately 8 h.

Indomethacin Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
75.00	1	Indomethacin	75.00
110.20	2	Sucrose	110.20
39.75	3	Cornstarch	39.75
36.20	4	Lactose	36.20
10.95	5	Polyvinylpyrrolidone	10.95
19.65	6	Talc	19.65
5.15	7	Magnesium Stearate	5.15
1.10	8	Eudragit L	1.10
2.00	9	Eudragit S	2.00
—	10	Ethyl Alcohol	98.55
—	11	Acetone	27.90

MANUFACTURING DIRECTIONS

I. Pellets
   A. Weigh and mix in a stainless steel mixer suitable quantities of sucrose and cornstarch in the proportion of 3:1 w/w. Sift through a screen of suitable size to break up possible lumps.
   B. Transfer the mixture to a stainless steel coating pan and adjust rotary speed between 20 and 30 rpm so as to obtain good tumbling action.
   C. By means of a suitable spray gun, spray over the powder a quantity of water equal to 15% w/w in very minute drops.
   D. Place the wet pellets over a thermostatic tray dryer and dry at 37°C to complete evaporation of water.
   E. Pass the dried pellets through sieves of suitable screens to ensure removal of dust and selection of cores of desirable size.

II. Active Pellets
   A. Dissolve polyvinylpyrrolidone in ethyl alcohol and add indomethacin previously mixed with lactose (No. 3) to it.
   B. Transfer 149.95 kg of neutral pellets obtained from Step I-E to a stainless steel coating pan and adjust the rotary speed between 20 and 30 rpm so as to obtain good tumbling action.
   C. Spray over the neutral pellets the result of Step II-A.
   D. Keep the pan rotating to allow partial evaporation of the solvent.
   E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.

III. Film-Coated Pellets
   A. Dissolve Eudragit L and Eudragit S in acetone.
   B. Transfer the active pellets obtained from Step II-E to a stainless steel coating pan, and adjust the rotary speed to obtain a good tumbling action.
   C. Spray the pellets as uniformly as possible with the solution obtained from Step II-E.
   D. Spray the wet pellets with talc and magnesium stearate to prevent agglutination.
   E. Keep the pan rotating to achieve solidification of the film coating and partial evaporation of the solvent.
   F. Complete evaporation of the solvent by drying the pellets in a thermostat for 35°C for 3 days.

IV. Blending of Pellets
   A. Transfer the film-coated pellets obtained from Step III-F to a stainless steel pan and add a suitable quantity of neutral pellets obtained from Step I-E so as to obtain the required dosage.
   B. Add a 0.5% w/w of talc to eliminate electrostatic charges and mix for 30–35 min.

V. Filling
   A. Fill the blended pellets obtained from Step IV-B into capsules (size 2) at the dose of 300 mg each.

Insulin Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
140.00 IU	1	Insulin[a]	140,000 IU
0.047	2	Dimyristyl Phosphatidyl Choline	0.047
3.39	3	Aprotinin[b]	3.39
3.76	4	Hydroxypropyl Cellulose-LF	3.76
3.76	5	Polyoxy-40 Stearate Myrj-52®	3.76
139.80	6	Polyethylene Glycol 400	139.80
15.57	7	Propylene Glycol	15.57
8.75	8	Water-Citrate Buffer for pH adjustment	8.75
31.20	9	Cholesterol	31.20
17.56	10	Tween 80	17.56
63.10	11	Egg Yolk Lecithin	63.10
27.90	12	Glyceryl Amino Oleate	27.90
19.60	13	d-alpha Tocopherol	19.60
249.10	14	Oleic Acid	249.10

[a] Insulin: 26 IU = 1 mg
[b] Aprotinin: 7500 KIU = mg

Manufacturing Directions

1. Insulin is a biologically active proteinaceous material. Insulin is a polypeptide consisting of 65 amino acids with an approximate molecular weight of 6000. In its preparations, there can be no use of heat or alcohol that can denature it.
2. The overall method is as follows: The surfactant Myrj-52 is slowly dispersed into the mixture of polyethylene glycol 400 and propylene glycol. Once it dissolves, hydroxypropyl cellulose as a stabilizer is also added, which is dispersed slowly into the preceding mixture. A separate solution of the proteinaceous material along with the phospholipid and the protease inhibitor is made in a portion of the preceding solvent mixture. The solution can then be added to the PEG/PG mixture at room temperature. The amount of any water is limited to 5% of the polyol solvent. When the water solution is used, citrate buffer is used to maintain the pH at a point where the protein is most stable. In this particular example, if insulin is used, it is suggested that the pH be maintained with a citrate buffer at or around 2.5. Separately, the ingredients of the lipid solvent are mixed together. Under gentle and constant stirring, the polyol solution is dispersed with the lipid solution.
3. The surfactant (Polyoxy-40 stearate) is slowly dispersed into a mixture of polyethylene glycol and propylene glycol.
4. Once it is dissolved, small amounts of hydroxypropyl cellulose are then added and dispersed into the same mixture.
5. Insulin is dissolved in water, and citric acid is dissolved in water for maintaining the pH at 2.5.
6. The water solution is added to the polyethylene glycol mixture. In a separate vessel, dissolve all the ingredients of the oil phase in oleic acid.
7. Cholesterol is added slowly to achieve faster dissolution.
8. Once both the phases are ready, the polyol solution is added slowly to lipid phase while mixing at low speed. The vessel should be preferably ice jacketed because heat may be produced. Once the addition is achieved, a transparent yellowish-brown solution is obtained.
9. The preemulsion solution is filled in a size 0 hard gelatin capsule, and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
10. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, 3.5–4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.

11. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers, such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate are used.
12. Anionic copolymers that are based on methacrylic acid and methyl methycralate, commercially available as Eudragit, are also very suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, and isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5–6% weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows:

    Methacrylic acid and methyl methycralate copolymer 10% w/w
    Diethyl butyl phthalate (plasticizer) 2% w/w
    Acetone 22% w/w
    Isopropanol 66% w/w

    Procedure:
    Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly, and let it dissolve.
    For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing-bed techniques. The fluid-bed sprayer/dryer is operated with the following parameters:
        Flow rate: 1.5 ml/min
        Inlet air temp.: 25°C
        Outlet air temp.: 25°C
        Air flap: 35

    Atomizer: 2.0 bar
    A size 0 capsule after the enteric coating will typically have the following composition:
        Preemulsion solution: 0.589 g
        Undercoat polymer: 0.027 g
        Enteric coat polymer: 0.032 g, 0.648 g

Iron-Polysaccharide Complex Capsules

Each bead-filled capsule contains 150 mg elemental iron as polysaccharide — iron complex, as cell-contracted akaganéite. Each capsule also contains the following inactive ingredients: D&C Red No. 7, D&C Red No. 28, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, hydrogenated castor oil, polysorbate 80 pharmaceutical glaze, povidone, sodium lauryl sulfate, starch, sucrose, and titanium dioxide. Each capsule may contain silicon dioxide.

Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules

Each red capsule with a pink band contains isometheptene mucate (65 mg), dichloralphenazone (100 mg), and acetaminophen (325 mg). Isometheptene mucate is a white crystalline powder that has a characteristic aromatic odor and bitter taste. It is an unsaturated aliphatic amine with sympathomimetic properties. Dichloralphenazone is a white, microcrystalline powder, with a slight odor; it tastes salty at first, and then becomes acrid. It is a mild sedative. Acetaminophen, a non-salicylate, occurs as a white, odorless, crystalline powder possessing a slightly bitter taste. Capsules contain FD&C Yellow No. 6 as a color additive.

Isosorbide Mononitrate Capsules 20 mg

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
20.00	1	Isosorbide-5-Mononitrate	20.00
60.00	2	Lactose	60.00
60.00	3	Sucrose and Cornstarch Microgranules	60.00
5.85	4	Shellac	5.85
1.20	5	Eudragit L 100	1.20
1.20	6	Eudragit RS 100	1.20
11.75	7	Talc	11.75
—	8	Alcohol	QS
—	9	Acetone	QD

MANUFACTURING DIRECTIONS

1. Charge neutral microgranules of Item 3 in a coating pan.
2. Prepare a 40% solution of shellac in alcohol, together with Item 1.
3. Maintain the temperature of microgranules at 25 ± 5°C. Apply Step 2 and dry granules, and repeat the process until all of the drug has been incorporated.
4. Sieve granules using a 1-mm aperture, and dry at 20–30°C for 8 h.
5. Prepare a 12.5% solution of equal parts of Items 5 and 6 in acetone. Spray the microgranules from Step 4 and incorporate.
6. Sieve the microgranules using a 1-mm aperture sieve.
7. Dry microgranules at 20–30°C for 8 h.
8. Spray the microgranules with balance of alcoholic shellac solution, adding talc simultaneously.
9. Adjust fill weight of granules based on assay.

Isradipine Capsules

Isradipine is a calcium antagonist available for oral administration in capsules containing 2.5 mg or 5 mg. Chemically, isradipine is 3,5-pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester. The inactive ingredients are: colloidal silicon dioxide, D&C Red No. 7 calcium lake, FD&C Red No. 40 (5 mg capsule only), FD&C Yellow No. 6 aluminum lake, gelatin, lactose, starch (corn), titanium dioxide, and other optional ingredients. The 2.5 mg and 5 mg capsules may also contain benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate.

Itraconazole Capsules

Itraconazole, a synthetic triazole antifungal agent, is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. The capsules contain 100 mg of itraconazole coated on sugar spheres. The inactive ingredients are: gelatin, hydroxypropyl methylcellulose, polyethylene glycol (PEG) 20,000, starch, sucrose, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22, and D&C Red No. 28.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	Itraconazole (used as pellets)	100.00
—	2	Empty Hard Gelatin Capsule, Size 0	1000
280.00	3	Sugar Spheres	280.00
32.00	4	Hydroxypropyl Cellulose	32.00
2.00	5	Polyethylene Glycol 6000	2.00
30.00	6	Cornstarch	30.00
6.00	7	Titanium Dioxide	6.00

MANUFACTURING DIRECTIONS

1. Check the assay of pellets to calculate the exact amount needed. Calculate the dose per capsule to fill.
2. Charge Items 1 and 3–7 in a suitable blender; mix for 10 min.
3. Set the capsule-filling machine with empty shells.
4. Fill the pellets as per assay.
5. Polish the capsules.

Ketoprofen and Misoprostol Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	Ketoprofen Delayed-Release Beads (40% Ketoprofen)	250.00
0.20	2	Misoprostol (dilute 1:100 on HPMC)	20.00
160.00	3	Lactose Anhydrous	160.00
4.00	4	Hydrogenated Vegetable Oil	4.00

MANUFACTURING DIRECTIONS

1. Item 1 beads are prepared by spray coating a suspension or solution of ketoprofen onto a nonpareil sugarcore, together with a binder (e.g., polyvinyl pyrrolidone or hydroxypropyl methylcellulose). The beads are subsequently coated with a delayed release coating (e.g., methylmethacrylate, for instance, Eudragit). Mixtures of beads with various levels of coating were used to give the required therapeutic release pattern.
   a. In a fluidized-bed apparatus, uniform spherical inert sugar cores were coated with a first layer consisting of the compounds, an inert water-soluble polymer, such as hydroxy-propylmethylcellulose or hydroxypropyl cellulose, and talc. The second layer consisted of an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, talc, and a pigment, such as titanium dioxide. The third and enteric coating layer consisted of an enteric coating polymer such as co-polymerized methacrylic acid/methacrylic acid methyl esters, a plasticizer, such as triethylacetate or similar plasticizers, and talc. The layers were applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions. Pseudo zero release is obtained by the use of a mixture of beads.
2. The beads in Item 1 contain 40% ketoprofen, giving a dose per capsule of 100 mg. The mix of Items 1–4 is filled into suitable hard gelatin capsules.

Ketoprofen Capsules

Ketoprofen is a nonsteroidal anti-inflammatory drug. The chemical name for ketoprofen is 2-(3-benzoylphenyl)-propionic acid. Capsules contain 25 mg, 50 mg, or 75 mg of ketoprofen for oral administration. The inactive ingredients present are: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25-mg dosage strength also contains D&C Red No. 28 and FD&C Red No. 40. Each 100 mg, 150 mg, or 200 mg capsule contains ketoprofen in the form of hundreds of coated pellets. The dissolution of the pellets is pH-dependent, with optimum dissolution occurring at pH 6.5–7.5. There is no dissolution at a pH of 1. In addition to the active ingredient, each 100 mg, 150 mg, or 200 mg capsule of Oruvail contains the following inactive ingredients: D&C Red No. 22, D&C Red No. 28, FD&C Blue No. 1, ethyl cellulose, gelatin, shellac, silicon dioxide, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other optional ingredients. The 100 and 150 mg capsules also contain D&C Yellow No. 10 and FD&C Green No. 3.

Lansoprazole Capsules

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
30.00	1	Lansoprazole	30.00
93.50	2	Neutral Pellets	93.50
22.86	3	Magnesium Carbonate	22.86
66.00	4	Sucrose	66.00
37.14	5	Cornstarch	37.14
46.34	6	Hydroxypropyl Cellulose	46.34
79.68	7	Eudragit L	79.68
13.68	8	Talc	13.86
4.36	9	Titanium Dioxide	4.36
4.36	10	Polyethylene Glycol 6000	4.36
1.80	11	Polysorbate 80	1.80
—	12	Water Purified	QS

MANUFACTURING DIRECTIONS

1. Charge Items 1 and 3–5, and half of Item 6 in a suitable mixer and confirm homogeneity of mixture.
2. In a separate mixer, add and dissolve balance of Item 6 and dissolve.
3. In rotary fluid-bed dryer, charge Item 2 and incorporate Step 2 into it.
4. Prepare a suspension with Item 9 in Item 12, and Items 8, 10, and 11, and keep agitating until dissolved or well dispersed.
5. Add Item 7 and mix until well suspended.
6. Start spraying it onto the pellets from Step 3 after passing the suspension before a fine mill.
7. Fill capsules 370 mg.

Lansoprazole Delayed-Release Capsules

The active ingredient is a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole (30 mg), hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include: gelatin, titanium dioxide, D&C Red No. 28, FD&C Blue No. 1, and FD&C Red No. 40.

Lincomycin Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
500.00	1	Lincomycin, USE Lincomycin Hydrochloride	560.00
7.00	2	Lactose	7.00
2.00	3	Aerosil 200	2.00
2.00	4	Magnesium Stearate	2.00
12.00	5	Sodium Starch Glycolate	12.00

MANUFACTURING DIRECTIONS

1. Charge all items after passing through No. 60 mesh in a low-humidity room (not more than 40%).
2. Mix for 30 min.
3. Fill 590 mg in size 0 capsules.

Linezolid Oral Suspension

Linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazo-lidinyl]methyl]-acetamide. The oral suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 ml contains 100 mg of linezolid. The inactive ingredients are: sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors. The sodium (Na^+) content is 8.52 mg per 5 ml (0.4 mEq per 5 ml).

Lipase, Amylase, and Protease Capsules

The pancrelipase capsules are orally administered and contain enteric-coated minitablets of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. Each capsule contains: lipase (12,000 USP units); amylase (39,000 USP units); and protease (39,000 USP units). Other combinations are 18,000/58,500/58,500 or 20,000/65,000/65,000. The capsules contain an amount of pancrelipase equivalent to but not more than 125% of the labeled lipase activity expressed in USP units. The inactive ingredients are: hydrogenated castor oil, silicon dioxide, sodium carboxymethylcellulose, magnesium stearate, microcrystalline cellulose, methacrylic acid copolymer (Type C), talc, simethicone, triethyl citrate, iron oxides, and titanium oxide.

Lithium Carbonate Capsules

Each capsule for oral administration contains lithium carbonate (150 mg, 300 mg, or 600 mg). The capsules contain talc, gelatin, FD&C Red No. 40, titanium dioxide. The imprinting ink contains FD&C Blue No. 2, FD&C Yellow No. 6, FD&C Red No. 40, synthetic black iron oxide, and pharmaceutical glaze.

Lopinavir-Ritonavir Capsules

This is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV protease. As co-formulated in KALETRA®, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. Lopinavir is chemically designated as [1S-[1R*,(R*),3R*,4R*]]-N-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide. Ritonavir is chemically designated as 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolymethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

Loracarbef Capsules and Oral Suspension

Loracarbef is a synthetic (β)-lactam antibiotic of the carbacephem class for oral administration. Chemically, carbacephems differ from cephalosporin-class antibiotics in the dihydrothiazine ring where a methylene group has been substituted for a sulfur atom. The chemical name for loracarbef is: (6 *R*,7 *S*)-7-[(*R*)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, monohydrate. Each Pulvule contains loracarbef equivalent to 200 mg (0.57 mmol) or 400 mg (1.14 mmol) anhydrous loracarbef activity. They also contain cornstarch, dimethicone, FD&C Blue No. 2, gelatin, iron oxides, magnesium stearate, titanium dioxide, and other inactive optional ingredients. After reconstitution, each 5 ml of lorabid for oral suspension contains loracarbef equivalent to 100 mg (0.286 mmol) or 200 mg (0.57 mmol) anhydrous loracarbef activity. The suspensions also contain cellulose, FD&C Red No. 40, flavors, methylparaben, propylparaben, simethicone emulsion, sodium carboxymethylcellulose, sucrose, and xanthan gum.

Loxapine Capsules

Loxapine, a dibenzoxazepine compound, represents a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Chemically, it is 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine. It is present as the succinate salt. Each capsule, for oral administration, contains loxapine succinate (6.8, 13.6, 34.0, or 68.1 mg) equivalent to 5, 10, 25, or 50 mg of loxapine base, respectively. It also contains the following inactive ingredients: gelatin, silicon dioxide, sodium lauryl sulfate, anhydrous lactose, D&C Yellow No. 10, FD&C Blue No. 1, polacrilin potassium, magnesium stearate, talc, and titanium dioxide. Additionally, the 5-mg capsule contains D&C Red No. 33, the 10-mg capsule contains D&C Red No. 28 and D&C Red No. 33, and the 25-mg capsule contains FD&C Yellow No. 6.

Loxapine Succinate Capsules

Loxapine, a dibenzoxazepine compound, represents a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Chemically, it is 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepine. It is present as the succinate salt. Each capsule for oral administration contains loxapine succinate 6.8, 13.6, 34.0, or 68.1 mg equivalent to 5, 10, 25, or 50 mg of loxapine base, respectively. It also contains the following inactive ingredients: gelatin, silicon dioxide, sodium lauryl sulfate, anhydrous lactose, D&C Yellow No. 10, FD&C Blue No. 1, polacrilin potassium, magnesium stearate, talc, and titanium dioxide. Additionally, the 5-mg capsule contains D&C Red No. 33, the 10 mg capsule contains D&C Red No. 28 and D&C Red No. 33, and the 25 mg capsule contains FD&C Yellow No. 6.

Magaldrate Instant Powder or Dry Syrup

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Sachets (g)**
800.00	1	Magaldrate	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol, Crystalline	200.00
40.00	4	Orange Flavor	40.00
40.00	5	Kollidon 90 F	40.00
4.00	6	Coconut Flavor	4.00
4.00	7	Banana Flavor	4.00
0.80	8	Saccharin Sodium	0.80
QS	9	Water	about 280 ml

MANUFACTURING DIRECTIONS

1. Granulate a mixture of Items 1–4 with solution of Items 5–9, and pass through a 0.8-mm sieve to obtain free-flowing granules.
2. Fill 2 g in sachets or 20 g in a 100-ml flask. For instant granules in sachets: suspend 2 g (= 1 sachet) in a glass of water (= 800 mg magaldrate).

Magnesium Oxide Capsules

Each capsule contains magnesium oxide (140 mg USP [Heavy]) or 84.5 mg of elemental magnesium (6.93 mEq).

Mefenamic Acid Capsules

Mefenamic acid is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each blue-banded, ivory capsule contains 250 mg of mefenamic acid for oral administration. Each capsule also contains lactose. The capsule shell and band contain citric acid, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, gelatin, glycerol monooleate, silicon dioxide, sodium benzoate, sodium lauryl sulfate, and titanium dioxide.

Mesalamine Capsules

Mesalamine for oral administration is a controlled-release formulation of mesalamine, an aminosalicylate anti-inflammatory agent for gastrointestinal use. Chemically, mesalamine is 5-amino-2-hydroxybenzoic acid. Each capsule contains 250 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains D&C Yellow No. 10, FD&C Blue No. 1, FD&C Green No. 3, gelatin, titanium dioxide, and other optional ingredients.

Mesalamine Colonic Delivery Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Mesalamine (5-ASA)	250.00
45.00	2	Lactose	45.00
5.20	3	Polyvinylpyrrolidone	5.20
10.80	4	Sodium Starch Glycolate	10.80
3.60	5	Magnesium Stearate	3.60
36.80	6	Talc	36.80
18.40	7	Eudragit S100	18.40
43.20	8	Eudragit NE 30D	43.20
0.40	9	Antifoam Emulsion SE 2	0.40

MANUFACTURING DIRECTIONS

1. Add Items 1 and 2 to a blending vessel; mix well.
2. Add Item 4 and blend.
3. Prepare an aqueous solution of Item 3, and granulate Step 2.
4. Dry and compress; reduce size by passing through 0.5–1.2-mm sieve.
5. The granules in Step 4 are loaded into a fluid-bed coater and then spray-coated with an aqueous suspension to provide a 20% or 25% dry weight gain based on an uncoated granule weight of a mixture of Eudragit S100 and Eudragit NE 30D (Rohm Pharma GmbH, Darmstadt, Germany) in the ratio of 3:7. Eudragit S100 is a copolymer of methacrylic acid and methylmethacrylate in the ratio of 1:2 in powder form and Eudragit NE 30D is a 30% aqueous dispersion of a copolymer of ethylacrylate and methylmethacrylate in the ratio 2:1.
6. Coated granules are packed into size 00 hard gelatin capsules in an amount of 400 mg granules per capsule.

   The capsules are then spray-coated with a coating solution of the following formula:

   Eudragit L powder, 3 g
   Diethyl phthalate, 0.75 ml
   Silicone fluid 200 cs, 0.75 ml
   Acetone, 100 ml

Methsuximide Capsules

Methsuximide is an anticonvulsant succinimide, chemically designated as *N*,2-dimethyl-2-phenylsuccinimide. Each capsule contains 150 mg or 300 mg methsuximide, as well as starch. The capsule contains colloidal silicon dioxide, D&C Yellow No. 10, FD&C Yellow No. 6, gelatin, and sodium lauryl sulfate.

Methylphenidate Capsules

Methylphenidate is a central nervous system (CNS) stimulant. Chemically, methylphenidate HCl is *d,l* racemic *threo*-methyl(alpha)-phenyl-2-piperidineacetate hydrochloride. It contains 20 mg of methylphenidate hydrochloride for oral administration. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose (6 mg) is provided by the IR component, and 70% of the dose (14 mg) is provided by the ER component. It also contains the following inert ingredients: sugar spheres, povidone, hydroxypropyl methylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, and FD&C Blue No. 2.

MANUFACTURING DIRECTIONS

1. Methylphenidate HCl (200 g) is slowly added to an aqueous solution (about 15% solids) of polyvinylpyrrolidone (10 g Povidone K-30) and mixed well.
2. About 25–30 mesh sugar spheres (770 g) were coated with the drug solution in a fluid-bed granulator. The drug-containing pellets are dried, and a sealcoat of Opadry Clear® (20 g) is first applied to produce instant-release or IR beads.
3. Extended-release (ER) beads are produced by taking IR beads and coating with the dissolution rate controlling polymer. A plasticized ethylcellulose coating is applied to the methylphenidate particles (893 g) by spraying Aquacoat ECD-30® (233 g) and dibutyl sebacate (16.8 g).
4. An outer seal coating formulation (20 g) of Opadry® is sprayed onto the coated active particles. The coated particles are cured at 60°C for 12 h so that polymer particles coalesce to form a smooth membrane on ER beads. The instant-release (IR) and ER beads are then filled into hard gelatin capsules with dual bead-filling hoppers.

Methylphenidate Immediate- and Extended-Release Capsules

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
25.00	1	Methylphenidate	25.00
1.25	2	Polyvinylpyrrolidone K-30	1.25
96.25	3	Sugar Spheres 25–30 Mesh	96.25
2.25	4	Opadry Clear	2.25
29.12	5	Aquacoat ECD-30	29.12
2.10	6	Dibutyl Sebacate	2.10
2.25	7	Opadry Clear	2.25
—	8	Alcohol	QS

MANUFACTURING DIRECTIONS

1. This product consists of two types of beads: instant release and extended release. The extended release beads are formed by further coating of instant release beads.
2. Instant release beads are produced by preparing a 15% solution of Item 2 in Item 8 and adding Item 1 to it slowly.
3. Charge Item 3 in a fluid-bed granulator, and load drug solution in Step 2 onto sugar pellets. Dry and apply seal coat of Item 4. This completes the process of preparing instant release beads.
4. Take an appropriate quantity (893 g) of beads in Step 3 and apply a coating of Item 6 in Item 8.
5. Apply Item 7 seal coat (as 15% aqueous solution), and cure at 60°C for 12 h for polymer particles to coalesce into a uniform film.
6. Fill in gelatin capsules using a 20:80, 30:70, or 40:60 mixture of instant release to extended release beads. Use equipment that is capable of filling beads simultaneously.

Methyltestosterone Capsules

Methyltestosterone, a synthetic derivative of testosterone, is an androgenic preparation given by the oral route in a capsule form. Each capsule contains 10 mg of methyltestosterone. Each capsule, for oral administration, contains 10 mg of methyltestosterone. In addition, each capsule contains the following inactive ingredients: cornstarch, gelatin, FD&C Blue No. 1, FD&C Red No. 40. Each capsule also contains the following inactive ingredients: cornstarch, gelatin, FD&C Blue No. 1, and FD&C Red No. 40.

Metoclopramide Hydrochloride Sustained-Release Capsules

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Metoclopramide, USE Metoclopramide Hydrochloride	21.00
183.90	2	Sucrose and Cornstarch Microgranules, Size 20	183.90
0.12	3	Disodium Edetate	0.12
0.19	4	Stearic Acid	0.19
1.30	5	Methacrylic Acid Copolymer Eudragit L100	1.30
0.42	6	Cornstarch	0.42
9.07	7	Shellac, bleached wax-free	9.07
15.00	8	Talc	15.00
1.00	9	Gelatin Capsules, Size 3	1000.00
—	10	Alcohol	QS
—	11	Water Purified	11.00

MANUFACTURING DIRECTIONS

1. The neutral microgranules (Item 2) are placed in an appropriate coating pan, and the pan is rotated.
2. In a separate vessel, prepare an alcoholic solution of Item 5. Spray in Step 1.
3. Prepare alcohol solution of Item 4 in alcohol, and spray into Step 2.
4. Prepare aqueous solution of Item 3, and spray into Step 3.
5. Mix Item 1 with Item 6, and add to Step 4 alternating with an alcoholic solution of Eudragit until all of the drug has been incorporated.
6. Sieve the microgranules.
7. Apply aqueous solution of Item 3 followed by an alcohol solution of Eudragit L and microgranules dried.
8. Apply alcoholic solution of shellac alternating with talc until all shellac solution is used.
9. Lubricate and fill in capsules; sieve and dry microgranules.

Metyrosine Capsules

Metyrosine is (-)-(α)-methyl-*L*-tyrosine or (α)-MPT. It is supplied as capsules for oral administration. Each capsule contains 250 mg of metyrosine. The inactive ingredients are: colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, magnesium stearate, and titanium dioxide. The capsules may also contain any combination of D&C Red No. 33, D&C Yellow No. 10, FD&C Blue No. 1, and FD&C Blue No. 2.

Miconazole Nitrate Foot and Itch Powder

Spray powder for athlete's foot contains miconazole nitrate 2%. It also contains alcohol SD-40 (10% w/w), isobutane, starch/acrylates/acrylamide copolymer, stearalkonium hectorite, and talc. Spray powder for jock itch contains miconazole nitrate 2%. It also contains alcohol SD-40 (10% w/w), isobutane, stearalkonium hectorite, and talc. Spray deodorant powder contains miconazole nitrate 2%. It also contains isobutane, alcohol SD-40 (10% w/w), talc, starch/acrylates/acrylamide copolymer, stearalkonium hectorite, and fragrance. Powder contains miconazole nitrate 2%. It also contains benzethonium chloride, cornstarch, kaolin, sodium bicarbonate, starch/acrylates/acrylamide copolymer, and zinc oxide.

Mineral Powder for Topical Herpes Simplex

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
14.00	1	Calcium Carbonate	14.00
14.00	2	Sodium Carbonate	14.00
14.00	3	Sodium Dihydrogen Phosphate Anhydrous	14.00
80.00	4	Calcium Hypochlorite	80.00
818.00	5	Cornstarch	818.00

MANUFACTURING DIRECTIONS

1. Mix all ingredients after passing through an 80-mesh screen.
2. Pack in bottles.

Minocycline Hydrochloride Capsules

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4*S*-(4(alpha),4a(alpha),5a(alpha),12a(alpha))]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride. Each minocycline hydrochloride capsule for oral administration contains the equivalent of 50 mg, 75 mg, or 100 mg of minocycline. In addition, each capsule contains the following inactive ingredients: magnesium stearate and starch (corn). The 50-mg, 75-mg, and 100-mg capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The 75-mg and 100-mg capsule shells also contains black iron oxide.

Mixed Amphetamine Salt Capsules

It is a once daily extended-release, single-entity amphetamine product. It combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and *d*,*l*-amphetamine aspartate monohydrate. The capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine compared to the conventional immediate-release tablet formulation. Each capsule contains equal quantities of four salts of amphetamine to give a total of 10, 20, or 30 mg of content (total amphetamine base equivalence of 6.3, 12.5, and 18.8 mg): dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, amphetamine sulfate. The inactive ingredients in the capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, Opadry beige, sugar spheres, talc, and triethyl citrate. The gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 10-mg capsules also contain FD&C Blue No. 2. The 20-mg and 30-mg capsules also contain red iron oxide and yellow iron oxide.

Mixed Amphetamine Salts Enteric-Release Capsules

Bill of Materials

Item	Material Name	Qty/kg (g)
	Immediate-Release Beads	
1	Amphetamine Mixed Salts[a]	88.00
2	Nonpareil Seeds (30/35 Mesh, Paulaur)	6.80
3	Hydroxypropyl Methylcellulose E5 Premium	0.60
4	Water Purified	QS
	Enteric-Release Pellets	
5	Immediate-Release Beads (see Items 1–4)	40.00
6	Eudragit L30-D-55	24.88
7	Triethyl Citrate	2.52
8	Talc	2.60
9	Water Purified	QS

[a] Mixed salts include: amphetamine sulfate, amphetamine aspartate, and dixtroamphetamine sulfate.

MANUFACTURING DIRECTIONS

1. Charge Item 2 in a fluid-bed processor, and fluidize at 60°C.
2. Prepare a suspension of Item 3 (prepare a 1% solution) and Item 1 using Item 4; assure it is free of agglomerates and contains no fines, with a yield of at least 98%.
3. Apply binder solution to Step 1, and load the drug.
4. Charge Item 5 into a fluid-bed processor.
5. Prepare the coating dispersion using Items 6–8 in Item 9, and mix for at least 30 min.
6. Spray the coating solution in Step 5 onto Step 1 until a target level of 20 µm is achieved.
7. Dry pellets at 30–35°C for 5 min before stopping the processor.
8. Fill to contain in each capsule base equivalent, 10 mg, 20 mg, and 30 mg (Adderall XR®).

Morphine Sulfate Capsules

Chemically, morphine sulfate is 7,8didehydro-4,5(alpha)-epoxy-17-methylmorphinan-3,6(alpha)-diolsulfate(2:1)(salt)pentahydrate. Each capsule for oral administration contains morphine sulfate 15 or 30 mg. The inactive ingredients are: FD&C Blue No. 1, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, hydroxypropyl methylcellulose, lactose, polyethylene glycol, polysorbate 80, polyvinylpyrrolidone, starch, sucrose, titanium dioxide, and other optional ingredients. In addition, the 30-mg capsule contains black iron oxide and D&C Red No. 28.

Morphine Sulfate Controlled-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
40.00	1	Morphine Hydrochloride	40.00
40.00	2	Lactose	40.00
20.00	3	Microcrystalline Cellulose	20.00
QS	4	Water Purified	QS
3.50–5.30	5	Ethyl Cellulose	3.50–5.30
2.20–3.40	6	Hydroxypropyl Methylcellulose	2.20–3.40
0.60–1.0	7	Triethyl Citrate	0.60–1.00
QS	8	Ethanol	QS
QS	9	Methyl Isobutyl Ketone	QS

MANUFACTURING DIRECTIONS

1. Mixing and Granulating: Morphine hydrochloride (40% w/w), lactose (40% w/w), and microcrystalline cellulose (Avicel PH-101) (20% w/w) totally 1500 gram are dry-mixed in a planetary type mixer (Kenwood Major®) at a low mixing speed (speed adjustment < 1) for 10 min. Water (585 g) is added and the mass is granulated for 5 min at speed adjustment 2.
2. Extrusion: Extrusion is performed in a Nica™ E-140 Extruder (Lejus Medical AB, Sweden) through a perforated screen with drilled orifices of 1.0 mm in diameter. The speed of the agitator and the feeder is set on the lowest values.
3. Spheronization: Spheronization is conducted in a mammerizer (Ferro Mecano AB, Sweden). The speed of the Marumerizer™ plate is adjusted to 450 rpm. The number of spheronization rounds is 5, with about 400 g of wet extrudates on the plates at each run.
4. Drying: Drying is performed in a fluid bed dryer (Aeromatic AG®, West Germany) at an IN-temperature of 50°C. The batch is divided into sub-batches of 600–700 g wet particulate cores. Each sub-batch is dried for 5 min at the air velocity adjustment 20 in order to obtain individual cores rather than aggregates. The sub-batches are then mixed and the whole batch is dried at adjustment 12 for 65 min. The end OUT-temperature is 36°C. The yield of dry cores after drying is 1437 g and 96% w/w.
5. Sieving: Sieving is performed by using analytical sieves with sieve sizes of 0.71 mm and 1.40 mm, respectively. The yield of dry cores after sieving is 1337 gram and 89% w/w. The yields are 96% and 89% w/w after drying and sieving, respectively.
6. A sieving analysis before and after abrasion of the cores shows that about 93% of the cores have a size between 0.71 and 1.0 mm. A crushing strength analysis shows that the mean crushing strength of 1.0-mm particles is 4.71 N. A hardness value at this level makes it possible to coat the particles in small as well as in large equipment.
7. Morphine hydrochloride cores manufactured as above are coated with controlled-release membranes. Hydroxypropyl methylcellulose (HPMC) (E5) and ethyl cellulose (EC) (10 cps) were used as film formers together with triethyl citrate (TEC) as a plasticizer. The coating solution contains 99.5% ethanol and methyl isobutyl ketone (MIBK).
8. The coating is performed using a spray coating equipment (Nica™ FB-coater, Sweden). The spray gun used is a Binks & Bullows with a J92R liquid nozzle and a J930 air nozzle. A net device is placed in the top of the fluidized bed to avoid loss of cores to the cyclone output. The spray gun is mounted on a height over the bottom of the bed for 185 min. Ethanol/MIBK mixture is pumped through the system before to the start of the coating, and there is consequently liquid present between the pump housing and the spray gun. The morphine hydrochloride cores prepared above are loaded. The cores are preheated at 55°C with an air velocity of 20–25 m^3/h for 4 min. At the start of the coating, the bed temperature is 32–36°C. The coating is started using the following process parameters: atomizing pressure 500 kPa, air velocity 85 m^3/h, and a solution flow of about 24 ml/min. The registered IN-temperature varies between 53–56°C, and the OUT-temperature varies between 34–38°C during the coating.

9. The coated spheres are sieved through a 1.4 mm-sieve, and spheres with a size less than 1.4 mm are collected.
10. The collected spheres are filled into hard gelatin capsules (hard gelatin capsule, color white, No. 2) with a normal weight of 0.17 g (net weight 108 mg). The mean content of active component in the capsules is between 36 and 44 mg.

Morphine Sulfate Sustained-Release Capsules

Each sustained-release capsule contains either 20, 30, 50, 60, or 100 mg of morphine sulfate and the following inactive ingredients that are common to all strengths: hydroxypropyl methylcellulose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, cornstarch, and sucrose. The 20-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C Yellow No. 10, titanium dioxide, and black ink (SW-9009). The 30-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, FD&C Red No. 3, FD&C Blue No. 1, titanium dioxide, and black ink (S-1-8114 or S-1-8115). The 50-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C Red No. 28, FD&C Red No. 40, FD&C Blue No. 1, titanium dioxide, and black ink (SW-9009). The 60-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C Red No. 28, FD&C Red No. 40, FD&C Blue No. 1, titanium dioxide, and black ink (S-1-8114 or S-1-8115). The 100-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C Yellow No. 10, FD&C Blue No. 1, titanium dioxide, and black ink (SW-9009).

Multivitamin Effervescent Granules

Bill of Materials			
Scale (mg/Sachet)	**Item**	**Material Name**	**Qty/1000 Tabs (g)**
2.600	1	Thiamin Hydrochloride (BASF)	0.26
3.000	2	Riboflavin (BASF)	0.30
11.000	3	Nicotinamide	1.10
2.500	4	Pyridoxine Hydrochloride (BASF)	0.25
15.000	5	Calcium D-Pantothenate (BASF)	1.50
200.000	6	Ascorbic Acid Powder (BASF)	20.00
500.000	7	Citric Acid	50.00
1300.000	8	Sucrose	130.00
800.000	9	Fructose	80.00
200.000	10	Kollidon CL-M	20.00
250.000	11	Flavors	25.00
20.000	12	Cyclamate Sodium	2.00
1.000	13	Saccharine Sodium	0.10
150.000	14	Kollidon VA 64	15.00
350.000	15	Isopropanol	35.00
15.000	16	Vitamin A Acetate Dry Powder 325,000 IU/g CWD (BASF)	1.50
8.000	17	Vitamin D3 Dry Powder 100,000 IU/g CWD (BASF)	0.80
21.000	18	Vitamin E Acetate Dry Powder 50%	2.10
0.066	19	Cyanocobalamin Gelatin Coated 0.1% (BASF)	0.66
400.000	20	Sodium Bicarbonate	40.00

MANUFACTURING DIRECTIONS

1. Granulate mixture of Items 1–13 with solution of Items 14 and 15; pass through a 0.8-mm sieve, dry well, and mix with Items 16–20.
2. Fill 4 g in sachets.

Multivitamin Instant Granules

Bill of Materials			
Scale (mg/6 g Sachet)	**Item**	**Material Name**	**Qty/30 kg (g)**
40.00	1	Vitamin A+D dry powder + 50,000 IU/g CWD (BASF)	200.00
5.00	2	Thiamine Mononitrate (BASF)	26.00
6.00	3	Riboflavin (BASF)	33.00
22.00	4	Nicotinamide	110.00
4.50	5	Pyridoxine Hydrochloride (BASF)	22.00
30.00	6	Calcium D-Pantothenate (BASF)	150.00
0.013	7	Cyanocobalamin, USE Cyanocobalamin 0.1% Gelatin Coated (BASF)	66.00
230.00	8	Ascorbic Acid Powder (BASF)	1150.00
42.00	9	Vitamin E Acetate Dry Powder	210.00
4000.00	10	Sucrose, finely ground	20,000.00
1000.00	11	Kollidon CL-M	5000.00
200.00	12	Orange Flavor	1000.00
400.00	13	Kollidon VA 64	2000.00
—	14	Ethanol or Isopropanol	Approx. 7 l

MANUFACTURING DIRECTIONS

1. Pass mixture through a 0.8-mm sieve, and granulate with solution of Items 13 and 14 in the fluidized bed. Fill the granules in sachets. If the technology of a fluidized bed is not available, the dry powders of vitamin A, E, and B12 should be added after the granulation of the other components. Suspend 6–12 g (= 1 sachet) in a glass of water corresponding to 2–4 RDA of vitamins. Double-strength sachet filled at 12 g.

Mycophenolate Mofetil Capsules and Oral Suspension

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor. The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. The inactive ingredients in 250-mg capsules include: croscarmellose sodium, magnesium stearate, povidone (K-90), and pregelatinized starch. The capsule shells contain black iron oxide, FD&C Blue No. 2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. The inactive ingredients in CellCept oral suspension include: aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin, and xanthan gum.

Nanoparticle Polymer Particle Powders

1. Preparation of Polymer Nanoparticles of Ketorolac: To 900 mg NIPAAM (N-isopropyl is acrylamide), 100 ml freshly distilled VP (vinyl pyrrolidone), and 50 ml freshly distilled AA (acrylic acid) in 100 ml of water, 300 ml MBA (methylene bis acrylamide) ([MBA] = 0.049 gm/ml) is added to cross-link the polymer chain. The dissolved oxygen is removed by passing nitrogen gas for 30 min; 50 ml of 0.5% w/v ferrous ammonium sulphate (FAS) and 50 ml saturated ammonium persulphate (APS) solutions are then added to initiate the polymerization reaction. The polymerization is done at 30°C, for 24 h in nitrogen atmosphere. Total aqueous solution of polymer is then dialyzed overnight using a spectrapore membrane dialysis bag (12 kD cut off). The dialyzed aqueous solution of polymeric micelles is frozen in liquid nitrogen and is lyophilized immediately to obtain dry powder for subsequent use. The yield of micelle nanoparticles is more than 80%. The lyophilized powder is easily redispersible in aqueous buffer; 100 mg of lyophilized powder of polymeric micelles is dispersed in 10 ml of water and is stirred well to disperse the micelles. The free acid form of ketorolac is dissolved in absolute ethanol ([ketorolac] = 50 mg/ml) and the alcoholic solution is added in polymeric micelles slowly with constant stirring. Ketorolac got directly loaded into hydrophobic core of micelles. The drug-loaded polymeric micelles are then lyophilized to get dry powder for subsequent use.
2. Preparation of Polymeric Nanoparticles Containing Indomethacin: In 100 mg of the lyophilized powder of the polymeric micelle nanoparticles, an alcoholic solution of indomethacin ([indomethacin] = 33 mg/ml) is added with constant stirring to get clear solution of polymeric micelles containing the drug of desired concentration dispersed in aqueous buffer. Maximum 10% w/w of the drug can be dissolved in polymeric micelles at room temperature. The drug-loaded polymeric micelles are then lyophilized to get dry powder for subsequent use.
3. Preparation of Polymeric Micelles Containing Nimesulide: In 100 mg of dry powder of polymeric micelles, an alcoholic solution of nimesulide ([nimesulide] = 10 mg/ml) is added with constant stirring to get a clear solution. Maximum 8% w/w of nimesulide could be dissolved in polymeric micelles at room temperature. The drug-loaded micelles are then lyophilized to get dry powder for subsequent use.

Nelfinavir Mesylate Oral Powder

Nelfinavir mesylate is an inhibitor of the human immunodeficiency virus (HIV) protease. Oral powder is available for oral administration in a 50 mg/g strength (as nelfinavir freebase) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame, sucrose palmitate, and natural and artificial flavors. The chemical name for nelfinavir mesylate is [3 *S*-[2(2 *S**, 3 *S**), 3(alpha),4a(beta),8a(beta)]]-N-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinolinecarboxamide monomethanesulfonate (salt) and the molecular weight is 663.90 (567.79 as the freebase).

Bill of Materials

Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Nelfinavir Mesylate	50.00
50.00	2	Sodium Carboxymethylcellulose	50.00
1.25 ml	3	Syrup	1.25 l
0.10 ml	4	Benzoic Acid Solution	0.10 l
QS	5	Flavor	QS
QS	6	Dye	QS
QS to 5 ml	7	Purfied Water	5 l

MANUFACTURING DIRECTIONS

The active ingredient is passed through a No. 45-mesh sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Nilvadipine Capsules

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
14.00	1	Nilvadipine	14.00
166.00	2	Polyethylene Glycol 400	166.00
20.00	3	Hydroxypropyl Methylcellulose	10.00

MANUFACTURING DIRECTIONS

1. Add and dissolve Item 1 in Item 2.
2. Add Item 3, and fill 200 mg in a size 4 hard gelatin capsule.

Nitrofurantoin Capsules

A nitrofurantoin macrocrystal is a synthetic chemical of controlled crystal size. Inactive ingredients: Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, and may contain FD&C Yellow No. 6 and D&C Yellow No. 10. Nitrofurantoin is an antibacterial agent specific for urinary tract infections. Another formulation of nitrofurantoin capsule is a hard gelatin capsule shell containing the equivalent of 100 mg of nitrofurantoin in the form of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate. Inactive ingredients: Each capsule contains carbomer 934P, cornstarch, compressible sugar, D&C Yellow No. 10, edible gray ink, FD&C Blue No. 1, FD&C Red No. 40, gelatin, lactose, magnesium stearate, povidone, talc, and titanium dioxide.

Nitrofurantoin Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
150.00	1	Nitrofurantoin Monohydrate (Norwich Eaton Pharmaceuticals, Inc.)	150.00
17.70	2	Carbopol 934P (B.F. Goodrich)	17.70
181.00	3	PVP C-15 (GAF Corporation)	181.00
3.50	4	Talc	3.50
1.80	5	Zinc Stearate	1.80

MANUFACTURING DIRECTIONS

1. The Carbopol 934P, PVP C-15 (mean molecular weight of about 8000, talc, and zinc stearate are combined in a mortar and triturated well.
2. The nitrofurantoin monohydrate is added to this mixture in the mortar and triturated well until a substantially uniform particulate mixture is achieved.
3. The resulting particulate mixture (354 mg) is filled into size 1 hard gelatin capsule shells.

Nizatidine Capsules

Nizatidine is a histamine H2-receptor antagonist. Chemically, it is N-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine. Each capsule contains pregelatinized starch, dimethicone, starch, titanium dioxide, yellow iron oxide, 150 mg (0.45 mmol) or 300 mg (0.91 mmol) of nizatidine, and other inactive ingredients. The 150-mg capsule also contains magnesium stearate, and the 300-mg capsule also contains croscarmellose sodium, povidone, red iron oxide, and talc.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
150.00	1	Nizatidine	150.00
33.70	2	Cornstarch	33.70
15.00	3	Pregelatinized Starch (Starch 1500)	15.00
0.70	4	Magnesium Stearate	0.70
0.60	5	Simethicone	0.60
	6	Empty Hard Gelatin Shell, Size 2 (Bovine Origin)	1000

MANUFACTURING DIRECTIONS

1. Add and blend Items 1–3 in a suitable blender, and mix for 20 min.
2. Add Item 4 and blend for 10 min
3. Add Item 5 and blend for 4 min.
4. Fill in 200 mg of hard gelatin capsules.

Nystatin Powder

Nystatin is a polyene antifungal antibiotic obtained from *Streptomyces noursei.* Nystatin Topical Powder is for dermatologic use and contains 100,000 USP nystatin units per gram dispersed in talc.

Omeprazole and Piroxicam Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
95.70	1	Omeprazole Enteric-Coated Pellets	95.70
122.70	2	Piroxicam Enteric-Coated Pellets	122.70

MANUFACTURING DIRECTIONS

1. This product requires preparation of enteric coated pellets of omeprazole and piroxicam separately.
2. The omeprazole pellets are prepared by applying drug solution (in HPMC) on non-pareil sugar beads, applying a separating layer consisting of HPMC alone and then applying an enteric coating that comprises methylacrylic acid copolymer 30% suspension with triethyl citrate, mono-, and diglycerides and polysorbate 80 in purified water. Finally an overcoat is applied.
   - Core material (omeprazole)
     - Magnesium omeprazole: 5.00 kg
     - Nonpareil cores: 10.00 kg
     - Hydroxypropyl methylcellulose: 0.75 kg
     - Water purified: 19.65 kg
   - Separating layer (omeprazole)
     - Core material (acc. to above): 14.60 kg
     - Hydroxypropyl cellulose: 1.46 kg
     - Talc: 2.5 kg
     - Magnesium stearate: 0.21 kg
     - Water purified: 29.2 kg
   - Enteric coating layer (omeprazole)
     - Pellets with separate layer (acc. to above): 9.00 kg
     - Methacrylic acid copolymer (30% suspension): 15.00 kg
     - Triethyl citrate: 1.35 kg
     - Mono- and diglycerides: 0.22 kg
     - Polysorbate 80: 0.02 kg
     - Water purified: 8.8 kg
   - Over-coating layer (omeprazole)
     - Enteric coating layered pellets: 9.0 kg
     - Hydroxypropyl methylcellulose: 0.18 kg
     - Mg-Stearate: 0.005 kg
     - Water purified: 3.6 kg
3. The piroxicam pellets are prepared by a similar method except using a hydro-alcoholic solution in the first instance, not using a separating layer and performing enteric coating using HPMC succinate.
   - Core material (piroxicam)
     - Piroxicam micronized: 35 g
     - Sugar seeds: 100 g
     - Hydroxypropyl methylcellulose: 6 cps, 25 g
     - Water purified: 250 g
     - Ethanol 99% (w/v): 250 g
   - Enteric coating layer (piroxicam)
     - Piroxicam pellets (acc. to above): 100 g
     - Hydroxypropyl methylcellulose acetate-succinate: 14.38 parts
     - Triethyl citrate: 2.87 parts
     - Sodium lauryl sulphate: 0.43 parts
     - Talc: 4.32 parts
     - Water purified: 183.3 parts
4. Coat with a suspension of the preceding composition to give a product with a content of 163 mg/g; suspension layering is performed in a fluid bed equipment. Micronized piroxicam is sprayed onto inert non-pareil cores from a water suspension containing the dissolved binder.

Omeprazole Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
40.00	1	Omeprazole	40.00
68.00	2	Sucrose and Cornstarch Neutral Microgranules, Size 26	68.00
4.00	3	Sodium Starch Glycollate (Explotab)	4.00
6.00	4	Sodium Lauryl Sulfate	6.00
7.12	5	Polyvidone	7.00
5.96	6	Hydroxypropyl Methylcellulose	5.96
36.15	7	Eudragit L30D	36.15
3.62	8	Triethyl Citrate	3.62
15.40	9	Talc	15.40
—	10	Alcohol	QS

Omeprazole Delayed-Release Capsules

The active ingredient in omeprazole delayed-release capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1 *H*-benzimidazole, a compound that inhibits gastric acid secretion. Each delayed-release capsule contains either 10 mg, 20 mg, or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate, and other ingredients. The capsule shells have the following inactive ingredients: gelatin NF, FD&C Blue No. 1, FD&C Red No. 40, D&C Red No. 28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C Blue No. 2, D&C Red No. 7 Calcium Lake, and, in addition, the 10-mg and 40-mg capsule shells also contain D&C Yellow No. 10.

Oral Rehydration Salt 45 mEq

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
811.90	1	Cerelose Powder	811.90
66.57	2	Sodium Chloride	66.57
31.82	3	Sodium Citrate Dihydrate	31.82
70.14	4	Potassium Citrate Monohydrate/Food Grade	70.14
19.57	5	Povidone (K 29-32)	19.57
—	6	Alcohol	500.00 ml
—	7	Water Purified	50.00 ml

MANUFACTURING DIRECTIONS

1. Mill the dextrose through a 1.2-mm aperture screen or similar on a comminuting mill, medium speed, knives forward.
2. Individually mill the sodium chloride, sodium citrate, and potassium citrate through a 1.2-mm aperture screen on a comminuting mill, medium speed, knives forward.
   Note: Do not mix the milled items until ready to add them to the dextrose.
3. Charge the powders from steps above into a suitable mass mixer and mix for 10 min. Screen the povidone through a 1.2-mm aperture screen and transfer to the mixer. Mix all the powders for 5 min.
4. Mix 500 ml of alcohol with 50 ml of water and slowly add to the mixer while mixing. Continue to mix for 5–10 min. Do not over wet the mass.
5. Granulate the wet mass through a 4.76-mm aperture screen using an oscillating granulator and spread on stainless steel trays.
6. Dry the granules at 45°C for approximately 16 h or until loss on drying is below 0.8%.
7. Turn the granules over after 3–4 h drying.
8. Screen dried granules through an 840-µm aperture screen.
9. Transfer the fine powder to a suitable blender.
10. Pass coarse granules through an 840-µm aperture screen using an oscillating granulator and transfer to the blender. Blend for 5–10 min.
11. Discharge into polyethylene-lined drums.
12. Fill 3.08 g for 100 ml, 7.70 g for 250 ml, and 30.80 g for 1000 ml of reconstituted solution; prorate weights for different volumes.

Orlistat Capsules

Orlistat is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Orlistat is available for oral administration in dark blue, hard gelatin capsules, with light blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C Blue No. 1, with printing of pharmaceutical glaze, titanium dioxide, and FD&C Blue No. 1 Aluminum Lake.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
120.00	1	Orlistat	120.00
93.60	2	Microcrystalline Cellulose	93.60
7.20	3	Sodium Starch Glycolate	7.20
12.00	4	Polyvinylpyrrolidone	12.00
7.20	5	Sodium Lauryl Sulfate	7.20

MANUFACTURING DIRECTIONS

1. Polyvinylpyrrolidone and sodium lauryl sulfate are dissolved in water.
2. Orlistat, microcrystalline cellulose, and sodium starch glycolate are mixed for 10 min and granulated with the solution of Step 1.
3. Granules are dried at or below 30°C and passed through a No. 20 mesh screen.
4. Granules are filled in a size 1 hard gelatin capsule.

Oseltamivir Phosphate Capsules and Oral Suspension

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt.

Oseltamivir phosphate is available as a capsule containing 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/ml oseltamivir. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, and sodium stearyl fumarate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C Blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains xanthan gum, monosodium citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide, and tutti-frutti flavoring.

Oxcarbazepine Oral Suspension

Oxcarbazepine is an antiepileptic drug available as a 300 mg/5 ml (60 mg/ml) oral suspension. Oxcarbazepine is 10,11-dihydro-10-oxo-5*H*-dibenz[b,*f*]azepine-5-carboxamide. The oral suspension contains the following inactive ingredients: ascorbic acid; dispersible cellulose; ethanol; macrogol stearate; methyl parahydroxybenzoate; propylene glycol; propyl parahydroxybenzoate; purified water; sodium saccharin; sorbic acid; sorbitol; yellow-plum-lemon aroma.

Oxycodone Hydrochloride and Acetaminophen Capsules

Each capsule contains oxycodone hydrochloride USP 5 mg and acetaminopohen 500 mg. Inactive ingredients: docusate sodium, gelatin, magnesium stearate, sodium benzoate, sodium metabisulfite, cornstarch, FD&C Blue No. 1, FD&C Red No. 3, FD&C Red No. 40, and titanium dioxide.

Oxytetracycline Hydrochloride Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Oxytetracycline, USE Oxytetracycline HCl BP 80	275.00
30.00	2	Starch (Cornstarch Dried)	30.00
1.00	3	Colloidal Silicon Dioxide (Aerosil 200)	1.00
3.00	4	Magnesium Stearate	3.00
3.00	5	Talc (Fine Powder)	3.00
1	6	Empty Hard Gelatin Capsule, Size 1	1000

MANUFACTURING DIRECTIONS

Note: The processing area must be under controlled room temperature and humidity. The limits are: RH 50–55%; temperature 22–27°C.

1. Pass Item 1 through a 630-µm sieve, using a sifter. Collect in stainless steel drum.
2. Mix Items 5, 3, and 2 in stainless steel drum. Pass through a 250-µm sieve, using a sifter. Collect in a stainless steel drum.
3. Add 66.67 g of sieved Item 1 (from Step 1) to the drum at Step 2, and mix for 5 min in drum blender.
4. Pass the mix through a 630-µm stainless steel sieve using sifter. Collect in stainless steel drum.
5. Pass Item 4 through a 250-µm sieve using sifter. Collect in stainless steel drum.
6. Add 8.0 g of sieved Item 1 (from Step 1) to the drum at Step 4 and mix for 5 min by rolling.
7. Pass the mix through a 630-µm stainless steel sieve using sifter. Collect in stainless steel drum.
8. Load the sieved powders to the blender. Mix for 5 min.
9. Unload the powder in stainless steel drum.
10. A fill weight of one capsule is 312 mg.

Oxytetracycline Hydrochloride, Sulfamethizole, and Phenazopyridine Hydrochloride Capsules

Each capsule contains: tetracycline hydrochloride equivalent to 250 mg oxytetracycline; sulfamethizole 250 mg; phenazopyridine hydrochloride 50 mg. Inert ingredients in the formulation are: hard gelatin capsules (which may contain FD&C Green No. 3, FD&C Yellow No. 6, D&C Yellow No. 10, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; and starch.

Pancrealipase Capsules

The delayed-release microsphere capsules for delayed release of pancrealipase, which is of porcine pancreatic origin, contain lipase (5000 USP units), protease (18,750 USP units), and amylase 16,600 (USP units) or pancrealipase (10,000 USP units), protease (37,500 USP units), and amylase (33,200 USP units) or contain lipase (20,000 USP units), protease (75,000 USP units), and amylase (66,400 USP units). Inactive ingredients include: dibutyl phthalate, dimethicone, hydroxypropyl methylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule shell contains FD&C Blue No. 2. In addition, the 10,000-unit capsule shell contains black iron oxide and the imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide.

Pancrealipase Capsules Enteric-Coated Microspheres

Pancrealipase capsules are orally administered capsules containing enteric-coated microspheres of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. The inactive ingredients are: povidone, talc, sugar, methacrylic acid copolymer (Type C), triethyl citrate, and simethicone emulsion.

Penicillamine Capsules

Penicillamine is a chelating agent used in the treatment of Wilson's disease. It is also used to reduce cystine excretion in cystinuria and to treat patients with severe, active rheumatoid arthritis unresponsive to conventional therapy. It is 3-mercapto-D-valine. Capsules of penicillamine for oral administration contain either 125 mg or 250 mg of penicillamine. Each capsule contains the following inactive ingredients: D&C Yellow No. 10, gelatin, lactose, magnesium stearate, and titanium dioxide. The 125-mg capsule also contains iron oxide.

Pentosan Polysulfate Sodium Capsules

Pentosan polysulfate sodium is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative, which chemically and structurally resembles glycosaminoglycans. It is a white odorless powder, slightly hygroscopic and soluble in water to 50% at pH 6. It has a molecular weight of 4000 to 6000 Da. It is supplied in white opaque hard gelatin capsules containing 100 mg of pentosan polysulfate sodium, microcrystalline cellulose, and magnesium stearate. It is formulated for oral use.

Pentostatin Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
5.00	1	Pentostatin	5.00
25.00	2	Gelatin	25.00
100.00	3	Lactose	100.00
2.00	4	Iron Oxide Red	2.00

MANUFACTURING DIRECTIONS

1. Pass Items 1–3 through 80 mesh and blend.
2. Add Item 4 and mix for 10 min.
3. Fill 132 mg in a size 1 capsule.

Phenobarbital and Hyoscyamine Sulfate Capsules

Each capsule contains phenobarbital (16.2 mg) and hyoscyamine sulfate (0.1037 mg). The inactive ingredients include: cornstarch, edible ink, D&C Yellow No. 10 and FD&C Green No. 3, or FD&C Blue No. 1 and FD&C Yellow No. 6, FD&C Blue No. 2 Aluminum Lake, gelatin, lactose, sucrose. Capsules may contain FD&C Red No. 40 and Yellow No. 6 aluminum lakes.

Phenoxybenzamine Hydrochloride Capsules

Each capsule, with a red cap and a red body contains phenoxybenzamine hydrochloride (10 mg). Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C Red No. 33, FD&C Red No. 3, FD&C Yellow No. 6, gelatin, lactose, sodium lauryl sulfate, and trace amounts of other inactive ingredients.

Phentermine Capsules

Each capsule contains 15 mg or 30 mg of phentermine as the cationic exchange resin complex. Phentermine is (alpha), (alpha)-dimethyl phenethylamine (phenyl-tertiary-butylamine). The inactive ingredients are: D&C Yellow No. 10, dibasic calcium phosphate, FD&C Yellow No. 6, gelatin, iron oxides (15 mg capsules only), lactose, magnesium stearate, and titanium dioxide.

Phentermine Hydrochloride Capsules

Phentermine hydrochloride has the chemical name of (α), (α)-dimethylphenethylamine hydrochloride. It is an anorectic agent for oral administration, is available as a capsule or tablet containing 37.5 mg of phentermine hydrochloride (equivalent to 30 mg of phentermine base). The capsules contain the following inactive ingredients: cornstarch, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, black iron oxide, FD&C Blue No. 1, FD&C Red No. 40, and D&C Red No. 33.

Phenytoin Sodium Extended-Release Capsules

Phenytoin sodium is an antiepileptic drug. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. Each extended phenytoin sodium capsule contains 30 mg or 100 mg phenytoin sodium. The capsule also contains lactose, confectioner's sugar, talc, and magnesium stearate. The capsule shell and band contain colloidal silicon dioxide, FD&C Red No. 3, gelatin, glyceryl monooleate, and sodium lauryl sulfate. The 30-mg capsule shell and band also contain citric acid, FD&C Blue No. 1, sodium benzoate, and titanium dioxide. The 100-mg capsule shell and band also contain FD&C Yellow No. 6, purified water, and polyethylene glycol 200. Product *in vivo* performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 h as contrasted with prompt phenytoin sodium capsules with a rapid rate of absorption with peak blood concentration expected in $1^1/_2$ to 3 h.

Piroxicam and Beta-cyclodextrin Topical Powder

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
100.00	1	Piroxicam	100.00
900.00	2	Beta-cyclodextrin	900.00

MANUFACTURING DIRECTIONS

1. Items 1 and 2 are screened through a 60-mesh screen and fed into the grinding chamber of a high-energy vibration mill together. While maintaining the mill at its minimum vibrational frequency, the powders are exposed for 15 min to a flow of steam by opening a connection valve between the chamber and a steam reservoir (mixing and activation stage).
2. After this operation, the true co-grinding stage is continued for 4 h. On termination, the product is discharged, screened through a 60-mesh screen, and homogenized by mixing.

Piroxicam Capsules

Piroxicam is a member of the oxicam group of nonsteroidal anti-inflammatory drugs. Each maroon and blue capsule contains 10 mg of piroxicam; each maroon capsule contains 20 mg of piroxicam for oral administration. The chemical name for piroxicam is 4-hydroxyl-2-methyl-*N*-2-pyridinyl-2 *H*-1, 2-benzothiazine-3-carboxamide 1,1-dioxide. The inactive ingredients in FELDENE capsules include: FD&C Blue No. 1, FD&C Red No. 3, lactose, magnesium stearate, sodium lauryl sulfate, and starch.

1.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
20.00	1	Piroxicam	20.00
233.23	2	Lactose	233.23
48.75	3	Cornstarch	48.75
1.36	4	Magnesium Stearate	1.36
0.15	5	Sodium Lauryl Sulfate	0.15

Note: For 5 and 10 mg strength, adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Charge Items 1–3 in a suitable blender in a low-humidity area.
2. Compress to make slugs, reduce slugs by passing through a No. 20 sieve.
3. Add and blend Items 4 and 5, and blend for 10–15 min.
4. Fill 305 mg in hard gelatin capsules.

2.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
50.00	1	Piroxicam	50.00
124.40	2	Lactose Anhydrous	124.40
50.00	3	Cornstarch	50.00
12.50	4	Sodium Starch Glycolate	12.50
2.50	5	Povidone	2.50
7.50	6	Polysorbate 80	7.50
0.625	7	Colloidal Silicon Dioxide	0.625
6.25	8	Glycine	6.25
1.25	9	Citric Acid	1.25
QS	10	Water Purified	QS

MANUFACTURING DIRECTIONS

1. An aqueous wet granulation process is whereby Item 1, lactose, cornstarch, sodium starch glycolate, colloidal silicon dioxide, and povidone are mixed and subsequently granulated with polysorbate dissolved in purified water.
2. Additional purified water is then added until granules form and no dry powder remains.
3. Glycine and citric acid are dissolved in the additional purified water.
4. Wet granules are dried at 60°C until loss on drying is not more than 2%.
5. The dried granules are milled with the sodium starch glycolate, blended and lubricated with screened magnesium stearate in a twinshell blender.
6. Fill 250 mg in size 2 capsules.

Polyethylene Glycol 3350 Powder for Reconstitution

A white powder. Polyethylene glycol 3350 is a synthetic polyglycol having an average molecular weight of 3350. The actual molecular weight is not less than 90% and not greater than 110% of the nominal value. At below 55°C it is a free-flowing white powder freely soluble in water. It is an osmotic agent for the treatment of constipation. Each dose consists of 17 g of polyethylene glycol 3350.

Polythiazide Capsules

Polythiazide is an orally effective, nonmercurial diuretic, saluretic, and antihypertensive agent. It is designated chemically as 2*H*-1,2,4-benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-2-methyl-3-[[(2,2,2-tri-fluoro-ethyl)thio]methyl]-,1,1-dioxide. Inert ingredients in the formulations are: hard gelatin capsules (which may contain FD&C Blue No. 1, FD&C Green No. 3, FD&C Red No. 3, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch; and sucrose.

Potassium Chloride Extended-Release Capsules

The extended release capsules contain microencapsulated potassium chloride 600 and 750 mg, respectively, of potassium chloride USP equivalent to 8 and 10 mEq of potassium. Dispersibility of potassium chloride (KCl) is accomplished by microencapsulation and a dispersing agent. The resultant flow characteristics of the KCl microcapsules and the controlled release of K + ions by the microcapsular membrane are intended to avoid the possibility that excessive amounts of KCl can be localized at any point on the mucosa of the gastrointestinal tract. Each crystal of KCl is microencapsulated by a patented process with an insoluble polymeric coating which functions as a semi-permeable membrane; it allows for the controlled release of potassium and chloride ions over an 8- to 10-h period. Fluids pass through the membrane and gradually dissolve the potassium chloride within the microcapsules. The resulting potassium chloride solution slowly diffuses outward through the membrane. The inactive ingredients present are edible ink, ethylcellulose, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6, gelatin, magnesium stearate, sodium lauryl sulfate, and titanium dioxide. The capsules may contain FD&C Red No. 40 and Yellow No. 6 Aluminum Lake.

Potassium Chloride for Oral Solution

Natural fruit-flavored potassium chloride for oral solution, USP is an oral potassium supplement offered in individual packets as a powder for reconstitution. Each packet of powder contains potassium 20 mEq and chloride 20 mEq provided by potassium chloride 1.5 g. It is an electrolyte replenisher. Inactive ingredients: FD&C Yellow No. 6, maltodextrin (contains corn derivative), malic acid, saccharin, silica gel, and natural flavoring.

Potassium Chloride Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
600.00	1	Potassium Chloride	600.00
900.00	2	Gelatin	900.00
QS	3	Water Purified	1.5 l
QS	4	Corn Oil	QS
QS	5	Petroleum Ether	QS
QS	6	Isopropyl Alcohol	QS
QS	7	Glutaryldehyde 1%	QS

MANUFACTURING DIRECTIONS

1. Item 2 is added to 1.5 l of Item 3 and the mixture is allowed to stand at 25°C for 1 h while the gelatin hydrates and swells.
2. To this mixture is added Item 1 and the preparation is heated to 60°C while it is stirred at 300 rpm for 30 min to effect dissolution of the gelatin and to assure even suspension of the calcium carbonate. Additional distilled water previously heated to 60°C is then added to bring the total volume to 100°C while the stirring is continued.
3. This preparation is slowly poured into 12 l of a mixture consisting of 20% by volume of corn oil in petroleum ether, which has previously been heated to 60°C while the petroleum ether solution is stirred at 500 rpm. This preparation is then cooled to 5°C with continued stirring, and the stirring is continued at 500 rpm for 1 h after the lower temperature is reached.
4. Isopropanol (6 l) is then added while stirring of the preparation at 5°C is continued. The solid microspheres are then collected by filtration and washed three times with isopropyl alcohol. The capsules are then immersed in 1.5 l of a 1% solution of glutaraldehyde in isopropyl alcohol for 8 h at 5°C, then washed again three times with isopropyl alcohol, filtered, and vacuum dried for 24 h.
5. The microspheres, which average between 200 and 300 μm in diameter, are filled into gelatin capsules for administration as a long-acting antacid product (1.5 g of the microsphere mix, which contains 600 mg of potassium chloride, are filled into each size 00 capsule). This final dosage form delivers a total dose of 600 mg of KCl, but over a sustained time period of 1–4 h and in such a way that the potassium chloride is in the solution state, rather than the more injurious solid state, when it contacts the gastrointestinal mucosa. Total dissolution of the microspheres occurs from 1–5 h after the drug content is depleted.

Potassium Chloride Powder 20 mEq

Bill of Materials			
Scale (g/3g Pack)	**Item**	**Material Name**	**Qty/kg (g)**
1.50	1	Potassium Chloride Powder	500.00
0.40	2	Calcium Cyclamate Granules	130.00
4.00 mg	3	Dye Yellow	1.33
0.16	4	Malic Acid	51.67
0.50	5	Hydrolyzed Cereal Solids	165.00
—	6	Alcohol Anhydrous	90.00
—	7	Water Purified	10.00
15.00	8	Silicon Dioxide Colloidal	15.00
0.25	9	Flavor	81.66
0.20	10	Flavor	65.33

MANUFACTURING DIRECTIONS

1. Pass Items 1–4 and, if necessary, Item 5 through a 686-μm mesh using a comminuting mill with impact forward.
2. Charge the materials from Step 1 and Item 5 in a suitable mixer and mix for 20 min.
3. Mix Items 6 and 7 separately and add to Step 2; mix for 5 min or until satisfactory mass is obtained.
4. Spread wet granules on paper-lined trays and dry at 40–60°C to not more than 1.5% loss on drying.
5. Sift granules through an 840-μm aperture, and grind through a 1.27-mm aperture.
6. Screen the flavors and, if necessary, Item 8 through 20 mesh.
7. Load half the granulation in a blender and add Step 6, followed by remainder granules and blend for 20–30 min.
8. Fill in suitable sachet 3 g.
9.

Prazosin and Polythiazide Capsules

Prazosin hydrochloride, a quinazoline derivative, is the first of the chemical class of antihypertensives. It is the hydrochloride salt of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl) piperazine. Each 1 mg capsule of contains drug equivalent to 1 mg free base. Inert ingredients in the formulations are: hard gelatin capsules (which may contain FD&C Blue No. 1, FD&C Red No. 3, FD&C Red No. 28, FD&C Red No. 40, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch; and sucrose.

Prednisolone Targeted-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
10.00	1	Prednisolone	10.00
100.00	2	Succinic Acid	100.00
30.00	3	Eudragit E100 (5%)	30.00
100.00	4	Hydroxypropyl Methylcellulose Acetate Succinate	100.00
QS	5	Ethanol	QS
QS	6	Purified Water	QS
QS	7	Talc	QS

MANUFACTURING DIRECTIONS

1. Add Items 1 and 2 to a suitable mixer, and blend well. Fill in a size 2 capsule, the core capsule.
2. Spray-coat the core capsule with a 5% by weight solution of Eudragit E100 dissolved in ethanol, in a coating amount of 30 mg per capsule (48% by weight, based on the weight of the used empty hard capsule) as Eudragit E100 to obtain a capsule coated with a low pH-soluble polymer film.
3. The coated capsule is further spray-coated with a coating solution prepared by dissolving Item 4 in a mixture of ethanol and water (5:3 [w/w]) to obtain a 5% by weight Item 4 solution and adding thereto talc in an amount of 2.5% by weight, based on the total weight of the 5% Item 4 solution, in a coating amount of 100 mg per capsule (159% by weight, based on the weight of the used empty hard capsule) as Item 4 by means of an appropriate coater.
4. The formulation described above releases in the lower part of the digestive tract.

Procarbazine Hydrochloride Capsules

Procarbazine hydrochloride, a hydrazine derivative antineoplastic agent, is available as capsules containing the equivalent of 50 mg of procarbazine as the hydrochloride. Each capsule also contains cornstarch, mannitol and talc. Gelatin capsule shells contain parabens (methyl and propyl), potassium sorbate, titanium dioxide, FD&C Yellow No. 6 and D&C Yellow No. 10. Chemically, procarbazine hydrochloride is N-isopropyl-(alpha)-(2-methylhydrazino)-p-toluamide monohydrochloride. It is a white to pale yellow crystalline powder, which is soluble but unstable in water or aqueous solutions. The molecular weight of procarbazine hydrochloride is 257.76.

Prochlorperazine Sustained-Release Capsules

Prochlorperazine is a phenothiazine derivative, present in *Spansule*® sustained release capsules as the maleate. Its chemical name is 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10 *H* phenothiazine *Z)*-2-butenedioate (1:2). Spansule sustained release capsules — each Compazine *Spansule* is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period. Food slows absorption of prochlorperazine and decreases C_{max} by 23% and AUC by 13%. Inactive ingredients consist of ammonio methacrylate co-polymer, D&C Green No. 5, D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, silicon dioxide, simethicone emulsion, sodium lauryl sulfate, sorbic acid, sugar spheres, talc, triethyl citrate, and trace amounts of other inactive ingredients.

Propoxyphene Hydrochloride, Caffeine, and Aspirin Capsules

Propoxyphene Hydrochloride is an odorless, white crystalline powder with a bitter taste. It is freely soluble in water. Chemically, it is (2 *S*,3 *R*)-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol propionate (ester) hydrochloride. Each capsule contains 65 mg (172.9 µmol) of propoxyphene hydrochloride, 389 mg (2159 µmol) of aspirin, and 32.4 mg (166.8 µmol) of caffeine. It also contains FD&C Red No. 3, FD&C Yellow No. 6, gelatin, glutamic acid hydrochloride, iron oxide, kaolin, silicone, titanium dioxide, and other inactive ingredients.

Propoxyphene Hydrochloride Capsules

Each Pulvule contains 65 mg (172.9 µmol) (No. 365) of propoxyphene hydrochloride. It also contains D&C Red No. 33, FD&C Yellow No. 6, gelatin, magnesium stearate, silicone, starch, titanium dioxide, and other inactive ingredients.

Propranolol Hydrochloride and Hydrochlorothiazide Capsules

Each capsule contains propranolol (80 mg) and hydrochlorothiazide (50 mg); alternately, the capsule may contain 120/50 or 160/50 mg, respectively. It contains the following inactive ingredients: calcium carbonate, ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, and D&C Yellow No. 10. In addition, 80/50-mg and 120/50-mg capsules contain D&C Red No. 33; 120/50-mg and 160/50-mg capsules contain FD&C Blue No. 1 and FD&C Red No. 40.

Propranolol Hydrochloride Long-Acting Capsules

Propranolol hydrochloride is a synthetic beta-adrenergic receptor-blocking agent chemically described as 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride. It is formulated to provide a sustained release of propranolol hydrochloride. It is is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules. The capsules contain the following inactive ingredients: cellulose, ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, and titanium dioxide. In addition, Inderal LA® 60 mg, 80 mg, and 120 mg capsules contain D&C Red No. 28 and FD&C Blue No. 1; Inderal LA 160 mg capsules contain FD&C Blue No. 1. These capsules comply with USP Drug Release Test 1.

Propranolol Hydrochloride Multiple Bead Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
160.00	1	Propranolol Hydrochloride [total]	160.00
		Powder Blend	
30.00	1	Propranolol Hydrochloride Powder	30.00
54.00	2	Lactose	54.00
15.00	3	Microcrystalline Cellulose	15.00
1.00	4	Magnesium Stearate	1.00
		pH Sensitive Coated Spheroids	
		Uncoated Spheroids (60% w/w Propranolol Hydrochloride)	3.00 kg
		Methacrylic Acid Copolymer Type B Eudragit S	0.75 kg
		Triacetin	0.112 kg
		Isopropyl Alcohol	1.64 kg
		Methylene Chloride	1.99 kg
		Water	0.50 kg
		Coated Spheroids	
		Uncoated Spheroids (60% w/w Propranolol Hydrochloride)	3.00 kg
		Hydroxypropyl Methylcellulose 2910, 4000 cps, Methocel	0.075 kg
		Methylene Chloride	4.98 kg
		Methanol Anhydrous	2.96
		Eudragit E 30D Aqueous Dispersion	1.00 kg
		Calcium Stearate	0.03 kg
		Simethicone Emulsion	0.0025 kg
		Water Purified	0.50 kg

MANUFACTURING DIRECTIONS

1. The finished dosage form consists of a hard gelatin capsule containing a powder blend of propranolol hydrochloride and two types of spheroids. The formulation particulars are based on 160 mg of propranolol hydrochloride per capsule, although they can be designed to provide other dosage strengths.
2. The propranolol hydrochloride powder blend (or first group of spheroids) provides the loading dose, (e.g., 25 mg of propranolol HCl). The second and third types of spheroids are categorized as:
   a. Propranolol hydrochloride (60 kg) and microcrystalline cellulose (Avicel-PH101; 40 kg) are blended together in a 450-l planetary mixer. Water (50 kg) is added, and the mixer is run for 10 min until a homogeneous plastic mass is obtained. The mass is extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1 mm in diameter. The damp extrudates (in batches of 15 to 20 kg) are placed in a spheronizer in which the rotating disc (diameter 68 cm) rotated at 300 to 400 rpm. The rotation is continued for 10 min, and the resulting spheroids are then dried at 60°C in a fluidized-bed dryer. The dried spheroids are passed over a 1.4-mm screen, and those which passed through are subjected to a 0.7-mm screen. The over- and undersized spheroids are discarded.
   b. pH sensitive coated spheroids are used to provide a second dose (pH 6.5) (e.g., 65 mg propranolol HCl). Uncoated spheroids are placed in a fluidized-bed coater. The Eudragit S solution is applied using a peristaltic pump. The spheroids are dried.
   c. Coated spheroids are used to provide a third dose (4–10 h post-ingestion) (e.g., 70 mg propranolol HCl). The uncoated spheroids are placed in a fluidized-bed coater. Methocel E4MP® solution is sprayed using a peristaltic pump. The spheroids are dried.

3. Process for applying overcoat: Eudragit E 30D suspension containing calcium stearate is sprayed on the Methocel E4MP coated spheroids using a peristaltic pump.
4. The spheroids are dried.
5. Capsules are filled with the powder blend, pH-sensitive coated spheroids, and coated spheroids on an encapsulating machine capable of dual filling powders and spheroids.

Propranolol Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
160.00	1	Propranolol Hydrochloride	160.00
128.92	2	Sucrose	128.92
42.97	3	Cornstarch	42.97
22.86	4	Shellac	22.86
35.25	5	Talc	35.25
—	6	Ethyl Alcohol	91.44
—	7	Water Purified	QS

MANUFACTURING DIRECTIONS

I. Neutral Pellets
   A. Weigh and mix in a stainless steel mixer suitable quantities of sucrose and cornstarch in the proportion of 3:1 w/w. Sift through a screen of suitable size to break up possible lumps.
   B. Transfer the mixture to a stainless steel coating pan and adjust rotary speed between 20 and 30 rpm to obtain a good tumbling action.
   C. By means of a suitable spray gun, spray over the powder a quantity of water equal to 15% w/w in very minute drops.
   D. Place the wet pellets over a thermostatic tray dryer and dry at 37°C to complete evaporation of water.
   E. Pass the dried pellets through sieves of suitable screens to ensure removal of dust and selection of cores of desired size.

II. Active Pellets
   A. Dissolve Shellac in Ethyl Alcohol. To 65% of this solution add propranolol hydrochloride. (Reserve the remaining 35% of the solution for the film coating.)
   B. Transfer 171.89 kg of neutral pellets obtained from Step I-E to a stainless steel coating pan and adjust the rotation speed between 20 and 30 rpm so as to obtain good tumbling action.
   C. Spray over the neutral pellets the result of Step II-A.
   D. Keep the pan rotating to allow partial evaporation of the solvent.
   E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.

III. Film-Coated Pellets
   A. Transfer the active pellets obtained from Step II-E to a stainless steel coating pan and adjust the rotatory speed so as to obtain a good tumbling action.
   B. Spray the pellets as uniformly as possible with the alcoholic solution of shellac reserved from Step II-A.
   C. Spread the wet pellets with talc to prevent agglutination.
   D. Keep the pan rotating to achieve solidification of the film-coating and partial evaporation of the solvent.
   E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.

IV. Blending of Pellets
   A. Transfer the film-coated pellets obtained from Step III-E to a stainless steel pan and add a suitable quantity of neutral pellets obtained from Step III-E to obtain the required dosage.
   B. Add a 0.5% w/w talc to eliminate electrostatic charges and mix for 30–35 min.

V. Assembly
   A. Fill the blended pellets obtained from Step IV-B into capsules of size 1 at the weight of 390 mg.

Propranolol Timed- and Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
80.00	1	Propranolol	80.00
4.14	2	Polyvinyl Pyrrolidone K-30	4.14
55.85	3	Nonpareil Sugar Beads 25–30 Mesh	55.85
2.80	4	Opadry Clear	2.80
2.33	5	Ethyl Cellulose	2.33
0.23	6	Diethyl Phthalate	0.23
—	7	Water Purified	QS
—	8	Acetone	QS
9.75	9	Ethyl Cellulose	9.75
8.57	10	Hydroxypropyl Methylcellulose Phthalate	8.57
3.10	11	Diethyl Phthalate	3.10

MANUFACTURING DIRECTIONS

1. Prepare a solution of Item 2 in Item 7, and add Item 1 slowly; mix well. This is the drug solution.
2. In a Glatt fluid-bed dryer, charge Item 3 and coat with Step 1 slowly, and then dry to less than 2% moisture.
3. Apply Item 4 coating to dried granules from Step 2 to obtain 2% weight gain.
4. In a separate vessel, prepare a solution of Items 5 and 6 in 98 parts of Item 8 and 2 parts of Item 7. Spray this inner coating on to Step 3.
5. Prepare an acetone:water solution of Items 9–11 and coat on Step 4.
6. Dry and fill in capsules to yield 80, 120, and 160 mg of Item 1. This product provides drug loading of 56% w/w based on core composition corresponding to 45.7% drug based on final time and sustained release beads.

Pseudoephedrine and Guaifenesin Capsules

Each capsule contains: pseudoephedrine hydrochloride 120 mg in a specially prepared base to provide prolonged action and guaifenesin 250 mg designed for immediate release to provide rapid action. Alternate dosing is 60 mg and 300 mg, respectively. The capsules also contain as inactive ingredients: calcium stearate, FD&C Blue No. 1 (for higher strength identification), gelatin, pharmaceutical glaze, starch, sucrose, talc, and titanium dioxide.

Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/Capsule)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
24.00	1	Pseudoephedrine Hydrochloride	24.00
15.00	2	Hydroxyethylcellulose NF	15.00
60.00	3	Lactose Anhydrous	60.00
1.00	4	Magnesium Stearate	1.00

MANUFACTURING DIRECTIONS

Blend all the ingredients in a twinshell blender for 10 min. Fill size 0 capsules with fill weight of 500 mg, using tamping force of 200 N.

Ranitidine Effervescent Granules

Ranitidine hydrochloride (HCl) is a histamine H2-receptor antagonist. Chemically, it is N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine, HCl. Granules for oral administration are effervescent formulations of ranitidine; these must be dissolved in water before use. Each packet contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate.

Ribavirin Capsules

Ribavirin is a nucleoside analog with antiviral activity. The chemical name of ribavirin is 1-(beta)-D-ribofuranosyl-1 *H*-1,2,4-triazole-3-carboxamide. Capsules consist of a white powder in a white opaque gelatin capsule. Each capsule contains 200 mg of ribavirin and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink, which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue No. 2 aluminum lake.

Rifabutin Capsules

The antimycobacterial agent rifabutin is a semisynthetic ansamycin antibiotic derived from rifamycin S. The capsules contain 150 mg of rifabutin, USP, per capsule, along with the following inactive ingredients: microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

Rifampicin Capsules

Rifampicin (rifampin) capsules contain 150 mg or 300 mg of rifampin per capsule. The 150-mg and 300-mg capsules also contain, as inactive ingredients: cornstarch, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, and titanium dioxide. Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin is a red-brown crystalline powder very slightly soluble in water at neutral pH, freely soluble in chloroform, soluble in ethyl acetate and in methanol.

Rifampin and Isoniazid Capsules

This is a combination capsule containing 300 mg of rifampin and 150 mg of isoniazid. The capsules also contain as inactive ingredients: colloidal silicon dioxide, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, sodium starch glycolate, and titanium dioxide. Rifampin is a semisynthetic antibiotic derivative of rifamycin B. The chemical name for rifampin is 3-(4-methyl-1-piperazinyliminomethyl) rifamycin SV. Isoniazid is the hydrazide of isonicotinic acid. It exists as colorless or white crystals or as a white crystalline powder that is water soluble, odorless, and slowly affected by exposure to air and light.

Rivastigmine Tartrate Capsules

Rivastigmine tartrate is a reversible cholinesterase inhibitor and is known chemically as (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2*R*,3*R*)-tartrate. Rivastigmine tartrate is commonly referred to in the pharmacological literature as SDZ ENA 713 or ENA 713. It is supplied as capsules containing rivastigmine tartrate, equivalent to 1.5, 3, 4.5, and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard gelatin capsule contains gelatin, titanium dioxide, and red and/or yellow iron oxides.

Salmeterol Xinafolate Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
2.00	1	Salmeterol Xinafolate	2.00
97.00	2	Starch 1500 DC	97.00
1.00	3	Magnesium Stearate	1.00

MANUFACTURING DIRECTIONS

Blend and fill 100 mg in each capsule.

Salmeterol Xinafolate Inhalation Powder

Salmeterol xinafolate inhalation powder contains salmeterol xinafolate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. The active component of the formulation is salmeterol base, a highly selective beta 2-adrenergic bronchodilator. The chemical name of salmeterol xinafolate is 4-hydroxy-(alpha) 1-[[[6-(4-phenylbutoxy) hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate. It is a specially designed plastic device containing a double-foil blister strip of a powder formulation of salmeterol xinafolate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50 mcg of salmeterol administered as the salmeterol xinafolate salt in 12.5 mg of formulation containing lactose. When a blister containing medication is opened by activating the device, the medication is dispersed into the air stream created when the patient inhales through the mouthpiece.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
0.05	1	Salmeterol Xinafolate Micronized	0.05
12.50	2	Lactose Anhydrous	12.50

Saquinavir Mesylate Capsules

Saquinavir mesylate is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name for saquinavir mesylate is N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide methanesulfonate. It is available as light brown and green, opaque hard gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients: lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc, and magnesium stearate. Each capsule shell contains gelatin and water with the following dye systems: red iron oxide, yellow iron oxide, black iron oxide, FD&C Blue No. 2, and titanium dioxide. Another formulation contains inactives. Each capsule also contains the inactive ingredients: medium chain mono- and diglycerides, povidone, and dl-alpha tocopherol. Each capsule shell contains gelatin and glycerol 85% with the following colorants: red iron oxide, yellow iron oxide, and titanium dioxide.

Selegiline Hydrochloride

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as l-deprenyl. The chemical name is: (R)-(-)-*N,2*-dimethyl-*N*-*2*-propynylphenethylamine hydrochloride. Each aqua blue capsule contains 5 mg of selegiline hydrochloride. The inactive ingredients are: citric acid, lactose, magnesium stearate, and microcrystalline cellulose.

Sevelamer Hydrochloride Capsules

Sevelamer hydrochloride is a polymeric phosphate binder intended for oral administration. Sevelamer hydrochloride is poly(allylamine hydrochloride) crosslinked with epichlorohydrin in which 40% of the amines are protonated. It is known chemically as poly(allylamine-co-N,N′-diallyl-1,3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic, but insoluble in water. Each hard gelatin capsule of Renagel® contains 403 mg of sevelamer hydrochloride on an anhydrous basis. The inactive ingredients are colloidal silicon dioxide and stearic acid. The capsule and imprint contain titanium dioxide and indigo carmine ink.

Sibutramine Hydrochloride Capsules

Sibutramine hydrochloride monohydrate is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (–) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-*N,N*-dimethyl-(alpha)-(2-methylpropyl)-, hydrochloride, monohydrate. Each capsule contains 5 mg, 10 mg, or 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule (which contains titanium dioxide, USP; gelatin; FD&C Blue No. 2 [5- and 10-mg capsules only]; D&C Yellow No. 10 [5- and 15-mg capsules only], and other inactive ingredients).

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Sibutramine Hydrochloride	5.00
78.50	2	Lactose Anhydrous	78.50
5.00	3	Polyvinylpyrrolidone	5.00
15.00	4	Cornstarch	15.00
1.50	5	Magnesium Stearate	1.50
QS	6	Alcohol	QS

MANUFACTURING DIRECTIONS

1. Mix Items 1, 2, and 4 and granulate with alcoholic solution of Item 3.
2. Dry, size, and blend with Item 5.
3. Fill 105 mg; adjust for higher dose with Item 2.

Stavudine Capsules

Stavudine (d4T), a synthetic thymidine nucleoside analog, is active against HIV. The chemical name for stavudine is 2′,3′-didehydro-3′-deoxythymidine. The stavudine capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. Each capsule also contains inactive ingredients: microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides.

Succimer Capsules

Succimer is an orally active, heavy metal chelating agent. The chemical name for succimer is *meso* 2,3-dimercaptosuccinic acid (DMSA). Each opaque white capsule for oral administration contains beads coated with 100 mg of succimer and is imprinted in black with CHEMET 100®. The inactive ingredients in medicated beads are: povidone, sodium starch glycolate, starch, and sucrose. The inactive ingredients in the capsule are: gelatin, iron oxide, titanium dioxide, and other ingredients.

Sucralafate Granules

Bill of Materials			
Scale (mg/Sachet) (2 g)	**Item**	**Material Name**	**Qty/2 kg (g)**
1000.00	1	Sucralafate	1000.00
100.00	2	Cornstarch	100.00
240.00	3	Povidone	240.00
QS	4	Lactose, QS to 2000	QS
—	5	Alcohol	QS

MANUFACTURING DIRECTIONS

1. Charge Items 1 and 2 in a fluid-bed granulator (e.g., Glatt) and mix for 5 min at inlet temperature of 30°C.
2. Dissolve Item 3 in a separate container in Item 5 and spray into Step 1 to granulate.
3. Dry granules at 50°C until the temperature reaches 30°C.
4. Sieve through No. 18.
5. Fill 1.9–2.1 g per sachet.

Tacrine Hydrochloride Capsules

Tacrine hydrochloride is a reversible cholinesterase inhibitor, known chemically as 1,2,3,4-tetrahydro-9-acridinamine monohydrochloride monohydrate. Each capsule contains tacrine as the hydrochloride. Inactive ingredients are hydrous lactose, magnesium stearate, and microcrystalline cellulose. The hard gelatin capsules contain: gelatin, silicon dioxide, sodium lauryl sulfate, and the following dyes: 10 mg: D&C Yellow No. 10, FD&C Green No. 3, titanium dioxide; 20 mg: D&C Yellow No. 10, FD&C Blue No. 1, titanium dioxide; 30 mg: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, titanium dioxide; 40 mg: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red No. 40, D&C Red No. 28, and titanium dioxide. Each 10-, 20-, 30-, and 40-mg capsule for oral administration contains 12.75, 25.50, 38.25, and 51.00 mg of tacrine hydrochloride, respectively.

Tacrolimus Capsules

Tacrolimus is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5 mg, 1 mg, or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide, the 1-mg capsule shell contains gelatin and titanium dioxide, and the 5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis.*

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
1.00	1	Tacrolimus	1.00
1.00	2	Hydroxypropyl Methylcellulose 2910	1.00
QS	3	Ethanol	QS
58.00	4	Lactose	58.00

MANUFACTURING DIRECTIONS

1. Item 1 is mixed with Items 2 and 3. The mixture is kneaded and granulated to pass through sieves to collect particle size 180–250 μm; the other particle size is regranulated.
2. Dry granulation in Step 1 is dried at room temperature.
3. In a suitable blending vessel, add Item 4 and gradually add the Step 2 granulation. Mix for 10 min and fill in size 0 capsules.

Talc, Crospovidone, and Starch Topical Powder

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
100.00	1	Croscarmellose Sodium (Crospovidone)	100.00
800.00	2	Cornstarch	800.00
100.00	3	Talc	100.00

MANUFACTURING DIRECTIONS

Mix and fill in bottles.

Tamsulosin Hydrochloride Capsules

Tamsulosin hydrochloride is an antagonist of alpha 1A adrenoceptors in the prostate. Tamsulosin HCl is (-)-(*R*)-5-[2-[[2-(0-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Each capsule for oral administration contains tamsulosin HCl 0.4 mg, and the following inactive ingredients: methacrylic acid copolymer, microcrystalline cellulose, triacetin, polysorbate 80, sodium lauryl sulfate, calcium stearate, talc, FD&C Blue No. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts of shellac, industrial methylated spirit 74 OP, *n*-butyl alcohol, isopropyl alcohol, propylene glycol, dimethylpolysiloxane, and black iron oxide (E172).

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
0.40	1	Tamsulosin Hydrochloride	0.40
35.60	2	Crystalline Cellulose	35.60
13.32	3	Eudragit L30D-55	13.32
4.00	4	Magnesium Stearate	4.00

MANUFACTURING DIRECTIONS

1. After sufficiently mixing Item 1 crystalline cellulose, and of magnesium stearate, a mixture of Eudragit L30D-55 and 40 ml of water was added to the aforementioned mixture, and the resultant mixture was kneaded and granulated by a centrifugal fluidized-bed granulator.
2. The granules obtained were spheres having particle sizes of 0.1 to 1.5 mm, mainly 0.2 to 1.0 mm.

Temazepam Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
7.50	1	Temazepam Micronized	7.50
7.50	2	Lactose Anhydrous	7.50
232.50	3	Lactose Anhydrous	232.50
2.50	4	Magnesium Stearate	2.50

MANUFACTURING DIRECTIONS

1. Item 1 is processed as follows: White crystalline temazepam having a purity of not less than 98% is fed into an Alpine 160 UPZ mill with a stainless steel pin at a rate of about 40 kg per hour using a mill speed of about 11,000 rpm to obtain temazepam particles having a specific surface area of 0.65 to 1.1 m^2/g area and 95% of the particles having a particle size diameter of less than 65 µm. The surface area measurement is made with the Quantector Gas Flow System and Quantasorb Surface Area Analyser at the temperature of liquid nitrogen (−196°C) using krypton as the absorbant and helium as the carrier gas. The particle size diameter is determined with the Malverne Particle Sizer at an obscuration value of 0.2 to 0.25 using a 0.1% Tween 80 solution in water saturated with temazepam in which 1 to 2 g of temazepam sample to be tested has been dispersed. After the feed rate and mill speed of the Alpine mill have been set, they are monitored at regular intervals to maintain the required particle size and surface area.
2. To prepare hard gelatin capsules containing 7.5 mg of the temazepam processed as in Step 1, charge Items 1 and 2 in a mill and pass through an 18-mesh screen.
3. Pass Item 3 through 18-mesh screen and add to Step 2.
4. Pass Item 4 through 18-mesh screen and add to Step 3 in a PK Mixer® without an intensity bar.
5. Mix for 30 min using tumbling action only.
6. The capsule mix is encapsulated in number 3 Lock hard gelatin capsules. Each capsule contains 250 mg of capsule mix and 7.5 mg of temazepam.

Temozolomide Capsules

The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-tetrazine-8-carboxamide. Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR® Capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. The gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.

Terazosin Hydrochloride Capsules

Terazosin hydrochloride, an alpha-1-selective adrenoceptor blocking agent, is a quinazoline derivative represented by the following chemical name and structural formula: (RS)-piperazine,1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]-,monohydrochloride, dihydrate. Terazosin hydrochloride capsules for oral ingestion are supplied in four dosage strengths containing terazosin hydrochloride equivalent to 1 mg, 2 mg, 5 mg, or 10 mg of terazosin. The inactive ingredients in the 1-mg capsules are: gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 2-mg capsules: D&C Yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 5-mg capsules: D&C Red No. 28, FD&C Red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 10-mg capsules: FD&C Blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
5.000	1	Terazosin Hydrochloride Anhydrous	5.471
174.529	2	Lactose Monohydrate	174.529
28.000	3	Microcrystalline Cellulose	28.000
14.000	4	Crospovidone	14.000
3.000	5	Magnesium Stearate	3.000

MANUFACTURING DIRECTIONS

1. Add and blend all Items 1–5 in a suitable blender.
2. Fill using size 3 capsules; fill weight of 225.00 mg.

Tetracycline Hydrochloride Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
250.00	1	Tetracycline, USE Tetracycline	275.00
46.00	2	Lactose Monohydrate (Dense)	46.00
2.00	3	Colloidal Silicon Dioxide (Aerosil 200)	2.00
2.00	4	Magnesium Stearate	2.00
1	5	Empty Hard Gelatin Capsule, Size 1	1000

MANUFACTURING DIRECTIONS

1. Check the temperature and relative humidity of the room before start of processing. Limits: RH 50–55%; temperature: 22–27°C.
2. Pass the Items 1, 2, and 3 through a 630-µm sieve, using a sifter. Collect in stainless steel drum.
3. Pass Item 4 through a 250-µm sieve, using a sifter. Collect in polythene bag. Load the sieved powder to the drum (Step 1) and mix for 5 min using drum mixer.
4. Load the empty capsule shells (size 1) in the hopper.
5. Run the machine and check the locking of shells.
6. Fill weight of one capsule = 325 mg + average weight of one empty shell.

Thalidomide Capsules

Thalidomide, α-(*N*-phthalimido) glutarimide, is an immunomodulatory agent. Thalidomide capsules are available in 50-mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

Theophylline Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
150.00	1	Theophylline Anhydrous (B.F. Goodrich)	150.00
26.60	2	Carbopol 934P (GAF Corporation)	26.60
172.10	3	PVP C-15	172.10
3.50	4	Talc	3.50
1.80	5	Zinc Stearate	1.80

MANUFACTURING DIRECTIONS

1. The Carbopol 934P, PVP C-15 (mean molecular weight of about 8000, talc, and zinc stearate are combined in a mixer and are mixed.
2. Theophylline anhydrous is added to this mixture and mixed well to achieve a uniform mixture.
3. The resulting particulate mixture, 354 mg, is filled into size 1 hard gelatin capsule shells.

Thiothixene Capsules

Thiothixene is a thioxanthene derivative. Specifically, it is the *cis* isomer of *N*,*N*-dimethyl-9-[3-(4-methyl-1-piperazinyl)-propylidene] thioxanthene-2-sulfonamide. Each capsule contains 1 mg, 2 mg, 5 mg, or 10 mg of thiothixene and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium (Type A), gelatin, magnesium stearate, microcrystalline cellulose, powdered cellulose, pregelatinized starch, sodium lauryl sulfate, titanium dioxide, and other inactive ingredients. The following coloring agents are employed: 1 mg — FD&C Blue No. 1, D&C Red No. 28, FD&C Red No. 40, FD&C Yellow No. 6; 2 mg — FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6, D&C Yellow No. 10; 5 mg — FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6; 10 mg — FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No. 6.

Tibolone Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
0.30	1	Tibolone (Org GD 14)	0.30
1.95	2	Hydroxypropyl Cellulose	1.95
32.50	3	Cornstarch	32.50
0.32	4	Magnesium Stearate	0.32
QS	5	Lactose, QS to	130.00
QS	6	Water Purified	QS

MANUFACTURING DIRECTIONS

1. Charge in a mixer Items 3 and 5 and mix well.
2. Prepare a suspension of Items 1 and 2 in Item 6 and mix thoroughly; add to Step 1 and granulate in a granulator by mixing for 2–3 min.
3. Dry the sieved wet material for 4 h in a vacuum dryer at 40°C.
4. Screen the dried granules through a 710-μm sieve in the drum.
5. Load the empty capsule shells (size 1) in the hopper.
6. Run the machine and check the locking of shells.
7. Fill 130 mg in suitable capsules.

Tiotropium Inhalation Powder

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
21.70	1	Tiotropium Bromide Micronized	21.70
270.00	2	Endothelin Antagonist 2	270.00
4708.30	3	Lactose	4708.30

MANUFACTURING DIRECTIONS

1. Item 1 should first be prepared in an inhalable powder form by the following method:
   a. 15.0 kg of tiotropium bromide are placed in 25.7 kg of water in a suitable reaction vessel.
   b. The mixture is heated to 80–90°C and stirred at constant temperature until a clear solution is formed.
   c. Activated charcoal (0.8 kg) moistened with water is suspended in 4.4 kg of water. This mixture is added to the solution containing the tiotropium bromide and the resulting mixture is rinsed with 4.3 kg of water.
   d. The mixture thus obtained is stirred for at least 15 min at 80–90°C. Then, it is filtered through a heated filter into an apparatus preheated to an external temperature of 70°C.
   e. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled at 3–5°C for every 20 min to a temperature of 20–25°C.
   f. The apparatus is cooled further to 10–15°C using cold water and crystallization is completed by stirring for at least another hour.
   g. The crystals are isolated using a suction filter dryer. The crystals are washed with cold water (10–15°C) and cold acetone (10–15°C).
   h. The crystals obtained are dried at 25°C in a nitrogen current over a period of 2 h. Yield: 13.4 μg of tiotropium bromide monohydrate (86% of theory).
2. Add and mix all items and mix well.
3. Fill 5.00 g per unit dose.

Tolmetin Sodium Capsules

Capsules for oral administration contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium and the following inactive ingredients: gelatin, magnesium stearate, cornstarch, talc, FD&C Red No. 3, FD&C Yellow No. 6, and titanium dioxide.

Tolterodine Capsules

The capsules contain tolterodine tartrate, a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-*N*,*N*-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. Capsules contain 2 mg or 4 mg of tolterodine tartrate. The inactive ingredients are: sucrose, starch, hydroxypropyl methylcellulose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, and FD&C Blue No. 2. The 2-mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac, titanium dioxide, propylene glycol, and simethicone.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
2.00	1	Tolterodine	2.00
186.00	2	Lactose Anhydrous	186.00
20.00	3	Cornstarch	20.00
15.00	4	Talc	15.00
2.00	5	Magnesium Stearate	2.00

Note: For 1-mg strength, adjust with Item 2.

MANUFACTURING DIRECTIONS

1. Item 1 is accordingly mixed with Items 2 and 3 and then milled.
2. The resulting mixture is then mixed with ingredients 4 and 5 and then filled into capsules of appropriate size.

Topiramate Capsules

Topiramate is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic drug. Topiramate capsules, Sprinkle capsules are available as 15 mg and 25 mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food. Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/ml. Its saturated solution has a pH of 6.3. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-(beta)-D-fructopyranose sulfamate. Sprinkle capsules contain topiramate coated beads in a hard gelatin capsule. The inactive ingredients are: sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

Tretinoin Capsules

Tretinoin is a retinoid that induces maturation of acute promyelocytic leukemia (APL) cells in culture. It is available in a 10-mg soft gelatin capsule for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils, and soybean oil. The gelatin capsule shell contains glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben, and propylparaben.

Triamterene and Hydrochlorothiazide Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
23.01	1	Triamterene	23.01
15.34	2	Hydrochlorothiazide	15.34
2.50	3	Glycine	2.50
7.50	4	Polysorbate 80	7.50
QS	5	Water Purified	QS
QS	6	Isopropyl Alcohol	QS
52.15	7	Lactic Acid	52.15

MANUFACTURING DIRECTIONS

1. Add and dissolve Item 3 in a suitable quantity of Item 5.
2. Add Items 1 and 2, and prepare a good wet mass.
3. Separately dissolve Item 4 in Item 6, and add to Step 2 until granules are formed.
4. Dry granules in vacuum and mill.
5. Fill in size 4 capsules.

Triamterene Capsules

Triamterene is a potassium-sparing diuretic. Triamterene is 2,4,7-triamino-6-phenyl-pteridine. Each capsule for oral use, with an opaque red cap and body, contains triamterene, 50 or 100 mg. The inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C Red No. 33, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, titanium dioxide, and trace amounts of other inactive ingredients.

Triclosan and Zinc Undecylenate Powder

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/1000 Tabs (g)**
3.0	1	Triclosan-Irgasan DP300	3.0
2.0	2	Zinc Undecylenate	2.0
0.2	3	Menthol	0.2
926.8	4	Talc	926.8
30.0	5	Magnesium Stearate	30.0
30.0	6	Cornstarch	30.0
8.0	7	Perfume	8.0

MANUFACTURING DIRECTIONS

1. Pass the following ingredients through a 250-μm aperture screen or similar screen: Triclosan-Irgasan DP300, zinc undecylenate, magnesium stearate, cornstarch, menthol, and approximately 10% of the total amount of talc.
2. Charge materials from first step into a suitable mixer. Mix until uniform.
3. Discharge powder from second step into another suitable mixer. Add and disperse perfume. Mix until uniform. Pass mixture from step above through a 250-μm aperture screen or similar screen. Charge mixture from Step 2 into a V-mixer or a similar mixer, and add balance of talc powder.
4. Mix for 30 min or until homogeneous.

Trientine Hydrochloride Capsules

Trientine hydrochloride is *N,N′*-bis (2-aminoethyl)-1,2-ethanediamine dihydrochloride. Trientine hydrochloride is a chelating compound for removal of excess copper from the body. It is available as 250-mg capsules for oral administration. It contains gelatin, iron oxides, stearic acid, and titanium dioxide as inactive ingredients.

Trimethoprim and Sulfamethoxazole Oral Suspension

Trimethoprim and sulfamethoxazole is a synthetic antibacterial combination product available in DS (double strength) pediatric suspension for oral administration. Each teaspoonful (5 ml) of the pediatric suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole in a vehicle containing 0.3% alcohol, edetate disodium, glycerin, microcrystalline cellulose, parabens (methyl and propyl), polysorbate 80, saccharin sodium, simethicone, sorbitol, sucrose, FD&C Yellow No. 6, FD&C Red No. 40, flavors, and water.

Trimipramine Maleate Capsules

Trimipramine maleate is 5-(3-dimethylamino-2-methylpropyl)-10,11-dihydro-5H-dibenz(b,f) azepine acid maleate (racemic form). Each capsule contains trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C Blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25 mg dosage strength also contains D&C Yellow No. 10 and FD&C Yellow No. 6; the 50 mg dosage strength also contains D&C Red No. 28, FD&C Red No. 40, and FD&C Yellow No. 6.

Troleandomycin Capsules

Troleandomycin is a synthetically derived acetylated ester of oleandomycin, an antibiotic elaborated by a species of *Streptomyces antibioticus.* It is a white crystalline compound, insoluble in water, but readily soluble and stable in the presence of gastric juice. Inert ingredients in the formulation are: hard gelatin capsules (which may contain inert ingredients); lactose; magnesium stearate; sodium lauryl sulfate; and starch.

Typhoid Vaccine Live Oral Capsules

Typhoid vaccine live oral Ty21a is a live attenuated vaccine for oral administration only. The vaccine contains the attenuated strain *Salmonella typhi* Ty21a (1,2). The vaccine is manufactured by the Swiss Serum and Vaccine Institute. The vaccine strain is grown in fermenters under controlled conditions in medium containing a digest of yeast extract, an acid digest of casein, dextrose, and galactose. The bacteria are collected by centrifugation, mixed with a stabilizer containing sucrose, ascorbic and amino acids, and lyophilized. The lyophilized bacteria are mixed with lactose and magnesium stearate and filled into gelatin capsules, which are coated with an organic solution to render them resistant to dissolution in stomach acid. The enteric-coated, salmon/white capsules are then packaged in 4-capsule blisters for distribution. The contents of each enteric-coated capsule are:

Viable *S. typhi* Ty21a	2–6 H 10^9 colony-forming units[a]
Nonviable *S. typhi* Ty21a	5–50 H 10^9 bacterial cells
Sucrose	26–130 mg
Ascorbic acid	1–5 mg
Amino acid mixture	1.4–7 mg
Lactose	100–180 mg
Magnesium stearate	3.6–4.4 mg

[a] Vaccine potency (viable cell counts per capsule) is determined by inoculation of agar plates with appropriate dilutions of the vaccine suspended in physiological saline.

Valsartan and Hydrochlorothiazide Capsules

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
80.00	1	Valsartan	80.00
12.50	2	Hydrochlorothiazide	12.50
1.50	3	Colloidal Anhydrous Silica Aerosil	1.50
31.50	4	Microcrystalline Cellulose Avicel	31.50
20.00	5	Polyvinylpyrrolidone Crospovidone	20.00
4.50	6	Magnesium Stearate	4.50

MANUFACTURING DIRECTIONS

1. The components, except for a portion of the magnesium stearate, are blended in a container mixer.
2. The blended material is sieved and preblended for an additional time period in a container mixer. The blended material is compacted using a roller compactor by applying a compaction force of 25–65 kN and a roller speed of 1.3–7.5 rpm.
3. The compacted material is sieved again and the remaining portion of the magnesium stearate is added and finally blended in a container mixer.
4. Then, 150 mg of the homogeneous mixture is filled in capsules, or compressed for tablets and subsequent coating.

Valsartan Capsules

Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT 1 receptor subtype. It is chemically described as *N*-(1-oxopentyl)-*N*-[[2'-(1 *H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine. It is available as capsules for oral administration, containing either 80 mg or 160 mg of valsartan. The inactive ingredients contained in the capsules are: cellulose compounds, crospovidone, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
80.00	1	Valsartan	80.00
1.50	2	Colloidal Anhydrous Silica Aerosil	1.50
31.50	3	Microcrystalline Cellulose Avicel	31.50
20.00	4	Polyvinylpyrrolidone Crospovidone	20.00
4.50	5	Magnesium Stearate	4.50

MANUFACTURING DIRECTIONS

1. The components, except for a portion of the magnesium stearate, are blended in a container mixer.
2. The blended material is sieved and preblended for an additional period of time in a container mixer. The blended material is compacted using a roller compactor by applying a compaction force of 25–65 kN and a roller speed of 1.3–7.5 rpm.
3. The compacted material is sieved again, and the remaining portion of the magnesium stearate is added and finally blended in a container mixer.
4. Then, 138.50 mg of the homogeneous mixture is filled in capsules or compressed for tablets and subsequent coating.

Vancomycin Hydrochloride Capsules

Vancomycin hydrochloride capsules contain chromatographically purified vancomycin hydrochloride, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). 500 mg of the base is equivalent to 0.34 mmol. Each capsule contains vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The Pulvules also contain FD&C Blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.

Verapamil Hydrochloride Capsules

Verapamil is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). It is available for oral administration as a 360-mg hard gelatin capsule (lavender cap/yellow body), a 240-mg hard gelatin capsule (dark blue cap/yellow body), a 180-mg hard gelatin capsule (light gray cap/yellow body), and a 120-mg hard gelatin capsule (yellow cap/yellow body). These pellet-filled capsules provide a sustained release of the drug in the gastrointestinal tract. In addition to verapamil HCl, the capsule contains the following inactive ingredients: fumaric acid, talc, sugar spheres, povidone, shellac, gelatin, FD&C Red No. 40, yellow iron oxide, titanium dioxide, methylparaben, propylparaben, silicon dioxide, and sodium lauryl sulfate. In addition, the 240-mg and 360-mg capsules contain FD&C Blue No. 1 and D&C Red No. 28; and the 180-mg capsule contains black iron oxide.

MANUFACTURING DIRECTIONS

1. Verapamil hydrochloride (30 kg), malic acid (10 kg), and talc (2.4 kg) are blended and passed through a No. 100 mesh screen, using a conventional milling machine.
2. A polymer suspension is prepared containing 5% hydroxypropyl methylcellulose in methanol/methylene chloride 60/40.
3. Sugar/starch seeds (0.4–0.5 mm) (9 kg) are placed in a standard coating pan and rotation commenced.
4. The seeds are wetted with sufficient polymer suspension to dampen them thoroughly and then an amount of the powder blend is dusted on until no more adhered. This step is repeated until all the powder blend has been applied.
5. The coated seeds are allowed to dry after each application of polymer suspension.
6. When all of the powder has been applied, the coated seeds are dried at 40–60°C until all of the solvent has been driven off.
7. A membrane suspension is prepared from the following components: 2 parts by volume 5% hydroxypropyl methylcellulose in methanol/methylene chloride 60/40; 8 parts by volume 5% ethylcellulose in methanol/methylene chloride 60/40; and 5 parts by weight talc.
8. The coated seeds, which are prepared previously and which define the active core of the pellets being prepared, are placed in a coating pan and rotation commenced. The membrane suspension is applied to the coated seeds in separate coats, each coat corresponding to 10 ml of the membrane suspension per kg of coated seeds. After each coat had been applied, the pellets are air dried in the coating pan.
9. After the final coat has been applied, the pellets are dried at 40–60°C to evaporate all traces of solvent. Rapid release pellets as used in the controlled absorption pharmaceutical formulation of the invention are prepared by forming active cores without the subsequent application of a membrane thereto.

Verapamil Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
120.00	1	Verapamil Hydrochloride	120.00
20.00	2	Sucrose and Cornstarch Neutral Microgranules	20.00
11.30	3	Shellac, Bleached, Wax-Free	11.30
0.75	4	Eudragit L100	0.75
3.60	5	Eudragit L30D	3.60
1.23	6	Eudrafit NE30D	1.23
0.37	7	Diethyl phthalate	0.37
1.60	8	Talc	1.60
—	9	Alcohol	QS
—	10	Acetone	QS
—	11	Water Purified	QS

Note: For 240-mg strength, scale to twice the formula.

MANUFACTURING DIRECTIONS

1. The neutral microgranules (Item 2) are placed in a coating pan and pan started.
2. Prepare a 20% solution of Item 3 in a mixture of acetone and alcohol.
3. Set temperature of Step 1 to 25 ± 5°C. Apply shellac solution, alternating with Item 1 powder until all the active ingredient is incorporated.
4. Sieve microgranules through a 0.85-mm aperture. Dry microgranules at 30–40°C for 8 h.
5. Sieve dried microgranules and dry again at 30–40°C for 8 h.
6. Prepare a 15% alcoholic solution of Eudragit L100, and apply with talc; dry and apply until all solution is incorporated.
7. Sieve microgranules using a 1.18-mm aperture sieve.
8. Prepare an aqueous dispersion of Item 5 (L30D) and Item 7. Apply part of suspension to microgranules together with part of Item 8. Allow to dry. Repeat operation until desired dissolution rate is obtained.
9. Sieve microgranules using 1.18-mm sieve and then dry at 30–40°C for 12 h.
10. Prepare aqueous solution of NE30D and Item 7, apply in parts with remaining talc, and then dry. Repeat until desired dissolution rate is obtained.
11. Sieve using a 1.18-mm sieve. Dry at 30–40°C for 12 h.
12. Fill appropriate quantity based on assay. Use approximately 158.85 mg for 120-mg strength and 317.70 mg for 240-mg strength.

Vincamine Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
30.00	1	Vincamine	30.00
17.50	2	Lactose	17.50
166.80	3	Sucrose and Cornstarch Microgranules, Size 20	166.80
3.30	4	Polyvinyl Pyrrolidone	3.30
1.30	5	Shellac	1.30
3.60	6	Eudragit L	3.60
7.50	7	Talc	7.50
—	8	Alcohol	QS

MANUFACTURING DIRECTIONS

1. Charge Item 3 in a coating pan and run the pan.
2. Prepare solution of Item 4 in Item 8.
3. Add and mix Items 1 and 2 in a separate container.
4. Heat Step 1 to 25 ± 5°C; apply solution in Step 2, and alternate with powder mixture in Step 3 until all of Step 3 is incorporated.
5. Sieve granules through a 1.18-mm sieve in Step 4, and dry at 30–40°C for 8 h.
6. Prepare an alcoholic solution of Item 5 in Item 8, and apply to Step 5 until all incorporated.
7. Sieve microgranules through a 1.18-mm sieve and dry at 30–40°C for 8 h.
8. Prepare a solution of Item 6 in Item 8 and apply in steps until all solution is incorporated.
9. Sieve microgranules through a 1.18-mm sieve and dry at 30–40°C for 8 h.
10. Fill appropriate quantity in capsules; approximately 230 mg.

Vinpocetine Multiple Bead Capsules

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
160.00	1	Vinpocetine	160.00
		Powder Blend	
5.00	1	Vinpocetine	5.00
0.10	2	Sodium Lauryl Sulfate	0.10
3.0	3	Sodium Starch Glycolate	3.00
6.00	4	Glutamic Acid	6.00
7.00	5	Cornstarch	7.00
62.00	6	Lactose	62.00
13.00	7	Microcrystalline Cellulose	13.00
1.00	8	Magnesium Stearate	1.00
		pH Sensitive Coated Spheroid	
		Uncoated Spheroids (10% w/w Vinpocetine)	3.00 kg
		Methacrylic Acid Copolymer Type B Eudragit S	0.75 kg
		Triacetin	0.112 kg
		Isopropyl Alcohol	1.64 kg
		Methylene Chloride	1.99 kg
		Water	0.50 kg
		Coated Spheroids	
		Uncoated Spheroid (24% w/w Vinpocetine)	3.00 kg
		Hydroxypropyl Methylcellulose 2910, 4000 cps	0.075 kg
		Methylene Chloride	4.98 kg
		Methanol Anhydrous	2.96 kg
		Eudragit E30D Aqueous Dispersion	1.00 kg
		Calcium Stearate	0.03 kg
		Simethicone Emulsion	0.0025 kg
		Water Purified	0.50 kg

MANUFACTURING DIRECTIONS

1. Vinpocetine hydrochloride (10.0 kg), microcrystalline cellulose (Avicel-PH-101) (80.0 kg), and citric acid monohydrate (10.0 kg) are blended together in a 450-l planetary mixer. Water (100 kg) is added, and the mixer is run for 10 min until a homogeneous plastic mass is obtained. The mass is extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1 mm in diameter.
2. The damp extrudates (in batches of 15–20 kg) are placed in a spheronizer in which the rotating disc (diameter 68 cm) rotated at 300–400 rpm. The rotation is continued for 20 min, and the resulting spheroids are then dried at 80°C in a fluidized-bed drier. The dried spheroids are passed over a 1.2-mm. screen, and those that passed through are subjected to a 0.5-mm screen. The over- and undersized spheroids are discarded.
3. The finished dosage form consists of a hard gelatin capsule containing a powder blend of vinpocetine and two types of spheroids. The formulation particulars are based on 30 mg per capsule, although they can be designed to provide other dosage strengths.
4. The vinpocetine powder blend (or first group of spheroids) provides the loading dose, (e.g., 5 mg of vinpocetine).
   a. Blend the vinpocetine, lactose microcrystalline cellulose, starch, glutamic acid, sodium starch glycolate, talc triturate, and the sodium lauryl sulfate into the PK® blender for 20 min with intensifier bar running.
   b. Pass the Step 1 blend through a Fitz mill using a No. 1B screen, medium speed, knives forward.
   c. Return the granulation from Step 2 to the PK blender and add the magnesium stearate and blend for 2 min without the intensifier bar on.

5. The second and third types of spheroids are categorized as:
   a. pH sensitive coated spheroids to provide a second dose (pH > 6.5) (e.g., 12 mg vinpocetine). Uncoated spheroids are placed in a fluidized-bed coater. The Eudragit S solution is applied using a peristaltic pump. The spheroids are dried.
   b. Coated spheroids to provide a third dose (4–10 h post-ingestion) (e.g., 13 mg vinpocetine). Process for applying undercoat: The uncoated spheroids are placed in a fluidized-bed coater). Methocel E4MP solution is sprayed using a peristaltic pump. The spheroids are dried. Process for applying overcoat: Eudragit E30D suspension containing calcium stearate is sprayed on the methocel E4MP-coated spheroids using a peristaltic pump. The spheroids are dried.
6. Capsules are filled with the powder blend, pH sensitive coated spheroids, and coated spheroids on an encapsulating machine capable of dual filling powders and spheroids.

Vitamin B-Complex, Amino Acids, and Magnesium Effervescent Granules (Sugar-Free)

Bill of Materials

Scale (mg/Tab)	Item	Material Name	Qty/1000 Tabs (g)
2.00	1	Thiamin Hydrochloride	2.00
2.00	2	Pyridoxine Hydrochloride	2.00
5.00	3	Cyanocobalamin Dry Powder 0.1%	5.00
20.00	4	L-Glutamine	20.00
10.00	5	Inositol	10.00
10.00	6	Potassium L-Aspartate	10.00
500.00	7	DL-Carnitine Hydrochloride	500.00
350.00	8	Magnesium L-Aspartate	350.00
600.00	9	Citric acid, Anhydrous	600.00
500.00	10	Sodium Bicarbonate	500.00
QS	11	Flavors	QS
50.00	12	Kollidon VA 64	50.00
—	13	Isopropanol	80.00

MANUFACTURING DIRECTIONS

1. Mix Items 1–6, add the mixture of Items 7–12, granulate mixture of these two combinations with Item 13, pass through a 0.8-mm sieve, dry well, and mix.
2. Fill 2.1 g of the granules in sachets.

Vitamin B-Complex and Vitamin C Instant Granules

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
3.60	1	Thiamine Hydrochloride	3.60
5.70	2	Riboflavin Phosphate Sodium	5.70
45.00	3	Nicotinamide	45.00
4.50	4	Pyridoxine Hydrochloride	4.50
15.00	5	Cyanocobalamin, Gelatin Coated 0.1%	15.00
150.00	6	Ascorbic Acid, Powder	150.00
723.00	7	Sucrose	723.00
51.00	8	Kollidon 30	51.00
QS	9	Ethanol	180 ml

MANUFACTURING DIRECTIONS

1. Mix Items 1–7, granulate with solution of Items 8 and 9, dry, and pass through a 0.8-mm sieve.
2. Fill 1 g of the granules in sachets, which corresponds to two daily vitamin B and vitamin C requirements of adults.

Vitamin C and Calcium Carbonate Effervescent Tablets

Bill of Materials			
Scale (mg/Tab)	**Item**	**Material Name**	**Qty/1000 Tabs (g)**
300.00	1	Calcium, USE Calcium Carbonate	315.00
450.00	2	Sodium Tartaric Acid, Powder Bicarbonate	450.00
600.00	3	Kollidon 30	600.00
35.00	4	Kollidon 30	35.00
200.00	5	Isopropanol	200.00
400.00	6	Sucrose Crystalline	400.00
500.00	7	Ascorbic Acid, Crystalline, with Excess	550.00
120.00	8	Kollidon CL	120.00
60.00	9	Polyethylene Glycol 6000, Powder	60.00

MANUFACTURING DIRECTIONS

1. Granulate mixture of Items 1–3 with solution of Items 4 and 5, mix with Item 6, and dry.
2. Add Items 7–9 and press with a high compression force at maximum 30% of relative atmospheric humidity.
3. Compress 2500 mg in 20 mm biplanar punches.

Zanamivir Powder

The chemical name of zanamivir is 5-(acetylamino)-4-[(aminoimino-methyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid. It is for administration to the respiratory tract by oral inhalation only. Each disc contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose. The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER®.

Bill of Materials			
Scale (mg/Disk)	**Item**	**Material Name**	**Qty/1000 Disks (g)**
5.00	1	Zanamivir	5.00
20.00	2	Lactose Anhydrous	20.00

The drug is also administered as aqueous solution (10%) with 0.04% benzalkonium chloride and 0.40% phenylethyl alcohol. In an aqueous cosolvent system, it contains 10% active drug, 0.04% benzalkonium chloride, 10% PEG 400, and 30% propylene glycol (balance purified water). In an aerosol formulation, there is 7.5% active drug, 25.6% propellant 11, and 66.5% propellant 12.

Zidovudine Capsules

Zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analog active against HIV. Each capsule contains 100 mg of zidovudine and the inactive ingredients cornstarch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C Blue No. 2.

Bill of Materials			
Scale (mg/Cap)	**Item**	**Material Name**	**Qty/1000 Caps (g)**
100.00	1	Zidovudine (3′-Azido-3′-Deoxythymidine)	100.00
200.00	2	Lactose	200.00
50.00	3	Cornstarch	50.00
5.00	4	Polyvinylpyrrolidone	5.00
4.00	5	Magnesium Stearate	4.00

MANUFACTURING DIRECTIONS

1. Sieve Items 1–4 through 80-mesh sieve and blend.
2. Pass Item 5 through a 100-mesh sieve, and add to Step 1 and blend for 2 min.
3. Fill 359 mg in capsules.

Zinc Oxide and Cornstarch Powder

Cornstarch baby powder combines zinc oxide (10%) with topical starch (cornstarch) for topical application. Also contains: fragrance and tribasic calcium phosphate.

Ziprasidone Hydrochloride Capsules

Ziprasidone hydrochloride is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1, 2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2 *H*-indol-2-one. Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2 *H*-indol-2-one, monohydrochloride, monohydrate. Capsules are supplied for oral administration in 20 mg, 40 mg, 60 mg, and 80 mg doses. Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Ziprasidone, USE Ziprasidone Hydrochloride	22.65
66.10	2	Lactose Monohydrate	66.10
10.00	3	Pregelatinized Cornstarch	10.00
0.75	4	Magnesium Stearate	0.75

MANUFACTURING DIRECTIONS

1. Pass Items 1–3 through 80-mesh screen and blend.
2. Pass Item 4 through 100-mesh screen, and add and blend for 2 min.
3. Fill in size 4 capsules (100 mg). For higher strengths, scale up the quantity and size of capsule. The lactose monohydrate weight is adjusted according to small potency changes in the ziprasidone hydrochloride monohydrate in order to maintain a constant capsule weight.

Zonisamide Capsules

Zonisamide is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents. The active ingredient is zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. It is supplied for oral administration as capsules containing 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

Bill of Materials

Scale (mg/Cap)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Zonisamide	100.00
35.00	2	Lactose Anhydrous	35.00
17.00	3	Cornstarch	17.00
40.00	4	Crystalline Cellulose	40.00
6.00	5	Hydroxypropyl Cellulose	6.00
1.00	6	Light Anhydrous Silicic Acid	1.00
1.00	7	Magnesium Stearate	1.00
QS	8	Water Purified	QS

MANUFACTURING DIRECTIONS

1. Among the preceding components, zoniamide, lactose, cornstarch, and crystalline cellulose are blended, and thereto is added hydroxypropyl cellulose being dissolved in water. The mixture is kneaded, dried, and granulated.
2. To these granules are added magnesium stearate and light anhydrous silicic acid, and the mixture is filled (200 mg) in each capsule.
3. A 20% powder formulation contains:

   Zonisamide, 200 g
   Lactose, 719 g
   Hydroxypropyl cellulose, 20 g
   Light anydrous silicic acid, 1 g
   Total, 940 g
4. Using a high-shear granulator, all the preceding components for powder formulation are blended, sprayed with an ethanolic solution (200 g) containing ethylcellulose (40 g) and hydroxypropyl cellulose (20 g) for granulation, and are then made into granules. These are dried and regulated in size to give 20% powders.