PHARMACEUTICALS

1. Introduction

Pharmaceuticals are best viewed as drug-containing products in dosage forms. These forms are designed and manufactured to deliver safe and effective therapeutic responses each time administered within appropriate regimens and even after storage under well-documented conditions in scientifically designed packaging for designated time periods (see PACKAGING, COSMETICS AND PHARMACEUTICALS). Thus, pharmaceuticals are actual drug delivery systems (qv). Pharmacokinetic and pharmacodynamic principles that influence the delivery of a drug from the pharmaceutical product to the body, routes of drug administration, and modes/technologies used for controlled drug delivery are covered elsewhere (see DRUG DELIVERY SYSTEMS; PHARMACODYNAMICS).

Various technologies are required to produce drug products. Both federal and state laws and regulations exist in the United States to control the manufacture and distribution of pharmaceuticals. The Food and Drug administration exists by the mandate of the U.S. Congress with the Food, Drug & Cosmetics Act (1) as the principal law to enforce. The Act, based on it regulations developed by the Agency, constitutes the basis of the drug approval process (2). The name Food and Drug Administration is relatively new. In 1931 the Food, Drug, and Insecticide Administration, then part of the U.S. Department of Agriculture, was renamed the Food and Drug Administration (3). The U.S. drug distribution system is multifaceted including drug usage within the community and hospitals, under long- or short-term home health care or pharmacy practice. Individual pharmaceuticals are covered elsewhere in the *Encyclopedia*.

2. Chronology of Drug Regulation in the United States

The history of food and drug law enforcement in the United States and the con secutive modifications of the 1906 Act are summarized below (from Ref. 4).

1820 Eleven physicians meet in Washington, DC, to establish the U.S. Pharmacopeia, the first compendium of standard drugs for the United States.

1846 Publication of Lewis Caleb Beck's Adulteration of Various Substances Used in Medicine and the Arts helps document problems in the drug supply.

1848 Drug Importation Act passed by Congress requires U.S. Customs Service inspection to stop entry of adulterated drugs from overseas.

1903 Lyman F. Kebler, M. D., Ph.C., assumes duties as Director of the Drug Laboratory, Bureau of Chemistry.

1905 Samuel Hopkins Adams' 10-part exposé of the patent medicine industry, "The Great American Fraud," begins in Collier's. The American Medical Association, through its Council on Pharmacy and Chemistry, initiates a voluntary program of drug approval that would last until 1955. To earn the right to advertise in AMA and related journals, companies submitted evidence, for review by the Council and outside experts, to support their therapeutic claims for drugs.

1906 The original Food and Drugs Act is passed by Congress on June 30 and signed by President Theodore Roosevelt. It prohibits interstate commerce in

misbranded and adulterated foods and drugs. The Meat Inspection Act is passed the same day. Shocking disclosures of unsanitary conditions in meat-packing plants, the use of poisonous preservatives and dyes in foods, and cure-all claims for worthless and dangerous patent medicines were the major problems leading to the enactment of these laws.

1911 In U.S. versus Johnson, the Supreme Court rules that the 1906 Food and Drugs Act does not prohibit false therapeutic claims but only false and misleading statements about the ingredients or identity of a drug.

1912 Congress enacts the Sherley Amendment to overcome the ruling in U.S. versus Johnson. It prohibits labeling medicines with false therapeutic claims intended to defraud the purchaser, a standard difficult to prove.

1914 The Harrison Narcotic Act imposes upper limits on the amount of opium, opium-derived products, and cocaine allowed in products available to the public; requires prescriptions for products exceeding the allowable limit of narcotics; and mandates increased record keeping for physicians and pharmacists that dispense narcotics. A separate law dealing with marihuana would be enacted in 1937.

1933 FDA recommends a complete revision of the obsolete 1906 Food and Drugs Act. The first bill is introduced into the Senate, launching a 5-year legislative battle. FDA assembles a graphic display of shortcomings in pharmaceutical and other regulation under the 1906 act, dubbed by one reporter as the Chamber of Horrors and exhibited nationwide to help draw support for a new law.

1937 Elixir Sulfanilamide, containing the poisonous solvent diethylene glycol, kills 107 persons, many of whom are children, dramatizing the need to establish drug safety before marketing and to enact the pending food and drug law.

1938 The Federal Food, Drug, and Cosmetic Act of 1938 is passed by Congress, containing new provisions:

Requiring new drugs to be shown safe before marketing; starting a new system of drug regulation.

Eliminating the Sherley Amendment requirement to prove intent to defraud in drug misbranding cases.

Extending control to cosmetics and therapeutic devices.

Providing that safe tolerances be set for unavoidable poisonous substances.

Authorizing standards of identity, quality, and fill-of-container for foods.

Authorizing factory inspections.

Adding the remedy of court injunctions to the previous penalties of seizures and prosecutions.

Under the Wheeler-Lea Act, the Federal Trade Commission is charged to oversee advertising associated with products, including pharmaceuticals, otherwise regulated by FDA.

FDA promulgates the policy in August that sulfanilamide and selected other dangerous drugs must be administered under the direction of a qualified expert, thus launching the requirement for prescription only (non-narcotic) drugs.

1941 Insulin Amendment requires FDA to test and certify purity and potency of this life-saving drug for diabetes.

Nearly 300 deaths and injuries result from distribution of sulfathiazole tablets tainted with the sedative phenobarbital. The incident prompts FDA to revise manufacturing and quality controls drastically, the beginning of what would later be called good manufacturing practices (GMPs).

1945 Penicillin Amendment requires FDA testing and certification of safety and effectiveness of all penicillin products. Later amendments would extend this requirement to all antibiotics. In 1983 such control would be found no longer needed and was abolished.

1948 Supreme Court rules in U.S. versus Sullivan that FDA's jurisdiction extends to the retail distribution, thereby permitting FDA to interdict in pharmacies illegal sales of drugs—the most problematical being barbiturates and amphetamines.

1951 Durham-Humphrey Amendment defines the kinds of drugs that cannot be used safely without medical supervision and restricts their sale to prescription by a licensed practitioner.

1952 In U.S. versus Cardiff, the Supreme Court rules that the factory inspection provision of the 1938 FDC Act is too vague to be enforced as criminal law.

A nationwide investigation by FDA reveals that chloramphenicol, a broad-spectrum antibiotic, has caused nearly 180 cases of often fatal blood diseases. Two years later, the FDA would engage the American Society of Hospital Pharmacists, the American Association of Medical Record Librarians, and later the American Medical Association in a voluntary program of drug reaction reporting.

1953 Factory Inspection Amendment clarifies previous law and requires FDA to give manufacturers written reports of conditions observed during inspections and analyses of factory samples.

1955 HEW Secretary Olveta Culp Hobby appoints a committee of 14 citizens to study the adequacy of FDA's facilities and programs. The committee recommends a substantial expansion of FDA staff and facilities, a new headquarters building, and more use of educational and informational programs.

1962 Thalidomide, a new sleeping pill, is found to have caused birth defects in thousands of babies born in western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouse public support for stronger drug regulation.

Kefauver-Harris Drug Amendments are passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers are required to prove to the FDA the effectiveness of their products before marketing them. In addition, the FDA is given closer control over investigational drug studies, FDA inspectors are granted access to additional company records, and manufacturers must demonstrate the efficacy of products approved before 1962.

1963 Advisory Committee on Investigational Drugs meets, the first meeting of a committee to advise FDA on product approval and policy on an ongoing basis.

1965 Drug Abuse Control Amendments are enacted to deal with problems caused by abuse of depressants, stimulants, and hallucinogens.

1966 FDA contracts with the National Academy of Sciences/National Research Council to evaluate the effectiveness of 4000 drugs approved on the basis of safety alone between 1938 and 1962.

1968 FDA Bureau of Drug Abuse Control and the Treasury Department's Bureau of Narcotics are transferred to the Department of Justice to form the Bureau of Narcotics and Dangerous Drugs (BNDD), consolidating efforts to police traffic in abused drugs. A reorganization of BNDD in 1973 formed the Drug Enforcement Administration.

The FDA forms the Drug Efficacy Study Implementation (DESI) to incorporate the recommendations of a National Academy of Sciences investigation of effectiveness of drugs marketed between 1938 and 1962.

Animal Drug Amendments place all regulation of new animal drugs under one section of the Food, Drug, and Cosmetic Act—Section 512—making approval of animal drugs and medicated feeds more efficient.

1970 In Upjohn versus Finch, the Court of Appeals upholds enforcement of the 1962 drug effectiveness amendments by ruling that commercial success alone does not constitute substantial evidence of drug safety and efficacy.

The FDA requires the first patient package insert: oral contraceptives must contain information for the patient about specific risks and benefits.

The Comprehensive Drug Abuse Prevention and Control Act replaces previous laws and categorizes drugs based on abuse and addiction potential vis-à-vis therapeutic value.

1972 Over-the-Counter Drug Review initiated to enhance the safety, effectiveness, and appropriate labeling of drugs sold without prescription.

1973 The U. S. Supreme Court upholds the 1962 drug effectiveness law and endorses FDA action to control entire classes of products by regulations rather than to rely only on time-consuming litigation.

1976 Vitamins and Minerals Amendments ("Proxmire Amendments") stop the FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs based solely on potency.

1982 Tamper-resistant packaging regulations issued by the FDA to prevent poisonings such as deaths from cyanide placed in Tylenol capsules. The Federal Anti-Tampering Act passed in 1983 makes it a crime to tamper with packaged consumer products.

1983 Orphan Drug Act passed, enabling FDA to promote research and marketing of drugs needed for treating rare diseases.

1984 Drug Price Competition and Patent Term Restoration expedites the availability of less costly generic drugs by permitting the FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective.

At the same time, the brand-name companies can apply for up to 5 years of additional patent protection for the new medicines they developed to

make up for time lost while their products were going through the FDA's approval process.

1987 The FDA revises investigational drug regulations to expand access to experimental drugs for patients with serious diseases with no alternative therapies.

1988 The Prescription Drug Marketing Act bans the diversion of prescription drugs from legitimate commercial channels. Congress finds that the resale of such drugs leads to the distribution of mislabeled, adulterated, subpotent, and counterfeit drugs to the public. The new law requires drug wholesalers to be licensed by the states; restricts reimportation from other countries; and bans sale, trade, or purchase of drug samples and traffic or counterfeiting of redeemable drug coupons.

1991 The FDA publishes regulations to accelerate reviews of drugs for life-threatening diseases.

1992 Generic Drug Enforcement Act imposes debarment and other penalties for illegal acts involving abbreviated drug applications.

Prescription Drug User Fee requires drug and biologics manufacturers to pay fees for product applications and supplements and other services. The act also requires the FDA to use these funds to hire more reviewers to assess applications.

1994 The FDA announces it could consider regulating nicotine in cigarettes as a drug, in response to a citizen's petition by the Coalition on Smoking and Health.

Uruguay Round Agreements Act extends the patent terms of U.S. drugs from 17 to 20 years.

1995 The FDA declares cigarettes to be "drug delivery devices." Restrictions are proposed on marketing and sales to reduce smoking by young people.

1997 Food and Drug Administration Modernization Act (FDAMA) reauthorizes the Prescription Drug User Fee Act of 1992 and mandates the most wide-ranging reforms in agency practices since 1938. Provisions include measures to accelerate review of devices, advertising unapproved uses of approved drugs and devices, health claims for foods in agreement with published data by a reputable public health source, and development of good guidance practices for agency decision-making. The fast track provisions are intended to speed up the development and the approval review process for ... "drug intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition."

3. FDA Basic Structure

Employing over 9000 employees, the FDA's structure reflects the tasks on hand and consists of a number of centers and offices.

Center for Biologics Evaluation and Research (CBER)

Center for Devices and Radiological Health (CDRH)

Center for Drug Evaluation and Research (CDER)
Center for Food Safety and Applied Nutrition (CFSAN)
Center for Veterinary Medicine (CVM)
National Center for Toxicological Research (NCTR)
Office of the Commissioner (OC)
Office of Regulatory Affairs (ORA)

As an agency of the U.S. Government, the FDA does not develop, manufacture, or test drugs. Drug approval is entirely based on sponsor's (manufacturer's) reports of a drug's studies so that the appropriate Center can evaluate its data. The evaluation of submitted data allows the Center reviewers (*1*) to establish whether the drug submitted for approval works for the proposed use, (*2*) to assess the benefit-to-risk relationship, and (*3*) to determine if the drug will be approved. The approval of low molecular weight molecular entities rests within the CDER authority (5) and is the subject of this chapter. An analogous center CBER regulates biological products like blood, vaccines, therapeutics, and related drugs and devices (6). The reader interested in other centers or aspects of FDA activities is advised to visit appropriate sites. In general outline, the drug approval process is divided into an Investigational New Drug (IND) Application Process (with its phases representing a logical and safe process of drug development); New Drug Approval, and the post-approval activities. For as long as an approved drug remains on the market, all aspects pertinent to its safety are under constant scrutiny by the FDA.

4. IND Application Process

The tests carried out in the pre-clinical investigation of a potential drug serve the purpose to determine whether the new molecule has the desired pharmacological activity and is reasonably safe to be administered to humans in limited, early-stage clinical studies. Before any new drug under pre-clinical investigation is administered to patients to determine its value as a therapeutic or diagnostic, the drug's sponsor must obtain permission from the FDA through the IND process (7). By definition, a sponsor is a person or entity who assumes responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act (the FDC Act) and related regulations and initiates a clinical investigation. A sponsor could be an individual, partnership, corporation, government agency, manufacturer, or scientific institution. In a way, the IND is an exemption from the legal requirement to transport or distribute across state lines only drugs approved for marketing. Although not approved, the molecule has to conform to specific requirements under the Federal Food, Drug, and Cosmetic Act as interpreted by the Code of Federal Regulations (CFR). The CFR, a codification of the general and permanent regulations published in the Federal Register by the Executive departments and agencies, provides detailed information of requirements for each step of the approval process (8). The Federal Register is the additional important source for information on what regulations FDA proposes and notices issues.

A sponsor wishing to submit an IND is assisted and guided by a number of regulatory mechanisms and documents created to secure the uniformity of applications and to guarantee consistency of the review process. The logical development of information and guidance is as follows: (*1*) from the Federal Food, Drug, and Cosmetic Act to (*2*) the Code of Federal Regulations to (*3*) the use of available guidance documents issued by the CDER/CBER and International Conference on Harmonization (ICH). In their review process the FDA reviewers also depend on Manuals of Policies and Procedures (MAPPs), which constitute approved instructions for internal practices and procedures followed by CDER staff. MAPPs are to help standardize the new drug review process and other activities and are available for the public (9).

4.1. Types of IND. The CFR does not differentiate between the "commercial" and "noncommercial," "research," or "compassionate" IND. The three general "types" of INDs below are often mentioned, but again the nomenclature used is not recognized by 21 CFR 312.3. The term Commercial IND is defined in CDER's MAPP 6030.1 as: "An IND for which the sponsor is usually either a corporate entity or one of the institutes of the National Institutes of Health (NIH). In addition, CDER may designate other INDs as *commercial* if it is clear the sponsor intends the product to be commercialized at a later date" (10). The term Screening IND is defined in CDER's MAPP 6030.4 (11) as "A single IND submitted for the sole purpose of comparing the properties of closely related active moieties to screen for the preferred compounds or formulations. These compounds or formulations can then become the subject of additional clinical development, each under a separate IND."

The same goes for the fast track programs of the FDA originating from the section 112(b) "Expediting Study and Approval of Fast Track Drugs" of the Food and Drug Administration Modernization Act (FDAMA) of 1997. The FDAMA amendments of the Act are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs (fast track products).

An Investigator IND. An investigator is an individual who conducts a clinical investigation or is a responsible leader of a team of investigators. Sponsor is a person who takes responsibility far and initiates a clinical investigation. Sponsor may be a person or an organization, company, university, etc. Sponsor-investigator is a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population. The investigator's name appears on the Investigational New Drug Application forms (Forms FDA 1571 and 1572) as the name of person responsible for monitoring the conduct and progress of clinical investigations.

Emergency Use IND. Emergency Use IND of an investigational new drug (21 CFR 312.36) allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with the Code of Federal Regulations. It is also used for patients who do not meet the criteria of an existing study protocol or if an approved study protocol does not exist.

Treatment IND. Treatment IND (21 CFR 312.34) is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place. An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For example, advanced cases of AIDS, herpes simplex encephalitis, and subarachnoid hemorrhage are all considered to be immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during phase III studies. Treatment INDs also allow FDA to obtain additional data on the drug's safety and effectiveness (12).

4.2. Parallel Track. Another mechanism used to permit wider availability of experimental agents is the "parallel track" policy (Federal Register of May 21, 1990) developed by the U.S. Public Health Service in response to AIDS. Under this policy, patients with AIDS whose condition prevents them from participating in controlled clinical trials can receive investigational drugs shown in preliminary studies to be promising.

4.3. Resources for Preparation of IND Applications. As listed above, to assist in preparation of IND, numerous resources are available on the Web to provide the sponsor with (*1*) the legal requirements of an IND application, (*2*) assistance from CDER/CBER to help meet those requirements, and (*3*) internal IND review principles, policies, and procedures.

Pre-IND Meeting. In addition to all documents available on the Web, under the FDAMA provisions and the resulting guidances (13), a sponsor can request all kinds of meetings with the FDA to facilitate the review and approval process. The pre-IND meetings (21 CFR 312.82) belong to type B meetings and should occur with the division of CDER responsible for the review of given drug therapeutic category within 60 days from when the Agency receives a written request. The list of questions and the information submitted to the Agency in the Information Package should be of sufficient pertinence and quality to permit a productive meeting.

Guidance Documents. Guidance documents representing the Agency's current thinking on a particular subject can be obtained from the Web (14) or from the Office of Training and Communications, Division of Communications Management (15). One should remember that the guidance documents merely provide direction and are not binding on either part. A Guidance for Industry "Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products" (14) is a place to start. This particular Guidance, based on 21CFR 312, provides a detailed clarification of CFR requirements for data and data presentation to be included in the initial phase I IND document, permitting its acceptance by the Agency for review.

Information Submitted with IND. To be acceptable for review by the FDA, the IND application must include the following groups of information.

Animal Pharmacology and Toxicology Studies. Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are the results of any previous experience with the drug in humans (often foreign use).

Manufacturing Information. Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

Clinical Protocols and Investigator Information. Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks needs to be provided. In addition, information on the qualifications of clinical investigators, professionals (generally physicians) who oversee the administration of the experimental compound, to assess whether they are qualified to fulfill their clinical trial duties is needed. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations are also required.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, the FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

4.4. The First Step, the Phase I IND Application. The content of the Phase I IND Application (14) must include the following:

A. FDA Forms 1571 (IND Application) and 1572 (Statement of Investigator)
B. Table of Contents
C. Introductory Statement and General Investigational Plan
D. Investigator's Brochure
E. Protocols
F. Chemistry, Manufacturing, and Control (CMC) Information
G. Pharmacology and Toxicology Information
H. Previous Human Experience with the Investigational Drug
I. Additional and Relevant Information

Ad C. It should succinctly describe what the sponsor attempts to determine by the first human studies. All previous human experience with the drug, other INDs, previous attempts to investigate followed by withdrawal, foreign marketing experience relevant to the safety of the proposed investigation, etc., should be described. Because the detailed development plans are contingent on the results of the initial studies, limited in scope and subject to change, that section should be kept as brief as possible.

Ad D. Before the investigation of a drug by participating clinical investigators may begin, the sponsor should provide them with an Investigator Brochure. The recommended elements of Investigator's Brochure are subject of ICH document ICH E6 (16) and should provide a compilation of the clinical and non-clinical data relevant to the study in human subjects. The brochure should include a brief description of the drug substance, summaries of pharmacological and toxicological effects, pharmacokinetics and biological disposition in animals, and if known, in humans.

Also included should be a summary of known safety and effectiveness in humans from previous clinical studies. Reprints of published studies may be attached. Based on prior experience or on related drugs, the brochure should describe possible risks and side effects and eventual precautions or need of special monitoring.

Ad E. Protocols for phase I studies need not be detailed and may be quite flexible compared with later phases. They should provide the following: (*1*) outline of the investigation, (*2*) estimated number of patients involved, (*3*) description of safety exclusions, (*4*) description of dosing plan, duration, and dose or method of determining the dose, and (*5*) specific detail elements critical to safety. Monitoring of vital signs and blood chemistry and toxicity-based stopping or dose adjustment rules should be specified in detail.

Ad F. Phase I studies are usually conducted with the drug substance of drug discovery origin. It is recognized that the synthetic methods may change and that additional information may be accumulated as the studies and development progress. Nevertheless, the application should provide CMC information sufficient to evaluate the safety of drug substance. The governing principle is that the sponsor should be able to relate the drug product proposed for human studies to the drug product used in animal toxicology studies. At issue is the comparability of the (im)purity profiles. Also addressed should be the issues of stability of the drug product and the polymorphic form of the drug substance as they might change with the change of synthetic methods. The CMC information section to be provided in the phase I application should consist of following sections.

1. CMC Introduction: Should address any potential human risks and the proposed steps to monitor such risks and describe the eventual chemical and manufacturing differences between batches used in animal and proposed for human studies.
2. Drug Substance:
   a. Brief description of the drug substance including some physicochemical characterization and proof of structure.
   b. The name and address of manufacturer.
   c. Brief description of manufacturing process with a flow chart and a list of reagents, solvents and catalysts.
   d. Proposed acceptable limits of assay and related substances (impurities) based on actual analytical results with the certificates of analysis for batches used in animal toxicological studies and stability studies and batches destined for clinical studies.
   e. Stability studies may be brief but should cover the proposed duration of the study. A tabular presentation of past stability studies may be submitted.
3. Drug Product:
   a. List of all components.
   b. Quantitative composition of the investigational drug product.
   c. The name and address of manufacturer.
   d. Brief description of manufacturing and packaging process.

e. Specifications and methods assuring identification, strength, quality and purity of drug product.
f. Stability and stability methods used. The stability studies should cover the duration of toxicologic and clinical studies.

4. Placebo (see part 3)
5. Labels and Labeling: Copies or mock-ups of proposed labeling that will be provided to each investigator should be provided.
6. A claim for Categorical Exclusion from submission or submission of Environmental Assessment. The FDA believes that the great majority of drug products should qualify for a categorical exclusion.

Ad G. The Pharmacology and Toxicology Information is usually divided into the following sections.

1. Pharmacology & Drug Distribution which should contain, if known: description of drug pharmacologic effects and mechanisms of action in animals and its absorption, distribution, metabolism and excretion.
2. Toxicology: Integrated Summary of toxicologic effects in animals and *in vitro*. In cases where species specificity may be of concern, the sponsor is encouraged to discuss the issue with the Agency. In the early phase of IND, the final fully quality-assured individual study reports may slow preparation and delay the submission of application. If the integrated summary is based on unaudited draft reports, the sponsor is required to submit an update by 120 days after the start of the human studies and identify the differences. Any new findings discovered in preparation of final document affecting the patient safety must be reported to FDA in IND safety reports. To support the safety of human investigation the integrated summary should include:
   a. Design of the toxicologic studies and deviations from it. The dates of trials. References to protocols and protocol amendments.
   b. Systematic presentation of findings highlighting the findings that may be considered by an expert as possible risk signals.
   c. Qualifications of individual who evaluated the animal safety data. That individual should sign the summary attesting that the summary accurately reflects the data.
   d. Location of animal studies and where the records of the studies are located, in case of an inspection.
   e. Declaration of compliance to Good Laboratory Practices (GLP) or explanation why the compliance was impossible and how it may affect the interpretation of findings.
3. Toxicology—Full Data Tabulation. Each animal toxicology study intended to support the safety of the proposed clinical study should be supported by a full tabulation of data suitable for detailed review. A technical report on methods used and a copy of the study protocol should be attached.

Ad H. Previous Human Experience with the Investigational Drug may be presented in an integrated summary report. The absence of previous human experience should be stated.

Ad I. Additional and Relevant Information may be needed if the drug has a dependence or abuse potential, is radioactive, or if pediatric safety and effectiveness assessment is planned. Any information previously submitted need not to be resubmitted but may be referenced.

Once the IND is submitted to FDA, an IND number is assigned, and the application is forwarded to the appropriate reviewing division. The reviewing division sends a letter to the Sponsor-Investigator providing the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of the FDA person to whom questions about the application should be directed. The IND studies shall not be initiated until 30 days after the date of receipt of the IND by the FDA. The sponsor may receive earlier notification by the FDA that studies may begin.

Phase I of IND. The initial introduction of an investigational new drug into humans may be conducted in patients, but is usually conducted in healthy volunteer subjects. Phase I studies are usually designed to obtain, in humans, sufficient information about the pharmacokinetics, pharmacological effects, and metabolism, the side effects associated with increasing doses, and perhaps, preliminary evidence on effectiveness of the drug. The information collected should permit the design of well-controlled, scientifically valid phase II studies. The studies might even attempt to study the structure-activity relationships and the mechanism of action. The total number of subjects in the phase I study may vary. Depending on intent, it is usually in the range of 20–80 and rarely exceeds 100. The phase lasts several months and 70% of investigated drugs pass that phase. Beginning with phase I studies, the CDER can impose a clinical hold (ie, prohibit the study from proceeding or stop a trial that has started) for reasons of safety or because of a sponsor's failure to accurately disclose the risk of study to investigators. The review process, illustrated in Fig. 1, begins with the moment the IND application is assigned to individual reviewers representing various disciplines.

Phase II of IND. The initial (phase I) studies can be conducted in a group of patients, but most likely are conducted in healthy volunteers. In phase II, the early clinical studies of the effectiveness of the drug for a particular indication or indications are conducted in patients with the disease or condition. They are also used to determine the common short-term side effects and risks associated with the drug. The number of patients in phase II studies is still small and does not exceed several hundred. The studies that have to be well-controlled and closely monitored last several months to 2 years. Approximately 33% of drugs investigated pass that phase.

Phase III of IND. Phase III studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in phase II and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit–risk relationship of the drug. Phase III studies also provide an adequate basis for extrapolating the results to the general population

and transmitting that information in the physician labeling. Phase III studies usually include several hundred to several thousand people.

In both phases II and III, CDER can impose a clinical hold if a study is unsafe (as in phase I), or if the protocol is clearly deficient in design in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, agency experience with the design of clinical trials, and experience with the class of drugs under investigation. Out of 100 drugs entering phase I, over 25 should pass phase III and go into the New Drug Application (NDA) approval process. According to FDA calculations (18), about 20% of drugs entering IND phase are eventually approved for marketing. The numbers agree with similar representation of Pharmaceutical Research and Manufacturers of America (PhRMA) (19), showing that on the average, it takes 12–15 years and over $500 million to discover and develop a new drug. Out of 5000 compounds entering the preclinical research, only 5 go to IND and only 1 is approved (20).

Phase IV of IND. 21 CFR 312 Subpart E provides for drugs intended to treat life-threatening and severely-debilitating illnesses. In that case, the end-of-phase I meetings would reach agreement on the design of phase II controlled clinical trials. If the results of preliminary analysis of phase II studies are promising, a treatment protocol may be requested and when granted would remain in effect until the complete data necessary for marketing application are assembled. Concurrent with the marketing approval, the FDA may seek agreement to conduct post-marketing, phase IV studies (21CFR312.85).

4.5. Meetings with the FDA. Section 119(a) of the FDAMA of the 1997 Act directs the FDA to meet with sponsors and applicants, provided certain conditions are met, for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim in a NDA submitted under section 505(b) of the Act. These meetings are considered special protocol assessment meetings. All in all, there are three categories of meetings between sponsors or applicants for PDUFA products and CDER staff listed in the above guidance: type A, type B, and type C (21).

Type A. A type A meeting is one that is immediately necessary for an otherwise stalled drug development program to proceed. Type A meetings generally will be reserved for dispute resolution meetings, meetings to discuss clinical holds, and special protocol assessment meetings that are requested by sponsors after the FDA's evaluation of protocols in assessment letters. Type A meetings should be scheduled to occur within 30 days of FDA's receipt of a written request for a meeting from a sponsor or applicant for a PDUFA product.

Type B. Type B meetings are (*1*) pre-IND meetings (21 CFR 312.82), (*2*) certain end of phase I meetings (21 CFR 312.82), (*3*) end of phase II/pre-phase III meetings (21 CFR 312.47), and (*4*) pre-NDA/BLA meetings (21 CFR 312.47). Type B meetings should be scheduled to occur within 60 days of the Agency's receipt of the written request for a meeting.

Type C. A type C meeting is any meeting other than a type A or type B meeting, but it should be regarding the development and review of a product in a human drug application as described in section 735 (1) of the Act.

5. Drug Development and Approval Time Frame

The development and approval process is presented in Fig. 2. In the preclinical phase, the sponsor conducts the short-term animal testing and begins more extensive long-term animal studies. It is advisable to meet with the appropriate division of CDER in a pre-IND meeting to clarify the content of an application. When a sufficient amount of necessary data is gathered into an IND document, the application is filed with the FDA. The Agency has 30 days from the date the document is received to review the IND application, request additional information, and reach the decision of whether the phase I studies using human subjects can begin (see Fig. 1). Depending on the amount of information available or developed about the investigated drug, the phases of IND can overlap. There is no time limit on the duration of IND phases, and the time limits are simply determined by the results and economics. Approval of a drug doesn't end the IND process, which may continue for as long the sponsor intends to accumulate additional information about the drug, which may lead to new uses or formulation (see Fig. 2).

Accelerated development/review (*Federal Register*, April 15, 1992) is a highly specialized mechanism for speeding the development of drugs that promise significant benefit over existing therapy for serious or life-threatening illnesses for which no therapy exists. This process incorporates several novel elements aimed at making sure that rapid development and review is balanced by safeguards to protect both the patients and the integrity of the regulatory process.

5.1. Accelerated Development/Review. Accelerated development/review can be used under two special circumstances: when approval is based on evidence of the product's effect on a "surrogate endpoint," and when the FDA determines that safe use of a product depends on restricting its distribution or use. A surrogate endpoint is a laboratory finding or physical sign that may not be a direct measurement of how a patient feels, functions, or survives, but is still considered likely to predict therapeutic benefit for the patient.

The fundamental element of this process is that the manufacturers must continue testing after approval to demonstrate that the drug indeed provides therapeutic benefit to the patient (21CFR314.510). If not, the FDA can withdraw the product from the market more easily than usual.

5.2. Fast Track Programs. Fast Track Programs (22,23), Section 112(b), of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amends the Federal Food, Drug, and Cosmetic Act (the Act) by adding section 506 (21 U.S.C. 356) and directing the FDA to issue guidance describing its policies and procedures pertaining to fast track products. Section 506 authorizes the FDA to take actions appropriate to facilitate the development and expedite the review of an application for such a product. These actions are not limited to those specified in the fast track provision but also encompass existing FDA programs to facilitate development and review of products for serious and life-threatening conditions.

The advantages of Fast Track consist of scheduled meetings with the FDA to gain Agency input into development plans, the option of submitting a New

Drug Application in sections, and the option of requesting evaluation of studies using surrogate endpoints (see ACCELERATED APPROVAL). "The Fast Track designation is intended for products that address an unmet medical need, but is independent of Priority Review and Accelerated Approval. An applicant may use any or all of the components of Fast Track without the formal designation. Fast Track designation does not necessarily lead to a Priority Review or Accelerated Approval" (24).

5.3. Safety of Clinical Trials. The safety and effectiveness of the majority of investigated, unapproved drugs in treating, preventing, or diagnosing a specific disease or condition can only be determined by their administration to humans. It is the patient that is the ultimate premarket testing ground for unapproved drugs. To assure the safety of patients in clinical trials, the CDER monitors the study design and conduct of clinical trials to ensure that people in the trials are not exposed to unnecessary risks. The information available on the Web refers the sponsors and investigators to the necessary CFR regulations and guidances. The most important parts of CFR regulating clinical trials are as follows.

1. Financial disclosure section under 21 CFR 54. This covers financial disclosure for clinical investigators to ensure that financial interests and arrangements of clinical investigators that could affect reliability of data submitted to the FDA in support of product marketing are identified and disclosed by the sponsor (25).
2. Parts of 21 CFR 312 that include regulations for clinical investigators (26) and further:
   312.60 General Responsibilities of Investigators
   312.61 Control of the Investigational Drug
   312.62 Investigator Record Keeping and Record Retention
   312.64 Investigator Records
   312.66 Assurance of Institutional Review Board (IRB) Review
   312.68 Inspection of Investigator's Records and Reports
   312.69 Handling of controlled Substances
   312.70 Disqualification of a Clinical Investigator

The important part of any clinical investigation is the presence and activity of an Institutional Review Board (27), a group that is formally designated to review and monitor biomedical research involving human subjects. An IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects. An IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To achieve that, IRBs use a group process to review research protocols and related materials (eg, informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects.

6. NDA Process

By submitting the NDA application to the FDA (28), the sponsor formally proposes to approve a new drug for sale and marketing in the United States. The information on the drug's safety and efficacy collected during the animal and human trials during the IND process becomes part of the NDA application. The review process of the submitted NDA (Fig. 3) is expected to answer the following questions:

1. Is the new drug safe and effective in its proposed use(s)? Do the benefits of the drug outweigh the risks?
2. Is the proposed labeling (package insert) of the drug appropriate and complete?
3. Are the manufacturing and control methods adequate to preserve drug's identity, strength, quality, and purity?

As for IND, the preparation of NDA submission is based on existing laws and regulations and is guided by various guidance documents representing the Agency's current thinking on particular subjects to be included in the NDA documentation. The preparation of NDA submission is based on the Federal Food, Drug, and Cosmetic Act (29), as amended, which is the basic drug law in the United States. Its interpretation is provided by the Code of Federal Regulations: 21CFR 314—Applications for FDA Approval to Market a New Drug or an Antibiotic Drug and is available in PDF format (see Ref. 30). Further help in understanding of the NDA process is obtained from the available online guidances (14) and CDER Manuals of Policies and Procedures (MAPPs, Ref. 31). The list of guidances is particularly long and needs constant monitoring because some of them may be updated or withdrawn. Many of them address the format and content of the application to assure uniformity and consistency of the review process and decision-making. Particularly useful are the following MAPPs (in PDF):

6050.1—Refusal to Accept Application for Filing from Applicants in Arrears

7211.1—Drug Application Approval 501(b) Policy

7600.6—Requesting and Accepting Non-Archivable Electronic Records for New Drug Applications

6.1. Review Priority Classification. Under the Food and Drug Administration Modernization Act (FDAMA), depending on the anticipated therapeutic or diagnostic value of the submitted NDA, its review might receive a "Priority" (P) or "Standard" (S) classification. The designations "Priority" (P) and "Standard" (S) are mutually exclusive. Both original NDAs and effectiveness supplements receive a review priority classification, but manufacturing supplements do not. The basics of classification, discussed in CDER's MAPP 6020.3 (32), are listed below.

6.2. P—Priority Review. The drug product, if approved, would be a significant improvement compared with marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis,

or prevention of a disease. Improvement can be demonstrated by (*1*) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (*2*) elimination or substantial reduction of a treatment-limiting drug reaction; (*3*) documented enhancement of patient compliance; or (*4*) evidence of safety and effectiveness of a new subpopulation. (The CBER definition of a priority review is stricter than the definition that CDER uses. The biological drug, if approved, must be a significant improvement in the safety or effectiveness of the treatment diagnosis or prevention of a serious or life-threatening disease).

6.3. S—Standard Review. All non-priority applications will be considered standard applications. The target date for completing all aspects of a review and the FDA taking an action on the "S" application (approve or not approve) is 10 months after the date it was filed. The "P" applications have the target date for the FDA action set at 6 months.

6.4. Accelerated Approval (21CFR Subpart H Sec. 314.510). Accelerated Approval is approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. The CFR clearly states that the FDA ... "may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Post-marketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence." Therefore, an approval, if it is granted, may be considered a conditional approval with a written commitment to complete clinical studies that formally demonstrate patient benefit.

7. U.S. Pharmacopeia and FDA

The USP Convention is the publisher of the *United States Pharmacopeia* and *National Formulary (USP/NF)*. These texts and supplements are recognized as official compendia under the Federal Food, Drug & Cosmetic Act (FD&C Act). As such, their standards of strength, quality, purity, packaging, and labeling are directly enforceable under the adulteration and misbranding provisions without further approval or adoption by the FDA (33).

The Federal Food, Drug, and Cosmetic Act §321(g) (1) states: "The term "drug" means (A) articles recognized in the official *United States Pharmacopoeia*, official *Homeopathic Pharmacopoeia of the United States*, or official *National Formulary*, or any supplement to any of them; and ... " (34). That statement and additional arguments evolving from it may lead to a misapprehension that the USP and the FDA are at loggerheads over the authority to regulate the quality of drugs marketed in the United States. Nothing could be further from the

truth. The harmonious collaboration of the FDA with many of the USP offices and committees may serve as a model of interaction between a federal agency and a non-governmental organization such as USP.

CDER's MAPP 7211.1 (35) establishes policy applicable to drug application approval with regard to official compendial standards and Section 501(b) of the Act: "When a USP monograph exists and an ANDA/NDA application is submitted to the Agency, reviewers are not to approve regulatory methods/specifications (ie, those which must be relied upon for enforcement purposes) that differ from those in the USP, unless a recommendation is being or has been sent to the USPC through Compendial Operations Branch (COB) to change the methods/specifications. Direct notification to the U.S. Pharmacopeial Convention, Inc. by applicants does not absolve reviewers of their obligation to notify COB. Each Office within the Center should determine its own standard operating procedures under the policy decision."

8. CDER Freedom of Information Electronic Reading Room

The 1996 amendments to the Freedom of Information (FOI) Act (FOIA) mandate publicly accessible "electronic reading rooms" (ERRs) with agency FOIA response materials and other information routinely available to the public, with electronic search and indexing features. The FDA (36) and many centers (37) have their ERRs on the Web.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, Ref. 38) brings together the regulatory authorities of European Union (EU-15), Japan, and the United States, and experts from the pharmaceutical industry in these three regions. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonization is a more economical use of human, animal, and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.

A series of guidances have been issued (such as Ref. 39) that provide recommendations for applicants preparing the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD) for submission to the FDA.

9. Manufacturing

Table 1 gives the common dosage forms of pharmaceuticals as including properties and uses (40). A comprehensive list and review of the varied types of dosage forms used in earlier years is also available (41). This treatise includes older forms of liquid preparations (decoctions, infusions, mucilages, fluid glycerates,

brandies, essences, balsams, and oleoresins); solid preparations (medicated cones, cachets, dragees, insufflations, pills, and wafers); semisolid preparations (cataplasms, cerates, glycerogelatins, plasters, and vesicotories); and suppository-type preparations (bougies and pessaries).

9.1. Compressed Tablets. This popular type of dosage form offers convenience, stability, accuracy and precision, and good bioavailability of active ingredients. After the best formulation has been established, compressed tablets can be manufactured at high rates of speed on advanced equipment. Tablets can be made to achieve rapid drug release or to produce delayed, repeat, or prolonged therapeutic action (Controlled release technology, pharmaceutical).

Quality control during manufacture and of the final product assures batch-to-batch consistency and reliability. Bioavailability is checked in early batches produced for clinical testing. Other tests include uniformity of weight and contents, hardness (qv), disintegration rate, dissolution rate, and friability.

During the preformulation stage, the chemical and physical properties of the drug moiety are studied exhaustively to ensure stability, safety, bioavailability, and therapeutic efficacy. Tablets are produced directly by compression of powder blends or granulations, which include a small percentage of fine, particle-sized powders.

9.2. Granulation. Granulation methods can be wet or dry. Wet granulation cannot be used for drugs that are sensitive to moisture and heat. The powered drug and diluent are blended with a dispersion of the binder excipient, eg, gelatin, to a consistency that can be screened to 840–1800-μm granules (10–20 mesh). These granules are dried on trays in hot-air ovens or fluid-bed dryers. The latter are more time efficient and can be modified by combining the granulating and drying stages. The dried granules are resieved, generally to 420–840 μm (20–40 mesh), and blended with powdered lubricants and disintegrants. In some instances a portion of the disintegrating agent can be added to the powder blend before the addition of the binder. The percentage of powdered ingredients, ie, the fines, should at this point be relatively small (ca 5%). The granulation blend is then compressed.

Dry granulation is used when the drug is not stable under the conditions of wet granulation and when the combined powders of a formulation cannot be compressed directly. One form, slugging, occurs when all the ingredients are blended and compressed on heavy-duty tablet presses. Generally, the pressure is greater than in regular compression and the resulting tablets or slugs are very large (2.5–5.0 cm dia) and weigh 20–30 g. These large, hard slugs are ground and screened to appropriate mesh size and then recompressed into final tablets. Chilsonation, another form of dry granulation, involves the use of roller compaction of the blended ingredients, followed by particle size reduction to appropriate sizes for compaction.

9.3. Direct Compression. This process is relatively simple and time saving. All the ingredients are blended and then compressed into the final tablet. This is an excellent method, but encumbered by a number of problems. Not all substances can be compressed directly, necessitating a granulation step. Likewise, the flow properties of many blends of fine, particle-sized powders are not such as to ensure even filling of the die cavities of tablet presses. In addition, air entrapment can occur.

The availability of spray-dried lactose, microcrystalline cellulose, and other excipients allows for the use of granular rather than powdered phases. This eliminates some of the problems of particle segregation according to size (demixing) and even flow to the die. Direct compression eventually may be the preferred method of tablet preparation.

9.4. Tablet Press. The main components of a tablet compression machine (press) are the dies, which hold a measured volume of material to be compressed (granulation), the upper punches which exert pressure on the down stroke, and the lower punches which move upward after compaction to eject the tablets from the dies. Mechanical components deliver the necessary pressure. The granulation is fed from a hopper with a feed-frame on rotary-type presses and a feeding shoe on single-punch presses. A smooth and even flow ensures good weight and compression uniformity. Using the proper formulation, demixing in the hopper is minimized.

The actual compression process is a cycle of die fill, compaction by intervention of the upper punch using great pressure on the granulation material in the die, and upward movement of both punches to achieve ejection of the tablet from the die. Singe-punch presses have only one die-and-punch arrangement and the compression is quick, with little dwell time of the top punch in die.

Rotary tablet presses can accommodate many punch/die units. The dies are set in a rotating, circular, metal table and the punches ride in appropriately designed cam tracks or channels in the head and foot areas of the press to achieve the necessary upward and downward stroking action. The central shaft mechanism drives these rotating components in synchrony, producing the designed number of tablets in each cycle. The granulation is fed from the hopper to the dies, passing below the feeder frame at a point when the lower punches are in their lowest position. The frame may contain some devices, such as rotating spindles, to induce or force granulation into the dies, as a means to ensure more accurate and uniform fills. Pressure-release devices allow a lift release if an overload at the die occurs.

Single-punch machines produce approximately 100–150 tablets per minute. Depending on numbers of die per punch units, standard rotary presses can produce 5000 tablets/min, and even more with a double-sided rotary press. The newest high speed presses can achieve 12,000 tablets/min.

Some presses are equipped with strain gauges at key points in the overall feed–compress–eject cycle. Thus, these measure compression and ejection forces. Tight specifications for punch lengths and well-designed and prepared granulations have led to better control of variations in tablet weight. In fully automated presses, weight variations are adjusted by computer.

Compressed tablets that are composed of several layers require specially adapted presses designed with several fed hoppers. For a two-layer tablet, one granulation is first fed to a die and partially compressed into a soft tablet. The second granulation is added, and the total die components then are compressed fully. Such procedures are used when the tablet ingredients may be incompatible, which requires separate granulations. If needed, a layer of inert ingredient, eg, lactose, is inserted between the two.

Layered tablets are also used for a prolonged or sustained therapeutic effect. In this case, one layer disintegrates and dissolves rapidly to provide the initial dosing, whereas the other is designed for controlled release.

9.5. Formulation. Compressed tablet formulations contain several types of inert, adjuvant ingredients necessary for proper preparation and therapeutic performance. Tablets designed to be swallowed need diluent, disintegrating, binding (adhesive), and lubricating inert ingredients, whereas troches or lozenges intended to be dissolved slowly in the mouth should not disintegrate quickly, need more binder, and no disintegrant. Lactose or dicalcium phosphate are common diluents, whereas starch and cellulose derivatives are used as disintegrating agents. Sublingual tablets are designed to dissolve rapidly under the tongue to provide rapid absorption as in the case of nitroglycerin usage.

Glidants are needed to facilitate the flow of granulation from the hopper. Lubricants ensure the release of the compressed mass from the punch surfaces and the release/ejection of the tablet from the die. Combinations of silicas, corn starch, talc (qv), magnesium stearate, and high molecular weight poly(ethylene glycols) are used. Most lubricants are hydrophobic and may slow down disintegration and drug dissolution.

Colors and flavors increase the elegance and acceptability of the product. Sometimes colors are used for identification.

Effervescent tablets disintegrate by virtue of the chemical reaction occurring in water between component ingredients, such as sodium bicarbonate and citric or tartaric acid, to achieve release of carbon dioxide. Interest exists in the pharmaceutical industry for technologies to produce fast dissolving tablets and various concepts are being investigated. One is the use of mildly effervescent bases and adaptation of technology similar to that used to make cotton candy. Another, intended to produce a product to dissolve very quickly in the mouth, involves preparation of a lyophilized porous wafer containing a therapeutic substance that dissolves in seconds in saliva, when placed on the tongue.

9.6. Coating. Sugar or film coatings offer protection from moisture, oxygen, or light and mask unpleasant taste or appearance. Enteric coatings delay the release of active ingredients in the stomach and may prolong the onset of therapeutic activity. The latter are used for drugs that are unstable to gastric pH or enzymes, cause nausea and vomiting or irritation to the stomach, or should be present in high concentration in the intestines, eg, preoperative sterilization of the gut or as anthelmintics. Effectiveness depends on the varying pH patterns of the gastrointestinal tract and the enzymes present for dissolution and aqueous solubility.

Enteric coating is also used for repeat-action tablets, which contain an enteric-coated core tablet and a sugar or film-coated second dose, permitting the administration of two doses simultaneously. The core dose is released several hours after the initial, outer dose.

Some tablets that provide a sustained period (up to 8–12 h) of therapy may be coated during processing. A portion is released first to bring the drug to the desired blood concentration (onset of activity), whereas a sustained-release portion maintains an effective level for a prolonged period of time (duration of activity), eg, by coating erosion or diffusion of drug through it.

Sugar Coating. Sugar coating is applied in rotating, pear-shaped or short cylindrical pans. The cores are usually somewhat harder than in uncoated tablets to withstand the rigors of tumbling. They are first dusted and then wetted with a solution of concentrated sucrose, gelatin, acacia, or methylcellulose that imparts adhesiveness to the surfaces. Next, powdered sugar is applied with continued tumbling. The batch is then dried with warm air. This alternative subcoating procedure that uses syrup and powder is continued until the tablet is rounded. The core tablet may need to be sealed with a thin coat of pure shellac before it is subcoated. Color may be added to the smoothing coats. Finally, the tablet is polished with a waxy composition such as carnauba wax.

Sugar coating is time-consuming, requires skilled operators, and increases the tablet weight, sometimes to twice that of the uncoated core.

Film Coating. Film coating in pans is a much quicker procedure than sugar coating. The coating is much thinner and the process is easily automated or programmed. Various polymer solutions (eg, cellulose derivatives) are used that form films upon drying. Plasticizers improve film flexibility. The polymer may be water soluble or produce an enteric effect. Until the late 1980s, organic solvents such as acetone were used. However, because of increased cost and disposal problems of such solvents, aqueous-based solutions or dispersions of the polymers have become popular.

Gelatin Coating. A more recent development in tablet coating involves the use of gelation as the coating material to produce geltabs. If a tablet is compressed as a capsule-shaped unit prior to gelatin coating it is called a gelcap. Such tablets are dipped into a reservoir of a molten gelatin mixture, similar to the production of empty, hard gelatin capsule shells. The gelatin coating facilitates swallowing.

Air-Suspension Coating. The Wurster process utilizes a cylindrical chamber in which the cores are suspended in a controlled stream of air. Film coatings are applied by introducing the coating solution into the airstream, where the solvent evaporates quickly. The process is much quicker than film coating; however, care must be taken to avoid destruction of the cores by attrition in the air stream.

Compression Coating. In this dry process an outer coating is compressed around a core tablet, producing a tablet within a tablet. This requires sophisticated tableting presses that cannot be run at high speeds. The granulations are similar to those for uncoated, compressed tablets. This procedure is employed for drugs that are sensitive to moisture, oxygen, or light. Likewise, if two active incompatible ingredients are present, one can be granulated in the core and the other incorporated in the coating. Pressure coating also can be used to achieve prolonged periods of therapeutic effect. For example, the core can be formulated as a slowly eroding matrix that provides the sustained portion of therapy, whereas the initial dose is included in the compression coat.

9.7. Capsules. Capsules are made in two types. In hard-gelatin capsules, powders or granules are enclosed in rigid gelatin shells. Soft-gelatin capsules contain glycerol as well as gelatin and maintain plastically even when dried. Hard-gelatin capsules are made in two sections, cap and body, which are then filled, whereas soft-gelatin capsules are formed and filled in succession in one manufacturing procedure. Soft-gelatin capsules are generally filled using

nonaqueous solutions, although powders can also be used. Most drug companies buy the hard-gelatin shells from external sources. These are made by dipping precisely tooled pins into controlled solutions of gelatin. A film of gelatin adheres to the pins. Upon drying, the units are trimmed to specified length, removed from the pins, and the cap and body portions are joined. Various colors can be incorporated (see GELATIN).

The formulations of filled, hard-gelatin capsules are generally less complex than those of compressed tablets, and require no binders or disintegrators. Upon swallowing, the capsule shell dissolves quickly and the powder ingredients are available for dissolution. Because no initial disintegration step is needed, bioavailability of drugs in capsule formulations is generally better than that of compressed tablets. The capsules are filled by various high speed machines. Occasionally the pharmacist has to perform this procedure manually.

The size system of capsules is inversely related to the volume. A No. 1 capsule is larger in volume than a No. 2; a No. 0 is larger than a No. 1. For human consumption, No. 0–2 are most common. Hard-shell gelatin capsules vary in size from those that contain 100 mg of drug to those for veterinary use, which contain several grams.

For prolonged action therapy, granular-sized encapsulated particles, ie, beads, are used and can be both uncoated or coated. The uncoated beads provide the initial dose; the others are made to dissolve at various rates depending on the coating type and thickness.

Hard-gelatin capsule shells, prepared from gelatin and water in various sizes, are made of two component parts, base and body. They can be compounded extemporaneously by pharmacists or manufactured by high speed machinery. Soft-gelatin capsules contain glycerin, as well as water and gelatin. These cannot be extemporaneously prepared owing to the gelatin character. Rather, these require heating process and sealing. As shown in Figure 4, for the soft-gelatin capsules two rolled sheets of gelatin are kept appropriately softened using minimal (40°C) heat. The rolled sheets meet in an injection wedge where the drug mix (solution; dispersion) is injected into its ultimate form upon sealing. Various shapes and sizes are possible by mold adaptations.

9.8. Prolonged Action/Controlled Release, Orally Administered Solid Dosage Forms. The therapeutic purpose of prolonged action and controlled release solid, oral drug products is to maintain safe and effective concentrations of the drug in the blood for 2–4 times longer than those times achieved using regular compressed tablets or capsules. This is accomplished by releasing one portion of the drug quickly, whereas the remaining portion is released at a rate that approaches the elimination rate. Ideally, the second portion should be released at a zero-order rate to achieve this profile. The technologies used for such controlled release only approach such a rate, but do accomplish the increased therapeutic period. These oral products mainly use diffusion-controlled or dissolution-controlled release profiles. The more recognized technologies used to achieve these methods include ion-exchange (qv) resins, coated micropellets, barrier coatings, drug embedment in either slowly eroding or plastic matrices, swelling hydrogels of various polymer resins, drug complexation, and osmotic pressure controlled tablets (42,43). Other technologies that have been attempted or tested include altered density micropellets, prodrugs, and bioadhesives.

The best drug candidates for incorporation into prolonged action systems are uniformly absorbed throughout the gastrointestinal (GI) tract, have medium (2–8 h) biological half-lives, and are prescribed for chronic maintenance use. Drugs in large doses are difficult to formulate into such products (see CONTROLLED RELEASE TECHNOLOGY, PHARMACEUTICAL).

Since the development of the Spansule brand (SmithKline Beecham) of coated beads and granules in the late 1960s, various drug product technologies have been developed and patented to achieve extended durations of therapeutic effects. Each of these does so by various mechanisms of control of drug release from administered dosage forms. Each method has its advantages and disadvantages, a discussion of which is available in the pharmaceutical literature (see DRUG DELIVERY SYSTEMS) (42).

Coated Beads or Granules. Coats of varying thickness are applied to beads containing the appropriate amounts of drug (see MICROENCAPSULATION). The rate of dissolution depends on the rate of dissolution or disintegration of the coating and thus varies with the thickness of the coating. Various proportions of such coated beads are incorporated in gelatin capsules or compressed tablets together with appropriate amounts of uncoated beads to initiate onset of activity.

Eroding of Slow-Releasing Core Tablets. The sustained-dose portion of a drug is granulated with hydrophobic materials such as waxes, fatty acids, or fatty alcohols and compressed into a core. The initial dose is added to the core by a modified sugar coating process or by compression coating. Thus, a tablet within a tablet is created. The core erodes slowly to release the active ingredient.

Leaching from Carriers. The drug is granulated with inert plastic resins and water-soluble channeling agents. This mixture is compressed to form a porous plastic tablet with drug and channeling agent(s) entrapped in many veins or channels. The water-soluble excipient, ie, the channeling agent, attracts water from the gastrointestinal tract to the drug in the channels. The drug dissolves and passes into the gastrointestinal fluid. Such a leaching effect apparently occurs at rates suitable to accomplish a rapid initial onset of activity followed by a prolonged period of therapy. The exhausted plastic core is excreted.

Ion-Exchange Resins. Catonic-exchange resins which are combined with an appropriate form of the drug for which sustained activity is desired may be used. In the gastrointestinal tract the drugs ions are exchanged for other ions. Using the appropriate ion-exchange resin, the drug is delivered to the gastrointestinal fluids at a rate that produces sustained therapeutic activity. The rate of release also depends on the size of the bead resins. Thus, smaller beads have larger total surface area, the drug is exchanged at a faster rate, and the activity is less prolonged. Anionic-exchange resins have also been used.

Tannate Complexation. Certain drugs, those that contain amine groups, complex readily with tannic acid. Such complexes release the drug gradually and uniformly. The rate seems to be affected by the pH and the electrolytes present in the gastrointestinal tract. At lower pH, the drug is released more quickly. Other complexing compounds have also been used.

Hydrogels. Controlled swelling of hydrophilic polymers, derived from the glossy/rubbery properties of polymers, is used to control the rate of drug release from matrices. In the rubbery state, accomplished by lowering the polymer's

glass-transition temperature to an appropriate level, the dispersed drug diffuses as the polymer swells in the presence of water.

Osmotic Pressure Controlled Oral Tablets. Alza Corp. developed a system that is dependent on osmotic pressure developed within a tablet. The core of the tablet is the water-soluble drug encapsulated in a hydrophobic, semipermeable membrane. Water enters the tablet through the membrane and dissolves the drug creating a greater osmotic pressure within the tablet. The drug solution exits at a zero-order rate through a laser drilled hole in the membrane. Should the drug itself be unable to provide sufficient osmotic pressure to create the necessary pressure gradient, other water-soluble salts or a layer of polymer can be added to the drug layer. The polymer swells and pushes the drug solution through the orifice in what is known as a push–pull system (Fig. 5). The exhausted drug unit then passes out of the body in fecal matter.

This technology is relatively expensive to produce. Special excipients and equipment, such as a laser unit to drill the necessary hole for drug release, are required. However, the achievement of very steady blood levels of a drug for sustained periods, ie, zero-order rate release, of therapy is advantageous.

Other Prolonged Action Drug Products. The USP/NF recognizes several nonorally administered, prolonged action/controlled release drug delivery systems including transdermal, ocular, and intrauterine systems (40). The transdermal systems include medicated adhesive patches of various types. One patch technology utilizes a drug reservoir from which the drug diffuses through a rate-controlling membrane to and through the skin (see MEMBRANE TECHNOLOGY). Another type involves embedment of appropriately coated drug pellets into the adhesive of the patch.

Ophthalmic drug delivery systems (qv) have been developed to deliver controlled drug quantities for a prolonged time (up to seven days) to the eye. Such a product known as Ocusert was originally marketed to treat glaucoma. This system utilizes specific membranes, between which the drug reservoir is enclosed (Fig. 6). A tiny elliptical disk, inserted into the cul-de-sac of the eye, releases pilocarpine steadily. The drug is delivered through selected polymeric membranes. The drug reservoir maintains a saturated solution between the membranes which acts osmotically as the driving force for the drug to diffuse through the rate-limiting membranes.

Alza Corp. also developed an intrauterine device, Progestasert, designed to release progesterone by diffusion through a rate-controlling membrane for up to one year. The drug reservoir is built into a T-shaped device that is inserted intravaginally (45).

A prolonged action/controlled release system developed to deliver levonorgestrel for contraceptive therapy involves implantation of a set of flexible closed capsules made of demethylsiloxane–methylvinyl–siloxane copolymer (see CONTRACEPTIVES). Each capsule measures 2.4 mm in diameter and 34 mm in length. A set of six such capsules is surgically implanted beneath the skin of the upper arm. These capsules are intended to be removed by the end of the fifth year after implantation.

Repeat and Delayed Action Oral Dosage Forms. Repeat action tablets provide prolonged periods of therapy, usually twice that of conventional release tablets, eg, eight hours instead of four. These are designed to release two portions

of drug. The first portion is incorporated in an outer shell and is released entirely at one time, as for conventional tablets. The second portion is incorporated in a coated compressed core unit. The coating is designed to erode or dissolve at a rate such that the core dose is completely released when the concentration of the drug in the blood from the first portion approaches the MEC, after reaching its peak concentration. However, the drug release is not controlled to be gradual over the eight hours.

Delayed action solid products are designed like conventional dosage forms to release all their drug contents at one time, but only after a delayed period. Thus, the duration of action and the blood concentration–time curve is like that of a conventional product. However, the onset time is purposely designed to be long.

Such products are generally used when the drug is nauseating, irritating to the stomach, or chemically degraded by stomach pH and/or enzymes. In such cases, coatings that do not erode or dissolve in the stomach, but do so in the small intestine (enteric coatings), are used. An example of such a coating ingredient is cellulose acetate phthalate.

9.9. Liquid Dosage Forms. Simple aqueous solutions, syrups, elixirs, and tinctures are prepared by dissolution of solutes in the appropriate solvent systems. Adjunct formulation ingredients include certified dyes, flavors, sweeteners, and antimicrobial preservatives. These solutions are filtered under pressure, often using selected filtering aid materials. The products are stored in large tanks, ready for filling into containers. Quality control analysis is then performed.

Dosage forms of naturally occurring materials having therapeutic activity are prepared by extractive processes, especially percolation and maceration. Examples of such dosage forms have included certain tinctures, syrups, fluid extracts, and powdered extracts.

Solutions for external or oral use do not require sterilization but generally contain antimicrobial preservatives. Ophthalmic solutions and parenteral solutions require sterilization (qv).

For the preparation of suspensions and emulsions, colloid mills and homogenizers, respectively, are used. Ultrasonic mills that utilize vibrating reeds in restricted chambers to reduce the particle size of the dispersed ingredients can also be employed (see COLLOIDS).

9.10. Semisolid Dosage Forms. The ingredients that constitute the base of ointments, eg, petrolatum and waxes, are melted together, powdered drug components are added, and the mass stirred with cooling. Generally, the product then is passed through a roller mill to achieve the particle-size range desired for the dispersed solid. Pastes are ointments having relatively large, dispersed solid content, and are prepared similarly.

Creams are semisolid emulsions either water-in-oil (w/o) or oil-in-water (o/w). Generally, the ingredients of the two phases are heated separately to ca 70–80°C. The phases are then mixed and stirred vigorously to achieve emulsification. Such stirring is continued until the product has been cooled sufficiently. For further reduction of the internal-phase droplets, the product may be passed through a homogenizer before final cooling. A solid ingredient can be added to

the appropriate phase before emulsification or may be dispersed at some point after the emulsification step.

Suppositories. These semi-rigid, plastic dosage forms are designed to deliver a unit dose of medication to body cavities, ie, rectum, vagina, or urethra. Depending on the base, suppositories either melt (cocoa butter) at body temperature or dissolve (poly(ethylene glycol)s, glycerogelatin) in the fluids of the cavity. They can be used for systemic therapy (rectal suppositories) or for localized treatment. Rectal suppositories are a route of administration in comatose conditions or after gastrointestinal surgery, and for pediatric patients.

Cocoa butter-based suppositories can be prepared manually by pharmacists by mixing the ingredients to a pliable consistency in a mortar. This mass is then rolled into a thin cylinder and cut into units that represent one dose each. Melting the ingredients together and molding them into appropriate units in metal or rigid plastic molds generally is preferred. Formulations utilizing poly(ethylene glycol) or glyerogelatin bases must be prepared by molding because of the character of the individual base ingredients. On a large scale, suppositories are produced by molding.

9.11. Parenteral Dosage Forms. The most commonly used forms for drug products designed and manufactured for injection through the skin include those meant for subcutaneous, intramuscular, and intravenous administration (45–49). Other types include intradermal, intraarticular, intrathecal, intraspinal, intracisternal, and intraocular. Such dosage forms generally are termed injections and can be grouped into several categories: solutions ready for injection; powdered, soluble ingredients in appropriate containers that are combined with an appropriate solvent prior to use; suspensions that are ready to be combined with a vehicle prior to use; and emulsions (qv) (46,47). The route of administration and the physical nature of the injection have direct bearing on the selection of parenteral therapy. Injectable suspension (USF/NF) for example, should not be administered intravenously because of the inherent danger of the suspended solid particles (46).

Intravenous aqueous injections provide an excellent means of achieving a rapid therapeutic response. Parenteral product design, eg, vehicle and other excipient selection, as well as choice of route of administration, can prolong therapeutic activity and increase onset times. Thus, oily solutions, suspensions, or emulsions can be administered by subcutaneous or intramuscular routes to create prolonged effect, ie, depot injection (48).

Several factors of design and manufacture are of great importance: sterility, absence of pyrogens and foreign particulate matter, and tonicity. The last, when adjusted to the osmotic pressure of body fluids in the case of aqueous solutions, reduces the risk of tissue irritation and pain. The USP/NF utilizes the designation “Large Volume Intravenous Solution” for single-dose injections for iv use packaged in containers containing more than 100 mL. “Small Volumes” injections are those iv solutions containing 100 mL or less (47).

The USP recognizes three forms of water for parenteral dosage forms. Water for injection is prepared by reverse osmosis or distillation, which removes nonvolatile pyrogens. It contains no added substances and is intended for solvent use in the preparation of parenteral solutions. When the solution is prepared

under aseptic conditions, ie, not sterilized by filtration or in the final container, such water must be sterilized and protected from microbial contamination.

Sterile water for injection is used mostly for the solution or suspension of drugs just before injection. In containers of 30-mL capacity or less, it may contain a bacteriostatic agent. Inclusion of such agents in larger volumes can cause toxicity.

Bacteriostatic water for injection is sterile and pyrogen-free and contains bacteriostatic agents. The drug involved must be compatible with the antimicrobial agents present.

In addition to these forms of water, several other official aqueous vehicles can be used. These are isotonic injections that can be sterilized, eg, sodium chloride, Ringer's, dextrose, dextrose and sodium chloride, and lactated Ringer's. Addition of water-miscible solvents such as ethanol or propylene glycol increases solubility and stability.

Some fixed oils, such as cottonseed oil or peanut oil, and esters, eg, isopropyl myristate, may be used as solvent systems for parenteral drugs. Mineral oil and paraffins should not be used, because these are not metabolized and may irritate tissue. Various other additives are needed for stability, sterility, and isotonicity: antimicrobial preservatives, antioxidants (qv), chelating agents (qv), and buffers. No parenteral container material is completely inert to parenteral solvent systems.

Plastic components can be leached into the product and the alkalinity also can be affected by certain types of glass (qv). Particulate matter can be introduced by flaking from container surfaces. The containers also must be able to withstand the heat and pressure of sterilization.

Containers should be clear in order to allow detection of foreign particles. Outer coverings minimize irradiation. Plugs used as stoppers are selected with care to prevent flaking into the contents and possible component leaching into the product.

Traditionally, glass has been the preferred container material. The USP has adopted a classification of glass types acceptable for drug container use: Type I, borosilicates glass; Type II, a soda–lime treated glass; Type III, a soda–lime glass; and NP (nonparenteral), a soda–lime glass that is not suitable for parenteral products. There are two official USP tests: the powdered glass and the water attack test. In general, Type I glass is preferred; it is expensive, however. Types II and III may also be used for parenteral products.

Increasingly, plastics are being used as parenteral packaging (qv) materials. Plastics such as poly(vinyl chloride), polyethylene, and polypropylene are employed. However, plastics may contain various additives that could leach into the product, such as plasticizers (qv) and antioxidants. Permeability of plastics to oxygen, carbon dioxide, and water vapor must be tested in the selection of plastic containers. Furthermore, the plastic should withstand sterilization. Flaking of plastic particles should not occur and clarity necessary for inspection should be present.

Rubber is a popular closure component, and additives such as vulcanizers, pigments (qv), or antioxidants may leach into the product. In cases where rubber closures are penetrated by needles in dosing, bits of the closure (coring) could

enter the product. Thus, such closure components must be sufficiently tested before use.

Commercially available containers for use with parenteral products include single-dose ampuls that are heat sealed and opened by snapping at the point of least diameter, vials for multidose use, and bottles and pliable bags that are used for large volumes such as needed in intravenous infusions. Container size can vary from 1 mL to 1 L. Generally volumes up to 100 mL are available as ampuls or vials.

Parenteral products are sterilized in containers soon after packaging by dry or moist heat under pressure (autoclaving). Drug solutions that are degraded chemically by heat can be sterilized by filtration through bacteria-retaining filters into sterilized containers under aseptic conditions, and then aseptically closed. Needles, syringes, and administration sets are sterilized with gas, ie, ethylene oxide. Ionized radiation has been used to sterilize sutures, dressings, needles, etc. However, gaseous and radiation sterilization are not suitable for liquid preparations.

Aseptic techniques must be scrupulously followed throughout the packaging stages of parenteral production. Sources of contamination are controlled strictly by using laminar-flow hoods having high efficiency particulate air (HEPA) filters. The availability of this technology, a spin-off of early aerospace research, has led to injectable products being prepared in hospital pharmacies. Ophthalmic solutions also can be prepared by this technique using bacterial filtration.

The industrial areas used for parenteral production call for careful design and conscientious maintenance of an aseptic environment.

Prolonged Action Parenterals Injections. Intramuscular injections have been developed to achieve prolonged therapeutic effects. This can be accomplished by suspension of drug particles in oils or flowable gels, from which the drug slowly diffuses. Aqueous suspensions can also provide such therapeutic response. In these cases, the solid drug crystals generally are quite water insoluble and of a controlled particle size and crystallized form. An example of such a product is Sterile Medroxyprogestrone Acetate Suspension used for its contraceptive property. Such an injection is designed to provide up to three months of contraceptive activity. Another such product is a depot injection of leuprolode acetate, an analogue of gonadatropin-releasing hormone (see DRUG DELIVERY SYSTEMS). In this case, the product is a sterilized powder of microspheres to be suspended upon the addition of an appropriate diluent and intended for monthly injection.

9.12. Lyophilization. Lyophilization is essentially a drying technology. Some drugs and biologicals are thermolabile and/or unstable in aqueous solution. Utilization of freeze drying permits the production of granules or powders that can be reconstituted by the addition of water, buffered solution, or mixed hydrophilic solvents just prior to use, eg, certain antibiotic suspensions.

Initially, the product to be made using lyophilization is prepared as an aqueous solution or suspension, which is then cooled rapidly to a predetermined temperature. Such temperature is below the eutectic point and generally approaches $-50^{\circ}C$. The freezing chamber is sealed and the frozen material subjected to heat under high vacuum conditions. The liquid portion sublimes, leaving the desired

solid drug or biological. The process continues until less than 1% moisture remains in the dried components. Reabsorption of moisture can occur, necessitating quick removal from the freezer chamber into appropriate containers in a low humidity environment. When the lyophilized product is to be prepared for parenteral use, sterile conditions are maintained throughout the process. The dried drug or biological residue is porous upon sublimation of the ice crystals. Such surface character increases its rate of dissolution.

9.13. Ophthalmic Dosage Forms. Ophthalmic preparations can be solutions, eg, eye drops, eyewashes, ointments, or aqueous suspensions (50). They must be sterile and any suspended drug particles must be of a very fine particle size. Solutions must be particle free and isotonic with tears. Thus, the osmotic pressure must equal that of normal saline (0.9% sodium chloride) solution. Hypotonic solutions are adjusted to be isotonic by addition of calculated amounts of tonicity adjusters, eg, sodium chloride, boric acid, or sodium nitrate.

Single-dose preparations intended for use in eye surgery do not contain excipient ingredients, in order to avoid tissue irritation. However, multiple-dose containers may require antioxidants (qv), antimicrobial preservatives, or buffers to maintain stability and sterility. Such solutions are packaged in polyethylene flexible dropper units called droptainers or in glass dropper bottles.

Ophthalmic ointments usually contain petrolatum as the base. The petrolatum is sterilized by dry heat and combined with the sterile drug powder under aseptic conditions. Ophthalmic suspensions contain very fine ($\sim$10μ) particle sized solids suspended in an aqueous vehicle. The vehicle is adjusted to isotonicity and viscosity-increasing excipients, chelating agents, and surfactants also may be needed. The aqueous vehicle in these cases is generally autoclaved and mixed with sterile drug powder asceptically (50).

9.14. Radiopharmaceuticals. Radioactive isotopes for human use in the diagnosis and treatment of disease states are called radiopharmaceuticals (qv) (45,51). Whereas the dosage form types used, eg, solutions or injections, are traditional, special handling of these products during compounding, transport, and use is vital. Most are administered intravenously and shortly after preparation. Examples of drugs used in such products include ^{57}Co-cyanocobalamin, ^{123}I-sodium iodide, ^{201}Tl-thallium chloride, ^{99}mTc-technetium, ^{131}I-sodium iodohipparate, and ^{32}P-sodium phosphate. A comprehensive review of radiopharmaceuticals is available (51). Specialized pharmacies prepare these products overnight and transport them to hospitals for early administration by members of nuclear medicine departments.

9.15. Aerosols. Pressurized containers to deliver aerosolized drug products through appropriate systems of valves and actuators have been available since the 1950s (see AEROSOLS). Such dosage forms are used as external applications of lotions and creams, for oral inhalation, or for treatment of the vaginal cavity, eg, contraceptive foams. Aerosols contain two- or three-phase systems, wherein a volatile liquid or admixture of liquids is sealed in a container in equilibrium with a vapor phase (propellant). The latter develops pressure to force the liquid from the container through a precisely designed value upon actuation. If the drug is soluble in the propellant, the system is two-phase. Upon actuation and delivery of the product, the propellant evaporates quickly, and fine dispersion of the drug settles on the area of application. For aerosol products that

need accurate dosing, metered valves are used with the valve chamber being recharged between each actuation or dose.

If the drug is not soluble in the propellant, it is dissolved or dispersed in a liquid vehicle. The propellant then constitutes the third phase of the system, and the container must be shaken before valve actuation. Emulsified aerosol products like lotions and creams are examples of such systems.

Aerosols are generally filled cold with chilled product and propellant. This reduces the vapor pressure of the propellant, allowing filling of appropriate containers by volume. The valves are then crimped to the container with the valve in place. The container is then charged with the propellant (under pressure) through the valve. The finished containers are checked for leaks.

The popularity of aerosols has been declining. A widely used group of propellants, the fluorinated hydrocarbons, have been restricted in use since it was found that they can harm the environment by reducing the ozone layer of the upper atmosphere (see AIR POLLUTION; ATMOSPHERIC MODELING; OZONE).

9.16. Biotechnology and Dosage Forms. In drug development, biotechnology (qv) generally is recognized as a term that identifies those technologies that utilize living organisms in the production and/or alteration of chemical entities that have potential therapeutic activity (52). Besides the production of pharmacologically or biochemically active moieties, these technologies also have been used to produce food ingredients, vaccines, diagnostic testing reagents, and agricultural products (see FERMENTATION; MEDICAL DIAGNOSTIC REAGENTS; VACCINE TECHNOLOGY).

Recombinant deoxyribonucleic (DNA) technology, gene-splicing, genetic engineering (qv), and research in molecular biology and immunology have contributed to biotechnology (53). To track such products that fall into its preview, the FDA considers biotechnology to also include direct DNA transfer technology, hybridoma procedures, cell fusion, molecular alteration of cellular receptors, and the application of cells, cellular components, and tissues that have had their biological activity altered by such technologies (see PROTEIN ENGINEERING) (54).

Drugs developed in the biotechnology arena are peptides and proteins. Erythropoietin, human insulin, and interferons are examples. Generally these chemical entities are present in very small quantities in living organisms or are modifications of such entities. The proteins are produced as solution or injection dosage forms or lyophilized powders to be reconstituted using appropriate vehicles before use.

Biotechnology drugs generally are expensive. Biotechnology also requires large investments, and the patient population needing such drug therapy generally is small which increases the per-dose cost.

10. Packaging

The packaging components of pharmaceutical products are vital to their safe and effective use. Besides serving the patient as a convenient unit of use, the composite package (unit container, labeling, and shipping components) must provide appropriate identification and necessary information for proper use (including

warnings and cautions) and preservation of the product's chemical and physical integrity (see PACKAGING, COSMETICS AND PHARMACEUTICALS).

10.1. Labeling. Labeling, controlled by FDA regulations, includes not only the affixed labels, but also the package inserts that provide more detailed information. Trade, generic, or common name, dose, number of dose units present, and name and address of manufacturer and distributor are required. For nonprescription products, adequate directions for use are required. Prescription products must bear the phrase, "Caution: Federal law prohibits use without a prescription" on their labels.

All drug labels must include batch or lot numbers. Using such coded information, products can be traced through all stages of manufacture. Furthermore, the nature of the drug product may require special cautionary phrases, eg, "store in cool place or refrigerator," "protect from light," and "shake well before using." In the 1990s, labels started to carry the expiration date, ie, shelf-life.

Labeling information also includes warnings as to possible side effects, eg, drowsiness, and potential harm if used with other drugs or certain foods (drug–drug or drug–food interactions). Inserts are generally intended for use by physicians or pharmacists and give name and description of the product, mode of administration, dosage regimen, therapeutic indications and contraindications, precautions and side effects, units of supply, and literature citations. All labeling must be approved by the FDA as part of the New Drug Application. The FDA has proposed the widespread use of patient package inserts (PPIs). These are separate sheets of information, written in layman's terms, providing more detailed information.

The use of over-the-counter (OTC) medications is increasing every year among consumers for symptomatic relief of ailments. Consumers have difficulties in reading and comprehending information on the OTC medication packages. A standardized format to present information on OTC medication packages was necessary; hence the FDA announced guidelines, Over-the-counter Human Drugs: Labeling Requirements, on 11 March 1999. Manufacturers have been given six years since 1999 to comply with the FDA guidelines.

A study found that some manufacturers have adopted the FDA guidelines. However, many manufacturers did not implement several aspects of the guidelines. Although manufacturers still have some time to adhere to the guidelines, early implementation could benefit the consumers (55).

10.2. Containers. The USPXXIII–NFXVIII lists container requirements such as well-closed, tight, or light-resistant. Most containers are light-resistant (amber) glass or plastic. The latter is break-resistant and lightweight, which reduces shipping costs and increases safety.

In hospitals and long-term care units, unit-dose packages are used more and more. This system allows better control of the dispensed drugs in institutional settings and precludes the dispensing of larger numbers of doses than needed.

11. Quality Control and Quality Assurance

Quality control (QC) involves the regular, daily assessment and/or analysis, according to established protocols and standards, of all ingredients, processes, and finished products (56,57). Official USP/NF monographs, for example, provide various chemical, physical, and biological tests and specifications for assurance of purity, potency, and stability of component ingredients used to prepare and package drug products. In-process testing performed at specified points during the production stages, eg, tablet disintegration, weight, fragility, and hardness tests, are part of the QC program. Likewise, the FDA requires process validation procedures as QC constituents. The FDA also monitors QC standards through the requirements of the Current Good Manufacturing Procedures regulations.

Quality assurance (QA) constitutes the broad, oversight functions that include the auditing of the various QC functions. This ensures that appropriate QC standards have been developed and are in regular use (56,57). It includes the acknowledgment of necessary change, when needed, to maintain quality, the education of personnel to be sure they know their assigned QC responsibility, the documentation of all such training programs, spot auditing as an assurance process, and appropriate action to assure and maintain compliance with all externally imposed regulations and internally established criteria and standards.

12. Economic Aspects

Sales of United States brand pharmaceuticals amounted to $\$217.4\times10^9$ for 2004. United States generic brand sales were $\$18.1\times10^9$. In 2004, the average price for a generic prescription was $28.4 and the average for a brand name was $96.01 (58).

Pharmaceutical and biotechnology companies added 38 new medicines to the market in 2004. Among the new therapeutics included treatments for cancer, infectious diseases, chronic kidney disease, Parkinson's, pain, and radiation contamination (58).

The average cost of each approved medicine was $\$802\times10^6$ as reported by Tufts Center for the Study of Drug Development in 2001. In 2004, drug companies spent $\$38.8\times10^9$ on research and development. It now takes 10–15 years for a new medicine to go from the laboratory to the pharmacy. The Pharmaceutical Research and Manufacturers of America (PhMRA) has reported that there are 1000 potential new treatments in the pipeline, and with the completion of the human genome map, more are expected (59).

13. End Notes

The views expressed are the author's and do not necessarily represent those of nor imply endorsement from the Food and Drug Administration or the U.S. Government.

The reader is reminded that almost all the information that is provided in this article is freely available on the Web from the government and other sources and subject to change. The bibliography lists the web addresses and they should be checked frequently.

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Table 1. **Pharmaceutical Dosage Forms**

Dosage form	Constituents, properties	Uses
	Liquid solutions	
aromatic waters	volatile solids or oils, water	flavoring agents, carminative action
liquors or solutions	water, chemicals	internally or externally
syrups	sweetener, solvent, medicinal agent	flavoring agent, medicinal
elixirs	sweetened hydroalcoholic soln, may be medicated	flavor or medicinal
spirits	alcohol, water, volatile substances	flavor or medicinal
tinctures	natural drugs, extracted with appropriate solvent; 10–20 g/cm^3[a]	external or internal
collodions	pyroxylin in ether, medicinal agent (castor oil, camphor)	external for corns and bunions
liniments	oily or alcoholic solutions, suspensions	external with rubbing
parenteral soln	sterile, pyrogen-free, isotonic, pH close to that of blood; oily[b] or aqueous suspension	intravenous, intramuscular, subcutaneous injection
ophthalmic	sterile, isotonic, pH close to that of tears; viscosity builder	eye treatment
nasal	aqueous, isotonic, pH close to that of nasal fluid; sprays or drops	nose treatment
otic	glycerol-based	ear treatment
mouthwash, gargles	aqueous, antiseptic	refreshment, short-term bacterial control
inhalations	administered with mechanical devices	medication of trachea or bronchioles
enemas, douches	aqueous soln or suspension, may include medicinal agent	irrigation of body cavity
	Liquid dispersions	
suspensions	powder suspended in water, alcohol, glycol, or an oil; viscosity builders, wetting agents, preservatives	oral dosing, skin application
emulsions, lotions	oil-in-water (o/w), or water-in-oil (w/o)	oral, external or injection
gels, jellies, magmas	viscous, colloidal dispersions	internal (oral), external
gaseous solutions, dispersions	delivered in atomizers, nebulizers, aerosols, inhalers	external or internal
	Semisolid and plastic dispersions	
ointments	hydrocarbon (oily), absorptive water-washable, or water-soluble bases; emulsifying agents; glycols; medicating agent	external
pastes and cerates	ointments with high dispersed solids or waxes, respectively	external
suppositories	theobroma oil, glycerinated gelatin, or polyethylene glycol base plus medicinal agent	insertion in body cavity

Table 1. (*Continued*)

Dosage form	Constituents, properties	Uses
	Solids	
powders		
bulk	comminuted or blended, dissolved in or mixed with water	external, internal
effervescent	CO_2-releasing base ingredients	oral
dusting	absorbents; lubricants	skin treatment
insufflations	insufflator propels medicated powder into body cavity	body cavities
lyophilized	reconstitution by pharmacist of unstable products	various uses, including parenteral and oral
capsules	small-dose bulk powder enclosed in gelatin shell; active ingredient plus diluent	internal
troches, lozenges	prepared by piping and cutting or disk candy technology; compounded with glycerogelatin	slow dissolution in mouth
tablet triturates	small molded tablets intended for quick complete dissolution, eg, nitroglycerin	oral (sublingual)
granules	particle size larger than powder	oral
compressed tablets	dissolved or mixed with water; great variety of shapes and formulations[c]	oral and external
pellets	for prolonged action	implantation
coated tablets	coating protective; slow release	oral

[a]Concentrations of 1 g/cm^3 are called fluid extracts.
[b]Repository dosage form.
[c]Common excipients: diluents, disintegrators, binders, and lubricants (glidants).

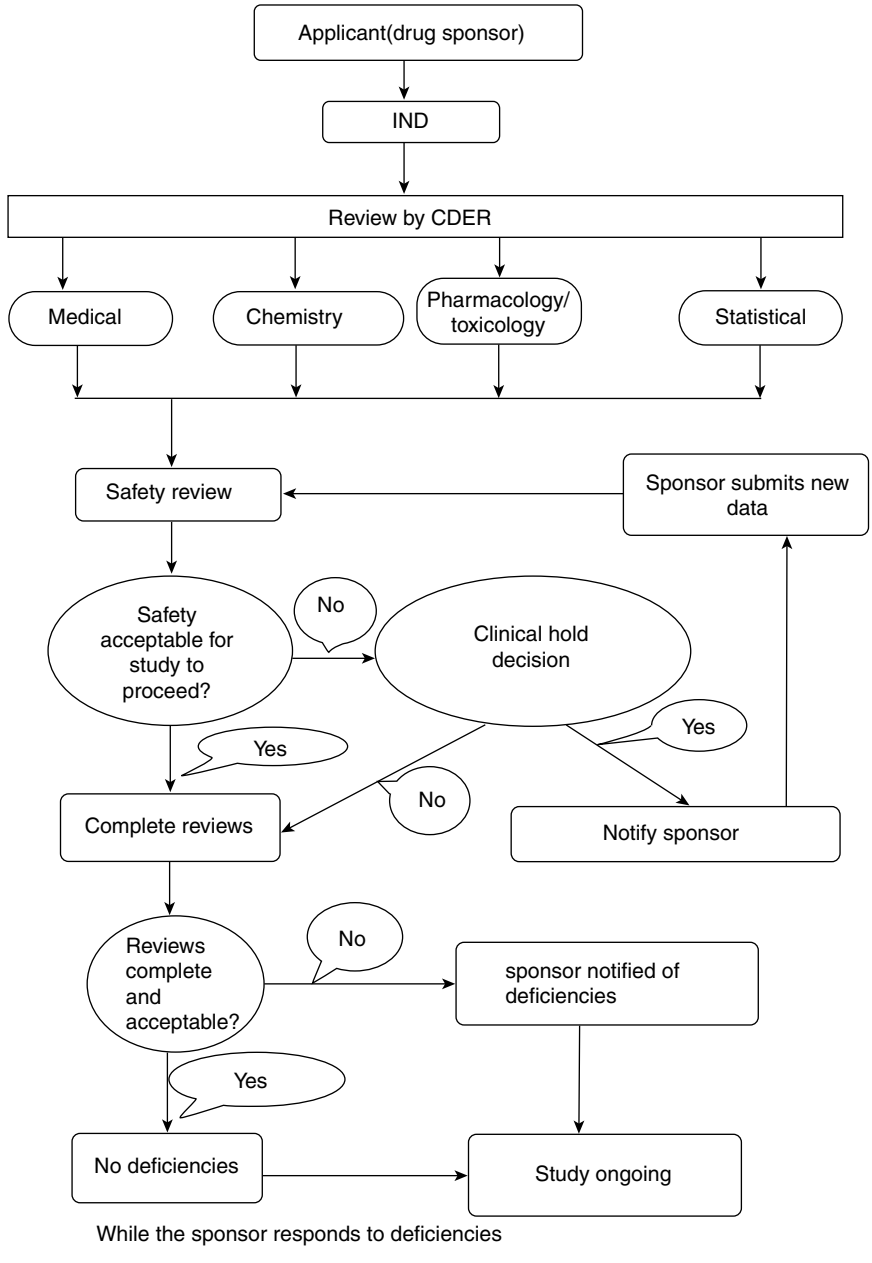

Fig. 1. IND review flow chart from Ref. 17.

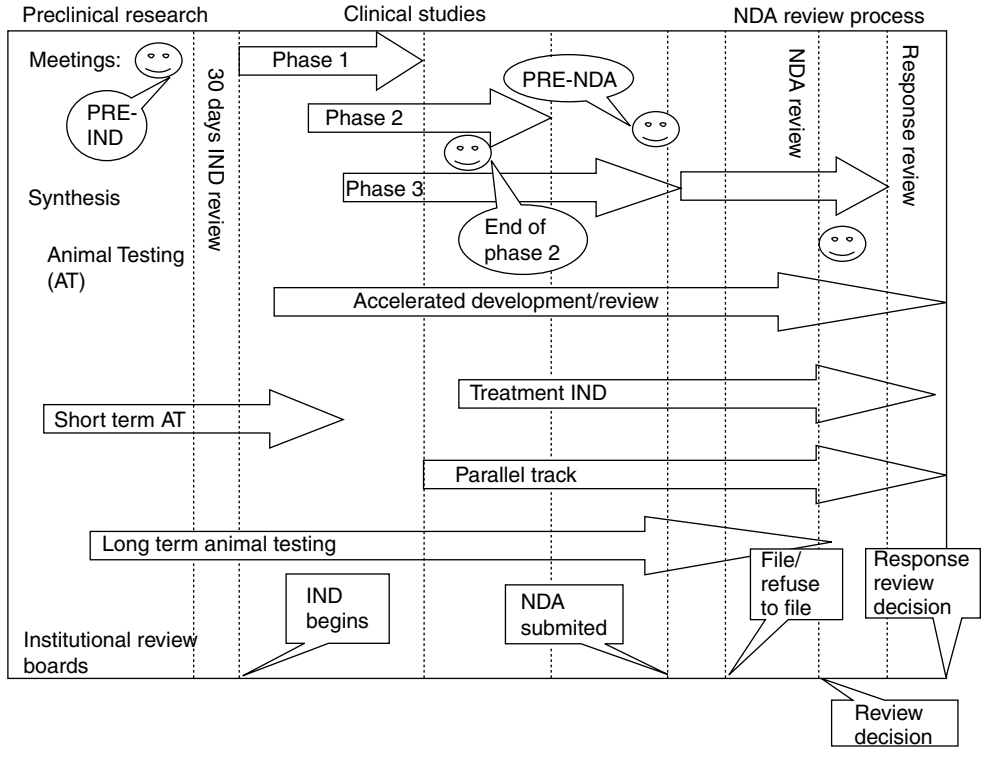

Fig. 2. New drug development and approval process.

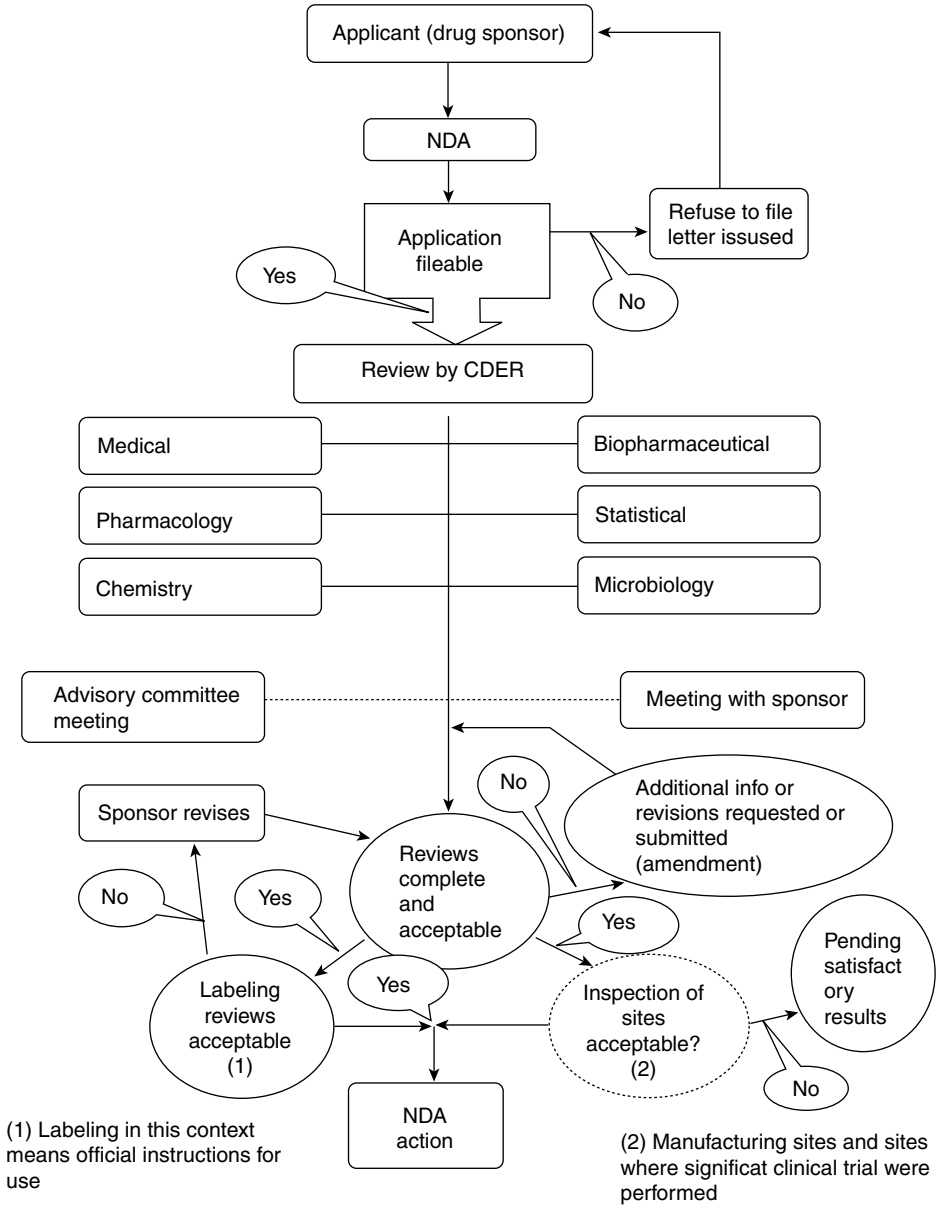

Fig. 3. NDA review process from Ref. 17.

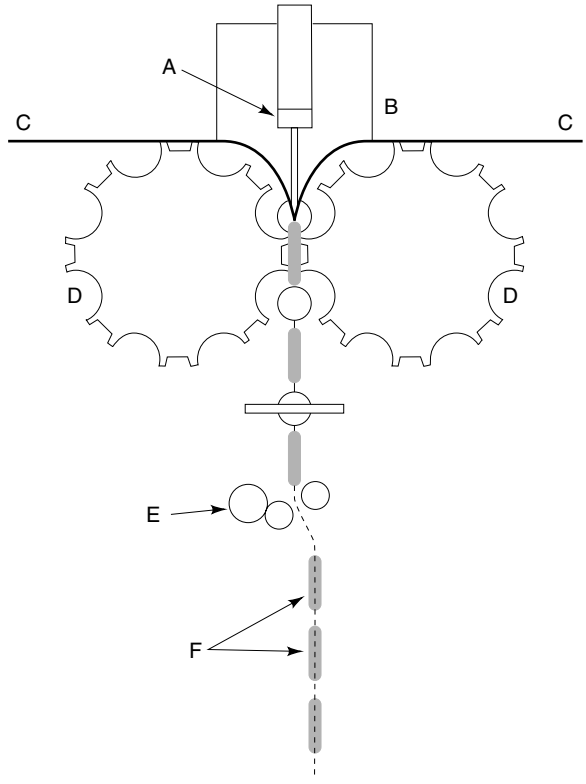

Fig. 4. Rotary die process of soft gelatin capsules where A represents the drug mix; B, the mold wedge; C, gelatin ribbons; D, die rolls; E, capsules; and F, scrap gelatin. Courtesy of R. P. Scherer Corp.

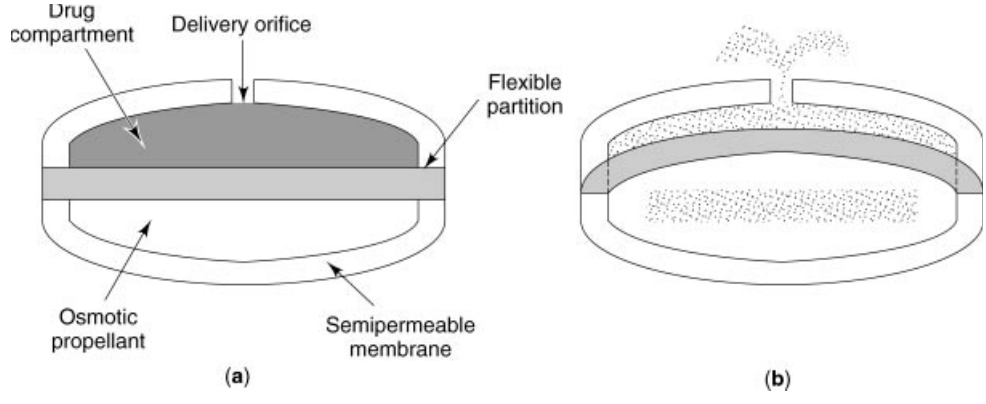

Fig. 5. (**a**) Cross section of the push–pull oral osmotic system (OROS), which has an inner flexible partition to segregate the osmotic propellant from the drug compartment. (**b**) Push–pull OROS in operation with the propellant imbibing water, increasing in volume, and pushing the drug out of the device through the delivery orifice (44).

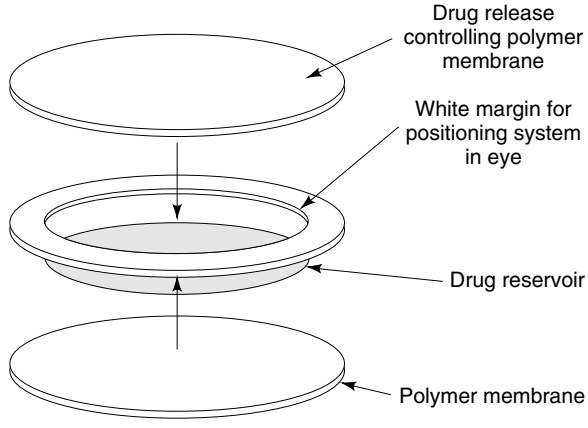

Fig. 6. Components of the Ocusert Pilo-40 therapeutic system (44).