SECTION I

INTRODUCTION TO DRUGS, DRUG DOSAGE FORMS, AND DRUG DELIVERY SYSTEMS

1 Introduction to Drugs and Pharmacy

OBJECTIVES

After reading this chapter, the student will be able to:

1. Describe the development and purpose of the *United States Pharmacopeia* (USP) and the *National Formulary* (NF)
2. Describe the central features of a typical drug monograph
3. Compare and contrast significant drug regulation and control federal laws and their impact on pharmacy
4. Explain the concept of pharmaceutical care
5. Summarize the Code of Ethics for Pharmacists of the American Pharmacists Association
6. Summarize the Code of Ethics of the American Association of Pharmaceutical Scientists (AAPS)

A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals (Food, Drug, and Cosmetic Act, 1938). One of the most astounding qualities of drugs is the diversity of their actions and effects on the body. This quality enables their selective use in the treatment of a range of common and rare conditions involving virtually every body organ, tissue, and cell.

Some drugs selectively stimulate the cardiac muscle, the central nervous system, or the gastrointestinal tract, whereas other drugs have the opposite effect. Mydriatic drugs dilate the pupil of the eye, and miotics constrict or diminish pupillary size. Drugs can render blood more coagulable or less coagulable; they can increase the hemoglobin content of the erythrocytes, reduce serum cholesterol, or expand blood volume.

Drugs termed emetics induce vomiting, whereas antiemetic drugs prevent vomiting. Diuretic drugs increase the flow of urine; expectorant drugs increase respiratory tract fluid; and cathartics or laxatives evacuate the bowel. Other drugs decrease the flow of urine, diminish body secretions, or induce constipation.

Drugs may be used to reduce pain, fever, thyroid activity, rhinitis, insomnia, gastric acidity, motion sickness, blood pressure, and mental depression. Other drugs can elevate mood, blood pressure, or activity of the endocrine glands. Drugs can combat infectious disease, destroy intestinal worms, or act as antidotes against the poisoning effects of other drugs. Drugs can assist in smoking cessation or alcohol withdrawal or can modify obsessive–compulsive disorders.

Drugs are used to treat common infections, AIDS, benign prostatic hyperplasia, cancer, cardiovascular disease, asthma, glaucoma, Alzheimer disease, and male impotence. They can protect against the rejection of transplanted tissues and organs and reduce the incidence of measles and mumps. Antineoplastic drugs provide one means of attacking the cancerous process; radioactive pharmaceuticals provide another. Drugs may be used to diagnose diabetes, liver malfunction,

tuberculosis, or pregnancy. They can replenish a body deficient in antibodies, vitamins, hormones, electrolytes, protein, enzymes, or blood. Drugs can prevent pregnancy, assist fertility, and sustain life itself.

Certainly, the vast array of effective medicinal agents available today is one of our greatest scientific accomplishments. It is difficult to conceive our civilization devoid of these remarkable and beneficial agents. Through their use, many of the diseases that have plagued humans throughout history, such as smallpox and poliomyelitis, are now virtually extinct. Illnesses such as diabetes, hypertension, and mental depression are effectively controlled with modern drugs. Today's surgical procedures would be virtually impossible without the benefit of anesthetics, analgesics, antibiotics, blood transfusions, and intravenous fluids.

New drugs may be derived from plant or animal sources, as by-products of microbial growth, or through chemical synthesis, molecular modification, or biotechnology. Computer libraries and data banks of chemical compounds and sophisticated methods of screening for potential biologic activity assist drug discovery.

The process of drug discovery and development is complex. It entails the collective contributions of many scientific specialists, including organic, physical, and analytical chemists; biochemists; molecular biologists; bacteriologists; physiologists; pharmacologists; toxicologists; hematologists; immunologists; endocrinologists; pathologists; biostatisticians; pharmaceutical scientists; clinical pharmacists; physicians; and many others.

After a potential new drug substance is discovered and undergoes definitive chemical and physical characterization, a great deal of biologic information must be gathered. The basic pharmacology, or the nature and mechanism of action of the drug on the biologic system, must be determined including toxicologic features. The drug's site and rate of absorption, its pattern of distribution and concentration within the body, its duration of action, and the method and rate of its elimination or excretion must be studied. Information on the drug's metabolic degradation and the activity of any of its metabolites must be obtained. A comprehensive study of the short-term and long-term effects of the drug on various body cells, tissues, and organs must be made. Highly specific information, such as the effect of the drug on the fetus of a pregnant animal or its ability to pass to a nursing baby through the breast milk of its mother, may be obtained. Many a promising new drug has been abandoned because of its potential to cause excessive or hazardous adverse effects.

The most effective routes of administration (e.g., oral, rectal, parenteral, topical) must be determined, and guidelines for the dosages recommended for persons of varying ages (e.g., neonates, children, adults, the elderly), weights, and states of illness have to be established. It has been said that the only difference between a drug and a poison is the dose. To facilitate administration of the drug by the selected routes, appropriate dosage forms, such as tablets, capsules, injections, suppositories, ointments, aerosols, and others, are formulated and prepared. Each of these dosage units is designed to contain a specified quantity of medication for ease and accuracy of dosage administration. These dosage forms are highly sophisticated delivery systems. Their design, development, production, and use are the product of application of the pharmaceutical sciences—the blending of the basic, applied, and clinical sciences with pharmaceutical technology.

Each particular pharmaceutical product is a formulation unique unto itself. In addition to the active therapeutic ingredients, a pharmaceutical formulation contains a number of nontherapeutic or pharmaceutical ingredients. It is through their use that a formulation achieves its unique composition and characteristic physical appearance. Pharmaceutical ingredients include such materials as fillers, thickeners, solvents, suspending agents, tablet coatings and disintegrants, penetration enhancers, stabilizing agents, antimicrobial preservatives, flavors, colorants, and sweeteners.

To ensure the stability of a drug in a formulation and the continued effectiveness of

the drug product throughout its usual shelf life, the principles of chemistry, physical pharmacy, microbiology, and pharmaceutical technology must be applied. The formulation must be such that all components are physically and chemically compatible, including the active therapeutic agents, the pharmaceutical ingredients, and the packaging materials. The formulation must be preserved against decomposition due to chemical degradation and protected from microbial contamination and the destructive influences of excessive heat, light, and moisture. The therapeutic ingredients must be released from the dosage form in the proper quantity and in such a manner that the onset and duration of the drug's action are that which are desired. The pharmaceutical product must lend itself to efficient administration and must possess attractive features of flavor, odor, color, and texture that enhance acceptance by the patient. Finally, the product must be effectively packaged and clearly and completely labeled according to legal regulations.

Once prepared, the pharmaceutical product must be properly administered if the patient is to receive maximum benefit. The medication must be taken in sufficient quantity, at specified intervals, and for an indicated duration to achieve the desired therapeutic outcomes. The effectiveness of the medication in achieving the prescriber's objectives should be reevaluated at regular intervals and necessary adjustments made in the dosage, regimen, schedule, or form, or indeed, in the choice of the drug administered. Patients' expressions of disappointment in the rate of progress or complaints of side effects to the prescribed drug should be evaluated and decisions made as to the continuance, adjustment, or major change in drug therapy. Before initially taking a medication, a patient should be advised of any expected side effects and of foods, beverages, and/or other drugs that may interfere with the effectiveness of the medication.

Through professional interaction and communication with other health professionals, the pharmacist can contribute greatly to patient care. An intimate knowledge of drug actions, pharmacotherapeutics, formulation and dosage form design, available pharmaceutical products, and drug information sources makes the pharmacist a vital member of the health care team. The pharmacist is entrusted with the legal responsibility for the procurement, storage, control, and distribution of effective pharmaceutical products and for the compounding and filling of prescription orders. Drawing on extensive training and knowledge, the pharmacist serves the patient as an advisor on drugs and encourages their safe and proper use through patient counseling. The pharmacist delivers pharmaceutical services in a variety of community and institutional health care environments and effectively uses medication records, patient monitoring, and assessment techniques in safeguarding the public health.

To appreciate the progress that has been made in drug discovery and development and to provide background for the study of modern drugs and pharmaceutical dosage forms, it is important to examine pharmacy's heritage.

THE HERITAGE OF PHARMACY

Drugs, in the form of vegetation and minerals, have existed as long as humans. Human disease and the instinct to survive have led to their discovery through the ages. The use of drugs, crude though they may have been, undoubtedly began long before recorded history, for the instinct of primitive man to relieve the pain of a wound by bathing it in cool water or by soothing it with a fresh leaf or protecting it with mud is within the realm of belief. From experience, early humans would learn that certain therapy was more effective than others, and from these beginnings came the practice of drug therapy.

Among many early races, disease was believed to be caused by the entrance of demons or evil spirits into the body. The treatment naturally involved ridding the body of the supernatural intruders. From the earliest records, the primary methods of removing spirits were through the use of spiritual incantations, the application of

noisome materials, and the administration of specific herbs or plant materials.

The First Apothecary

Before the days of the priestcraft, the wise man or woman of the tribe, whose knowledge of the healing qualities of plants had been gathered through experience or handed down by word of mouth, was called upon to attend to the sick or wounded and prepare the remedy. It was in the preparation of the medicinal materials that the art of the apothecary originated.

The art of the apothecary has always been associated with the mysterious, and its practitioners were believed to have connection with the world of spirits and thus performed as intermediaries between the seen and the unseen. The belief that a drug had magical associations meant that its action, for good or for evil, did not depend upon its natural qualities alone. The compassion of a god, the observance of ceremonies, the absence of evil spirits, and the healing intent of the dispenser were individually and collectively needed to make the drug therapeutically effective. Because of this, the tribal apothecary was one to be feared, respected, trusted, sometimes mistrusted, worshipped, and revered, for it was through his potions that spiritual contact was made, and upon that contact the cures or failures depended.

Throughout history, the knowledge of drugs and their application to disease has always meant power. In the Homeric epics, the term *pharmakon* (Gr.), from which our word pharmacy was derived, connotes a charm or a drug that can be used for good or for evil. Many of the tribal apothecary's failures were doubtless due to impotent or inappropriate medicines, underdosage, overdosage, and even poisoning. Successes may be attributed to experience, mere coincidence of appropriate drug selection, natural healing, inconsequential effect of the drug, or placebo effects, that is, successful treatment due to psychologic rather than therapeutic effects. Even today, placebo therapy with inert or inconsequential chemicals is used successfully to treat individual patients and is a routine practice in the clinical evaluation of new drugs, in which subjects' responses to the effects of the actual drug and the placebo are compared and evaluated.

As time passed, the art of the apothecary combined with priestly functions, and among the early civilizations, the priest–physician became the healer of the body as well as of the soul. Pharmacy and medicine are indistinguishable in their early history because their practice was the combined function of the tribal religious leaders.

Early Drugs

Because of the patience and intellect of the archaeologist, the types and specific drugs used in the early history of drug therapy are not as indefinable as one might suspect. Numerous ancient tablets, scrolls, and other relics as early as 3000 BC have been uncovered and deciphered by archaeologic scholars to the gratitude of historians of both medicine and pharmacy (Fig. 1.1).

Perhaps the most famous of these surviving artifacts is the Ebers papyrus, a continuous scroll some 60 feet long and a foot wide dating to the 16th century BC. This document, which is now preserved at the University of Leipzig, is named for the noted German Egyptologist Georg Ebers, who discovered it in the tomb of a mummy and partly translated it during the last half of the 19th century. Since that time, many scholars have participated in the translation of the document's challenging hieroglyphics, and although they are not unanimous in their interpretations, there is little doubt that by 1550 BC, the Egyptians were using some drugs and dosage forms that are still used today.

The text of the Ebers papyrus is dominated by drug formulas, with more than 800 formulas or prescriptions being described and more than 700 drugs mentioned. The drugs are chiefly botanical, although mineral and animal drugs are also noted. Such botanical substances as acacia, castor bean (from which we express castor oil), and fennel are mentioned along with

FIGURE 1.1 Sumerian clay tablet from the third millennium BC on which are believed to be the world's oldest written prescriptions. Among them are a preparation of the seed of carpenter plant, gum resin of markhazi, and thyme, all pulverized and dissolved in beer, and a combination of powdered roots of "Moon plant" and white pear tree, also dissolved in beer. (Courtesy of the University Museum, University of Pennsylvania.)

apparent references to such minerals as iron oxide, sodium carbonate, sodium chloride, and sulfur. Animal excrements were also used in drug therapy.

The vehicles of the day were beer, wine, milk, and honey. Many of the pharmaceutical formulas employed two dozen or more medicinal agents, a type of preparation later called polypharmacy. The Egyptians commonly used mortars and pestles, hand mills, sieves, and balances in their compounding of suppositories, gargles, pills, inhalations, troches, lotions, ointments, plasters, and enemas.

Introduction of the Scientific Viewpoint

Throughout history, many individuals have contributed to the advancement of the health sciences. Notable among those whose genius and creativeness had a revolutionary influence on the development of pharmacy and medicine were Hippocrates (ca. 460–377 BC), Dioscorides (first century AD), Galen (ca. 130–200 AD), and Paracelsus (1493–1541 AD).

Hippocrates, a Greek physician, is credited with the introduction of scientific pharmacy and medicine. He rationalized medicine, systematized medical knowledge, and put the practice of medicine on a high ethical plane. His thinking on the ethics and science of medicine dominated the medical writings of his and successive generations, and his concepts and precepts are embodied in the renowned Hippocratic oath of ethical behavior for the healing professions. His works included the descriptions of hundreds of drugs, and it was during this period that the term *pharmakon* came to mean a purifying remedy for good only, transcending the previous connotation of a charm or drug for good or for evil purposes. Because of his pioneering work in medical science and his inspirational teachings and advanced philosophies that have become a part of modern medicine, Hippocrates is honored by being called the Father of Medicine.

Dioscorides, a Greek physician and botanist, was the first to deal with botany as an applied science of pharmacy. His work, *De Materia Medica*, is considered a milestone in the development of pharmaceutical botany and in the study of naturally occurring medicinal materials. This area of study is today known as natural products chemistry and/or pharmacognosy, a term formed from two Greek words, *pharmakon*, drug, and *gnosis*, knowledge. Some of the drugs Dioscorides described, including opium, ergot, and hyoscyamus, continue to have use in medicine. His descriptions of the art of identifying and collecting natural drug products, the methods of their proper storage, and the means of detecting adulterants or contaminants were the standards of the period, established the

need for additional work, and set guidelines for future investigators.

Claudius Galen, a Greek pharmacist–physician who attained Roman citizenship, aimed to create a perfect system of physiology, pathology, and treatment. Galen formulated doctrines that were followed for 1,500 years. He was one of the most prolific authors of his or any other era, having been credited with 500 treatises on medicine and some 250 others on philosophy, law, and grammar. His medical writings include descriptions of numerous drugs of natural origin with a profusion of drug formulas and methods of compounding. He originated so many preparations of vegetable drugs by mixing or melting the individual ingredients that the field of pharmaceutical preparations was once commonly referred to as "Galenic pharmacy." Perhaps the most famous of his formulas is one for a cold cream, called Galen's Cerate, which has similarities to some in use today, including theatrical cold cream and others that are slight modifications of his formula.

Pharmacy remained a function of medicine until the increasing variety of drugs and the growing complexity of compounding demanded specialists who could devote full attention to the art. Pharmacy was officially separated from medicine for the first time in 1240 AD, when a decree of Emperor Frederick II of Germany regulated the practice of pharmacy within the part of his kingdom called the Two Sicilies. His edict separating the two professions acknowledged that pharmacy required special knowledge, skill, initiative, and responsibility if adequate care to the medical needs of the people was to be guaranteed. Pharmacists were obligated by oath to prepare reliable drugs of uniform quality according to their art. Any exploitation of the patient through business relations between the pharmacist and the physician was strictly forbidden. Between that time and the evolution of chemistry as an exact science, pharmacy and chemistry became united as pharmacy and medicine had been.

Perhaps no person in history exercised such a revolutionary influence on pharmacy and medicine as did Aureolus Theophrastus Bombastus von Hohenheim (1493–1541), a Swiss physician and chemist who called himself Paracelsus. He influenced the transformation of pharmacy from a profession based primarily on botanical science to one based on chemical science. Some of his chemical observations were astounding for his time and for their anticipation of later discoveries. He believed it was possible to prepare a specific medicinal agent to combat each specific disease and introduced a host of chemical substances to internal therapy.

Early Research

As the knowledge of the basic sciences increased, so did their application to pharmacy. The opportunity was presented for the investigation of medicinal materials on a firm scientific basis, and the challenge was accepted by numerous pharmacists who conducted their research in the back rooms and basements of their pharmacies. Noteworthy among them was the Swede Karl Wilhelm Scheele (1742–1786), perhaps the most famous of all pharmacists because of his scientific genius and dramatic discoveries. Among his discoveries were the chemicals lactic acid, citric acid, oxalic acid, tartaric acid, and arsenic acid. He identified glycerin, invented new methods of preparing calomel and benzoic acid, and discovered oxygen a year before Priestley.

The isolation of morphine from opium by the German pharmacist Friedrich Sertürner (1783–1841) in 1805 prompted a series of isolations of other active materials from medicinal plants by a score of French pharmacists. Joseph Caventou (1795–1877) and Joseph Pelletier (1788–1842) combined their talents and isolated quinine and cinchonine from cinchona and strychnine and brucine from nux vomica. Pelletier together with Pierre Robiquet (1780–1840) isolated caffeine, and Robiquet independently separated codeine from opium. Methodically, one chemical after another was isolated from plant drugs and identified as an agent responsible for the plants' medicinal activity. Today we are still engaged in this fascinating activity as we probe nature for more useful and more specific therapeutic agents. Contemporary

examples of drugs isolated from a natural source include paclitaxel (Taxol), an agent with antitumor activity derived from the Pacific yew tree (*Taxus baccata*) and employed in the treatment of metastatic carcinoma of the ovary; vincaleukoblastine, another antineoplastic drug, from *Vinca rosea*; and digoxin, a cardiac glycoside, from *Digitalis lanata*.

Throughout Europe during the late 18th century and the beginning of the 19th century, pharmacists like Pelletier and Sertürner were held in great esteem because of their intellect and technical abilities. They applied the art and the science of pharmacy to the preparation of drug products with the highest standards of purity, uniformity, and efficacy possible at that time. The extraction and isolation of active constituents from crude (unprocessed) botanical drugs led to the development of dosage forms of uniform strength containing singly effective therapeutic agents of natural origin. Many pharmacists of the period began to manufacture quality pharmaceutical products on a small but steadily increasing scale to meet the growing needs of their communities. Some of today's largest pharmaceutical research and manufacturing companies developed from these progressive prescription laboratories of two centuries ago.

Although many of the drugs indigenous to America and first used by the American Indians were adopted by the settlers, most drugs needed in this country before the 19th century were imported from Europe, either as the raw materials or as finished products. With the Revolutionary War, however, it became more difficult to import drugs, and the American pharmacist was stimulated to acquire the scientific and technologic expertise of his European contemporary. From this period until the Civil War, pharmaceutical manufacture was in its infancy in this country. A few of the pharmaceutical firms established during the early 1800s are still in operation. In 1821, the Philadelphia College of Pharmacy was established as the nation's first school of pharmacy. In 1820, the *United States Pharmacopeia* (USP) was created to aid in establishing standards for drugs in the United States.

DRUG STANDARDS

As the scientific basis for drugs and drug products developed, so did the need for uniform standards to ensure quality. This need led to the development and publication of monographs and reference books containing such standards to be used by those involved in the production of drugs and pharmaceutical products. Organized sets of monographs or books of these standards are called pharmacopeias or formularies.

The *United States Pharmacopeia* and the *National Formulary*

The term pharmacopeia comes from the Greek *pharmakon*, meaning drug, and *poiein*, meaning make, and the combination indicates any recipe or formula or other standards required to make or prepare a drug. The term was first used in 1580 in connection with a local book of drug standards in Bergamo, Italy. From that time on, countless city, state, and national pharmacopeias were published by various European pharmaceutical societies. As time passed, the value of a uniform set of national drug standards became apparent. In Great Britain, for example, three city pharmacopeias—the London, the Edinburgh, and the Dublin—were official until 1864, when they were replaced by the *British Pharmacopoeia* (BP).

In the United States, drug standards were first provided on a national basis in 1820, when the first USP was published. However, the need for drug standards was recognized in this country long before the first USP was published. For convenience and because of their familiarity with them, colonial physicians and apothecaries used the pharmacopeias and other references of their various homelands. The first American pharmacopeia was the so-called *Lititz Pharmacopeia*, published in 1778 at Lititz, Pennsylvania, for use by the Military Hospital of the United States Army. It was a 32-page booklet containing information on 84 internal and 16 external drugs and preparations.

During the last decade of the 18th century, several attempts were made by various

local medical societies to collate drug information, set appropriate standards, and prepare an extensive American pharmacopeia of the drugs in use at that time. In 1808, the Massachusetts Medical Society published a 272-page pharmacopeia containing information or monographs on 536 drugs and pharmaceutical preparations. Included were monographs on many drugs indigenous to America, which were not described in the European pharmacopeias of the day.

On January 6, 1817, Lyman Spalding, a physician from New York City, submitted a plan to the Medical Society of the County of New York for the creation of a national pharmacopeia. Spalding's efforts were later to result in his being recognized as the Father of the *United States Pharmacopeia*. He proposed dividing the United States as then known into four geographic districts—northern, middle, southern, and western. The plan provided for a convention in each of these districts, to be composed of delegates from all medical societies and medical schools within them. Where there was as yet no incorporated medical society or medical school, voluntary associations of physicians and surgeons were invited to assist in the undertaking. Each district's convention was to draft a pharmacopeia and appoint delegates to a general convention to be held later in Washington, DC. At the general convention, the four district pharmacopeias were to be compiled into a single national pharmacopeia.

Draft pharmacopeias were submitted to the convention by only the northern and middle districts. These were reviewed, consolidated, and adopted by the first United States Pharmacopeial Convention assembled in Washington, DC, on January 1, 1820 (Fig. 1.2). The first USP was published on December 15, 1820, in English and Latin, then the international language of medicine, to render the book more intelligible to physicians and pharmacists of any nationality. Within its 272 pages were listed 217 drugs considered worthy of recognition; many of them were taken from the *Massachusetts Pharmacopeia*, which is considered by some to be the precursor to the USP. The objective of the first USP was stated in its preface and remains important. It reads in part

FIGURE 1.2 The first United States Pharmacopeial Convention, held on January 1, 1820 in Washington, DC. (Reprinted with permission from the United States Pharmacopeial Convention.)

> It is the object of a Pharmacopeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries (1).

Before adjourning, the convention adopted a constitution and bylaws, with provisions for subsequent meetings of the convention leading to a revised USP every 10 years. As many new drugs entered use, the need for more frequent issuance of standards became increasingly apparent. In 1900, the Pharmacopeial Convention granted authority to issue supplements to the USP whenever necessary to maintain satisfactory standards. At the 1940 meeting of the convention, it was decided to revise the USP every 5 years while maintaining the use of periodic supplements.

The first United States Pharmacopeial Convention was composed exclusively of physicians. In 1830 and again in 1840, prominent pharmacists were invited to assist in the revision, and in recognition of their contributions pharmacists were awarded full membership in the convention of 1850 and have

participated regularly ever since. By 1870, the USP was so nearly in the hands of pharmacists that vigorous efforts were required to revive interest in it among physicians. The present constitution and bylaws of the United States Pharmacopeial Convention provide for accredited delegates representing educational institutions, professional and scientific organizations, divisions of governmental bodies, non–United States international organizations and pharmacopeial bodies, persons who possess special scientific competence or knowledge of emerging technologies, and public members (2). Of the eight elected members of the board of trustees, at least two must be representatives of the medical sciences, two others must be representatives of the pharmaceutical sciences, one must be a public member, and three shall serve without restriction concerning their affiliation.

After the appearance of the first USP, the art and science of both pharmacy and medicine changed remarkably. Before 1820, drugs to treat disease had been the same for centuries. The USP of 1820 reflected the fact that the apothecary of that day was competent at collecting and identifying botanical drugs and preparing from them the mixtures and preparations required by the physician. The individual pharmacist seemed fulfilled as he applied his total art to the creation of elegant pharmaceutical preparations from crude botanical materials. It was a time that would never be seen again because of the impending upsurge in technologic capabilities and the steady development of the basic sciences, particularly synthetic organic chemistry.

The second half of the 19th century brought great and far-reaching changes. The industrial revolution was in full swing in the United States. The steam engine, which used water power to turn mills that powdered crude botanical drugs, was replaced by the gas, diesel, or electric motor. New machinery was substituted for the old whenever possible, and often machinery from other industries was adapted to the special needs of pharmaceutical manufacturing. Mixers from the baking industry, centrifugal machines from the laundry industry, and sugarcoating pans from the candy industry were a few examples of improvisations. Production increased rapidly, but the new industry had to wait for the scientific revolution before it could claim newer and better drugs for mankind. A symbiosis between science and the advancing technology was needed.

By 1880, the industrial manufacture of chemicals and pharmaceutical products had become well established in this country, and the pharmacist was relying heavily on commercial sources for drug supply. Synthetic organic chemistry began to have its influence on drug therapy. The isolation of some active constituents of plant drugs led to the knowledge of their chemical structure. From this arose methods of synthetically duplicating the same structures, as well as manipulating molecular structure to produce organic chemicals yet undiscovered in nature. In 1872, the synthesis of salicylic acid from phenol inaugurated the synthesis of a group of analgesic compounds including acetylsalicylic acid (aspirin), which was introduced into medicine in 1899. Among other chemicals synthesized for the first time were sleep-producing derivatives of barbituric acid called barbiturates. This new source of drugs—synthetic organic chemistry—welcomed the turn into the 20th century.

Until this time, drugs created through the genius of the synthetic organic chemist relieved a host of maladies, but none had been found to be curative—none, that is, until 1910, when arsphenamine, a specific agent against syphilis, was introduced to medical science. This was the start of an era of chemotherapy, an era in which the diseases of humans became curable through the use of specific chemical agents. The concepts, discoveries, and inspirational work that led mankind to this glorious period are credited to Paul Ehrlich, the German bacteriologist who together with a Japanese colleague, Sahachiro Hata, discovered arsphenamine. Today many of our drugs originate in the flask of the synthetic organic chemist.

The advancement of science, both basic and applied, led to drugs of a more complex nature and to more of them. The standards advanced by the USP were more than ever needed to protect the public by ensuring the purity and uniformity of drugs.

When the American Pharmaceutical Association (APhA) was organized in 1852, the only authoritative and recognized book of drug standards available was the third revision of the USP. To serve as a therapeutic guide to the medical profession, its scope, then as now, was restricted to drugs of established therapeutic merit. Because of strict selectivity, many drugs and formulas that were accepted and used by the medical profession were not granted admission to early revisions of the USP. As a type of protest, and in keeping with the original objectives of the APhA to standardize drugs and formulas, certain pharmacists, with the sanction of their national organization, prepared a formulary containing many of the popular drugs and formulas denied admission to the USP. The first edition was published in 1888 under the title *National Formulary of Unofficial Preparations* (3). The designation "unofficial preparations" reflected the protest mood of the authors, since the USP had earlier adopted the term "official" as applying to the drugs for which it provided standards. The title was changed to *National Formulary* (NF) on June 30, 1906, when President Theodore Roosevelt signed into law the first federal Pure Food and Drug Act, designating both the USP and NF as establishing legal standards for medicinal and pharmaceutical substances. Thus the two publications became official compendia. Among other things, the law required that whenever the designation USP or NF was used or implied on drug labeling, the products must conform to the physical and chemical standards set forth in the compendium monograph.

The early editions of the NF served mainly as a convenience to practicing pharmacists by providing uniform names of drugs and preparations and working directions for the small-scale manufacture of popular pharmaceutical preparations prescribed by physicians. Before 1940, the NF, like the USP, was revised every 10 years. After that date, new editions appeared every 5 years, with supplements issued periodically as necessary.

In 1975, the United States Pharmacopeial Convention, Inc. purchased the NF, unifying the official compendia and providing the mechanism for a single national compendium.

Today, the United States Pharmacopeia-National Formulary (USP-NF) is continuously revised. Revisions are available annually in hard copy and as online editions, including twice-yearly supplements and update notices on the USP Web site. Monographs for drug substances, dietary supplements, dosage forms, and compounded preparations are contained in the USP sections of the combined compendium whereas monographs for pharmaceutical excipients are contained in the NF section.

A *Spanish* edition of the USP-NF was introduced in 2006. Presently, USP standards are used in more than 140 countries worldwide.

The standards advanced by the USP and the NF are put to active use by all members of the health care industry who share the responsibility and enjoy the public's trust for ensuring the availability of quality drugs and pharmaceutical products and preparations. The term "products" is now generally used to refer to manufactured drugs and "preparations" to compounded drugs. The USP-NF is used by pharmacists, physicians, dentists, veterinarians, nurses, producers, and suppliers of bulk chemicals for use in drug production; large and small manufacturers of pharmaceutical products; drug procurement officers of various private and public health agencies and institutions; drug regulatory and enforcement agencies; and others.

USP and NF Monographs

The USP and NF adopt standards for drug substances, pharmaceutical ingredients, and dosage forms reflecting the best in the current practices of medicine and pharmacy and provide suitable tests and assay procedures for demonstrating compliance with these standards. In fulfilling this function, the compendia become legal documents, every statement of which must be of a high degree of clarity and specificity.

In the United States, a drug with a name recognized in the USP-NF must comply with compendial identity standards or be deemed adulterated, misbranded, or both. To avoid being deemed adulterated, such drugs also must comply with compendial standards for

strength, quality, or purity, unless labeled to show all respects in which the drug differs. In addition, to avoid being deemed misbranded, drugs recognized in the USP-NF also must comply with compendial standards for packaging and labeling.

Many pharmaceutical products on the market, especially combinations of therapeutic ingredients, are not described in formulation or dosage form monographs in the official compendia. However, the individual components in these products are described in monographs in the compendia, in supplements to the compendia, or in drug applications for marketing approved by the U.S. Food and Drug Administration (FDA).

An example of a typical monograph for a drug substance appearing in the USP is shown in Figure 1.3. This monograph demonstrates the type of information that appears for organic medicinal agents.

The initial part of the monograph consists of the official title (generic or nonproprietary name) of the drug substance. This is followed by its graphic or structural formula, empirical formula, molecular weight, established chemical names, and the drug's Chemical Abstracts Service (CAS) registry number. The CAS registry number identifies each compound uniquely in the CAS computer information retrieval system. Appearing next in the monograph is a statement of chemical purity, a cautionary statement that reflects the toxic nature of the agent, packaging and storage recommendations, and chemical and physical tests, and the prescribed method of assay to substantiate the identification and purity of the chemical.

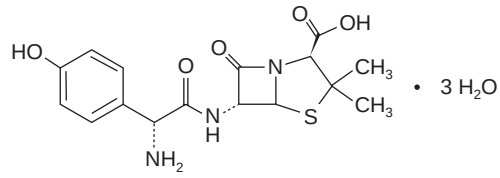
In each monograph, the standards set forth are specific to the individual therapeutic agent, pharmaceutical material, or dosage form product/preparation to ensure purity, potency, and quality.

Other Pharmacopeias

In addition to the USP and the NF, other references to drug standards, such as the *Homeopathic Pharmacopeia of the United States* (HPUS) and the *Pharmacopeia Internationalis*, or *International Pharmacopeia* (IP), provide additional guidelines for drug quality required by certain practitioners and agencies. HPUS is used by pharmacists and homeopathists as well as by law enforcement agencies that must ensure the quality of homeopathic drugs. The term homeopathy was coined by Samuel Hahnemann (1755–1843) from the Greek *homoios*, meaning similar, and *pathos*, meaning disease. In essence, the basis of homeopathy is the law of similars, or that like cures like: that is, a drug that produces symptoms of the illness in healthy persons will also be capable of treating those same symptoms and curing the disease. Embodied in the homeopathic approach are (*a*) the testing of a drug on healthy persons to find the drug's effects so that it may be employed against the same symptoms manifesting a disease in an ill person; (*b*) the use of only minute doses of drugs in therapy, employed in dilutions expressed as "1X" (a 1:10 dilution), "2X" (a 1:100 dilution), and so on; (*c*) the administration of not more than one drug at a time; and (*d*) the treatment of the entire symptom complex of the patient, not just one symptom (4–6). The HPUS is essential for pharmacists who prepare drugs to be used in the practice of homeopathy.

The IP is published by the World Health Organization (WHO) of the United Nations with the cooperation of member countries. It is intended as a recommendation to national pharmacopeial revision committees to modify their pharmacopeias according to international standards. It has no legal authority, only the respect and recognition accorded it by the participating countries in their effort to provide acceptable drug standards on an international basis. The first volume of the IP was published in 1951. It has been revised periodically since that time.

Over the years, a number of countries have published their own pharmacopeias, including the United Kingdom, France, Italy, Japan, India, Mexico, Norway, and the People's Republic of China. These pharmacopeias and the *European Pharmacopeia* (EP or Ph Eur) are used within their legal jurisdictions and by multinational pharmaceutical companies that develop and market products



$C_{16}H_{19}N_3O_5S{\cdot}3H_2O$ 419.45

4-Thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid, 6-[[amino (4-hydroxyphenyl) acetyl]amino]-3, 3-dimethyl-7-oxo-,trihydrate [2*S*-[2α,5α,6β(*S**)]]-;
(2*S*,5*R*,6*R*)-6-[(*R*)-(–)-2-Amino-2-(*p*-hydroxyphenyl) acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid trihydrate [61336-70-7].
Anhydrous 365.41 [26787-78-0].

Definition—Amoxicillin contains NLT 900 µg and NMT 1,050 µg of $C_{16}H_{19}N_3O_5S$ per milligram, calculated on the anhydrous basis.
Identification—*Infrared absorption* (197K)

Assay

- **Procedure**

Diluent: 6.8 g/L of monobasic potassium phosphate in water. Adjust with a 45% (w/w) solution of potassium hydroxide to a pH of 5.0 ± 0.1.
Mobile phase: Acetonitrile and *Diluent* (1:24)
Standard solution: 1.2 mg/mL of USP Amoxicillin RS in *Diluent*. (Note—Use this solution within 6 hours.)
Sample solution: 1.2 mg/mL of Amoxicillin in *Diluent*. (Note—Use this solution within 6 hours.)
Chromatographic system (see *Chromatography* [621], *System Suitability*)
Mode: LC
Detector: UV 230 nm
Column: 4-mm × 25-cm; packing L1
Flow rate: 1.5 mL/min
Injection size: 10 µL
System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the quantity, in µg/mg, of $C_{16}H_{19}N_3O_5S$ in the portion of Amoxicillin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Amoxicillin RS in the *Standard solution* (mg/mL)
C_U = concentration of *Sample solution* (mg/mL)
P = potency of amoxicillin in USP Amoxicillin RS (µg/mg)

Acceptance criteria: 900 to 1050 µg of $C_{16}H_{19}N_3O_5S$ per milligram on the anhydrous basis

Impurities

Organic Impurities

- **Procedure**

Solution A: 2.72 g/L of monobasic potassium phosphate. Adjust with 1 N potassium hydroxide or 20% phosphoric acid to a pH of 5.0 ± 0.1.
Solution B: Methanol
Mobile phase: See the gradient table below.

TIME (MIN)	SOLUTION A (%)	SOLUTION B (%)
0	97	3
10	97	3
22	75	25
26	97	3

Standard solution: 12.5 µg/mL of USP Amoxicillin RS in *Solution A*
System suitability solution: 12.5 µg/mL each of USP Amoxicillin Related Compound A RS and USP Amoxicillin Related Compound D RS in *Solution A*
Sample solution: 1.25 mg/mL of Amoxicillin in *Solution A*. (Note—Store this solution at 4 degrees and use within 4 hours)
Chromatographic system (see *Chromatography* [621], *System Suitability*)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 10-cm; 5-µm packing L1
Column temperature: 40 degrees
Flow rate: 1.5 mL/min
Injection size: 10 µL
Autosampler temperature: 4 degrees
System suitability
Samples: Standard solution and System suitability solution

Suitability requirements

(Note—Identify peaks by the relative retention times in *Impurity Table 1*.)
Resolution: NLT 1.5 between Amoxicillin related compound A and the second peak for Amoxicillin related compound D, *System suitability solution*
Relative standard deviation: NMT 10%, *Standard solution*

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of *Amoxicillin taken:*

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times F \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of amoxicillin from the *Standard solution*
C_S = concentration of USP Amoxicillin RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of Amoxicillin in the *Sample solution* (mg/mL)
F = unit conversion factor (0.001 mg/µg)

(*Continued*)

FIGURE 1.3 Amoxicillin.

Impurity Table 1

NAME	RELATIVE RETENTION TIME	ACCEPTANCE CRITERIA, NMT (%)
Amoxicillin related compound I[a] (D-hydroxyphenylglycine)	0.32	1.0
Amoxicillin related compound D[b,c] (amoxicillin open ring)	0.53	1.0
	0.68	1.0
Amoxicillin related compound A[d] (6-aminopenicillanic acid)	0.78	0.5
Amoxicillin related compound B[e,f] (L-amoxicillin)	0.87	—
Amoxicillin	1.0	—
Amoxicillin related compound G[g] (D-hydroxyphenylglycylamoxicillin)	2.9	1.0
Amoxicillin related compound E[h,i] (amoxicillin penilloic derivative)	4.5	1.0
Amoxicillin related compound M[j] (*N*-(penicillan-6-yl) open ring amoxicillinamide)	6.0	1.0
Amoxicillin related compound F[e,k] (phenylpyrazinediol)	6.3	—
Amoxicillin related compound C[l] (amoxicillin rearrangement product)	6.4	1.0
Amoxicillin related compound E[h,i] (amoxicillin penilloic derivative)	6.7	1.0
Amoxicillin related compound J[m] (amoxicillin open ring dimer)	8.8	1.0
Amoxicillin related compound L[n] (*N*-(penicillan-6-yl) amoxicillinamide)	9.0	1.0
Any unspecified individual impurity	—	1.0

[a](*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.
[b]The chromatographic system resolves two penicilloic acids from each other.
[c](4*S*)-2-{[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.
[d](2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
[e]These compounds are listed for information only and are not to be reported.
[f](2*S*,5*R*,6*R*)-6-[(*S*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
[g](2*S*,5*R*,6*R*)-6-{(*R*)-2-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
[h]The chromatographic system resolves two penilloic acids from each other.
[i](4*S*)-2-{[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.
[j](2*S*,5*R*,6*R*)-6-(2-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-((4*S*)-4-carboxy-5,5-dimethylthiazolidin-2-yl)acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
[k]3-(4-Hydroxyphenyl)pyrazin-2-ol.
[l](4*S*)-2-[5-(4-Hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid.
[m](2*S*,5*R*,6*R*)-6-((2*R*)-2-{2-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-[(4*S*)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido}-2-(4-hydroxyphenyl)acetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.
[n](2*S*,5*R*,6*R*)-6-{(2*S*,5*R*,6*R*)-6-[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Acceptance criteria

(Note—The reporting limit is 0.03% of the amoxicillin peak from the *Standard solution*.)
Individual impurities: See *Impurity Table 1*.
Total impurities: NMT 5.0%

Specific Tests

- *Crystallinity* (*695*): Meets the requirements
- D*imethylaniline* (*223*): Meets the requirement
- pH *(791)*: 3.5–6.0
  Sample solution: 2 mg/mL
- *Water determination*, *Method I* (*921*): 11.5% to 14.5%
- S*terility tests (71)*: Where the label states that Amoxicillin is sterile, it meets the requirements when tested as directed in *Test for Sterility of the Product to Be Examined, Direct Inoculation of the Culture Medium*, except to use fluid thioglycollate medium containing polysorbate 80 solution (5 mg/mL) and an amount of sterile penicillinase sufficient to inactivate the amoxicillin in each tube, to use soybean–casein digest medium containing polysorbate 80 solution (5 mg/mL) and an amount of sterile penicillinase sufficient to inactivate the amoxicillin in each tube, and to shake the tubes once daily.
- B*acterial endotoxins test (85)*: Where the label states that Amoxicillin is sterile or Amoxicillin must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.25 USP Endotoxin Unit/mg of amoxicillin.

Additional Requirements

- P*ackaging and storage*: Preserve in tight containers, and store at controlled room temperature.
- L*abeling*: Where it is intended for use in preparing injectable dosage forms, the label states that it is intended for veterinary use only and that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. Label all other Amoxicillin to indicate that it is to be used in the manufacture of nonparenteral drugs only.
- USP *reference standards (11)*
  USP Amoxicillin RS
  USP Amoxicillin Related Compound A RS
  (2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; 6-aminopenicillanic acid.
  $C_8H_{12}N_2O_3S$ 216.26
  USP Amoxicillin Related Compound D RS
  (4*S*)-2-{[(*R*)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl}-5,5-dimethylthiazolidine-4-carboxylic acid; amoxicillin open ring.
  $C_{16}H_{21}N_3O_6S$ 383.42
  USP Endotoxin RS

FIGURE 1.3 (*Continued*).

internationally. Countries not having a national pharmacopeia frequently adopt one of another country for use in setting and regulating drug standards. Selection of the pharmacopeia is usually based on geographic proximity, a common heritage or language, or a similarity of drugs and pharmaceutical products used. For example, Canada, which does not have its own national pharmacopeia, has traditionally used USP–NF standards. The Mexican pharmacopeia (*Farmacopea de los Estados Unidos Mexicanos*) and the Brazilian Pharmacopeia (*Farmacopeia Brasilieira*) are the only other actively maintained pharmacopeias in this hemisphere. The Brazilian Pharmacopoeia is part of the MERCOSUR Pharmacopoeia, comprising Argentina, Brazil, Paraguay, and Uruguay (7).

Standards Set Forth in FDA-Approved New Drug Applications

In the United States, in addition to the official compendia, some initial drug and drug product standards and assay methods are established as set forth in new drug applications approved by the FDA (see Chapter 2). The manufacturer must rigidly adhere to these initial standards to maintain product quality and continued FDA approval for marketing. Ultimately, these or subsequently developed standards are adopted as new monographs by the USP–NF.

International Organization for Standardization

The International Organization for Standardization (ISO) is an international consortium of representative bodies constituted to develop and promote uniform or harmonized international standards. Representing the United States in the consortium is the American National Standards Institute.

Among the various ISO standards used in the pharmaceutical industry are those in the series ISO 9000 to ISO 9004. Included here are standards pertaining to development, production, quality assurance (QA), quality control (QC), detection of defective products, quality management (QM), and other issues, such as product safety and liability. Industry compliance with the standards is voluntary. However, many firms find it advantageous to their business to comply with ISO standards and to be identified within their industry as having an internationally recognized QM system. Some companies choose to become ISO certified through a rigorous evaluation and accreditation process (8).

DRUG REGULATION AND CONTROL

The first federal law in the United States designed to regulate drug products manufactured domestically was the Food and Drug Act of 1906. The law required drugs marketed interstate to comply with their claimed standards for strength, purity, and quality. Manufacturers' claims of therapeutic benefit were not regulated until 1912, when the passage of the Sherley Amendment specifically prohibited false claims of therapeutic effects, declaring such products misbranded.

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT OF 1938

The need for additional drug standards was tragically demonstrated in 1938. The then-new wonder drug sulfanilamide, which was not soluble in most common pharmaceutical solvents of the day, was prepared and distributed by an otherwise reputable manufacturer as an elixir using as the solvent diethylene glycol, a highly toxic agent used in antifreeze solutions. Before the product could be removed from the market, more than 100 persons died of diethylene glycol poisoning. The necessity for proper product formulation and thorough pharmacologic and toxicologic testing of the therapeutic agent, pharmaceutical ingredients, and the completed product was painfully recognized. Congress responded with the passage of the Federal Food, Drug, and Cosmetic Act of 1938 and the creation of the FDA to administer and enforce it.

The 1938 Act prohibits the distribution and use of any new drug or drug product without

the prior filing of a New Drug Application (NDA) and approval of the FDA. It became the responsibility of the FDA to either grant or deny permission to manufacture and distribute a new product after reviewing the applicant's filed data on the product's ingredients, methods of assay and quality standards, formulation and manufacturing processes, preclinical (animal, tissue, or cell culture) studies including pharmacology and toxicology, and clinical trials on human subjects.

Although the Act of 1938 required manufactured pharmaceutical products to be safe for human use, it did not require them to be efficacious. Subsequent legislation, as described later in this chapter, requires that a drug approved for marketing in the United States be both safe and effective for the condition for which it is intended. Many drugs that had been on the market prior to this Act were allowed to remain on the market if their formula was unchanged and they were "grandfathered" in by the Act: examples include selected dosage forms of acetaminophen, codeine phosphate, codeine sulfate, hydrocodone, levothyroxine, morphine, nitroglycerin, oxycodone, pilocarpine hydrochloride, potassium chloride, potassium iodide, sodium fluoride, and others.

Durham-Humphrey Amendment of 1951

The Durham-Humphrey Amendment of the Federal Food Drug and Cosmetic Act established a legal distinction between prescription and over-the-counter (OTC) or nonprescription drugs. Until that time, all drugs could be purchased over the counter by consumers.

Medications deemed safe enough by the FDA for self-treatment are made available to consumers for direct purchase whereas medications requiring professional diagnosis for their safe and effective use must be dispensed only upon a valid prescription or institutional medication order. Prescription drugs must bear the symbol "R_x Only" or the legend "Caution: Federal Law Prohibits Dispensing Without Prescription." New drug substances are limited to prescription-only dispensing. However, their legal status may be changed to OTC, albeit usually at lower recommended dosage, should they later be considered useful and safe enough for the lay person's discretionary use. Examples of such drugs include ibuprofen, ketoprofen, cimetidine, loratadine, and ranitidine.

According to the Durham-Humphrey Amendment, prescriptions for legend drugs may not be refilled (dispensed again after the initial filling of the prescription) without the express consent of the prescriber. The refill status of prescriptions for certain legend drugs known to be subject to public abuse was further regulated with the passage of the Drug Abuse Control Amendments of 1965 and then by the Comprehensive Drug Abuse Prevention and Control Act of 1970.

Kefauver-Harris Amendments of 1962

A tragedy in 1960 led to the passage of the Kefauver-Harris Amendments to the Federal Food Drug and Cosmetic Act of 1938. A new synthetic drug, thalidomide, recommended as a sedative and tranquilizer, was being sold OTC in Europe. It was a drug of special interest because of its apparent lack of toxicity even at extreme dosage levels. It was hoped that it would replace the barbiturates as a sedative and therefore prevent the frequent deaths caused from accidental and intentional barbiturate overdosage. A pharmaceutical company was awaiting FDA approval for marketing in the United States when reports of a toxic effect of the drug's use in Europe began to appear. Thalidomide given to women during pregnancy produced birth defects, most notably phocomelia, an arrested development of the limbs of the affected newborn. Thousands of children were affected to various extents (9). Some were born without arms or legs and others, with partially formed limbs. The more fortunate were born with only disfigurations of the nose, eyes, and ears. The most severely afflicted died of malformation of the heart or gastrointestinal tract. This drug catastrophe spurred the Congress to strengthen the existing laws regarding new drugs. Without

dissent, on October 10, 1962, the Kefauver-Harris Drug Amendments to the Food, Drug, and Cosmetic Act of 1938 were passed by both houses of Congress. The purpose of the enactment was to ensure a greater degree of safety for approved drugs, and manufacturers were now required to prove a drug both safe and effective before it would be granted FDA approval for marketing.

Under the Food, Drug, and Cosmetic Act as amended, the sponsor of a new drug is required to file an investigational new drug application (IND) with the FDA before the drug may be clinically tested on human subjects. Only after carefully designed and structured human clinical trials, in which the drug is evaluated for safety and effectiveness, may the drug's sponsor file an NDA seeking approval for marketing. The FDA was given authority to issue good manufacturing practice (GMP) guidelines governing how drugs were to be manufactured, access to facilities for inspection, and jurisdiction over prescription drug advertising. The requirements for these and other submissions to the FDA are presented in Chapter 2.

Interestingly, WHO now considers thalidomide to be the standard treatment for the fever and painful skin lesions associated with erythema nodosum leprosum (ENL) in patients with leprosy and the FDA has approved its use for this purpose. Further, research into potential uses for thalidomide has determined that it is effective in the treatment of multiple myeloma, a blood and bone marrow cancer, and shows promise in certain inflammatory diseases, and in Kaposi sarcoma, a cancer of the blood vessel walls mostly found in people with HIV (10).

Comprehensive Drug Abuse Prevention and Control Act of 1970

The Comprehensive Drug Abuse Prevention and Control Act of 1970 (now referred to as the Controlled Substances Act [CSA]) served to consolidate and codify control authority over drugs of abuse into a single statute. Under its provisions, the Drug Abuse Control Amendments of 1965, the Harrison Narcotic Act of 1914, and other related laws governing stimulants, depressants, narcotics, and hallucinogens were repealed and replaced by regulatory framework now administered by the Drug Enforcement Administration (DEA) in the Department of Justice.

The Comprehensive Drug Abuse Prevention and Control Act of 1970 established five "schedules" for the classification and control of drug substances that are subject to abuse. These schedules provide for decreasing levels of control, from schedule I to schedule V. The drugs in the five schedules may be described as follows:

- Schedule I: Drugs with no accepted medical use, or other substances with a high potential for abuse. In this category are agents including heroin, lysergic acid diethylamide (LSD), mescaline, peyote, methaqualone, marijuana, and similar items. Any nonmedical substance that is being abused can be placed in this category.
- Schedule II: Drugs with accepted medical uses and a high potential for abuse that if abused may lead to severe psychologic or physical dependence. In this category are morphine, cocaine, methamphetamine, amobarbital, and other such drugs.
- Schedule III: Drugs with accepted medical uses and a potential for abuse less than those listed in schedules I and II that if abused may lead to moderate psychologic or physical dependence. In this category are specified quantities of codeine, hydrocodone, and similar agents.
- Schedule IV: Drugs with accepted medical uses and low potential for abuse relative to those in Schedule III that if abused may lead to limited physical dependence or psychologic dependence relative to drugs in schedule III. In this category are specified quantities of difenoxin, diazepam, oxazepam, and similar agents.
- Schedule V: Drugs with accepted medical uses and low potential for abuse relative to those in schedule IV that if abused may lead to limited physical dependence or psychologic dependence relative to drugs in schedule IV. Included in this category are specified quantities of dihydrocodeine, diphenoxylate, and similar agents.

FDA Pregnancy Categories

Appropriate prescribing and use of medications requires a risk-versus-benefit assessment of the medication for a specific patient. There are many risk factors that must be evaluated, including pregnancy. In 1979, the United States FDA introduced a classification of fetal risks due to pharmaceuticals. This was based on a similar system that was introduced in Sweden just 1 year earlier.

The FDA has established five categories that can be used to estimate the potential of a systemically absorbed drug for causing birth defects. The reliability of the documentation is the key differentiation factor among the categories for determining the risk-versus-benefit ratio. The Pregnancy Category "X" is the strongest and states that if any data exist that a drug may be implicated as a teratogen and the risk-versus-benefit ratio does not support the use of the drug, then the drug is contraindicated during pregnancy.

The FDA-assigned pregnancy categories are as follows:

- Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
- Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
- Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
- Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Medication Exposures During Pregnancy and Lactation

Every woman in the general population has a 3% to 5% risk of having a child with a birth defect or mental retardation. Birth defects are the leading cause of infant mortality in the United States. Two important factors to consider when assessing the teratogenic potential of a medication are the stage of pregnancy at which the exposure occurred and the amount of medication taken. It is critical to evaluate each exposure on a case-by-case basis in order to give an accurate risk assessment. Some of the known, possible, and unlikely human teratogens are listed in Table 1.1. In a pregnant or breast-feeding patient who is currently taking, or considering taking, a medication, the patient needs to be counseled about potential adverse effects the medication could have on her fetus or infant (11). This counseling needs to be documented.

Black Box Warnings

A *black box warning* in prescription drug labeling is used to call attention to one of the following situations: (*a*) there is an adverse reaction so serious in proportion to the potential benefit that it be considered in assessing the risks and benefits of using the drug, (*b*) the risk of a serious adverse reaction can be prevented or reduced in severity by careful use of the drug (e.g., patient selection, special monitoring, certain concomitant therapy), or (*c*) the FDA has approved the drug *with restrictions* to prescribing/distribution to ensure its safe use (12).

Drug Listing Act of 1972

The Drug Listing Act was enacted to provide the FDA with the legislative authority to compile a list of marketed drugs to assist in the enforcement of federal laws requiring that drugs be safe and effective and not

Table 1.1 SOME KNOWN TERATOGENS

RADIATION

Atomic weapons
Radioiodine
Therapeutic radiation

INFECTIONS

Cytomegalovirus
Herpes simplex virus I and II
Parvovirus B-19 (erythema infectiosum)
Rubella virus
Syphilis
Toxoplasmosis
Varicella virus
Venezuelan equine encephalitis virus

MATERNAL AND METABOLIC IMBALANCE

Alcoholism
Amniocentesis, early (before day 70 post conception)
Chorionic villus sampling (before day 60 post conception)
Cretinism, endemic
Diabetes
Folic acid deficiency
Hyperthermia
Myasthenia gravis
Phenylketonuria
Rheumatic disease
Sjögren syndrome
Virilizing tumors

DRUGS AND ENVIRONMENTAL CHEMICALS

ACE inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril)
Aminopterin
Androgenic hormones
Busulfan
Chlorobiphenyls
Cigarette smoking
Cocaine
Coumarin anticoagulants
Cyclophosphamide
Diethylstilbestrol
Etretinate
Fluconazole (high doses)
Iodides
Isotretinoin (Accutane)
Lithium
Mercury, organic
Methimazole
Methotrexate (methylaminopterin)
Methylene blue (via intra-amniotic injection)
Misoprostol
Penicillamine
Phenytoin
Tetracyclines
Thalidomide
Toluene (abuse)
Trimethadione
Valproic acid

POSSIBLE TERATOGENS

Binge drinking
Carbamazepine
Colchicine
Disulfiram
Ergotamine
Glucocorticoids
Lead
Primidone
Quinine (suicidal doses)
Streptomycin
Vitamin A (high doses)
Zidovudine (AZT)
Zinc deficiency

UNLIKELY TERATOGENS

Agent Orange
Anesthetics
Aspartame
Aspirin (but aspirin in the second half of pregnancy may increase cerebral hemorrhage during delivery)
Bendectin (antinauseant)
Electromagnetic waves
Hydroxyprogesterone
LSD
Marijuana
Medroxyprogesterone
Metronidazole
Oral contraceptives
Progesterone
Rubella vaccine
Spermicides
Video display terminals
Ultrasound

adulterated or misbranded. Under the regulations of the act, each firm that manufactures or repackages drugs for ultimate sale or distribution to patients or consumers must register with the FDA and submit appropriate information for listing. All foreign drug manufacturing and distributing firms whose products are imported into the United States are also included in this regulation. Exempt from the registration and listing requirements are hospitals, clinics, and the various health practitioners who compound pharmaceutical preparations for use in their respective institutions and practices. Also exempt are research and teaching institutions in which drug products are prepared for purposes other than sale. Each registrant is assigned a permanent registration number, following the format of the National Drug Code (NDC) numbering system. Under this system, the first four numbers, the labeler code of the 10-character code, identify the manufacturer or distributor. The last six numbers identify the drug formulation and the trade package size and type. The segment that identifies the drug formulation is the product code, and the segment that identifies the trade package size and type is the package code. The manufacturer or distributor determines the ratio of use of the last six digits for the two codes, as a 3:3 digit product code to package code configuration (e.g., 542–112) or a 4:2 digit configuration (e.g., 5421–12). Only one such type of configuration may be selected for use by a manufacturer or distributor, who then assigns a code number to each product to be included in the drug listing. A final code number is presented as the example: NDC 0081-5421-12.

The NDC numbers appear on all manufacturers' drug labeling. In some instances, manufacturers imprint the NDC number, or a part of the NDC number, directly on the dosage units, such as capsules and tablets, for rapid and positive identification when the number is matched in the NDC Directory or against a decoding list provided by the manufacturer. Once a number is assigned to a drug product, it is a permanent assignment. Even when a drug manufacturer discontinues the manufacture and distribution of a product, the number may not be used again. If a drug product is substantially changed, as through an alteration in the active ingredients, dosage form, or product name, the registrant assigns a new NDC number and advises the FDA accordingly.

The product information is now received by the FDA electronically from each registrant, processed and stored in computer files, and made available in web-based format. A search of the Drug Code Directory may be done online by proprietary name, application number, active ingredient, NDC number, or labeler name.

Orphan Drug Act of 1983

Drugs intended for the treatment of "rare diseases and conditions" may be designated *orphan* drugs to help promote research on rare diseases. "Rare" diseases are defined as diseases affecting fewer than 200,000 people or diseases that affect more than 200,000 people but where circumstances are such that a company is unlikely to recover its research and development costs. The law provides tax credits and designated years of marketing exclusivity as incentives.

Drug Price Competition and Patent Term Restoration Act of 1984

Changes to speed FDA approval of generic drugs and the extension of patent life for innovative new drugs were the major components of the Drug Price Competition and Patent Restoration Act of 1984.

Under the provisions of the legislation, applications for generic copies of an originally approved new drug can be filed through an abbreviated new drug application (ANDA), and the extensive animal and human studies of an NDA are not required. This reduces considerably the time and expense of bringing a generic version of the drug to market. The FDA evaluates the chemistry, manufacturing, control (CMC) standards, and the drug's bioavailability in determining that the generic version is

equivalent to the originally approved drug. Since 1984, over 10,000 generic drug products have entered the market, and generic drugs now account for about 70% of prescriptions dispensed.

For holders of patented drugs, the legislation provides an extension of patent life equal to the time required for FDA review of the NDA plus half the time spent in the testing phase, up to a maximum of 5 years and not to exceed the usual 20-year patent term. This extends the effective patent life and exclusive marketing period for innovative new drug products, thereby encouraging pioneering research and development.

Prescription Drug Marketing Act of 1987 and Prescription Drug Amendments of 1992

The Prescription Drug Marketing Act of 1987 established new safeguards on the integrity of the nation's supply of prescription drugs. The act is intended to reduce the risks of adulterated, misbranded, repackaged, or mislabeled drugs entering the legitimate marketplace through "secondary sources." The primary sections of the Act are summarized as follows:

1. Reimportation: Prohibits the reimportation of drug products manufactured in the United States except by the manufacturer of the product.
2. Sales restrictions: Prohibits selling, trading, purchasing, or the offer to sell, trade, or purchase a drug sample. It also prohibits resale by health care institutions of pharmaceuticals purchased explicitly for the use of the institution. Charitable institutions that receive drugs at reduced prices or no cost cannot resell the drugs.
3. Distribution of samples: Samples may be distributed only to (*a*) practitioners licensed to prescribe such drugs and (*b*) at the written request of the practitioner, to pharmacies of hospitals or other health care institutions.
4. Wholesale distributors: Manufacturers are required to maintain a list of their authorized distributors.

Prescription Drug User Fee Act of 1992

The Prescription Drug User Fee Act, first passed in 1992 and subsequently renewed, allows the FDA to accept *user fees* from drug and biologic companies in return for committing to review new drug and biologic applications within certain time frames. The Act is credited with a more rapid application review process and the speedier approval of new drug products. The third enactment, passed as part of the "Public Health Security and Bioterrorism Preparedness and Response Act of 2002," included designated resources for postmarketing studies to monitor the continuing safety and efficacy of new drug products.

Dietary Supplement Health and Education Act of 1994 and the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006

In passing the Dietary Supplement Health and Education Act (DSHEA) of 1994, Congress recognized the growing interest in the use of various herbs and dietary supplements and addressed the need to regulate the labeling claims made for these products. These products, which include vitamins, minerals, amino acids, and botanicals, legally are not considered drugs if they have not been submitted for review on NDAs and thus have not been evaluated for safety and efficacy by the FDA. However, as with drugs, their safe use is a concern to the FDA.

The act forbids manufacturers or distributors of these products to make any advertising or labeling claims that indicate that the use of the product can prevent or cure a specific disease. In fact, a disclaimer must appear on the product: "This product is not intended to diagnose, treat, cure, or prevent any disease." However, the law does permit claims of benefit as they may properly relate to a nutrient deficiency disease or, based on scientific evidence, how an ingredient may affect the body's "structure or function" (e.g., increase circulation or lower cholesterol) or

how use of the product can affect a person's general well-being. But before any promotional or labeling claims may be made, they first must be submitted to the FDA as being truthful and not misleading (13).

The use of herbs and nutritional supplements is part of today's milieu of "alternative" therapies, and as such is receiving increased attention on the part of the scientific community and the FDA. Many of these agents, including ginseng, *Ginkgo*, saw palmetto, St. John's wort, and *Echinacea*, are used worldwide and have been the subject of literature reports and research conducted in Europe and Asia. In 1997, a report of the U.S. Presidential Commission on Dietary Supplement Labels called for more research in this country on the health benefits of dietary supplements. In response, academic and National Institutes of Health (NIH) studies are assessing the therapeutic usefulness of some of these agents and to determine their safety. The USP–NF has adopted standards for many of these products using marker ingredients that must be present within specified ranges if the product is labeled USP–NF. The USP also has a voluntary Dietary Supplement Verification program in place. Participants who meet USP's criteria can place a logo on the label of their product signifying their compliance with USP standards (Fig. 1.4).

FIGURE 1.4 USP Verified Mark on dietary supplement label assures consumers receive expected value. (Reprinted with permission of *United States Pharmacopeia*.)

The "Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006" enabled the FDA to implement a policy of GMPs for dietary supplements similar to those in place for pharmaceutical products. This requires that dietary supplements are manufactured according to quality standards, that all ingredients listed are in the declared amounts, that they are properly packaged and accurately labeled, and that complete manufacturing and QC records are maintained along with a system for the identification and reporting of serious adverse events.

The FDA and the Food and Drug Administration Modernization Act of 1997 and the Food and Drug Administration Amendments Act of 2007

As noted previously, the FDA was established in 1938 to administer and enforce the Federal Food Drug and Cosmetic Act. Starting with this initial authority, today the FDA is responsible for enforcing many additional pieces of legislation.

The mission of the FDA is to protect the public health against risks associated with the production, distribution, and sale of food and food additives, human drugs and biologicals, radiologic and medical devices, animal drugs and feeds, and cosmetics. In carrying out the intent of legislation it is mandated to enforce, the FDA

- Sets policies, establishes standards, issues guidelines, and promulgates and enforces rules and regulations governing the affected industries and their products
- Monitors for regulatory compliance through reporting requirements, product sampling and testing, and establishment inspections
- Establishes product labeling requirements, disseminates product use and safety information, issues product warnings, and directs product recalls
- Acts as the government's gatekeeper in making safe and effective new drugs, clinical laboratory tests, and medical devices available through a carefully conducted application and review process

The FDA, an agency of the Department of Health and Human Services, is organized into appropriate units to support its various responsibilities and functions. A complete and detailed FDA organizational chart may be found on the agency's Web site: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/default.htm.

A listing of some primary offices include

- Office of the Commissioner
- Office of Policy and Planning
- Office of the Chief Scientist
- National Center for Toxicological Research
- Office of Women's Health
- Office of Minority Health
- Office of Foods
- Center for Veterinary Medicine
- Center for Food Safety and Applied Nutrition
- Office of Medical Products and Tobacco
- Center for Devices and Radiological Health
- Center for Biologics Evaluation and Research (CBER)
- Center for Drug Evaluation and Research (CDER)
- Office of Global Regulatory Operations and Policy
- Office of Regulatory Affairs

Each of these offices and centers has a highly organized substructure and personnel to address agency policy, regulations, and operational responsibilities.

The CDER and the CBER are responsible for the drug and biologicals approval process as described in Chapter 2.

The FDA Modernization Act of 1997 was enacted to streamline FDA policies and to codify many of the agency's newer regulations (14). The bill expanded patient access to investigational treatments for AIDS, cancer, Alzheimer disease, and other serious or life-threatening illnesses. It also provided for faster new drug approvals by using drug sponsors' fees to hire additional internal reviewers, by the authorized use of external reviewers, and by changes in the requirements demonstrating a drug's clinical effectiveness. It also provided incentives for investigations of drugs for children.

The legislation included provisions to track clinical trial data in a joint program with the NIH, established a system to follow and review studies of the safety and efficacy of marketed drug products, established a program for the dissemination of information on off-label uses of marketed drugs and encouraged applications for additional therapeutic indications, and fostered the expansion of the FDA's information management system and the agency's progress toward paperless systems for human drug applications.

To codify, enable, and enforce legislative authority, the FDA develops relevant guidelines and regulations. These are first published in the *Federal Register* (FR) for public comment, and when finalized, in the *Code of Federal Regulations* (CFR).

Globalization and the FDA

The responsibility of the Federal Food and Drug Administration to protect the public health by assuring the safety and efficacy of the drugs and other products it regulates has become increasingly complex in recent years by the rapidly expanding globalization of the marketplace. Data indicate that 80% of the active pharmaceutical ingredients used in the manufacture of pharmaceutical products and 40% of the finished dosage forms used in the United States are imported (15). FDA-regulated products originate in over 150 countries, are produced in approximately 300,000 foreign facilities and are distributed by 130,000 importers (15).

In addressing this challenge, the FDA has established foreign operational offices in receptive supplier countries around the world and has increased inspections of foreign supplier facilities. In addition, the FDA is working to develop internationally accepted quality and safety standards through coalitions with foreign counterpart agencies and together, they are generating global data information systems and mechanisms to identify and quickly address potential risks irrespective of geographic location (15).

It should be noted that the activities of the United States Pharmacopeia are also

worldwide in scope nowadays, with physical operations in key international manufacturing and distribution sites.

Drug Product Recall

If the FDA or a manufacturer finds that a marketed product presents a threat or a potential threat to consumer safety, that product may be recalled or sought for return to the manufacturer from its depth of distribution. The pharmaceutical manufacturer is legally bound to report serious unlabeled adverse reactions to the FDA through the FDA MedWatch Program (800-FDA-1088 or www.FDA.gov). A practitioner also has a responsibility to report a problem with any drug product or medical device using the MedWatch program. Reported problems may include product defects, product adulteration, container leakage, improper labeling, unexpected adverse reactions, and others.

A drug product recall may be initiated by the FDA or by the manufacturer, the latter being termed a voluntary recall. A numerical classification, as follows, indicates the degree of hazard associated with the product being recalled:

- Class I: There is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.
- Class II: The use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or the probability of serious adverse health consequences is remote.
- Class III: The use of or exposure to a violative product is not likely to cause adverse health consequences.

The depth of recall, or the level of market removal or correction (e.g., wholesaler, retailer, consumer), depends on the nature of the product, the urgency of the situation, and depth to which the product has been distributed. The lot numbers of packaging control numbers on the containers or labels of the products help in identifying the product to be recalled.

Drug Products Removed or Withdrawn

The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found to be unsafe or not effective. Thus, the products, as listed may not be compounded under the provisions of section 503A(a) of the Federal Food, Drug, and Cosmetic Act. It is important to note that not all dosage forms of the drugs listed have been removed or cannot be compounded because in some situations, it is select dosage forms.

Adenosine phosphate: All drug products containing adenosine phosphate

Adrenal cortex: All drug products containing adrenal cortex

Azaribine: All drug products containing azaribine

Benoxaprofen: All drug products containing benoxaprofen

Bithionol: All drug products containing bithionol

Bromfenac sodium: All drug products containing bromfenac sodium

Butamben: All parenteral drug products containing butamben

Camphorated oil: All drug products containing camphorated oil

Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate

Casein, iodinated: All drug products containing iodinated casein

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for use as a patient preoperative skin preparation

Chlormadinone acetate: All drug products containing chlormadinone acetate

Chloroform: All drug products containing chloroform

Cobalt: All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives)

Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine hydrochloride

Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride

Dibromsalan: All drug products containing dibromsalan

Diethylstilbestrol: All oral and parenteral drug products containing 25 mg or more of diethylstilbestrol per unit dose

Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin sulfate

Dipyrone: All drug products containing dipyrone

Encainide hydrochloride: All drug products containing encainide hydrochloride

Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride

Flosequinan: All drug products containing flosequinan

Gelatin: All intravenous drug products containing gelatin

Glycerol, iodinated: All drug products containing iodinated glycerol

Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of animal origin

Mepazine: All drug products containing mepazine hydrochloride or mepazine acetate

Metabromsalan: All drug products containing metabromsalan

Methamphetamine hydrochloride: All parenteral drug products containing methamphetamine hydrochloride

Methapyrilene: All drug products containing methapyrilene

Methopholine: All drug products containing methopholine

Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatologic application)

Nomifensine maleate: All drug products containing nomifensine maleate

Oxyphenisatin: All drug products containing oxyphenisatin

Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate

Phenacetin: All drug products containing phenacetin

Phenformin hydrochloride: All drug products containing phenformin hydrochloride

Pipamazine: All drug products containing pipamazine

Potassium arsenite: All drug products containing potassium arsenite

Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 mg or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion)

Povidone: All intravenous drug products containing povidone

Reserpine: All oral dosage form drug products containing more than 1 mg of reserpine

Sparteine sulfate: All drug products containing sparteine sulfate

Sulfadimethoxine: All drug products containing sulfadimethoxine

Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use)

Suprofen: All drug products containing suprofen (except ophthalmic solutions)

Sweet spirits of nitre: All drug products containing sweet spirits of nitre

Temafloxacin hydrochloride: All drug products containing temafloxacin

Terfenadine: All drug products containing terfenadine

3,3′,4′,5-tetrachlorosalicylanilide: All drug products containing 3,3′,4′,5-tetrachlorosalic ylanilide

Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 mg/mL

Ticrynafen: All drug products containing ticrynafen

Tribromsalan: All drug products containing tribromsalan

Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane

Urethane: All drug products containing urethane

Vinyl chloride: All aerosol drug products containing vinyl chloride

Zirconium: All aerosol drug products containing zirconium

Zomepirac sodium: All drug products containing zomepirac sodium

THE PHARMACIST'S CONTEMPORARY ROLE

Pharmacy graduates holding the Bachelor of Science (BS) in Pharmacy degree or the Doctor of Pharmacy (PharmD) degree practice in a variety of settings, applying the basic pharmaceutical sciences, the clinical sciences, and professional training and experience. This includes practice in community pharmacies, patient care institutions, managed care, home health care, military and government service, academic settings, professional associations, and the pharmaceutical research and manufacturing industry, as well as in other positions requiring the pharmacist's expertise.

Historically, the abbreviation RPh (registered pharmacist) has been used as the professional designation of a pharmacist licensed by a state board of pharmacy to practice in that state. Doctors of Pharmacy use the PharmD after their name in place of RPh. To minimize any confusion from patients, some states instituted the title DPh (Doctor of Pharmacy) to designate licensed pharmacists. This designation is used by pharmacists who have earned a BS in Pharmacy. Under this format, all pharmacists in the states where this has been implemented can be called doctors as are those who have earned the PharmD degree; one is a professional degree designation and the other a licensure designation.

Most pharmacists practice within an ambulatory care or community pharmacy setting. In either setting, the pharmacist plays an active role in the patient's use of prescription and nonprescription medication, diagnostic agents, durable medical equipment and devices, and other health care products. The pharmacist develops and maintains individual patient medication profiles, compounds drug preparations, dispenses drug products, issues patient information leaflets (PILs), counsels patients on their health status, and provides information on the use of drug and nondrug measures. As members of the health care team, pharmacists serve as an expert source of drug information and participate in the selection, monitoring, and assessment of drug therapy.

A substantial number of pharmacists practice in institutional settings, such as hospitals, clinics, extended care facilities, and health maintenance organizations (HMOs). In these settings, pharmacists manage drug distribution and control systems and provide a variety of clinical services, including drug utilization reviews (DURs), drug use evaluations, therapeutic drug monitoring, intravenous admixture programs, pharmacokinetic consulting services, investigational drug supplies, and poison control and drug information.

For most of its history as a profession, pharmacy was relatively undifferentiated. The emergence of practice differentiation was in the late 1960s and early 1970s with the professional literature describing hospital pharmacists who had developed unique roles that were distinctive from the traditional dispensing roles of the pharmacist. These pioneering "clinical pharmacists" participated with physicians in therapeutic decision making, and it was suggested that their level of knowledge and practice skills required special educational and experiential preparation. Further, hospital pharmacists were encouraged to organize their departments to recognize and utilize these emerging "specialties" and proposed that the medical model of service organization might be applicable to pharmacy. Shortly thereafter, the Study Commission on Pharmacy (*syn* the Millis commission) was commissioned by the American Association of Colleges of Pharmacy (AACP). Its 1975 report acknowledged that differentiation in pharmacy practice was occurring and that this differentiation was, in general, expected and desirable. While not specifying specialty practice areas, the commission suggested that a structure be established to oversee all pharmacist credentialing.

The Board of Pharmaceutical Specialties (BPS) was officially established on January 5, 1976, when the American Pharmacists Association (APhA) membership approved the BPS bylaws under the aegis of the APhA structure. The initial mission of BPS was based on responsibilities outlined in its bylaws. The BPS recognizes appropriate

specialties in pharmacy practice using specific criteria developed for this purpose. The BPS establishes standards for certification and recertification of pharmacists in designated areas of specialty practice. This is achieved primarily by individual specialty councils, within the BPS structure, that make recommendations to the full Board. The BPS administers the process of examination and evaluation of individuals who seek certification and recertification as specialists, and it serves as an information clearinghouse and coordinating agency for organizations and pharmacists with regard to the specialty practice of pharmacy. To date, there are six specialty areas as follows: nuclear pharmacy, nutrition support pharmacy, pharmacotherapy, psychiatric pharmacy, ambulatory care, and oncology pharmacy.

In recent years, managed health care programs have grown extraordinarily. Managed health care organizations have enrolled a large and rapidly growing base of patients and thus have assumed major responsibilities in the delivery of health care, including the delivery of pharmaceutical services. Many new positions have evolved for pharmacists within the managed care industry, including positions for pharmacy benefits managers, disease management specialists, drug formulary managers, therapeutic outcomes researchers, DUR specialists, and others (16). In these functions, managed care pharmacists apply administrative, epidemiological, clinical, financial, research, information technology, and communication skills to their practice.

A number of pharmacy graduates, particularly those having an interest in institutional practice, participate in postgraduate residency and/or fellowship programs to enhance their practice and/or research skills. A pharmacy residency is an organized, directed postgraduate training program in a defined area of practice. The chief purpose is to train pharmacists in professional practice and management skills. Residency programs are conducted primarily in institutional practice settings. A fellowship to develop skill in research is a directed, highly individualized postgraduate program designed to prepare the participant to become an independent researcher. Both pharmacy residencies and fellowships last 12 months or longer and require the close direction of a qualified preceptor.

Pharmacists working for pharmaceutical research, development, and manufacturing firms can participate in a range of activities, including drug discovery, drug analysis and QC, product development and production, clinical studies and drug evaluation, labeling and drug literature, marketing and sales, regulatory affairs, and management. The pharmacist's knowledge of the basic chemical, biological, and pharmaceutical sciences, along with technical knowledge of product formulation, dosage form design, and clinical use meshes well with the requirements of the pharmaceutical industry. Pharmacists with advanced degrees (Master of Science [MS] or Doctor of Philosophy [PhD]) in the basic or pharmaceutical sciences or in health care administration are highly sought in the pharmaceutical industry.

In government service, pharmacists perform professional and administrative functions in the development and implementation of pharmaceutical care delivery programs and in the design and enforcement of regulations involving drug distribution and drug quality standards. Career opportunities for pharmacists in government service at the federal level include positions in the military service, in the U.S. Public Health Service, and in such civil service agencies as the FDA, Veterans Administration, Department of Health and Human Services, DEA, NIH, the Indian Health Service, and others. At the state and local levels, many pharmacists find rewarding careers in health departments, family and children's services, drug investigation and regulatory control, clinics and other health care institutions, and with state boards of pharmacy.

Schools of pharmacy enlist pharmacists, some with and some without advanced degrees (MS, PhD), to serve as preceptors within the practice setting, to teach specific courses and/or laboratories within the academic institution, to participate in extramural research, and to contribute to

the service and continuing education mission of the school. Some pharmacists work full-time in the academic setting, whereas many others provide part-time professional instruction in community or hospital pharmacies, teaching hospitals and clinics, drug information centers, nursing homes and extended care facilities, health departments, home health care, managed care, and other areas in which pharmaceutical services are delivered.

A number of pharmacists serve their profession in volunteer or professional positions with local, state, and national pharmaceutical associations. For example, the APhA, the American Society of Health-Systems Pharmacists (ASHP), American College of Apothecaries (ACA), International Academy of Pharmaceutical Compounding, American College of Clinical Pharmacy (ACCP), the American Society of Managed Care Pharmacy (AMCP), and the AACP are national organizations with pharmacists in key leadership positions. Pharmacists are also active in international pharmacy organizations including International Pharmaceutical Federation (FIP) and the International Society of Pharmaceutical Compounding (ISPhC).

Pharmacists exercise a vital service health education role in their communities through participation in drug and health education community forums, by conducting "brown bag" sessions, by speaking on drug issues in schools, by conducting in-service education programs in patient care settings, and by providing input on drug and health issues to state and federal legislators and community leaders and officials.

The Mission of Pharmacy

In 1991, the House of Delegates of the APhA adopted the following mission statement for pharmacy practice (17):

> *To serve society as the profession responsible for the appropriate use of medications, devices, and services to achieve optimal therapeutic outcomes.*

And, in 2011, APhA's Board of Trustees adopted the following vision statement for the profession of pharmacy (17):

> *Pharmacists are essential for optimizing medication use and improving patient health.*

Definition of Pharmaceutical Care

Today, the role of the pharmacist in contemporary practice is the delivery of pharmaceutical care, which was first proposed in 1975 by Mikeal and others as "the care that a given patient requires and receives which assures rational drug usage" (18). Since then, the term has been redefined by many authors, including Strand and others who in 1992 stated (19):

> Pharmaceutical care is that component of pharmacy practice which entails the direct interaction of the pharmacist with the patient for the purpose of caring for that patient's drug-related needs.

The ASHP, a national organization that represents pharmacists who practice in hospitals, HMOs, long-term care facilities, home care agencies, and other components of health care systems, advanced the following statement on pharmaceutical care in 1993 (20):

> The mission of the pharmacist is to provide pharmaceutical care. Pharmaceutical care is the direct, responsible provision of medication-related care for the purpose of achieving definite outcomes that improve a patient's quality of life.

The APhA in 1996 issued its Principles of Practice for Pharmaceutical Care, including the following general statement (21):

> Pharmaceutical care is a patient-centered, outcomes-oriented pharmacy practice that requires the pharmacist to work in concert with the patient and the patient's other healthcare providers to promote health, to prevent disease, and to assess, monitor, initiate, and modify medication use to assure that drug therapy regimens are safe and effective.
>
> The goal of pharmaceutical care is to optimize the patient's health-related quality of life and achieve positive clinical outcomes, within realistic economic expenditures.

Implicit in all of these statements is the requirement of pharmacists to participate fully in all aspects of medication distribution (manufactured and compounded drugs)

and their appropriate clinical use to achieve optimal therapeutic outcomes. The contemporary pharmacy literature is replete with research papers and articles in support of the concept and practice of pharmaceutical care, including clinical skill development (22), pharmaceutical care databases (23), information technology (24), literature retrieval (25), therapeutic drug monitoring and outcomes assessment (26–29), DUR (30), pharmacotherapy and medication therapy management (MTM) (31,32), drug treatment protocols (33), adverse drug reaction monitoring (34), pharmacokinetic services (35), and strategies to implement pharmaceutical care (36).

In 1997, the AACP's Janus Commission issued a report, *Approaching the Millennium*, which stated that to provide pharmaceutical care, the successful pharmacy graduate must be (37)

- A problem solver, capable of adapting to changes in health care
- Able to achieve health outcomes through effective medication use that are valued by the health care system
- Able to collaborate with and be a resource to physicians, nurses, and other health care team members
- A committed lifelong learner

Pharmacy Practice Standards

The scope and standards of pharmacy practice are established in each state through laws and regulations promulgated by the state's board of pharmacy. Together with applicable federal laws, they constitute the basis for the legal practice of pharmacy.

Over the years, various professional associations in pharmacy have developed documents termed standards of practice. One such document, *Practice Standards of the ASHP*, is updated and published annually. In 1991, the APhA, the AACP, and the National Association of Boards of Pharmacy studied the scope of pharmacy practice to revalidate the Standards of Practice for the Profession of Pharmacy, which were published in 1979 and updated in 1986 as Competency Statements for Pharmacy Practice (38). They can be summarized as follows:

- General management and administration of the pharmacy: Selects and supervises pharmacists and nonprofessionals for pharmacy staff; establishes a pricing structure for pharmaceutical services and products; administers budgets and negotiates with vendors; develops and maintains a purchasing and inventory system for all drugs and pharmaceutical supplies; initiates a formulary system. In general, establishes and administers pharmacy management, personnel, and fiscal policy.
- Processing the prescription: Verifies the prescription for legality and physical and chemical compatibility; checks the patient's record before dispensing prescription; measures quantities needed to dispense the prescription; performs final check of the finished prescription; dispenses the prescription.
- Patient care functions: Clarifies the patient's understanding of dosage; integrates drug with patient information; advises the patient of potential drug-related conditions; refers the patient to other health care resources; monitors and evaluates therapeutic response of the patient; reviews and/or seeks additional drug-related information.
- Education of health care professionals and patients: Organizes, maintains, and provides drug information to other health care professionals; organizes and/or participates in in-pharmacy education programs for other pharmacists; makes recommendations regarding drug therapy to the physician or patient; develops and maintains system for drug distributions and QC.

In 1998, a consortium of 10 pharmacy organizations undertook a pharmacy practice activity classification project to develop uniform language in describing practice activities in such areas as pharmacotherapy, monitoring and therapeutic outcomes, dispensing

medications, health promotion and disease prevention, and health systems management (39). The developed classification is intended to provide the common language to be used and understood within and outside of the profession in describing the practice activities of pharmacists.

The Omnibus Budget Reconciliation Act of 1990

The Omnibus Budget Reconciliation Act of 1990 (OBRA 90), which became effective on January 1, 1993, established a requirement for each state to develop and mandate DUR programs to improve the quality of pharmaceutical care provided to patients covered by the federal medical assistance (Medicaid) program (40). The statute was designed to ensure that prescriptions are appropriate, medically necessary, and not likely to result in adverse medical effects. The statute required that each state's plan provide for a review of drug therapy before each prescription is dispensed and delivered to an eligible patient.

The regulations required patient medication monitoring for therapeutic appropriateness, therapeutic duplication, overuse, underuse, drug–disease contraindications, drug–drug interactions with other prescribed and OTC medications, drug–allergy interactions, correct drug dosage, duration of treatment, and clinical abuse or misuse. They also required that pharmacists offer therapeutic counseling to each recipient of a prescription or the recipient's caregiver regarding the drug, dosage and duration of use, route of administration, side effects, contraindications, techniques for self-monitoring drug therapy, proper storage, refill information, and action to be taken in the event of a missed dose. Pharmacists are to maintain patient medication profiles and therapeutic counseling records.

In designing the DUR programs, state boards of pharmacy commonly included the federal requirements in the state's pharmacy practice regulations, thereby applying them to each recipient of a prescription, not only to patients receiving benefits under the Medicaid program. Many states used the model regulations for the practice of pharmaceutical care developed by the National Association of Boards of Pharmacy.

Patient Protection and Affordable Care Act of 2010

The Patient Protection and Affordable Care Act (PPACA) was enacted to decrease the number of medically uninsured while improving the quality and reducing the overall costs of health care in the United States. Among its many provisions are expanded prescription drug coverage for Medicare and Medicaid patients, programs for innovative methods of health care delivery, and a pathway for the approval of *biosimilars* (generic biological products) (41).

CODE OF ETHICS FOR PHARMACISTS OF THE AMERICAN PHARMACISTS ASSOCIATION

By definition, a profession is founded on an art, built on specialized intellectual training, and has as its primary objective the performing of a service. The principles on which the professional practice of pharmacy is based are embodied in the Code of Ethics of the APhA.

The APhA Code of Ethics has been revised over the years to reflect dynamic changes in the profession. The current version is as follows (42):

> Code of Ethics for Pharmacists
>
> PREAMBLE
> Pharmacists are health professionals who assist individuals in making the best use of medications. This Code, prepared and supported by pharmacists, is intended to state publicly the principles that form the fundamental basis of the roles and responsibilities of pharmacists. These principles, based on moral obligations and virtues, are established to guide pharmacists in relationships with patients, health professionals, and society.
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> **I. A pharmacist respects the covenantal relationship between the patient and pharmacist.**
> Considering the patient-pharmacist relationship as a covenant means that a pharmacist has moral obligations in response to the gift of trust received from society. In return for this gift, a pharmacist

promises to help individuals achieve optimum benefit from their medications, to be committed to their welfare, and to maintain their trust.

II. A pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner.
A pharmacist places concern for the well-being of the patient at the center of professional practice. In doing so, a pharmacist considers needs stated by the patient as well as those defined by health science. A pharmacist is dedicated to protecting the dignity of the patient. With a caring attitude and a compassionate spirit, a pharmacist focuses on serving the patient in a private and confidential manner.

III. A pharmacist respects the autonomy and dignity of each patient.
A pharmacist promotes the right of self-determination and recognizes individual self-worth by encouraging patients to participate in decisions about their health. A pharmacist communicates with patients in terms that are understandable. In all cases, a pharmacist respects personal and cultural differences among patients.

IV. A pharmacist acts with honesty and integrity in professional relationships.
A pharmacist has a duty to tell the truth and to act with conviction of conscience. A pharmacist avoids discriminatory practices, behavior or work conditions that impair professional judgment, and actions that compromise dedication to the best interests of patients.

V. A pharmacist maintains professional competence.
A pharmacist has a duty to maintain knowledge and abilities as new medications, devices, and technologies become available and as health information advances.

VI. A pharmacist respects the values and abilities of colleagues and other health professionals.
When appropriate, a pharmacist asks for the consultation of colleagues or other health professionals or refers the patient. A pharmacist acknowledges that colleagues and other health professionals may differ in the beliefs and values they apply to the care of the patient.

VII. A pharmacist serves individual, community, and societal needs.
The primary obligation of a pharmacist is to individual patients. However, the obligations of a pharmacist may at times extend beyond the individual to the community and society. In these situations, the pharmacist recognizes the responsibilities that accompany these obligations and acts accordingly.

VIII. A pharmacist seeks justice in the distribution of health resources.
When health resources are allocated, a pharmacist is fair and equitable, balancing the needs of patients and society.

CODE OF ETHICS OF THE AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS

Like pharmacy practitioners, pharmaceutical scientists recognize their special obligation to society and to the public welfare. Members of the American Association of Pharmaceutical Scientists (AAPS) have adopted the following code of ethics (43).

In their scientific pursuits, they

Conduct their work in a manner that adheres to the highest principles of scientific research so as to merit the confidence and trust of peers and the public in particular regarding the rights of human subjects and concern for the proper use of animals involved and provision for suitable safeguards against environmental damage.

Avoid scientific misconduct and expose it when encountered. AAPS uses the current federal definition of scientific misconduct, 65 FR 76260–76264: Fabrication, falsification, and plagiarism in proposing, performing, or reviewing research or reporting research results.

Recognize latitude for differences of scientific opinion in the interpretation of scientific data and that such differences of opinion do not constitute unethical conduct.

Disclose sources of external financial support for, or significant financial interests in the content of, research reports/publications and avoid the manipulation of the release of such information for illegal financial gain.

Report results accurately, stating explicitly any known or suspected bias, opposing efforts to improperly modify data or conclusions and offering professional advice only on those subjects concerning which they regard themselves competent through scientific education, training or experience.

Respect the known ownership rights of others in scientific research and seek prior authorization from the owner before disclosure or use of such information including the contents of manuscripts submitted for prepublication review.

Support in their research and among their employers the participation and employment of all qualified persons regardless of race, gender, creed or national origin.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Develop a comparison chart of the drug regulations and control laws described in this chapter. Include when the law was initiated, why the law was created, what the law entails, and how the law affects everyday pharmacy practice.
2. Research and present a pharmacy practice area you are not familiar with and would desire to learn more about. Possibilities include ambulatory care, nuclear pharmacy, managed care, etc.
3. With a partner, role play a provider–patient dialogue example of pharmaceutical care. Be sure the example encompasses all aspects of the definition.
4. After reviewing the APhA Code of Ethics, do you believe the principles are complete and inclusive? Are there any new aspects in the practice of pharmacy that may need to be incorporated in the future version of the Code of Ethics? Discuss, present, and defend your conclusions.

Individual Activities

1. Describe the evolution of the USP and the NF since its inception up to the current date.
2. After reviewing the Competency Statements for Pharmacy Practice, evaluate how well the college/school of pharmacy you attend will prepare you to practice the profession of pharmacy.

REFERENCES

1. Mission and Preface. USP 31-NF 26: History. In: United States Pharmacopeia. 31st Rev. Rockville, MD: United States Pharmacopeial Convention, Inc., 2008:v–x.
2. Constitution and Bylaws. USP 35-NF 30. Rockville, MD: United States Pharmacopeial Convention, Inc., 2012. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/aboutUSP/governance/article5.pdf. (Accessed September 18, 2012)
3. History of the National Formulary. In: National Formulary. 18th Ed. Rockville, MD: United States Pharmacopeial Convention, Inc., 1995:2196–2200.
4. Chavez ML. Homeopathy. Hosp Pharm 1998;33:41–49.
5. Der Marderosian AH. Understanding homeopathy. J Am Pharm Assoc 1996;NS36:317–321.
6. Pray WS. The challenge to professionalism presented by homeopathy. Am J Pharm Educ 1996;60:198–204.
7. International Meeting of World Pharmacopeias, World Health Organization, 2012. Available at: http://www.who.int/medicines/areas/quality_safety/quality_assurance/resources/Brazil_Pharmacopoeia.pdf. (Accessed September 14, 2012)
8. International Organization for Standardization. Available at: http://www.iso.org/iso/home/about.htm. (Accessed September 14, 2012)
9. FDA The thalidomide tragedy—25 years ago. FDA Consum 1987;21:14–17.
10. Thalidomide: Research advances in cancer and other conditions. Mayo Clinic. Available at http://www.mayoclinic.com/health/thalidomide/HQ01507. (Accessed September 14, 2012)
11. Summary of Proposed Rule on Pregnancy and Lactation Labeling U.S. Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093310.htm. (Accessed September 15, 2012)
12. Guidance for Industry, Warnings and Precautions, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products. Food and Drug Administration. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidelines/default.htm. (Accessed September 15)
13. Bonnell L. Packaging nutritional supplements. Pharm Med Packag News 1997;5:42–50.
14. Berger MS, Berger BA. FDA Overview. Available at: http://www.emedicinehealth.com/fda_overview/article_em.htm. (Accessed September 19, 2012)
15. Autor DM. Globalization and the FDA. Presented at the 36th Good International Manufacturing Practices Conference. The University of Georgia, Athens, GA. March 12, 2012.
16. Vogenberg FR. Managed health care: A review. Hosp Pharm 1997;32:975–982.
17. Vision and mission for the pharmacy profession. Available at: http://www.pharmacist.com/vision-and-mission-pharmacy-profession. (Accessed September 18, 2012)
18. Mikeal RL, Brown TP, Lazarus HL, et al. Quality of pharmaceutical care in hospitals. Am J Hosp Pharm 1975;32:567–574.
19. Strand LM, Cipolle RJ, Morley PC. Pharmaceutical Care: An introduction. Current Concepts. Kalamazoo, MI: Upjohn, 1992.

20. American Society of Health-System Pharmacists. ASHP guidelines on a standardized method of pharmaceutical care. Am J Health Syst Pharm 1996;53:1713–1716.
21. American Pharmacists Association. Principles of Practice for Pharmaceutical Care. Washington, DC: American Pharmacists Association. http://www.aphanet.org/pharmcare/prinprac.html. (Accessed September 8, 2003)
22. Barnette DJ, Murphy CM, Carter BL. Clinical skill development for community pharmacists. J Am Pharm Assoc 1996;NS36:573–579.
23. Rodriquez de Bittner M, Michocki R. Pharmaceutical care databases. J Am Pharm Assoc 1997;NS37:595–596.
24. West DS, Szeinbach S. Information technology and pharmaceutical care. J Am Pharm Assoc 1997;NS37:497–501.
25. Grant KL, Herrier RN, Armstrong EP. Teaching a systematic search strategy improves literature retrieval skills of pharmacy students. Am J Pharm Educ 1996;60:281–286.
26. Madan PL. Therapeutic drug monitoring. US Pharm 1996;21:92–105.
27. McDonough RP. Interventions to improve patient pharmaceutical care outcomes. J Am Pharm Assoc 1996;NS36:453–459.
28. Fera T, Bluml BM, Ellis WM, et al. The Diabetes Ten City Challenge: Interim clinical and humanistic outcomes of a multisite community pharmacy diabetes care program. J Am Pharm Assoc 2008;48(2):181–190.
29. Isetts BJ, Schondelmeyer SW, Artz MB, et al. J Am Pharm Assoc 2008;48(2):203–211.
30. Kubacka RT. A primer on drug utilization review. J Am Pharm Assoc 1996;NS36:257–261.
31. McGivney MS, Meyer SM, Duncan-Hewitt W, et al. Medication therapy management: Its relationship to patient counseling, disease management, and pharmaceutical care. J Am Pharm Assoc 2007;47(5):620–625.
32. Nkansah NT, Brewer JM, Connores R, et al. Clinical outcomes of patients with diabetes mellitus receiving medication management by pharmacists in an urban private physician practice. Am J Health Syst Pharm 2008;65(2):145–149.
33. American Pharmacists Association. APhA Guide to Drug Treatment Protocols. Washington, DC: American Pharmacists Association, 1997.
34. American Society of Health-System Pharmacists. ASHP Guidelines on Adverse Drug Reaction Monitoring and Reporting. Bethesda, MD: American Society of Health-System Pharmacists, 1995.
35. American Society of Health-System Pharmacists. ASHP Statement on the Pharmacist's Role in Clinical Pharmacokinetic Services. Bethesda, MD: American Society of Health-System Pharmacists, 1998.
36. Berdine HJ, O'Neil CK. Development and implementation of a pharmacist-managed university-based wellness center. J Am Pharm Assoc 2007;47(3):390–397.
37. American Association of Colleges of Pharmacy. Approaching the Millennium: The Report of the AACP Janus Commission. Alexandria, VA: American Association of Colleges of Pharmacy, 1997.
38. Pancorbo SA, Campagna KD, Davenport JK, et al. Task force report of competency statements for pharmacy practice. Am J Pharm Educ 1987;51:196–206.
39. Maine LL. Pharmacy Practice Classification. J Am Pharm Assoc 1998;38:139–148.
40. Health Care Financing Administration. Medicaid program: Drug use review program and electronic claims management system for outpatient drug claims. Washington, DC: Health Care Financing Administration, Department of Health and Human Services, 1992; Federal Register 57:49397–49412.
41. PUBLIC LAW 111–148—MAR. 23, 2010. Available at: http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf. (Accessed September 17, 2012)
42. Code of Ethics. American Pharmacists Association. Available at: http://www.pharmacist.com/code-ethics. (Accessed September 18, 2012)
43. Code of Ethics. American Association of Pharmaceutical Scientists. Available at: http://www.aaps.org/uploadedFiles/Content/About_AAPS/Policies_and_Governance/AAPSCodeofEthics.pdf. (Accessed September 18, 2012)

2 New Drug Development and Approval Process

OBJECTIVES

After reading this chapter, the student will be able to:

1. Compare and contrast an Investigational New Drug (IND) Application from a New Drug Application (NDA)
2. Differentiate between Phase 1, Phase 2, Phase 3, and Phase 4 clinical trials
3. Give examples of the sources of new drugs
4. Differentiate between the various methods of drug discovery
5. Delineate the circumstances whereby an old drug could be classified as "new"
6. Define pharmacology, drug metabolism, and toxicology
7. Explain a treatment IND
8. Define an orphan drug
9. Define a package insert and the information contained therein

The federal Food, Drug, and Cosmetic Act, as regulated through Title 21 of the U.S. Code of Federal Regulations, requires a new drug to be approved by the Food and Drug Administration (FDA) before it may be legally introduced in the interstate commerce (1). The regulations apply to the drug products manufactured domestically and those imported into the United States.

To gain approval for marketing, a drug's sponsor (e.g., a pharmaceutical company) must demonstrate, through supporting scientific evidence, that the new drug or drug product is safe and effective for its proposed use. The sponsor must also demonstrate that the various processes and controls used in producing the drug substance and in manufacturing, packaging, and labeling are properly controlled and validated to ensure that the product meets the established standards of quality. The process and time course from drug discovery to approval for marketing can be lengthy and tedious but are well defined and understood in the pharmaceutical industry. A schematic representation of the process for new drug development is shown in Figure 2.1, and the usual time course is depicted in Figure 2.2. Although these representations demonstrate the course for *new chemical entities* (usually small-molecule drugs), similar developmental schemes are followed for *new biological entities*, as described later in this chapter. After the discovery (e.g., synthesis) of a proposed new drug, the agent is biologically characterized for pharmacologic and toxicologic effects and for potential therapeutic application. Preformulation studies are initiated to define the physical and chemical properties of the agent. Formulation studies follow to develop the initial features of the proposed pharmaceutical product or dosage form. To obtain the required evidence demonstrating the drug's safety and effectiveness for its proposed use, a carefully designed and progressive sequence of preclinical (e.g., cell culture, whole animal) and clinical (human) studies is undertaken.

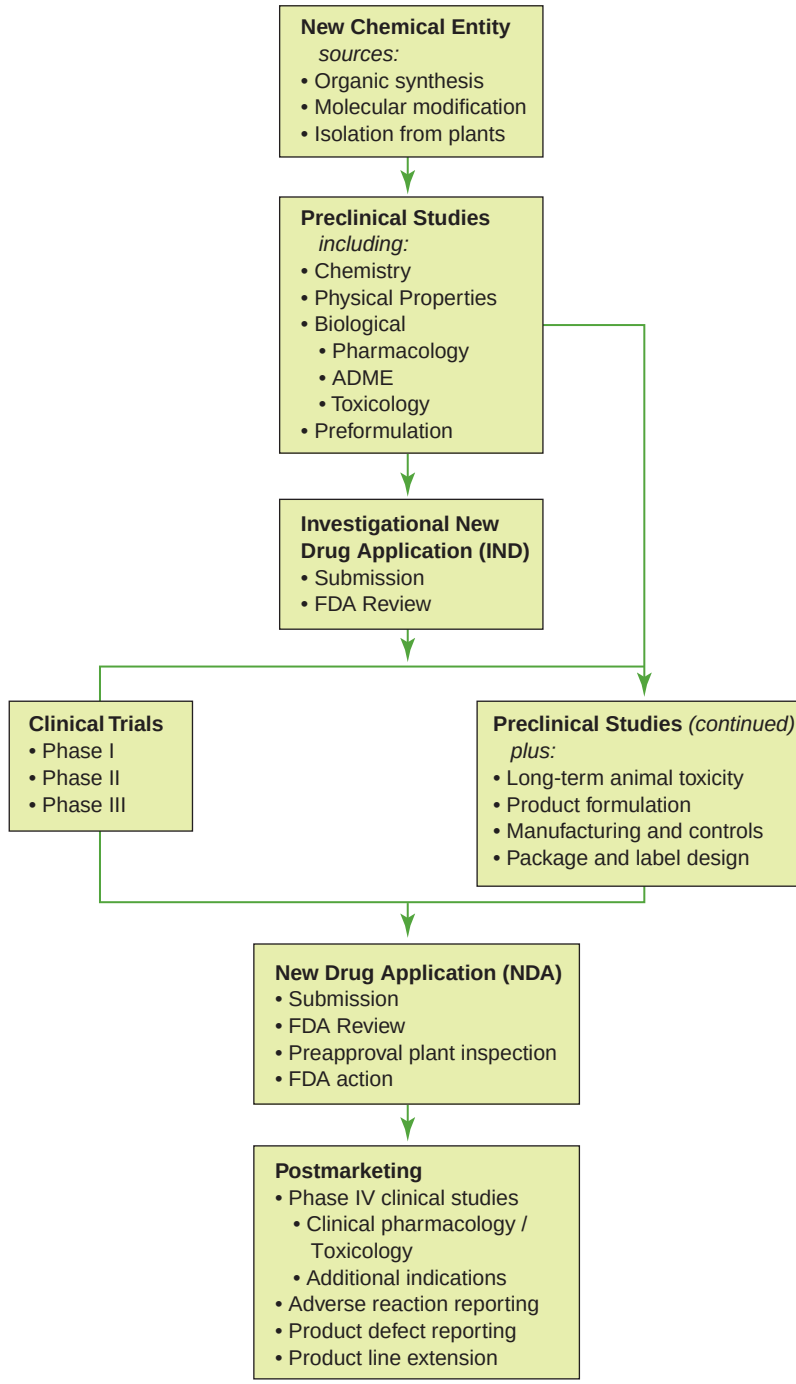


FIGURE 2.1 The new drug development process of a new chemical entity from discovery through preclinical and clinical studies, FDA review of the NDA, and postmarketing activities. A variation of this process is followed for the discovery and development of new biological entities, as described later in this chapter.

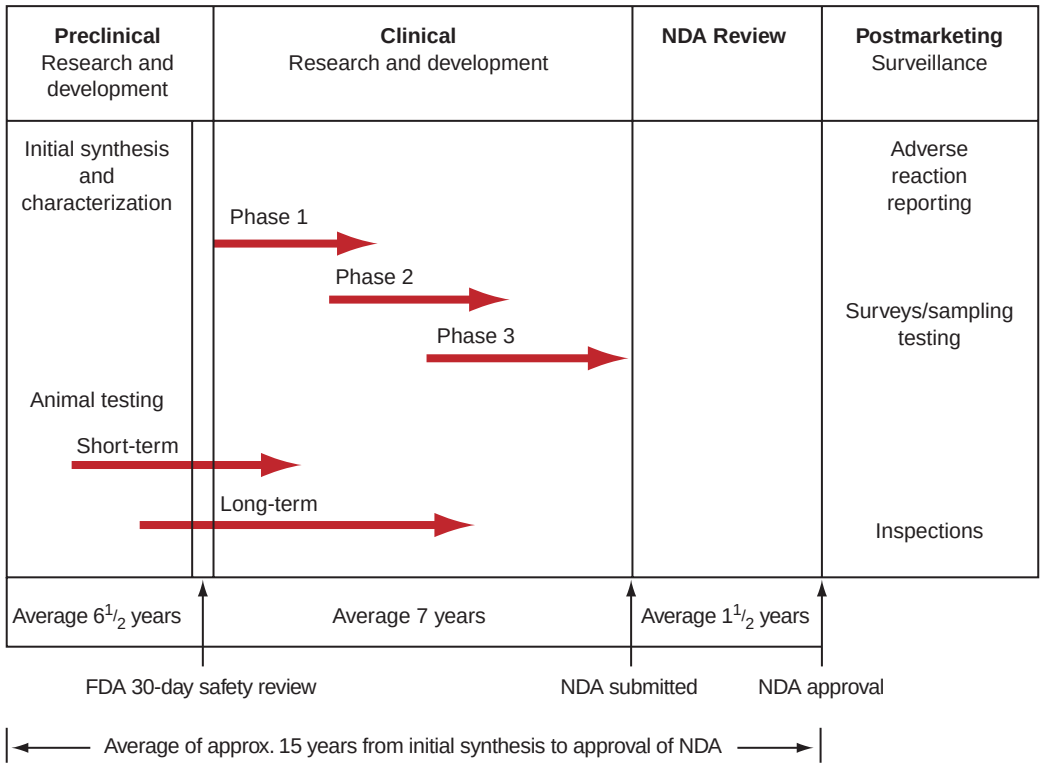


FIGURE 2.2 Time course for the development of a new drug. (Adapted from The Pharmaceutical Research and Manufacturers of America (PhRMA), 2012; http://www.phrma.org/research).

Only when the preclinical studies demonstrate adequate safety and the new agent shows promise as a useful drug will the drug's sponsor file an *Investigational New Drug* (*IND*) *Application* with the FDA for initial testing in humans. If the drug demonstrates adequate safety in these initial human studies, termed Phase 1, progressive human trials through Phases 2 and 3 are undertaken to assess safety and efficacy. As the clinical trials progress, laboratory work continues toward defining the agent's basic and clinical pharmacology and toxicology, product design and development, manufacturing scale-up and process controls, analytical methods development, proposed labeling and package design, and initial plans for marketing. At the completion of the carefully designed preclinical and clinical studies, the drug's sponsor may file a *New Drug Application* (*NDA*) seeking approval to market the new product. The FDA's approval of an NDA indicates that the body of scientific evidence submitted sufficiently demonstrates that the drug or the drug product is safe and effective for the proposed clinical indications, that there is adequate assurance of its proper manufacture and control, and that the final labeling accurately presents the necessary information for its proper use. Some products, however, have been approved and later removed from the market for safety reasons, including alosetron HCl (Lotrovec), astemizole (Hismanal), bromfenac sodium (Duract), cerivastatin (Baycol), cisapride (Propulsid), dexfenfluramine HCl (Redux), fenfluramine HCl (Pondimin), grepafloxacin HCl (Raxar), mibefradil (Posicor), natalizumab (Tysabri), pemoline (Cylert), phenylpropanolamine (Propagest, Dexatrim), rofecoxib (Vioxx), terfenadine (Seldane), and troglitazone (Rezulin).

The content of a product's approved labeling, represented by the package insert, is a summary of the entire drug development process because it contains the essential chemistry, pharmacology, toxicology, indications and contraindications for use, adverse

effects, formulation composition, dosage, and storage requirements, as ascertained during the research and development (R&D).

In addition to the general new drug approval process, special regulations apply for the approval of certain new drugs to treat serious or life-threatening illnesses, such as AIDS and cancer. These may be placed on an accelerated or fast-track program for approval. Also, if there are no satisfactory approved drugs or treatment alternatives for a serious medical condition, special protocols may be issued permitting the use of an investigational drug to treat some patients prior to approval of the NDA. This type of protocol is termed a treatment IND. Treatment INDs often are sought for orphan drugs, which are targeted for small numbers of patients who have rare conditions or diseases for which there are no satisfactory alternative treatments.

An abbreviated new drug application (ANDA) is used to gain approval to market a generic equivalent of a product that is already approved and being marketed by the pioneer, or the original sponsor, of the drug. In these instances, the sponsor of the ANDA provides documentation on the chemistry, manufacturing, controls (CMCs), and bioavailability of the proposed product to demonstrate biologic equivalency to the original product (2). Clinical data on the drug's safety and efficacy are not required because clinical studies were provided by the pioneer sponsor.

Federal regulations are varied and specific for orphan drugs (3); for biologics, such as human blood products and vaccines, which require approval of a biologics licensing application (BLA) for distribution (4); for over-the-counter (OTC) drugs (5); and for animal drugs, which may require an investigational new animal drug application (INADA), a new animal drug application (NADA), or a supplemental new animal drug application (SNADA) (6). Medical devices, such as catheters and cardiac pacemakers, follow a separate approval process (7). These regulations and others governing foods and drugs are found in the Code of Federal Regulations (CFR) Title 21 and may be accessed at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm.

The following sections are intended to serve as an overview of the new drug development and approval process. More specific and detailed information may be obtained directly from the referenced sections of the CFR (1–7), from relevant entries in the Federal Register (8), and from other treatises on the topic (9–13).

DRUG DISCOVERY AND DRUG DESIGN

The discovery of new drugs and their development into commercial products take place across the broad scope of the pharmaceutical industry. The basic underpinning for this effort is the cumulative body of scientific and biomedical information generated worldwide in research institutes, academic centers, and industry. The combined efforts of chemists, biologists, molecular biologists, pharmacologists, toxicologists, statisticians, physicians, pharmacists and pharmaceutical scientists, engineers, and many others participate in drug discovery and development.

Some pharmaceutical firms focus their R&D activities on new prescription drugs for human use, whereas other firms concentrate on the development of OTC medications, generic drugs, biotechnology products, animal health care drugs, diagnostic products, and/or medical devices. Many of the large pharmaceutical companies develop and manufacture products of various types, with some firms having subsidiary companies for specialized functions and products.

The pharmaceutical industry in the United States grew rapidly during World War II and in the years immediately following. The upsurge in the domestic production of drugs and pharmaceutical products stemmed in part from the wartime hazards and consequent undependability of overseas shipping, the unavailability of drugs from previous sources, and the increased need for drugs of all kinds, but especially those with lifesaving capabilities. One such drug is penicillin, the antibiotic that became commercially available in 1944, 15 years after its discovery in England by Sir Alexander Fleming and 1 year before the end of the war. In every year since, scientific

discoveries and technological advancements have enabled the development of new drugs and therapies that have enhanced the lives of countless millions worldwide. Today, the scientific exploration of *disease mechanisms* is leading to the discovery and development of agents that specifically impact these mechanisms, resulting in new therapeutic modalities. There is a dramatic advance in the development of *biologic drugs*, including monoclonal antibodies, therapeutic proteins, immunotherapies, and vaccines, which is transforming the treatment of many diseases. Presently, biologics is the fastest growing segment within the new prescription drug market and is expected to continue as such in the years ahead. Annually, approximately 40 new molecular entities receive FDA approval for marketing. In addition, many new dosage strengths and dosage forms of previously approved drugs, new generic products, and new biologics are approved each year.

Not all drugs are discovered, developed, and first approved in the United States. Many pharmaceutical companies do drug R&D in other countries, and many drugs are first marketed abroad. Many of the world's largest pharmaceutical companies are multinational firms with facilities for R&D, manufacturing, and distribution in countries around the world. Irrespective of the country of origin, a drug may be proposed by its sponsor for regulatory approval for marketing in the United States and/or in other countries. These approvals do not occur simultaneously, as they are subject to the laws, regulations, and requirements peculiar to each country's governing authority. However, the international effort to harmonize the regulations through the work of the International Conference on Harmonization (ICH) as described at the end of this chapter fosters multinational drug approvals.

Sources of New Drugs

New drugs may be discovered from a variety of natural sources (e.g., plants), synthesized in the laboratory, or created through processes of biotechnology. Historically, some drugs were found by accident, others by serendipity, but most through years of largely random but tireless pursuit by the synthetic organic chemist. Nowadays, new drugs are the chemical or engineered biologic material resulting from research that is more targeted; that is, directed specifically toward the identified physiologic/metabolic process or biomolecular target of a disease. Current methods of drug discovery are discussed later in this chapter.

Throughout history, plant materials have served as a reservoir of potential new drugs. Yet, only a small portion of the approximately 270,000 known plants thus far have been investigated for medicinal activity. Certain major contributions to modern drug therapy may be attributed to the successful conversion of botanic folklore remedies into modern wonder drugs. The chemical reserpine, a tranquilizer and a hypotensive agent, is an example of a medicinal chemical isolated by design from the folklore remedy *Rauwolfia serpentina*. Another plant drug, periwinkle, or *Vinca rosea*, was first scientifically investigated as a result of its reputation in folklore as an agent useful in the treatment of diabetes mellitus. Plant extracts from *V. rosea* yield two potent drugs that, when screened for pharmacologic activity, surprisingly exhibited antitumor capabilities. These two materials, vinblastine and vincristine, since have been used successfully in the treatment of certain types of cancer, including acute leukemia, Hodgkin disease, lymphocytic lymphoma, and other malignancies. Another example, paclitaxel (Taxol), prepared from an extract of the Pacific yew tree, is used in the treatment of ovarian cancer.

After the isolation and structural identification of active plant constituents, organic chemists may recreate them by total synthesis in the laboratory or, more importantly, use the natural chemical as the starting material in the creation of slightly different chemical structures through molecular manipulation. The new structures, termed semisynthetic drugs, may have a slightly or vastly different pharmacologic activity from that of the starting substance, depending on the nature and extent of chemical alteration. Other plant constituents that in themselves may be inactive or rather unimportant therapeutically may

be chemically modified to yield important drugs with profound pharmacologic activity. For example, the various species of *Dioscorea*, popularly known as Mexican yams, are rich in the chemical steroid structure from which cortisone and estrogens are semisynthetically produced.

Animals have served humans in their search for drugs in a number of ways. They not only have yielded to drug testing and biologic assay but also have provided drugs that are mannered from their tissues or through their biologic processes. Hormonal substances, such as thyroid extract, insulin, and pituitary hormone obtained from the endocrine glands of cattle, sheep, and swine, are lifesaving drugs used daily as replacement therapy in the human body. The urine of pregnant mares is a rich source of estrogens. Knowledge of the structural architecture of the individual hormonal substances has produced a variety of synthetic and semisynthetic compounds with hormone-like activity. The synthetic chemicals used as oral contraceptives are notable examples.

The use of animals in the production of various biologic products, including serums, antitoxins, and vaccines, has had lifesaving significance ever since the pioneering work of Edward Jenner on the smallpox vaccine in England in 1796. Today the poliomyelitis vaccine is prepared in cultures of renal monkey tissue, the mumps and influenza vaccines in fluids of chick embryo, the rubella (German measles) vaccine in duck embryo, and the smallpox vaccine from the skin of bovine calves inoculated with vaccinia virus. New vaccines for diseases such as AIDS and cancer are being developed through the use of cell and tissue cultures.

Today we are witnessing a new era in the development of pharmaceutical products as a result of the advent of genetic engineering, the submicroscopic manipulation of the double helix, the spiral DNA chain of life. Through this process will come more abundant and vastly purer antibiotics, vaccines, and yet unknown chemical and biologic products to combat human diseases.

The two basic technologies that drive the genetic field of drug development are recombinant DNA and monoclonal antibody (mAb) production (14–16). Common to each technique is the ability to manipulate and produce proteins, the building blocks of living matter. Proteins are an almost infinite source of drugs. Made up of long chains of amino acids, their sequence and spatial configuration offer a staggering number of possibilities. Both recombinant rDNA and mAb production techniques influence cells' ability to produce proteins.

The more fundamental of the two techniques is recombinant DNA. It has the potential to produce almost any protein. Genetic material can be transplanted from higher species, such as humans, into a lowly bacterium. This so-called gene splicing can induce the lower organism to make proteins it would not otherwise have made. Such drug products as human insulin, human growth hormone, hepatitis B vaccine, epoetin alfa, and interferon are being produced in this manner. Human insulin was the first recombinant biopharmaceutical approved in the United States, in 1982.

Whereas recombinant DNA techniques involve the manipulation of proteins within the cells of lower animals, mAb production is conducted entirely within the cells of higher animals, including the patient. The technique exploits the ability of cells with the potential to produce a desired antibody and stimulates an unending stream of pure antibody production. These antibodies have the capacity to combat the specific target.

The development and use of monoclonal antibodies is having a profound impact in both diagnostic medicine and in the treatment of disease. Diagnostically, for example, monoclonal antibodies are used in home pregnancy testing products. In these tests, the mAb is highly sensitive to binding on one site on the human chorionic gonadotropin (HCG) molecule, a specific marker to pregnancy because in healthy women, HCG is synthesized exclusively by the placenta. The first FDA-approved therapeutic mAb was muromonab, a transplant rejection drug, approved in 1986. Since then, many additional mAbs have received FDA approval for marketing with hundreds of others undergoing clinical

trials. Among those in current use are belimumab (lupus erythematosus), brentuximab (Hodgkin lymphoma), cetuximab (colorectal cancer), natalizumab (multiple sclerosis), ofatumumab (lymphocytic leukemia), ranibizumab (macular degeneration), and tocilizumab (rheumatoid arthritis).

Human gene therapy, used to prevent, treat, cure, diagnose, or mitigate human diseases caused by genetic disorders, is another promising new technology. The human body contains up to 100,000 genes. Genes that are aligned on a double strand of DNA in the nucleus of every cell control all of the body's functions. Base pairs of adenine and thymine (A and T, respectively) and cytosine and guanine (C and G, respectively) constitute the instructions on a gene. Only genes necessary for a specific cell's function are active or expressed. When a gene is expressed, a specific type of protein is produced. In genetic diseases, gene expression may be altered and/or gene sequences may be mismatched, partly missing, or repeated too many times, causing cellular malfunction and disease.

Gene therapy is a medical intervention based on the modification of the genetic material of living cells. Cells may be modified outside the body (ex vivo) for subsequent administration, or they may be modified within the body (in vivo) by gene therapy products given directly to the patient. In either case, gene therapy entails the transfer of new genetic material to the cells of a patient with a genetic disease. The genetic material, usually cloned DNA, may be transferred into the patient's cells physically, as through microinjection, through chemically mediated transfer procedures, or through disabled retroviral gene transfer systems that integrate genetic material directly into the host cell chromosomes (17–19).

The first human gene therapy used was to treat adenosine deaminase (ADA) deficiency, a condition that results in abnormal functioning of the immune system. Therapy consisted of the administration of genetically modified cells capable of producing ADA (18). Many emerging biopharmaceutical companies are exploring the application of gene therapy to treat sickle cell anemia, malignant melanoma, renal cell cancer, heart disease, familial hypercholesterolemia, cystic fibrosis, lung and colorectal cancer, and AIDS (20). The FDA has established guidelines for cellular and gene therapy (21).

A Goal Drug

In theory, a goal drug would produce the specifically desired effect, be administered by the most desired route (generally orally) at minimal dosage and dosing frequency, have optimal onset and duration of activity, exhibit no side effects, and following its desired effect would be eliminated from the body efficiently, completely, and without residual effect. It would also be easily produced at low cost, pharmaceutically elegant, and physically and chemically stable in various conditions of use and storage. Although not completely attainable in practice, these qualities and features are sought in drug and dosage form design.

Methods of Drug Discovery

Although some drugs may be the result of fortuitous discovery, most drugs are the result of carefully designed research programs of screening, molecular modification, and mechanism-based drug design (11–13, 22–25).

Random or untargeted screening involves the testing of large numbers of synthetic organic compounds or substances of natural origin for biologic activity. Random screens may be used initially to detect an unknown activity of the test compound or substance or to identify the most promising compounds to be studied by more sophisticated nonrandom or targeted screens to determine a specific activity.

Although random and nonrandom screening programs can examine a host of new compounds for activity, sometimes promising compounds may be overlooked if the screening models are not sensitive enough to reflect accurately the specific disease against which the agent or its metabolites may be useful (25).

To detect and evaluate biologic activity, bioassays are used to differentiate the effect

and potency (strength of effect) of the test agent from those of controls of known action and effect. The initial bioassays may be performed in vitro using cell cultures to test the new agent's effect against enzyme systems or tumor cells, whereas subsequent bioassays may be performed in vivo and may use more expensive and disease-specific animal models.

Newer methods, such as high-throughput screening, are capable of examining 15,000 chemical compounds a week using 10 to 20 biologic assays (23). To be effective, this requires a sizable and chemically diverse collection of compounds to examine, which many pharmaceutical and chemical companies have in chemical libraries. Frequently these libraries, which may contain hundreds of thousands of compounds, are purchased or licensed from academic or commercial sources. With the advent of techniques like combinatorial chemistry, it has become feasible to increase substantially the size and diversity of a chemical library (23).

Molecular modification is a chemical alteration of a known and previously characterized organic compound (frequently a lead compound; see "A Lead Compound") for the purpose of enhancing its usefulness as a drug. This could mean enhancing its specificity for a particular body target site, increasing its potency, improving its rate and extent of absorption, modifying to advantage its time course in the body, reducing its toxicity, or changing its physical or chemical properties (e.g., solubility) to provide desired features (23). The molecular modifications may be slight or substantial, involving changes in functional groups, ring structures, or configuration. Knowledge of chemical structure–pharmacologic activity relationships plays an important role in designing new drug molecules. Molecular modification produces new chemical entities and improved therapeutic agents. Figure 2.3A and B shows the molecular modifications that led to the discoveries of the first commercial beta-blocker, propranolol, and the first commercial histamine H2-receptor blocking agent, cimetidine.

Mechanism-based drug design is molecular modification to design a drug that interferes specifically with the known or suspected biochemical pathway or mechanism of a disease process. The intention is the interaction of the drug with specific cell receptors, enzyme systems, or the metabolic processes of pathogens or tumor cells, resulting in a blocking, disruption, or reversal of the disease process. For this, it is essential to understand the biochemical pathway of the disease process and the manner in which it is regulated. Molecular graphics, the use of computer graphics to represent and manipulate the structure of the drug molecule to fit the simulated molecular structure of the receptor site, is a useful complementary tool in drug molecule design.

An example of mechanism-based drug design is the compound enalaprilat, the active metabolite of enalapril (Vasotec), which inhibits the angiotensin-converting enzyme (ACE) that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Inhibition of the enzyme results in decreased plasma angiotensin II, leading to decreased vasopressor effects and lower blood pressure. Another example is ranitidine (Zantac), an inhibitor of histamine at the histamine H2-receptors, including receptors on the gastric cells. This inhibits gastric acid secretion, making the drug effective in the treatment of gastric ulcers and other gastrointestinal conditions related to the production of gastric acid. A third example is sertraline (Zoloft), which inhibits the central nervous system's neuronal uptake of serotonin, making the drug useful in the treatment of depression.

A Lead Compound

A lead compound is a prototype chemical compound that has a fundamental desired biologic or pharmacologic activity. Although active, the lead compound may not possess all of the features desired, such as potency, absorbability, solubility, low toxicity, and so forth. Thus, the medicinal chemist may seek to modify the lead compound's chemical structure to achieve the desired features while reducing the undesired ones. The chemical modifications produce analogs with

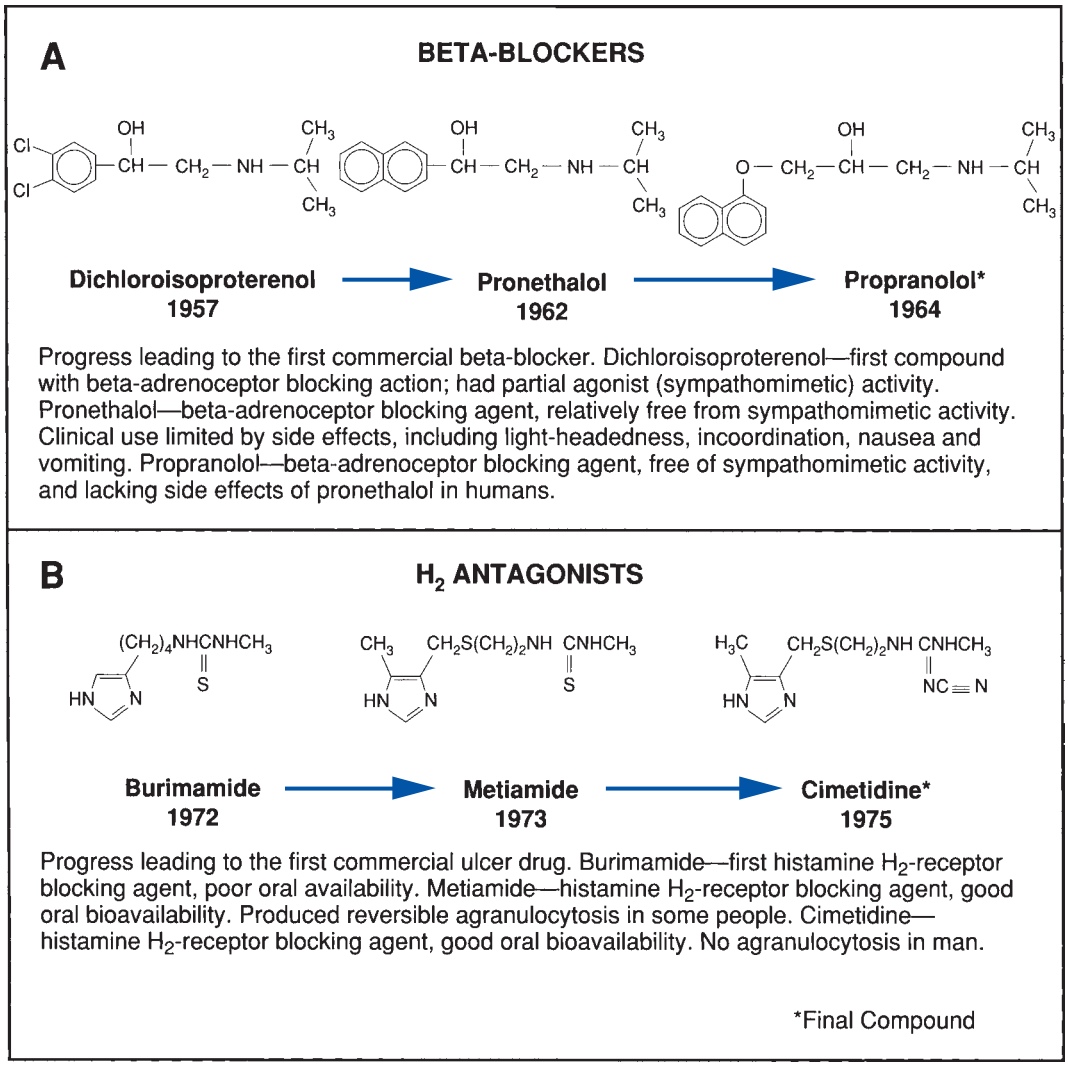


FIGURE 2.3 Molecular modifications leading to the development of the first commercial beta-blocker, propranolol, and the first commercial histamine H2-receptor blocking agent, cimetidine. (Reprinted with permission from Maxwell RA. The state of the art of the science of drug discovery. Drug Develop Res 1984;4:375–389; through Pharmaceutical Research: Therapeutic and Economic Value of Incremental Improvements, 1990;12. Courtesy of National Pharmaceutical Council, Reston, VA. Reprinted with permission of John Wiley & Sons, Inc.)

additional or different functional chemical groups, altered ring structures, or different chemical configurations. The results are modified chemical compounds capable of having different interactions with the body's receptors, thereby eliciting different actions and intensities of action.

The synthesis of derivatives of the prototype chemical may ultimately lead to successive generations of new compounds of the same pharmacologic type. This may be exemplified by the development of new generations of cephalosporin antibiotics, additional H2-antagonists from the pioneer drug cimetidine, and the large series of antianxiety drugs derived from the benzodiazepine structure and the innovator drug chlordiazepoxide (Librium).

Most drugs exhibit activities secondary to their primary pharmacologic action. It is fairly common to take advantage of a secondary activity by using molecular modification

to develop new compounds that amplify the secondary use of the drug or by gaining approval to market the drug for a secondary indication. For example, the drug finasteride (Proscar) was originally developed and approved to treat benign prostatic hyperplasia. Later, the same drug (as Propecia) was approved at a lower recommended dosage to treat male pattern baldness.

Prodrugs

Prodrug is a term used to describe a compound that requires metabolic biotransformation after administration to produce the desired pharmacologically active compound. The conversion of an inactive prodrug to an active compound occurs primarily through enzymatic biochemical cleavage. Depending on the specific prodrug–enzyme interaction, the biotransformation may occur anywhere along the course of drug transit or at the body site where the requisite enzymes are sufficiently present. An example of a prodrug is enalapril maleate (Vasotec), which, after oral administration, is bioactivated by hydrolysis to enalaprilat, an ACE inhibitor used in the treatment of hypertension. Prodrugs may be designed preferentially for solubility, absorption, biostability, and prolonged release (24).

Solubility

A prodrug may be designed to possess solubility advantages over the active drug, enabling the use of specifically desired dosage forms and routes of administration. For example, if an active drug is insufficiently soluble in water to prepare a desired intravenous injection, a water-soluble prodrug, for example, hydrocortisone sodium succinate, could be prepared through the addition of a functional group that later would be detached by the metabolic process to yield, once again, the active drug molecule.

Absorption

A drug may be made more water or lipid soluble, as desired, to facilitate absorption via the intended route of administration. For example, for patients requiring prolonged antipsychotic therapy, the addition of the decanoate ester to the haloperidol molecule makes the molecule less water soluble. Subsequently, when it is administered by a deep intramuscular injection, the molecule provides a sustained effect that lasts up to 4 weeks.

Biostability

If an active drug is prematurely destroyed by biochemical or enzymatic processes, the design of a prodrug may protect the drug during its transport in the body. For example, valacyclovir is a prodrug of acyclovir. Normally, the bioavailability of acyclovir is 10% to 20% after oral administration. Valacyclovir is converted to acyclovir by liver esterases via the first pass metabolism resulting in a 55% bioavailability. In addition, the use of a prodrug could result in site-specific action of greater potency. For example, dopamine in the treatment of Parkinson disease is unable to cross the blood–brain barrier. However, its prodrug, levodopa, is able to cross the blood–brain barrier and then is converted to dopamine.

Prolonged Release

Depending on a prodrug's rate of metabolic conversion to an active drug, it may provide prolonged drug release and extended therapeutic activity.

FDA'S Definition of a New Drug

A New Molecular Entity (NME) is defined by the FDA as an active ingredient that has never before been marketed in the United States in any form (26). However, a drug need not be a new chemical entity to be considered new. A change in a previously approved drug product's formulation or method of manufacture constitutes newness under the law since such changes can alter the therapeutic efficacy and/or safety of a product.

A combination of two or more old drugs or a change in the usual proportions of drugs in an established combination product is considered new if the change introduces a question of safety or efficacy.

A proposed new use for an established drug, a new dosage schedule or regimen,

a new route of administration, or a new dosage form makes a drug or a drug product's status new and triggers reconsideration for safety and efficacy.

Drug Nomenclature

When first synthesized or identified from a natural source, an organic compound is represented by an empirical formula, for example, $C_{16}H_{19}N_3O_5S{\cdot}3H_2O$ for amoxicillin, which indicates the number and relationship of the atoms in the molecule. As knowledge of the relative locations of these atoms increases, the compound receives a systematic chemical name, such as 4-thia-1-azabicylco[3.2.0]heptane-2-carboxylic acid, 6-[amino(4-hydroxyphenyl) acetyl]amino-3, 3-dimethyl-7-oxo, trihydrate 2S-[2[alpha], [5[alpha], 6[beta](S*)]]. To be adequate and fully specific, the name must reveal every part of the compound's molecular structure, so that it describes only that compound and no other. The systematic name is generally so formidable that it soon is replaced in scientific communication by a shortened name, which, although less descriptive chemically, is understood to refer only to that chemical compound. This shortened name is the chemical's nonproprietary (or generic) name (e.g., amoxicillin; see Fig. 1.3). A nonproprietary name of a drug serves numerous and varied purposes, its principal function being to identify the substance to which it applies by means of a designation that may be used by the professional and lay public free from the restrictions associated with registered trademarks.

Today, many companies give their new compounds code numbers before assigning a nonproprietary name. These code numbers take the form of an identifying prefix letter or letters that identify the drug's sponsor, followed by a number that further identifies the test compound (e.g., SQ 14,225, the investigational code number for the drug captopril, initially developed by Squibb). The code number frequently stays with a compound from its initial preclinical laboratory investigation through human clinical trials.

When the results of testing indicate that a compound shows sufficient promise of becoming a drug, the sponsor may formally propose a nonproprietary name to the U.S. Adopted Names (USAN) Council. The Council is tri-sponsored by the American Medical Association (AMA), the United States Pharmacopeial Convention (USP), and the American Pharmacists Association (APhA). In addition, the FDA cooperates with and is represented on the Council. Should the drug receive recognition in an official compendium, the nonproprietary name established during the drug's early usage is adopted. Nonproprietary names are issued only for single agents. An updated list of adopted names may be found on the Web site: http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/adopted-names.page.

Guiding principles for the coining of a nonproprietary name are comprehensive (27). Among the stated principles are the following: (*a*) the name should be useful primarily to health care practitioners particularly in its safety for use in the routine processes of prescribing, dispensing, and administering drugs; (*b*) the name should be a single word, preferably with no more than four syllables, and should be free from conflict with other nonproprietary names and should be neither confusing nor misleading; and (*c*) distinctive terminology should be used for specific drugs or drug groups (e.g., beta-blockers).

With the creation of the USAN Council and the cooperation of the interested parties on a worldwide basis, nonproprietary drug nomenclature is becoming standardized.

BIOLOGIC CHARACTERIZATION

Prospective drug substances must undergo preclinical testing for biologic activity to assess their potential as useful therapeutic agents. These studies, which fall into the general areas of pharmacology, drug metabolism, and toxicology, involve many types of scientists, including general biologists, microbiologists, molecular biologists, biochemists, geneticists, pharmacologists, physiologists, pharmacokineticists, pathologists, toxicologists, statisticians, and others. Their work leads to the determination of whether

a chemical agent possesses adequate features of safety and sufficient promise of usefulness to pursue as a prospective new drug.

To judge whether a drug is safe and effective, information must be gained on how it is absorbed, distributed throughout the body, stored, metabolized, and excreted and how it affects the action of the body's cells, tissues, and organs. Scientists have developed studies that may be conducted outside the living body by using cell and tissue culture and computer programs that simulate human and animal systems. Cell cultures are being used increasingly to screen for toxicity before progressing to whole-animal testing.

Pharmacology

Within its broad definition, pharmacology is the science concerned with drugs, their sources, appearance, chemistry, actions, and uses. The term in general can be expanded to include biochemical and physiologic effects, mechanisms of action, absorption, distribution, biotransformation, and excretion. From this basic field of study come such subareas as pharmacodynamics, the study of the biochemical and physiologic effects of drugs and their mechanisms of action; pharmacokinetics, which deals with the absorption, distribution, metabolism or biotransformation, and excretion (ADME) of drugs; and clinical pharmacology, which applies pharmacologic principles to the study of the effects and actions of drugs in humans.

Today's emphasis in the development of new drugs is on identifying the cause and process of a disease and then designing molecules capable of interfering with that process. Although the precise cause of each disease is not yet known, what is known is that most diseases arise from a biochemical imbalance, an abnormal proliferation of cells, an endogenous deficiency, or an exogenous chemical toxin or invasive pathogen.

The biochemical processes in the body's cells involve intricate enzymatic reactions. An understanding of the role of a particular enzyme system in the body's healthy state and disease state can lead to the design of drugs that affect the enzyme system with positive results, as exemplified earlier in this chapter for the drug enalaprilat.

Different drug substances produce different effects on the biologic system because of the specific interactions between a drug's chemical structure and specific cells or cellular components of a particular tissue or organ, termed receptor sites (Fig. 2.4). The action of most drugs takes place at the molecular level, with the drug molecules interacting with the molecules of the cell structure or its contents. The selectivity and specificity of drugs for a certain body tissue—for example, drugs that act primarily on the nerves, heart, or kidney—are related to specific sites on or within the cells, receptive only to chemicals of a particular chemical structure and configuration. This is the basis for structure–activity relationships established for drugs and for families of drugs within therapeutic categories. Studies of the pharmacologic activities of a series of analogs with varied functional groups and side chains can reveal the most specific structure for a given drug–cell or drug–enzyme interaction.

Although receptors for many drugs have yet to be identified, they, like the active centers of enzymes, are considered to be carboxyl, amino, sulfhydryl, phosphate, and similar reactive groups oriented on or in the cell in a pattern complementary to that of the drugs with which they react. The binding of a drug to the receptor is thought to be accomplished mainly by ionic, covalent, and other relatively weak reversible bonds. Occasionally, firm covalent bonding is involved, and the drug effect is then slowly reversible.

There is a relationship between the quantity of drug molecules available for interaction and the capacity of the specific receptor site. For instance, after a dose of drug and its transit to the site of action, the cell's receptors may or may not become fully saturated with the interacting drug. When the receptors are saturated, the effects of the specific interaction are maximized. Any additional drug present (as in the circulation) and not participating in the interaction may serve as a reservoir to replace the drug molecules released from the complex. Two drugs in a

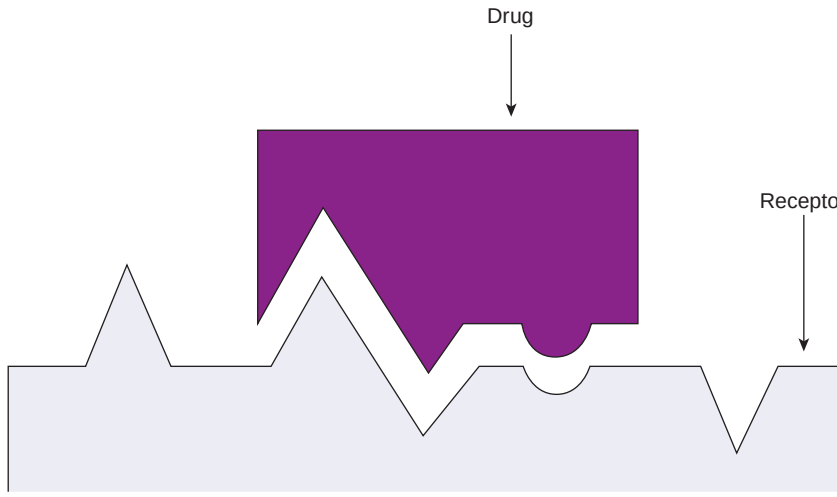


FIGURE 2.4 Receptor site and substrate (drug). (Reprinted with permission from Clark FH, ed. How Modern Medicines are Discovered. Courtesy of Futura Publishing.)

biologic system may compete for the same binding sites, with the drug having the stronger bonding attraction for the site generally prevailing. Already bound molecules of the more weakly bound drug may be displaced from the binding site and left free in the circulation.

Certain cells within the body are capable of binding drugs without eliciting a drug effect. These cells act as carriers and may be important to a drug's transport to active sites or to sites of the drug's biotransformation and elimination.

The process of evaluating chemical compounds for biologic activity and the determination of their mechanisms of action are the responsibilities of the pharmacologist. In vitro cultures of cells and enzymes systems and in vivo animal models are used to define a chemical's pharmacologic profile.

To define a pharmacologic profile, pharmacologists progress stepwise through increasingly sophisticated levels of evaluation, based on the test compound's success in prior studies. Whole-animal studies are reserved for the test compounds that have demonstrated reasonable potential as a drug candidate.

Among the early studies are the determination of a compound's selectivity for various receptors and its activity against select enzyme systems. Studies of the compound's effects on cell function are then performed to detect evidence of efficacy and to determine whether the compound is an agonist or antagonist. These are followed by studies with isolated animal tissues to define further the compound's activity and selectivity. Then whole-animal studies are used to evaluate the pharmacologic effects of the agent on specific organ systems. Finally, studies are undertaken using animal models of human disease for which the compound is considered a drug candidate.

Most animal testing is performed on small animals, usually rodents (mouse, rat) for a number of reasons including cost, availability, the small amount of drug required for a study, the ease of administration by various routes (oral, inhalation, and intravenous), and experience with drug testing in these species. However, in final pharmacologic and toxicologic studies, two or more animal species are used as required by the FDA, including a rodent and an animal from another order. Drugs are studied at various dose levels to determine the effect, potency, and toxicity.

The primary objective of the animal studies is to obtain basic information on the drug's effects that may be used to predict safe and effective use in humans. This is a difficult task because of species variation

and the fact that animals are not absolute predictors of human response. However, a number of animal models have been developed to mimic certain human diseases, and these are used effectively. For instance, there are animal models for type I diabetes and hypertension, using genetically diabetic and hypertensive animals, respectively, and for tumor growth, using tumor transplants in various species. Certain animal species have been determined to be the best for certain studies of organ systems, or as human disease models, including dogs and rats for hypertension, dogs and guinea pigs for respiratory effects, dogs for diuretic activity, rabbits for blood coagulation, and mice and rats for central nervous system studies (28). Unfortunately, useful animal models are not available for every human disease. As a drug candidate progresses in its preclinical pharmacologic evaluation, drug metabolism and toxicity tests are initiated.

Drug Metabolism

A series of animal studies of a proposed drug's ADME are undertaken to determine (*a*) the extent and rate of drug absorption from various routes of administration, including the one intended for human use; (*b*) the rate of distribution of the drug through the body and the site or sites and duration of the drug's residence; (*c*) the rate, primary and secondary sites, the mechanism of the drug's metabolism in the body, and the chemistry and pharmacology of any metabolites; and (*d*) the proportion of administered dose eliminated from the body and its rate and route of elimination. In these studies, a minimum of two animal species are employed (generally the same as used in the pharmacologic and toxicologic studies), a rodent and one other, usually a dog.

The biochemical transformation or metabolism of drug substances is the body's means of transforming nonpolar drug molecules into polar compounds, which are more readily eliminated. Specific and nonspecific enzymes participate in drug metabolism, primarily in the liver but also in the kidneys, lungs, and gastrointestinal tract. Drugs that enter the hepatic circulation after absorption from the gut, as after oral administration, are particularly exposed to rapid drug metabolism. This transit through the liver and exposure to the hepatic enzyme system is termed the first-pass effect. If the first-pass effect is to be avoided, other routes of administration (buccal, rectal) may be used that allow the drug to be absorbed into the systemic circulation through blood vessels other than hepatic.

Drug metabolism or biotransformation frequently results in the production of one or more metabolites of the administered drug, some of which may be pharmacologically active compounds, while others may not. As noted previously, drug metabolism may be essential to convert prodrugs to active compounds. For reasons of safety, it is important to determine whether a drug's metabolic products are toxic or nontoxic to the animal and later to the human. When metabolites are found, they are chemically and biologically characterized for activity and toxicity. Some new drugs have been discovered as metabolic by-products, or metabolites, of parent compounds.

ADME studies are performed through the timely collection and analysis of urine, blood, and fecal samples and through a careful examination of animal tissues and organs upon autopsy. In addition, special studies are undertaken to determine the presence, if any, of a test drug or its metabolites in the milk of lactating animals; the ability of the drug to cross the placental barrier and enter the fetal blood supply; and the long-term retention of drugs or metabolites in the body. In studying the formation and disposition of metabolites, a radioactive label is commonly incorporated into the administered compound and traced in the animal's waste products and tissues.

The relationship between ADME and drug product development is discussed in Chapter 5.

Toxicology

Toxicology deals with the adverse or undesired effects of drugs. Although the ability to predict the safe use of a new drug in humans based on preclinical animal studies is desirable, it is not entirely achievable. The direct extrapolation of preclinical animal

safety data to humans is difficult because of species variation, different dose–response relationships, immunologic differences, subjective reactions that are not deducible in animals (such as headache), and other reasons. Although many adverse reactions in humans cannot be predicted in advance through animal studies, the greater the number of animal species tested that demonstrate a toxic effect, the greater the likelihood that the effect will also be seen in humans.

In drug development programs, preclinical drug safety evaluation or toxicity studies are undertaken to determine (*a*) the substance's potential for toxicity with short-term (acute effects) or long-term use (chronic effects); (*b*) the substance's potential for specific organ toxicity; (*c*) the mode, site, and degree of toxicity; (*d*) dose–response relationships for low, high, and intermediate doses over a specified time; (*e*) gender, reproductive, or teratogenic toxicities; and (*f*) the substance's carcinogenic and genotoxic potential.

As a part of an application to initiate human studies (IND), the FDA requires an integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug, the application is required to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; and any special toxicity test related to the drug's particular mode of administration or conditions of use, for example, inhalation, dermal, or ocular toxicology (9,29,30).

Acute or Short-Term Toxicity Studies

These studies are designed to determine the toxic effects of a test compound when administered in a single dose and/or in multiple doses over a short period, usually a single day. Although various routes of administration may be used (such as lavage dosing via gastric tube), the studies should be conducted to represent the intended route for human use.

The test compound is administered at various dose levels, with toxic signs observed for onset, progression or reversal, severity, mortality, and rates of incidence. Doses are ranged to find the largest single dose of the test compound that will not produce a toxic effect, the dose level at which severe toxicity occurs, and intermediate toxicity levels. The animals are observed and compared with controls for eating and drinking habits, weight change, toxic effects, psychomotor changes, and any other signs of untoward effects, usually over a 30-day postdose period. Feces and urine specimens are collected and clinical laboratory tests performed to detect changes in clinical chemistry and other changes that could indicate toxicity. When they occur, animal deaths are recorded, studied by histology and pathology, and statistically evaluated on the basis of dose–response, gender, age, and intraspecies and interspecies findings and against laboratory controls.

Subacute or Subchronic Studies

In designing an animal toxicology program, relationships to projected human clinical studies for safety must be considered. For example, animal toxicity studies of a minimum of 2 weeks of daily drug administration at three or more dosage levels to two animal species are required to support the initial administration of a single dose in human clinical testing (8). These studies are termed subacute or subchronic. The initial human dose is usually one tenth of the highest nontoxic dose (in milligrams per kilogram of subject's weight) shown during the animal studies. For drugs intended to be given to humans for a week or more, animal studies of 90 to 180 days must demonstrate safety. These are termed chronic toxicity studies. And if the drug is to be used for a chronic human illness, animal studies for 1 year or longer must be undertaken to support human use. Some animal toxicity studies last 2 years or longer and may be used to corroborate findings obtained during the course of the human clinical trials.

Included in the subchronic and chronic studies are comparative data of test and control animal species, strain, sex, age, dose levels and ranges, routes of administration, duration of treatment, observed effects, mortality, body weight changes, food and water consumption, physical examinations (e.g., electrocardiography, ophthalmic examination),

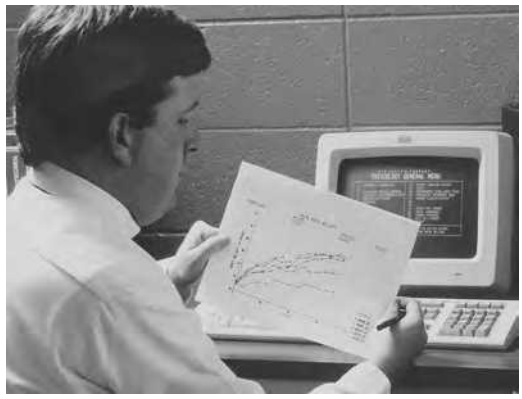


FIGURE 2.5 A toxicologist examining research data of body weight changes during preclinical studies in mice. (Courtesy of Toxicology Research Laboratories, Lilly Research Laboratories, Division of Eli Lilly and Company.)

hematology, clinical chemistry, organ weights, gross pathology, neoplastic pathology, histopathology, urinalysis, ADME data, and other factors. Figure 2.5 shows a toxicologist examining research data of body weight changes during preclinical rodent studies.

Carcinogenicity Studies

Carcinogenicity testing is usually a component of chronic testing and is undertaken when the compound has shown sufficient promise as a drug to enter human clinical trials. Carcinogenicity studies are usually carried out in a limited number of rat and mouse strains for which there is reasonable information on spontaneous tumor incidence.

Dose-ranging studies are done with female and male animals using high, intermediate, and low doses over a 90-day period. For carcinogenicity studies, the high dose should be only high enough (the maximum tolerated dose) to elicit signs of minimal toxicity without significantly altering the animal's normal lifespan by effects other than carcinogenicity (31).

Carcinogenicity studies are long term (18 to 24 months), with surviving animals killed and studied at defined weeks during the test period. Data on the causes of animal death (other than killing), tumor incidence, type and site, and necropsy findings are collected and evaluated. Any preneoplastic lesions and/or tissue-specific proliferative effects are important findings.

Reproduction Studies

Reproduction studies are undertaken to reveal any effect of an active ingredient on mammalian reproduction. Included in these studies are fertility and mating behavior; early embryonic, prenatal, and postnatal development; multigenerational effects; and teratology. The combination of studies allows exposure from conception to sexual maturity and allows immediate and latent effects to be detected through complete life cycles and through successive generations.

In these studies, the maternal parent, fetus, neonates, and weaning offspring are evaluated for anatomic abnormalities, growth, and development. The same species of animal used in other toxicity studies are used in reproductive studies, usually the rat. In embryotoxicity studies only, a second mammalian species traditionally has been required.

In reproductive studies, as is the case for other toxicity studies, the doses selected and the routes of administration used are critical. A high dose, based on previous acute and chronic toxicity and pharmacokinetic studies, is selected, with lower dosages chosen in descending sequence. Setting close dosage intervals is useful to reveal trends in dose-related toxicity. Although once-daily dosing is usual, the drug's pharmacokinetics may influence the frequency of dosing (32). The route or routes of administration used should be similar to those intended for human use. A single route of administration may be acceptable if it can be shown that a similar drug distribution (kinetic profile) results from different routes of administration.

Genotoxicity or Mutagenicity Studies

Genotoxicity studies are performed to determine whether the test compound can affect gene mutation or cause chromosome or DNA damage. Strains of *Salmonella*

typhimurium are routinely used in assays to detect mutations (9,33).

EARLY FORMULATION STUDIES

As a promising compound is characterized for biologic activity, it is also evaluated with regard to chemical and physical properties that have a bearing on its ultimate and successful formulation into a stable and effective pharmaceutical product. This is the area of responsibility of pharmaceutical scientists and formulation pharmacists. When sufficient information is gleaned on the compound's physical and chemical properties, initial formulations of the dosage form are developed for use in human clinical trials. During the course of the clinical trials, the proposed product is developed further, from initial formulation to final formulation and from pilot plant (or small-scale production) to scale-up, in preparation for large-scale manufacturing.

To provide sufficient quantities of the bulk chemical (drug) compound for the sequence of preclinical studies, clinical trials, and small-scale and large-scale dosage form production, the careful planning, scheduling, and implementation of the bulk chemical's production must be undertaken by chemical engineers. Quality control and validation must be built into each step of the process.

Full documentation of the CMCs is an essential part of all drug applications filed with the FDA (1,34).

Preformulation Studies

Each drug substance has intrinsic chemical and physical characteristics that must be considered before the development of a pharmaceutical formulation. Among these are the drug's solubility, partition coefficient, dissolution rate, physical form, and stability. These and other factors, discussed in detail in Chapter 4 and throughout the text, are briefly noted here as an introduction to their importance in the preparation of dosage forms for drug evaluation in human clinical trials and in the development of a final product submitted to the FDA for marketing approval. The FDA's protocols seek to correlate in vitro drug product dissolution and in vivo bioavailability, since drug dissolution and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption (35).

Drug Solubility

A drug substance administered by any route must possess some aqueous solubility for systemic absorption and therapeutic response. Poorly soluble compounds (e.g., less than 10 mg/mL aqueous solubility) may exhibit incomplete, erratic, and/or slow absorption and thus produce a minimal response at desired dosage. Enhanced aqueous solubility may be achieved by preparing more soluble derivatives of the parent compound, such as salts or esters, by chemical complexation, or by reducing the drug's particle size.

Partition Coefficient

To produce a pharmacologic response, a drug molecule must first cross a biologic membrane of protein and lipid, which acts as a lipophilic barrier to many drugs. The ability of a drug molecule to penetrate this barrier is based in part on its preference for lipids (lipophilic) versus its preference for an aqueous phase (hydrophilic). A drug's partition coefficient is a measure of its distribution in a lipophilic–hydrophilic phase system and indicates its ability to penetrate biologic multiphase systems.

Dissolution Rate

The speed at which a drug substance dissolves in a medium is called its dissolution rate. Dissolution rate data, when considered along with data on a drug's solubility, dissolution constant, and partition coefficient, can provide an indication of the drug's absorption potential. For a chemical entity, its acid, base, or salt forms, as well as its physical form (e.g., particle size), may result in substantial differences in the dissolution rate.

Physical Form

The crystal or amorphous forms and/or the particle size of a powdered drug can affect the dissolution rate, and thus the rate and

extent of absorption, for a number of drugs. For example, by reducing the particle size and increasing the powder fineness and therefore the surface area of a poorly soluble drug, its dissolution rate in the gut is enhanced (through greater exposure of the drug to gastrointestinal fluid) and its biologic absorption increased. Small and controlled particle size is also critical for drugs administered to the lung by inhalation. The smaller the particle, the deeper is the penetration into the alveoli. Thus, by selective control of the physical parameters of a drug, biologic response may be optimized.

Stability

The chemical and physical stability of a drug substance alone, and when combined with formulation components, is critical to preparing a successful pharmaceutical product. For a given drug, one type of crystal structure may provide greater stability than other structures and may therefore be preferred. For drugs susceptible to oxidative decomposition, the addition of antioxidant stabilizing agents to the formulation may be required to protect the potency. For drugs destroyed by hydrolysis, protection against moisture in formulation, processing, and packaging may be required to prevent decomposition. In every case, drug stability testing at various temperatures, conditions of relative humidity (RH)—as 40°C 75% RH/30°C 60% RH—durations, and environments of light, air, and packaging is essential in assessing drug and drug product stability. Such information is vital in developing label instructions for use and storage, assigning product expiration dating, and packaging and shipping.

Initial Product Formulation and Clinical Trial Materials

An initial product is formulated using the information gained during the preformulation studies and with the consideration of the dose or doses, dosage form, and route of administration desired for the clinical studies and for the proposed marketed product. Thus, depending upon the design of the clinical protocol and desired final product, formulation pharmacists are called upon to develop a specific dosage form (e.g., capsule, suppository, solution) of one or more dosage strengths for administration by the intended route of administration (e.g., oral, rectal, intravenous). Additional dosage forms for other than the initial route of administration may later be developed, depending on patients' requirements, therapeutic utility, and marketing assessments. This is especially important if the drug may be administered to children.

The initial formulations prepared for Phase 1 and Phase 2 of the clinical trials, although not as sophisticated and elegant as the final formulation, should be of high pharmaceutical quality, meet analytical specifications for composition, manufacturing, and control, and be sufficiently stable for the period of use.

Often during Phase 1 studies, for orally administered drugs, capsules are employed containing the active ingredient alone, without pharmaceutical excipients. Excipients are included in the formulation for Phase 2 trials. During human trials, studies of the drug's ADME are undertaken to obtain a profile of the drug's human pharmacokinetics and biologic availability from the formulation administered. Different formulations may be prepared and examined to develop the one having the desired characteristics. During Phase 2, the final dosage form is selected and developed for Phase 3 trials; this is the formulation that is submitted to the FDA for marketing approval.

Clinical supplies or clinical trial materials comprise all dosage formulations used in the clinical evaluation of a new drug. This includes the proposed new drug, placebos (inert substances), and drug products against which the new drug is to be compared (comparator drugs or drug products). They all must be prepared in indistinguishable dosage forms (look alike, taste alike, and so on) and packaged with coded labels to reduce possible bias when blinded studies are called for in the clinical protocol. Blinded studies

are controlled studies in which at least one of the parties (e.g., patient, physician) does not know which product is being administered. At the conclusion of the clinical study, the codes for the products administered are broken and the clinical results statistically evaluated. Some studies are open label, in which case, all parties may know what products are administered.

Some pharmaceutical companies have special units for the preparation, analytical control, coding, packaging, labeling, shipping, and record maintenance of clinical supplies. Other companies integrate this activity within their existing drug product development and production operations. Still other companies employ contract firms specializing in this field to prepare and manage their clinical trial materials program.

In all clinical study programs, the package label of the investigational drug must bear the statement "Caution: new drug—limited by federal [or United States] law to investigational use." Once received by the investigator, the clinical supplies may be administered only to subjects in the study. Blister packaging is commonly used in clinical studies, with immediate labels containing the clinical study or protocol number, patient identification number, sponsor number, directions for use, code number to distinguish between investigational drug, placebo, and/or comparator product, and other relevant information. Records of the disposition of the drug must be maintained by patient number, dates, and quantities administered. When there is a department of pharmacy at the site of the clinical study (e.g., university teaching hospital), pharmacists frequently assist in the control and management of clinical supplies. When an investigation is terminated, suspended, discontinued, or complete, all unused clinical supplies must be returned to the sponsor and an accounting made of used and unused products.

All formulations, from those developed initially through the final marketed version, must be prepared under the conditions and procedures set out by the FDA in its Current Good Manufacturing Practice guidelines (36), as outlined in Chapter 3.

THE INVESTIGATIONAL NEW DRUG APPLICATION

Under the Food, Drug, and Cosmetic Act as amended, the sponsor of a new drug is required to file with the FDA an IND before the drug may be given to human subjects (1). This is to protect the rights and safety of the subjects and to ensure that the investigational plan is sound and is designed to achieve the stated objectives. The sponsor of an IND takes responsibility for and initiates a clinical investigation. The sponsor may be an individual (a sponsor–investigator), a pharmaceutical company, governmental agency, academic institution, or some other private or public organization. The sponsor may actually conduct the study or employ, designate, or contract other qualified persons to do so. Nowadays, many contract research organizations conduct all or designated portions of clinical studies or clinical drug trials for others through contractual arrangements.

After submission of the IND, the sponsor must delay the use of the drug in human subjects for not less than 30 days from the date the FDA acknowledges the receipt of the application. An IND automatically goes into effect following this period unless the FDA notifies the sponsor that as a result of its review of the submission, it is waiving the period and the sponsor may initiate the study early or the investigation is being placed on a clinical hold (37).

A *clinical hold* is an order issued by the FDA to delay the start of a clinical investigation or to suspend an ongoing study. During a clinical hold, the investigational drug may not be administered to human subjects (unless specifically permitted by the FDA for individual patients in an ongoing study). A clinical hold is issued when there is concern that human subjects will be exposed to unreasonable and significant risk of illness or injury, when there is a question of the qualifying credentials of the clinical investigators, or when the IND is considered incomplete, inaccurate, or misleading. If the concerns raised are addressed to the FDA's

satisfaction, a clinical hold may be lifted and clinical investigations resumed; if not, an IND may be maintained in a clinical hold, declared inactive, withdrawn by the sponsor, or terminated by the FDA.

Content of the IND

The content of an IND is prescribed in the CFR and is submitted under a cover sheet (Form FDA-1571) (38).

Among the items required

- Name, address, and telephone number of the sponsor of the drug
- Date of submission
- Name (s) of the drug, including all available names (generic, trade name, chemical, code)
- IND number (if one has been previously assigned)
- Indications for the proposed drug's use
- Indication of whether the application is a new submission, a response to a clinical hold, or an amendment to a previously submitted IND application
- Name and title of the person responsible for monitoring the conduct and progress of the investigation
- Names and titles of the persons responsible for the review and evaluation of the information relevant to the safety of the drug
- Name and address of any contract research organization involved in the study
- Identification of the phase or phases of the clinical investigation to be conducted
- Introductory statement and general investigational plan: the name of the drug and all active ingredients, the drug's structural formula and pharmacologic class, the formulation of the dosage form and route of administration, and the broad objectives and planned duration of the study
- Description of the investigational plan: the rationale for the drug or research study, the indication or indications to be studied, the approach to evaluating the drug, the types of studies to be conducted, the estimated number of subjects to be given the drug, and any serious risks anticipated based on animal studies or other human experiences with the drug
- Brief summary of previous human experience with the drug (domestic or foreign), including the reasons if the drug has been withdrawn from any other investigation and/or marketing
- CMC information: a complete description of the drug substance, including its physical, chemical, and biologic characteristics; its method of preparation and analytical methods to ensure its identity, strength, quality, purity, and stability; a quantitative list of the active and inactive components of the dosage form to be administered; the methods, facilities, and controls employed in the manufacture, processing, packaging, and labeling of the new drug to ensure appropriate qualitative and quantitative standards; and product stability during the clinical investigation
- Pharmacology and toxicology information: the drug's mechanism of action if known; information on the drug's absorption, distribution, metabolism, and excretion; and acute, subacute, chronic, and reproductive and developmental toxicity studies
- If the new drug is a combination of previously investigated components, a complete preclinical and clinical summary of these components when administered singly and any data or expectations relating to the effect when combined
- Clinical protocol for each planned study
- Commitment that an Institutional Review Board (IRB) has approved the clinical study and will continue to review and monitor the investigation (discussed in the next section)
- Investigator brochure (discussed in the next section)
- Indication if any part of the study is to be conducted by a contract research organization, and, if so, the name and address of that organization
- Commitment not to begin clinical investigations until the IND is in effect, the signature of the sponsor or authorized representative, and the date of the signed application

The Clinical Protocol

As a part of the IND application, a clinical protocol must be submitted to ensure the appropriate design and conduct of the investigation. Clinical protocols include

- Statement of the purpose and objectives of the study
- Outline of the investigational plan and study design, including the kind of control group and methods to minimize bias on the part of the subjects, investigators, and analysts
- Estimate of the number of patients to be involved
- Basis for subject selection, with inclusion and exclusion criteria
- Description of the dosing plan, including dose levels, route of administration, and duration of patient exposure
- Description of the patient observations, measurements, and tests to be used
- Clinical procedures, laboratory tests, and monitoring to be used in minimizing patient risk
- Names, addresses, and credentials of the principal investigators and coinvestigators
- Locations and descriptions of the clinical research facilities to be used
- Approval of the authorized IRB

Once an IND is in effect, a sponsor must submit an amendment for approval of any proposed changes. This may involve changes of dosing levels, testing procedures, the addition of new investigators, additional sites for the study, and so on.

For many years, women and the elderly were included only rarely in clinical drug investigations. Women of childbearing age were excluded from early drug tests out of fear that the subject would become pregnant during the investigation with possible harm to the fetus. Exceptions were made only in cases of potentially lifesaving drugs. However, in recognition that the general exclusion of women from drug investigations results in inadequate data on any gender-based differences in a drug's effects, the FDA now calls for the inclusion of women in numbers adequate to allow detection of clinically significant differences in drug response.

The FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs issued in 1993 states the agency's gender inclusion policy (39). Although the guideline does not require participation of women in any particular trial, it sets forth FDA's general expectations regarding the inclusion of both women and men in drug development, analysis of clinical data by gender, and assessment of potential pharmacokinetic differences between genders. In 1994, the National Institutes of Health (NIH) similarly issued its policy that women and minorities be included in all NIH-supported biomedical and behavioral research projects involving human subjects "unless there is a clear and compelling rationale and justification that their inclusion is inappropriate with respect to the health of the subjects or the purpose of the research" (40).

Pregnancy is a concern in drug investigations because drugs are readily transported from the maternal to the fetal circulation. Because of undeveloped drug detoxication and excretion mechanisms in the fetus, concentrations of drugs may actually reach a higher level in the fetus than in the maternal circulation, with toxic levels resulting. To reduce the risk of fetal exposure to investigational drugs in women of childbearing age, the FDA guideline calls for pregnancy testing, use of contraception, and full information disclosure of potential fetal risks to prospective study subjects. The FDA has made a special effort to ensure that women who have a life-threatening disease (e.g., AIDS-related) are not automatically excluded from investigational trials of drug products for that disease because of a perceived risk of reproductive or developmental toxicity from use of the investigational drug. There are other instances in which drug studies or drug use during pregnancy is justified, for example, agents intended to prevent Rh immunization and hemolytic disease of the newborn (41).

When a proposed drug is likely to have significant use in the elderly, elderly patients are required to be included in clinical studies to

yield age-related data of a drug's effectiveness and any adverse effects. Older people handle a drug differently because of altered body functions such as diminished liver and kidney function, reduced circulation, and changes in drug ADME. Furthermore, the elderly have a greater incidence of chronic illness and multiple disease states than younger adults, and as a result, take multiple medications daily, increasing the potential for drug–drug interactions. This potential is studied and defined.

Recognition of the need to examine in children new drugs intended for the pediatric patient has a similar requirement to ensure a drug's safe and effective use in this population. Also, differentiation in a drug's activity in minority groups and their subpopulations is important in the full assessment of a drug's potential. It is well known that there are interethnic variations both in disease incidence and in biologic response to some medications, and these factors must be considered in the clinical evaluation of drug substances (42).

Each IND submission must have the prior approval of the IRB with jurisdiction over the site of the proposed clinical investigation. An IRB is a body of professional and public members that has the responsibility for reviewing and approving any study involving human subjects in the institution they serve. The purpose of the IRB is to protect the safety of human subjects by assessing a proposed clinical protocol, evaluating the benefits against risks, and ensuring that the plan includes all needed measures for subject protection. By law, the IRB shall be constituted to include persons competent to review clinical research proposals and be diverse in membership, with consideration of race, gender, cultural background, and sensitivity to issues affecting the subjects and the community (43). Any substantive change or amendment to an originally approved clinical protocol must be submitted, reviewed, and approved by the IRB and the FDA before implementation.

Each clinical investigator must receive from the sponsor an investigator's brochure, which contains all of the pertinent information developed during the preclinical studies, including summary information on the drug's chemistry, pharmacology, toxicology, and pharmacokinetics; formulation of the clinical trial materials; any known information related to the drug's safety and effectiveness; a description of possible risks and side effects that may be anticipated and special monitoring required; the clinical protocol and study design; criteria for patient inclusion and exclusion; laboratory and clinical tests to be performed; and drug control and record-keeping information.

Each study has defined criteria for subject inclusion or exclusion. These criteria may relate to age, sex (as qualified earlier), smoking, health status (e.g., liver and/or renal function), and other factors deemed necessary in a given phase of investigation. Each subject in a clinical investigation must participate willingly and with full knowledge of the benefits and risks associated with the investigation.

The sponsor of the study must certify that each person who will receive the investigational drug has given informed consent—that is, he or she has been informed of the following: participation in the study is voluntary; the purpose and nature of the study; the procedures involved; a description of any foreseeable risks or discomforts; the potential benefits for patients; disclosure of alternative procedures or courses of treatments, if any; the extent of confidentiality of records; conditions under which the subject's participation in the study may be terminated; consequences of a patient's decision to withdraw from the study; the approximate number of subjects to be enrolled; and whom to contact for answers to pertinent questions and/or in case of research-related illness or injury. These elements of informed consent, and additional protections that apply to prisoners in clinical investigations, must be in conformance with the CFR (44). Individuals who agree to be subjects in an investigation indicate their consent by signing the form or document containing this information.

Investigators selected by the sponsor to conduct a clinical investigation must be qualified as experts by training and experience to investigate a particular drug. Each investigator's qualifications are submitted to the FDA

as a part of the IND application. To participate in an investigation, each investigator signs a form agreeing to comply with and to be responsible for ensuring that the study is conducted according to the IND's investigational plan and clinical protocol; protecting the rights, safety, and welfare of the human subjects; control of the investigational drug; written records of case histories and clinical observations; and the timely submission of progress reports, safety reports, and a final report. It is the responsibility of the sponsor to monitor the progress of all clinical investigations under its IND. If a sponsor discovers that an investigator is not in compliance with the investigational plan, it is the sponsor's responsibility to gain compliance or to terminate the investigator's participation in the study.

Any serious, unexpected, life-threatening, or fatal adverse experience that may be associated with the use of the drug during a clinical investigation must be reported promptly to the sponsor and subsequently to the FDA for investigation. Depending on the severity and assessment of the adverse experience, an alert notice may be sent to other investigators, a clinical hold may be placed on the study for further evaluation and assessment, or the IND may be withdrawn by the sponsor, placed on inactive status, or terminated by the FDA.

Pre-IND Meetings

On request, the FDA will advise a sponsor on scientific, technical, or formatting concerns relating to the preparation and submission of an IND. This may include advice on the adequacy of data to support an investigational plan, the design of a clinical trial, or whether the proposed investigation is likely to produce the data needed to meet the requirements of the next step, the filing of an NDA to gain approval for marketing.

FDA Review of an IND Application

The FDA's objectives in reviewing an IND are to protect the safety and rights of the human subjects and to help ensure that the study allows the evaluation of the drug's safety and effectiveness. These objectives are best met by the accuracy and completeness of the IND submission, the design and conduct of the investigational plan, and the expertise and diligence of the investigators.

When received by the FDA, the IND submission is stamped with the date of receipt, assigned an application number, and forwarded to either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) for review. Applications for chemical agents are sent to CDER and applications for biologics to CBER.

Within CDER, applications are forwarded to the appropriate office of drug evaluation and then to one of its divisions for review (45).

After assignment to one of the divisions, the content of the application is thoroughly reviewed to determine whether the preclinical data indicate that the drug is sufficiently safe for administration to human subjects and that the proposed clinical studies are designed to provide the desired data on drug safety and efficacy while not exposing the human subjects to unnecessary risks.

Although the discussion in this chapter is based principally on the evaluation and approval of new chemical entities and products, for biologic products, there is a similar but necessarily distinct procedure of application review and product licensing for biologics through CBER and its divisions (4):

FDA Drug Classification System

The FDA's CDER has established a drug classification system for the review of drug applications. Within 14 days of receipt of an original new drug or new biologic application, the agency determines whether the application will receive a *Priority* (*P*) *Review* or a *Standard* (*S*) *Review* (45). A priority review is considered if the proposed drug product provides a significant improvement compared to marketed products or provides safe and effective therapy where no satisfactory alternative therapy exists.

Phases of a Clinical Investigation

An IND may be submitted for one or more phases of a clinical investigation, namely Phase 1, Phase 2, or Phase 3 (Fig. 2.2, Table 2.1).

Table 2.1 PHASES OF CLINICAL TESTING

	NUMBER OF PATIENTS	LENGTH	PURPOSE	PERCENT SUCCESSFULLY COMPLETING[a]
Phase 1	20–100	Several months	Mainly safety	67
Phase 2	Up to several hundred	Several months to 2 years	Some short-term safety but mainly effectiveness	45
Phase 3	Several hundred to several thousand	1–4 years	Safety, effectiveness, dosage	5–10

Presentation 4 (Clinical Trials: A Closer Look), found at http://www.ncabr.org/bioman/,2002.
[a]For example, of 20 drugs entering the clinical testing, 13 or 14 successfully complete Phase 1 trials and go on to Phase 2; about nine will complete Phase 2 and go to Phase 3; only one or two will clear Phase 3, and on average, about 1 of the original 20 will ultimately be approved for marketing.

Although the phases are conducted sequentially, certain studies may overlap.

Phase 1 includes the initial introduction of an investigational drug into humans and is primarily for the purpose of assessing safety. The studies are closely monitored by clinicians expert in such investigations. The human subjects are usually healthy volunteers, although, in certain protocols, they may be patients. The total number of subjects included in Phase 1 studies varies with the drug but is usually in the range of 20 to 100. The initial dose of the drug is usually low, usually one tenth of the highest no-effect dose observed during the animal studies. If the first dose is well tolerated, the investigation continues with the administration of progressively greater doses (to new subjects) until some evidence of the drug's effects is observed.

Phase 1 studies are designed to determine the human pharmacology of the drug, structure–activity relationships, side effects associated with increasing doses, and, if possible, early evidence of effectiveness. Among the basic data collected are the rate of absorption; the concentration of drug in the blood over time; the rate and mechanism of drug metabolism and elimination; toxic effects, if any, in body tissues and major organs; and changes in physiologic processes from baseline. The subjects' ability to tolerate the drug and any unpleasant effects of the drug is observed and recorded. Phase 1 studies are often useful in selecting from among different chemical analogs of a lead compound. As noted previously, capsules without excipients are used for orally administered drugs in Phase 1 studies. If the studies demonstrate sufficient merit and if the order of drug toxicity is low, Phase 2 begins, studying up to several hundred patients.

Phase 2 trials are controlled clinical studies to evaluate the effectiveness of a drug in patients with the condition for which the drug is intended and to assess side effects and risks that may be revealed. Because this phase uses patients as subjects, side effects or toxicity symptoms that were not shown in the preclinical animal studies or in Phase 1 studies with healthy volunteers may be revealed for the first time. Only clinicians expert in the disease being treated are used as investigators during Phase 2 studies (Fig. 2.6). During this phase, additional data are collected on the drug's pharmacokinetics and studies undertaken to determine dose–response and dose ranging (often called Phase 2a studies). Each patient is monitored for the appearance of the drug's effects while the dose is carefully increased to determine the minimal effective dose. Then the dose is extended beyond the minimally effective dose to the level at which a patient reveals extremely undesirable or intolerable toxic or adverse effects. The greater the range between the dose of the drug determined to be minimally effective and that which causes severe side effects, the greater is the drug's safety margin. These dose determination studies (often called Phase 2b studies) result in the specific doses and the dose range to be used in Phase 3 studies. During Phase 2 trials,

FIGURE 2.6 Monitoring the effects for cardiac function of an investigational drug as a part of its clinical evaluation. (Courtesy of Eli Lilly and Company.)

the drug product is refined, with the final formulation developed for use during late Phase 2 and Phase 3 trials.

If the clinical results of Phase 2 trials indicate continued promise for the new drug and if the margin of safety appears to be good, end-of-Phase 2 meetings between the drug's sponsor and the FDA's review division are held to analyze the data from Phases 1 and 2. This resolves any questions and issues and to establish investigational plans for Phase 3 studies.

Phase 3 studies may include several hundred to several thousand patients in controlled and uncontrolled trials. The objective is to determine the usefulness of the drug in an expanded patient base. Many additional clinicians having patients with the condition for drug's intended use are recruited to participate in this trial. Several dosage strengths of the proposed drug may be evaluated during this phase, using formulations intended to be proposed in the NDA and for marketing. Sufficient information on the drug's effectiveness and safety is expected to be gathered during Phase 3 to evaluate the overall benefit–risk relationship of the drug and to file a complete NDA.

It is fairly common for certain Phase 3 studies to be continued after an NDA is filed but prior to approval. In these instances, the completed studies (Phase 3a studies) are considered sufficient for the NDA. The additional studies (Phase 3b studies) are used to gather supplemental information that may support certain labeling requests, provide information on patients' quality of life issues, reveal product advantages over already marketed competing drugs, provide evidence in support of possible additional drug indications, or provide other clues for prospective postmarketing studies (Phase 4).

Clinical Study Controls and Designs

As indicated, Phase 2 and some Phase 3 studies are controlled, that is, the effects of the investigational drug are compared with another agent. The second agent may be a placebo (placebo control) or an active drug (positive control), a standard or comparator drug product. Both a placebo and an active drug may be used as controls in the same study. For studies that are blinded, the identities of the investigational drug and the control or controls are not revealed to certain participants to decrease bias. In single blind studies, the patient is unaware of the agent administered. In double-blind studies, neither the patient nor the clinician is aware of the agent administered. In preparing dosage forms for blinded studies, all of the agents administered, investigational drug, placebo, and/or comparator drug, must be indistinguishable to the blinded individuals. This requires the preparation of clinical trial materials of the same dosage form, having the same size, shape, color, flavor, texture, and so forth. Indistinguishable clinical trial materials are not necessary for open-label studies, in which all parties are aware of the identities of the agents administered.

In designing a clinical trial, many additional factors are considered, including the scheme of the study design and the duration of the treatment period. Before treatment, baseline data are obtained on each subject through physical examination and appropriate laboratory tests and procedures. Subjects are randomly assigned to different treatment

groups to allow treatment comparisons. Some common parallel and crossover study designs are depicted in Figure 2.7 (46). These studies may be blinded or not, using placebo and/or active drug controls. The parallel designs are applicable to most clinical trials. Crossover designs are useful in comparing different treatments within individuals since following one treatment, a patient is crossed over to a different treatment. Between treatment periods, subjects may be given no drugs as a washout period to allow return to baseline.

Drug Dosage and Terminology

A major part of any clinical drug study is the determination of a drug's safe and effective dose. As noted earlier, dose and dose-ranging studies are conducted during Phase 2 and concluded during Phase 3 clinical trials.

The safe and effective dose of a drug depends on a number of factors, including characteristics of the drug substance, the dosage form and its route of administration, and a variety of patient factors including age, body weight, general health status, any pathologic conditions, and concomitant drug therapy. All of these factors and others are integral to clinical drug trials.

For convenience of dosage administration, most products are formulated to contain a drug's usual dose within a single unit (e.g., capsule) or within a specified volume (e.g., 5 mL or a teaspoonful) of a liquid dosage form. To serve varying dosage requirements, manufacturers often formulate a drug into more than one dosage form and in more than a single strength.

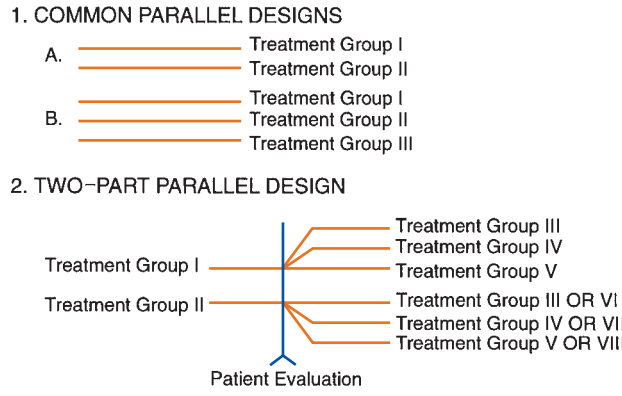
The dose of a drug may be described as an amount that is enough but not too much; the idea is to achieve the drug's optimum therapeutic effect with safety but at the lowest possible dose. The effective dose of a drug may be different for different patients. The familiar bell curve presented in Figure 2.8 shows that in a normal distribution sample, a drug's dose will provide what might be called an average effect in most individuals. However, in a portion of the population, the drug will produce little effect, and in another portion, the drug will produce an effect greater than average. The amount of drug that will produce the desired effect in most adult patients is considered the drug's usual adult dose and the likely starting dose for a patient. From this initial dose, the physician may, if necessary, increase or decrease subsequent doses to meet the particular requirements of the patient. Certain drugs may produce more than one effect, depending on the dose. For example, a low dose of a barbiturate produces sedation, whereas a larger dose produces hypnotic effects. The usual dosage range indicates the quantitative range or amounts of the drug that may be prescribed safely within the framework of usual medical practice. Doses falling outside of the usual range may result in underdosage or overdosage or may reflect a patient's special requirements. For drugs administered to children, a usual pediatric dose may be determined, as discussed later in this section.

The schedule of dosage, or the dosage regimen, is determined during the clinical investigation and is based largely on a drug's inherent duration of action, its pharmacokinetic profile, and the characteristics of the dosage form (e.g., immediate release or modified release). Because of these factors, some drugs are recommended for once-a-day dosage and others more frequently.

For certain drugs, an initial, priming, or loading dose may be required to attain the desired concentration of the drug in the blood or tissues, after which the blood level may be maintained through subsequent administration of regularly scheduled maintenance doses.

Certain biologic products, such as tetanus immune globulin, may have two usual doses, a prophylactic dose, or the amount administered to protect the patient from contracting the illness, and the therapeutic dose, which is administered to a patient after exposure or contraction of the illness. The doses of vaccines and other biologic products often are expressed in units of activity rather than in specific quantitative amounts of the drug. This is because the unavailability of suitable chemical assay methods for the active biologic component necessitates the use of

SOME CLINICAL TRIAL PARALLEL STUDY DESIGNS



SOME CLINICAL TRIAL CROSSOVER STUDY DESIGNS

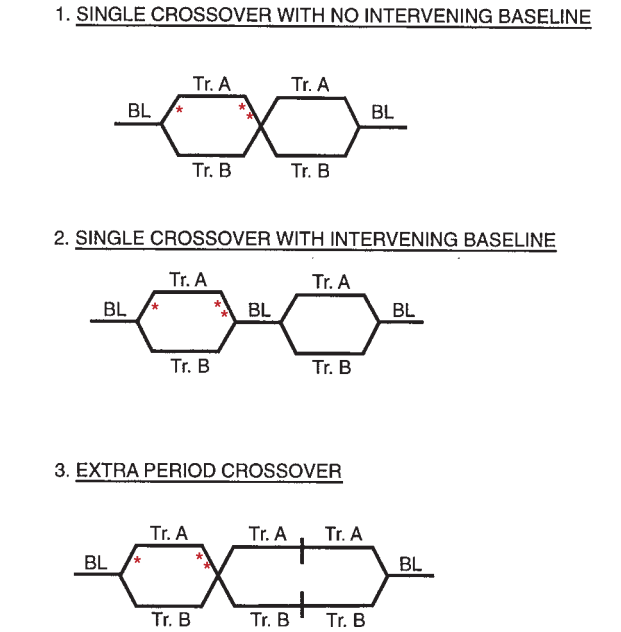


FIGURE 2.7 Some common clinical study designs. (Reprinted with permission from Spilker B. Guide to Clinical Trials. New York, NY: Raven, 1991).

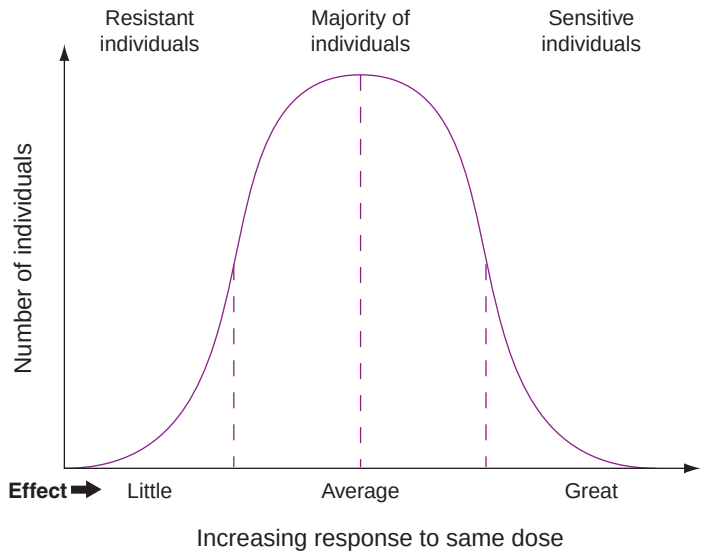


FIGURE 2.8 Drug effect in a population sample.

biologic assays to determine a product's potency.

To provide systemic effects, a drug must be absorbed from its route of administration at a suitable rate, be distributed in adequate concentration to the receptor sites, and remain there for a sufficient period. One measure of a drug's absorption characteristics is its blood serum concentration at various intervals after administration. Certain drugs have a correlation between blood serum concentration and the presentation of drug effects. For these drugs, an average blood serum concentration represents the minimum concentration that can be expected to produce the drug's desired effects in a patient. This concentration is the minimum effective concentration (MEC). As shown in Figure 2.9, the serum concentration of a hypothetical drug reaches the MEC 2 hours after its administration, achieves a peak concentration in 4 hours, and decreases below the MEC in 10 hours. If it were desired to maintain the drug serum concentration above the MEC for a longer period, a second dose of the drug would be required at approximately 8 hours. The time–blood level curve presented in Figure 2.9 is hypothetical. In practice, the curve would vary, depending on the nature of the drug substance, its chemical and physical characteristics, the dosage form

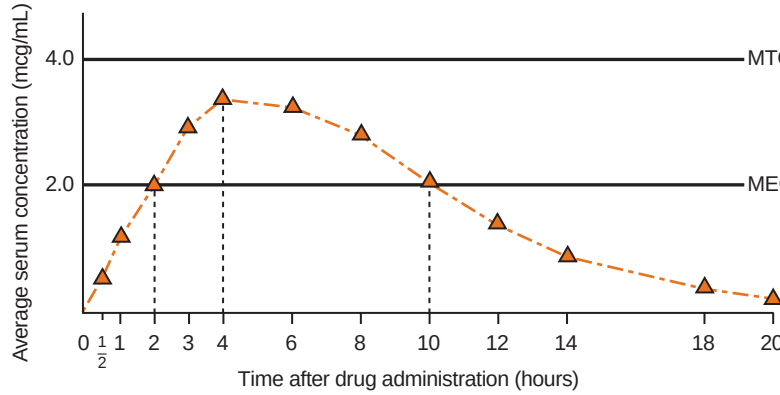


FIGURE 2.9 Example of a blood level curve for a hypothetical drug as a function of time following oral administration. MEC, minimum effective concentration; MTC, minimum toxic concentration.

administered, and the individual patient factors. The second level of serum concentration of drug refers to the minimum toxic concentration (MTC). Drug serum concentrations above this level would be expected to produce dose-related toxic effects in the average individual. Ideally, the serum drug concentration in a well-dosed patient would be maintained between the MEC and the MTC (the therapeutic window for the drug) for the period that drug effects are desired. Table 2.2 presents examples of therapeutic, toxic, and considered lethal concentrations for some selected drug substances. The values in this table do not apply to infants and children. Further, the portrayed values should not be considered absolute but used as a guideline. Actual values of drugs can be influenced by a number of factors that are described later in this section. The median effective dose of a drug is the amount that will produce the desired intensity of effect in 50% of the individuals tested. The median toxic dose is the amount that will produce a defined toxic effect in 50% of the individuals tested. The relationship between the desired and undesired effects of a drug is commonly expressed as the therapeutic index and is defined as the ratio between a drug's median toxic dose and its median effective dose, TD50/ED50. Thus, a drug with a therapeutic index of 15 would be expected to have a greater margin of safety in its use than a drug with a therapeutic index of 5. For certain drugs, the therapeutic index may be as low as 2, and extreme caution must be exercised in their administration. Table 2.3 demonstrates drugs and pharmacological classes of drugs that have narrow therapeutic indices and, therefore, should be monitored closely in patients receiving them. Some factors of patients considered in determining a drug's dose in clinical investigations and in medical practice include the following:

Age

The age of the patient may be a consideration in the determination of drug dosage. Age is particularly important in the treatment of

Table 2.2 THERAPEUTIC AND TOXIC BLOOD LEVEL CONCENTRATIONS OF SOME DRUG SUBSTANCES

	DRUG SUBSTANCE CONCENTRATION, MILLIGRAMS/LITER		
DRUG SUBSTANCE	**THERAPEUTIC**	**TOXIC**	**LETHAL**
Acetaminophen	10–20	400	1,500
Amitriptyline	0.5–0.20	0.4	10–20
Barbiturates			
Short acting	1	7	10
Intermediate acting	1–5	10–30	30
Long acting	~10	40–60	80–150
Dextropropoxyphene	0.05–0.2	5–10	57
Diazepam	0.5–2.5	5–20	50
Digoxin	0.0006–0.0013	0.002–0.009	—
Imipramine	0.05–0.16	0.7	2
Lidocaine	1.2–5.0	6	—
Lithium	4.2–8.3	13.9	13.9–34.7
Meperidine	0.6–0.65	5	30
Morphine	0.1	—	0.05–4
Phenytoin	5–22	50	100
Quinidine	3–6	10	30–50
Theophylline	20–100	—	—

Table 2.3 THERAPEUTIC INDICES FOR VARIOUS DRUG SUBSTANCES

LESS THAN 5	BETWEEN 5 AND 10	GREATER THAN 10
Amitriptyline	Barbiturates	Acetaminophen
Chlordiazepoxide	Diazepam	Bromide
Diphenhydramine	Digoxin	Chloral hydrate
Ethchlorvynol	Imipramine	Glutethimide
Lidocaine	Meperidine	Meprobamate
Methadone	Paraldehyde	Nortriptyline
Procainamide	Primidone	Pentazocine
Quinidine	Thioridazine	Propoxyphene

Source: Niazi S. Textbook of Biopharmaceutics and Clinical Pharmacokinetics. New York, NY: Appleton-Century-Crofts, 1979:254.

neonatal, pediatric, and geriatric patients. Infants, especially newborns and those born prematurely, have immature hepatic and renal function, the means by which drugs are normally inactivated and eliminated from the body. A reduced capacity to detoxify and eliminate drugs can result in drug accumulation in the tissues to toxic levels. Often, drug blood levels are determined in these patients and are carefully monitored.

Before there was sufficient understanding of the capacity of the young to detoxify and eliminate drugs, infants and children were dosed by fractions of the adult dose determined by age-based or weight-based formulas. Age or weight alone is no longer considered to be a particularly valid criterion in the determination of pediatric dosage. Today, doses for many drugs are determined through pediatric clinical trials under special protocols and subject safeguards (47). Many pediatric doses are based on body weight or body surface area (BSA), as noted later in this section.

Elderly persons also present unique therapeutic and dosing problems that require special attention. Most physiologic functions begin to diminish in adults after the third decade of life. For example, cardiac output declines approximately 1% per year from age 20 to age 80. Glomerular filtration rate falls progressively until age 80, at which time it is only about half of what it was at age 20. Vital capacity, immune capacity, and liver microsomal enzyme function also decrease (48). The decline in renal and hepatic function in the elderly slows the drug clearance rate and increases the possibility of drug accumulation and toxicity. Elderly persons may also respond differently to drugs than do younger patients because of changes in drug receptor sensitivity or because of age-related alterations in target tissues or organs (49).

Furthermore, the chronic disorders in most geriatric patients require concomitant drug therapy, increasing the possibility of drug–drug interactions and adverse drug effects. In the clinical evaluation of a new drug, consideration is given to other drugs most likely to be taken concomitantly by the intended patient, with studies directed toward determining the potential drug–drug effects or interactions.

Among the references to assist the prescriber and pharmacist in neonatal, pediatric, and geriatric dosing are the following: *Pediatric and Neonatal Dosing* and *Geriatric Dosing* (50).

Pharmacogenetics

Pharmacogenetic research in the last two decades has uncovered significant differences among racial and ethnic groups in the metabolism, clinical effectiveness, and adverse effects of therapeutically important drugs. Clinical studies have been conducted on cardiovascular agents, for example, beta-blockers, diuretics, calcium channel blockers, ACE inhibitors, or psychotropic and central nervous system agents, for

example, tricyclic antidepressants (51) and neuroleptics. Antihistamines, alcohol, and analgesics, for example, acetaminophen and codeine, have also demonstrated varying effects among different ethnic and racial populations. Common genetic polymorphisms, that is, multiple forms of enzymes governing drug metabolism, affect the clearance from the blood of many therapeutically important drugs used in large patient populations. These polymorphisms are the rule rather than the exception, and genetic diversity is a major source of interindividual, interethnic, and racial differences in drug response. These genetic polymorphisms may influence a drug's action by altering its pharmacokinetic profile and/or pharmacodynamic properties. The result could be an increase or a decrease in the intensity of the patient's response and duration of the drug activity. Thus, dosage adjustments may be necessary for individuals from minority populations.

Body Weight

The usual doses for drugs are considered generally suitable for 70-kg (150 lb) individuals. The ratio between the amount of drug administered and the size of the body influences drug concentration in body fluids. Therefore, drug dosage may require adjustment from the usual adult dose for abnormally lean or heavy patients. The doses for certain drugs are based on body weight and are expressed on a milligram (drug) per kilogram (body weight) basis (e.g., 1 mg/kg).

As noted earlier, body weight is considered more dependable than age as determinant of drug dosage for youngsters, and for many drugs, the dose is based on milligrams per kilogram. In some instances, a pediatric dose may be based on a combination of age and weight (e.g., 6 months to 2 years of age: 3 mg/kg/day).

Body Surface Area

Because of the correlation between a number of physiologic processes and BSA, some drug doses are based on this relationship (e.g., 1 mg/M^2 BSA). The BSA for a child or adult may be determined using a nomogram (Fig. 2.10). The BSA is determined at the intersect of a straight line drawn to connect an individual's height and weight. For example, an adult measuring 67 in. in height and weighing 132 lb would have a BSA of approximately 1.7 m^2.

Sex

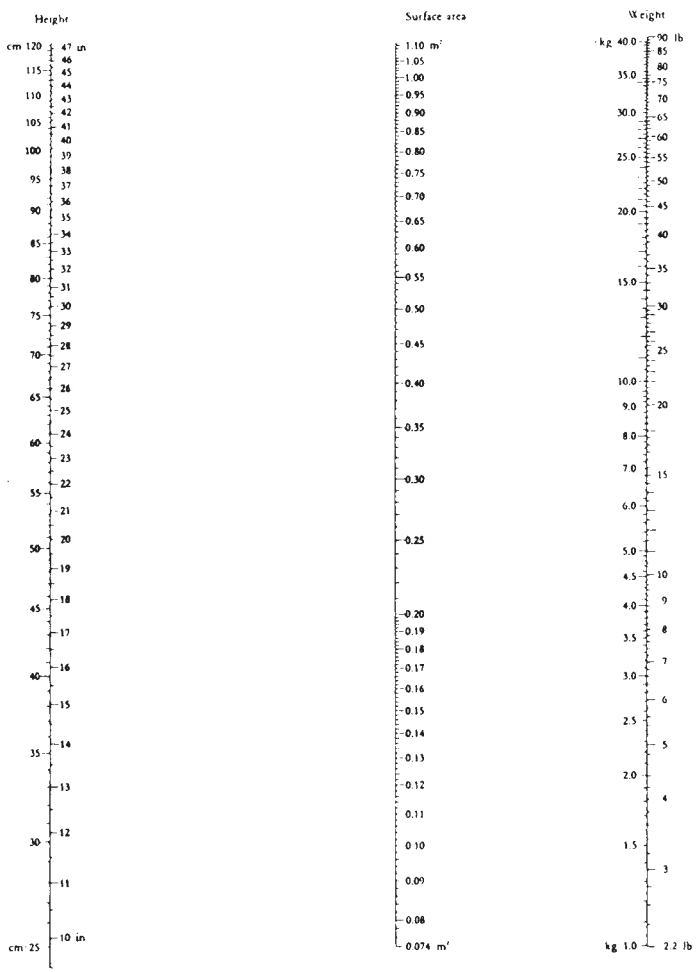
Because biochemical and physiologic factors produce different responses to certain drugs and drug dosages in men and women, both sexes should be included in clinical drug trials. Pharmacokinetic differences between women and men may be particularly important for drugs having a narrow therapeutic index, in which the smaller average size of women may necessitate modified dosing. Drugs with narrow therapeutic indices carry the inherent risk that drug blood levels may increase to toxic levels or decrease to ineffective levels with minimal dosing changes. Other important studies on women include the effects of the menstrual cycle and menopausal status on a drug's pharmacokinetics and the drug interaction potential of concomitant estrogen or oral contraceptive use (52).

Because virtually no clinical investigations have included pregnant women in their study protocols and thus drug effects are undetermined in these circumstances, great caution is advised for the use of most drugs during pregnancy and in women of childbearing age. Similar caution is applicable to drug use in nursing mothers because transfer from mother's milk to an infant is well documented for a variety of drugs (53,54).

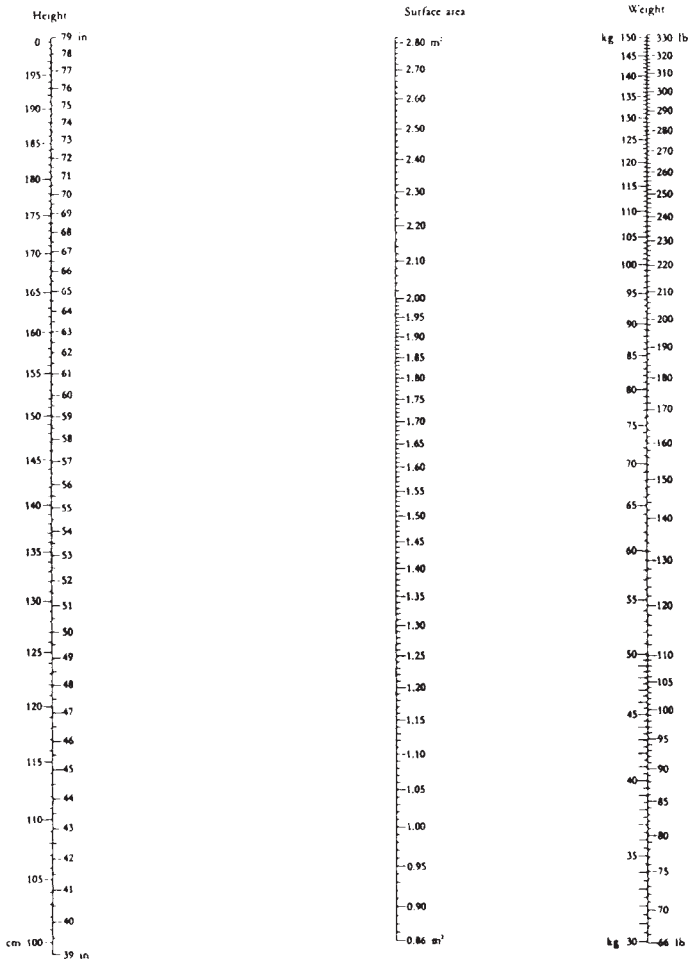
Pathologic State

The effects of certain drugs may be modified by the pathologic condition of the patient. For example, if certain drugs are used in the presence of renal impairment, excessive systemic accumulation of the drug may occur, risking toxicity. In such conditions, lower than usual doses are indicated, and if therapy is prolonged, blood serum levels of the drug should be assessed and the patient monitored at regular intervals to ensure the maintenance of nontoxic levels of the drug. In these instances, pharmacokinetic dosing is an integral part of the clinical study protocol and of the approved product labeling.

A. Nomogram for Calculating the Body Surface Area of Children[1]



B. Nomogram for Calculating the Body Surface Area of Adults[1]



[1]From the formula of DuBois and DuBois, *Arch Intern. Med.*,17, 863 1916 $S = W^{0.425} \times H^{0.725} \times 71.84$ or $\log S = 0.425 \log W + 0.725 \log H + 1.8564$ where S = body surface area in square centimeters, W = weight in kilograms, H = height in centimeters

FIGURE 2.10 Nomograms for calculating the BSA. **A:** For children. **B:** For adults. (From the formula of DuBois and DuBois, Arch Intern Med 1916;17:863: S = W0.425 × H0.725 × 71.84, or log S = log W × 0.425 + log H × 0.725 + 1.8564, where S = body surface in square centimeters, W = weight in kilograms, H = height in centimeters.) (Reprinted with permission from J.R. Geigy SA. Documenta Geigy Scientific Tables. 7th Ed. Basel: Ciba-Geigy, 537–538.)

Tolerance

The ability to endure the influence of a drug, particularly during continued use, is referred to as drug tolerance. It is usually developed to a specific drug and to its chemical congeners; in the latter instance, it is referred to as cross-tolerance. The result is that drug dosage must be increased over time to maintain a desired therapeutic response. Tolerance is common with the use of antihistamines and narcotic analgesics. After the development of tolerance, normal response may be regained by suspending the drug's administration for a while.

Concomitant Drug Therapy

The effects of a drug may be modified by the prior or concurrent administration of another drug. Such interference, a drug–drug interaction, may be due to a chemical or physical interaction between the drugs or to an alteration of the absorption, distribution, metabolism, or excretion patterns of one of the drugs. Certain clinical protocols include the evaluation of a new drug in the presence of other drugs most likely to be included in the target patient's therapeutic regimen.

Important drug–drug interactions that are identified during a drug's clinical trials are included in approved product labeling. Additional drug interactions that become known after the drug is marketed are added in labeling revisions. Drug–drug interactions may include "social" agents such as tobacco and alcohol, which affect the pharmacokinetics of a number of drugs and require an alteration in a drug's usual dose.

Time and Conditions of Administration

The time at which a drug is administered may influence the dosage. This is true especially for oral therapy in relation to meals. Absorption proceeds more rapidly if the stomach and the upper portions of the intestinal tract are empty of food. A dose of a drug that is effective when taken before a meal may be less effective if administered during or after eating. Drug–food interactions can affect a drug's usual absorption pattern. When such interactions are determined, appropriate guidance is provided in the product and professional literature.

Dosage Form and Route of Administration

The effective dose of a drug may vary with the dosage form and the route of administration. Drugs administered intravenously enter the bloodstream directly and completely. In contrast, drugs administered orally are rarely, if ever, fully absorbed into the bloodstream because of the various physical, chemical, and biologic barriers to their absorption. Thus, in many instances, a lower parenteral (injectable) dose of a drug is required than the oral dose to achieve the same blood levels or clinical effects. Varying rates and degrees of absorption can occur from drug administration in the rectum, in the gastrointestinal tract, under the tongue, via the skin, and to other sites. Therefore, for a given drug, different dosage forms and routes of administration are considered new by the FDA and must be evaluated individually through clinical studies to determine the effective doses.

Treatment IND

A treatment IND or a treatment protocol permits the use of an investigational drug in the treatment of patients who are not enrolled in the clinical study but who have a serious or immediately life-threatening disease for which there is no satisfactory alternative therapy. The objective is to make promising new drugs available to desperately ill patients as early as possible in the drug development process. By FDA definition, "immediately life-threatening" 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" (1). This includes such conditions as advanced cases of AIDS, herpes simplex encephalitis, advanced metastatic refractory cancers, bacterial endocarditis, Alzheimer disease, advanced multiple sclerosis, advanced Parkinson disease, and others.

For products to be considered for a treatment IND, the drug must be under active

investigation in a controlled clinical trial with sufficient evidence of its safety and efficacy demonstrated to support its use in the intended patients. Depending on the sponsor's clinical safety and efficacy data, a drug may be approved for treatment use during Phase 2 or Phase 3 of the clinical trials. In applying for a drug's treatment use, a sponsor must submit a treatment protocol in addition to the information normally included in an IND application. In making its decision, the FDA renders a risk–benefit judgment after considering the severity of the disease, any alternative therapy, and the potential benefits of the drug against the known and possible risks.

A "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the NIH under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. Because administration of Group C drugs is not done with research intent, FDA has generally granted a waiver from the IRB review requirements (55).

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize an "emergency use IND" and shipment of the drug for a specified use. Such authorization is usually conditioned upon the sponsor filing an appropriate application as soon as practicable. Prospective IRB review and informed consent are required (55).

IND for an Orphan Drug

Under the Orphan Drug Act of 1983 as amended, an orphan disease is defined as a rare disease or condition that affects fewer than 200,000 people in the United States and for which there is no reasonable expectation that costs of R&D for the indication can be recovered by sales of the product in the United States. Examples of such illnesses are chronic lymphocytic leukemia, Gaucher disease, cystic fibrosis, and conditions related to AIDS.

The FDA Office of Orphan Products Development was established to identify and facilitate the development of orphan products, including drugs, biologics, and medical devices. To foster the necessary R&D, the FDA provides support grants to conduct clinical trials on safety and effectiveness. Applicants first request orphan status designation for the disease and file an IND or an investigational device exemption with their grant application. In most cases, grants are awarded for Phase 2 and Phase 3 clinical studies based on preliminary clinical research. Regular and treatment IND protocols may be included in orphan drug clinical trials. An incentive to orphan product development is a provision for a 7-year period of exclusive marketing rights after regulatory approval of a product.

Withdrawal or Termination of an IND

A sponsor may withdraw an IND at any time, ending all clinical investigations. All stock of clinical supplies must be returned to the sponsor or otherwise destroyed. If an IND is withdrawn for safety reasons, the FDA, IRB, and all investigators must be so advised.

If no subjects are entered in an IND for 2 years or more or if investigations remain on a clinical hold for 1 year or more, the FDA may place the IND on inactive status upon proper notification of the sponsor. An IND may also be placed on inactive status on the initiative of the sponsor.

The FDA may terminate an IND and end related clinical investigations for reasons of safety, efficacy, or regulatory compliance.

CLINICAL STUDY REGISTRY

The National Library of Medicine (NLM) at the U.S. NIH at the website *ClinicalTrials.gov*,

provides a registry and database of clinical studies conducted around the world. This Web-based resource provides the general public, patients, their family members, health care professionals, and researchers with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The Web site facilitates basic and advanced searches and is continually updated by the sponsor or principal investigator of the clinical study.

THE NEW DRUG APPLICATION

If the three phases of clinical testing during the IND period demonstrate sufficient drug safety and therapeutic effectiveness, the sponsor may file an NDA with the FDA. This filing may be preceded by a pre-NDA meeting between the sponsor and the FDA to discuss the content and format of the NDA. The purpose of the NDA is to gain permission to market the drug product in the United States.

General Content of the NDA Submission

An NDA contains a complete presentation of all of the preclinical and clinical results that the sponsor has obtained during the investigation of the drug. It is a highly organized document that may contain several hundred volumes of information. In recent years, a computer-assisted NDA process has been implemented whereby the sponsor may interact by computer with the FDA reviewers to facilitate the application review.

The applicant submits three copies of the NDA: an archival copy, maintained by the FDA as the reference document; a review copy, used by the FDA review division; and a field copy, used by the FDA district office and field inspectors in an on-site preapproval inspection (1). The preapproval inspection is conducted in the facilities in which the approved product is to be produced. The inspectors assess the sponsor's capability to comply with all control and quality standards contained in the application, including the FDA's Current Good Manufacturing Practice standards (discussed in Chapter 3). Final approval of an NDA can be contingent upon this inspection.

In part, an application for a new chemical entity contains the following components:

- Application form (form FDA 356 h) with the name, address, date, and signature of the applicant or the applicant's authorized representative
- Chemical, nonproprietary, code, and proprietary names of the drug, the dosage form, its strength, and route of administration
- Statement regarding the applicant's proposal to market the drug product as prescription only or as an OTC product
- Detailed summary of all aspects of the application, including the proposed text of the product's intended labeling, CMCs, nonclinical and clinical pharmacology and toxicology, human pharmacokinetics and bioavailability, statistical analysis, clinical trial data, benefit and risk considerations, and proposed additional or planned postmarketing studies
- Detailed technical sections on the CMCs for the drug substance, including its physical and chemical characteristics, methods of identification, assay, and controls, and the drug product, including its composition, specifications, methods of manufacture and equipment used, in-process controls, batch and master production records, container and closure systems, stability, and expiration dating
- Detailed technical sections for nonclinical pharmacology and toxicology in relation to the proposed therapeutic indication, including acute, subacute, and chronic toxicology, carcinogenicity, reproductive toxicology, and animal studies of absorption, distribution, metabolism, and excretion
- Detailed technical sections for human pharmacokinetics and bioavailability along with microbiology for antibiotic applications
- Detailed technical sections for clinical data for each controlled and uncontrolled study relating to the proposed indication, a copy of the study protocol, effectiveness

and safety data including any updates on safety information, comparison of human and animal pharmacology and toxicology data, and support for the dosage and dose intervals and modifications for specific subgroups such as pediatric, geriatric, and renally impaired subjects
- Statement regarding compliance to IRB and informed consent requirements
- Statistical methods and analysis of the clinical data
- Samples of the drug substance, drug product proposed for marketing, reference standards, and finished market package, as requested
- Clinical case report forms for the archival copy of the application

The FDA accepts foreign clinical data if they are applicable to the U.S. population and domestic medical practice, if the studies were conducted by clinical investigators of recognized competence, and if the FDA considers the data to be valid without the need for an on-site inspection. The FDA has entered into bilateral agreements with some countries whereby inspections performed by the regulatory personnel of those countries are acceptable to the FDA.

Drug Product Labeling

The labeling of all drug products distributed in the United States must meet the specific labeling requirements set forth in the CFR and approved for each product by the FDA (56). Specific labeling requirements differ for prescription drugs, nonprescription drugs, and animal drugs. In each instance, however, the objective is the same—to ensure the appropriate and safe use of the approved product.

According to federal regulations, drug labeling includes not only the labels placed on an immediate container but also the information on the packaging, in package inserts, and in company literature, advertising, and promotional materials.

For prescription drugs, labeling is a summary of all of the preclinical and clinical studies conducted over the period from drug discovery through product development to FDA approval. The essential prescribing information for a human prescription drug is provided in the package insert, which by law contains a balanced presentation of the usefulness and the risks associated with the product to enable safe and effective use. The package insert is required to contain the following summary information in the order listed.

1. Description of the product, including the proprietary and nonproprietary names, dosage form and route of administration, quantitative product composition, pharmacologic or therapeutic class of the drug, chemical name and structural formula of the drug compound, and important chemical and physical information (e.g., pH, sterility).
2. Clinical pharmacology, including a summary of actions of the drug in humans, relevant in vitro and animal studies essential to the biochemical and/or physiologic basis for action, pharmacokinetic information on rate and degree of absorption, biotransformation, and metabolite formation, degree of drug binding to plasma proteins, rate or half-time of elimination, uptake by a particular organ or fetus, and any toxic effects.
3. Indications and usage, including the FDA-approved indications in the treatment, prevention, or diagnosis of a disease or condition, evidence of effectiveness demonstrated by results of controlled clinical trials, and special conditions to the drug's use for short-term or long-term use.
4. Contraindications, situations in which the drug should not be used because the risk of use clearly outweighs any possible beneficial effect. Contraindications may be associated with drug hypersensitivity, concomitant therapy, disease state, pregnancy, and/or factors of age or gender.
5. Warnings, including descriptions of serious adverse reactions and potential safety hazards, limitations to use imposed by them, and steps to be taken if they occur. Especially serious warnings are called black box warnings, as they are set off in the product's labeling within a black box. See Figure 2.11 for an example.

WARNING

An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of REGRANEX Gel in a post-marketing retrospective cohort study. REGRANEX Gel should only be used when the benefits can be expected to outweigh the risks. REGRANEX Gel should be used with caution in patients with known malignancy. (See **CONTRAINDICATIONS** and **WARNINGS**)

FIGURE 2.11 Example warning for REGRANEX® Gel 0.01% (becaplermin).

6. Precautions, including special care to be exercised by prescriber and patient in the use of the drug; these include drug–drug, drug–food, and drug–laboratory test interactions, effects on fertility, use in pregnancy, and use in nursing mothers and children.
7. Adverse reactions, including predictable and potential unpredictable undesired (side) effects, categorized by organ system or severity of reaction and frequency of occurrence.
8. Drug abuse and dependence, including legal schedule if a controlled substance, types of abuse and resultant adverse reactions, psychologic and physical dependence potential, and treatment of withdrawal.
9. Overdosage, including signs, symptoms, and laboratory findings of acute overdosage, along with specifics or principles of treatment.
10. Dosage and administration, stating the recommended usual dose, the usual dosage range, the safe upper limit of dosage, duration of treatment, modification of dosage in special patient populations (children, elders, and patients with kidney and/or liver dysfunction), and special rates of administration (as with parenteral medications).
11. How supplied, including information on available dosage forms, strengths, and means of dosage form identification, as color, coating, scoring, and National Drug Code.

FDA Review and Action Letters

The completed NDA is carefully reviewed by the FDA, which decides whether to allow the sponsor to market the drug, to disallow marketing, or to require additional data before rendering a judgment. By regulation, the FDA must respond within 180 days of receipt of an application. This 180-day period is called the review clock and is often extended by agreement between the applicant and the FDA, as additional information, studies, or clarifications are sought.

The NDA is reviewed by the same FDA division that reviewed the sponsor's original IND. However, for the NDA review, the FDA also obtains the recommendation of an outside advisory review committee composed of persons of recognized competence and stature in the clinical area of the proposed drug's use. Although not binding, this committee's recommendation has influence in the FDA's decision to issue an action letter after the entire review of the application is completed. The FDA can respond to a sponsor of an NDA with one of the following types of letters:

1. Approval, meaning the drug has met agency standards for safety and efficacy and the drug can be marketed for sale in the United States.
2. Complete response, letting a company know that the review period for a drug is complete and that the application is not yet ready for approval. The letter will describe specific deficiencies and, when possible, will outline the recommended actions the applicant might take to get the application ready for approval.

After an NDA is approved and the product marketed, the FDA requires periodic safety and other reports, schedules plant inspections, and requires continued compliance with control and quality standards and current good manufacturing practices.

Phase 4 Studies and Postmarketing Surveillance

The receipt of marketing status for a new drug product does not necessarily end a sponsor's investigation of the drug. Continued clinical investigations, often called Phase 4 studies, may contribute to the understanding of the drug's mechanism or scope of action, may

indicate possible new therapeutic uses for the drug, and/or may demonstrate the need for additional dosage strengths, dosage forms, or routes of administration. Postmarketing studies may also reveal additional side effects, serious and unexpected adverse effects, and/or drug interactions.

In applying for a new use, strength, dosage form, or route of administration for a previously approved drug, the sponsor must file a new IND, conduct all necessary additional nonclinical and clinical studies, and file a new NDA for FDA review.

Postmarketing Reporting of Adverse Drug Experience

A drug's sponsor is required to report to the FDA each adverse drug experience that is both serious (life threatening or fatal) and unexpected (not contained in the approved drug product labeling), regardless of the source of the information, within 15 working days of receipt of the information. These 15-day alert reports must then be investigated by the sponsor with a follow-up report submitted to the FDA, again within 15 working days. Other adverse events, not considered serious and unexpected, are reported quarterly for 3 years following the date of approval of the NDA and annually thereafter. Practicing pharmacists and other health care professionals participate in adverse drug experience reporting through the FDA's MedWatch program, using forms provided for this purpose at http://fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm (57). Two forms are available: Form FDA 3500 is for voluntary reporting by healthcare professionals, consumers, and patients; Form FDA 3500 A is for mandatory reporting by IND reporters, manufacturers, distributors, importers, and other specified parties.

Depending on the nature, causal relationship, and seriousness of an adverse drug reaction report, the FDA may require revised product labeling to reflect the new findings, ask the sponsor to issue special warning notices to health care professionals, undertake or require the sponsor to undertake a review of all available clinical data, restrict the marketing of the product during a review period, issue a product recall notice, or withdraw the product approval for marketing.

In the event of information on or a confirmed incident of a mislabeled, contaminated, or deteriorated product in distribution, the sponsor is required to file an NDA field alert report to the FDA district office by telephone or other rapid communication within 3 working days of receipt of the information. The FDA follows up with appropriate action.

Annual Reports

Each year, the sponsor of an approved drug must file with the FDA division responsible for the NDA review a report containing the following information:

- An annual summary of significant new information that might affect the safety, effectiveness, or labeling of the drug product
- Data on the quantity of dosage units of the drug product distributed domestically and abroad
- A sample of professional labeling, patient brochures, or package inserts, and a summary of any changes since the previous report
- Reports of experiences, investigations, studies, or tests involving chemical or physical properties of the drug that may affect its safety or effectiveness
- A full description of any manufacturing and controls changes not requiring a Supplemental New Drug Application (SNDA)
- Copies of unpublished reports and summaries of published reports of new toxicologic findings in vitro and animal studies conducted or obtained by the sponsor
- Full or abstract reports on published clinical trials of the drug, including studies on safety and effectiveness; new uses; biopharmaceutical, pharmacokinetic, clinical pharmacologic, and epidemiologic reports; pharmacotherapeutic and lay press articles on the drug; and summaries of unpublished clinical trials or prepublication manuscripts, as available, conducted or obtained by the sponsor

- A statement on the current status of any postmarketing studies performed by or on behalf of the sponsor
- Specimens of mailing pieces or other forms of promotion of the drug product

Failure to make required reports may lead to FDA withdrawal of approval for marketing.

SUPPLEMENTAL, ABBREVIATED, AND OTHER APPLICATIONS

In addition to the IND and NDA, the following types of applications are filed with the FDA for the purposes described.

Supplemental New Drug Application

A sponsor of an approved NDA may make changes in that application through the filing of an SNDA. Depending on the changes proposed, some require FDA approval before implementing; others do not. Among the changes requiring prior approval are the following:

- A change in the method of synthesis of the drug substance
- Use of a different facility to manufacture the drug substance where the facility has not been approved through inspection for Current Good Manufacturing Practice standards within the previous 2 years
- Change in the formulation, analytical standards, method of manufacture, or in-process controls of the drug product
- Use of a different facility or contractor to manufacture, process, or package the drug product
- Change in the container and closure system for a drug product
- Extension of the expiration date for a drug product based on new stability data
- Any labeling change that does not add to or strengthen a previously approved label statement

Examples of changes that may be made without prior approval are minor editorial or other changes in the labeling that add to or strengthen an approved label section, any analytical changes made to comply with the USP–NF, an extension of the product's expiration date based on full shelf-life data obtained from a protocol in the approved application, and a change in the size (not the type of system) of the container for a solid dosage form.

Abbreviated New Drug Application

An ANDA is one in which nonclinical laboratory studies and clinical investigations may be omitted, except those pertaining to the drug's bioavailability. These applications are usually filed for duplicates (generic copies) of drug products previously approved under a full NDA and for which the FDA has determined that information on the exempted nonclinical and clinical studies is already available at the agency. ANDAs commonly are filed by competing companies following the expiration of patent term protection of the innovator drug or drug product. Bioavailability and product bioequivalency are discussed in Chapter 5.

The Patient Protection and Affordable Care Act of 2010 created an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. Under the Act, a biological product may be deemed to be "biosimilar" if data show that, among other things, the product is "highly similar" to an already-approved biological product.

Biologics License Application

BLAs are submitted to the FDA's CBER for the manufacture of biologics such as blood products, vaccines, and toxins. The applications for biologics approvals follow the regulatory requirements as stated specifically for these products in the relevant parts of the CFR (4).

Animal Drug Applications

The Federal Food, Drug, and Cosmetic Act, as amended, contains specific regulations pertaining to the approval for the marketing and labeling of drugs intended for animal use (6).

Included are NADAs, supplemental applications to an approved drug (SNADA), abbreviated new animal drug applications (ANADAs) for generic equivalents, and CNADAs, which are applications for conditional approval of new animal drugs which allow a drug sponsor to legally market a new animal drug intended for a minor use or a minor species after proving it is safe but before collecting all the necessary effectiveness data. The drug's sponsor can keep the product on the market for up to 5 years, while collecting the effectiveness data required for an NADA application.

Medical Devices

The FDA has regulatory authority over the manufacture and licensing of all medical devices, from surgical gloves and catheters to cardiac pacemakers and cardiopulmonary bypass blood gas monitors (7). Included in the regulations are standards and procedures for manufacturer registration, investigational studies, good manufacturing practices, and premarket approval.

INTERNATIONAL CONFERENCE ON HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

In recognition of the international marketplace for pharmaceuticals and in an effort to achieve global efficiencies for both regulatory agencies and the pharmaceutical industry, the FDA, counterpart agencies of the European Union and Japan, and geographic representatives of the pharmaceutical industry formed a tripartite organization in 1991 to discuss, identify, and address relevant regulatory issues. This organization, named the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, has worked toward harmonizing, or bringing together, the regulatory requirements with the long-range goal of establishing a uniform set of standards for drug registration within these geographic areas.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Given a new FDA approval, research and present its progression from a new chemical entity to its NDA. Identify pertinent dates, preclinical trials, and clinical trials.
2. Within the last 2 years, identify a drug that was given a treatment IND, a drug approved for an SNDA, a drug that was approved for an ANDA, and an example of a drug that was withdrawn from its IND.
3. Draw a timeline of the steps taken for a drug to gain approval after an IND is submitted to the FDA.
4. Create a table of patient factors considered in determining a drug's dose in clinical investigations and in medical practice, and provide three examples of drug dosages/regimens influenced by the specific factor.

Individual Activities

1. Identify a drug that had previous FDA approval; however, it has recently been submitted as a new drug under the FDA definition.
2. Identify a drug that had postmarketing reporting that resulted in the drug being withdrawn from the market; identify a drug whose postmarketing surveillance reporting resulted in the addition of a black-box warning.
3. Determine how much money a drug company typically spends before a drug is FDA approved. How much does a drug company allocate for marketing a new product? Explain how this accounts for the cost of new prescription medications.

REFERENCES

1. Code of Federal Regulations, Title 21, Parts 300–314.
2. Code of Federal Regulations, Title 21, Part 320.
3. Code of Federal Regulations, Title 21, Part 316.
4. Code of Federal Regulations, Title 21, Parts 600–680.
5. Code of Federal Regulations, Title 21, Part 330.
6. Code of Federal Regulations, Title 21, Parts 510–555.
7. Code of Federal Regulations, Title 21, Parts 800–895.
8. Federal Register, U.S. Washington: Government Printing Office, Superintendent of Documents. Available at: http://www.gpo.gov/fdsys/browse/collection.action?collectionCode=FR. (Accessed September 23, 2012).
9. Mathieu M. New Drug Development: A Regulatory Overview. 8th Ed. Cambridge, MA: PAREXEL International, 2008.
10. Mathieu M. Biologics Development: A Regulatory Overview. 1348321086 false -1 5 5 4 Cambridge, MA: PAREXEL International, 2004.
11. Chorghade MS, Ed. Drug Discovery and Development, Volume 1 (Drug Discovery), 2006, Volume 2 (Drug Development), Hoboken, NJ: Wiley-Interscience, 2007.
12. Kayser O, Warzecha H, Eds. Pharmaceutical Biotechnology: Drug Discovery and Clinical Applications, 2nd Ed. Hoboken, NJ: Wiley, 2012.
13. Ng R. Drugs, from Discovery to Approval. 2nd Ed., Hoboken, NJ: Wiley-Blackwell, 2008.
14. Portfolio management solutions. JamesSamanenConsulting.com. Available at: http://www.portfoliomanagementsolutions.com/overall-outline/. (Accessed September 20, 2012)
15. Tami JA, Parr MD, Brown SA, et al. Monoclonal antibody technology. Am J Hosp Pharm 1986;43:2816–2826.
16. Brodsky FM. Monoclonal antibodies as magic bullets. Pharm Res 1988;5:1–9.
17. Parasrampuria DA, Hunt CA. Therapeutic delivery issues in gene therapy, part 2: Targeting approaches. Pharm Technol 1998;22:34–43.
18. Chew NJ. Cellular and gene therapies, part 1: Regulatory health. BioPharmacy 1995;8:22–23.
19. Smith TJ. Gene therapy: Opportunities for pharmacy in the 21st century. Am J Pharm Ed 1996;60:213–215.
20. Milestones in gene therapy. BioPharmacy 1997;10:17.
21. Cellular and Gene Therapy Guidance Documents. Rockville, MD: Food and Drug Administration. Available at: http://www.portfoliomanagementsolutions.com/overall-outline/. (Accessed September 20, 2012)
22. Kauvar LM. Affinity fingerprinting: Implications for drug discovery. Pharm News 1996;3:12–15.
23. Harris AL. High throughput screening and molecular diversity. Pharm News 1995;2:26–30.
24. Silverman RB. Drug discovery, design, and development. In: The Organic Chemistry of Drug Design and Drug Action. New York, NY: Academic Press, 1992:4–51.
25. Perun TJ, Propst CL, Eds. Computer-aided Drug Design: Methods and Applications. New York, NY: Marcel Dekker, 1989.
26. FDA Glossary of Terms. Rockville, MD: Food and Drug Administration. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm. (Accessed September 22, 2012)
27. United States Adopted Names. Chicago, IL: American Medical Association. Available at: USAN http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/adopted-names.page. (Accessed September 22, 2012)
28. Spilker B. Extrapolation of preclinical safety data to humans. Drug News Perspect 1991;4:214–216.
29. Code of Federal Regulations Title 21, 312.23. Rockville, MD: Food and Drug Administration. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.23. (Accessed September 22, 2012)
30. 60 Federal Register 11263–11268. International conference on harmonization; guideline on the assessment of systemic exposure in toxicity studies, 1995.
31. 60 Federal Register 11277–11281. International conference on harmonization; guidance on dose selection for carcinogenicity study of pharmaceuticals, 1995.
32. 58 Federal Register 21073–21080. International conference on harmonization; draft guideline on detection of toxicity to reproduction for medicinal products, 1993.
33. 59 Federal Register 48734–48737. International conference on harmonization, draft guideline on specific aspects of regulatory genotoxicity tests, 1994.
34. Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application. Rockville, MD: Food and Drug Administration, 1987.
35. The Biopharmaceutics Classification System. Rockville, MD: Food and Drug Administration. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf. (Accessed September 23, 2012)
36. Code of Federal Regulations, Title 21, Parts 210–211.
37. IND Process and Review Procedures. Manual of Policies and Procedures. Center for Drug Evaluation and Research, Rockville, MD: Food and Drug Administration. Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM082022.pdf. (Accessed September 23, 2012)
38. Investigational New Drug Application (FDA Form 1571). Available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf. (Accessed September 23, 2012)

39. 58 Fedral Register 39405-39416. Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs, 1993.
40. 59 Federal Register 11145-11151. NIH guidelines on the inclusion of women and minorities as subjects in clinical research, 1994.
41. Wright DT, Chew NJ. Women as subjects in clinical research. Appl Clin Trials 1996;5:44–52.
42. Wick JY. Culture, ethnicity, and medications. JAPhA 1996;NS36:555–563.
43. Code of Federal Regulations, Title 21, Part 56.
44. Code of Federal Regulations, Title 21, Part 50.
45. Manual of Policies & Procedures (CDER). Rockville, MD: Food and Drug Administration. Available at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedical ProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm#ode2. (Accessed September 23, 2012)
46. Spilker B. Guide to Clinical Trials. New York, NY: Raven, 1991.
47. Bush C. When your subject is a child. Appl Clin Trials 1997;6:54–56.
48. Cohen HJ. The elderly patient: A challenge to the art and science of medicine. Drug Ther 1983;13:41.
49. Futerman SS. The geriatric patient: Pharmacy care can make a difference. Apothecary 1982;94:34.
50. Taketomo CK, ed. Pediatric and Neonatal Dosage Handbook. 19th Ed., 2012, and Semla TP, Beizer JL, Higbee MD, eds. Geriatric Dosage Handbook. 17th Ed., 2012. Hudson OH: Lexi-Comp Inc.
51. Kim H, Lim SW, Kim S, et al. Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression. JAMA 2006;296:1609–1618.
52. Food and Drug Administration. FDA Med Bull 1993;23:2–4.
53. Logsdon BA. Drug use during lactation. JAPhA 1997;NS37:407–418.
54. Drug safety in lactation. Available at: http://www.medsafe.govt.nz/Profs/PUarticles/lactation.htm. (Accessed September 23, 2012)
55. Treatment Use of Investigational Drugs—Information Sheet. Rockville, MD: Food and Drug Administration. Available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126495.htm. (Accessed September 23, 2012)
56. Code of Federal Regulations, Title 21. Part 201.
57. MedWatch. Rockville, MD: Food and Drug Administration.

3 Current Good Manufacturing Practices and Current Good Compounding Practices

OBJECTIVES

After reading this chapter, the student will be able to:

1. List common terms used in the Current Good Manufacturing Practice (cGMP) for finished pharmaceuticals
2. Describe the organization and personnel required by cGMP
3. Describe the intent and importance of written procedures within the various components of cGMP
4. Describe the various types of tamper-evident packaging, and provide a product example of each type
5. Differentiate between pharmaceutical manufacturing and extemporaneous compounding
6. Describe Chapter 795 of the current United States Pharmacopeia (USP)
7. Describe Chapter 797 of the current USP

STANDARDS FOR CURRENT GOOD MANUFACTURING PRACTICE

Current Good Manufacturing Practice (cGMP or GMP) regulations are established by the Food and Drug Administration (FDA) to ensure that minimum standards are met for drug product quality in the United States (1). The first GMP regulations were promulgated in 1963 under the provisions of the Kefauver-Harris Drug Amendments, and since then, they have been periodically revised and updated.

The cGMP regulations establish requirements for all aspects of pharmaceutical manufacture. They apply to domestic and to foreign suppliers and manufacturers whose bulk components and finished pharmaceutical products are imported, distributed, or sold in this country. To ensure compliance, the FDA inspects the facilities and production records of all firms covered by these regulations.

The Code of Federal Regulations (CFR) contains (*a*) requirements for the "Current Good Manufacturing Practice for Finished Pharmaceuticals" and (*b*) additional cGMP requirements for biologic products, (*c*) medicated articles, and (*d*) medical devices. Currency and compliance with cGMP regulations are supported through notices in the Federal Register and through the FDA's Compliance Policy Guide and various other guidances issued by the FDA.

A topical outline of the cGMP regulations for finished pharmaceuticals is presented in Table 3.1 and summarized in the sections that follow.

cGMP FOR FINISHED PHARMACEUTICALS

General Provisions: Scope and Definitions

The regulations in 21 CFR, part 211, contain the minimum GMP requirements for

Table 3.1 TOPICAL OUTLINE OF CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS

A. General Provisions
- Scope
- Definitions

B. Organization and Personnel
- Responsibilities of quality control unit
- Personnel qualifications
- Personnel responsibilities
- Consultants

C. Buildings and Facilities
- Design and construction features
- Lighting
- Ventilation, air filtration, air heating and cooling
- Plumbing
- Sewage and refuse
- Washing and toilet facilities
- Sanitation
- Maintenance

D. Equipment
- Equipment design, size, and location
- Equipment construction
- Equipment cleaning and maintenance
- Automatic, mechanical, and electronic equipment
- Filters

E. Control of Components and Drug Product Containers and Closures
- General requirements
- Receipt and storage of untested components, drug product containers, and closures
- Testing and approval or rejection of components, drug product containers, and closures
- Use of approved components, drug product containers, and closures
- Retesting of approved components, drug product containers, and closures
- Rejected components, drug product containers, and closures
- Drug product containers and closures

F. Production and Process Controls
- Written procedures, deviations
- Charge-in of components
- Calculation of yield
- Equipment identification
- Sampling and testing of in-process materials and drug products
- Time limitations on production
- Control of microbiological contamination
- Reprocessing

G. Packaging and Labeling Control
- Materials examination and usage criteria
- Labeling issuance
- Packaging and labeling operations
- Tamper-resistant packaging requirements for OTC human drug products
- Drug product inspection
- Expiration dating

H. Holding and Distribution
- Warehousing procedures
- Distribution procedures

I. Laboratory Controls
- General requirements
- Testing and release for distribution
- Stability testing
- Special testing requirements
- Reserve samples
- Laboratory animals
- Penicillin contamination

J. Records and Reports
- General requirements
- Equipment cleaning and use log
- Component, drug product container, closure, and labeling records
- Master production and control records
- Batch production and control records
- Production record review
- Laboratory records
- Distribution records
- Complaint files

K. Returned and Salvaged Drug Products
- Returned drug products
- Drug product salvaging

Code of Federal Regulations 21, part 211, revised April 1, 2012. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart = 211. (Accessed September 25, 2012)

the preparation of finished pharmaceutical products for administration to humans or animals.

Common terms used in these regulations are defined as follows:

Active ingredient or active pharmaceutical ingredient (API): Any component that is intended to furnish pharmacologic activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body of man or other animals

Batch: A specific quantity of a drug of uniform specified quality produced according to a single manufacturing order during the same cycle of manufacture

Batchwise control: The use of validated in-process sampling and testing methods in such a way that results prove that the process has done what it purports to do for the specific batch concerned

Certification: Documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are acceptable

Compliance: Determination through inspection of the extent to which a manufacturer is acting in accordance with prescribed regulations, standards, and practices

Component: Any ingredient used in the manufacture of a drug product, including those that may not be present in the finished product

Drug product: A finished form that contains an active drug and inactive ingredients. The term may also include a form that does not contain an active ingredient, such as a placebo.

Inactive ingredient: Any component other than the active ingredients in a drug product

Lot: A batch or any portion of a batch having uniform specified quality and a distinctive identifying lot number

Lot number, control number, or batch number: Any distinctive combination of letters, numbers, or symbols from which the complete history of the manufacture, processing, packaging, holding, and distribution of a batch or lot of a drug product may be determined

Master record: Record containing the formulation, specifications, manufacturing procedures, quality assurance requirements, and labeling of a finished product

Quality assurance: Provision to all concerned the evidence needed to establish confidence that the activities relating to quality are being performed adequately

Quality audit: A documented activity performed in accordance with established procedures on a planned and periodic basis to verify compliance with the procedures to ensure quality

Quality control: The regulatory process through which industry measures actual quality performance, compares it with standards, and acts on the difference

Quality control unit: An organizational element designated by a firm to be responsible for the duties relating to quality control

Quarantine: An area that is marked, designated, or set aside for the holding of incoming components prior to acceptance testing and qualification for use

Representative sample: A sample that accurately portrays the whole

Reprocessing: The activity whereby the finished product or any of its components is recycled through all or part of the manufacturing process

Strength: The concentration of the drug substance per unit dose or volume

Verified: Signed by a second individual or recorded by automated equipment

Validation: Documented evidence that a system (e.g., equipment, software, controls) does what it purports to do

Process validation: Documented evidence that a process (e.g., sterilization) does what it purports to do

Validation protocol: A prospective experimental plan to produce documented evidence that the system has been validated

Organization and Personnel

The organization and personnel section of the regulations deals with the responsibilities of the quality control unit, employees,

and consultants. The regulations require that a quality control unit have the authority and responsibility for all functions that may affect product quality. This includes accepting or rejecting product components, product specifications, finished products, packaging, and labeling. Adequate laboratory facilities shall be provided, written procedures followed, and all records maintained.

All personnel engaged in the manufacture, processing, packing, or holding of a drug product, including those in supervisory positions, are required to have the education, training, and/or experience needed to fulfill the assigned responsibility. Appropriate programs of skill development, continuing education and training, and performance evaluations are essential for maintaining quality assurance. Any consultants advising on scientific and technical matters should possess requisite qualifications for the tasks.

Buildings and Facilities

As outlined in Table 3.1, the regulations in this section include the design, structural features, and functional aspects of buildings and facilities. Each building's structure, space, design, and placement of equipment must be such to enable thorough cleaning, inspection, and safe and effective use for the designated operations. Proper considerations must be given to such factors as water quality standards; security; materials used for floors, walls, and ceilings; lighting; segregated quarantine areas for raw materials and product components subject to quality control approval; holding areas for rejected components; storage areas for released components; weighing and measuring rooms; sterile areas for ophthalmic and parenteral products; flammable materials storage areas; finished products storage; control of heat, humidity, temperature, and ventilation; waste handling; employee facilities and safety procedures in compliance with the Occupational Safety and Health Administration regulations; and procedures and practices of personal sanitation.

All work in the manufacture, processing, packaging, or holding of a pharmaceutical product must be logged in, inspected by a supervisor, and signed off. Similarly, a log of building maintenance must be kept to document this component of the regulations.

Equipment

Each piece of equipment must be of appropriate design and size and suitably located to facilitate operations for its intended use, cleaning, and maintenance. The equipment's surfaces and parts must not interact with the processes or product's components so as to alter the purity, strength, or quality.

Standard operating procedures must be written and followed for the proper use, maintenance, and cleaning of each piece of equipment, and appropriate logs and records must be kept. Automated equipment and computers used in the processes must be routinely calibrated, maintained, and validated for accuracy.

Filters used in the manufacture or processing of injectable drug products shall not release fibers into such products. If fiber-releasing filters must be used, non–fiber-releasing filters also must be used to reduce any fiber content.

Control of Components, Containers, and Closures

Written procedures describing the receipt, identification, storage, handling, sampling, testing, and approval or rejection of all drug product components, product containers, and closures must be maintained and followed. Bulk pharmaceutical chemicals, containers, and closures must meet the exact physical and chemical specifications established with the supplier at the time of ordering.

When product components are received from a supplier, each lot must be logged in with the purchase order number, date of receipt, bill of lading, name and vital information of the supplier, supplier's stock or control number, and quantity received. The component is assigned a control number that identifies both the component and the intended product. Raw materials are quarantined until they are verified through representative sampling and careful qualitative

and quantitative analysis. The quality control unit approves and releases for use in manufacture only those that meet the specifications. The assigned control number follows the component throughout production so it can be traced if necessary.

Rejected components, drug product containers, and closures are identified and controlled under a quarantine system to prevent their use in manufacturing and processing operations. As the majority of bulk chemicals (APIs) are synthesized overseas (primarily in China and India), it is important to confirm their identity and purity and conformance with United States Pharmacopeia (USP) and National Formulary (NF) standards prior to use in finished pharmaceuticals.

Production and Process Controls

Written procedures are required for production and process controls to ensure that the drug products have the correct identity, strength, quality, and purity. These procedures, which include the charge-in of all components, use of in-process controls, sample testing, and process and equipment validation, must be followed for quality assurance. Any deviation from the written procedures must be recorded and justified. In most instances, the operator records time and date of each key operation, and the supervisor signs off on it. When operations are controlled by automated equipment, such equipment must be validated regularly for precision.

All product ingredients, equipment, and drums or other containers of bulk finished product must be distinctively identified by labeling as to content and/or status. In-process samples are taken from production batches periodically for product control. In-process controls are of two general types: (*a*) those performed by production personnel at the time of operation to ensure that the machinery is producing output within preestablished control limits (e.g., tablet size, hardness) and (*b*) those performed by the quality control laboratory personnel to ensure compliance with all product specifications (e.g., tablet content, dissolution) and batch-to-batch consistency. Product found out of standard sometimes may be reprocessed for subsequent use. However, in this, as in all instances, procedures must be performed according to established protocol, and all materials must be accounted for, all specifications met, and all records meticulously maintained.

Packaging and Labeling Control

Written procedures are required for the receipt, identification, storage, handling, sampling, and testing of drug product and issuance of labeling and packaging materials. Labeling for each variation in drug product—strength, dosage form, or quantity of contents—must be stored separately with suitable identification. Obsolete and outdated labels and other packaging materials must be destroyed. Access to the storage area must be limited to authorized personnel.

All materials must be withheld for use in the packaging and labeling of product until approved and released by the quality control unit. Control procedures must be followed and records maintained for the issuance and use of product labeling. Quantities issued, used, and returned must be reconciled and discrepancies investigated. Before labeling operations commence, the labeling facilities must be inspected to ensure that all drug products and labels have been removed from the previous operations. There must be dedication of labeling and packaging lines to *each different strength of each different drug product*. There must be use of appropriate electronic or electromechanical equipment to conduct a 100% examination for correct labeling during or after completion of finishing operations or use of visual inspection to conduct a 100% examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person. All of these procedures are essential to avoid label mix-ups and the mislabeling of products. All records of inspections and controls must be documented in the batch production records.

Labels must meet the legal requirements for content as outlined in Chapter 2 and later

in this chapter. Each label must contain expiration dating and the production batch or lot number to facilitate product identification.

Expiration Dating

To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it must bear an expiration date determined by appropriate stability testing. Exempt from this requirement are homeopathic drug products, allergenic extracts, and investigational drugs that meet the standards established during preclinical and clinical studies.

Tamper-Evident Packaging

On November 5, 1982, the FDA published initial regulations on tamper-resistant packaging in the *Federal Register*. These regulations were promulgated after criminal tampering with over-the-counter (OTC) drug products earlier in that year resulted in illness and deaths. In the primary incident, cyanide was surreptitiously placed in acetaminophen capsules in commercial packages.

Today, the cGMP regulations require tamper-evident packaging for OTC drug products to improve their security and to assure their safety and effectiveness. All OTC drug products offered for retail sale are required to have tamper-evident packaging except for some categories, such as dentifrices, dermatologicals, insulin, and throat lozenges. For other product categories, a manufacturer may file with the FDA a Request for Exemption from Tamper-Evident Rule. The petition is required to contain specific information on the drug product, the reasons the requirement is unnecessary or cannot be achieved, and alternative steps the petitioner has taken or may take to reduce the likelihood of malicious adulteration of the product. Generally exempt from these regulations are products not packaged for retail sale but rather distributed to hospitals, nursing homes, and health care clinics for institutional use.

A tamper-evident package is defined as "one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred" (1). The indicators or barriers may involve the immediate drug product container and/or an outer container or carton. For two-piece hard gelatin capsule products, a minimum of two tamper-evident packaging features is required unless the capsules are sealed with tamper-resistant technology.

Even with these safeguards in effect, the possibility of drug product tampering requires the pharmacist and consumer to remain constantly vigilant for signs of product entry. Pharmaceutical manufacturers have the option of determining the type of tamper-resistant packaging to use. Table 3.2 presents some examples of tamper-evident packaging.

Holding and Distribution

Written procedures must be established and followed for the holding and distribution of product. Finished pharmaceuticals must be quarantined in storage until released by the quality control unit. Products must be stored and shipped under conditions that do not affect product quality. Ordinarily, the oldest approved stock is distributed first. The distribution control system must allow the distribution point of each lot of drug product to be readily determined to facilitate its recall if necessary.

Laboratory Controls

Laboratory controls are requirements for the establishment of and conformance to written specifications, standards, sampling plans, test procedures, and other such mechanisms. The specifications, which apply to each batch of drug product, include provisions for sample size, test intervals, sample storage, stability testing, and special testing requirements for certain dosage forms, including parenterals, ophthalmics, controlled-release products, and radioactive pharmaceuticals. Reserve samples must be retained for distributed products for specified periods depending on their category. Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall

Table 3.2 EXAMPLES OF TAMPER-EVIDENT PACKAGING

PACKAGE TYPE	TAMPER PROTECTION
Film wrapper	Sealed around product and/or product container; film must be cut or torn to remove product.
Blister/strip pack	Individually sealed dose units; removal requires tearing or breaking individual compartment.
Bubble pack	Product and container sealed in plastic, usually mounted on display card; plastic must be cut or broken open to remove product.
Shrink seal, band	Band or wrapper shrunk by heat or drying to conform to cap; must be torn to open package
Bottle seal	Paper or foil sealed to mouth of container under cap; must be torn or broken to reach product
Tape seal	Paper or foil sealed over carton flap or bottle cap; must be torn or broken to reach product
Breakable cap	Plastic or metal tearaway cap over container; must be broken to remove
Sealed tube	Seal over mouth of tube; must be punctured to reach product
Sealed carton	Carton flaps sealed; carton cannot be opened without damage.
Aerosol container	Tamper-resistant by design

be identified, and adequate records shall be maintained showing the history of their use.

Records and Reports

Production, control, and distribution records must be maintained for at least a year following the expiration date of a product batch. This includes equipment cleaning and maintenance logs; specifications and lot numbers of product components, including raw materials and product containers and closures; and label records. Complete master production and control records for each batch must be kept.

These master records must document that each step in the production, control, packaging, labeling, and distribution of the product was accomplished and approved by the quality control unit. Depending on the operation, the operator's and/or supervisor's full signatures, initials, or other written or electronic identification codes are required.

Records of written and oral complaints regarding a drug product (e.g., product failure, adverse drug experience) must also be maintained, along with information regarding the internal disposition of each complaint. All records must be made available at the time of inspection by FDA officials.

Returned and Salvaged Drug Products

Returned drug products (e.g., from wholesalers) must be identified by lot number and product quality determined through appropriate testing. Drug products that meet specifications may be salvaged or reprocessed. Those that do not, along with those that have been subjected to improper storage (e.g., extremes in temperature), shall not be returned to the marketplace. Records for all returned products must be maintained and must include the date and reasons for the return; quantity and lot number of product returned; procedures employed for holding, testing, and reprocessing the product; and the product's disposition.

Information Technology and Automation

Although not part of the cGMP requirements, the effective deployment of information technologies and automated systems can enhance pharmaceutical process development, production efficiencies, product quality, and regulatory compliance (2).

Computers are used extensively in plant operations such as production scheduling,

in-process manufacturing, quality control, and packaging and labeling. The networking of computers in the production and quality control areas fully integrates laboratory information and manufacturing operations into sophisticated management systems. These integrated systems support cGMP compliance, process validation, resource management, and cost control. Figure 3.1 presents an example of computer use in the pharmaceutical industry for the management of plant operations. Robotic devices increasingly are being employed to replace manual operations in production lines, analytical sampling, and packaging. Figure 3.2 presents an example of robot use in the laboratory. Laboratory robotics provides automation in areas such as sample preparation and handling, wet chemistry procedures, laboratory process control, and instrumental analysis (3). Pharmaceutical applications of robotics include automated product handling in production lines and in procedures such as sampling and analysis, tablet content uniformity, and dissolution testing.

ADDITIONAL cGMP REGULATORY REQUIREMENTS

Active Pharmaceutical Ingredients and Pharmaceutical Excipients

The manufacture of APIs comes under the *aegis* of cGMP regulations and requirements. The FDA publication *Guide to the Inspection of Bulk Pharmaceutical Chemicals* (4) identifies the inspection program for manufacture of chemical components of pharmaceutical products to assure that all required standards for quality are met. Because the quality of any finished pharmaceutical product depends on the quality of the various components, including the active ingredients, compliance with cGMPs is a critical part of the FDA's preapproval inspection program for new drug applications (NDAs) and abbreviated new drug applications (ANDAs).

The broad cGMP areas described previously for finished pharmaceuticals apply but are directed toward the process-specific aspects of bulk pharmaceutical chemicals. The application of the regulations is focused on all of the defining elements of chemical purity and quality, including the following (5):

- Specifications and analytical methods for all reactive and nonreactive components used in synthesis
- Critical chemical reaction steps
- Handling of chemical intermediates
- Effect of scale-up of chemical batches on the yield
- Quality of the water systems
- Solvent handling and recovery systems
- Analytical methods to detect impurities or chemical residues and the limits set
- Stability studies of the bulk pharmaceutical chemical

Pharmaceutical excipients, as they, too, are components of finished pharmaceutical products, must be produced in accordance with cGMP standards as certified on the application by each sponsor of an NDA or ANDA (6,7).

FIGURE 3.1 Example of computer use in the pharmaceutical industry. The machine shown is an Allen Bradley Advisor 21 operator interface. This allows the plant operator to communicate with the main programmable logical controller. The Advisor 21 gives a constant real-time update of the process on a series of screens and allows an operator to perform programmed operations at the push of a button. (Courtesy of Elan Corporation, plc.)

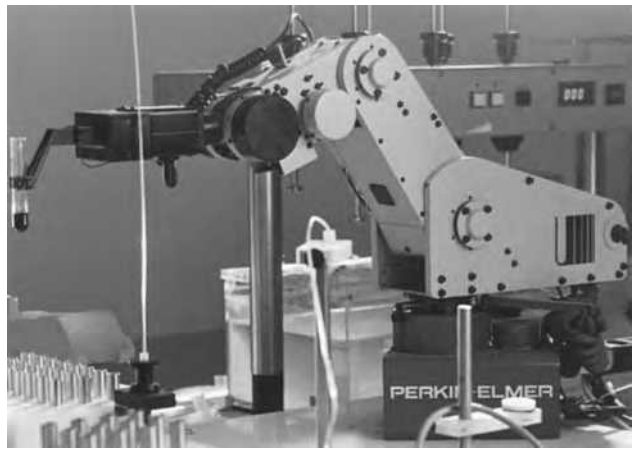


FIGURE 3.2 Robotics in laboratory use. Perkin-Elmer Robotic Arm and Perkin-Elmer Lambda 1a UV/VIS Spectrophotometer. (Courtesy of Elan Corporation, plc.)

Clinical Trial Materials

Clinical trial materials (CTMs) must be produced in conformance with cGMP regulations. This applies to both the production of the APIs and investigational drug products.

The API used in a clinical investigation is subject to all of the requirements for the production of bulk pharmaceutical chemicals. However, the batch size is different from the commercial scale used in the production of an FDA-approved product. In some cases, technology transfer in the production of an API from one production site or laboratory to another may require validation to ensure purity and quality standards.

The CTMs used in clinical investigations must be produced in compliance with the cGMP regulatory requirements and standardized as to identity, purity, strength, and quality (8). However, during preclinical testing and the early phases of clinical evaluation, a product's formulation and many of the production processes and analytical controls are under development. Thus, during this period, the regulatory requirements are applied with flexibility. As the clinical trials progress from Phase 1 to Phase 2, the processes are being characterized and refined, and during Phase 3, they are expected to meet all regulatory requirements. It is during Phase 3 that process optimization is demonstrated to the FDA by the production of at least one tenth of a commercial-size batch (e.g., 100,000 capsules) of the proposed product. Prior to that, adequate supplies of dosing units from a few hundred to a few thousand may be prepared by hand or in pilot plant–scale operations as is necessary for the clinical trials (8).

In addition to the active drug product, matching placebo and/or comparator products must be prepared. Specific labeling, coding, packaging design, assembly, and distribution protocols are in effect for CTMs to accommodate the clinical trial design and the requirements for investigational drugs as discussed in Chapter 2.

Biologics

As noted previously, cGMP standards are defined for biologic products in the *Code of Federal Regulations* (1). While the basic regulations for finished pharmaceuticals apply to biologic products as well, the nature of blood, bacterial, and viral products requires specific additional mandates, which are detailed in the regulations.

Medical Devices

Medical devices follow a path for FDA approval that resembles that for pharmaceuticals. For instance, clinical investigations of devices are conducted on approval of an investigational device exemption and approved for marketing when shown to be safe and

effective through a premarket approval application, similar to an investigational new drug and NDA, respectively. Medical devices also are subject to the reporting of adverse events, to recall, and to termination of approval.

The regulations for "good manufacturing practice for medical devices" are similar in organizational structure to those for finished pharmaceuticals. Literally, thousands of medical devices are regulated by the provisions of the *Code of Federal Regulations* (1). Each device has a specific design with individual performance features and utility. For many devices, specific standards are stated in the regulations. Devices covered by cGMP regulations include intraocular lenses, hearing aids, intrauterine devices, cardiac pacemakers, clinical chemistry analyzers, catheters, cardiopulmonary bypass heart–lung machine console, dental X-ray equipment, surgical gloves, condoms, prosthetic hip joints, traction equipment, computed tomography equipment, and powered wheelchairs.

Noncompliance with cGMP Regulations

Noncompliance with cGMP regulations can lead to a number of regulatory actions by the FDA. Noncompliance determined during a premarket approval inspection of facilities as part of an NDA or ANDA application likely would result in a delay of approval of an otherwise approvable application. Noncompliance with cGMP regulations during a regularly scheduled FDA inspection can lead to various actions, depending on the severity of the offenses. In most instances, time for corrective action is given, with the firm required to institute and document corrective measures and undergo another inspection. In a worst-case scenario, the FDA is empowered to remove violative products from the market, withdraw product approvals, and restrict further applications. All FDA actions are subject to appeal.

cGMP Requirements for Manufacturing in Pharmacies

The FDA's cGMP regulations apply to community or institutional pharmacies engaged in the manufacture, repackaging, or relabeling of drugs and drug products in a supplier function and beyond the usual conduct of professional dispensing. Pharmacies that engage in such activities must register with the FDA as a manufacturer or distributor and be subject to FDA inspection at regular intervals. Included are hospital pharmacies that repackage drug products for their own use and for the use of other hospitals, chain pharmacy operations that repackage and relabel bulk quantities of products for distribution in the chain, and similar repackaging and relabeling by individual pharmacists or pharmacies for distribution to other pharmacies or retailers.

Professional, legislative, and regulatory attention has been directed toward differentiating between pharmaceutical manufacturing and compounding as practiced by community pharmacists (9). Pharmaceutical manufacturing is large-scale production of drugs or drug products for distribution and sale, whereas compounding is professional preparation of prescriptions for specific patients as a part of the traditional practice of pharmacy. This was affirmed by provision in the Food and Drug Administration Modernization Act of 1997.

CURRENT GOOD COMPOUNDING PRACTICES

In recent years, pharmacists have increased the practice of compounding patient-specific medications. A number of reasons have been presented for the increase in preparing patient-specific medications, including the following:

1. Many patients need drug dosages or strengths that are not commercially available.
2. Many patients need dosage forms, such as suppositories, oral liquids, or topicals, that are not commercially available.
3. Many patients are allergic to excipients in commercially available products.
4. Children's medications must be prepared as liquids, flavored to enhance compliance, and prepared in alternative

dosage forms, such as lozenges, gumdrops, popsicles, and lollipops.
5. Some medications are not very stable and require preparation and dispensing every few days; they are not suitable to be manufactured products.
6. Many physicians desire to deliver products in innovative ways, and pharmacists can work with them to solve medication problems.
7. Most products are not available for veterinary patients and must be compounded.
8. Home health care and the treatment of an increasing number of patients at home have resulted in many community pharmacies and home health care pharmacies preparing sterile products for home use.
9. Hospice care has resulted in new approaches to pain management and higher concentrations and combinations of drugs that are now used.
10. Many drugs are reported in the literature but are not yet manufactured, so pharmacists can compound them for their physicians' and patients' use.

As the extent of compounding increased, many standard-setting agencies and regulatory bodies wanted to ensure quality compounded products; consequently, there was a lot of activity during the mid-1990s to establish guidelines for pharmaceutical compounding.

U.S. Pharmacopeia–National Formulary

In 1990, the U.S. Pharmacopeial Convention initiated a number of activities to bring the compounding provisions of the USP–NF up-to-date. Chapters related to pharmacy compounding were developed and published starting in 1996 (10). In addition, the first of the compounding monographs became official in 1998, and they provide a tested, uniform formulation with valid beyond-use dating.

The USP–NF presently contains the following chapters directly related to pharmaceutical compounding:

<795> Pharmaceutical Compounding-Nonsterile Preparations

<797> Pharmaceutical Compounding-Sterile Preparations

<1160> Pharmaceutical Calculations in Prescription Compounding

<1163> Quality Assurance in Pharmaceutical Compounding

<1176> Prescription Balances and Volumetric Apparatus

In addition, the following are supporting chapters:

<85> Bacterial Endotoxins Test

<1151> Pharmaceutical Dosage Forms

Additional chapters on Compounding for Investigational Studies and Compounding with Hazardous Drugs are being developed. Our present discussion will highlight chapters <795> and <797>. As these chapters are numbered less than <1000>, they are enforceable standards and must be followed.

Chapter <795> Pharmacy Compounding-Nonsterile Preparations contains the following sections: (1) Introduction; (2) Definitions; (3) Categories of Compounding; (4) Responsibilities of the Compounder; (5) Compounding Process; (6) Compounding Facilities; (7) Compounding Equipment; (8) Component Selection, Handling and Storage; (9) Stability Criteria and Beyond-Use Dating; (10) Packaging and Drug Preparation Containers; (11) Compounding Documentation; (12) Quality Control; (13) Patient Counseling; (14) Training; and (15) Compounding for Animal Patients. The purpose of this chapter is to include information to enhance the compounder's ability to extemporaneously compound preparations that are of acceptable strength, quality, and purity.

Chapter <797> Pharmacy Compounding-Sterile Preparations contains the following sections: (1) Definitions; (2) Responsibility of Compounding Personnel; (3) CSP Microbial Contamination Risk Levels; (4) Personnel Training and Evaluation in Aseptic Manipulation Skills; (5) Immediate-Use CSPs; (6) Single-Dose and Multiple-Dose Containers; (7) Hazardous Drugs as CSPs; (8) Radiopharmaceuticals as CSPs; (9) Allergen Extracts as CSPs; (10) Verification of Compounding Accuracy and Sterility; (11) Environmental Quality and Control; (12) Suggested Standard Operating Procedures;

(13) Elements of Quality Control; (14) Verification of Automated Compounding Devices for Parenteral Nutrition Compounding; (15) Finished Preparation Release Checks and Tests; (16) Storage and Beyond-Use Dating; (17) Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs; (18) Patient or Caregiver Training; (19) Patient Monitoring and Adverse Events Reporting; (20) Quality-Assurance Program; (21) Abbreviations and Acronyms; and four appendices. The overall objective of the chapter is to describe conditions and practices to prevent harm, including death, to patients that could possibly result from microbial contamination, excessive bacterial endotoxins, variability in the intended strength and composition, unintended chemical and physical contaminants, and ingredients of inappropriate quality in CSPs (10).

National Association of Boards of Pharmacy

"The Good Compounding Practices Applicable to State-Licensed Pharmacies" (11), developed by the National Association of Boards of Pharmacy, discusses eight recommendations. The subparts include (A) General Provisions and Definitions; (B) Organization and Personnel; (C) Drug Compounding Facilities; (D) Equipment; (E) Control of Components and Drug Product Containers and Closures; (F) Drug Compounding Controls; (G) Continuous Quality Improvement Program; (H) Labeling Control of Excess Products; and (I) Records and Reports.

Subpart (A), General Provisions, provides two important definitions (11):

> "Compounding" means the preparation of Components into a Drug product (*a*) as the result of a Practitioner's Prescription Drug Order based on the Practitioner/patient/Pharmacist relationship in the course of professional practice, or (*b*) for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or Dispensing. Compounding includes the preparation of limited amounts of Drugs or Devices in anticipation of receiving Prescription Drug Orders based on routine, regularly observed prescribing patterns.
>
> "Manufacturing" means the production, preparation, propagation, conversion, or processing of a Drug or Device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis. Manufacturing includes the packaging or repackaging of a Drug or Device or the labeling or relabeling of the container of a Drug or Device for resale by pharmacies, Practitioners, or other Persons.

Subpart (B), Organization and Personnel, discusses the responsibilities of pharmacists and other personnel engaged in compounding. It also stresses that only personnel authorized by the responsible pharmacist shall be in the immediate vicinity of the drug compounding operation.

Subpart (C), Drug Compounding Facilities, describes the areas that should be set aside for compounding, either sterile or not. Special attention is required for radiopharmaceuticals and for products requiring special precautions to minimize contamination, such as penicillin.

Subpart (D), Equipment, states that equipment used must be of appropriate design, adequate size, and suitably located to facilitate operation for its intended use and for its cleaning and maintenance. If mechanical or electronic equipment is used, controls must be in place to ensure proper performance.

Subpart (E), Control of Components and Drug Product Containers and Closures, describes the packaging requirements for compounded products.

Subpart (F), Drug Compounding Controls, discusses the written procedures to ensure that the finished products are of the proper identity, strength, quality, and purity, as labeled.

Subpart (G), Labeling Control of Excess Products and Records and Reports, describes the various records and reports that are required under these guidelines.

Many individual states have used this model and implemented their own version. All pharmacists and pharmacy students should become familiar with the individual state requirements in the state in which they practice.

It will be important as compounding pharmacy increases to ensure reasonable agreement between the national and state agencies so pharmacists will have a set of guidelines within which they can work to

provide their patients the needed individualized medications.

PACKAGING, LABELING, AND STORAGE OF PHARMACEUTICALS

The proper packaging, labeling, and storage of pharmaceutical products are all essential for product stability and efficacious use.

Containers

Standards for the packaging of pharmaceuticals by manufacturers are contained in the "Current Good Manufacturing Practice" section of the *Code of Federal Regulations* (1), in the USP–NF (12), and in the FDA's *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics* (13). When submitting an NDA, the manufacturer must include all relevant specifications for packaging the product. During the initial stages of clinical investigations, the packaging must be shown to provide adequate drug stability for the duration of the clinical trials. As the clinical trials advance to their final stage, information on the chemical and physical characteristics of the container, closure, and other component parts of the package system for the proposed product must be developed to ensure drug stability for its anticipated shelf life.

Different specifications are required for parenteral, nonparenteral, pressurized, and bulk containers and for those made of glass, plastic, and metal. In each instance, the package and closure system must be shown to be effective for the particular product for which it is intended. Depending on the intended use and type of container, among the qualities tested are the following:

- Physicochemical properties
- Light transmission for glass or plastic
- Drug compatibility
- Leaching and/or migration
- Vapor transmission for plastics
- Moisture barrier
- Toxicity for plastics
- Valve, actuator, metered dose, particle size, spray characteristics, and leaks for aerosols
- Sterility and permeation for parenteral containers
- Drug stability for all packaging

Compendial terms applying to types of containers and conditions of storage have defined meanings (12). According to the USP, a container is "that which holds the article and is or may be in direct contact with the article." The immediate container is "that which is in direct contact with the article at all times." The closure is part of the container. The container, including the closure, should be clean and dry before it is filled with the drug. The container must not interact physically or chemically with the drug so as to alter its strength, quality, or purity beyond the official requirements. An example would be the sorption of lipophilic drugs, such as diazepam, to low-density plastics resulting in a loss of drug that is available for administration. The problem can be avoided with the use of glass containers.

The USP classifies containers according to their ability to protect their contents from external conditions (12). The minimally acceptable container is termed a well-closed container. It "protects the contents from extraneous solids and from loss of the article under ordinary conditions of handling, shipment, storage, and distribution." A tight container "protects the contents from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution and is capable of tight reclosure." A hermetic container "is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution." Sterile hermetic containers generally hold preparations intended for injection or parenteral administration. A single-dose container is one that holds a quantity of drug intended as a single dose and, when opened, cannot be resealed with assurance that sterility has been maintained. These containers include fusion-sealed ampuls and prefilled syringes and cartridges. A multiple-dose container is a hermetic container that

permits withdrawal of successive portions of the contents without changing the strength or endangering the quality or purity of the remaining portion. These containers are commonly called vials. Examples of single-dose and multiple-dose products are shown in Figure 3.3.

Dosage forms, such as tablets, capsules, and oral liquids, may be packaged in single-unit or multiple-unit containers. A single-unit container is designed to hold a quantity of drug intended for administration as a single dose promptly after the container is opened (Fig. 3.4). Multiple-unit containers contain more than a single unit or dose of the medication. A single-unit package is termed a unit-dose package. The single-unit packaging of drugs may be performed on a large scale by a manufacturer or distributor or on a smaller scale by the pharmacy dispensing the medication. In either instance, the single-unit package must be appropriately labeled with the product identity, quality and/or strength, name of manufacturer, and lot number to ensure positive identification of the medication.

Although single-unit packaging has a particular usefulness in institutional settings, for example, hospitals and extended care facilities, it is not limited to them. Many outpatients find single-unit packages a convenient and sanitary means of maintaining and using their medication. Among the advantages cited for single-unit packaging and unit-dose dispensing are positive identification of each dosage unit and reduction of medication errors (many are bar-coded), reduced contamination of the drug because of its protective wrapping, reduced dispensing time, greater ease of inventory control in the pharmacy

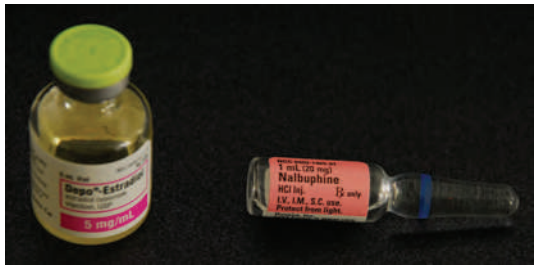


FIGURE 3.3 Injectable products packaged in multiple-dose (vial) and single-dose (ampul) containers.

FIGURE 3.4 Single-unit packaging, including patient cup and blister packaging of single capsule. (Reprinted with permission from Lacher BE. Pharmaceutical Calculations for the Pharmacy Technician. Baltimore, MD: Lippincott Williams & Wilkins, 2008.)

or nursing station, and elimination of waste through better medication management with less discarded medication.

Many hospitals with unit-dose systems strip-package oral solids (Fig. 3.5). Such equipment seals solid dosage forms into four-sided pouches and imprints dose identification on each package at the same time. The equipment can be adjusted to produce individual single-cut packages or perforated strips or rolls of doses. The packaging materials may be combinations of paper, foil, plastic, or cellophane. Some drugs must be packaged in foil-to-foil wrappings to prevent the deteriorating effects of light or permeation of moisture. The packaging of solid dosage forms in clear plastic or aluminum blister wells is perhaps the most popular method of single-unit packaging (Fig. 3.6).

Oral liquids may be dispensed in single units in paper, plastic, or foil cups or prepackaged and dispensed in glass containers having threaded caps or crimped aluminum caps. A number of hospital pharmacies package oral liquids for children's use in disposable plastic oral syringes with rubber or plastic tips on the orifice for closure. In these instances, the nursing staff must be fully aware of the novel packaging and special labeling used to indicate that they are not for injection. These oral syringes are designed so they will not accept a needle. Other dosage forms, such as suppositories, powders, ointments, creams, and ophthalmic solutions, are also commonly found in single-unit packages provided by their manufacturers. However, the relatively

FIGURE 3.5 Strip packaging equipment capable of producing 50 packages per minute. Seals solid dosage units in a variety of wrapping materials and labels each package simultaneously. (Courtesy of Packaging Machinery Associates.)

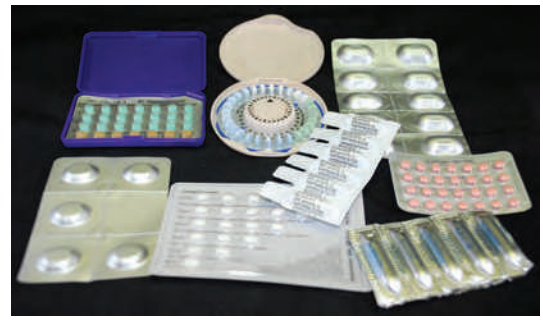


FIGURE 3.6 Commercial blister packaging of pharmaceuticals.

infrequent use of these dosage forms in a given hospital, extended care facility, or community pharmacy does not generally justify the expense of purchasing the specialized packaging machinery necessary for the small-scale repackaging of these forms.

Some pharmaceutical manufacturers use unit-of-use packaging, that is, the quantity of drug product prescribed is packaged in a container. For example, if certain antibiotic capsules are usually prescribed to be taken two times a day for 10 days, unit-of-use packaging would contain 20 capsules. Other products may be packaged to contain a month's supply.

Many pharmaceutical products require light-resistant containers. In most instances, a container made of a good quality of amber glass or a light-resistant opaque plastic will reduce light transmission sufficiently to protect a light-sensitive pharmaceutical. Agents termed ultraviolet absorbers may be added to plastic to decrease the transmission of short ultraviolet rays. The USP provides tests and standards for glass and plastic containers with respect to their ability to prevent the transmission of light (12). Containers intended to provide protection from light or those offered as light-resistant containers must meet the USP standards that define the acceptable limits of light transmission at any wavelength between 290 and 450 nm. A recent innovation in plastic packaging is the coextruded two-layer high-density polyethylene bottle, which has an inner layer of black polyethylene coextruded with an outer layer of white polyethylene. The container

provides light resistance (exceeding amber glass) and moisture protection. It is increasingly being used in the packaging of tablets and capsules.

The glass used in packaging pharmaceuticals falls into four categories, depending on the chemical constitution of the glass and its ability to resist deterioration. Table 3.3 presents the chemical makeup of the various glasses; types I, II, and III are intended for parenteral products, and type NP is intended for other products. Each type is tested according to its resistance to water attack. The degree of attack is determined by the amount of alkali released from the glass in the specified test conditions. Obviously, leaching of alkali from the glass into a pharmaceutical solution or preparation could alter the pH and, thus, the stability of the product. Pharmaceutical manufacturers must use containers that do not adversely affect the composition or stability of their products. Type I is the most resistant glass of the four categories.

Today, most pharmaceutical products are packaged in plastic. The modern compact-type container used for oral contraceptives, which contains sufficient tablets for a monthly cycle of administration and permits the scheduled removal of one tablet at a time, is a prime example of contemporary plastic packaging (Fig. 3.6). Plastic bags for intravenous fluids, plastic ointment tubes, plastic film–protected suppositories, and plastic tablet and capsule vials are other examples of plastics used in pharmaceutical packaging.

The widespread use of plastic containers arose from a number of factors, including the following:

- Its advantage over glass in lightness of weight and resistance to impact, which reduces transportation costs and losses due to container damage
- The versatility in container design and consumer acceptance
- Consumer preference for plastic squeeze bottles in administration of ophthalmics, nasal sprays, and lotions
- The popularity of blister packaging and unit-dose dispensing, particularly in health care institutions

Table 3.3 CONSTITUTION OF OFFICIAL GLASS TYPES

TYPE	GENERAL DESCRIPTION
I	Highly resistant borosilicate glass
II	Treated soda lime glass
III	Soda lime glass
NP	General purpose soda lime glass

The term *plastic* does not apply to a single type of material but rather to a vast number of materials, each developed to have desired features. For example, the addition of methyl groups to every other carbon atom in the polymer chains of polyethylene will give polypropylene, a material that can be autoclaved, whereas polyethylene cannot. If a chlorine atom is added to every other carbon in the polyethylene polymer, polyvinyl chloride (PVC) is produced. This material is rigid and has good clarity, making it particularly useful in the blister packaging of tablets and capsules. However, it has a significant drawback for packaging medical devices (e.g., syringes): it is unsuitable for *gamma* sterilization, a method that is being used increasingly. The placement of other functional groups on the main chain of polyethylene or added to other types of polymers can give a variety of alterations to the final plastic material. Among the newer plastics are polyethylene terephthalate (PET), amorphous polyethylene terephthalate glycol (APET), and polyethylene terephthalate glycol (PETG). Both APET and PETG have excellent transparency and luster and can be sterilized with *gamma* radiation (14).

Among the problems encountered in the use of plastics in packaging are (*a*) permeability of the containers to atmospheric oxygen and to moisture vapor, (*b*) leaching of the constituents of the container to the internal contents, (*c*) absorption of drugs from the contents to the container, (*d*) transmission of light through the container, and (*e*) alteration of the container upon storage. Agents frequently added to alter the properties of plastic include plasticizers, stabilizers, antioxidants, antistatic agents, antifungal agents, colorants, and others.

Permeability is considered a process of solution and diffusion, with the penetrant dissolving in the plastic on one side and diffusing through to the other side. Permeability should not be confused with porosity, in which minute holes or cracks in the plastic allow gas or moisture vapor to move through directly. The permeability of a plastic is a function of several factors, including the nature of the polymer itself; the amounts and types of plasticizers, fillers, lubricants, pigments, and other additives; pressure; and temperature. Generally, increases in temperature, pressure, and the use of additives tend to increase the permeability of the plastic. Glass containers are less permeable than plastic containers.

The movement of moisture vapor or gas, especially oxygen, through a pharmaceutical container can pose a threat to the stability of the product. In the presence of moisture, solid dosage forms may lose their color or physical integrity. A host of pharmaceutical adjuncts, especially those used in tablet formulations, as diluents, binders, and disintegrating agents, are affected by moisture. Most of these adjuncts are carbohydrates, starches, and natural or synthetic gums, and because of their hygroscopicity, they hold moisture and may even serve as nutrient media for the growth of microorganisms. Many of the tablet-disintegrating agents act by swelling, and if they are exposed to high moisture vapor during storage, they can cause tablet deterioration. Many medicinal agents, including aspirin and nitroglycerin, are adversely affected by moisture and require special protection. Sublingual nitroglycerin tablets must be dispensed in their original glass container.

Specially developed high-barrier packaging can provide added protection to pharmaceutical products against the effects of humidity. Such packaging meets the drug stability requirements adopted by the International Committee on Harmonization, which call for testing of packaged products for a minimum for 12 months at 25°C (77°F) at 60% relative humidity (15). Many capsule and other products are liable to deteriorate in humidity unless protected by high-barrier packaging. Desiccant protectants, such as silica gel in small packets, are commonly included in solid-form packaging as added protection against the effects of moisture vapor.

Drug substances that are subject to oxidative degradation may undergo a greater degree of degradation when packaged in plastic than in glass. In glass, the container's void space is confined and presents only a limited amount of oxygen to the drug contents, whereas a drug packaged in a gas-permeable plastic container may be constantly exposed to oxygen because of the replenished air supply entering through the container. Liquid pharmaceuticals packaged in permeable plastic may lose drug molecules or solvent to the container, altering the concentration of the drug in the product and affecting its potency. An example of solvent loss involves large volume parenterals that are packaged in 1-L plastic bags that are packaged with an "overwrap" that is removed to yield the container of fluid that is actually used. The inside bag may feel slightly damp due to the loss of fluid from the primary container that is entrapped between the primary container and the overwrap.

Leaching is a term used to describe the movement of components of a container into the contents. Compounds leached from plastic containers are generally the polymer additives, such as the plasticizers, stabilizers, or antioxidants. The leaching of these additives occurs predominantly when liquids or semisolids are packaged in plastic. Little leaching occurs when tablets or capsules are packaged in plastic.

Leaching may be influenced by temperature, excessive agitation of the filled container, and the solubilizing effect of liquid contents on one or more of the polymer additives. The leaching of polymer additives from plastic containers of fluids intended for intravenous administration is a special concern that requires careful selection of the plastic used. Leached material, whether dissolved in an intravenous fluid or in minute particles, poses a health hazard to the patient. Thus, studies of the leaching characteristics of each plastic considered for use are undertaken as

a part of the drug development process. Soft-walled plastic containers of PVC are used to package intravenous solutions and blood for transfusion.

Sorption, a term used to indicate the binding of molecules to polymer materials, includes both adsorption and absorption. Sorption occurs through chemical or physical means due to the chemical structure of the solute molecules and the physical and chemical properties of the polymer. Generally, the un-ionized species of a solute has a greater tendency to be bound than the ionized species. Because the degree of ionization of a solute may be affected by the pH of a solution, the pH may influence the sorption tendency of a particular solute. Furthermore, the pH of a solution may affect the chemical nature of a plastic container so as to increase or decrease the active bonding sites available to the solute molecules. Plastic materials with polar groups are particularly prone to sorption. Because sorption depends on the penetration or diffusion of a solute into the plastic, the pharmaceutical vehicle or solvent used can also play a role by altering the integrity of the plastic.

Sorption may occur with active pharmacologic agents or with pharmaceutical excipients. Thus, each ingredient must be examined in the proposed plastic packaging to determine its tendency. Sorption may be initiated by the adsorption of a solute to the inner surface of a plastic container. After saturation of the surface, the solute may diffuse into the container and be bound within the plastic. The sorption of an active pharmacologic agent from a pharmaceutical solution would reduce its effective concentration and render the product's potency unreliable. The sorption of pharmaceutical excipients such as colorants, preservatives, or stabilizers would likewise alter the quality of the product. Methylparaben may be sorbed to some types of plastics, resulting in a decrease in the available concentration of the preservative; this may be reflected in a lowering of its preservative effectiveness.

Deformations, softening, hardening, and other physical changes in plastic containers can be caused by the action of the container's contents or external factors, including changes in temperature and the physical stress placed upon the container in handling and shipping.

It is always good practice to dispense medication to patients in the same type and quality of container as that used by the manufacturer. In some instances, the original container may be used to dispense the medication.

Child-Resistant and Adult–Senior Use Packaging

The U.S. Consumer Product Safety Commission (CPSC) was created in 1972 through the Consumer Product Safety Act to protect "against unreasonable risks of injuries associated with consumer products." Today, the CPSC regulates the sale and manufacture of more than 15,000 different consumer products, including the packaging of legend and OTC medications. At present, all legend drugs intended for oral use must be dispensed by the pharmacist to the patient in a container having a child-resistant closure unless the prescriber or the patient specifically requests otherwise or unless the product is specifically exempt from the requirement.

The CPSC may propose exemption of certain drugs and drug products from the regulations based on toxicologic data or on practical considerations. For instance, certain cardiac drugs, such as sublingual tablets of nitroglycerin, are exempt from the regulations because of the importance of a patient's immediate access to the medication. Exemptions are also permitted in the case of OTC products for one package size or specially marked package to be available to consumers for whom safety closures are unnecessary or too difficult to manipulate. These consumers include childless persons, arthritic patients, and the debilitated. These packages must be labeled "This package for households without young children" or "Package not child-resistant."

A child-resistant container is defined as one that is significantly difficult for children under 5 years of age to open or to obtain a harmful amount of its contents within a reasonable time and that is not difficult for

"normal adults" to use properly (16,17). The CPSC evaluates the effectiveness of such containers using children aged 42 to 51 months. The four basic designs commonly used are align the arrows, press down and turn, squeeze and turn, and latch top. A child-resistant prescription container is shown in Figure 3.7.

In recognition that many adults, particularly the elderly and those with arthritis or weakened hand strength, have difficulty opening child-resistant packages, the regulations were amended to require that child-resistant containers be readily opened by senior adults.

Drugs that are used or dispensed in patient care institutions, including hospitals, nursing homes, and extended care facilities, need not be dispensed with safety closures unless they are intended for patients who are leaving the institution.

Compliance Packaging

Many patients are not compliant with the prescribed schedule for taking their medications. The many factors associated with noncompliance include misunderstanding the dosing schedule, confusion because the patient is taking multiple medications, forgetfulness, and a feeling of well-being leading to premature discontinuance of medication.

To assist patients in taking their medications on schedule, manufacturers and pharmacists have devised numerous educational techniques, reminder aids, compliance packages, and devices. The oral contraceptive compact was among the earliest packages developed to assist adherence to a prescribed dosing schedule. Many subsequent packaging innovations, as the methylprednisolone "dose pack," provide scheduled doses. For prescriptions dispensed in traditional containers (e.g., capsule vials), pharmacists often provide calendar medication schedules or commercial pillboxes with daily or weekly compartments. These medication compliance techniques and devices are particularly useful for patients taking multiple medications.

FIGURE 3.7 Child-resistant safety closure on a prescription container. (Courtesy of Owens-Brockway Prescription Products.)

Labeling

All drug products distributed in the United States must meet the labeling requirements in the *Code of Federal Regulations* (1,18,19). Different labeling requirements apply to investigational drugs, manufacturer's prescription drugs, controlled substances, dispensed prescription medication, OTC products, products for animals, medical devices, and other specific categories and specific products. In every instance, federal labeling requirements may be strengthened by state law.

According to federal regulations, manufacturers' drug product labeling includes not only the labels on the immediate container and packaging but also inserts; company literature; advertising and promotional material, including brochures, booklets, mailing pieces, file cards, bulletins, price lists, catalogs, sound recordings, film strips, motion picture films, slides, exhibits, displays, literature reprints, and computer-accessed information; and other materials related to the product.

Important information for a prescription-only drug is provided to health professionals through the manufacturer's product package insert. As discussed in Chapter 2, the package insert must provide full disclosure, that is, a full and balanced presentation of the drug product to enable the prescriber to use the drug with sufficient knowledge of important benefit to risk factors.

Manufacturer's Label

Included in the information usually appearing on the manufacturer's or distributor's

immediate label affixed to the container of legend drugs is the following:

1. The established or nonproprietary name of the drug or drugs and the proprietary name of the product if one is used
2. The name of the manufacturer, packer, or distributor of the product
3. A quantitative statement of the amount of each drug per unit of weight, volume, or dosage unit, whichever is most appropriate
4. The pharmaceutical type of dosage form constituting the product
5. The net amount of drug product contained in the package, in units of weight, volume, or number of dosage units, as appropriate
6. The logo "Rx only" or the federal legend "Caution—Federal law prohibits dispensing without prescription" or a similar statement
7. A label reference to refer to the accompanying package insert or other product literature for dosage and other information
8. Special storage instructions when applicable
9. The National Drug Code identification number for the product and a bar code
10. An identifying lot or control number
11. An expiration date
12. For controlled drug substances, the DEA symbol "C" together with the schedule assigned (e.g., III). The statement "Warning—May be habit forming" may also appear.

Prescription Label

When dispensing a prescription, by federal law, the pharmacist must include the following information on the label of the dispensed medication:

- The name and address of the pharmacy
- The serial number of the prescription
- The date of the prescription or the date of its filling or refilling (state law often determines which date is to be used)
- The name of the prescriber
- The name of the patient
- Directions for use, including any precautions, as indicated on the prescription

In addition, state laws may require additional information:

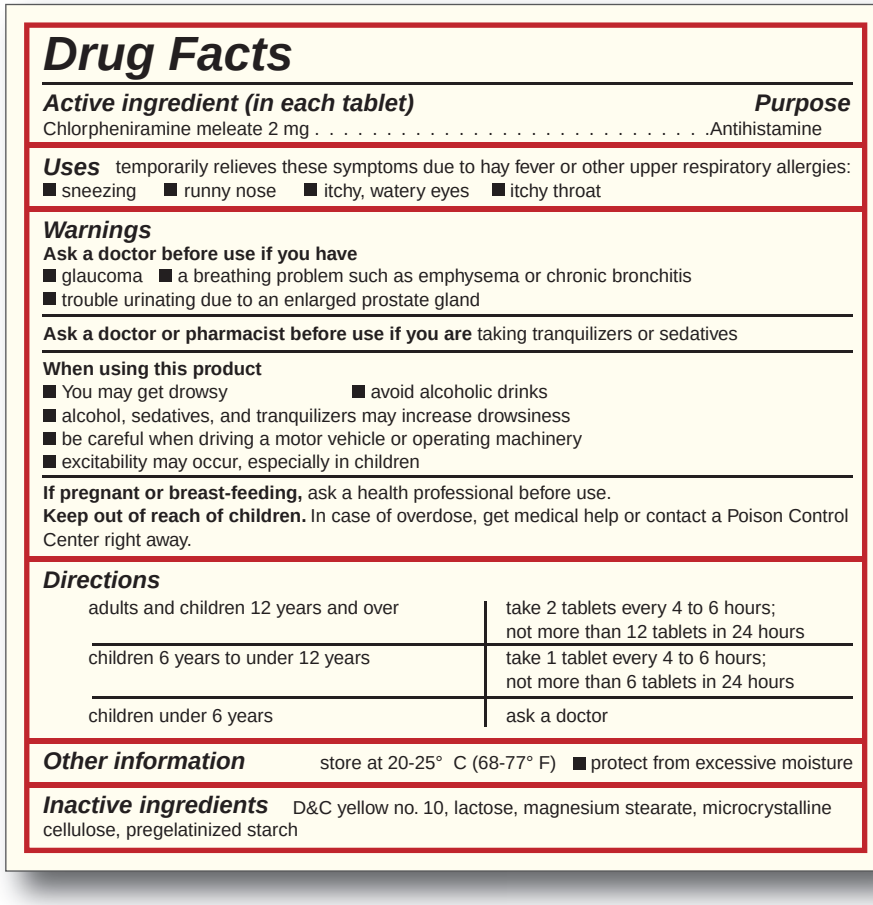
- The address of the patient
- The initials or name of the dispensing pharmacist
- The telephone number of the pharmacy
- The drug name, strength, and manufacturer's lot or control number
- The expiration date of the drug
- The name of the manufacturer or distributor
- In an effort to decrease medication errors, there is thought to include the "indication" on the prescription label to help the pharmacist assure the prescribed drug is appropriate.

Over-the-Counter Labeling

The FDA now requires a standardized format for the manufactures' labeling of more than 100,000 OTC products (20,21). In addition to the name of the product, the name and address of the manufacturer or distributor, the quantity of net contents, the bar code and other product-identifying items, the expiration date, and the other drug-specific required information, the following "drug facts" (Fig. 3.8) must appear in this listed order (21):

- The product's active ingredients, including the amount in each dosage unit
- The purpose of the product
- The uses (indications) for the product
- Specific warnings, including when the product should not be used under any circumstances and when it is appropriate to consult with a doctor or pharmacist. This section also describes side effects that could occur and substances or activities to avoid.
- Dosage instructions—when, how, and how often to take the product
- The product's inactive ingredients and important information to help consumers avoid ingredients that may cause an allergic reaction

The format and design of the label are intended to be easily read and understood, particularly by seniors who purchase over 30%



Drug Facts

Active ingredient (in each tablet) — **Purpose**
Chlorpheniramine meleate 2 mg . . . . . .Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings
Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland

Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives

When using this product
■ You may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Other information store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

FIGURE 3.8 Example drug facts label.

of the OTC pharmaceutical products sold in the United States.

Dietary Supplement Labeling

Dietary supplements are defined, in part, as products intended to supplement the diet that bear or contain one or more of the following dietary ingredients (22):

- A vitamin
- A mineral
- An herb or other botanical
- An amino acid
- A dietary substance for use by man to supplement the diet by increasing the total dietary intake
- A concentrate, metabolite, constituent, extract, or a combination of any ingredient mentioned above

The manufacturers of dietary supplements must follow the FDA's cGMP guidelines for dietary supplements, including labeling requirements (22). Labels must include, on the principal display panel or on the "supplement facts" panel (Fig. 3.9), a statement of identity (name of the dietary supplement), the net quantity of contents statement (amount of the dietary supplement), the nutrition values, the ingredient list, and the name and place of business of the manufacturer, packer, or distributor.

Under the Dietary Supplement Health Education Act (1994), supplement manufacturers are permitted to make certain label claims. However, the claims must be accurate and truthful. This act disallows "disease claims" that infer or imply that the product can be used to prevent, treat, cure, mitigate,

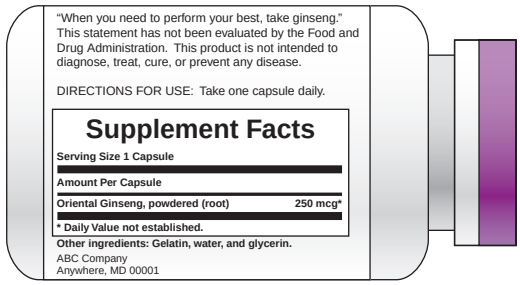


FIGURE 3.9 Example dietary supplement label.

or diagnose a disease. Thus, "structure/function" claims are allowed on the label. An example would be a claim that a product helps "improve mood" rather than treat depression. Statements can also be made relative to classical dietary nutrient deficiency disease and state of the prevalence of the disease in the United States.

In those instances when a manufacturer makes a permissible claim, the label must also bear the disclaimer, "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease." For herbal products, the label must also state the part of the plant used to make the product, for example, root, stem, or leaf. A standardized format provides the patient with certain minimum information about the product prior to its use. See Figure 3.9 for an example.

In 2009, the U.S. Pharmacopeial Convention initiated publication of the USP Dietary Supplements Compendium (DSC), a collection of standards designed to assist dietary supplement manufacturers in providing quality products to consumers. The DSC contains quality specifications for the identity, strength, purity, and performance characteristics (e.g., dissolution, disintegration) of dietary supplements included in the monographs. It also includes general and regulatory information and guidance to help manufacturers comply with FDA's cGMPs. Since its first publication, the DSC has been expanded and continually updated (23).

The USP also offers *verification services* for dietary supplement finished products and the ingredients used to make them. Products and ingredients that meet all USP verification requirements—including a GMP audit, product and ingredient testing, and manufacturing documentation review—are awarded use of a distinctive "USP Verified Mark" or logo, which may be displayed on product labeling. Participation is voluntary.

Storage

To ensure the stability of a pharmaceutical preparation for the period of its intended shelf life, the product must be stored in proper conditions. The labeling of each product includes the desired conditions of storage. The terms generally employed in such labeling have meanings defined by the USP (12):

> Cold: Any temperature not exceeding 8°C (46°F). A refrigerator is a cold place in which the temperature is maintained thermostatically between 2°C and 8°C (36°F and 46°F). A freezer is a cold place in which the temperature is maintained thermostatically between – 25°C and – 10°C (– 13°F and 14°F).
>
> Cool: Any temperature between 8°C and 15°C (46°F and 59°F). An article for which storage in a cool place is directed may alternatively be stored in a refrigerator unless otherwise specified in the individual monograph.
>
> Room temperature: The temperature prevailing in a working area. A controlled room temperature encompasses the usual working environment of 20°C to 25°C (68°F to 77°F) but also allows for temperature variations between 15°C and 30°C (59°F and 86°F) that may be found in pharmacies, hospitals, and drug warehouses.
>
> Warm: Any temperature between 30°C and 40°C (86°F and 104°F).
>
> Excessive heat: Above 40°C (104°F).
>
> Protection from freezing: Where in addition to the risk of breakage of the container, freezing subjects a product to loss of strength or potency or to destructive alteration of the dosage form, the container label bears an appropriate instruction to protect the product from freezing.

Transportation

The stability protection of a pharmaceutical product during transportation is an important consideration. Temperature and humidity variations may occur during shipment from a manufacturer to a wholesaler or to a pharmacy and from a pharmacy to a patient, during mail order shipment of prescriptions and their time in the mailbox, and in emergency care vehicles. Transportation to and within geographic areas of extreme temperatures and humidity requires special consideration.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Make a listing of issues that prevent pharmacies from compounding more than they do currently.
2. Compare and contrast pharmaceutical manufacturing and extemporaneous compounding. Give examples of each.
3. Develop a chart summarizing the eight recommendations of "The Good Compounding Practices Applicable to State-Licensed Pharmacies."
4. Provide examples of drugs that have been demonstrated to interact with their container and describe the type of interaction.
5. Compare and contrast a label from a prescription drug product with that of a nonprescription product label and a dietary supplement label.

Individual Activities

1. Given a specific dosage form, determine why the container used to hold the drug is important.
2. What are the problems encountered in the use of plastics in packaging drugs?
3. Given an OTC drug, identify and list all FDA-required labeling information.
4. Create a product prescription label. Include all information required by federal law and respective state laws.

REFERENCES

1. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm
2. A Strategic View of Information Technology in the Pharmaceutical Industry. Philadelphia, PA: Deloitte & Touche, 1994. Available at: http://www.pharmait.co.uk/. (Accessed August 14, 2009)
3. Laboratory Robotics Handbook. Hopkinton, MA: Zymark, 1988. Available at: http://www.labautopedia.com/mw/index.php/The_Zymark_Story. (Accessed August 14, 2009)
4. Guide to Inspection of Bulk Pharmaceutical Chemicals. Rockville, MD: Food and Drug Administration, 1991.
5. Moore RE. FDA's guideline for bulk pharmaceutical chemicals: A consultant's interpretation. Pharm Technol 1992;16:88–100.
6. Guidance for Industry: Nonclinical Studies for the safety Evaluation of Pharmaceutical Excipients. Rockville, MD: Food and Drug Administration, 2005. Available at: http://www.scribd.com/doc/80945199/FDA-Guidance-on-Excipients. (Accessed September 25, 2012)
7. Mercill A. A good manufacturing practices guide for bulk pharmaceutical excipients. Pharm Technol 1995;19:34–40.
8. Bernstein DF. Investigational clinical trial material supply operations in new product development. Appl Clin Trials 1993;2:59–69.
9. Compliance Policy Guidance for FDA Staff and Industry: Pharmacy Compounding. Rockville, MD: Food and Drug Administration, 2002.
10. United States Pharmacopeial Convention, Inc. USP 35/NF 30. Rockville, MD: US Pharmacopeial Convention, Inc.; 2012, 344–386.
11. Model State Pharmacy Act and Model Rules of the National Association of Boards of Pharmacy. Mount Prospect, IL: National Association of Boards of Pharmacy, 2008.
12. United States Pharmacopeia 32–National Formulary 27. Rockville, MD: United States Pharmacopeial Convention, 2009.
13. Guideline for Submitting Documentation for Packaging Drug Products. Rockville MD: Food and Drug Administration, 1999. (Accessed August 14, 2009)
14. Hacker D. Extruder sees future of medical market: Rigid PET. Pharm Med Pack News 1994;2:22.
15. Wagner J. Pending ICH guidelines and sophisticated drugs add up to the need for higher moisture protection. Pharm Med Pack News 1996;4:20–24.
16. 60 Federal Register 38671–38674.
17. 60 Federal Register 37709–37744.
18. Code of Federal Regulations, Title 21, Parts 111, 201, 210–211. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm
19. Code of Federal Regulations, Title 21, Part 1302. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm
20. Code of Federal Regulations, Title 21, Section 201, 2012. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR = 201.66. (Accessed September 25, 2012)
21. OTC Facts Label. Rockville, MD: Food and Drug Administration, 2002. Available at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143551.htm. (Accessed September 25, 2012)
22. General Dietary Supplement Labeling. Rockville, MD: Food and Drug Administration, 2005.

Available at: http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/DietarySupplements/DietarySupplementlabelingguide/ucm070519.htm. (Accessed September 26, 2012)

23. USP Dietary Supplements Compendium. Rockville, MD: The United States Pharmacopeial Convention, 2012. Available at: http://www.usp.org/store/products-services/dietary-supplements-compendium. (Accessed September 26, 2012)

SECTION II

DRUG DOSAGE FORM AND DRUG DELIVERY SYSTEM DESIGN

4 Dosage Form Design: Pharmaceutical and Formulation Considerations

OBJECTIVES

After reading this chapter, the student will be able to:

1. List reasons for the incorporation of drugs into various dosage forms
2. Compare and contrast the advantages/disadvantages of various drug dosage forms
3. Describe the information needed in preformulation studies to characterize a drug substance for possible inclusion into a dosage form
4. Describe the mechanisms of drug degradation and provide examples of each
5. Describe the five types of drug instability of concern to the practicing pharmacist
6. Describe the purpose and general protocol for accelerated stability studies
7. Summarize approaches employed to stabilize drugs in pharmaceutical dosage forms
8. Calculate rate reactions for various liquid dosage forms
9. Categorize various pharmaceutical ingredients and excipients

Drug substances are seldom administered alone; rather they are given as part of a formulation in combination with one or more nonmedicinal agents that serve varied and specialized pharmaceutical functions. Selective use of these nonmedicinal agents, referred to as pharmaceutical ingredients or excipients, produces dosage forms of various types. The pharmaceutical ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing and compounding pharmacist with the challenges of formulation and the physician with the choice of drug and delivery system to prescribe. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed pharmaceutics.

The proper design and formulation of a dosage form require consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe. The product should be manufactured with appropriate measures

of quality control and packaged in containers that keep the product stable. The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.

Methods for the preparation of specific types of dosage forms and drug delivery systems are described in subsequent chapters. This chapter presents some general considerations regarding physical pharmacy, drug product formulation, and pharmaceutical ingredients.

THE NEED FOR DOSAGE FORMS

The potent nature and low dosage of most of the drugs in use today preclude any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. Most drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive prescription or electronic analytical balance. For instance, how could the lay person accurately obtain from a bulk supply the 325 mg of aspirin found in the common tablet? Not possible. Yet compared with many other drugs, the dose of aspirin is formidable (Table 4.1). For example, the dose of ethinyl estradiol, 0.05 mg, is 1/6,500 the amount of aspirin in an aspirin tablet. To put it another way, 6,500 ethinyl estradiol tablets, each containing 0.05 mg of drug, could be made from an amount of ethinyl estradiol equal to the amount of aspirin in just one standard tablet. When the dose of the drug is minute, as with ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with fillers or diluents so that the dosage unit is large enough to pick up with the fingertips. Table 4.1 presents some examples of drugs with low dosage that are formulated and manufactured into capsules and tablets for oral administration.

Besides providing the mechanism for the safe and convenient delivery of accurate dosage, dosage forms are needed for additional reasons:

- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampuls)
- To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric-coated tablets)
- To conceal the bitter, salty, or offensive taste or odor of a drug substance (capsules, coated tablets, flavored syrups)
- To provide liquid preparations of drug substances, either as dispersions (suspensions) or as clear preparations (solutions)
- To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions)
- To provide optimal drug action from topical administration sites (ointments, creams, transdermal patches, and ophthalmic, ear, and nasal preparations)
- To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories)

Table 4.1 EXAMPLES OF LOW-DOSAGE DRUGS MANUFACTURED INTO CAPSULE OR TABLET DOSAGE FORMS[a]

DRUG CONTENT PER CAPSULE OR TABLET	INDICATION OR CATEGORY
Donepezil hydrochloride 5 mg	Dementia
Lisinopril 5 mg	Antihypertensive
Trandolapril 2 mg	Antihypertensive
Rivastigmine tartrate 1.5 mg	Dementia
Colchicine 0.6 mg	Gout
Rasagiline mesylate 0.5 mg	Parkinson disease
Nitroglycerine 0.3 mg	Angina pectoris
Everolimus 0.25 mg	Organ rejection (transplant)
Digoxin 0.125 mg (125 µg)	Heart failure; atrial fibrillation
Fentanyl 0.100 mg (100 µg)	Pain (severe)
Levothyroxine sodium 0.025 mg (25 µg)	Hypothyroidism
Lubiprostone 0.008 mg (8 µg)	Irritable bowel syndrome
Paricalcitol 0.002 mg (2 µg)	Hyperparathyroidism

[a]Examples are of the lowest strength capsule or tablet commercially available for each listed drug.

- To provide for placement of drugs directly in the bloodstream or body tissues (injections)
- To provide for optimal drug action through inhalation therapy (inhalants and inhalation aerosols)

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Before formulating a drug substance into a dosage form, the desired product type must be determined insofar as possible to establish the framework for product development. Then, various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness) and for pilot plant studies and production scale-up. The formulation that best meets the goals for the product is selected to be its *master formula*. Each batch of product subsequently prepared must meet the specifications established in the master formula.

There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease. Most commonly, a manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease (Fig. 4.1). Before a medicinal agent is formulated into one or more dosage forms, among the factors considered are the physical and chemical properties of the drug substance (discussed later in this chapter) and various therapeutic considerations.

If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are usually prepared because they are easily handled by the patient and are most convenient in the self-administration of medication. If a drug substance has application in an emergency in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared. Many other examples of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and vomiting, for which tablets and skin patches are used for prevention and suppositories and injections for treatment.

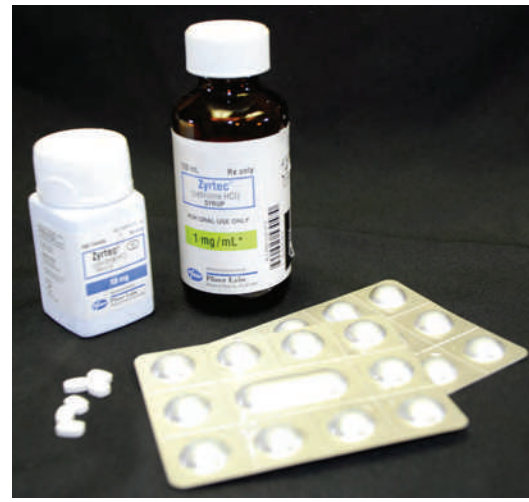


FIGURE 4.1 Various forms of a drug substance marketed by a pharmaceutical company to meet the special requirements of the patient.

The age of the intended patient also plays a role in dosage form design. For infants and children younger than 5 years of age, pharmaceutical liquids rather than solid forms are preferred for oral administration. These liquids, which are flavored aqueous solutions, syrups, or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser (Fig. 4.2) or incorporated into the child's food. The palatability of some commercial products may not be acceptable to some patients so different flavoring additives may be indicated to enhance compliance; an example would be the FLAVORx flavoring system. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When a young patient has a productive cough or is vomiting, gagging, or simply rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instances, injections may be required. Infant-size rectal suppositories may also be employed, although drug absorption from the rectum is often erratic.

FIGURE 4.2 Oral dosage devices to assist in measuring doses for children.

During childhood and even adulthood, a person may have difficulty in swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant-tasting creamy material. Newly available tablets dissolve in the mouth in about 10 to 15 seconds; this allows the patient to take a tablet but actually swallow a liquid. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water. Also, a teaspoonful of gelatin dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them. Also, if a person has difficulty in swallowing a capsule, the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask the taste of the medication and swallowed. There is also a device called the Pill Glide that can be used to help swallow solid dosage forms. Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. In many patient-care facilities, as nursing homes, tablet-crushing devices are utilized by the nursing staff preparatory to mixing with food (as applesauce) for administration. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance.

Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is proper identification of the medications. Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight. Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

In dealing with the problem of formulating a drug substance into a proper dosage form, research pharmacists employ knowledge gained through experience with other chemically similar drugs and through the proper use of the physical, chemical, biologic, and pharmaceutical sciences. The early stages of any new formulation include studies to collect basic information on the physical and chemical characteristics of the drug substance. These basic studies are the *preformulation* work needed before actual product formulation begins.

Preformulation Studies

Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized. The following *preformulation studies* (1) and others provide the type of information needed to define the nature of the drug substance. This information provides the framework for the drug's combination with pharmaceutical

ingredients in the fabrication of a dosage form.

Physical Description

It is important to understand the physical description of a drug substance prior to dosage form development. Most drug substances in use today are solid materials, pure chemical compounds of either crystalline or amorphous constitution. The purity of the chemical substance is essential for its identification and for evaluation of its chemical, physical, and biologic properties. Chemical properties include structure, form, and reactivity. Physical properties include such characteristics as its physical description, particle size, crystalline structure, melting point, and solubility. Biologic properties relate to its ability to get to a site of action and elicit a biologic response.

Drugs can be used therapeutically as solids, liquids, and gases. Liquid drugs are used to a much lesser extent than solid drugs, gases even less frequently.

Liquid drugs pose an interesting problem in the design of dosage forms and delivery systems. Many liquids are volatile and must be physically sealed from the atmosphere to prevent evaporation loss. Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is kept for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilation. Propylhexedrine is another volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for its vasoconstrictor action. A cylindrical roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, usually plastic, sealed nasal inhaler. The inhaler's cap must be securely tightened each time it is used. Even then, the inhaler maintains its effectiveness for only a limited time because of the volatility of the drug.

Another problem associated with liquid drugs is that those intended for oral administration cannot generally be formulated into tablet form, the most popular form of oral medication, without chemical modification. An exception to this is the liquid drug nitroglycerin, which is formulated into sublingual tablets that disintegrate within seconds after placement under the tongue. However, because the drug is volatile, it has a tendency to escape from the tablets during storage, and it is critical that the tablets be stored in a tightly sealed glass container. For the most part, when a liquid drug is to be administered orally and a solid dosage form is desired, one of two approaches is used. First, the liquid substance may be sealed in a soft gelatin capsule. Vitamins A, D, and E, and ergoloid mesylates are liquids commercially available in capsule form. Second, the liquid drug may be developed into a solid ester or salt form that will be suitable for tablets or drug capsules. For instance, scopolamine hydrobromide is a solid salt of the liquid drug scopolamine and is easily pressed into tablets. Another approach to formulate liquids into solids is by mixing the drug with a solid or melted semisolid material, such as a high molecular weight polyethylene glycol. The melted mixture is poured into hard gelatin capsules to harden, and the capsules are sealed.

For certain liquid drugs, especially those taken orally in large doses or applied topically, their liquid nature may have some advantage in therapy. For example, 15-mL doses of mineral oil may be administered conveniently as such. Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin. However, for the most part, pharmacists prefer solid materials in formulation work because they can easily form them into tablets and capsules.

Formulation and stability difficulties arise less frequently with solid dosage forms than with liquid preparations, and for this reason, many new drugs first reach the market as tablets or dry-filled capsules. Later, when the pharmaceutical problems are resolved, a

liquid form of the same drug may be marketed. This procedure is doubly advantageous, because for the most part, physicians and patients alike prefer small, generally tasteless, accurately dosed tablets or capsules to the analogous liquid forms. Therefore, marketing a drug in solid form first is more practical for the manufacturer and suits most patients. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

Microscopic Examination

Microscopic examination of the raw drug substance is an important step in preformulation work. It gives an indication of particle size and size range of the raw material along with the crystal structure. Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information in case of problems in formulation processing attributable to changes in particle or crystal characteristics of the drug. During some processing procedures, the solid drug powders must flow freely and not become entangled. Spherical and oval powders flow more easily than needle-shaped powders and make processing easier.

Heat of Vaporization

The use of vapor pressure is important in the operation of implantable pumps delivering medications as well as in aerosol dosage forms. Another application is the use of nasal inhalants (propylhexedrine with menthol and lavender oil—Benzedrex) for treating nasal congestion. In this latter dosage form, the quantity of drug required for effectiveness and a reasonable estimate of time of usefulness can be determined. Also, in the case of spills in inaccessible places, the time to evaporation of a substance can also be calculated. Some volatile drugs can even migrate within a tablet dosage form so the distribution may not be uniform any longer. This may have an impact in tablets that are scored for dosing where the drug in one portion may be higher or lower than in the other portion.

Exposure of personnel to hazardous drugs due to handling, spilling, or aerosolizing of drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment. Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil, as illustrated in Physical Pharmacy Capsule 4.1, Heat of Vaporization.

PHYSICAL PHARMACY CAPSULE **4.1**

Heat of Vaporization

The amount of heat absorbed when 1 g of a liquid vaporizes is known as the heat of vaporization of that liquid and is measured in calories. The heat of vaporization of water at 100°C is 540 cal/g or about 9.720 cal/mole. This is the same quantity of heat energy that is released when 1 g of steam condenses to water at 100°C. This energy exchange is important in processes like steam sterilization as it is this energy transfer that results in death of microorganisms.

The movement of molecules varies with temperature. In liquids, this results in a tendency of the molecules to escape the liquid environment into a gaseous environment and possibly loss of the liquid. In the case of solids that sublime, the movement of the molecules is from the solid state to the vapor state. As an example, if one looks at an older bottle containing aspirin, there may be crystals of aspirin on the inside walls of the container. With ibuprofen, the walls of the container may become cloudy as the ibuprofen sublimes.

PHYSICAL PHARMACY CAPSULE 4.1 CONT.

The use of vapor pressure is important in the operation of implantable pumps delivering medications as well as in aerosol dosage forms. Exposure of personnel to hazardous drugs due to handling, spilling, or aerosolizing of drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment. Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil, as illustrated in the table below. Particle size affects vapor pressure; the smaller the particle size, the greater the vapor pressure. This demonstrates the importance of personnel protection with working with micronized hazardous powders. The time to evaporation of a substance can also be calculated.

The variation of vapor pressure with temperature is described by the form of the Clausius-Clapeyron equation, as follows:

$$\frac{d \ln P}{dT} = \frac{\Delta H_{vap}}{RT^2}$$

assuming that δH_{vap} is constant, integration of the equation gives:

$$\log P = \frac{-\Delta H_{vap}}{2.303\ RT} + \text{constant}$$

A plot of the log of the vapor pressure versus 1/T should be linear and the slope will be equal $-\Delta H_{vap}/2.303R$ from which the enthalpy of vaporization can be calculated. With data obtained from Kiffmeyer et al. (2002), the following table can be constructed:

	MEASURED VAPOR PRESSURE (PA)	
COMPOUND	**20°C**	**40°C**
Carmustine	0.019	0.530
Cisplatin	0.0018	0.0031
Cyclophosphamide	0.0033	0.0090
Etoposide	0.0026	0.0038
Fluorouracil	0.0014	0.0039

Source: Kiffmeyer TK, Kube C, Opiolka S, et al. Vapour pressures, evaporation behaviour and airborne concentrations of hazardous drugs: implications for occupational safety. Pharm J. 2002;68:331–337.

Melting Point Depression

A characteristic of a pure substance is a defined melting point or melting range. If not pure, the substance will exhibit a change in melting point. This phenomenon is commonly used to determine the purity of a drug substance and in some cases, the compatibility of various substances before inclusion in the same dosage form. This characteristic is further described in Physical Pharmacy Capsule 4.2, Melting Point Depression.

The Phase Rule

Phase diagrams are often constructed to provide a visual picture of the existence and extent of the presence of solid and liquid phases in binary, ternary, and other mixtures. Phase diagrams are normally two-component (binary) representations, as shown in Physical Pharmacy Capsule 4.3, The Phase Rule, but can also be three-component representations, as shown in Physical Pharmacy Capsule 4.4, Triangular Phase Diagram.

PHYSICAL PHARMACY CAPSULE 4.2

Melting Point Depression

The *melting point*, or *freezing point*, of a pure crystalline solid is defined as the temperature at which the pure liquid and solid exist in equilibrium. Drugs with a low melting point may soften during a processing step in which heat is generated, such as particle size reduction, compression, sintering, and so on. Also, the melting point or range of a drug can be used as an indicator of purity of chemical substances (a pure substance is ordinarily characterized by a very sharp melting peak). An altered peak or a peak at a different temperature may indicate an adulterated or impure drug. This is explained as follows.

The *latent heat of fusion* is the quantity of heat absorbed when 1 g of a solid melts; the molar heat of fusion (ΔH_f) is the quantity of heat absorbed when 1 mole of a solid melts. High–melting-point substances have high heat of fusion, and low–melting-point substances have low heat of fusion. These characteristics are related to the types of bonding in the specific substance. For example, ionic materials have high heats of fusion (NaCl melts at 801°C with a heat of fusion of 124 cal/g), and those with weaker van der Waals forces have low heats of fusion (paraffin melts at 52°C with a heat of fusion of 35.1 cal/g). Ice, with weaker hydrogen bonding, has a melting point of 0°C and a heat of fusion of 80 cal/g.

The addition of a second component to a pure compound (A), resulting in a mixture, will result in a melting point that is lower than that of the pure compound. The degree to which the melting point is lowered is proportional to the mole fraction (N_A) of the second component that is added. This can be expressed thus:

$$\Delta T = \frac{2.303\ RTT_0}{\Delta H_f} \log N_A$$

where

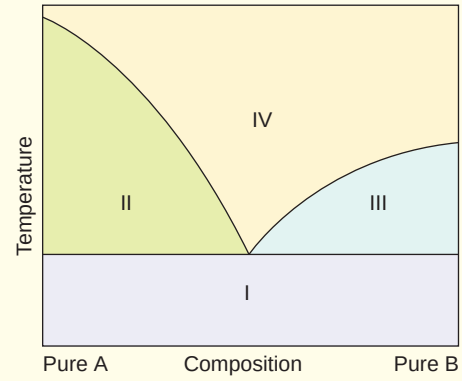
ΔH_f is the molar heat of fusion,
T is the absolute equilibrium temperature,
T_0 is the melting point of pure A, and
R is the gas constant.

Two noteworthy things contribute to the extent of lowering of the melting point:

1. Evident from this relationship is the inverse proportion between the melting point and the heat of fusion. When a second ingredient is added to a compound with a low molar heat of fusion, a large lowering of the melting point is observed; substances with a high molar heat of fusion will show little change in melting point with the addition of a second component.
2. The extent of lowering of the melting point is also related to the melting point itself. Compounds with low melting points are affected to a greater extent than compounds with high melting points upon the addition of a second component (i.e., low–melting-point compounds will result in a greater lowering of the melting point than those with high melting points).

PHYSICAL PHARMACY CAPSULE 4.3

The Phase Rule



A phase diagram, or temperature–composition diagram, represents the melting point as a function of composition of two or three component systems. The figure is an example of such a representation for a two-component mixture.

This phase diagram depicts a two-component mixture in which the components are completely miscible in the molten state and no solid solution or addition compound is formed in the solid state. As is evident, starting from the extremes of either pure component A or pure component B, as the second component is added, the melting point of the pure component decreases. There is a point on this phase diagram at which a minimum melting point occurs (i.e., the eutectic point). As is evident, four regions, or phases, in this diagram, represent the following:

I. Solid A + solid B
II. Solid A + melt
III. Solid B + melt
IV. Melt

Each phase is a homogenous part of the system, physically separated by distinct boundaries.

A description of the conditions under which these phases can exist is called the *Phase Rule*, which can be presented thus:

$$F = C - P + X$$

where

F is the number of degrees of freedom,
C is the number of components,
P is the number of phases, and
X is a variable dependent upon selected considerations of the phase diagram (1, 2, or 3).

C describes the minimum number of chemical components to be specified to define the phases. F is the number of independent variables that must be specified to define the complete system (e.g., temperature, pressure, concentration).

EXAMPLE 1

In a mixture of menthol and thymol, a phase diagram similar to that illustrated can be obtained. To describe the number of degrees of freedom in the part of the graph moving from the curved line starting at pure A, progressing downward to the eutectic point, and then following an increasing melting point to pure B, it is evident from this presentation that either temperature or composition will describe this system since it is assumed in this instance that pressure is constant. Therefore, the number of degrees of freedom to describe this portion of the phase diagram is given thus:

$$F = 2 - 2 + 1 = 1$$

In other words, along this line either temperature or composition will describe the system.

EXAMPLE 2

When in the area of a single phase of the diagram, such as the melt (IV), the system can be described thus:

PHYSICAL PHARMACY CAPSULE 4.3 CONT.

$$F = 2 - 1 + 1 = 2$$

In this portion of the phase diagram, two factors, temperature and composition, can be varied without a change in the number of phases in the system.

EXAMPLE 3

At the eutectic point,

$$F = 2 - 3 + 1 = 0$$

and any change in the concentration or temperature may cause disappearance of one of the two solid phases or the liquid phase.

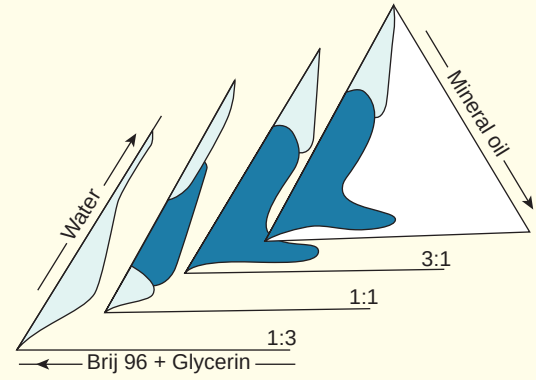
Phase diagrams are valuable for interpreting interactions between two or more components, relating not only to melting point depression and possible liquefaction at room temperature but also to the formation of solid solutions, coprecipitates, and other solid-state interactions.

PHYSICAL PHARMACY CAPSULE **4.4**

Triangular (Three-Component) Phase Diagram

A three-component phase diagram has four degrees of freedom: F = 3 – 1 + 2 = 4. In this case, temperature and pressure are two of the conditions and the concentrations of two of the three components make up the rest. Only two concentrations are required because the third will be the difference between 100% and the sum of the other two components.

These systems are used for determining miscibility/solubility, coacervation regions, gel-forming regions for multicomponent mixtures, etc. To read a three-phase diagram, each of the three corners of the triangle represent 100% by weight of one of the components (A, B, C) and 0% by weight of the other two (A, B, C). The lines joining the corner points forming the triangle each represent two component mixtures of the three possible combinations (AB, BC, and CA). If two of the components are known, the third is known by difference. Any combination of the three components is described by a single point on the diagram. Combining different proportions of the three components and observing for an end point (solubility, gel formation, haziness, etc.), the phase differences can be visualized, as follows.



The following is a stack of four separate pseudoternary phase diagrams for a quaternary system composed of Brij 96, glycerin, mineral oil, and water. The Brij 96:glycerin ratio is noted on the diagram and is considered one of the three components. The shaded regions represent gel systems while the clear regions represent fluid systems.

In addition to observing the phase changes in a single plane, the use of stacked ternary phase diagrams enables one to visualize the change using different ratios of one of the components (in this case, the Brij 96:glycerin ratios). Constructions like this enable a pharmaceutical scientist to select the best ratios and combinations of components for a formulation.

Particle Size

Certain physical and chemical properties of drug substances, including dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability, are affected by the particle size distribution. In addition, flow characteristics and sedimentation rates, among other properties, are important factors related to particle size. It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and efficacy. Of special interest is the effect of particle size on absorption. Particle size significantly influences the oral absorption profiles of certain drugs, including griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin. Also, satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation. Particle size is discussed further in Chapter 6. Figure 4.3 shows a particle size analyzer.

Polymorphism

An important factor on formulation is the crystal or amorphous form of the drug substance. Polymorphic forms usually exhibit different physicochemical properties, including melting point and solubility. Polymorphic forms in drugs are relatively common. It has been estimated that at least one third of all organic compounds exhibit polymorphism.

FIGURE 4.3 Mastersizer 2000E particle size analyzer. (Courtesy of Malvern Instruments Ltd.)

In addition to polymorphic forms, compounds may occur in noncrystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than is required to escape from an amorphous powder. Therefore, the amorphous form of a compound is always more soluble than a corresponding crystal form.

Evaluation of crystal structure, polymorphism, and solvate form is an important preformulation activity. The changes in crystal characteristics can influence bioavailability and chemical and physical stability and can have important implications in dosage form process functions. For example, it can be a significant factor relating to tablet formation because of flow and compaction behaviors, among others. Various techniques are used to determine crystal properties. The most widely used methods are hot stage microscopy, thermal analysis, infrared spectroscopy, and x-ray diffraction.

Solubility

An important physicochemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation and exert a therapeutic effect, it must first be in solution. Relatively insoluble compounds often exhibit incomplete or erratic absorption. If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility. The methods to accomplish this depend on the chemical nature of the drug and the type of drug product under consideration. Chemical modification of the drug into salt or ester forms is frequently used to increase solubility.

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Chemical analysis of the drug content in solution is performed to determine degree of solubility.

PHYSICAL PHARMACY CAPSULE 4.5

Solubility and Particle Size

The particle size and surface area of a drug exposed to a medium can affect actual solubility within reason, for example, in the following relationship:

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303\ RTr}$$

where

S is the solubility of the small particles,
S_0 is the solubility of the large particles,
γ is the surface tension,
V is the molar volume,
R is the gas constant,
T is the absolute temperature, and
r is the radius of the small particles.

The equation can be used to estimate the decrease in particle size required to increase solubility. For example, a desired increase in solubility of 5% would require an increase in the S/S_0 ratio to 1.05; that is, the left term in the equation would become log 1.05. If a powder has a surface tension of 125 dynes/cm, molar volume of 45 cm^3, and temperature of 27°C, what is the particle size required to obtain the 5% increase in solubility?

$$\log 1.05 = \frac{(2)\ (125)\ (45)}{(2.303)\ \left(8.314 \times 10^{7}\right)(300)r}$$

$$r = 9.238 \times 10^{-6}\ \text{cm or } 0.0238\ \mu$$

A number of factors are involved in actual solubility enhancement, and this is only an introduction to the general effects of particle size reduction.

Solubility and Particle Size

Although solubility is normally considered a physicochemical constant, small increases in solubility can be accomplished by particle size reduction as described in the Physical Pharmacy Capsule 4.5, Solubility and Particle Size.

Solubility and pH

Another technique, if the drug is to be formulated into a liquid product, is adjustment of the pH of the solvent to enhance solubility. However, for many drug substances, pH adjustment is not an effective means of improving solubility. Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients. Adjustment of pH usually has little effect on the solubility of substances other than electrolytes. In many cases, it is desirable to use cosolvents or other techniques such as complexation, micronization, or solid dispersion to improve aqueous solubility. A review of pH is provided in Physical Pharmacy Capsule 4.6, Principles of pH. The effect of pH on solubility is illustrated in Physical Pharmacy Capsule 4.7, Solubility and pH.

PHYSICAL PHARMACY CAPSULE 4.6

Principles of pH

pH is a critical variable in pharmaceutics, and a basic understanding of its principles and measurement is important. Let's begin with a definition of the term pH. The p comes from the word power. The H, of course, is the symbol for hydrogen. Together, the term pH means the hydrogen ion exponent.

The pH of a substance is a measure of its acidity, just as a degree is a measure of temperature. A specific pH value tells the exact acidity. Rather than stating general ideas, such as cherry syrup is acidic or the water is hot, a specific pH value gives the same relative point of reference, thus providing more exact communication. "The cherry juice has a pH of 3.5" or "the water is at 80°C" provides an exact common language.

pH is defined in terms of the hydrogen ion activity:

$$pH = -\log_{10} a_{H+} \text{ or } 10^{-pH} = a_{H+}$$

pH equals the negative logarithm of the hydrogen ion activity or the activity of the hydrogen ion is 10 raised to the exponent – pH. The latter expression renders the use of the p exponent more obvious. The activity is the effective concentration of the hydrogen ion in solution. The difference between effective and actual concentration decreases as one moves toward more dilute solutions, in which ionic interaction becomes progressively less important.

Normally, reference is made to the hydrogen ion when reference should be made to the hydronium ion (H_3O^+). It is a matter of convenience and brevity that only the hydrogen ion is mentioned, even though it is normally in its solvated form:

$$H^+ + H_2O = H_3O^+$$

The complexing of the hydrogen ion by water affects activity and applies to other ions, which partially complex or establish an equilibrium with the hydrogen ion. In other words, equilibrium such as

$$H_2CO_3 = H^+ + HCO_3^-$$
$$HC_2H_3O_2 = H^+ + C_2H_3O_2^-$$

complexes the hydrogen ion so that it is not sensed by the pH measuring system. This is why an acid–base titration is performed if the total concentration of acid (H^+) is needed. These effects on hydrogen ion activity are obvious, but other more subtle effects are involved in the correlation of activity and concentration.

The activity of the hydrogen ion can be defined by its relation to concentration (C_{H^+}, molality) and the activity coefficient f_{H^+}:

$$aH^+ = f_H + C_{H+}$$

If the activity coefficient is unity, activity is equal to concentration. This is nearly the case in dilute solutions, whose ionic strength is low. Since the objective of most pH measurements is to find a stable and reproducible reading that can be correlated with the results of some process, it is important to know what influences the activity coefficient and therefore the pH measurement.

The factors that affect the activity coefficient are the temperature (T), the ionic strength (μ), the dielectric constant (ε), the ion charge (Z_i), the size of the ion in angstroms (Å), and the density of the solvent (d). All of these factors are characteristics of the solution that relate the activity to the concentration by two main effects: the salt effect and the medium effect; the latter relates the influence that the solvent can have on the hydrogen ion activity. Thus, hydrogen activity is

PHYSICAL PHARMACY CAPSULE 4.6 CONT.

related to concentration through a salt effect and a solvent effect. Because of these influences, a sample pH value cannot be extrapolated to another temperature or dilution. If the pH value of a particular solution is known at 40°C, it is not automatically known at 25°C.

THE pH SCALE

In pure water, hydrogen and hydroxyl ion concentrations are equal at 10^{-7} M at 25°C. This is a neutral solution. Since most samples encountered have less than 1 M H^+ or OH^-, the extremes of pH 0 for acids and pH 14 for bases are established. Of course, with strong acids or bases, pH values below 0 and above 14 are possible but infrequently measured.

MEASUREMENT OF pH

The activity of the hydrogen ion in solution is measured with a glass electrode, a reference electrode, and a pH meter.

COMBINATION ELECTRODES

A combination electrode is a combination of the glass and reference electrodes into a single probe. The main advantage in using a combination electrode is with the measurement of small volume samples or samples in limited-access containers.

PHYSICAL PHARMACY CAPSULE **4.7**

Solubility and pH

pH is one of the most important factors in the formulation process. Two areas of critical importance are the effects of pH on solubility and stability. The effect of pH on solubility is critical in the formulation of liquid dosage forms, from oral and topical solutions to intravenous solutions and admixtures.

The solubility of a weak acid or base is often pH dependent. The total quantity of a monoprotic weak acid (HA) in solution at a specific pH is the sum of the concentrations of both the free acid and salt (A^-) forms. If excess drug is present, the quantity of free acid in solution is maximized and constant because of its saturation solubility. As the pH of the solution increases, the quantity of drug in solution increases because the water-soluble ionizable salt is formed. The expression is

$$HA \overset{K_a}{\leftrightarrow} H^+ + A^-$$

where K_a is the dissociation constant.

There may be a certain pH level reached where the total solubility (S_T) of the drug solution is saturated with respect to both the salt and acid forms of the drug, that is, the pH_{max}. The solution can be saturated with respect to the salt at pH values higher than this but not with respect to the acid. Also, at pH values less than this, the solution can be saturated with respect to the acid but not to the salt. This is illustrated in the accompanying figure.

To calculate the total quantity of drug that can be maintained in solution at a selected pH, either of two equations can be used, depending on whether the product is to be in a pH region

PHYSICAL PHARMACY CAPSULE 4.7 CONT.

above or below the pH_{max}. The following equation is used when below the pH_{max}:

$$S_T = S_a\left[1+\frac{K_a}{H^+}\right] \qquad \textit{(Equation 4.1)}$$

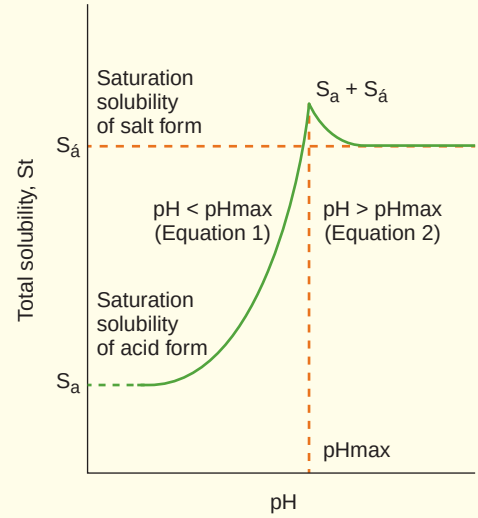
The next equation is used when above the pH_{max}:

$$S_T = S'_a\left[1+\frac{K_a}{H^+}\right] \qquad \textit{(Equation 4.2)}$$

where

S_a is the saturation solubility of the free acid and

S'_a is the saturation solubility of the salt form.



EXAMPLE

A pharmacist prepares a 3% solution of an antibiotic as an ophthalmic solution and dispenses it to a patient. A few days later, the patient returns the eye drops to the pharmacist because the product contains a precipitate. The pharmacist, checking the pH of the solution and finding it to be 6, reasons that the problem may be pH related. The physicochemical information of interest on the antibiotic includes the following:

Molecular weight	285 (salt) 263 (free acid)
3% solution of the drug	0.1053-M solution
Acid form solubility (S_a)	3.1 mg/mL (0.0118 M)
K_a	5.86×10^{-6}

Using Equation (Equation 4.1, the pharmacist calculates the quantity of the antibiotic in solution at a pH of 6 (*Note*: pH of 6.0 = $[H^+]$ of 1×10^{-6})

$$S_T = 0.0118\left[1+\left(5.86\times10^{-6}\right)/\left(1\times10^{-6}\right)\right] = 0.0809\ molar$$

From this, the pharmacist knows that at a pH of 6, a 0.0809-M solution can be prepared. However, the concentration that was to be prepared was a 0.1053-M solution; consequently, the drug will not be in solution at that pH. The pH may have been all right initially but shifted to a lower pH over time, resulting in precipitation of the drug. The question is at what pH (hydrogen ion concentration) the drug will remain in solution. This can be calculated using the same equation and information. The S_T value is 0.1053 M.

$$0.1053 = 0.0118\left[1+\frac{5.86\times10^{-6}}{H^+}\right]$$

$$\left[H^+\right] = 7.333\times10^{-7},\ \text{or a pH of } 6.135$$

The pharmacist prepares a solution of the antibiotic, adjusting the pH to above about 6.2, using a suitable buffer system, and dispenses the solution to the patient—with positive results.

An interesting phenomenon concerns the close relationship of pH to solubility. At a pH of 6, only a 0.0809-M solution could be prepared, but at a pH of 6.13, a 0.1053-M solution could be prepared. In other words, a difference of 0.13 pH units resulted in

PHYSICAL PHARMACY CAPSULE 4.7 CONT.

$$\frac{01053 - 0.0809}{0.0809} = 30.1\%$$

more drugs going into solution at the higher pH than at the lower pH. In other words, a very small change in pH resulted in about 30% more drugs going into solution. According to the figure, the slope of the curve would be very steep for this example drug, and a small change in pH (x-axis) results in a large change in solubility (y-axis). From this, it can be reasoned that if one observes the pH–solubility profile of a drug, it is possible to predict the magnitude of the pH change on its solubility.

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in different types of practice, especially those involved in compounding and pharmacokinetic monitoring.

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in different types of practice, especially those who compound and do pharmacokinetic monitoring.

Dissolution

Variations in the biologic activity of a drug substance may be brought about by the rate at which it becomes available to the organism. In many instances, dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption. This is true for drugs administered orally in solid forms, such as tablets, capsules, or suspensions, and for those administered intramuscularly. When the dissolution rate is the rate-limiting step, anything that affects it will also affect absorption. Consequently, dissolution rate can affect the onset, intensity, and duration of response and control the overall bioavailability of the drug from the dosage form, as discussed in the previous chapter.

The dissolution rate of drugs may be increased by decreasing the drug's particle size. It may also be increased by increasing its solubility in the diffusion layer. The most effective means of obtaining higher dissolution rates is to use a highly water-soluble salt of the parent substance. Although a soluble salt of a weak acid will precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid, it will do so in the form of fine particles with a large surface area.

The dissolution rates of chemical compounds are determined by two methods: the constant surface method, which provides the intrinsic dissolution rate of the agent, and particulate dissolution, in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

The constant surface method uses a compressed disc of known area. This method eliminates surface area and surface electrical charges as dissolution variables. The dissolution rate obtained by this method, the *intrinsic dissolution rate*, is characteristic of each solid compound and a given solvent in the fixed experimental conditions. The value is expressed as milligrams dissolved per minute per square centimeter. It has been suggested that this value is useful in predicting probable absorption problems due to dissolution rate. In particulate dissolution, a weighed amount of powdered sample is added to the dissolution medium in a constant agitation system. This method is frequently used to study the influence of particle size, surface area, and excipients upon the active agent. Occasionally, the surface properties of the drug produce an inverse relationship of particle size to dissolution. In these instances,

surface charge and/or agglomeration results in the reduced particle size form of the drug presenting a lower effective surface area to the solvent due to incomplete wetting or agglomeration. Fick's laws describe the relationship of diffusion and dissolution of the active drug in the dosage form and when administered in the body, as shown in Physical Pharmacy Capsule 4.8, Fick's Laws of Diffusion and the Noyes-Whitney Equation.

PHYSICAL PHARMACY CAPSULE 4.8

Fick's Laws of Diffusion and the Noyes-Whitney Equation

All drugs must diffuse through various barriers when administered to the body. For example, some drugs must diffuse through the skin, gastric mucosa, or some other barrier to gain access to the interior of the body. Parenteral drugs must diffuse through muscle, connective tissue, and so on, to get to the site of action; even intravenous drugs must diffuse from the blood to the site of action. Drugs must also diffuse through various barriers for metabolism and excretion.

Considering all the diffusion processes that occur in the body (passive, active, and facilitated), it is not surprising that the laws governing diffusion are important to drug delivery systems. In fact, diffusion is important not only in the body but also in some quality control procedures used to determine batch-to-batch uniformity of products (dissolution test for tablets based on the Noyes-Whitney equation, which can be derived from Fick's law).

When individual molecules move within a substance, diffusion is said to occur. This may occur as the result of a concentration gradient or by random molecular motion.

Probably the most widely used laws of diffusion are known as Fick's first and second laws. Fick first law involving steady-state diffusion (where dc/dx does not change) is derived from the following expression for the quantity of material (M) flowing through a cross section of a barrier (S) in unit time (t) expressed as the flux (J):

$$J = dM/(Sdt)$$

Under a concentration gradient (dc/dx), Fick's first law can be expressed thus:

$$J = D\left[(C_1 - C_2)/h\right] \text{ or } J = -D(dC/dx)$$

where

J is the flux of a component across a plane of unit area,
C_1 and C_2 are the concentrations in the donor and receptor compartments,
h is the membrane thickness, and
D is the diffusion coefficient (or diffusivity).

The sign is negative, denoting that the flux is in the direction of decreasing concentration. The units of J are grams per square centimeter; C, grams per cubic centimeter; M, grams or moles; S, square centimeters; x, centimeters; and D, square centimeters per second.

D is appropriately called a diffusion coefficient, not a diffusion constant, as it is subject to change. D may change in value with increased concentrations. Also, D can be affected by temperature, pressure, solvent properties, and the chemical nature of the drug itself. To study the rate of change of the drug in the system, one needs an expression that relates the change in concentration with time at a definite location in place of the mass of drug diffusing across a unit area of barrier in unit time; this expression is known as Fick's second law. This law can be summarized as stating that the change in concentration in a particular place with time is proportional to the change in concentration gradient at that particular place in the system.

PHYSICAL PHARMACY CAPSULE 4.8 CONT.

In summary, Fick's first law relates to a steady-state flow, whereas Fick second law relates to a change in concentration of drug with time, at any distance, or an unsteady state of flow.

The diffusion coefficients ($D \times 10^{-6}$) of various compounds in water (25°C) and other media have been determined as follows: ethanol, 12.5 cm^2/s; glycine, 10.6 cm^2/s; sodium lauryl sulfate, 6.2 cm^2/s; glucose, 6.8 cm^2/s.

The concentration of drug in the membrane can be calculated using the partition coefficient (K) and the concentration in the donor and receptor compartments.

$$K = (C_1 / C_d) = (C_2 / C_r)$$

where

C_1 and C_d are the concentrations in the donor compartment (g/cm^3)
and C_2 and C_r are the concentrations in the receptor compartment (g/cm^3).

K is the partition coefficient of the drug between the solution and the membrane. It can be estimated using the oil solubility of the drug versus the water solubility of the drug. Usually, the higher the partition coefficient, the more the drug will be soluble in a lipophilic substance. We can now write the expression:

$$dM/dt = \left[DSK(C_d - C_r)\right]/h$$

or in sink conditions,

$$dM/dt = DSKC_d/h = PSC_d$$

The permeability coefficient (centimeters per second) can be obtained by rearranging to:

$$P = DK/h$$

EXAMPLE 1

A drug passing through a 1-mm-thick membrane has a diffusion coefficient of 4.23×10^{-7} cm^2/s and an oil–water partition coefficient of 2.03. The radius of the area exposed to the solution is 2 cm, and the concentration of the drug in the donor compartment is 0.5 mg/mL. Calculate the permeability and the diffusion rate of the drug.

h = 1 mm = 0.1 cm
$D = 4.23 \times 10^{-7}$ cm^2/s
K = 2.03
r = 2 cm, $S = \pi(2\text{ cm})^2 = 12.57$ cm^2
Cd = 0.5 mg/mL
$P = [(4.23 \times 10^{-7}\ cm^2/s)\ (2.03)]/0.1\ cm = 8.59 \times 10^{-6}$ cm/s
$dM/dt = (8.59 \times 10^{-6}\ cm/s)\ (12.57\ cm^2)(0.5\ mg/mL) = 5.40 \times 10^{-5}$ mg/s
$(5.40 \times 10^{-5}\ mg/s)(3{,}600\ s/h) = 0.19$ mg/h

In the dissolution of particles of drug, the dissolved molecules diffuse away from the individual particle body. An expression to describe this, derived from Fick equations, is known as the Noyes and Whitney expression, proposed in 1897. It can be written as follows:

$$dC/dt = (DS/Vh)(Cs - C)$$

where

C is the concentration of drug dissolved at time t,
D is the diffusion coefficient of the solute in solution,

PHYSICAL PHARMACY CAPSULE 4.8 CONT.

S is the surface area of the exposed solid,
V is the volume of solution,
h is the thickness of the diffusion layer,
Cs is the saturation solubility of the drug, and
C is the concentration of solute in the bulk phase at a specific time, t.

It is common practice to use sink conditions in which C does not exceed about 20% of the solubility of the drug being investigated. Under these conditions, the expression simplifies to

$$dC/dt = (DSCs/Vh)$$

and incorporating the volume of solution (V), the thickness of the diffusion layer (h), and the diffusivity coefficient (D) into a coefficient k (to take into account the various factors in the system), the expression becomes

$$dC/dt = kSCs$$

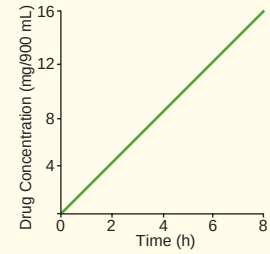
As the factors are held constant, it becomes apparent that the dissolution rate of a drug can be proportional to the surface area exposed to the dissolution medium. A number of other expressions have been derived for specific application to various situations and conditions.

These relationships expressed as Fick first and second laws, and the Noyes-Whitney equation have great importance and relevance in pharmaceutical systems.

EXAMPLE 2

The following information was obtained using the USP 32–NF 27 dissolution apparatus I. The drug is soluble at 1 g in 3 mL of water, so sink conditions were maintained; the surface area of the tablet exposed was 1.5 cm^2 (obtained by placing the tablet in a special holder exposing only one side to the dissolution medium); and the dosage form studied was a 16-mg sustained-release tablet; the release pattern should be zero order. What is the rate of release of drug?

TIME (HOURS)	DRUG CONCENTRATION (MG/900 ML OF SOLUTION)	GRAPH OF RELEASE PROFILE
0.0	0.0	
0.5	1.0	
1.0	1.9	
2.0	4.1	
4.0	8.0	
6.0	11.8	
8.0	15.9	



In this problem, since the surface area (S) was maintained constant at 1.5 cm^2 and the solubility (Cs) of the drug is constant at 1 g in 3 mL of water, the plot of concentration versus time (t) yields a slope with a value of kSCs, or k_2, expressing the rate of release of the drug as

$$dC/dt = kSCs$$

$$\text{The slope of the line} = \Delta y/\Delta x = (y_2 - y_1)/(x_2 - x_1)$$
$$= (15.9\,\text{mg} - 0\,\text{mg})/(8.0\,\text{h} - 0\,\text{h})$$
$$= 15.9/8 = 1.99\,\text{mg/h}$$

Therefore, the rate of release of the sustained-release preparation is 1.99 or approximately 2 mg/hour. From this, the quantity of drug released at any time (t) can be calculated.

Early formulation studies should include the effects of pharmaceutical ingredients on the dissolution characteristics of the drug substance.

Membrane Permeability

Modern preformulation studies include an early assessment of passage of drug molecules across biologic membranes. To produce a biologic response, the drug molecule must first cross a biologic membrane. The biologic membrane acts as a lipid barrier to most drugs and permits the absorption of lipid-soluble substances by passive diffusion, while lipid-insoluble substances can diffuse across the barrier only with considerable difficulty if at all. The interrelationship of the dissociation constant, lipid solubility, and pH at the absorption site with the absorption characteristics of various drugs are the basis of the pH partition theory.

Data obtained from the basic physicochemical studies, specifically, pK_a, solubility, and dissolution rate, provide an indication of absorption. To enhance these data, a technique using the everted intestinal sac may be used to evaluate absorption characteristics of drug substances. In this method, a piece of the intestine is removed from an intact animal, is everted, and is filled with a solution of the drug substance, and the degree and rate of passage of the drug through the membrane sac are determined. This method allows evaluation of both passive and active transport.

In the latter stages of preformulation testing or early formulation studies, animals and humans must be studied to assess the absorption efficiency and pharmacokinetic parameters and to establish possible in vitro and in vivo correlation for dissolution and bioavailability.

Partition Coefficient

The use of the partition coefficient is described in some detail in Physical Pharmacy Capsule 4.9, Partition Coefficient. Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns. The octanol–water partition coefficient is commonly used in formulation development. Following the illustrations provided earlier, it is defined as

$$P = \frac{(\text{Concentration of drug in octanol})}{(\text{Concentration of drug in water})}$$

P depends on the drug concentration only if the drug molecules have a tendency to associate in solution. For an ionizable drug, the following equation is applicable:

$$P = \frac{(\text{Concentration of drug in octanol})}{[1-\alpha](\text{Concentration of drug in water})}$$

where α equals the degree of ionization.

PHYSICAL PHARMACY CAPSULE 4.9

Partition Coefficient

The oil–water partition coefficient is a measure of a molecule's lipophilic character; that is, its preference for the hydrophilic or lipophilic phase. If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach an equilibrium at a constant temperature. The distribution of the solute (unaggregated and undissociated) between the two immiscible layers can be described thus:

$$K = C_U / C_L$$

where

K is the distribution constant or partition constant,

PHYSICAL PHARMACY CAPSULE 4.9 CONT.

C_U is the concentration of the drug in the upper phase, and
C_L is the concentration of the drug in the lower phase.

This information can be effectively used in the

1. Extraction of crude drugs
2. Recovery of antibiotics from fermentation broth
3. Recovery of biotechnology-derived drugs from bacterial cultures
4. Extraction of drugs from biologic fluids for therapeutic drug monitoring
5. Absorption of drugs from dosage forms (ointments, suppositories, and transdermal patches)
6. Study of the distribution of flavoring oil between oil and water phases of emulsions
7. In other applications

This basic relationship can be used to calculate the quantity of drug extracted from or remaining behind in a given layer and to calculate the number of extractions required to remove a drug from a mixture.

The concentration of drug found in the upper layer (U) of the two immiscible layers is given thus:

$$U = Kr/(Kr+1)$$

where

K is the distribution partition constant and
r is V_u/V_1 or the ratio of the volume of upper and lower phases.

The concentration of drug remaining in the lower layer (L) is given thus:

$$L = 1/(Kr+1)$$

If the lower phase is successively extracted again with *n* equal volumes of the upper layer, each upper phase (U_n) contains the following fraction of the drug:

$$U_n = Kr/(Kr+1)^n$$

where

U_n is the fraction contained in the nth extraction and
n is the nth successive volume.

The fraction of solute remaining in the lower layer (L_n) is given thus:

$$L_n = 1/(Kr+1)^n$$

More efficient extractions are obtained using successive small volumes of the extraction solvent than single larger volumes. This can be calculated as follows when the same volume of extracting solvent is used in divided portions. For example, the fraction L_n remaining after the *n*th extraction:

$$L_n = \frac{1}{\left(\frac{Kr}{n}+1\right)^n}$$

EXAMPLE 1

At 25°C and pH 6.8, the K for a second-generation cephalosporin is 0.7 between equal volumes of butanol and the fermentation broth. Calculate the U, L, and L_n (using the same volume divided into fourths).

PHYSICAL PHARMACY CAPSULE 4.9 CONT.

U = 0.7 / (0.7 + 1) = 0.41, the fraction of drug extracted into the upper layer
L = 1 / (0.7 + 1) = 0.59, the fraction of drug remaining in the lower layer

The total of the fractions in the U and L = 0.41 + 0.59 = 1.

If the fermentation broth is extracted with four successive extractions accomplished by dividing the quantity of butanol used into fourths, the quantity of drug remaining after the fourth extraction is

$$L_{4th} = \frac{1}{\left(\frac{0.7 \times 1}{4} + 1\right)^4} = 0.525$$

From this, the quantity remaining after a single volume, single extraction is 0.59, but when the single volume is divided into fourths and four successive extractions are done, the quantity remaining is 0.525; therefore, more was extracted using divided portions of the extracting solvent. Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns.

pK_a/Dissociation Constants

Among the physicochemical characteristics of interest is the extent of dissociation or ionization of drug substances. This is important because the extent of ionization has an important effect on the formulation and pharmacokinetic parameters of the drug. The extent of dissociation or ionization in many cases is highly dependent on the pH of the medium containing the drug. In formulation, often the vehicle is adjusted to a certain pH to obtain a certain level of ionization of the drug for solubility and stability. In the pharmacokinetic area, the extent of ionization of a drug has a strong effect on its extent of absorption, distribution, and elimination. The dissociation constant, or pK_a, is usually determined by potentiometric titration. For the practicing pharmacist, it is important in predicting precipitation in admixtures and in calculating the solubility of drugs at certain pH values. Physical Pharmacy Capsule 4.10, pK_a/Dissociation Constants, presents a brief summary of dissociation and ionization concepts.

PHYSICAL PHARMACY CAPSULE 4.10

pK_a/Dissociation Constants

The dissociation of a weak acid in water is given by this expression:

$$HA \leftrightarrow H^+ + A^-$$
$$K_1[HA] \leftrightarrow K_2[H^+][A^-]$$

At equilibrium, the reaction rate constants K_1 and K_2 are equal. This can be rearranged, and the dissociation constant is defined as

$$K_a = \frac{K_1}{K_2} = \frac{[H^+][A^-]}{[HA]}$$

PHYSICAL PHARMACY CAPSULE 4.10 CONT.

where K_a is the acid dissociation constant.

For the dissociation of a weak base that does not contain a hydroxyl group, the following relationship can be used:

$$BH^+ \leftrightarrow H^+ + B$$

The dissociation constant is described by

$$K_a = \frac{[H^+][B]}{[BH^+]}$$

The dissociation of a hydroxyl-containing weak base,

$$B + H_2O \leftrightarrow OH^- + BH^+$$

The dissociation constant is described by

$$K_b = \frac{[OH^-][BH^+]}{B}$$

The hydrogen ion concentrations can be calculated for the solution of a weak acid using

$$[H^+] = \sqrt{K_a C}$$

Similarly, the hydroxyl ion concentration for a solution of a weak base is approximated by

$$[OH^-] = \sqrt{K_b C}$$

Some practical applications of these equations are as follows.

EXAMPLE 1

The K_a of lactic acid is 1.387×10^{-4} at 25°C. What is the hydrogen ion concentration of a 0.02 M solution?

$$[H^+] = \sqrt{1.387 \times 10^{-4} \times 0.02} = 1.665 \times 10^{-3} \text{ G- ion / L}$$

EXAMPLE 2

The K_b of morphine is 7.4×10^{-7}. What is the hydroxyl ion concentration of a 0.02 M solution?

$$[OH^-] = \sqrt{7.4 \times 10^{-7} \times 0.02} = 1.216 \times 10^{-4} \text{ G- ion / L}$$

Hydrates and Solvates

Many active pharmaceutical agents exist as hydrates or solvates; some are hygroscopic, deliquescent, and/or efflorescent. Hygroscopic powders are those that will tend to absorb moisture from the air. Deliquescent powders are those that will absorb moisture from the air and even liquefy. Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty. When working with these powders, extra care must be taken. Generally, the USP description of a powder will state whether it has hygroscopic, deliquescent, or efflorescent properties.

One other factor is that if a hygroscopic or deliquescent powder is being weighed on a balance, the powder may absorb moisture from the air and weigh heavier than it should. Therefore, weighings should be

PHYSICAL PHARMACY CAPSULE 4.11

Hydrates and Solvates

When a substance is a hydrate and water is present in the molecule, more of the chemical must be weighed to obtain the actual active drug. As a drug example that is available with different amounts of water, let us look at different forms of dexamethasone.

- Dexamethasone contains less than 0.5% of its weight in water.
- Dexamethasone acetate has one molecule of water of hydration and contains between 3.5% and 4.5% of water; the anhydrous form contains less than 0.4% water.
- Dexamethasone sodium phosphate contains a sum of water and alcohol that may be up to 16%

Another example is lidocaine hydrochloride. Lidocaine hydrochloride occurs as a monohydrate and as the anhydrous form. The water content may be between 5% and 7%

CALCULATIONS

How much adjustment should be made if using lidocaine hydrochloride monohydrate in place of lidocaine hydrochloride anhydrous for a compounded prescription?

Lidocaine HCl monohydrate $C_{14}H_{22}N_2O \cdot HCl.H_2O$ MW 288.81

Lidocaine HCl anhydrous $C_{14}H_{22}N_2O \cdot HCl$ MW 270.80

A comparison of the molecular weights reveals a factor of 1.066 can be used for the adjustment:

$$(288.81) / (270.80) = 1.066$$

EXAMPLE:

If a prescription for lidocaine hydrochloride 2% gel (100 g) is to be made, then 2 g of anhydrous lidocaine HCl could be used, OR:

2 g × 1.066 = 2.132 g of lidocaine HCl monohydrate.

Also, a direct comparison of the molecular weights and the physical quantity required can be used, as follows:

$$\frac{\text{MW hydrate}}{\text{MW anhydrous}} = \frac{\text{weight of hydrated form}}{\text{weight of anhydrous form}}$$

$$\frac{288.81}{270.80} = \frac{X}{2\text{g}}$$

$$X = 2.133\ \text{g}$$

Further, the USP monograph for lidocaine hydrochloride Jelly, USP states "It contains not less than 95% and not more than 105.09% of the labeled amount of lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$)." Note that this is the anhydrous form. It is important to also check the C of A for the lidocaine hydrochloride being used to determine the water content. Fortunately, most pure powders (anhydrous) generally only contain 0.2% to 0.5% moisture, which can be insignificant but need to be checked, nevertheless.

made quickly after opening the bulk chemical containers and then resealing them.

Solvates and hydrates must be packaged in "tight" containers to prevent the loss or gain of moisture. In fact, it is best to have all chemicals stored in "tight" containers and to keep them thoroughly closed at all times except for the short time when a weighing step is involved. Storage at the indicated temperatures is also important and to minimize any exposure to very high humidity levels. More on hydrates and solvates is presented in Physical Pharmacy Capsule 4.11, Hydrates and Solvates.

Organic Salt Considerations

Because many drugs are either weak acids or weak bases and have limited water solubility, they are often used as their "salts" to increase their aqueous solubility. For example, sodium salts are often made from weak acids (sodium salicylate is the salt of the weak acid, salicylic acid, and a strong base, sodium hydroxide). Also, a salt such as ephedrine hydrochloride can be prepared between a weak base, ephedrine, and a strong acid, hydrochloric acid. Third, the combination of a weak base, codeine, and a weak acid, phosphoric acid, can be used, as in codeine phosphate.

When salts are placed in an aqueous environment, they will dissolve to some extent, based upon their solubility in the aqueous media and the pH of the media. There will be a portion of the drug that is dissolved and some may remain undissolved. Of the dissolved portion, there will be a part that is "ionized" and the remainder will be "unionized," depending upon the pH of the media. Generally, it is the "unionized" portion of the drug in solution that will be absorbed for systemic effect. This is described by the "dissociation constant" or "pK_a" of the drug.

Since the bulk substance or active pharmaceutical ingredient (API) in a salt form is not 100% active drug, it is important to know whether or not the dose of the drug is based upon the drug salt or drug base form. Many drugs are "salts," and the dose may be based on the "total salt" form or just the "base" form of the drug.

Sources of information that can be used to determine the "form" of the drug (base, salt, or ester) include the wording of commercial products (package inserts) and the USP/NF. For example, Albuterol Sulfate Tablets USP are based on the "albuterol" content (present as the sulfate form). The USP states "Albuterol Tablets USP contain an amount of albuterol sulfate equivalent to not less than 90% and not more than 110% of the labeled amount of albuterol ($C_{13}H_{21}NO_3$)." In other words, sufficient albuterol sulfate is present to provide the labeled amount of the albuterol base.

In another scenario, the dose of Diphenhydramine Hydrochloride Capsules USP is based on the total molecule, that is, diphenhydramine hydrochloride. The USP states "Diphenhydramine Hydrochloride Capsules USP contain not less than 90% and not more than 110% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$)." As one can see, the weight of the "HCl" is considered in the dose of the drug.

The purpose of the "salt" form is usually to enhance the solubility of the drug; but it may also enhance the stability and change other attributes of the drug that make it easier to handle and manipulate for producing dosage forms. Also, it is the "unionized" portion of the drug that will ultimately exert its effect in the body, as the remainder of the salt molecule may no longer follow the base, or unionized, form of the drug into the body.

Why do we have some drugs that are dosed on the "base" form of the drug and some drugs that are dosed on the total weight of the "salt" form of the drug? In reviewing the USP revisions, it appears that this has always been an issue for many years with no apparent basis for which way the salts are dosed. However, both the official monographs and the U.S. Food and Drug Administration (FDA)–approved drug products appear to be inconsistent in how they determine how a drug is dosed. It is the responsibility of the pharmacist to know whether or not the base/acid of the salt form of the drug is to be used in the calculations for the amount of API to actually be used, if compounding.

The new "Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Medications" (USP General Chapter <1121> Nomenclature) states the following:

> "The titles of USP monographs for drug products and compounded preparations formulated with a salt of an acid or base use the name of the active moiety, as defined below. The strength of the product or preparation also is expressed in terms of the active moiety.
>
> An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt

PHYSICAL PHARMACY CAPSULE 4.12

Organic Salts

It is important to know whether or not a drug is "dosed" on the base or the salt form. Consider that the fentanyl dose is calculated on the "base" form but the "salt" is the form that is used in the dosage form. For example:

A prescription calls for 10 mL of fentanyl 50 µg/0.1 mL (as the citrate) topical gel. How much fentanyl citrate will be required?

1. 50 µg/0.1 mL = X µg/10 mL, X = 5 mg
2. Fentanyl MW = 336.47
   Fentanyl citrate MW = 528.59
3. 336.47/5 mg = 528.59/X, X = 7.85 mg
4. Each mg of fentanyl equals 528.59/336.47 = 1.57 mg fentanyl citrate

In a different example, Diphenhydramine Hydrochloride Capsules USP are based on the total molecule, that is, diphenhydramine hydrochloride. The USP states "Diphenhydramine Hydrochloride Capsules USP contain not less than 90% and not more than 110% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$)." As one can see, the weight of the "HCl" is considered in the dose of the drug. For example:

A prescription calls for 30 capsules of diphenhydramine hydrochloride 35 mg each. How much diphenhydramine hydrochloride will be required?

1. Since the total salt molecule is part of the dose:
2. 30 × 35 mg = 1.05 g of diphenhydramine hydrochloride is required.

UXP XII (1942) lists about 20 tablet monographs that are all based on the "salt" form of the drug, for example, Morphine Sulfate Tablets USP contain not less than 93% and not more than 107% of the labeled amount of morphine sulfate [$(C_{17}H_{19}O_3N)_2 \cdot H_2SO_4 \cdot 5H_2O$]. The names of the monographed items in this time period were quite clear as the salt names were a part of the official name if it was to be used. For example, Barbital Tablets USP are based on the labeled amount of barbital ($C_8H_{12}N_2O_3$), but Barbital Sodium Tablets were based on the labeled amount of barbital sodium ($C_8H_{11}N_2O_3Na$).

USP XVI (1960) monograph for Amodiaquine Hydrochloride Tablets USP states "Amodiaquine Hydrochloride Tablets contain an amount of amodiaquine hydrochloride ($C_{20}H_{22}ClN_3O \cdot 2HCl \cdot 2H_2O$) equivalent to not less than 93% and not more than 107% of the labeled amount of amodiaquine base ($C_{20}H_{22}ClN_3O$)." It is evident in this monograph that the dose is calculated on the "base" form of the drug.

It is the responsibility of the formulator to determine whether or not the base/acid of the salt form of the drug is to be used in the calculations for the amount of API to actually be used.

with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance without regard to the actual charged state of the molecule in vivo.

For example, the active moiety of a hydrochloride salt of a base will be the free base and not the protonated form of the base. The active moiety of a metal acid salt will be the free acid.

This Policy is followed by USP in naming drug products and compounded preparations that are newly recognized in the USP. Revising existing monographs to conform to this Policy is not intended, except where the USP Council of Experts determines that, for reasons such as safety, a nomenclature change is warranted."

See example organic salt considerations in Physical Pharmacy Capsule 4.12, Organic Salts.

Organic Ester Considerations

Many drugs are available as the base form or as an "ester," and the dose may be based on the total ester form or just the base form of the drug. If a number of factors are not considered, a final manufactured product or compounded preparation may not fall within the strength requirements, for example, 90% to 110% for compounded preparations or the USP monographs.

Some drugs are esters by virtue of their internal chemical structure (atropine, cocaine, many local anesthetics, etc.), and others are esters by the addition of a moiety that will form an ester for certain purposes. It is only the latter that are discussed here; those that are esters because of their basic molecular structure are not included.

An ester is a compound of the general formula R-C-O-R1 where R and R1 may be the same or different and may be either aliphatic or aromatic. The term "aliphatic" refers to an acyclic or cyclic, saturated or unsaturated carbon compounds excluding aromatic compounds; the term "aromatic" was originally used to describe compounds that "smelled" but were later found to contain either benzene or a fused benzene rings in the structure. The term has been generalized to include aromatic heterocyclic structures.

The dehydration of a molecule of an alcohol and a molecule of an organic acid can form an ester. For example, ethanol reacts with acetic acid to form ethyl acetate, an ester:

$$C_2H_5OH + CH_3COOH \rightarrow CH_3CH_2 - O - CO - CH_3 + H_2O$$

Following salts, esters are the most important acid derivatives used in pharmacy. Esters can be prepared for a number of reasons, including solubility, stability, resistance to degradation after administration, use as prodrugs, etc.

Some drugs are very soluble but tend to degrade rapidly when in solution. One approach to increase their stability, and shelf-life, is to prepare esters that are poorly soluble. This results in a "suspension" dosage form in place of a "solution" dosage form. A drug in a suspension dosage form degrades at a much slower rate than one in solution. After oral administration, the ester is cleaved and the active drug moiety released for absorption, etc.

Some drugs may cause pain at the site of injection, especially if they precipitate and damage the surrounding tissue. This can be overcome by preparing a drug with increased solubility. Chloramphenicol has low water solubility, but the succinate ester is formed to increase the water solubility of the drug and facilitate parenteral administration. This succinate ester is inactive but is hydrolyzed to release the active chloramphenicol moiety.

Esters are an important means of preparing prodrugs due to the number of esterases present in various parts of the body that will cleave the ester linkage, releasing the active moiety. Carboxylic acid esters are common in pharmacy and are neutral liquids or solids, which can be hydrolyzed slowly by water and rapidly by acids or alkalis into their components. Some of the simple esters are soluble in water, but those with more than four carbon atoms are practically insoluble in water. See examples in Physical Pharmacy Capsule 4.13, Organic Esters.

PHYSICAL PHARMACY CAPSULE 4.13

Organic Esters

Esters are quite interesting because one cannot simply look at the title and determine whether or not the drug is a salt or an ester. For example, "*acetate salts*" include calcium acetate, chlorhexidine acetate, desmopressin acetate, flecainide acetate, gonadorelin acetate, guanabenz acetate, leuprolide acetate, lysine acetate, mafenide acetate, and zinc acetate, and "*acetate esters*" include cortisone acetate, desoxycorticosterone acetate, dexamethasone

PHYSICAL PHARMACY CAPSULE 4.13 CONT.

acetate, fludrocortisones acetate, fluorometholone acetate, hydrocortisone acetate, isoflupredone acetate, medroxyprogesterone acetate, megestrol acetate, melengestrol acetate, methylprednisolone acetate, norethindrone acetate, paramethasone acetate, prednisolone acetate, trenbolone acetate, and betamethasone acetate.

Further, "*succinate salts*" include sumatriptan succinate, doxylamine succinate, loxapine succinate, and metoprolol succinate, and "*succinate esters*" include chloramphenicol sodium succinate, hydrocortisone sodium succinate, hypromellose acetate succinate, methylprednisolone sodium succinate, and prednisolone sodium succinate.

Let's look at cefuroxime axetil as an example of an ester that is dosed on the base form.

1. Cefuroxime axetil is $C_{20}H_{22}N_4O_{10}S$, with a molecular weight of 510.47. Cefuroxime axetil is described as a mixture of the diastereoisomers of cefuroxime axetil and contains the equivalent of not less than 745 µg and not more than 875 µg of cefuroxime ($C_{16}H_{16}N_4O_8S$) per mg, calculated on the anhydrous basis.
2. Cefuroxime Axetil Tablets USP contain the equivalent of not less than 90% and not more than 110% of the labeled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$).
3. Ceftin Tablets (cefuroxime axetil tablets) provide the equivalent of 250 or 500 mg of cefuroxime as cefuroxime axetil.
4. Ceftin for Oral Suspension (cefuroxime axetil powder for oral suspension) provides the equivalent of 125 or 250 mg of cefuroxime as cefuroxime axetil per 5 mL of suspension.
5. After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime; the axetil moiety is metabolized to acetaldehyde and acetic acid.
6. The molecular weight of cefuroxime axetil is 510.47. The molecular weight of cefuroxime is 424.39. Therefore, 1 mg of cefuroxime is contained in 510.47/424.39 = 1.2 mg of cefuroxime axetil. A 250 mg of cefuroxime tablet will contain 250 × 1.2 = 300 mg of cefuroxime axetil.
7. Therefore, if using a commercial product to prepare a dosage form, no conversion should be required. However, if using a bulk active ingredient, then the required amount of cefuroxime axetil that is equivalent to the desired dosage of cefuroxime must be calculated.

Dexamethasone-labeled strengths pose an interesting problem as they are not consistent in naming either the base or the ester form, for example

"Dexamethasone" dosage form monographs are based on the labeled amount of "dexamethasone."

"Dexamethasone acetate" dosage form monograph is based on the labeled amount of "dexamethasone."

"Dexamethasone sodium phosphate" dosage form monographs are based upon the labeled amount of "dexamethasone phosphate," not "dexamethasone."

An example of a drug that occurs both as salt and ester forms is the drug erythromycin: Erythromycin estolate is a salt; erythromycin ethylsuccinate is an ester; erythromycin gluceptate is a salt; erythromycin lactobionate is a salt; and erythromycin stearate is a salt.

Potency-Designated Active Pharmaceutical Ingredients

In the case of "potency-designated drugs," the bulk substance, or API, is not 100% active drug in all cases. It is important to know the assayed potency designation of the ingredient so that appropriate allowances can be made to obtain the correct amount. This may be on the label or on the Certificate of Analysis.

Some APIs, including some antibiotics, endocrine products, biotechnology-derived products, biologics, etc., have potencies that are based on "activity" and are expressed in terms of "units of activity," "micrograms per milligram," or other standard terms of

measurements. These are described for each API in the USP.

Regarding biologicals, the following is found in the General Notices of the USP:

"5.50.10 Units of Potency (Biological)"

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as "USP Units." For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not International Units or USP Units have been defined.

There is no relationship between the units of potency of one drug with that of another different drug.

In the case of potency-designated drugs, there must be a "reference standard" for comparison. In actual usage, the potency specifications often include a range or "not less than __" and "not more than ___." In some cases, only a lower range is given, and in a few cases, there is no upper limit.

The determinations of potency are generally done on the "dried or anhydrous basis." In the case of hygroscopic APIs, one must exercise precautions to maintain the substance in a dried state in tight containers. In some cases, there is a designation of specified solvent-free conditions.

See examples in Physical Pharmacy Capsule 4.14, Potency-Designated Active Pharmaceutical Ingredients.

PHYSICAL PHARMACY CAPSULE **4.14**

Potency-Designated Active Pharmaceutical Ingredients

For those APIs, including some antibiotics, endocrine products, biotechnology-derived products, biologics, etc., that have potencies that are based on "activity" and are expressed in terms of "units of activity," "micrograms per milligram," or other standard terms of measurements, calculations must be made to ensure that the correct quantity of active drug is used.

In the case of dihydrostreptomycin, there are different potencies depending upon the use of the API. The potency may be not less than 450, 650, or 725 µg, depending upon its form or usage (route of administration).

In some cases, as in erythromycin ethylsuccinate and erythromycin stearate, the potency is based on the sum of the percentages of three different erythromycins that make up the API. Generally, the potency designation is determined on the "base" of the drug, but in few instances, the salt or ester form is used.

The potency of antibiotics is commonly expressed as "µg of activity per mg of substance." Obviously, there will be different equivalents for the base versus the salt forms of the drug. Tobramycin has not less than 900 µg of tobramycin per mg, and tobramycin sulfate has a potency of not less than 634 µg of tobramycin per mg, all on the anhydrous basis. As another example, ampicillin contains not less than 900 µg and not more than 1,050 µg of ampicillin per mg, and ampicillin sodium contains not less than 845 µg and not more than 988 µg of ampicillin per mg, both calculated on the anhydrous basis. So, one can tell that it is extremely important to check the labels accompanying each batch of each API for the necessary values to be used in calculations.

PHYSICAL PHARMACY CAPSULE 4.14 CONT.

In some drugs, the actual dose may be expressed in units instead of mg. Examples of this include heparin and insulin. Other examples include enzymes (pancreatin, pancrelipase, papain) and antibiotics.

Each container must be labeled with the actual potency, and this information is to be used in calculations involving dosing prior to compounding activities. These calculations must be done and checked and documented, as different lots of the same API may have different potencies. An example of a calculation follows.

EXAMPLE

A formula calls for 500 mg of neomycin sulfate. The label on the API shows 650 µg of neomycin activity per mg of powder. How much of this powder is required to provide the 500 mg of neomycin sulfate?

$$\frac{650\,\mu g}{1000\,\mu g} = \frac{500\,mg}{X}$$

X = 769 mg of the powder is required to provide 500 mg of actual neomycin sulfate.

Complex Organic Molecules

Most complex molecules and biotechnology products are proteins; however, some may be smaller peptide-like molecules. Proteins are inherently unstable molecules and require special handling; also, their degradation profiles can be quite complex. Pharmacists involved in working with or handling biologically active proteins must be interested in their stabilization, formulation, and delivery to the site of action.

In working with complex molecules, one must be cognizant of both the active drug constituent and the total drug formulation in which it is contained. This is true when converting a commercial product into a compounded preparation. Protein drugs are very potent and are generally used in quite low concentrations. The bulk of many manufactured products and compounded preparations may be the excipients. These excipients include the vehicle, buffers, stabilizers, and others that are often incorporated in these products. A number of different stabilizers can be used from different chemical classes and include surfactants, amino acids, polyhydric alcohols, fatty acids, proteins, antioxidants, reducing agents, and metal ions. See Physical Pharmacy Capsule 4.15, Complex Organic Molecules for further considerations.

PHYSICAL PHARMACY CAPSULE **4.15**

Complex Organic Molecules

Most complex molecules and biotechnology products are proteins; however, some may be smaller peptide-like molecules. Proteins are inherently unstable molecules and require special handling; also, their degradation profiles can be quite complex. Pharmacists involved in compounding with biologically active proteins must be interested in their stabilization, formulation, and delivery to the site of action.

Protein drugs are potent and are generally used in low concentrations; consequently, the bulk of many manufactured products and compounded preparations may be the excipients,

PHYSICAL PHARMACY CAPSULE 4.15 CONT.

including the vehicle, buffers, stabilizers, and others that are often incorporated in these products.

FACTORS

pH: pH is one of the key important factors in formulating a stable preparation. The optimal pH range can be achieved through the selection of appropriate physiologic buffers, usually in buffer concentration ranges of 0.01 to 0.1 M. In general, an increase in the buffer concentration means an increase in pain on injection so is generally kept as low as reasonable.

Chelating agents: Chelating agents are incorporated to bind trace metals such as copper, iron, calcium, and manganese and minimize rates of degradation. Ethylenediaminetetraacetic acid (EDTA) is commonly used at a concentration of about 0.01% to 0.05%.

Antioxidants: Antioxidants are often used since oxidation is one of the major factors in protein degradation. Examples include ascorbic acid, sodium disulfide, monothioglycerol, and α-tocopherol are frequently used at a concentration of about 0.05% to 0.1%.

Preservatives: Preservatives are used, especially if multiple dose vials are indicated. Examples include phenol (0.3% to 0.5%), chlorobutanol (0.3% to 0.5%), and benzyl alcohol (1% to 3%).

Others: Others may include the polyols, which are good stabilizers and are commonly used in concentrations from 1% to 10%, and tonicity-adjusting agents, which include sodium chloride and dextrose in concentrations necessary to achieve isotonicity of approximately 290 mOsm/L.

The use of filters in manipulating biotechnology products can result in "sorption" or the loss of some of the drug available to the patient. Sorption is "sticking" either by "absorption" into the filter or by "adsorption" onto the surface of the filter. Special filters have been prepared to minimize this problem. For example, muromonab-CD3 (Orthoclone OKT3) injection should be filtered with a low–protein-binding filter of 0.2 to 0.22 μm. Many biotechnology products should not be filtered at all. If a filtration device is part of the IV administration apparatus, large molecule drugs should generally be administered distal to the site of the filter. Filters that have been shown to minimize protein adsorption are those made from polyvinylidene difluoride, polycarbonate, polysulfone, and regenerated cellulose. As a precaution, low–protein-binding filters should be used.

Sorption of proteins to containers (glass or plastic) can result in drug loss. This loss can be minimized either by the use of albumin or by siliconization. Adding about 0.1% albumin to the product can decrease the sorption of proteins to containers. If glass containers are used, the albumin solution should be added and manipulated to coat the interior surface before adding the drug. If siliconization is used, one can prepare a silicon solution or emulsion and soak or rinse the glass vials in it. The drained vials should then be placed in an oven at about 250°C for 5 to 6 hours. This procedure will minimize protein adsorption to the glass; it can be used for both the preparation equipment and the packaging containers.

Specific issues relevant to large molecule drugs include the following:

- effect of agitation and/or frothing on a preparation's stability;
- high molecular weight and potential for aggregation (i.e., a small change in structure can result in a change in activity);
- assignment of potency to the reference standards (when traditional pharmaceuticals are about 98% pure, these materials may be only 0.1% to 1% active, with their activity assigned by potentially variable assays);
- use of micropipets, which can require frequent calibration;
- stability may be less than lyophilized preparations;
- interaction of the product with the inner wall of the glass vial and with the elastomeric closure;
- effectiveness of the preservative if a multidose product is mixed with other products; and

PHYSICAL PHARMACY CAPSULE 4.15 CONT.

- immunogenic potential, because some are produced by a fermentation-type process and proteins can copurify with proteins.

Sorption is a problem with colony-stimulating factors and with aldesleukin (Proleukin) at low concentrations. To minimize "sticking" of the protein to the glass, the addition of about 0.1% albumin to the product to occupy the potential binding sites in the container is often helpful. Pharmacists must consider this problem before making any changes in packaging.

Agitation resulting in frothing can create difficulties in two ways. First, frothing can cause difficulties in using a syringe to withdraw the required amount of drug from a vial. To avoid this problem, the formulator should mix the product by rolling the vial in the hands or gently swirling it. Second, excessive agitation can cause changes in a protein's quaternary structure that often reduce or eliminate a drug's therapeutic activity. Some products, such as filgrastim (Neupogen) and sargramostim (Leukine), are reconstituted by directing a soft stream of diluent against the inside of the container wall. Others, such as recombinant tissue plasminogen activator (tPA; alteplase), are reconstituted by directing a stream of diluent directly into the product at the bottom of the vial.

Storage: The recommended storage temperature depends on the specific preparation and may include room temperature (15°C to 25°C), refrigerator temperature (2°C to 8°C), frozen (–20°C), or ultra frozen temperature (down to –80°C). Freezing does affect the activity of certain products; for instance, the activity of filgrastim decreases if it is frozen. Some products can retain potency at room temperature after reconstitution. Sargramostim retains potency for up to 30 days at 25°C. However, most manufacturers recommend refrigeration at 2°C to 8°C, regardless of the product's potency at room temperature.

The short shelf life of these products after reconstitution can be due to chemical, physical, or microbiological instability. The manufacturer's recommendations or those validated by the published literature should be followed for products after they are reconstituted and manipulated. One example is tPA, which has been used in treating intraocular fibrin formation after a vitrectomy and in managing subconjunctival hemorrhage after glaucoma filtration surgery. The prepared solution is stable in a pH range of 5 to 7.5 and is incompatible with bacteriostatic agents. To prepare a compounded preparation, the commercial product is reconstituted according to the manufacturer's directions, using sterile water for injection without preservatives to yield a concentration of 1 mg/mL. This solution is further diluted with 0.9% sodium chloride injection to yield a concentration of 25 µg/100 µL. Aliquots of 0.3 mL are withdrawn into 1-mL tuberculin syringes and capped. The syringes are stored in an ultra freezer at –70°C. This product has been shown, by both bioassay and clinical use, to retain its activity for at least 1 year. This type of specific product information is not included in the manufacturer's label information and is usually obtained from the literature or by asking the manufacturer directly.

Physical stability: This can involve degradation by aggregation, denaturation, and precipitation. *Aggregation* can be the result of covalent or noncovalent processes and can be either physical or chemical in nature. Aggregate formation can actually begin when primary particles are formed from protein molecules as a result of Brownian movement.

Denaturation can result from heat, cold, extreme pH values, organic solvents, hydrophilic surfaces, shear, agitation, mixing, filtering, shaking, freeze–thaw cycles, ionic strength, and other factors. Denaturation can be quite complex and can be either reversible or irreversible.

Precipitation can result from shaking, heating, filtration, pH, and chemical interactions. The first step in a precipitation process is generally aggregation. When the aggregates gain a sufficient size, they precipitate out of solution and are clearly evident. Precipitation can occur on membrane filters, in equipment, in tubing, and in contact with other equipment and supplies.

Drug and Drug Product Stability

One of the most important activities of preformulation work is evaluation of the physical and chemical stability of the pure drug substance. It is essential that these initial studies be conducted using drug samples of known purity. The presence of impurities can lead to erroneous conclusions in such evaluations. Stability studies conducted in the preformulation phase include solid-state stability of the drug alone, solution-phase stability, and stability in the presence of expected excipients. Initial investigation begins with knowledge of the drug's chemical structure, which allows the preformulation scientist to anticipate the possible degradation reactions.

Drug Stability: Mechanisms of Degradation

Chemical instability of medicinal agents may take many forms because the drugs in use today are of such diverse chemical constitution. Chemically, drug substances are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with reactive chemical groups having different susceptibilities to chemical instability. Chemically, the most frequently encountered destructive processes are hydrolysis and oxidation.

Hydrolysis is a solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products. For example, aspirin, or acetylsalicylic acid, combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid.

Hydrolysis is probably the most important single cause of drug decomposition, mainly because a great number of medicinal agents are esters or contain such other groupings as substituted amides, lactones, and lactams, which are susceptible to the hydrolytic process (2).

Another destructive process is oxidation, which destroys many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils. Chemically, oxidation is loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, reducing the recipient. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element, for example, ferrous (+2) oxidizing to ferric (+3). In organic chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. Oxidation frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, such as molecular (atmospheric) oxygen (•O—O•) and free hydroxyl (•OH). These radicals tend to take electrons from other chemicals, thereby oxidizing the donor.

Many of the oxidative changes in pharmaceutical preparations have the character of autoxidations. Autoxidations occur spontaneously under the initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly. The process has been described as a type of chain reaction commencing with the union of oxygen with the drug molecule and continuing with a free radical of this oxidized molecule participating in the destruction of other drug molecules and so forth.

In drug product formulation work, steps are taken to reduce or prevent deterioration due to hydrolysis, oxidation, and other processes. These techniques are discussed later.

Drug and Drug Product Stability: Kinetics and Shelf Life

Stability is the extent to which a product retains within specified limits and throughout its period of storage and use (i.e., its shelf life) the same properties and characteristics that it possessed at the time of its manufacture.

Five types of stability concern pharmacists:

1. *Chemical*: Each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. *Physical*: The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
3. *Microbiologic*: Sterility or resistance to microbial growth is retained according to

the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. *Therapeutic*: The therapeutic effect remains unchanged.
5. *Toxicologic*: No significant increase in toxicity occurs.

Chemical stability is important for selecting storage conditions (temperature, light, humidity), selecting the proper container for dispensing (glass versus plastic, clear versus amber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms. Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical species and by factors such as solvent, pressure, and temperature.

In considering chemical stability of a pharmaceutical, one must know the reaction order and reaction rate. The reaction order may be the overall order (the sum of the exponents of the concentration terms of the rate expression) or the order with respect to each reactant (the exponent of the individual concentration term in the rate expression).

Rate Reactions

The reaction rate is a description of the drug concentration with respect to time. Most commonly, zero-order and first-order reactions are encountered in pharmacy. These are presented in Physical Pharmacy Capsule 4.16, Rate Reactions, along with some appropriate examples.

PHYSICAL PHARMACY CAPSULE 4.16

Rate Reactions

ZERO-ORDER RATE REACTIONS

If the loss of drug is independent of the concentration of the reactants and constant with respect to time (i.e., 1 mg/mL/h), the rate is called zero order. The mathematical expression is

$$\frac{-dC}{dt} = k_0$$

where k_0 is the zero-order rate constant [concentration (C)/time (t)].

The integrated and more useful form of the equation:

$$C = -k_0 t + C_0$$

where C_0 is the initial concentration of the drug.

The units for a zero rate constant k_0 are concentration per unit time, such as moles per liter-second or milligrams per milliliter per minute.

It is meaningless to attempt to describe the time required for *all* material in a reaction to decompose, that is, infinity. Therefore, reaction rates are commonly described by k or by their half-life, $t_{1/2}$.

The half-life equation for a zero-order reaction:

$$t_{1/2} = (1/2)(C_0 / k_0)$$

If the C_0 changes, the $t_{1/2}$ changes. There is an inverse relationship between the $t_{½}$ and k.

EXAMPLE 1

A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/h. What is the concentration of intact drug remaining after 3 days (72 hours), and what is its $t_{1/2}$?

PHYSICAL PHARMACY CAPSULE 4.16 CONT.

$$C = -(0.5\,mg/mL/h)(72\,h) + 125\,mg/mL$$
$$C = 89\,mg/mL \text{ after } 3\,d$$
$$t_{1/2} = 1/2(125\,mg/mL)/(0.5\,mg/mL/h)$$
$$t_{1/2} = 125\,h$$

EXAMPLE 2

How long will it take for the suspension to reach 90% of its original concentration?

$$90\% \times 125\ mg/mL = 112.5\ mg/mL$$

$$t = \frac{C - C_0}{-k_0} - \frac{112.5\ mg/mL - 125\ mg/mL}{-0.5\ mg/mL/h} = 25\ h$$

Drug suspensions are examples of pharmaceuticals that ordinarily follow zero-order kinetics for degradation.

FIRST-ORDER RATE REACTIONS

If the loss of drug is directly proportional to the concentration remaining with respect to time, it is called a first-order reaction and has the units of reciprocal time, that is, time^{-1}. The mathematical expression is

$$\frac{-dC}{dt} = kC$$

where

C is the concentration of intact drug remaining,
t is time,
(dC/dt) is the rate at which the intact drug degrades, and
k is the specific reaction rate constant.

The integrated and more useful form of the equation:

$$\log C = \frac{-kt}{2.303} + \log C_0$$

where C_0 is the initial concentration of the drug.

In natural log form, the equation is

$$\ln C = -kt + \ln C_0$$

The units of k for a first-order reaction are per unit of time, such as per second.

The half-life equation for a first-order reaction is

$$t_{1/2} = 0.693/k$$

and can be easily derived from the first-order equation by substituting values of C = 50% and C_0 = 100%, representing a decrease in concentration by 50%.

EXAMPLE 3

An ophthalmic solution of a mydriatic drug at 5 mg/mL exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?

PHYSICAL PHARMACY CAPSULE 4.16 CONT.

$$\ln C = -(0.0005/d)(120) + \ln(5\,mg/mL)$$
$$\ln C = -0.06 + 1.609$$
$$\ln C = 1.549$$
$$C = 4.71\ mg/mL$$
$$t_{1/2} = 0.693/0.0005/d$$
$$t_{1/2} = 1{,}386\ d$$

EXAMPLE 4

In Example 3, how long will it take for the drug to degrade to 90% of its original concentration?

$$90\%\ \text{of}\ 5\ mg/mL = 4.5\ mg/mL$$
$$\ln 4.5\ mg/mL = -(0.0005/d)t + \ln(5\ mg/mL)$$
$$t = \frac{\ln 4.5\ mg/mL - \ln 5\ mg/mL}{-0.0005/d}$$
$$t = 210\ d$$

ENERGY OF ACTIVATION: ARRHENIUS EQUATION

Stability projections for shelf life (t_{90} or the time required for 10% of the drug to degrade with 90% of the intact drug remaining) are commonly based on the Arrhenius equation:

$$\log = \frac{k_2}{k_1} = \frac{Ea(T_2 - T_1)}{2.3RT_1T_2}$$

which relates the reaction rate constants (k) to temperatures (T) with the gas constant (R) and the energy of activation (Ea).

The relationship of the reaction rate constants at two different temperatures provides the energy of activation for the degradation. By performing the reactions at elevated temperatures instead of allowing the process to proceed slowly at room temperature, the Ea can be calculated and a k value for room temperature determined with the Arrhenius equation.

EXAMPLE 5

The degradation of a new cancer drug follows first-order kinetics and has first-order degradation rate constants of 0.0001 per hour at 60°C and 0.0009 per hour at 80°C. What is its Ea?

$$\log = \frac{(0.0009)}{(0.0001)} = \frac{Ea(353 - 333)}{(2.3)(1.987)(353)(333)}$$
$$Ea = 25{,}651\ kcal/mol$$

Q_{10} Method of Shelf Life Estimation

The Q_{10} method of shelf life estimation lets the pharmacist estimate shelf life for a product that has been stored or is going to be stored under a different set of conditions. It is explained in Physical Pharmacy Capsule 4.19, Q_{10}, Method of Shelf Life Estimation.

Enhancing Stability of Drug Products

Many pharmaceutical ingredients may be used to prepare the desired dosage form of a drug substance. Some of these agents may be used to achieve the desired physical and chemical characteristics of the product or to enhance its appearance, odor, and taste.

Other substances may be used to increase the stability of the drug substance, particularly against hydrolysis and oxidation. In each instance, the added pharmaceutical ingredient must be compatible with and must not detract from the stability of the drug substance.

There are several approaches to the stabilization of pharmaceutical preparations containing drugs subject to hydrolysis. Perhaps the most obvious is the reduction or elimination of water from the pharmaceutical system. Even solid dosage forms containing water-labile drugs must be protected from humidity in the atmosphere. This may be accomplished by applying a waterproof protective coating over tablets or by keeping the drug in a tightly closed container. It is fairly common to detect hydrolyzed aspirin by noticing an odor of acetic acid upon opening a bottle of aspirin tablets. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

Decomposition by hydrolysis may be prevented in other liquid drugs by suspending them in a nonaqueous vehicle rather than dissolving them in an aqueous solvent. In still other instances, particularly for certain unstable antibiotic drugs, when an aqueous preparation is desired, the drug may be supplied to the pharmacist in a dry form for *reconstitution* by adding a specified volume of purified water just before dispensing. The dry powder is actually a mixture of the antibiotic, suspending agents, flavorants, and colorants; when reconstituted by the pharmacist, it remains stable for the period over which the preparation is normally consumed. Refrigeration is advisable for most preparations considered subject to hydrolysis. Together with temperature, pH is a major determinant of the stability of a drug prone to hydrolytic decomposition. Hydrolysis of most drugs depends on the relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolyzable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through judicious use of buffering agents, the stability of otherwise unstable compounds can be increased. Buffers are used to maintain a certain pH, as described in Physical Pharmacy Capsule 4.17, Buffer Capacity.

PHYSICAL PHARMACY CAPSULE **4.17**

Buffer Capacity

pH, buffers, and buffer capacity are especially important in drug product formulation, since they affect the drug's solubility, activity, absorption, and stability and the patient's comfort.

A buffer is a system, usually an aqueous solution, that can resist changes in pH upon addition of an acid or a base. Buffers are composed of a weak acid and its conjugate base or a weak base and its conjugate acid. Buffers are prepared by one of these processes:

1. Mixing a weak acid and its conjugate base or a weak base and its conjugate acid
2. Mixing a weak acid and a strong base to form the conjugate base or a weak base and a strong acid to form the conjugate acid

Using the Henderson-Hasselbalch equation:

$$pH = pK_a + \log(\text{base} / \text{acid})$$

PHYSICAL PHARMACY CAPSULE 4.17 CONT.

Remember that the acid is the proton donor and the base is the proton acceptor.

EXAMPLE 1

A buffer is prepared by mixing 100 mL of 0.2 M phosphoric acid with 200 mL of 0.08 M sodium phosphate monobasic. What is the pH of this buffer? (K_a of phosphoric acid = 7.5×10^{-3})

Moles acid = (0.2 mol/1,000 mL) (100 mL) = 0.02 mol; (0.02 mol)/(0.3 L) = 0.067 M
Moles base = (0.08 mol/1,000 mL) (200 mL) = 0.016 mol; (0.016 mol)/(0.3 L) = 0.053 M
pKa = $-\log 7.5 \times 10^{-3} = 2.125$
pH = 2.125 + log (0.016 mol/0.02 mol) = 2.028

EXAMPLE 2

Determine the pH of the buffer prepared as shown:

Sodium acetate 50 g
Conc. HCl 10 mL
Water qs 2 L
Helpful numbers:
pK_a acetic acid = 4.76
m.w. sodium acetate = 82.08
m.w. acetic acid = 60.05
m.w. HCl = 36.45
Conc. HCl, 44% HCl w/v

$$NaAc + HCl \rightarrow NaCl + HAc + NaAc$$
$$(0.609\ mol)\ (0.121\ mol)\ (0.121\ mol)\ (0.121\ mol)\ (0.488\ mol)$$
$$HCl: \{(10\ mL)[(44\ g)/(100\ mL)](1\ mol)/(36.45\ g)\} = 0.121\ mol$$
$$NaAc: \{(50\ g)[(1\ mol)/(82.08\ g)] = 0.609\ mol\ (0.609\ mol) - (0.121\ mol) = 0.488\ mol$$
$$pH = 4.76 + \log (0.488\ mol)/(0.121\ mol) = 5.367$$

The ability of a buffer solution to resist changes in pH upon the addition of an acid or a base is called buffer capacity (β) and is defined thus:

$$\beta = \Delta B / \Delta pH$$

where

ΔB is molar concentration of acid or base added,
ΔpH is change in pH due to addition of acid or base, and
ΔpH can be determined experimentally or calculated using the Henderson-Hasselbalch equation.

EXAMPLE 3

If 0.2 mole of HCl is added to a 0.015 M solution of ammonium hydroxide and the pH falls from 9.5 to 8.9, what is the buffer capacity?

$$\Delta pH = 9.5 - 8.9 = 0.6$$
$$\Delta B = 0.2\ mol/L = 0.2\ M$$
$$\beta = 0.2\ M/0.6 = 0.33\ M$$

EXAMPLE 4

If 0.002 mole of HCl is added to the buffer in Example 1, what is its buffer capacity? After adding 0.002 mole HCl:

PHYSICAL PHARMACY CAPSULE 4.17 CONT.

$$H_3PO_4 : 0.02\ mol + 0.002\ mol = 0.022\ mol$$
$$NaH_2PO_4 : 0.016\ mol - 0.002\ mL = 0.014\ mol$$
$$pH = 2.125 + \log(0.014\ mol / 0.022\ mol) = 1.929$$
$$\Delta pH = 2.028 - 1.929 = 0.099$$
$$\Delta AB = 0.002\ mol / 0.3\ L = 0.0067\ M$$
$$\beta = 0.0067\ M / 0.099 = 0.067\ M$$

Another approach to calculating buffer capacity involves the use of Van Slyke equation:

$$\beta = 2.3C\{Ka[H^+] / (Ka[H^+])^2\}$$

where

C is the sum of the molar concentrations of the acid and base, and $[H^+] = 10^{-pH}$.

EXAMPLE 5

What is the Van Slyke buffer capacity of the buffer prepared in Example 1?

$C = 0.0067\ M + 0.0053\ M = 0.12\ M$

$Ka = 7.5 + 10^{-3}$

$[H^+] = 10^{-2.028} = 9.38 \times 10^{-3}\ M$

$\beta = 2.3\,(0.12\ M)\ \{[(7.5 \times 10^{-3}\ M)(9.38 \times 10^{-3}\ M)]/[(7.5 \times 10^{-3}\ M)/(9.38 \times 10^{-3}\ M)^2]\} = 0.68\ M$

Pharmaceutically, oxidation of a susceptible drug substance is most likely to occur when it is not kept dry in the presence of oxygen or when it is exposed to light or combined with other chemical agents without proper regard to their influence on oxidation. Oxidation of a chemical in a pharmaceutical preparation is usually accompanied by an alteration in the color of that preparation. It may also result in precipitation or a change in odor.

The oxidative process is diverted and the stability of the drug is preserved by agents called *antioxidants*, which react with one or more compounds in the drug to prevent progress of the chain reaction. In general, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy. Among those, most frequently used in aqueous preparations are sodium sulfite (Na_2SO_3, at high pH values), sodium bisulfite ($NaHSO_3$, at intermediate pH values), sodium metabisulfite ($Na_2S_2O_5$, at low pH values), hypophosphorous acid (H_3PO_2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butyl hydroxy anisole, and ascorbyl palmitate find application.

In its labeling regulations for pharmaceutical products containing sulfites, the FDA requires a warning about possible allergic-type reactions, including possible life-threatening anaphylaxis symptoms and/or asthma episodes, in susceptible persons (3). Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who are subject to allergic reactions to the chemicals. Many sulfite-sensitive persons have asthma or other allergic conditions. Previous to the regulations dealing with prescription medication, the FDA issued regulations for the use of sulfites in food. Asthmatics and other patients who may be sulfite sensitive should be reminded to read the labels of packaged

foods and medications to check for the presence of these agents. Sulfite agents covered by the regulations are potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide. The FDA permits the use of sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes for sulfites to maintain potency in certain medications. Some but not all epinephrine injections contain sulfites.

The proper use of antioxidants permits their specific application only after appropriate biomedical and pharmaceutical studies. In certain instances, other pharmaceutical additives can inactivate a given antioxidant. In other cases, certain antioxidants can react chemically with the drugs they were intended to stabilize without a noticeable change in the appearance of the preparation.

Because oxygen may adversely affect their stability, certain pharmaceuticals require an oxygen-free atmosphere during preparation and storage. Oxygen may be present in pharmaceutical liquids in the airspace within the container or may be dissolved in the liquid vehicle. To avoid these exposures, oxygen-sensitive drugs may be prepared in the dry state and packaged in sealed containers with the air replaced by an inert gas such as nitrogen, as may liquid preparations. This is a common practice in commercial production of vials and ampuls of easily oxidizable preparations intended for parenteral use.

Trace metals originating in the drug, solvent, container, or stopper are a constant source of difficulty in preparing stable solutions of oxidizable drugs. The rate of formation of color in epinephrine solutions, for instance, is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions. Great care must be taken to eliminate these trace metals from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process. These chelating agents are exemplified by calcium disodium edetate and EDTA.

Light can also act as a catalyst to oxidation reactions, transferring its energy (photons) to drug molecules, making the latter more reactive through increased energy capability. As a precaution against acceleration of oxidation, sensitive preparations are packaged in light-resistant or opaque containers.

Because most drug degradations proceed more rapidly as temperature increases, it is also advisable to maintain oxidizable drugs in a cool place. Another factor that can affect the stability of an oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at the pH most favorable to its stability. This varies from preparation to preparation and must be determined on an individual basis for the drug in question.

Statements in the USP warn of the oxidative decomposition of susceptible drugs and preparations. In some instances, the specific agent to employ as a stabilizer is mentioned in the monograph, and in others, the term "suitable stabilizer" is used. An example in which a particular agent is designated for use is in the monograph for Potassium Iodide Oral Solution, USP. Potassium iodide in solution is prone to photocatalyzed oxidation and the release of free iodine, with a resultant yellow-to-brown discoloration of the solution. The use of light-resistant containers is essential to its stability. As a further precaution against decomposition if the solution is not to be used within a short time, the USP recommends the addition of 0.5 mg of sodium thiosulfate for each gram of potassium iodide. In the event, free iodine is released during storage, and the sodium thiosulfate converts it to colorless and soluble sodium iodide:

$$I_2 + 2Na_2S_2O_3 \rightarrow 2NaI + Na_2S_4O_6$$

In summary, for easily oxidizable drugs, the formulation pharmacist may stabilize the preparation by the selective exclusion from the system of oxygen, oxidizing agents, trace metals, light, heat, and other chemical catalysts to the oxidation process. Antioxidants, chelating agents, and buffering agents may be added to create and maintain a favorable pH.

In addition to oxidation and hydrolysis, destructive processes include polymerization, chemical decarboxylation, and deamination. However, these processes occur less frequently and are peculiar to only small groups of chemical substances.

Stability Testing

FDA's Current Good Manufacturing Practice regulations include sections on stability and stability testing of pharmaceutical components and finished pharmaceutical products (4). In addition, FDA and International Conference on Harmonization guidelines and guidances provide working recommendations to support the regulatory requirements. Among these are the following (5):

- "Stability Testing of New Drug Substances and Products"
- "Quality of Biotechnological Products: Stability Testing of Biotechnology/Biological Drug Products"
- "Photostability Testing of New Drug Substances and Products"
- "Stability Testing of New Dosage Forms"

Drug and drug product stability testing during every stage of development is critical to the quality of the product. Physical Pharmacy Capsule 4.18, Analytical Methods and Standard Curves provides a summary of the procedures required for the analysis of drug substances. Drug stability is important during preclinical testing and in clinical (human) trials to obtain a true and accurate assessment of the product being evaluated. For a marketed drug product, assurance of stability is vital to its safety and effectiveness during the course of its shelf life and use.

PHYSICAL PHARMACY CAPSULE **4.18**

Analytical Methods and Standard Curves

Any study involving concentration of a drug requires an analytical method and the development of standard curves. There are numerous analytical methods used in pharmacy. It is important for pharmacists to have a basic understanding of pharmaceutical analysis to ensure that valid results are obtained when tests are being conducted. It is important to know (*a*) when to test, (*b*) what to test, (*c*) what method(s) to use, (*d*) how to interpret the results, (*e*) the limits of the test, and (*f*) the importance of analytical testing in the overall quality program in pharmacy.

The goal in analytical testing is to produce results as accurately, efficiently, and quickly as possible. Any analytical method used should have accuracy, speed, reproducibility, and specificity. No single analytical method is ideally suited for all drugs; each method has its own strengths and weaknesses, and there are a number of factors that determine the validity and reliability of results.

SELECTION OF AN ANALYTICAL METHOD

One general consideration in analytical method selection is the type of information that is needed: quantitative (potency, concentration), semiquantitative (where a "cutoff" level is involved, as in endotoxin levels), or qualitative (yes/no type of testing, including substance identification, sterility). Another consideration involves the physical and chemical characteristics of the analyte, including its solubility, partition coefficient, dissociation constant (pK_a), volatility, binding, and the quantity present.

One must consider the degree of quantitative measurement in the validation process, for example, accuracy, repeatability/reproducibility, and precision are required; generally, the greater the level that is required, the more sophisticated and expensive the analytical methods that must be used. This is also governed by the types of instrumentation that are on hand or available and the standards available for comparison.

PHYSICAL PHARMACY CAPSULE 4.18 CONT.

FACTORS INVOLVED IN METHODS SELECTION

The ultimate analytical method selected depends upon a number of factors, including sample requirements, sample handling/preparation/purification requirements, type of data needed, and levels of specificity and accuracy required.

SAMPLING REQUIREMENTS

In any analytical method, there may be certain sample requirements that impact one's choice, such as the number of samples needed, the difficulty in obtaining a representative sample, the physical state of the sample (solid, liquid, or gas), the type of container required for collection and storage of the sample (some analytes may sorb to the walls or cap liner of the sample containers), and leaching of the container material into the sample, if a liquid, may occur. All these may cause problems in analysis. In the event of sorption, siliconization of the sample vials may sometimes help.

The storage requirements for the sample after collection must be specified (type of container, material used, UV protection, latex contamination, etc.). The effects of air, such as oxidation of the sample ingredients, the presence of carbon dioxide and the formation of insoluble carbonates, pH changes, free versus bound drug, etc., must be considered. The sample must be stored at the proper temperature (refrigerated, frozen, or controlled room) prior to shipment and during shipment. Procedures to follow if the sample is accidentally frozen or experiences a freeze–thaw cycle should be detailed.

In considering the chemical and physical stability of the sample, the effects of water must also be considered. If the sample must be maintained in a dry environment, including a desiccant, this should be detailed. The stability of the sample during storage, extraction, and preparation must be determined. The potential for enzymatic breakdown, or other adverse effects of pH, temperature, solvents, bacterial growth, etc., must be addressed. If volatile solvents are required, special handling must be implemented to prevent evaporation because if some of the solvent is allowed to evaporate, the resulting concentration may be falsely elevated.

The sample matrix effects must be determined. Any effects caused by sample viscosity (pipetting, aspiration), ionic strength (immunoassays, dialysis), buffers (ionized/unionized ratio can alter the extraction efficiency of an analyte prior to analysis), and vapor pressure, where drug can be lost, must be considered. If any sample pretreatment is required prior to shipment or working in-house, consider any inaccuracies that may occur from pipetting, which is one of the most common sources of analytical errors when working with small volumes.

There must be a consideration of any physical methods of separation and purification that might be used. Most analytical methods require some degree of sample pretreatment to prepare it for analysis. These may include crystallization from solution, distillation, sublimation, solvent extraction, solid-phase extraction, chromatography, and centrifugation; the proper choice of separation and purification depends upon the physical and chemical properties of the sample, including its solubility, volatility, binding, quantity present, etc. The effect of any substances in the formulation that may interfere or alter the results must be known beforehand.

DATA INTERPRETATION REQUIREMENTS

The collection of raw data from the analytical process must be done appropriately. One must ensure that appropriate and valid descriptive statistics are used to analyze the data and that the operating parameters of the analytical instruments are well established. Reference values, if available, should be provided with the analytical results. A description of the analytical controls used by the laboratory is important for documentation, as well as the source of reference standards used to establish standard curves.

PHYSICAL PHARMACY CAPSULE 4.18 CONT.

ANALYTICAL METHODS

In pharmaceutical analysis, analytical methods can be generally divided into physical testing methods, methods that interact with electromagnetic radiation, conductometric techniques, immunoassay methods, separation techniques, and others.

Nonspecific methods generally include melting, freezing and boiling points, density, refractive index, polarimetry, ultraviolet/visible spectroscopy, and pH. Methods that are somewhat more specific include infrared spectroscopic, mass spectroscopy, ion-selective electrodes, immunoassay methods, and chromatographic methods (high-performance liquid chromatography [HPLC] and gas chromatography [GC]), provided proper standards are used.

Methods that can be routinely used for testing incoming bulk materials, whether active or excipients, include melting, freezing and boiling points, density, refractive index, UV/visible spectroscopy, infrared spectroscopy, polarimetry, pH, and the separation methods. Final products may generally require a method such as HPLC or GC. A classification of analytical methods follows along with suggested analytical methods that can be used for different dosage forms.

CLASSIFICATION OF ANALYTICAL AND MICROBIOLOGICAL METHODS

Physical testing procedures
- Melting point
- Freezing point
- Boiling point
- Density
- Refractive index
- Optical rotation (polarimetry)
- Thermal analysis
- Color change
- Precipitate formation
- Viscosity change

Interaction of electromagnetic radiation
- Ultraviolet/visible spectroscopy
- Infrared spectroscopy
- Fluorescence/phosphorescence spectroscopy
- Raman spectroscopy
- X-ray spectroscopy
- Flame emission and atomic absorption spectroscopy
- Polarimetry
- Refractometry
- Interferometry

Conductance methods
- pH
- Ion-selective electrodes
- Polarography

Immunoassay
- Radioimmunoassay
- Enzyme-multiplied immunoassay technique
- Enzyme-linked immunosorbent assay
- Fluorescent immunoassay

Separation techniques
- HPLC
- GC
- Thin-layer chromatography

PHYSICAL PHARMACY CAPSULE 4.18 CONT.

Paper chromatography
Column chromatography
Gravimetric
Balance
Others
Osmolality
Microbiological methods
Sterility testing
Endotoxin testing
Preservative effectiveness testing

Suggested analytical methods for various dosage forms, depending upon the active drug:

DOSAGE	ANALYTICAL METHOD												
FORM	WT	VOL	PH	OSM	RI	SP GR	MP	UV/VIS	HPLC	GC	IR	STERIL	ENDO
Bulk substances	—	—	*	—	*	—	*	*	*	*	*	—	—
Powders	*	—	—	—	—	—	—	—	*	*	—	—	—
Capsules	*	—	—	—	—	—	—	—	*	*	—	—	—
Tablets	*	—	—	—	—	—	—	—	*	*	—	—	
Lozenges	*	—	—	—	—	—	—	—	*	*	—	—	—
Suppositories	*	—	—	—	—	*	*	—	*	*	—	—	—
Sticks	*	—	—	—	—	*	*	—	*	*	—	—	—
Solutions	*	*	*	*	*	*	—	*	*	*	—	—	—
Suspensions	*	*	*	—	—	*	—	—	*	*	—	—	—
Emulsions	*	*	*	—	—	*	—	—	*	*	—	—	—
Semisolids	*	—	—	—	—	*	*	—	*	*	—	—	—
Gels	*	*	*	—	*	*	—	—	*	*	—	—	—
Ophthalmics, Otics, and Nasals	*	*	*	*	*	*	—	*	*	*	—	*(Ophthalmic only)	—
Inhalations	*	*	*	*	*	—	—	*	*	*	—	*	—
Injections	*	*	*	*	*	*	—	*	*	*	—	*	*

CONSTRUCTION OF A STANDARD CURVE

A standard curve is constructed by analyzing samples (standards) of known composition, generally in increasing concentrations. As each standard is analyzed, an instrumental response (absorbance, peak height, peak area, other numerical value) will be obtained. The standard concentrations are plotted as the "x" axis on a graph and the instrumental responses are plotted on the "y" axis. As an example,

The following table represents the results from an HPLC analytical method of methotrexate.

Concentration (μg/mL)	0	10	20	30
Response (Peak Height in units)	0	2,600	5,190	7,780

When plotted on a graph, one obtains the following:

PHYSICAL PHARMACY CAPSULE 4.18 CONT.

The next step involves analyzing the unknown sample to obtain a response from the instrument. For example, if the unknown sample provided an instrumental response of 3,895, checking that value on the y-axis and moving toward the right on the graph until it intersects the plotted line and dropping down to the x-axis, we can read a value of 15 µg/mL of the methotrexate. As an option, the equation of the line can be calculated and the concentration determined by substituting the values of "y" and "b" with the slope of the line to obtain the drug concentration, as follows:

$$m = \Delta y / \Delta / x = (7780 - 0) / (30 - 0) = 7780 / 30 = 259.3$$

$$y = mx + b$$
$$3{,}895 = 259.3x + 0$$
$$x = 15.02\ \mu g/mL$$

The FDA-required demonstration of drug stability is necessarily different for each stage of drug development, such as for a 2-week preclinical study, an early phase I study, a limited phase II trial, a pivotal phase III clinical study, or for a new drug application. As a drug development program progresses, so do the requisite data to demonstrate and document the product's stability profile. Before approval for marketing, a product's stability must be assessed with regard to its formulation; the influence of its pharmaceutical ingredients; the influence of the container and closure; the manufacturing and processing conditions (e.g., heat); packaging components; conditions of storage; anticipated conditions of shipping, temperature, light, and humidity; and anticipated duration and conditions of pharmacy shelf life and patient use. Holding intermediate product components (such as drug granulations for tablets) for long periods before processing into finished pharmaceutical products can affect the stability of both the intermediate component and the finished product. Therefore, in-process stability testing, including retesting of intermediate components, is important.

Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles require different stability test protocols from those for blister packs or strip packaging. Drugs particularly subject to hydrolysis or oxidative decomposition must be evaluated accordingly. And sterile products must meet sterility test standards to ensure protection against microbial contamination. All preservatives must be tested for effectiveness in the finished product.

As noted elsewhere in this section, drug products must meet stability standards for long-term storage at room temperature and relative humidity. Products are also subjected to accelerated stability studies as an indication of shelf life stability. Drug instability in pharmaceutical formulations may be detected in some instances by a change in the physical appearance, color, odor, taste, or texture of the formulation, whereas in other instances, chemical changes may not be self-evident and may be ascertained only through chemical analysis. Scientific data pertaining to the stability of a formulation can lead to prediction of the expected shelf life of the proposed product, and when necessary to redesign of the drug (e.g., into more stable salt or ester form) and to reformulation of the dosage form. Obviously, the rate at which a drug product degrades is of prime importance. The study of the rate of chemical change and the way it is influenced by such factors as the concentration of the drug or

reactant, the solvent, temperature and pressure, and other chemical agents in the formulation is reaction kinetics.

In general, a kinetic study begins by measuring the concentration of the drug at given intervals under a specific set of conditions, including temperature, pH, ionic strength, light intensity, and drug concentration. The measurement of the drug's concentration at the various times reveals the stability or instability of the drug under the specified conditions with the passage of time. From this starting point, each of the original conditions may be varied to determine the influence of such changes on the drug's stability. For example, the pH of the solution may be changed while the temperature, light intensity, and original drug concentration are held constant.

The findings may be presented graphically, by plotting the drug concentration as a function of time. From the experimental data, the reaction rate may be determined and a rate constant and half-life calculated.

Accelerated Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and where appropriate, oxidation, light and microbial exposure. Stability testing is also used to establish the shelf life for a drug product and recommended storage conditions (6,7).

Among the definitions applied in stability testing are (7):

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of long-term, intermediate, and accelerated studies. Data from these studies are used to assess degradation that might occur under normal (nonexaggerated) or slight deviations in storage conditions as during shipping and storage. Results allow the development of product labeling with regard to expiration dating and recommended conditions for storage.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated withexcipients to produce the dosage form.

Excipient: Anything other than the drug substance in the dosage form.

Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of a drug substance. Such testing is part of the drug development process and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing as well as the specific testing of certain product types (e.g., metered dose inhalers, creams, emulsions).

For the drug substance, the testing should evaluate its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. Data should be obtained from at least three pilot-scale batches of the drug substance, manufactured by the method and procedures that mirror the process to be used for final full-scale production batches. Stability studies also should be conducted on the drug substance packaged in the container closure system that is the same or simulates the packaging proposed for the final product.

For the drug product, the design of the stability studies should be based on knowledge gained from those studies of the drug substance. Stability studies should be conducted

Table 4.2 EXAMPLE PROTOCOL FOR DRUG AND/OR DRUG PRODUCT STABILITY STUDIES[a]

STUDY TYPE	STORAGE CONDITION	MINIMUM TIME PERIOD
Long term	25°C ± 2°C @ 60% RH[b]± 5% RH	12 mo
Intermediate	30°C ± 2°C @ 65% RH[a]± 5% RH	6 mo
Accelerated	40°C ± 2°C @ 75% RH[a]± 5% RH	6 mo

[a]For chemical entities. Adapted from Stability and Testing of New Drug Substances and Products. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf. (Accessed September 28, 2012).
[b]RH, relative humidity.

on at least three batches of the manufactured dosage form, packaged in the container and closure system, including all secondary packaging (e.g., outer carton) proposed for marketing. The studies should include testing of those attributes of the product that are susceptible to change during storage, thereby affecting quality and efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes; preservative content (e.g., antioxidant, antimicrobial preservative); and functionality tests (e.g., metered-dose delivery system).

Table 4.2 presents an example protocol for long-term, intermediate, and accelerated stability studies for a chemical drug entity and dosage form product. Protocols vary for products intended to be maintained under conditions of refrigeration, for those to be frozen, for products known to be destined for geographic areas of temperature extremes, and for biotechnological/biological products, which have separate protocols for stability studies. Physical Pharmacy Capsule 4.19 presents the Q_{10} Method of Shelf Life Estimation.

PHYSICAL PHARMACY CAPSULE 4.19

Q_{10} Method of Shelf Life Estimation

The Q_{10} approach, based on Ea, which is independent of reaction order, is described as

$$Q_{10} = e^{\{(Ea/R)[(1/T+10)-(1/T)]\}}$$

where

Ea is the energy of activation,
R is the gas constant, and
T is the absolute temperature.

In usable terms, Q_{10}, the ratio of two different reaction rate constants, is defined thus:

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$

The commonly used Q values of 2, 3, and 4 relate to the energies of activations of the reactions for temperatures around room temperature (25°C). For example, a Q value of 2 corresponds to an Ea (kcal/mol) of 12.2, a Q value of 3 corresponds to an Ea of 19.4, and a Q value of 4 corresponds to an Ea of 24.5. Reasonable estimates can often be made using the value of 3.

PHYSICAL PHARMACY CAPSULE 4.19 CONT.

The equation for Q_{10} shelf life estimates is

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

where

$t_{90}T_2$ is the estimated shelf life,
$t_{90}T_1$ is the given shelf life at a given temperature, and
ΔT is the difference in the temperatures T_1 and T_2.

As is evident from this relationship, an increase in ΔT will decrease the shelf life and a decrease in ΔT will increase the shelf life. This is the same as saying that storing at a warmer temperature will shorten the life of the drug and storing at a cooler temperature will increase the life of the drug.

EXAMPLE 1

An antibiotic solution has a shelf life of 48 hours in the refrigerator (5°C). What is its estimated shelf life at room temperature (25°C)?

Using a Q value of 3, we set up the relationship as follows:

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} = \frac{48}{3^{[(25-5)/10]}} = \frac{48}{3^2} = 5.33 \text{ hours}$$

EXAMPLE 2

An ophthalmic solution has a shelf life of 6 hours at room temperature (25°C). What is the estimated shelf life in a refrigerator at 5°C? (*Note*: Since the temperature is decreasing, ΔT will be negative.)

$$t_{90}(T_2) = \frac{6}{3^{[(5-25)/10]}} = \frac{6}{3^{-2}} = 6 \times 3^2 = 54 \text{ hours}$$

These are estimates, and actual energies of activation can often be obtained from the literature for more exact calculations.

Following FDA product approval and initial marketing, pharmaceutical manufacturers retain production samples of drug/drug product for 5 years or longer and continue studies for signs of degradation under various conditions of storage. Pharmacy practitioners should also observe signs of product instability (e.g., color change, distorted capsules, softened tablets, etc.) and report such findings.

Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf life that commercially manufactured and distributed products do because they are intended to be used immediately on receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of use, and the compounding pharmacist must employ formulative components and techniques that will result in a stable product (7).

Today, there are a number of literature sources for the pharmacist to utilize in the compounding of high quality and

stable prescriptions. Several of these are listed among the references, including the USP chapters on the compounding of sterile and nonsterile preparations (8–12).

USP guidelines on stability of extemporaneous compounded formulations state that in the absence of stability information applicable to a specific drug and preparation, the following guidelines can be used: nonaqueous liquids and solid formulations in which the manufactured drug is the source of the active ingredient, not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier; nonaqueous liquids and solid formulations in which a USP or National Formulary (NF) substance is the source of active ingredient, a beyond-use date of 6 months; for water-containing formulations prepared from ingredients in solid form, a beyond-use date not later than 14 days in storage at cold temperatures; and for all other formulations, a beyond-use date of the intended duration of therapy or 30 days, whichever is earlier (8). Thus, if an oral aqueous liquid preparation is made from a tablet or capsule formulation, the pharmacist should make up only at most 14 days' supply, and it must be stored in a refrigerator. Furthermore, the pharmacist must dispense the medication in a container conducive to stability and use and must advise the patient of the proper method of use and conditions of storage of the medication.

Finally, when compounding on the basis of extrapolated or less than concrete information, the pharmacist is well advised to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.

PHARMACEUTICAL INGREDIENTS AND EXCIPIENTS

Definitions and Types

To produce a drug substance in a final dosage form requires pharmaceutical ingredients. For example, in the preparation of solutions, one or more *solvents* are used to dissolve the drug substance, *flavors* and *sweeteners* are used to make the product more palatable, *colorants* are added to enhance appeal, *preservatives* may be added to prevent microbial growth, and *stabilizers*, such as antioxidants and chelating agents, may be used to prevent decomposition, as previously discussed. In the preparation of tablets, *diluents* or *fillers* are commonly added to increase the bulk of the formulation, *binders* to cause adhesion of the powdered drug and pharmaceutical substances, *antiadherents* or *lubricants* to assist smooth tablet formation, *disintegrating agents* to promote tablet breakup after administration, and coatings to improve stability, control disintegration, or enhance appearance. Ointments, creams, and suppositories acquire their characteristic features from their pharmaceutical bases. Thus, for each dosage form, the pharmaceutical ingredients establish the primary features of the product and contribute to the physical form, texture, stability, taste, and overall appearance.

Table 4.3 presents the principal categories of pharmaceutical ingredients, listing some of the official and commercial agents in use. Additional discussion of many ingredients may be found in the chapters where they are most relevant; for example, pharmaceutical materials used in tablet and capsule formulations are discussed in Chapters 7 and 8, and those used in modified-release solid oral dosage forms and drug delivery systems in Chapter 9.

All drug products should be labeled to state the identity of all added substances (excipients). Such listing should be in alphabetical order by name and be distinguished from the identification statement of the active ingredient(s). The name of the inactive ingredient should be taken from the current edition of one of the following references works (in the following order of precedence): (*a*) the USP or the NF, (*b*) USAN and the USP Dictionary of Drug Names, (*c*) CTFA Cosmetic Ingredient Dictionary, and (*d*) Food Chemicals codes. If not listed in the above, then the reference works should be identified by the common or usual name or, if no common or usual name is available, by its chemical or other technical name. If an ingredient

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS

INGREDIENT TYPE	DEFINITION	EXAMPLES
Acidifying agent	Used in liquid preparations to provide acidic medium for product stability	Citric acid Acetic acid Fumaric acid Hydrochloric acid Nitric acid
Alkalinizing agent	Used in liquid preparations to provide alkaline medium for product stability	Ammonia solution Ammonium carbonate Diethanolamine Monoethanolamine Potassium hydroxide Sodium bicarbonate Sodium borate Sodium carbonate Sodium hydroxide Trolamine
Adsorbent	An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means	Powdered cellulose Activated charcoal
Aerosol propellant	Agent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened	Carbon dioxide Dichlorodifluoromethane Dichlorotetrafluoroethane Trichloromonofluoromethane
Air displacement	Agent employed to displace air in a hermetically sealed container to enhance product stability	Nitrogen Carbon dioxide
Antifungal preservative	Used in liquid and semisolid preparations to prevent growth of fungi. Effectiveness of parabens is usually enhanced by use in combination	Butylparaben Ethylparaben Methylparaben Benzoic acid Propylparaben Sodium benzoate Sodium propionate
Antimicrobial preservative	Used in liquid and semisolid preparations to prevent growth of microorganisms	Benzalkonium chloride
Antioxidant	Used to prevent deterioration of preparations by oxidation	Ascorbic acid Ascorbyl palmitate Butylated hydroxyanisole Butylated hydroxytoluene Hypophosphorous acid Monothioglycerol Propyl gallate Sodium ascorbate Sodium bisulfite Sodium formaldehyde Sulfoxylate Sodium metabisulfite
Buffering agent	Used to resist change in pH upon dilution or addition of acid or alkali	Potassium metaphosphate Potassium phosphate, monobasic Sodium acetate Sodium citrate, anhydrous and dihydrate

(*Continued*)

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
Chelating agent	Substance that forms stable water-soluble complexes (chelates) with metals; used in some liquid pharmaceuticals as stabilizers to complex heavy metals that might promote instability. In such use, they are also called *sequestering* agents	Edetic acid Edetate disodium
Colorant	Used to impart color to liquid and solid (e.g., tablets and capsules) preparations	FD&C Red No. 3 FD&C Red No. 20 FD&C Yellow No. 6 FD&C Blue No. 2 D&C Green No. 5 D&C Orange No. 5 D&C Red No. 8 Caramel Ferric oxide, red
Clarifying agent	Used as a filtering aid for its adsorbent qualities	Bentonite
Emulsifying agent	Used to promote and maintain dispersion of finely subdivided particles of liquid in a vehicle in which it is immiscible. End product may be a liquid emulsion or semisolid emulsion (e.g., a cream)	Acacia Cetomacrogol Cetyl alcohol Glyceryl monostearate Sorbitan monooleate Polyoxyethylene 50 stearate
Encapsulating agent	Used to form thin shells to enclose a drug for ease of administration	Gelatin
Flavorant	Used to impart a pleasant flavor and often odor to a preparation. In addition to the natural flavorants listed, many synthetic ones are used	Anise oil Cinnamon oil Cocoa Menthol Orange oil Peppermint oil Vanillin
Humectant	Used to prevent drying of preparations, particularly ointments and creams	Glycerin Propylene glycol Sorbitol
Levigating agent	Liquid used as an intervening agent to reduce the particle size of a powder by grinding, usually in a mortar	Mineral oil Glycerin Propylene glycol
Ointment base	Semisolid vehicle for medicated ointments	Lanolin Hydrophilic ointment Polyethylene glycol ointment Petrolatum Hydrophilic petrolatum White ointment Yellow ointment Rose water ointment
Plasticizer	Component of film-coating solutions to make film more pliable, enhance spread of coat over tablets, beads, and granules	Diethyl phthalate Glycerin

Table 4.3 **EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)**

INGREDIENT TYPE	DEFINITION	EXAMPLES
Solvent	Used to dissolve another substance in preparation of a solution; may be aqueous or not (e.g., oleaginous). Cosolvents, such as water and alcohol (hydroalcoholic) and water and glycerin, may be used when needed. Sterile solvents are used in certain preparations (e.g., injections)	Alcohol Corn oil Cottonseed oil Glycerin Isopropyl alcohol Mineral oil Oleic acid Peanut oil Purified water Water for injection Sterile water for injection Sterile water for irrigation
Stiffening agent	Used to increase thickness or hardness of a preparation, usually an ointment	Cetyl alcohol Cetyl esters wax Microcrystalline wax Paraffin Stearyl alcohol White wax Yellow wax
Suppository base	Vehicle for suppositories	Cocoa butter Polyethylene glycols (mixtures) PEG 3350
Surfactant (*surface active agent*)	Substances that absorb to surfaces or interfaces to reduce surface or interfacial tension. May be used as wetting agents, detergents, or emulsifying agents	Benzalkonium chloride Nonoxynol 10 Octoxynol 9 Polysorbate 80 Sodium lauryl sulfate Sorbitan monopalmitate
Suspending agent	Viscosity-increasing agent used to reduce sedimentation rate of particles in a vehicle in which they are not soluble; suspension may be formulated for oral, parenteral, ophthalmic, topical, or other route	Agar Bentonite Carbomer (e.g., Carbopol) Carboxymethylcellulose sodium Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Kaolin Methylcellulose Tragacanth Veegum
Sweetening agent	Used to impart sweetness to a preparation	Aspartame Dextrose Glycerin Mannitol Saccharin sodium Sorbitol Sucrose
Tablet antiadherents	Prevent tablet ingredients from sticking to punches and dies during production	Magnesium stearate

(*Continued*)

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
Tablet binders	Substances used to cause adhesion of powder particles in tablet granulations	Acacia Alginic acid Carboxymethylcellulose sodium Compressible sugar (e.g., Nu-Tab) Ethylcellulose Gelatin Liquid glucose Methylcellulose Povidone Pregelatinized starch
Tablet and capsule diluent	Inert filler to create desired bulk, flow properties, and compression characteristics of tablets and capsules	Dibasic calcium phosphate Kaolin Lactose Mannitol Microcrystalline cellulose Powdered cellulose Precipitated calcium carbonate Sorbitol Starch
Tablet-coating agent	Used to coat a tablet to protect against decomposition by atmospheric oxygen or humidity, to provide a desired release pattern, to mask taste or odor, or for aesthetic purposes. Coating may be sugar, film, or thick covering around a tablet. Sugar-coated tablets generally start to break up in the stomach. Film forms a thin cover around a formed tablet or bead. Unless it is enteric, film dissolves in the stomach. Enteric coating passes through the stomach to break up in the intestines. Some water-insoluble coatings (e.g., ethylcellulose) are used to slow the release of drug in the gastrointestinal tract	
Sugar coating		Liquid glucose Sucrose
Film coating		Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Methylcellulose (e.g., Methocel) Ethylcellulose (e.g., Ethocel)
Enteric coating		Cellulose acetate phthalate Shellac (35% in alcohol, pharmaceutical glaze)
Tablet direct compression excipient	Used in direct compression tablet formulations	Dibasic calcium phosphate (e.g., Ditab)
Tablet disintegrant	Used in solid forms to promote disruption of the mass into smaller particles more readily dispersed or dissolved	Alginic acid Polacrilin potassium (e.g., Amberlite) Sodium alginate Sodium starch glycolate Starch

Table 4.3 **EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)**

INGREDIENT TYPE	DEFINITION	EXAMPLES
Tablet glidant	Used in tablet and capsule formulations to improve flow properties of the powder mixture	Colloidal silica Cornstarch Talc
Tablet lubricant	Used in tablet formulations to reduce friction during tablet compression	Calcium stearate Magnesium stearate Mineral oil Stearic acid Zinc stearate
Tablet or capsule opaquant	Used to render a coating opaque. May be used alone or with a colorant	Titanium dioxide
Tablet polishing agent	Used to impart an attractive sheen to coated tablets	Carnauba wax White wax
Tonicity agent	Used to render solution similar in osmotic-dextrose characteristics to physiologic fluids, for example, in ophthalmic, parenteral, and irrigation fluids	Sodium chloride
Vehicle	Carrying agent used in formulating a variety of liquids for oral and parenteral administration Generally, oral liquids are aqueous (e.g., syrups) or hydroalcoholic (e.g., elixirs). Solutions for intravenous use are aqueous, whereas intramuscular injections may be aqueous or oleaginous	
Flavored, sweetened		Acacia syrup Aromatic syrup Aromatic elixir Cherry syrup Cocoa syrup Orange syrup Syrup
Oleaginous		Corn oil Mineral oil Peanut oil Sesame oil
Sterile		Bacteriostatic sodium chloride injection
Viscosity-increasing agent	Used to render preparations more resistant to flow. Used in suspensions to deter sedimentation, in ophthalmic solutions to enhance contact time (e.g., methylcellulose), to thicken topical creams, etc.	Alginic acid Bentonite Carbomer Carboxymethylcellulose Sodium Methylcellulose Povidone Sodium alginate Tragacanth

may or may not be present, it should be qualified by words such as "or" or "may also contain." If an ingredient is a trade secret, it may be omitted from the list if the list states "and other ingredients." If an ingredient is only present in a trace amount and has no functional or technical effect on the product, it does not need to be listed unless it has been shown to cause sensitivity reactions or allergic responses.

Handbook of Pharmaceutical Excipients

The *Handbook of Pharmaceutical Excipients* (10) presents monographs on more than 300 excipients used in dosage form preparation. Each monograph includes such information as nonproprietary, chemical, and commercial names; empirical and chemical formulas and molecular weight; pharmaceutical specifications and chemical and physical properties; incompatibilities and interactions with other excipients and drug substances; regulatory status; safety, stability, and handling information; and applications in pharmaceutical formulation or technology.

Appearance and Palatability

Although most drug substances in use today are unpalatable and unattractive in their natural state, their preparations present them to the patient as colorful, flavorful formulations attractive to the sight, smell, and taste. These qualities, which are the rule rather than the exception, have virtually eliminated the natural reluctance of many patients to take medications because of disagreeable odor or taste. In fact, the inherent attractiveness of today's pharmaceuticals has caused them to acquire the dubious distinction of being a source of accidental poisonings in the home, particularly among children who are lured by their organoleptic appeal.

There is some psychologic basis to drug therapy, and the odor, taste, and color of a pharmaceutical preparation can play a part. An appropriate drug has its most beneficial effect when it is accepted and taken properly by the patient. The proper combination of flavor, fragrance, and color in a pharmaceutical product contributes to its acceptance.

An "electronic tongue" is used to aid in providing a global "taste fingerprint" during formulation development. It provides information on bitterness levels and the stability of flavors in terms of taste (Figure 4.4).

FIGURE 4.4 Electronic tongue to assist in formulation development. (Courtesy of Alpha MOS.)

Flavoring Pharmaceuticals

The flavoring of pharmaceuticals applies primarily to liquids intended for oral administration. The 10,000 taste buds on the tongue, roof of the mouth, cheeks, and throat have 60 to 100 receptor cells each (13). These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Medication in liquid form comes into immediate and direct contact with these taste buds. The addition of flavoring agents to liquid medication can mask the disagreeable taste. Drugs placed in capsules or prepared as coated tablets may be easily swallowed with no contact between the drug and the taste buds. Tablets containing drugs that are not especially distasteful may remain uncoated and unflavored. Swallowing them with water usually is sufficient to avoid undesirable taste sensations. However, chewable tablets, such as certain antacid and vitamin products, usually are sweetened and flavored to improve acceptance.

The flavor sensation of a food or pharmaceutical is actually a complex blend of taste and smell, with lesser influences of texture, temperature, and even sight. In flavor-formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation. It would be incongruous, for example, to color a liquid pharmaceutical red and give it a banana taste and a mint odor. The color of a pharmaceutical must have a psychogenic balance with the taste, and the odor must also enhance that taste. Odor greatly affects the flavor of a preparation or foodstuff. If one's sense of smell is impaired, as during a head cold, the usual flavor sensation of food is similarly diminished.

The medicinal chemist and the formulation pharmacist are well acquainted with the taste characteristics of certain chemical types of drugs and strive to mask the unwanted taste through the appropriate use of flavoring agents. Although there are no rules for unerringly predicting the taste sensation of a drug based on its chemical constitution, experience permits the presentation of several observations. For instance, although we recognize and assume the salty taste of sodium chloride, the formulation pharmacist knows that not all salts are salty but that their taste is a function of both cation and anion. Whereas salty tastes are evoked by chlorides of sodium, potassium, and ammonium and by sodium bromide, bromides of potassium and ammonium elicit bitter and salty sensations, and potassium iodide and magnesium sulfate (epsom salt) are predominantly bitter. In general, low molecular weight salts are salty, and high molecular weight salts are bitter.

With organic compounds, an increase in the number of hydroxyl groups (—OH) seems to increase the sweetness of the compound. Sucrose, which has eight hydroxyl groups, is sweeter than glycerin, another pharmaceutical sweetener, which has three hydroxyl groups. In general, the organic esters, alcohols, and aldehydes are pleasant to the taste, and since many of them are volatile, they also contribute to the odor and thus the flavor of preparations in which they are used. Many nitrogen-containing compounds, especially the plant alkaloids (e.g., quinine), are extremely bitter, but certain other nitrogen-containing compounds (e.g., aspartame) are extremely sweet. The medicinal chemist recognizes that even the most simple structural change in an organic compound can alter its taste. D-Glucose is sweet, but L-glucose has a slightly salty taste; saccharin is very sweet, but *N*-methyl-saccharin is tasteless (14).

Thus, prediction of the taste characteristics of a new drug is only speculative. However, it is soon learned and the formulation pharmacist is then put to the task of increasing the drug's palatability in the environment of other formulative agents. The selection of an appropriate flavoring agent depends on several factors, primarily the taste of the drug substance itself. Certain flavoring materials are more effective than others in masking or disguising the particular bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, cocoa-flavored vehicles are considered effective for masking the taste of bitter drugs. Fruit or citrus flavors are frequently used to combat sour or acid-tasting drugs, and cinnamon, orange, raspberry, and other flavors have been successfully used to make preparations of salty drugs more palatable.

The age of the intended patient should also be considered in the selection of the flavoring agent, because certain age groups seem to prefer certain flavors. Children prefer sweet candy-like preparations with fruity flavors, but adults seem to prefer less sweet preparations with a tart rather than a fruit flavor.

Flavors can consist of oil- or water-soluble liquids and dry powders; most are diluted in carriers. Oil-soluble carriers include soybean and other edible oils; water-soluble carriers include water, ethanol, propylene glycol, glycerin, and emulsifiers. Dry carriers include maltodextrins, corn syrup solids, modified starches, gum arabic, salt, sugars, and whey protein. Flavors can degrade as a result of exposure to light, temperature, headspace oxygen, water, enzymes, contaminants, and other product components, so they must be carefully selected and checked for stability.

Flavoring agents may be derived from natural sources (e.g., fruit components) or prepared artificially. They may be either water soluble or oil soluble. Their selected use in pharmaceutical products is based on desired flavor, their solubility characteristics, and their chemical and physical compatibility with the active therapeutic agent and other components of the formulation.

Flavoring agents in liquid pharmaceutical products are added to the solvent or vehicle component of the formulation in which it is most soluble or miscible. That is, water-soluble flavorings are added to the aqueous

component of a formulation and oil-soluble flavorings are added to the nonaqueous components. In general, artificial flavors are used in liquid pharmaceutical at levels of 0.1% to 0.2%, whereas natural flavors are used within the 1% to 2% range.

Sweetening Pharmaceuticals

In addition to sucrose, a number of artificial sweetening agents have been used in foods and pharmaceuticals over the years. Some of these, including aspartame, saccharin, and cyclamate, have faced challenges over their safety by the FDA and restrictions to their use and sale.

A review of the history of safety concerns over the use of artificial sweeteners, current scientific findings, and related FDA and legislative actions, may be found at the Web site: http://www.cancer.gov/cancertopics/factsheet/Risk/artificial-sweeteners.

At the present time, the following artificial sweeteners are approved by the FDA with, in parenthesis, the number of times (×) each one is sweeter than table sugar:

- Acesulfame potassium (~200 ×)
- Aspartame (~180 to 200 ×)
- Sucralose (~600 ×)
- Saccharin (~300 ×)

Most large pharmaceutical manufacturers have special laboratories for taste-testing proposed formulations of their products. Panels of employees or interested community participants participate in evaluating the various formulations, and their assessments become the basis for the firm's flavoring decisions.

Coloring Pharmaceuticals

Coloring agents are used in pharmaceutical preparations for esthetics. A distinction should be made between agents that have inherent color and those that are employed as colorants. An example of a natural substance with inherent color that is employed as a colorant is red ferric oxide. It is mixed in small proportions with zinc oxide powder to give calamine its characteristic pink color, which is intended to match the skin tone upon application.

Most agents employed today to impart color to foods, drugs, cosmetics, and medical devices are synthetic. Synthetic coloring agents were first prepared in the middle of the 19th century from principles of coal tar. Coal tar (*pix carbonis*), a thick, black viscid liquid, is a by-product of the destructive distillation of coal. Its composition is extremely complex, and many of its constituents may be separated by fractional distillation. Among its products are anthracene, benzene, naphtha, creosote, phenol, and pitch. About 90% of the dyes used in the products FDA regulates are synthesized from a single colorless derivative of benzene called aniline. These aniline dyes are also known as synthetic organic dyes or as coal tar dyes, since aniline was originally obtained from bituminous coal. Aniline dyes today come mainly from petroleum.

Many coal tar dyes were originally used indiscriminately in foods and beverages to enhance their appeal without regard to their toxic potential. It was only after careful scrutiny that some dyes were found to be hazardous to health because of either their own chemical nature or the impurities they carried. As more dyestuffs became available, some expert guidance and regulation were needed to ensure the safety of the public. After passage of the Food and Drug Act in 1906, the U.S. Department of Agriculture established regulations by which a few colorants were *permitted* or *certified* for use in certain products. Today, the FDA regulates the use of color additives in foods, drugs, and cosmetics through the provisions of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1960 with the Color Additive Amendments. Lists of color additives *exempt* from certification and those *subject* to certification are codified into law and regulated by the FDA (15). Certified color additives are classified according to their approved use: (*a*) FD&C color additives, which may be used in foods, drugs, and cosmetics; (*b*) D&C color additives, some of which are approved for use in drugs, some in cosmetics, and some in medical devices; and (*c*) external D&C color additives, the use of which is restricted to external parts of the body, not including

the lips or any other body surface covered by mucous membrane. Each certification category has a variety of basic colors and shades for coloring pharmaceuticals. A current list of certified color additives may be found at 21CFR74 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart = 74). One may select from a variety of FD&C, D&C, and external D&C reds, yellows, oranges, greens, blues, and violets. Each is identified by category, color, and number, as for example, "D&C Yellow No. 8" and "FD&C Red No. 4." By selective combinations of the colorants, one can create distinctive colors (Table 4.4).

As a part of the National Toxicology Program of the U.S. Department of Health and Human Services, various substances, including color additives, are studied for toxicity and carcinogenesis. For color additives, the study protocols usually call for a 2-year study in which groups of male and female mice and rats are fed diets containing various quantities of the colorant. The killed and surviving animals are examined for evidence of long-term toxicity and carcinogenesis. Five categories of evidence of carcinogenic activity are used in reporting observations: (*a*) "clear evidence" of carcinogenic activity; (*b*) "some evidence"; (*c*) "equivocal evidence," indicating uncertainty; (*d*) "no evidence," indicating no observable effect; and (*e*) "inadequate study," for studies that cannot be evaluated because of major flaws.

The certification status of the colorants is continually reviewed, and changes are made in the list of certified colors in accordance with toxicology findings. These changes may be (*a*) the withdrawal of certification, (*b*) the transfer of a colorant from one certification category to another, or (*c*) the addition of new colors to the list. Before gaining certification, a color additive must be demonstrated to be safe. By FDA definition, "*safe*" means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive (16).

It should be borne in mind, however, that on an individual basis, some persons may demonstrate an allergic-type response to certain color additives and should avoid such agents accordingly.

Each certified color additive is subject to a host of chemical standards which must be met, including: chemical identity, purity, and specifically stated levels of allowable impurities (17).

Table 4.4 EXAMPLES OF COLOR FORMULATIONS

SHADE OR COLOR	FD&C DYE	% OF BLEND
Orange	Yellow No. 6	95
	or	
	Yellow No. 5	5
	Red No. 40	100
Cherry	Red No. 40	100
	or	
	Red No. 40	99
	Blue No. 1	1
Strawberry	Red No. 40	100
	or	
	Red No. 40	95
	Red No. 3	5
Lemon	Yellow No. 5	100
Lime	Yellow No. 5	95
	Blue No. 1	5
Grape	Red No. 40	80
	Blue No. 1	20
Raspberry	Red No. 3	75
	Yellow No. 6	20
	Blue No. 1	5
Butterscotch	Yellow No. 5	74
	Red No. 40	24
	Blue No. 1	2
Chocolate	Red No. 40	52
	Yellow No. 5	40
	Blue No. 1	8
Caramel	Yellow No. 5	64
	Red No. 3	21
	Yellow No. 6	9
	Blue No. 1	6
Cinnamon	Yellow No. 5	60
	Red No. 40	35
	Blue No. 1	5

In addition, they must be shown to not interfere with the therapeutic efficacy of a pharmaceutical product nor should they interfere with the performance of quality control assay procedures.

A colorant becomes an integral part of a pharmaceutical formulation, and its exact quantitative amount must be reproducible each time the formulation is prepared or else the preparation would have a different appearance from batch to batch. This requires a high degree of skill, for the amount of colorant generally added to liquid preparations ranges from 0.0005% to 0.001% depending upon the colorant and the depth of color desired. Because of their color potency, dyes generally are added to pharmaceutical preparations in the form of diluted solutions rather than as concentrated dry powders. This permits greater accuracy in measurement and more consistent color production (18).

In addition to liquid dyes in the coloring of pharmaceuticals, lake pigments may also be used. An FD&C lake is a pigment consisting of a substratum of alumina hydrate on which the dye is adsorbed or precipitated. Having aluminum hydroxide as the substrate, the lakes are insoluble in nearly all solvents.

Lakes in pharmaceuticals are commonly used in the form of fine dispersions or suspensions. The pigment particles may range in size from <1 μm up to 30 μm. The finer the particle, the less chance for color speckling in the finished product. Blends of various lake pigments may be used to achieve a variety of colors, and various vehicles, such as glycerin, propylene glycol, and sucrose-based syrup, may be employed to disperse the colorants.

Colored empty gelatin capsule shells may be used to hold a powdered drug mixture. Many commercial capsules are prepared with a capsule body of one color and a cap of a different color, resulting in a two-colored capsule. This makes certain commercial products more readily identifiable than solid-colored capsules. For powdered drugs dispensed as such or compressed into tablets, a generally larger proportion of dye is required (about 0.1%) to achieve the desired hue than with liquid preparations.

Both dyes and lakes are used to color sugar-coated tablets, film-coated tablets, direct compression tablets, pharmaceutical suspensions, and other dosage forms (19). Traditionally, sugar-coated tablets have been colored with syrup solutions containing varying amounts of the water-soluble dyes, starting with very dilute solutions, working up to concentrated color syrup solutions. As many as 30 to 60 coats are common. With the lakes, fewer color coats are used. Appealing tablets have been made with as few as 8 to 12 coats using lakes dispersed in syrup. Water-soluble dyes in aqueous vehicles or lakes dispersed in organic solvents may be effectively sprayed on tablets to produce attractive film coatings. There is continued interest today in chewable tablets, because of the availability of many direct compression materials such as dextrose, sucrose, mannitol, sorbitol, and spray-dried lactose. The direct compression colored chewable tablets may be prepared with 1 lb of lake per 1,000 lb of tablet mix. For aqueous suspensions, FD&C water-soluble colors or lakes may be satisfactory. In other suspensions, FD&C lakes are necessary. The lakes, added to either the aqueous or the nonaqueous phase, generally at a level of 1 lb of color per 1,000 lb of suspension, require homogenization or mechanical blending to achieve uniform coloring.

For the most part, ointments, suppositories, and ophthalmic and parenteral products assume the color of their ingredients and do not contain color additives. Should a dye lose the certification status it held when a product was first formulated, manufactured, and marketed, the manufacturer must reformulate within a reasonable length of time, using only color additives certified at the new date of manufacture.

In addition to esthetics and the certification status of a dye, a formulation pharmacist must select the dyes to be used in a particular formula on the basis of their physical and chemical properties. Of prime importance is the solubility of a prospective dye in the vehicle to be used for a liquid formulation or in a solvent to be employed during a pharmaceutical process, as when the dye is sprayed on a batch of tablets. In general, most dyes are broadly grouped into those that are water

soluble and those that are oil soluble; few if any dyes are both. Usually, a water-soluble dye is also adequately soluble in commonly used pharmaceutical liquids like glycerin, alcohol, and glycol ethers. Oil-soluble dyes may also be soluble to some extent in these solvents and in liquid petrolatum (mineral oil), fatty acids, fixed oils, and waxes. No great deal of solubility is required, since the concentration of dye in a given preparation is minimal.

Another important consideration when selecting a dye for use in a liquid pharmaceutical is the pH and pH stability of the preparation to be colored. Dyes can change color with a change in pH, and the dye must be selected so that no anticipated pH change will alter the color during the usual shelf life. The dye also must be chemically stable in the presence of the other formulative ingredients and must not interfere with the stability of the other agents. To maintain their original colors, FD&C dyes must be protected from oxidizing agents, reducing agents (especially metals, including iron, aluminum, zinc, and tin), strong acids and alkalis, and excessive heating. Dyes must also be reasonably photostable; that is, they must not change color when exposed to light of anticipated intensities and wavelengths under the usual conditions of shelf storage. As required, amber or opaque glass or plastic containers may be used to protect photolabile ingredients, including active therapeutic ingredients and colorants.

Preservatives

In addition to the stabilization of pharmaceutical preparations against chemical and physical degradation due to changed environmental conditions within a formulation, certain liquid and semisolid preparations must be preserved against microbial contamination.

Sterilization and Preservation

Although some types of pharmaceutical products, for example, ophthalmic and injectable preparations, are sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C, dry heat at 180°C for 1 hour, or bacterial filtration) during manufacture, many of them also require an antimicrobial preservative to maintain their aseptic condition throughout storage and use. Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative. Preparations that provide excellent growth media for microbes are most aqueous preparations, especially syrups, emulsions, suspensions, and some semisolid preparations, particularly creams. Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth. Generally, 15% v/v alcohol will prevent microbial growth in acid media and 18% v/v in alkaline media. Most alcohol-containing pharmaceuticals, such as elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation. The same applies to other individual pharmaceuticals that by virtue of their vehicle or other formulative agents may not permit the growth of microorganisms.

Preservative Selection

When experience or shelf storage experiments indicate that a preservative is required in a pharmaceutical preparation, its selection is based on many considerations, including some of the following:

- The preservative prevents the growth of the type of microorganisms considered the most likely contaminants of the preparation.
- The preservative is soluble enough in water to achieve adequate concentrations in the aqueous phase of a system with two or more phases.
- The proportion of preservative remaining undissociated at the pH of the preparation makes it capable of penetrating the microorganism and destroying its integrity.
- The required concentration of the preservative does not affect the safety or comfort of the patient when the pharmaceutical preparation is administered by the usual

or intended route; that is, it is nonirritating, nonsensitizing, and nontoxic.
- The preservative has adequate stability and will not be reduced in concentration by chemical decomposition or volatilization during the desired shelf life of the preparation.
- The preservative is completely compatible with all other formulative ingredients and does not interfere with them nor do they interfere with the effectiveness of the preservative agent.
- The preservative does not adversely affect the preparation's container or closure.

General Preservative Considerations

Microorganisms include molds, yeasts, and bacteria, with bacteria generally favoring a slightly alkaline medium and the others an acid medium. Although few microorganisms can grow below pH 3 or above pH 9, most aqueous pharmaceutical preparations are within the favorable pH range and therefore must be protected against microbial growth. To be effective, a preservative agent must be dissolved in sufficient concentration in the aqueous phase of a preparation. Furthermore, only the undissociated fraction or molecular form of a preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism. Thus, the preservative selected must be largely undissociated at the pH of the formulation being prepared. Acidic preservatives like benzoic, boric, and sorbic acids are more undissociated and thus more effective as the medium is made more acid. Conversely, alkaline preservatives are less effective in acid or neutral media and more effective in alkaline media. Thus, it is meaningless to suggest preservative effectiveness at specific concentrations unless the pH of the system is mentioned and the undissociated concentration of the agent is calculated or otherwise determined. Also, if formulative materials interfere with the solubility or availability of the preservative agent, its chemical concentration may be misleading, because it may not be a true measure of the effective concentration. It is essential for the research pharmacist to examine all formulative ingredients as one affects the other to ensure that each agent is free to do its job. In addition, the preservative must not interact with a container or closure.

The FDA recommends that in the pharmaceutical development process, the lowest effective concentration of an antimicrobial preservative should be used and that it should be demonstrated to be effective by an antimicrobial preservative effectiveness test. The concentration used should be validated in terms of efficacy and safety, with the effectiveness confirmed to last throughout the intended shelf life of the product (19).

Mode of Action

Preservatives interfere with microbial growth, multiplication, and metabolism through one or more of the following mechanisms:

- Modification of cell membrane permeability and leakage of cell constituents (partial lysis)
- Lysis and cytoplasmic leakage
- Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)
- Inhibition of cellular metabolism, such as by interfering with enzyme systems or inhibition of cell wall synthesis
- Oxidation of cellular constituents
- Hydrolysis

Examples of the preservatives and their concentrations commonly employed in pharmaceutical preparations are benzoic acid (0.1% to 0.2%), sodium benzoate (0.1% to 0.2%), alcohol (15% to 20%), phenylmercuric nitrate and acetate (0.002% to 0.01%), phenol (0.1% to 0.5%), cresol (0.1% to 0.5%), chlorobutanol (0.5%), benzalkonium chloride (0.002% to 0.01%), and combinations of methylparaben and propylparaben (0.1% to 0.2%), the latter being especially good against fungus. The required proportion varies with the pH, dissociation, and other factors already indicated as well with the presence of other formulative ingredients with inherent preservative capabilities.

For each type of preparation to be preserved, the research pharmacist must

consider the influence of the preservative on the comfort of the patient. For instance, a preservative in an ophthalmic preparation must have an extremely low degree of irritant qualities, which is characteristic of chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate, frequently used in ophthalmic preparations. In all instances, the preserved preparation must be biologically tested to determine its safety and efficacy and shelf-tested to determine its stability for the intended shelf life of the product.

CLINICAL CASE STUDY

SUBJECTIVE INFORMATION

HPI: Jen, an 8-year-old female is 4'1" tall, weighs 27 kg and has no known allergies.

She was brought to the clinic by her mother to seek advice on treating a "dry hacking" cough. Her mother states that Jen has had the cough for the past 4 weeks; it is a dry, hacking cough that does not produce any mucous. She experiences these coughs in 2- to 3-minute bouts once or twice daily, after coming in from recess or playing outside. At school, the nurse's office gives her water and a lozenge. After school and at bedtime, she also occasionally experiences the cough. Jen does not complain of stuffiness or increased nasal discharge. However, she has recently complained of a headache that was successfully treated with acetaminophen.

PMH: Over the past 2 months, Jen has had two episodes of sinusitis requiring antibiotic treatment. Her vaccinations are up to date and the rest of her history is negative.

MEDICATION RECORD

1/21 Augmentin 400/5 100 mL 1 tsp bid × 10 days.

4/14 Cefdinir 125/5 200 mL 7 mL bid × 10 days.

FH: The father (age 44) has diabetes mellitus type 2 treated with oral agents and high blood pressure. The mother (age 39) denies any health problems. Two other siblings are reported healthy.

OBJECTIVE INFORMATION

A physical exam reveals a well-nourished, well-developed female child who appears normal for her age. BP, 92/64; HR, 74 bpm; RR, 23 rpm; and temperature of 38°C.

ASSESSMENT

Patient is an 8-year-old female with a dry, hacking cough. She is not on any medications at this time. Cough seems to be aggravated after periods of exertion or exercise. The mother says she is concerned that some medicines might make Jen tired or drowsy while she is at school so she would like one that is least likely to produce drowsiness/sedation.

Jen's mother also wants a product she can give to Jen before school (7:30 AM) that will last until the evening when she returns home. Also, she says that Jen does not like the taste of many medications and is concerned that Jen may not like what is recommended and refuse to take it. Also, she says that Jen prefers strawberry flavors.

PLAN

Three commonly used systemic antitussive medications include codeine, dextromethorphan, and diphenhydramine. Only dextromethorphan will not cause significant drowsiness as will codeine and diphenhydramine. One product that last up to 12 hours is Delsym. Dextromethorphan products do not necessarily taste very good. An option for improving the flavor of Delsym would be to add a commercial flavor. For example, FLAVORx flavorings could be used as follows: For Delsym, 120 mL, strawberry cream 24 drops or 0.7 mL, with vanilla 24 drops or 0.7 mL

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Develop a listing of examples where patients misunderstand the intent of the administration of a pharmaceutical dosage form.
2. Develop a listing of examples where patients misuse/abuse a pharmaceutical dosage form.
3. Explain the appropriate use of specific dosage forms for different patient types, for example, geriatric, pediatric, visually impaired, hearing impaired. Identify and list the most common hurdles or obstacles for these patient populations with respect to medication compliance and discuss ways to overcome these barriers, that is, FLAVORx for liquids for children and PillGlide for children transitioning to tablets.
4. Identify four ophthalmic products with differing preservative agents and provide a rationale for the selection of the specific preservative in the product.
5. Identify elixir dosage form products that contain minimal or no alcohol content. Explain the reasons for this misnomer.
6. Prepare a chart listing which flavors pair well with certain medications based upon their chemical structure and their palatability issues (bitter, salty, etc.). Different groups can select medications with different chemical structures.

Individual Activities

1. Given a specific dosage form, list the signs of degradation a pharmacist might observe indicating product instability.
2. Given a concentration of drug in a liquid dosage form, determine its type of degradation rate and calculate its half-life and when its concentration will be 90% of the labeled amount.
3. Compare and contrast a zero-order rate of degradation and a first-order rate of degradation.
4. Make a listing of drugs that follow a zero-order rate of degradation in a liquid dosage form.
5. Make a listing of drugs that follow first-order rates of degradation in a liquid dosage form.

REFERENCES

1. Poole JW. Preformulation. FMC Corporation, 1982.
2. Brange J, Langkjaer L, Havelund S, et al. Chemical stability of insulin: Hydrolytic degradation during storage of pharmaceutical preparations. Pharm Res 1991;9:715–726.
3. 21CFR201.22. Drugs: Labeling. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr = 201. (Accessed September 28, 2012)
4. 21CFR211. Current Good Manufacturing Practice For Finished Pharmaceuticals. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart = 211. (Accessed September 28, 2012)
5. Stability. International Conference on Harmonization. Available at: http://www.ich.org/about/organisation-of-ich/coopgroup/gcc.html. (Accessed September 28, 2012)
6. FDA & ICH Guidelines on Accelerated Shelf-life Testing. Available at: http://www.fdaregulatory.net/index.php/component/content/article/115-fda-a-ich-guidelines-on-accelerated-shelf-life-testing.html. (Accessed September 28, 2012)
7. Stability and Testing of New Drug Substances and Products. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf. (Accessed September 28, 2012)
8. General Chapter <795 > Pharmaceutical Compounding-Nonsterile Preparations, and General Chapter <797 > Pharmaceutical Compounding-Sterile Preparations. U.S. Pharmacopoeia 31-National Formulary 26, Rockville MD, U.S. Pharmacopoeial Convention, Inc., 2008, pp. 315–336.
9. Trissel L. Trissel's Stability of Compounded Formulations. 3rd Ed. Washington, DC: American Pharmaceutical Association, 2005.
10. Rowe RC, ed. Handbook of Pharmaceutical Excipients. 7th Ed. London: Pharmaceutical Press, 2012.
11. Allen LV Jr. Editor-in-Chief, International Journal of Pharmaceutical Compounding. Edmond, OK. Available at: http://www.ijpc.com/
12. Allen, LV Jr. The Art, Science, and Technology of Pharmaceutical Compounding. 3rd Ed.Washington, DC: American Pharmacists Association, 2008.

13. Lewis R. When smell and taste go awry. FDA Consum 1991;25:29–33.
14. Hornstein I, Teranishi R. The chemistry of flavor. Chem Eng News 1967:45:92–108.
15. 21CFR172 Food Additives. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart = 172&showFR = 1&subpartNode = 21:3.0.1.1.3.9. (Accessed October 1, 2012)
16. 21CFR80 Color Additive Certification. Available at: http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol1/pdf/CFR-2011-title21-vol1-part80.pdf. (Accessed October 1, 2012)
17. 21CFR 74. Listing of Color Additives Subject to Certification. Available at: http://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol1/pdf/CFR-2011-title21-vol1-part80.pdf. (Accessed October 1, 2012)
18. No author listed. Colorants for drug tablets and capsules. Drug Cosmet Ind 1983;133(2):44–48, 107.
19. Guidance for Industry: Pharmaceutical Development. Rockville, MD: Food and Drug Administration, 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073507.pdf. (Accessed October 1, 2012)

5 Dosage Form Design: Biopharmaceutical and Pharmacokinetic Considerations

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate between *passive drug diffusion* and *active drug transport*
2. Discuss key data points in a blood plasma concentration–time curve following the oral administration of a drug
3. Differentiate between the terms *biopharmaceutics*, *bioavailability*, and *bioequivalence*
4. Discuss the importance of a drug's dissolution rate following the oral administration of a solid dosage form
5. Describe the sequence of events and the processes that occur to a drug during its course of bodily transit, from the time of its oral administration and absorption through its excretion
6. Perform various basic pharmacokinetic calculations
7. List the factors that a pharmacist must consider when determining a dosage regimen for a specific patient

As discussed in Chapter 2, the biologic response to a drug is the result of an interaction between the drug substance and functionally important cell receptors or enzyme systems. The response is due to an alteration in the biologic processes that were present prior to the drug's administration. The magnitude of the response is related to the concentration of the drug achieved at the site of its action. This drug concentration depends on the dosage of the drug administered, the extent of its absorption and distribution to the site, and the rate and extent of its elimination from the body. The physical and chemical constitution of the drug substance—particularly its lipid solubility, degree of ionization, and molecular size—determines to a great extent its ability to carry out its biologic activity. The area of study embracing this relationship between the physical, chemical, and biologic sciences as they apply to drugs, dosage forms, and drug action has been given the descriptive term *biopharmaceutics*.

In general, for a drug to exert its biologic effect, it must be transported by the body fluids, traverse the required biologic membrane barriers, escape widespread distribution to unwanted areas, endure metabolic attack, penetrate in adequate concentration to the sites of action, and interact in a specific fashion, causing an alteration of cellular function. A simplified diagram of this complex series of events between a drug's administration and its elimination is presented in Figure 5.1.

The absorption, distribution, biotransformation (metabolism), and elimination of a drug from the body are dynamic processes that continue from the time a drug is taken

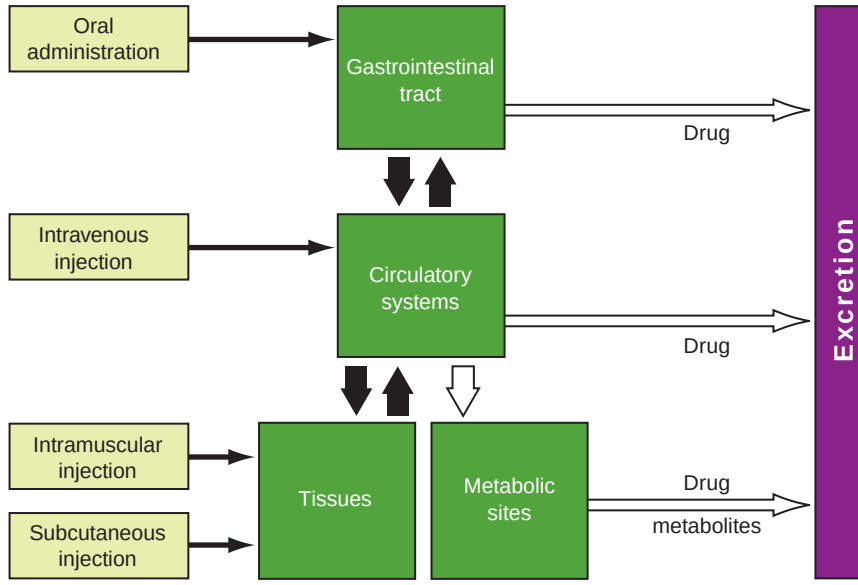


FIGURE 5.1 Events of absorption, metabolism, and excretion of drugs after their administration by various routes.

until drug has been removed from the body entirely. The *rates* at which these processes occur affect the onset, intensity, and duration of the drug's activity within the body. The area of study that elucidates the time course of drug concentration in the blood and tissues is termed *pharmacokinetics*. It is the study of the kinetics of absorption, distribution, metabolism, and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic effects in animals and man. Furthermore, because one drug may alter the ADME of another drug, pharmacokinetics may be applied in the study of interactions between drugs.

Once a drug is administered and absorption begins, the drug does not remain in a single body location but rather is distributed throughout the body until its ultimate elimination. For instance, following the oral administration of a drug and its entry into the gastrointestinal tract, a portion of the drug is absorbed into the circulatory system, from which it is distributed to the various other body fluids, tissues, and organs. From these sites, the drug may return to the circulatory system and be excreted through the kidney as such or be metabolized by the liver or other cellular sites and be excreted as one or more metabolites. As demonstrated in Figure 5.1, drugs administered by intravenous injection are introduced directly into the circulatory system, avoiding absorption, which is required for systemic effects from all other routes of administration.

The various body locations to which a drug travels may be viewed as separate compartments, each containing some fraction of the administered dose of drug. The transfer of drug from the blood to other body locations is generally a rapid and reversible process; that is, the drug may diffuse back into the circulation. The drug in the blood therefore exists in equilibrium with the drug in the other compartments. However, in this equilibrium state, the concentration of the drug in the blood may be quite different (greater or lesser) than the concentration of the drug in the other compartments. This is due largely to the physicochemical properties of the drug and its resultant ability to leave the blood and traverse the biologic membranes. Certain drugs leave the circulatory system rapidly and completely, whereas other drugs do so slowly and with difficulty. A number of drugs become bound to blood proteins, particularly the albumins, and only a small fraction of the drug administered may actually be found outside of the circulatory system at a given time. The transfer of drug from one compartment

to another is mathematically associated with a specific rate constant describing that particular transfer. Generally, the rate of transfer of a drug from one compartment to another is proportional to the concentration of the drug in the compartment from which it exits; the greater the concentration, the greater is the amount of drug transfer.

Metabolism is the major process by which foreign substances, including drugs, are eliminated from the body. During metabolism a drug substance may be biotransformed into pharmacologically active or inactive metabolites, or both. Often, both the drug substance and its metabolite or metabolites are active and exert pharmacologic effects. For example, the anticonvulsant drug carbamazepine is metabolized in the liver to an active epoxide metabolite. In some instances, a pharmacologically inactive drug (termed a *prodrug*) may be administered for the known effects of its active metabolites. Dipivefrin, for example, is a prodrug of epinephrine formed by the esterification of epinephrine and pivalic acid. This enhances the lipophilic character of the drug, and as a consequence, its penetration into the anterior chamber of the eye is 17 times that of epinephrine. Within the eye, dipivefrin HCl is converted by enzymatic hydrolysis to epinephrine.

Usually, the metabolism of a drug to inactive products is an irreversible process that culminates in the excretion of the drug from the body, usually via the urine. The pharmacokineticist may calculate an elimination rate constant (Kel) for a drug to describe its rate of elimination from the body. The term *elimination* refers to both metabolism and excretion. For drugs that are administered intravenously and, therefore, are not absorbed, the task is much less complex than for drugs administered by other routes. Except with intravenous administration, absorption and elimination occur simultaneously but at different rates.

PRINCIPLES OF DRUG ABSORPTION

Before an administered drug can arrive at its site of action in effective concentrations, it must surmount a number of barriers. These barriers are chiefly a succession of biologic membranes such as those of the gastrointestinal epithelium, lungs, blood, and brain. Body membranes are generally classified as three main types: (*a*) those composed of several layers of cells, like the skin; (*b*) those composed of a single layer of cells, like the intestinal epithelium; and (*c*) those less than one cell thick, like the membrane of a single cell. In most instances, a drug substance must pass more than one of these membrane types before it reaches its site of action. For instance, a drug taken by mouth must first traverse the gastrointestinal membranes (stomach and intestines), gain entrance to the general circulation, pass to the organ or tissue with which it has affinity, gain entrance to that tissue, and then enter its individual cells.

Although the chemistry of body membranes differs one from another, the membranes may be viewed in general as a bimolecular lipoid (fat containing) layer attached on both sides to a protein layer. Drugs are thought to penetrate these biologic membranes in two general ways: (*a*) by passive diffusion and (*b*) through specialized transport mechanisms. Within each of these main categories, more clearly defined processes have been ascribed to drug transfer.

Passive Diffusion

The term *passive diffusion* is used to describe the passage of (drug) molecules through a membrane that does not actively participate in the process. Drugs absorbed according to this method are said to be *passively absorbed*. The absorption process is driven by the concentration gradient (i.e., the differences in concentration) across the membrane, with the passage of drug molecules occurring primarily from the side of high concentration. Most drugs pass through biologic membranes by diffusion.

Passive diffusion is described by *Fick first law* (Physical Pharmacy Capsule 4.8), which states that the rate of diffusion or transport across a membrane (dc/dt) is proportional to the difference in drug concentration on both sides of the membrane:

$$-\frac{dc}{dt} = P(C_1 - C_2)$$

where

C_1 and C_2 are the drug concentrations on each side of the membrane and

P is a permeability coefficient or constant.

The term C_1 is customarily used to represent the compartment with the greater concentration of drug, and thus the transport of drug proceeds from compartment 1 (e.g., absorption site) to compartment 2 (e.g., blood).

The concentration of drug at the site of absorption (C_1) is usually much greater than on the other side of the membrane because of the rapid dilution of the drug in the blood and its subsequent distribution to the tissues, so for practical purposes, the value of $C_1 - C_2$ may be taken simply as that of C_1 and the equation written in the standard form for a first-order rate equation:

$$-\frac{dc}{dt} = PC_1$$

The gastrointestinal absorption of most drugs from solution occurs in this manner in accordance with *first-order kinetics*, in which the rate depends on drug concentration; that is, doubling the dose doubles the transfer rate. The magnitude of the permeability constant depends on the diffusion coefficient of the drug, the thickness and area of the absorbing membrane, and the permeability of the membrane to the particular drug.

Because of the lipoid nature of the cell membrane, it is highly permeable to lipid-soluble substances. The rate of diffusion of a drug across the membrane depends not only on its concentration but also on the relative extent of its affinity for lipid and rejection of water (a high lipid partition coefficient). The greater its affinity for lipid and the more hydrophobic it is, the faster will be its rate of penetration into the lipid-rich membrane. Erythromycin base, for example, possesses a higher partition coefficient than other erythromycin compounds, for example, estolate and gluceptate. Consequently, the base is the preferred agent for the topical treatment of acne where penetration into the skin is desired.

Because biologic cells are also permeated by water and lipid-insoluble substances, it is thought that the membrane also contains water-filled pores or channels that permit the passage of these types of substances. As water passes in bulk across a porous membrane, any dissolved solute with small enough molecules to traverse the pores passes in by *filtration*. Aqueous pores vary in size from membrane to membrane and thus in their individual permeability characteristics for certain drugs and other substances.

Most drugs today are weak organic acids or bases. Knowledge of their individual ionization or dissociation characteristics is important, because their absorption is governed to a large extent by their degrees of ionization as they are presented to the membrane barriers. Cell membranes are more permeable to the un-ionized forms of drugs than to their ionized forms, mainly because of the greater lipid solubility of the un-ionized forms and the highly charged nature of the cell membrane, which results in binding or repelling of the ionized drug and thereby decreases cell penetration. Also, ions become hydrated through association with water molecules, resulting in larger particles than the undissociated molecule and again decreased penetrating capability.

The degree of a drug's ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pK_a, or dissociation constant, of the drug (whether an acid or base). The concept of pK_a is derived from the Henderson-Hasselbalch equation.

For an acid,

$$pH = pK_a + \log \frac{\text{ionized conc.(salt)}}{\text{un-ionized conc.(acid)}}$$

For a base,

$$pH = pK_a + \log \frac{\text{un-ionized conc.(base)}}{\text{ionized conc.(acid)}}$$

Because the pH of body fluids varies (stomach, pH 1; lumen of the intestine, pH 6.6; blood plasma, pH 7.4), the absorption of a drug from various body fluids will differ and may dictate to some extent the type of dosage form and the route of administration preferred for a given drug.

Rearranging the equation for an acid yields

$$pK_a - pH = \log \frac{\text{un-ionized concentration (acid)}}{\text{ionized concentration (acid)}}$$

and one can theoretically determine the relative extent to which a drug remains un-ionized under various conditions of pH. This is particularly useful when applied to body fluids. For instance, if a weak acid having a pK_a of 4 is assumed to be in an environment of gastric juice with a pH of 1, the left side of the equation yields the number 3, which means that the ratio of un-ionized to ionized drug particles is about 1,000:1 and gastric absorption is excellent. At the pH of plasma, the reverse is true, and in the blood, the drug is largely in the ionized form. Table 5.1 presents the effect of pH on the ionization of weak electrolytes, and Table 5.2 offers some representative pK_a values of common drug substances.

The equation and Table 5.1 show that a drug substance is half ionized at a pH value equal to its pK_a. Thus, pK_a may be defined as the pH at which a drug is 50% ionized. For example, phenobarbital has a pK_a value of about 7.4, and in plasma (pH 7.4), it is present as ionized and un-ionized forms in equal amounts. However, a drug substance cannot reach the blood plasma unless it is placed there directly through intravenous injection or is favorably absorbed from a site along its route of entry, such as the gastrointestinal tract, and allowed to pass into the general circulation. As shown in Table 5.2, phenobarbital, a weak acid with a pK_a of 7.4, would be largely undissociated in the gastric environment of pH 1 and would likely be well absorbed. A drug may enter the circulation rapidly and at high concentrations if membrane penetration is easily accomplished

Table 5.1 THE EFFECT OF pH ON THE IONIZATION OF WEAK ELECTROLYTES pK_a–pH % UN-IONIZED

	IF WEAK ACID	IF WEAK BASE
– 3.0	0.10	99.90
– 2.0	0.99	99.00
– 1.0	9.09	90.90
– 0.7	16.60	83.40
– 0.5	24.00	76.00
– 0.2	38.70	61.30
0.0	50.00	50.00
+ 0.2	61.30	38.70
+ 0.5	76.00	24.00
+ 0.7	83.40	16.60
+ 1.0	90.90	9.09
+ 2.0	99.00	0.99
+ 3.0	99.90	0.10

Table 5.2 pK_a VALUES FOR SOME ACIDIC AND BASIC DRUGS

		pK_a
Acids		
	Acetylsalicylic acid	3.5
	Barbital	7.9
	Benzylpenicillin	2.8
	Boric acid	9.2
	Dicoumarol	5.7
	Phenobarbital	7.4
	Phenytoin	8.3
	Sulfanilamide	10.4
	Theophylline	9.0
	Thiopental	7.6
	Tolbutamide	5.5
	Warfarin sodium	4.8
Bases		
	Amphetamine	9.8
	Apomorphine	7.0
	Atropine	9.7
	Caffeine	0.8
	Chlordiazepoxide	4.6
	Cocaine	8.5
	Codeine	7.9
	Guanethidine	11.8
	Morphine	7.9
	Procaine	9.0
	Quinine	8.4
	Reserpine	6.6

or at a low rate and low level if the drug is not readily absorbed from its route of entry. The pH of the drug's current environment influences the rate and degree of its further distribution because under one condition of pH it becomes more or less un-ionized and therefore more or less lipid penetrating than under another. If an un-ionized molecule is able to diffuse through the lipid barrier and remain un-ionized in the new environment, it may return to its former location or go on to a new one. However, if in the new environment it is greatly ionized because of the influence of the pH of the second fluid, it likely will be unable to cross the membrane with its former ability. Thus, a concentration gradient of a drug usually is reached at equilibrium on each side of a membrane because different degrees of ionization occur on each side. A summary of the concepts of dissociation and ionization is found in Physical Pharmacy Capsules 4.8 and 4.10.

It is often desirable for pharmaceutical scientists to make structural modifications in organic drugs and thereby favorably alter their lipid solubility, partition coefficients, and dissociation constants while maintaining the same basic pharmacologic activity. These efforts frequently result in increased absorption, better therapeutic response, and lower dosage.

Specialized Transport Mechanisms

In contrast to the passive transfer of drugs and other substances across a biologic membrane, certain substances, including some drugs and biologic metabolites, are conducted across a membrane through one of several postulated *specialized transport* mechanisms. This type of transfer seems to account for substances, many naturally occurring as amino acids and glucose, that are too lipid insoluble to dissolve in the boundary and too large to flow or filter through the pores. This type of transport is thought to involve membrane components that may be enzymes or some other type of agent capable of forming a complex with the drug (or other agent) at the surface membrane. The complex moves across the membrane,

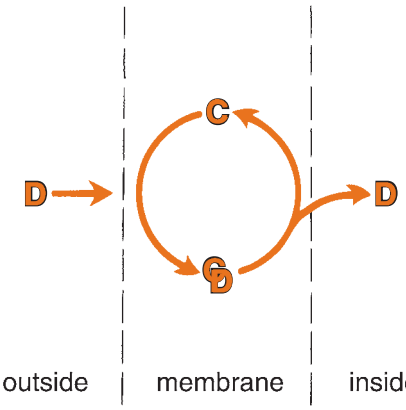


FIGURE 5.2 Active transport mechanism. D, drug molecule; C, the carrier in the membrane. (Adapted with permission from O'reilly WJ. Biological Factors in Dosage Design I: Membranes and Drug Absorption. Aust J Pharm 1966;47(Supp 42):S51.)

where the drug is released, with the carrier returning to the original surface. Figure 5.2 presents the simplified scheme of this process. Specialized transport may be differentiated from passive transfer in that the former process may become saturated as the amount of carrier for a given substance becomes completely bound with that substance, resulting in a delay in transport. Other features of specialized transport include the specificity by a carrier for a particular type of chemical structure, so that if two substances are transported by the same mechanism or carrier, one will competitively inhibit the transport of the other. Furthermore, the transport mechanism is inhibited in general by substances that interfere with cell metabolism. The term *active transport* as a subclassification of specialized transport denotes a process with the additional feature of the solute or drug being moved across the membrane against a concentration gradient, that is, from a solution of lower concentration to one of a higher concentration, or if the solute is an ion, against an electrochemical potential gradient. In contrast to active transport, *facilitated diffusion* is a specialized transport mechanism having all of the described characteristics except that the solute is not transferred against a concentration gradient and may attain the same concentration inside the cell as on the outside.

Many body nutrients, such as sugars and amino acids, are transported across the membranes of the gastrointestinal tract by carrier processes. Certain vitamins, such as thiamine, niacin, riboflavin, and pyridoxine, and drug substances, such as methyldopa and 5-fluorouracil, require active transport mechanisms for their absorption.

Investigations of intestinal transport have often used in situ (at the site) or in vivo (in the body) animal models or ex vivo (outside the body) transport models; however, recently cell culture models of human small intestine absorptive cells have become available to investigate transport across intestinal epithelium (1). Both passive and transport-mediated studies have been conducted to investigate mechanisms and rates of transport.

DISSOLUTION AND DRUG ABSORPTION

For a drug to be absorbed, it must first be dissolved in the fluid at the absorption site. For instance, a drug administered orally in tablet or capsule form cannot be absorbed until the drug particles are dissolved by the fluids in the gastrointestinal tract. When the solubility of a drug depends on either an acidic or basic medium, the drug dissolves in the stomach or intestines, respectively (Fig. 5.3). The process by which a drug particle dissolves is termed *dissolution*.

As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution, creating a saturated layer of drug solution that envelops the surface of the solid drug particle. This layer of solution is the *diffusion layer*. From this diffusion layer, the drug molecules pass throughout the dissolving fluid and make contact with the biologic membranes, and absorption ensues. As the molecules of drug continue to leave the diffusion layer, the layer is replenished with dissolved drug from the surface of the drug particle, and the process of absorption continues.

If the dissolution of a given drug particle is rapid or if the drug is administered as a solution and remains present in the body as such, the rate at which the drug becomes

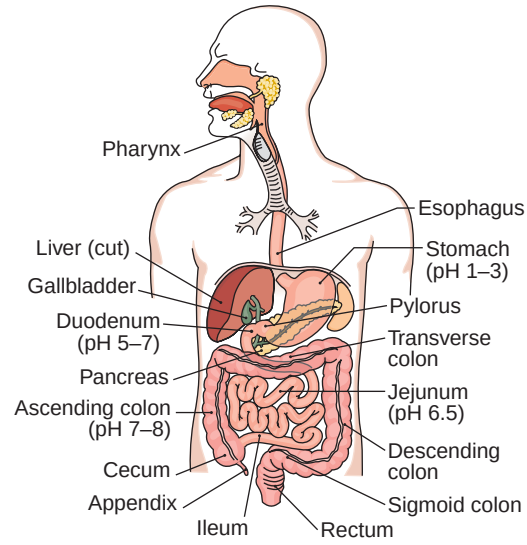


FIGURE 5.3 The digestive system, including the locations of drug absorption and their respective pH values. (Adapted with permission from Cohen BJ, Wood DL. Memmler's the Human Body in Health and Disease. 11th Ed. Baltimore, MD: Lippincott Williams & Wilkins, 2009.)

absorbed depends mainly on its ability to traverse the membrane barrier. However, if the rate of dissolution for a drug particle is slow because of the physicochemical characteristics of the drug substance or the dosage form, dissolution itself is a rate-limiting step in absorption. Slowly soluble drugs such as digoxin may not only be absorbed at a slow rate; they may be incompletely absorbed or in some cases largely unabsorbed following oral administration because of the natural limitation of time that they may remain within the stomach or the intestinal tract. Thus, poorly soluble drugs or poorly formulated drug products may be incompletely absorbed and pass unchanged out of the system via the feces.

Under normal circumstances, a drug may be expected to remain in the stomach for 2 to 4 hours (*gastric emptying time*) and in the small intestine for 4 to 10 hours, although there is substantial variation between people and even in the same person on different occasions. Various techniques have been used to determine gastric emptying time and the gastrointestinal passage of drug from various oral dosage forms, including tracking

dosage forms labeled with gamma-emitting radionuclides through gamma scintigraphy (2,3). The gastric emptying time for a drug is most rapid with a fasting stomach, becoming slower as the food content is increased. Changes in gastric emptying time and/or in intestinal motility can affect drug transit time and thus the opportunity for drug dissolution and absorption.

These changes can be affected by drugs. Certain drugs with anticholinergic properties, for example, dicyclomine HCl and amitriptyline HCl, can slow gastric emptying. This can enhance the rate of absorption of drugs normally absorbed from the stomach and reduce the rate of absorption of drugs that are primarily absorbed from the small intestine. Alternatively, drugs that enhance gastric motility, for example, laxatives, may cause some drugs to move through the gastrointestinal system and past their absorptive site at such a rate as to reduce the amount of drug absorbed. This effect has been demonstrated with digoxin, whose absorption is significantly decreased by accelerating gastrointestinal motility.

Aging may also influence gastrointestinal absorption. In the elderly, gastric acidity, the number of absorptive cells, intestinal blood flow, the rate of gastric emptying, and intestinal motility are all decreased. However, drugs in which absorption depends on passive processes are not affected by these factors as much as those that depend on active transport mechanisms, such as calcium, iron, thiamine, and sugars. A decrease in gastric emptying time is advantageous for drugs that are absorbed from the stomach but disadvantageous for those that are prone to acid degradation, such as penicillins and erythromycin, or inactivated by stomach enzymes, such as L-dopa.

The dissolution of a substance may be described by the modified Noyes-Whitney equation:

$$\frac{dc}{dt} = kS(c_S - c_t)$$

where

dc/dt is the rate of dissolution,

k is the dissolution rate constant,

S is the surface area of the dissolving solid,

c_s is the saturation concentration of drug in the diffusion layer (which may be approximated by the maximum solubility of the drug in the solvent, because the diffusion layer is considered saturated), and

c_t is the concentration of the drug in the dissolution medium at time t ($c_s - c_t$ is the concentration gradient).

The rate of dissolution is governed by the rate of diffusion of solute molecules through the diffusion layer into the body of the solution. The equation reveals that the dissolution rate of a drug may be increased by increasing the surface area (reducing the particle size) of the drug, by increasing the solubility of the drug in the diffusion layer, and by factors embodied in the dissolution rate constant, k, including the intensity of agitation of the solvent and the diffusion coefficient of the dissolving drug. For a given drug, the diffusion coefficient and usually the concentration of the drug in the diffusion layer will increase with increasing temperature. Also, increasing the rate of agitation of the dissolving medium will increase the rate of dissolution. A reduction in the viscosity of the solvent employed is another means to enhance the dissolution rate of a drug. Changes in the pH or the nature of the solvent that influence the solubility of the drug may be used to advantage in increasing dissolution rate. Effervescent, buffered aspirin tablet formulations use some of these principles to their advantage. The alkaline adjuvants in the tablet enhance the solubility of the aspirin within the diffusional layer, and the evolution of carbon dioxide agitates the solvent system, that is, gastric juices. Consequently, the rate of absorption of aspirin into the bloodstream is faster than from a conventional aspirin tablet formulation. If this dosage form is acceptable to the patient, it provides a quicker means for the patient to gain relief from a troublesome headache. Many manufacturers use a particular amorphous, crystalline, salt, or ester form of a drug that will exhibit the solubility characteristics needed to achieve the desired dissolution characteristics. Some of these factors that affect drug dissolution briefly are discussed in the following paragraphs,

PHYSICAL PHARMACY CAPSULE **5.1**

Particle Size, Surface Area, and Dissolution Rate

Particle size has an effect on dissolution rate and solubility. As shown in the Noyes-Whitney equation,
where

$$\frac{dC}{dT} = kS(C_s - C_t)$$

dC/dT is the rate of dissolution (concentration with respect to time);
k is the dissolution rate constant;
S is the surface area of the particles;
C_s is the concentration of the drug in the immediate proximity of the dissolving particle, that is, the solubility of the drug; and
C_t is the concentration of the drug in the bulk fluid.

It is evident that C_s cannot be significantly changed, C_t is often under sink conditions (an amount of the drug is used that is less than 20% of its solubility), and k comprises many factors, such as agitation and temperature. This leaves the S, surface area, as a factor that can affect the rate of dissolution.

An increase in the surface area of a drug will, within reason, increase the dissolution rate. Circumstances in which it may decrease the rate include a decrease in the effective surface area, that is, a condition in which the dissolving fluid cannot wet the particles. Wetting is the first step in dissolution. This can be demonstrated by visualizing a tablet of diameter 0.75 inch by thickness 0.25 inch. The surface area of the tablet can be increased by drilling a series of 0.0625-inch holes in the tablet. However, even though the surface area has been increased, the dissolution fluid—water—because of surface tension and so on cannot necessarily penetrate the new holes and displace the air. Adsorbed air and other factors can decrease the effective surface area of a dosage form, including powders. This is the reason that particle size reduction does not always raise the dissolution rate. One can also visualize a powder that has been comminuted to a very fine state of subdivision; when it is placed in a beaker of water, the powder floats because of the entrapped and adsorbed air. The effective surface area is not the same as the actual surface area of the powder.

whereas others will be discussed in succeeding chapters in which they are relevant.

The chemical and physical characteristics of a drug substance that can affect safety, efficacy, and stability must be carefully defined by appropriate standards in an application for U.S. Food and Drug Administration (FDA) approval and then sustained and controlled throughout product manufacture.

Surface Area

When a drug particle is broken up, the total surface area is increased. For drug substances that are poorly or slowly soluble, this generally results in an increase in the *rate* of dissolution. This is explained in Physical Pharmacy Capsule 5.1, Particle Size, Surface Area, and Dissolution Rate.

Increased therapeutic response to orally administered drugs due to smaller particle size has been reported for a number of drugs, among them theophylline, a xanthine derivative used to treat bronchial asthma; griseofulvin, an antibiotic with antifungal activity; sulfisoxazole, an anti-infective sulfonamide; and nitrofurantoin, a urinary anti-infective drug. To increase surface area,

pharmaceutical manufacturers frequently use *micronized* powders in their solid products. Although not officially defined, micronized powders generally consist of drug particles reduced in size to about 5 mm and smaller. A slight variation on this is accomplished by blending and melting poorly water-soluble powders with a water-soluble polymer, such as polyethylene glycol (PEG). In the molten state and if the drug dissolves in the carrier, a molecular dispersion of the drug in the carrier results. Solidification produces a solid dispersion that can be pulverized and formed into tablets or capsules. When this powder is placed in water, the water-soluble carrier rapidly dissolves, leaving the poorly soluble drug molecules enveloped in water, thus forming a solution.

The use of micronized drugs is not confined to oral preparations. For example, ophthalmic and topical ointments use micronized drugs for their preferred release characteristics and nonirritating quality after application.

Because of the different rates and degrees of absorption obtainable from drugs of various particle sizes, products of the same drug substance prepared by two or more reliable pharmaceutical manufacturers may result in different degrees of therapeutic response in the same individual. A classic example of this occurs with phenytoin sodium capsules, which have two distinct forms. The first is the rapid-release type, that is, Prompt Phenytoin Sodium Capsules, USP, and the second is the slow-dissolution type, that is, Extended Phenytoin Sodium Capsules, USP. The former has a dissolution rate of not less than 85% in 30 minutes and is recommended for use three to four times per day. The latter has a slower dissolution rate, for example, 15% to 35% in 30 minutes, which lends itself to use in patients who can be dosed less frequently. Because of such differences in formulation for a number of drugs and drug products, it is generally advisable for a person to continue taking the same brand of medication, provided it produces the desired therapeutic effect. Patients who are stabilized on one brand of drug should not be switched to another unless necessary. However, when a change is necessary, appropriate blood or plasma concentrations of the drug should be monitored until the patient is stabilized on the new product.

Occasionally, a rapid rate of drug absorption is not desired in a pharmaceutical preparation. Research pharmacists who wish to provide sustained rather than rapid action may employ agents of varying particle size to provide controlled dissolution and absorption. Summaries of the physicochemical principles of particle size reduction and the relation of particle size to surface area, dissolution, and solubility may be found in Physical Pharmacy Capsule 4.5.

Crystal or Amorphous Drug Form

Solid drug materials may occur as pure crystalline substances of definite identifiable shape or as amorphous particles without definite structure. The amorphous or crystalline character of a drug substance may be of considerable importance to its ease of formulation and handling, its chemical stability, and as has been recently demonstrated, even its biologic activity. Certain medicinal agents may be produced to exist in either a crystalline or an amorphous state. Because the amorphous form of a chemical is usually more soluble than the crystalline form, different extents of drug absorption may result with consequent differences in the degree of pharmacologic activity obtained from each. Two antibiotic substances, novobiocin and chloramphenicol palmitate, are essentially inactive when administered in crystalline form, but when they are administered in the amorphous form, absorption from the gastrointestinal tract proceeds rapidly, with good therapeutic response. In other instances, crystalline forms of drugs may be used because of greater stability than the corresponding amorphous forms. For example, the crystalline forms of penicillin G as the potassium salt or sodium salt are considerably more stable than the analogous amorphous forms. Thus, in formulation work on penicillin G, the crystalline forms are preferred and result in excellent therapeutic response.

The hormone insulin presents another striking example of the different degree of

activity that may result from the use of different physical forms of the same medicinal agent. Insulin is the active principle of the pancreas and is vital to the body's metabolism of glucose.

It is indispensable in the treatment of patients with type 1 diabetes, who depend upon an external source of the hormone for survival.

Prior to the development of insulin by the biosynthetic process using recombinant DNA technology, insulin was obtained for therapeutic use through its extraction and purification from animal pancreas glands, primarily pork. Today, the vast majority of insulin currently used worldwide is biosynthetic recombinant "human" insulin and its analogs. Although the therapeutic use of insulin from animal origin is largely diminished, the discussion, which follows, remains important from the physical pharmacy standpoint.

Insulin is a protein that forms an extremely insoluble zinc–insulin complex when combined with zinc in the presence of acetate buffer. The complex may be crystalline or amorphous, depending upon the pH of the buffer solution. Each form of the complex has been utilized in the formulation of insulin products to take advantage of the different absorption and retention rates following injection. The amorphous form (or prompt insulin suspension) is rapidly absorbed following intramuscular or subcutaneous injection, whereas the larger crystalline form (extended insulin zinc suspension) is more slowly absorbed and has a longer retention time and duration of action. By combining the two types, 70% of the crystalline form and 30% of the amorphous form, an intermediate-acting insulin product is prepared.

Nowadays, different absorption and retention rates for insulin are achieved through analogs of human insulin developed though biotechnology.

Some crystalline medicinal chemicals are capable of forming different types of crystals, depending on the conditions (temperature, solvent, time) under which crystallization is induced. This property, whereby a single chemical substance may exist in more than one crystalline form, is polymorphism. Only one form of a pure drug substance is stable at a given temperature and pressure, with the other higher-energy forms, called metastable forms, converting in time to the stable crystalline form. It is therefore fairly common for a metastable form of a medicinal agent to change form even in a completed pharmaceutical preparation, although the time required for a complete change may exceed the normal shelf life of the product. However, from a pharmaceutical point of view, any change in the crystal structure of a medicinal agent may critically affect the stability and even the therapeutic efficacy of the product in which the conversion takes place.

The various polymorphic forms of the same chemical generally differ in many physical properties, including solubility and dissolution, which are of prime importance to the rate and extent of absorption. These differences are manifest so long as the drug is in the solid state. Once solution is effected, the different forms become indistinguishable one from another. Therefore, differences in drug action, pharmaceutically and therapeutically, can be expected from polymorphs contained in solid dosage forms as well as in liquid suspension. The use of metastable forms generally results in higher solubility and dissolution rates than the respective stable crystal forms of the same drug. If all other factors remain constant, more rapid and complete drug absorption will likely result from the metastable forms than from the stable form of the same drug. On the other hand, the stable polymorph is more resistant to chemical degradation and because of its lower solubility, is frequently preferred in pharmaceutical suspensions of insoluble drugs. If metastable forms are employed in the preparation of suspensions, their gradual conversion to the stable form may be accompanied by an alteration in the consistency of the suspension itself, which affects its permanency. In all instances, the advantages of the metastable crystalline forms in terms of increased physiologic availability of the drug must be balanced against the increased product stability when stable polymorphs are employed. Sulfur and cortisone acetate exist in more than one crystalline form and are frequently

prepared in pharmaceutical suspensions. In fact, cortisone acetate is reported to exist in at least five crystalline forms. It is possible for the commercial products of two manufacturers to differ in stability and therapeutic effect, depending on the crystalline form of the drug used in the formulation.

Salt Forms

The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound. Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the respective free acids or bases. The result is a more rapid saturation of the diffusion layer surrounding the dissolving particle and the consequent more rapid diffusion of the drug to the absorption sites.

Numerous examples could be cited to demonstrate the increased rate of drug dissolution due to the use of the salt form of the drug rather than the free acid or base, but the following will suffice: The addition of the ethylenediamine moiety to theophylline increases the water solubility of theophylline fivefold. The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline and diminished the need to use hydroalcoholic mixtures such as elixirs.

Other Factors

The *state of hydration* of a drug molecule can affect its solubility and pattern of absorption. Usually, the anhydrous form of an organic molecule is more readily soluble than the hydrated form. This characteristic was demonstrated with the drug ampicillin, when the anhydrous form was found to have a greater rate of solubility than the trihydrate form (4). The rate of absorption for the anhydrous form was greater than that for the trihydrate form of the drug.

A drug's solubility in the gastrointestinal tract can be affected not only by the pH of the environment but also by the normal components of the tract and any foodstuffs. A drug may interact with one of the other agents present to form a chemical complex that may result in reduced drug solubility and decreased drug absorption. The classic example of this complexation is the one between tetracycline analogs and certain cations, for example, calcium, magnesium, and aluminum, resulting in decreased absorption of the tetracycline derivative. Also, if the drug becomes *ad*sorbed onto insoluble material in the tract, its availability for absorption may be correspondingly reduced.

BIOAVAILABILITY AND BIOEQUIVALENCE

The term *bioavailability* describes the *rate* and *extent* to which an active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of action. The term *bioequivalence* refers to the *comparison* of bioavailabilities of different formulations, drug products, or batches of the same drug product.

The availability to the biologic system of a pharmaceutical product is integral to the goals of dosage form design and paramount to the effectiveness of the medication. The study of a drug's bioavailability depends on the drug's absorption or entry into the systemic circulation, and it is necessary to study the pharmacokinetic profile of the drug or its metabolite or metabolites over time in the appropriate biologic system, for example, blood, plasma, and urine. Graphically, bioavailability of a drug is portrayed by a concentration time curve of the administered drug in an appropriate tissue system, for example, plasma (Fig. 5.4). Bioavailability data are used to determine (*a*) the amount or proportion of drug absorbed from a formulation or dosage form, (*b*) the rate at which the drug was absorbed, (*c*) the duration of the drug's presence in the biologic fluid or tissue correlated with the patient's response, and (*d*) the relationship between drug blood levels and clinical efficacy and toxicity.

During the product development stages of a proposed drug product, pharmaceutical manufacturers employ bioavailability studies to compare different formulations of the drug substance to ascertain which one allows the most desirable absorption pattern. Later

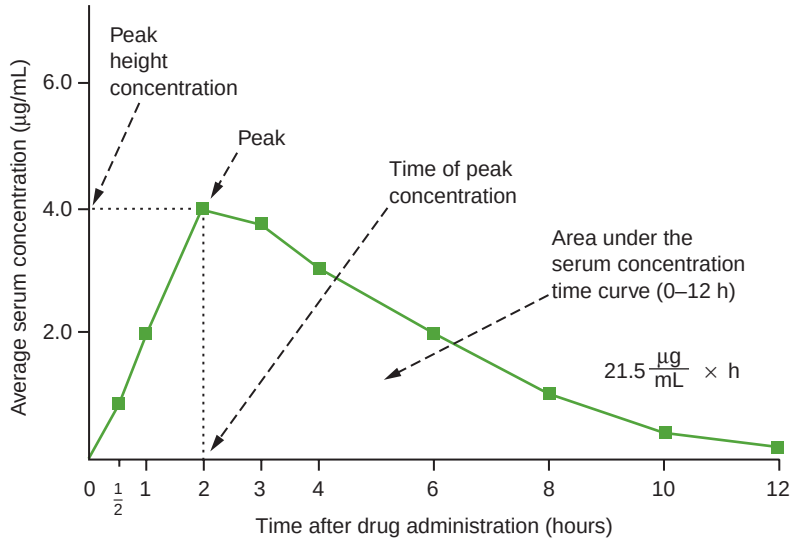


FIGURE 5.4 Serum concentration–time curve showing peak height concentration, time of peak concentration, and AUC. (Courtesy of D. J. Chodos and A. R. Disanto, Upjohn.)

bioavailability studies may be used to compare the availability of the drug substance in different production batches. They may also be used to compare the availability of the drug substance in different dosage forms (e.g., tablets, capsules, elixirs) or in the same dosage form produced by different (competing) manufacturers.

According to the FDA (5), the in vivo bioavailability of a drug product may be determined by measurements of the concentration of the active drug ingredient, its therapeutic moiety, or its metabolite(s) in the blood or urine or by pharmacological effects. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements of the rate and extent to which the active drug moiety becomes available at the site of action. Two drug products may be considered *bioequivalent* if their rates and extents of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose.

Single-Dose and Multiple-Dose Bioavailability Studies

Single-dose bioavailability studies compare the drug product to be tested against the appropriate reference material. Studies are conducted in normal adults generally in the fasting state. A single-dose study is usually crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons (refer to Fig. 2.7 for study designs). The sampling time for blood and/or urine is usually at least three times the half-life of the active drug ingredient or therapeutic moiety, its metabolite(s), or at least three times the half-life of the acute pharmacological effect. Measured are the peak concentration in the blood and the total area under the curve (discussed later in this chapter).

Multiple-dose bioavailability studies compare the test product and the reference material after repeated administration to determine steady-state levels of the active drug ingredient or therapeutic moiety in the body. Studies are conducted in human subjects in the fasting or nonfasting state, depending upon the conditions reflected in the proposed labeling of the test product.

A multiple-dose study may be required for a test product if (*a*) there is a difference in the rate of absorption but not in the extent of absorption; (*b*) there is excessive variability in bioavailability from subject to subject; (*c*) the concentration of the active drug ingredient or therapeutic moiety, or its metabolites, in the blood resulting from a single dose is too low

for accurate determination by the analytical method; or (*d*) the drug product is an extended-release dosage form. A multiple-dose study is generally crossover in design unless scientific reasons dictate otherwise (e.g., if the study is designed to establish the pharmacokinetic profile of a new drug product, a new drug delivery system, or an extended-release dosage form). At least five times the half-life of the active drug ingredient, its therapeutic moiety or its active metabolite(s) is measured in the blood or urine.

FDA Bioavailability Submission Requirements

The FDA requires bioavailability data submissions in the following instances (5):

1. *New Drug Applications* (*NDAs*): A section of each NDA is required to describe the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the bioavailability data requirement (see waiver provisions following).
2. *Abbreviated New Drug Applications* (*ANDAs*): In vivo bioavailability data are required unless information is provided and accepted supporting a waiver of this requirement (see waiver provisions following).
3. *Supplemental Applications*: In vivo bioavailability data are required if there is a change in the following:
   a. Manufacturing process, product formulation, or dosage strength beyond the variations provided for in the approved NDA
   b. Labeling to provide for a new indication for use of the drug product and if clinical studies are required, to support the new indication
   c. Labeling to provide for a new or additional dosage regimen for a special patient population (e.g., infants) if clinical studies are required to support the new or additional dosage regimen

Conditions under which the FDA *may* waive the in vivo bioavailability requirement are as follows:

1. The drug product is a parenteral, ophthalmic, or otic solution and contains the same active agent in the same concentration and solvent as a product previously approved through a full NDA.
2. The drug product is administered by inhalation as a gas or vapor and contains the same active agent in the same dosage form as a product previously approved through a full NDA.
3. The drug product is an oral solution, elixir, syrup, tincture, or similar other solubilized form and contains the same active agent in the same concentration as a previously approved drug product through a full NDA and contains no inactive ingredient known to significantly affect absorption of the active drug ingredient.
4. The drug product is a topically applied preparation (e.g., ointment) intended for local therapeutic effect.
5. The drug product is an oral form that is not intended to be absorbed (e.g., antacid or radiopaque medium).
6. The drug product is a solid oral form that has been demonstrated to be identical or sufficiently similar to a drug product that has met the in vivo bioavailability requirement.

Most bioavailability and bioequivalence studies are applied to drugs prepared into solid dosage forms intended to be administered orally. This is due to the fact that the majority of new pharmaceutical products are first developed and marketed as tablets and capsules and later, competing nonproprietary (generic) products are developed in the same forms. Consequently, much of the discussion, which follows, focuses on studies of orally administered dosage forms. However, this is not to imply that other dosage forms and routes of administration are free from bioavailability studies.

Blood, Serum, or Plasma Concentration–Time Curve

Following oral administration of a medication, if blood samples are drawn from the patient at specific time intervals and analyzed for drug content, the resulting data may be

plotted on ordinary graph paper to yield the type of drug blood level curve presented in Figure 5.4. The vertical axis of this type of plot characteristically presents the concentration of drug in the blood (or serum or plasma), and the horizontal axis presents the time the samples were obtained following the administration of the drug. When the drug is first administered (time zero), the blood concentration of the drug should also be zero. As the drug passes into the stomach and/or intestine, it is released from the dosage form, eventually dissolves, and is absorbed. As the sampling and analysis continue, the blood samples reveal increasing concentrations of drug (positive slope of the curve) until the maximum (peak) concentration (C_{max}) is reached. Then the blood level of the drug decreases (negative slope of the curve), and if no additional dose is given, it eventually falls to zero. The diminished blood level of drug after the peak height is reached indicates that the rate of elimination from the bloodstream is greater than the rate of absorption into the circulatory system. Absorption does not terminate after the peak blood level is reached; it may continue for some time. Similarly, the process of drug elimination is continuous. It begins as soon as the drug first appears in the bloodstream and continues until all of the drug has been eliminated. The positive or negative slope of the curve indicates which process is faster. When the drug leaves the blood, it may be found in various body tissues and cells for which it has an affinity until ultimately it is excreted as such or as drug metabolites in the urine or via some other route (Fig. 5.5). A urinalysis for the drug or its metabolites may be used to indicate the extent of absorption and/or the rate of elimination.

Parameters for Assessment and Comparison of Bioavailability

In discussing the important parameters to be considered in the comparative evaluation of the blood level curves following the oral administration of single doses of two formulations of the same drug entity, Chodos and DiSanto (6) list the following:

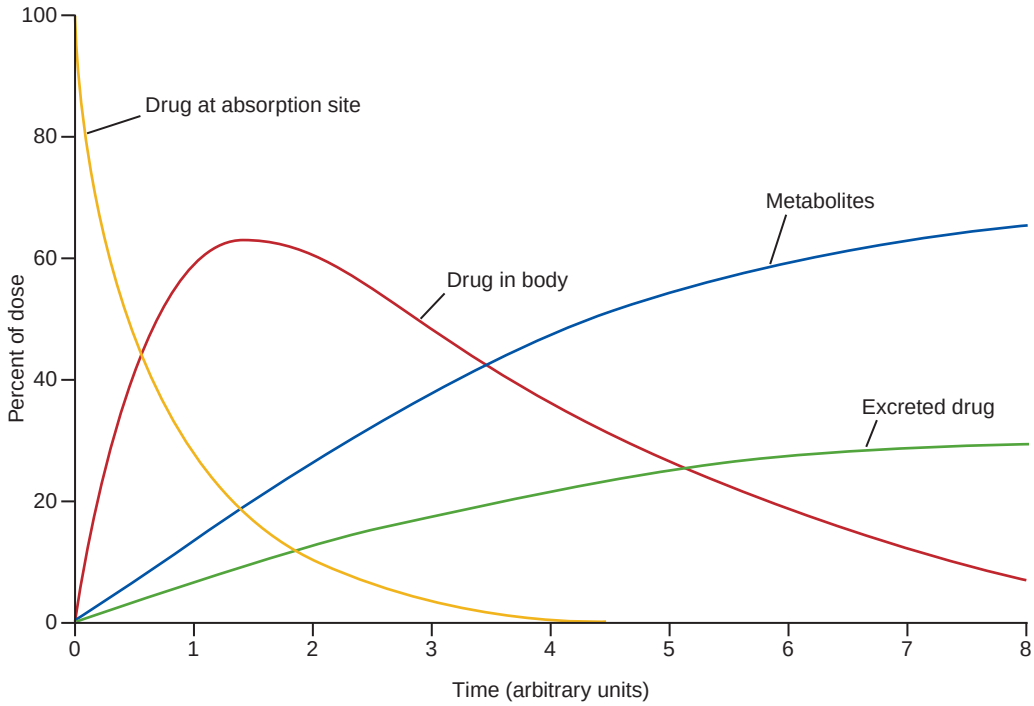


FIGURE 5.5 Time course of drug in the body. (Adapted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 3rd Ed. Baltimore, MD: Lippincott Williams & Wilkins, 1995.)

- The peak height concentration (C_{max})
- The time of the peak concentration (T_{max})
- The area under the blood (or serum or plasma) concentration–time curve (AUC)

Using Figure 5.4 as an example, the height of the peak concentration is equivalent to 4.0 mg/mL of drug in the serum, the time of the peak concentration is 2 hours after administration, and the AUC from 0 to 12 hours is calculated as 21.5 mg/mL × hours. The meaning and use of these parameters are further explained as follows.

Peak Height

Peak height concentration is the C_{max} observed in the blood plasma or serum following a dose of the drug, indicating a slope of zero, meaning the rates of absorption and elimination are equal. For conventional dosage forms, such as tablets and capsules, the C_{max} will usually occur at only a single time, T_{max}. The amount of drug is usually expressed in terms of its concentration in relation to a specific volume of blood, serum, or plasma. For example, the concentration may be expressed as grams per 100 mL, micrograms per milliliter, or milligrams per 100 mL. Figure 5.6 depicts concentration–time curves showing different peak height concentrations for *equal* amounts of drug from two different formulations following oral administration. The horizontal line drawn across the figure indicates that the minimum effective concentration (MEC) for the drug substance is 4.0 mg/mL. This means that for the patient to exhibit an adequate response to the drug, this concentration in the blood must be achieved. Comparing the blood levels of drug achieved after oral administration of equal doses of formulations A and B in Figure 5.6, formulation A will achieve the required blood levels of drug to produce the desired pharmacologic effect, whereas formulation B will not. On the other hand, if the MEC for the drug is 2.0 mg/mL and the minimum toxic concentration (MTC) is 4.0 mg/mL, as depicted in Figure 5.7, equal doses of the two formulations result in toxic effects produced by formulation A but only desired effects by formulation B. The objective in the individual dosing of a patient is to achieve the MEC but not the MTC.

The *size* of the dose influences the blood level concentration and C_{max} for that substance. Figure 5.8 depicts the influence of dose on the blood level–time curve for a hypothetical drug administered by the same route and in the same dosage form. In this example, it is assumed that all doses are completely absorbed and eliminated at the same rates. As

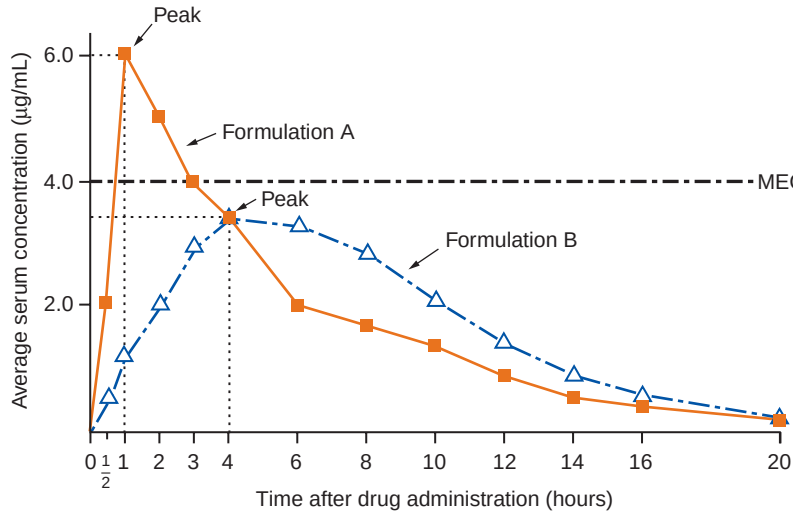


FIGURE 5.6 Serum concentration–time curve showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration. (Courtesy of D. J. Chodos and A. R. Disanto, Upjohn. With permission from Elsevier.)

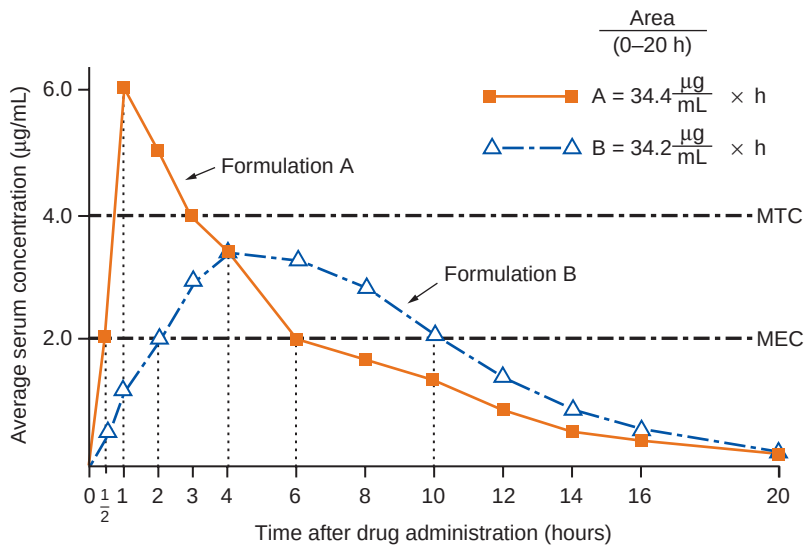


FIGURE 5.7 Serum concentration–time curve showing peak height concentrations, peak height times, times to reach MEC, and areas under the curves for equal amounts of drug from two different formulations following oral administration. MEC, minimum effective concentration; MTC, minimum toxic concentration. (Courtesy of D. I. Chodos and A. R. Disanto, Upjohn.)

the dose increases, the C_{max} is proportionately higher and the AUC proportionately greater. T_{max} is the same for each dose.

Time of Peak

The second important parameter in assessing the comparative bioavailability of two formulations is T_{max}. In Figure 5.6, T_{max} is 1 hour for formulation A and 4 hours for formulation B. This parameter reflects the *rate* of absorption from a formulation, which determines the time needed for the MEC to be reached and thus for initiation of the desired effect. The rate of absorption also influences the period over which the drug enters the bloodstream and therefore affects the duration that the drug is maintained in the blood. In Figure 5.7, formulation A allows the drug to reach the MEC within 30 minutes following administration and a peak concentration in 1 hour. Formulation B has a slower rate of release. Drug from this formulation reached the MEC 2 hours after administration and its peak concentration 4 hours after administration. Thus, formulation A permits the greater rate of drug absorption; it allows drug to reach both the MEC and its peak height sooner than formulation B. On the other hand, formulation B provides more time for drug concentrations maintained above the MEC, 8 hours (2 to 10 hours following administration) compared to 5.5 hours (30 minutes to 6 hours following administration) for formulation A. Thus, if a rapid onset of action is desired, a formulation similar to A is preferred, but if a long duration rather than a rapid onset of action is desired, a formulation similar to B is preferred.

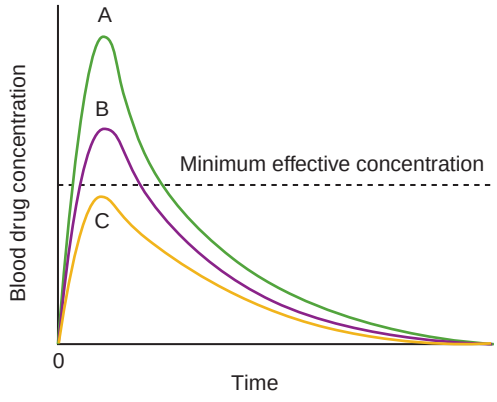


FIGURE 5.8 The influence of dose size on the blood drug concentration–time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A, 100 mg; B, 80 mg; C, 50 mg. (Adapted with permission from Ueda CT. Concepts in Clinical Pharmacology: Essentials of Bioavailability and Bioequivalence. Upjohn, 1979.)

In summary, changes in the *rate* of drug absorption change the values of both C_{max} and T_{max}. Each product has its own characteristic rate of absorption. When the *rate* of absorption is decreased, the C_{max} is lowered and T_{max} occurs at a later time. If the doses of the drugs are the same and presumed completely absorbed, as in Figure 5.7, the AUC for each is essentially the same.

Area Under the Serum Concentration–Time Curve

The AUC of a concentration–time plot (Fig. 5.4) is considered representative of the total amount of drug absorbed into the circulation following the administration of a single dose of that drug. Equivalent doses of a drug, when fully absorbed, produce the same AUC. Thus, two curves dissimilar in terms of peak height and time of peak, like those in Figure 5.7, may be similar in terms of AUC and thus in the amount of drug absorbed. As indicated in Figure 5.7, the AUC for formulation A is 34.4 mg/mL × hours and for formulation B is 34.2 mg/mL × hours, essentially the same. If equivalent doses of drug in different formulations produce *different* AUC values, differences exist in the *extent* of absorption between the formulations. Figure 5.9 depicts concentration–time curves for three different formulations of equal amounts of drug with greatly different AUC. In this example, formulation A delivers a much greater amount of drug to the circulatory system than do the other two formulations. In general, the smaller the AUC, the lesser drug absorbed.

The fraction (F) (or bioavailability) of an orally administered drug may be calculated by comparison of the AUC after oral administration with that obtained after intravenous administration:

$$F = (AUC)_{oral}/(AUC)_{intravenous}$$

In practice, it is rare for a drug to be completely absorbed into the circulation following oral administration. As noted earlier, many drugs undergo a first-pass effect resulting in some degree of metabolic degradation before entering the general circulation. In addition, factors of product formulation, dissolution, chemical and physical interactions with the gastrointestinal contents, gastric emptying time, intestinal motility, and others limit the absorption of an administered dose of a drug. The oral dosage strengths of many commercial products are based on considerations of the proportion of the dose administered that is expected to be absorbed and available to its site of action to produce the desired drug blood level and/or therapeutic response. The absolute bioavailability following oral dosing is generally compared

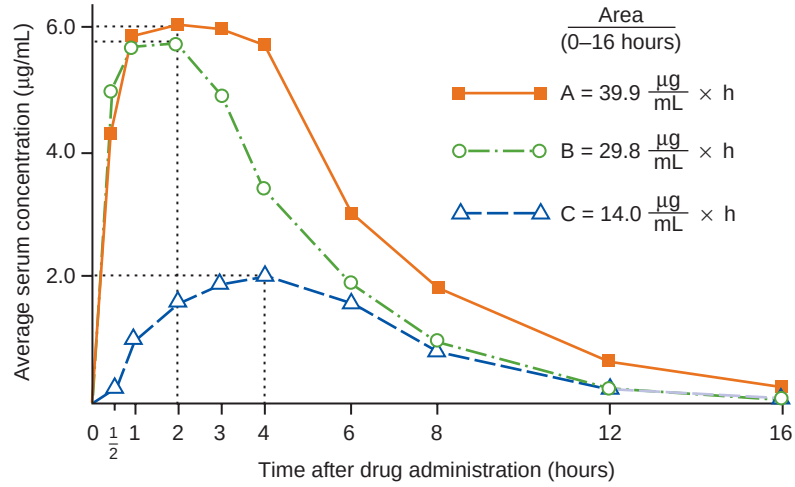


FIGURE 5.9 Serum concentration–time curve showing peak height concentrations, peak height times, and areas under the curves for equal amounts of drugs from three different formulations following oral administration. (Courtesy of D. I. Chodos and A. R. Disanto, Upjohn.)

to intravenous dosing. As examples, the reported mean oral bioavailability of ciprofloxacin hydrochloride tablets (Cipro) is 70%, levothyroxine sodium tablets (Synthroid) is 40% to 80%, fentanyl buccal tablets (Fentora) is 65%, lisinopril tablets (Prinivil) is 25%, and alendronate sodium tablets (Fosamax) is 0.64%. However, for most drugs, there is large intersubject variability, and the absorbed doses may vary from patient to patient.

BIOEQUIVALENCE OF DRUG PRODUCTS

A great deal of discussion and scientific investigation have been devoted recently to the problem of determining the equivalence between drug products of competing manufacturers.

The rate and extent to which a drug in a dosage form becomes available for biologic absorption or use depend in great measure on the materials in the formulation and on the method of manufacture. Thus, the same drug when formulated in *different* dosage forms may be found to possess different bioavailability characteristics and hence exhibit different clinical effectiveness. Furthermore, two seemingly identical or equivalent products of the same drug in the same dosage strength and in the *same* dosage form but differing in formulative materials or method of manufacture may vary widely in bioavailability and thus, in clinical effectiveness.

Dissolution requirements for capsules and tablets are included in the USP and are integral to bioavailability. Experience has shown that where bioinequivalence has been found between two supposedly equivalent products, dissolution testing can help to define the product differences. According to the USP, significant bioavailability and bioinequivalence problems that may be revealed through dissolution testing are generally the result of one or more of the following factors: the drug's particle size, excessive amounts of a lubricant such as magnesium stearate in the formulation, coating materials, and inadequate amounts of tablet or capsule disintegrants.

The FDA uses the following terms to define the type or level of equivalency between drug products (5).

Pharmaceutical equivalents are drug products that contain identical amounts of the identical active drug ingredient, that is, the same salt or ester of the same therapeutic moiety, in identical dosage forms but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable content uniformity, disintegration times, and/or dissolution rates.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety or its precursor but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable, content uniformity, disintegration times, and/or dissolution rates.

Bioequivalent drug products are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

In addition, the term *therapeutic equivalents* has been used to indicate pharmaceutical equivalents that provide essentially the same therapeutic effect when administered to the same individuals in the same dosage regimens.

Differences in bioavailability have been demonstrated for a number of products involving the following and other drugs: tetracycline, chloramphenicol, digoxin, warfarin sodium, diazepam, and L-dopa. Not only has bio *in*equivalence been demonstrated to exist in products of different manufacturers; there have also been variations in the bioavailability of different batches of drug products from the same manufacturer. Variations in the bioavailability of certain drug products have resulted in some therapeutic failures in patients who took two inequivalent drug products in the course of their therapy.

The most common experimental plan to compare the bioavailability of two drug products is the simple *crossover design study*. In this method, each of the 12 to 24 individuals in the group of carefully matched subjects (usually healthy men aged 18 to 40 years and having similar height and weight) is administered both products under fasting conditions and essentially serves as his own control. To avoid bias of the test results, each test subject is randomly assigned one of the two products for the first phase of the study. Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time. The same procedure is then repeated (*crossover*) with the second product after an appropriate interval, that is, a washout period to ensure that there is no residual drug from the first administered product that would artificially inflate the test results of the second product. Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability; that is, C_{max}, T_{max}, and AUC are analyzed with statistical procedures. Statistical differences in bioavailability parameters may not always be clinically significant in therapeutic outcomes.

Inherent differences in individuals result in different patterns of drug absorption, metabolism, and excretion. These differences must be statistically analyzed to separate them from the factors of bioavailability related to the products themselves. The value in the crossover experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences between individuals are minimized.

Absolute bioequivalency between drug products rarely if ever occurs. Such absolute equivalency would yield serum concentration–time curves for the products that would be exactly superimposable. This simply is not expected of products that are made at different times, in different batches, or indeed by different manufacturers. However, some expectations of bioequivalency are expected of products considered to have equivalent merit for therapy.

In most studies of bioavailability, the originally marketed product (often called the prototype, pioneer, innovator, or brand name drug product) is recognized as the established product of the drug and is used as the standard for the bioavailability comparative studies.

As is recalled from Chapter 2, an applicant seeking FDA approval for the marketing of a generic version of a previously approved drug product must file an Abbreviated New Drug Application (ANDA). The application is reviewed and acted upon by FDA's Center for Drug Evaluation and Research, Office of Generic Drugs. An approved generic product must be comparable to the innovator drug product in active ingredient, strength, dosage form, intended route of administration, therapeutic indication, and manufacturing and quality standards.

An ANDA application must contain data from in vitro studies, which demonstrate that the proposed product is "bioequivalent" to the approved comparator product. The applicant may request the FDA to *waive* the requirement for the submission of in vivo bioequivalence data based on an assessment that such bioequivalence may be considered self-evident as demonstrated by other data in the application or based on some of the following criteria (5):

- The drug product contains the same active drug ingredient, in the same concentration and dosage form as the comparator-approved product, and is intended to be administered by the same route.

- The drug product contains no inactive ingredient or other change in formulation from the approved drug product that may significantly affect the systemic absorption or therapeutic effectiveness of the active ingredient/product.
- The drug product is a parenteral, ophthalmic, nasal, oral, or otic solution; an inhalation; or a dermatologic preparation.
- The drug product is not a delayed-release or extended-release dosage form.
- The drug product meets an approved in vitro test comparable to the in vitro test of the approved drug, which has been correlated with in vivo data.
- The drug product is manufactured in accord with all Current Good Manufacturing Practice regulations.

The FDA may require in vivo studies if the agency determines that some differences between the proposed drug product and the previously approved drug product may affect the bioavailability, bioequivalence, or therapeutic equivalence of the proposed product.

The variables that can contribute to the differences between products are many (Table 5.3). For instance, in the manufacture of a tablet, different materials or amounts of such formulative components as fillers, disintegrating agents, binders, lubricants, colorants, flavorants, and coatings may be used. The particle size or crystalline form of a therapeutic or pharmaceutical component may vary between formulations. The tablet may vary in shape, size, and hardness, depending on the punches, dies, and compression forces used in the process. During packaging, shipping, and storage, the integrity of the tablets may be altered by physical impact, changes in humidity and temperature, or through interactions with the components of the container. Each of these factors may affect the rates of tablet disintegration, drug dissolution, and consequently the rate and extent of drug absorption. Although the bioequivalency problems are perhaps greater among tablets than for other dosage forms because of the multiplicity of variables, the same types of problems exist for the other dosage forms and must be considered in assessing bioequivalency.

Table 5.3 SOME FACTORS THAT INFLUENCE BIOAVAILABILITY OF ORAL DRUGS

DRUG SUBSTANCE PHYSIOCHEMICAL PROPERTIES
Particle size
Crystalline or amorphous form
Salt form
Hydration
Lipid or water solubility
pH and pK_a
PHARMACEUTICAL INGREDIENTS
Fillers
Binders
Coatings
Disintegrating agents
Lubricants
Suspending agents
Surface active agents
Flavoring agents
Coloring agents
Preservative agents
Stabilizing agents
DOSAGE FORM CHARACTERISTICS
Disintegration rate (tablets)
Dissolution time of drug in dosage form
Product age and storage conditions
PHYSIOLOGIC FACTORS AND PATIENT CHARACTERISTICS
Gastric emptying time
Intestinal Transit Time
Gastrointestinal abnormality or pathologic condition
Gastric contents
Other drugs
Food
Fluids
Gastrointestinal pH
DRUG METABOLISM (GUT AND DURING FIRST PASSAGE THROUGH LIVER)

Sometimes even therapeutically equivalent drugs are not equally suitable for a particular patient. For example, a patient may

be hypersensitive to an inert ingredient in one product (brand name or generic) that another product does not contain. Or a patient may become confused or upset if dispensed an alternative product that differs in color, flavor, shape, or packaging from that to which he or she is accustomed. Switching between products can generate concern, and thus pharmacists need to be prudent in both initial selection and interchange of products.

ROUTES OF DRUG ADMINISTRATION

Drugs may be administered using a variety of dosage forms and routes of administration, as presented in Tables 5.4 and 5.5. One of the fundamental considerations in dosage form design is whether the drug is intended for local or systemic effects. *Local* effects are achieved by direct application of the drug to the desired site of action, such as the eye, nose, or skin. *Systemic* effects result from the entrance of the drug into the circulatory system and transport to the cellular site of its action. For systemic effects, a drug may be placed directly in the bloodstream via intravenous injection or absorbed into the venous circulation following oral or other route of administration.

An individual drug substance may be formulated into multiple dosage forms that result in different drug absorption rates and times of onset, peak, and duration of action. Figure 5.10 and Table 5.6 demonstrate this for the drug nitroglycerin in various dosage forms. The sublingual, intravenous, and buccal forms present extremely rapid onsets of action, whereas the oral (swallowed), topical ointment, and topical patch present slower onsets of action but greater durations of action. The patch provides the longest duration of action, up to 14 hours following application of a single patch to the skin. The transdermal nitroglycerin patch allows a single daily dose, whereas the other forms require multiple dosing to maintain drug levels within the therapeutic window.

The difference in absorption between dosage forms is a function of the formulation and the route of administration. For example, a problem associated with the oral administration of a drug is that once absorbed through the lumen of the gastrointestinal tract into the portal vein, the drug may pass directly to the liver and undergo the *first-pass effect*. In essence, some or all of the drug may be metabolized by the liver. Consequently, its bioavailability is decreased. Thus, the bioavailable fraction is determined by the fraction of drug that is absorbed from the gastrointestinal tract and the fraction that escapes metabolism during its first pass through the liver. The bioavailable fraction (f) is the product of these two fractions as follows:

Table 5.4 ROUTES OF DRUG ADMINISTRATION

TERM	SITE
Oral	Mouth
Peroral (per os[a])	Gastrointestinal tract via mouth
Sublingual	Under the tongue
Parenteral	Other than the gastrointestinal tract (by injection)
Intravenous	Vein
Intra-arterial	Artery
Intracardiac	Heart
Intraspinal or intrathecal	Spine
Intraosseous	Bone
Intra-articular	Joint
Intrasynovial	Joint fluid area
Intracutaneous, intradermal	Skin
Subcutaneous	Beneath the skin
Intramuscular	Muscle
Epicutaneous (topical)	Skin surface
Transdermal	Skin surface
Conjunctival	Conjunctiva
Intraocular	Eye
Intranasal	Nose
Aural	Ear
Intrarespiratory	Lung
Rectal	Rectum
Vaginal	Vagina

[a]The abbreviation *po* is commonly used on prescriptions to indicate oral administration.

Table 5.5 ROUTE OF ADMINISTRATION AND DELIVERY SYSTEM OF PRIMARY DOSAGE FORMS

ORAL	Tablets
	Capsules
	Solutions
	Syrups
	Elixirs
	Suspensions
	Magmas
	Gels
	Powders
SUBLINGUAL	Tablets
	Troches, lozenges
	Drops (solutions)
PARENTERAL	Solutions
	Suspensions
EPICUTANEOUS, TRANSDERMAL	Ointments, gels
	Creams
	Infusion pumps
	Pastes
	Plasters
	Powders
	Aerosols
	Lotions
	Transdermal patches, disks, solutions
CONJUNCTIVAL	Contact lens inserts
	Ointments
INTRAOCULAR, INTRAAURAL	Solutions
	Suspensions
INTRANASAL	Solutions
	Sprays
	Inhalants
	Ointments
INTRARESPIRATORY	Aerosols
RECTAL	Solutions
	Ointments
	Suppositories
	Gels
VAGINAL	Solutions
	Ointments
	Emulsion foams
	Gels
	Tablets
	Inserts, suppositories, sponge
URETHRAL	Solutions
	Suppositories

$$f = \text{fraction of drug absorbed} \times \text{fraction escaping first-pass metabolism}$$

The bioavailability is lowest, then, for drugs that undergo a significant first-pass effect. For these drugs, a hepatic extraction ratio, or the fraction of drug metabolized, E, is calculated. The fraction of drug that enters the systemic circulation and is ultimately available to exert its effect then is equal to the quantity (1 − E). Table 5.7 lists some drugs according to their pharmacologic class that undergo a significant first-pass effect when administered by the oral route.

To compensate for this marked effect, the manufacturer may consider other routes of administration, for example, intravenous, intramuscular, or sublingual, that avoid the first-pass effect. Use of these routes must be accompanied by a corresponding adjustment in the dosage.

Another consideration centers on the metabolites themselves and whether they are pharmacologically active or inactive. If they are inactive, a larger oral dose is required to attain the desired therapeutic effect than with a lower dosage in a route with no first-pass effect. The classic example of drug that exhibits this effect is propranolol. However, if the metabolites are the active species, the oral dosage must be carefully tailored to the desired therapeutic effect. First-pass metabolism in this case will result in a quicker therapeutic response than that achieved by a route with no first-pass effect.

Also, the flow of blood through the liver can be decreased under certain conditions. Consequently, the bioavailability of drugs that undergo a first-pass effect can be expected to increase. For example, during cirrhosis, the blood flow to the kidney is dramatically decreased, and efficient hepatic extraction by enzymes responsible for a drug's metabolism also falls off. Consequently, in cirrhotic patients, the dosage of drug that undergoes a first-pass effect from oral administration will have to be reduced to avoid toxicity.

Oral Route

Drugs are most frequently taken by oral administration. Although a few drugs taken

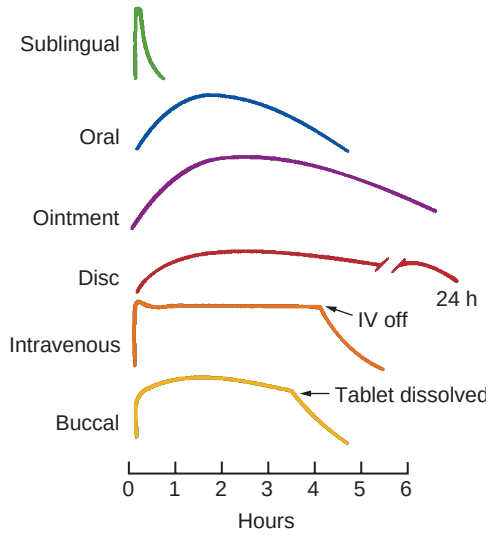


FIGURE 5.10 Blood level curves of nitroglycerin following administration of dosage forms by various routes. (Adapted with permission from Abrams J. Nitroglycerin and long-acting nitrates in clinical practice. Am J Med: Proceedings of the First North American Conference on Nitroglycerin Therapy. June 27, 1983. With permission from Elsevier.)

orally are intended to be dissolved in the mouth, nearly all drugs taken orally are swallowed. Of these, most are taken for the *systemic* drug effects that result after absorption from the various surfaces along the gastrointestinal tract. A few drugs, such as antacids, are swallowed for their local action in the gastrointestinal tract.

Compared with alternative routes, the oral route is considered the most natural, uncomplicated, convenient, and safe means of administering drugs. Disadvantages of the oral route include slow drug response (compared with parenterally administered drugs); chance of irregular absorption of drugs, depending upon such factors as constitutional makeup and the amount or type of food in the gastrointestinal tract; and the destruction of certain drugs by the acid reaction of the stomach or by gastrointestinal enzymes.

Dosage Forms Applicable

Drugs are administered by the oral route in a variety of pharmaceutical forms. The most popular are tablets, capsules, suspensions, and various pharmaceutical solutions. Briefly, *tablets* are solid dosage forms prepared by compression or molding that contains medicinal substances with or without suitable diluents, disintegrants, coatings, colorants, and other pharmaceutical adjuncts. Diluents are fillers used to prepare tablets of the proper size and consistency. Disintegrants are used for the breakup or separation of the tablet's compressed ingredients. This ensures prompt exposure of drug particles to the dissolution process, enhancing drug absorption, as demonstrated in Figure 5.11. Tablet coatings are of several types and for several purposes. Some, called *enteric coatings*, are employed to permit safe passage of a tablet through the acid environment of the stomach, where certain drugs may be destroyed, to the more suitable juices of the intestines, where tablet dissolution

Table 5.6 DOSAGE AND KINETICS OF NITROGLYCERIN IN VARIOUS DOSAGE FORMS

NITROGLYCERIN, DOSAGE FORM	USUAL DOSE (MG)	ONSET OF ACTION (MIN)	PEAK ACTION (MIN)	DURATION
Sublingual	0.3–0.8	2–5	4–8	10–30 min
Buccal	1–3	2–5	4–10	30–300 min[a]
Oral	6.5–19.5	20–45	45–120	2–6 h[b]
Ointment (2%)	0.5–2 in.	15–60	30–120	3–8 h
Transdermal Infusion System	20–160	30–60	60–180	12–14 h

[a]Effect persists so long as tablet is intact.
[b]Some short-term dosing studies have demonstrated effects to 8 h.
Reprinted with permission from Abrams J. Nitroglycerin and long-acting nitrates in clinical practice. Am J Med. Proceedings of First North American Conference of Nitroglycerin Therapy, June 27, 1983:88. With permission from Elsevier.

Table 5.7 SOME DRUGS THAT UNDERGO SIGNIFICANT LIVER METABOLISM AND EXHIBIT LOW BIOAVAILABILITY WHEN ADMINISTERED BY FIRST-PASS ROUTES

DRUG CLASS	EXAMPLES
Analgesic	Aspirin, meperidine, pentazocine, propoxyphene
Antianginal	Nitroglycerin
Antiarrhythmic	Lidocaine
Beta-adrenergic blocker	Labetalol, metoprolol, propranolol
Calcium channel blocker	Verapamil
Sympathomimetic amine	Isoproterenol
Tricyclic antidepressant	Desipramine, imipramine, nortriptyline

safely takes place. Other coatings protect the drug substance from the destructive influences of moisture, light, and air during storage or to conceal a bad or bitter taste from the taste buds of a patient. Commercial tablets, because of their distinctive shapes, colors, and frequently employed monograms of company symbols and code numbers, facilitate identification by persons trained in their use and serve as an added protection to public health.

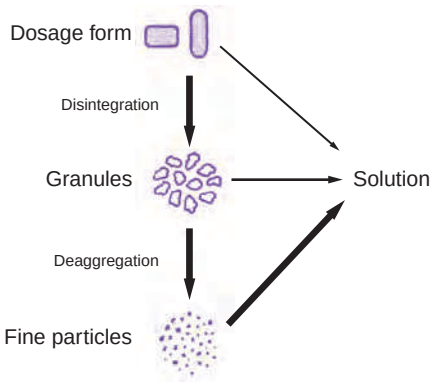


FIGURE 5.11 Disintegration of a tablet dosage form and direct availability of the contents in a capsule dosage form for dissolution and drug absorption after oral administration. (Adapted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 2nd Ed. Philadelphia, PA: Lea & Febiger, 1989.)

Capsules are solid dosage forms in which the drug substance and appropriate pharmaceutical adjuncts, such as fillers, are enclosed in either a hard or a soft shell, generally composed of a form of gelatin. Capsules vary in size, depending on the amount of drug to be administered, and have distinctive shapes and colors when produced commercially. Drug materials are released from capsules faster than from tablets. Capsules of gelatin, a protein, are rapidly disfigured within the gastrointestinal tract, permitting the gastric juices to permeate and reach the contents. Because unsealed capsules have been subject to tampering by unscrupulous individuals, many capsules nowadays are sealed by fusion of the two capsule shells. Also, capsule-shaped and coated tablets, called caplets, are increasingly used. These are easily swallowed, but their contents are sealed and protected from tampering like tablets.

Suspensions are preparations of finely divided drugs in a suitable fluid vehicle. Suspensions taken orally generally employ an aqueous vehicle, whereas those employed for other purposes may use a different vehicle. Suspensions of certain drugs to be used for intramuscular injection, for instance, may be maintained in a suitable oil. To be suspended, the drug particles must be insoluble in the vehicle. Nearly all suspensions must be shaken before use because they tend to settle. This ensures both uniformity of the preparation and, more importantly, the administration of the proper dosage. Suspensions are a useful means to administer large amounts of solid drugs that would be inconvenient to take in tablet or capsule form. In addition, suspensions have the advantage over solid dosage forms in that they are presented to the body in fine particle size, ready for dissolution immediately upon administration. However, not all oral suspensions are intended to be dissolved and absorbed by the body. For instance, some antidiarrheal preparations contain a kaolin mixture with pectin or attapulgite. The suspended kaolin or attapulgite acts in the intestinal tract by

adsorbing excessive intestinal fluid on the large surface area of its particles.

Drugs administered in aqueous *solution* are absorbed much more rapidly than those administered in solid form, because disintegration and dissolution are not required. Pharmaceutical solutions may differ in the type of solvent employed and therefore in their fluidity characteristics. Among the solutions frequently administered orally are *elixirs*, which are solutions in a sweetened hydroalcoholic vehicle and are more mobile than water; *syrups*, which generally use a sucrose solution as the sweet vehicle, resulting in a viscous preparation; and *solutions* themselves, which officially are preparations in which the drug substance is dissolved predominantly in an aqueous vehicle and do not for reasons of their method of preparation (e.g., injections, which must be sterilized) fall into another category of pharmaceutical preparations.

Absorption

Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum. In general, the higher up a drug is absorbed along the alimentary tract, the more rapid will be its action, a desirable feature in most instances. Because of the differences in chemical and physical nature among drug substances, a given drug may be better absorbed from one site than from another in the alimentary tract.

Sometimes the oral cavity is the absorption site. Physically, oral absorption of drugs is managed by allowing the drug substance to dissolve within the oral cavity with little or no swallowing until the taste of the drug has dissipated. This process is accommodated by providing the drug as extremely soluble and rapidly dissolving uncoated tablets. Drugs capable of being absorbed in the mouth present themselves to the absorbing surface in a much more concentrated form than when swallowed, because drugs become progressively more diluted with gastrointestinal secretions and contents as they pass along the alimentary tract.

The oral or *sublingual* (beneath the tongue) administration of drugs is regularly used for only a few drugs, with nitroglycerin and certain steroid sex hormones being the best examples. Nitroglycerin, a coronary vasodilator used in the prophylaxis and treatment of angina pectoris, is available in the form of tiny tablets that are allowed to dissolve under the tongue, producing therapeutic effects a few minutes after administration. The dose of nitroglycerin is so small (usually 400 mg) that if it were swallowed, the resulting dilute gastrointestinal concentration might not result in reliable and sufficient drug absorption. Even more important, however, is the fact that nitroglycerin is rapidly destroyed by the liver through the *first-pass effect*. Many sex hormones have been shown to be absorbed materially better from sublingual administration than when swallowed. Although the sublingual route is probably an effective absorption route for many other drugs, it has not been extensively used, primarily because other routes have proven satisfactory and more convenient for the patient. Retaining drug substances in the mouth is unattractive because of the bitter taste of most drugs.

Drugs may be altered within the gastrointestinal tract to render them less available for absorption. This may result from the drug's interaction with or binding to some normal constituent of the gastrointestinal tract or a foodstuff or even another drug. For instance, the absorption of the tetracycline group of antibiotics is greatly interfered with by the simultaneous presence of calcium. Because of this, tetracycline drugs must not be taken with milk or other calcium-containing foods or drugs.

Sometimes the pharmacist intends to prepare a formulation that releases the drug slowly over an extended time. There are many methods by which slow release is accomplished, including the complexation of the drug with another material, the combination of which is only slowly released from the dosage form. An example of this is slow-release wax-matrix potassium chloride tablets. These are designed to release their contents gradually as they are shunted through the gastrointestinal tract. Because their contents are leached out gradually, there is little incidence of gastric irritation. The intermingling

of food and drug generally results in delayed drug absorption. Since most drugs are absorbed more effectively from the intestines than from the stomach, when rapid absorption is intended, it is generally desirable to have the drug pass from the stomach into the intestines as rapidly as possible. Therefore, gastric emptying time is an important factor in drug action dependent on intestinal absorption. Gastric emptying time may be increased by a number of factors, including the presence of fatty foods (more effect than proteins, which in turn have more effect than carbohydrates) or lying on the back when bedridden (lying on the right side facilitates passage in many instances), or decreased, as by the presence of drugs (e.g., morphine) that have a quieting effect on the movements of the gastrointestinal tract. If a drug is administered in the form of a solution, it may be expected to pass into the intestines more rapidly than drugs administered in solid form. As a rule, large volumes of water taken with medication facilitate gastric emptying and passage into the intestines.

The pH of the gastrointestinal tract increases progressively along its length from about pH 1 in the stomach to approximately pH 8 at the far end of the intestines. pH has a definite bearing on the degree of ionization of most drugs, and this in turn affects lipid solubility, membrane permeability, and absorption. Because most drugs are absorbed by passive diffusion through the lipoid barrier, the lipid–water partition coefficient and the pK_a of the drugs are of prime importance to both the degree and the site of absorption within the gastrointestinal tract. As a general rule, weak acids are largely *un-ionized* in the stomach and are absorbed fairly well from this site, whereas weak bases are highly ionized in the stomach and are not significantly absorbed from the gastric surface. Alkalinization of the gastric environment by artificial means (simultaneous administration of alkaline or antacid drugs) would be expected to decrease the gastric absorption of weak acids and to increase that of weak bases. Strong acids and bases are generally poorly absorbed because of their high degree of ionization.

The small intestine serves as the major absorption pathway for drugs because of its suitable pH and the great surface area available for drug absorption along its approximately 20-foot length from the pylorus at the base of the stomach to the large intestine at the cecum. The pH of the lumen of the intestine is about 6.5 (Fig. 5.3), and both weakly acidic and weakly basic drugs are well absorbed from the intestinal surface, which behaves in the ionization and distribution of drugs between it and the plasma on the other side of the membrane as though its pH were about 5.3.

Rectal Route

Some drugs are administered rectally for their local effects and others for their systemic effects. Drugs given rectally may be administered as solutions, suppositories, or ointments. *Suppositories* are solid bodies of various weights and shapes intended for introduction into a body orifice (usually rectal, vaginal, or urethral) where they soften, melt, or dissolve; release their medication; and exert their drug effects. These effects simply may be the promotion of laxation (as with glycerin suppositories), the soothing of inflamed tissues (as with various commercial suppositories used to relieve the discomfort of hemorrhoids), or the promotion of systemic effects (as antinausea or anti–motion sickness). The composition of the suppository base, or carrier, can greatly influence the degree and rate of drug release and should be selected on an individual basis for each drug. The use of rectal ointments is generally limited to the treatment of local conditions. Rectal solutions are usually employed as enemas or cleansing solutions.

The rectum and the colon can absorb many soluble drugs. Rectal administration for systemic action may be preferred for drugs destroyed or inactivated by the environments of the stomach and intestines. The administration of drugs by the rectal route may also be indicated when the oral route is precluded because of vomiting or when the patient is unconscious or incapable of swallowing drugs safely without choking.

Approximately 50% of a dose of drug absorbed from rectal administration is likely to bypass the liver, an important factor when considering orally administered drugs that are rapidly destroyed in the liver by the first-pass effect. On the negative side, compared with oral administration, rectal administration of drugs is inconvenient and offensive to some patients, and the absorption of drugs from the rectum is frequently irregular and difficult to predict.

Parental Route

The term *parenteral* is derived from the Greek words *para*, meaning beside, and *enteron*, meaning intestine, which together indicate something done outside of the intestine and not by way of the alimentary tract. A drug administered parenterally is one injected through the hollow of a fine needle into the body at various sites and to various depths. The three primary routes of parenteral administration are subcutaneous, intramuscular, and intravenous, although there are others, such as intracardiac and intraspinal.

Drugs destroyed or inactivated in the gastrointestinal tract or too poorly absorbed to provide satisfactory response may be parenterally administered. The parenteral route is also preferred when rapid absorption is essential, as in emergencies. Absorption by the parenteral route is not only faster than after oral administration, but also the blood levels of drug that result are far more predictable, because little is lost after subcutaneous or intramuscular injection and virtually none by intravenous injection; this also generally permits the administration of smaller doses. The parenteral route of administration is especially useful in treating patients who are uncooperative, unconscious, or otherwise unable to accept oral medication.

One disadvantage of parenteral administration is that once the drug is injected, there is no retreat. That is, once the substance is in the tissues or bloodstream, removal of the drug warranted by an untoward or toxic effect or an inadvertent overdose is most difficult. By other means of administration, there is more time between drug administration and drug absorption, which becomes a safety factor by allowing for the extraction of unabsorbed drug (as by the induction of vomiting after an orally administered drug). Also, because of the strict sterility requirements for all injections, they are more expensive than other dosage forms and require competent trained personnel for proper administration.

Dosage Forms Applicable

Pharmaceutically, most injectable preparations are either a sterile suspension or solution of a drug substance in water or in a suitable vegetable oil. Drugs in solution act more rapidly than drugs in suspension, with an aqueous vehicle providing faster action in each instance than an oleaginous vehicle. As in other instances of drug absorption, a drug must be in solution to be absorbed, and a suspended drug must first submit to dissolution. Also, because body fluids are aqueous, they are more receptive to drugs in an aqueous vehicle than those in an oily one. For these reasons, the rate of drug absorption can be varied in parenteral products by selective combinations of drug state and supporting vehicle. For instance, a suspension of a drug in a vegetable oil is likely to be much more slowly absorbed than an aqueous solution of the same drug. Slow absorption means prolonged drug action, and when this is achieved through pharmaceutical means, the resulting preparation is referred to as a *depot* or *repository* injection, because it provides a storage reservoir of the drug substance within the body from which it is slowly removed into the systemic circulation. In this regard, even more sustained drug action may be achieved through the use of subcutaneous implantation of compressed tablets, termed pellets, that are only slowly dissolved from their site of implantation, releasing their medication at a fairly constant rate over several weeks to many months. The repository type of injection is mainly limited to the subcutaneous or intramuscular route. It is obvious that drugs injected intravenously do not encounter absorption barriers and thus produce only rapid drug effects. Preparations for intravenous injection must not interfere with

the blood components or with circulation and therefore, with few exceptions, are aqueous solutions.

Subcutaneous Injections

The subcutaneous (hypodermic) administration of drugs entails injection through the skin into the loose subcutaneous tissue. Subcutaneous injections are prepared as aqueous solutions or as suspensions and are administered in relatively small volumes, 2 mL or less. Insulin is an example of a drug administered by the subcutaneous route. Subcutaneous injections are generally given in the forearm, upper arm, thigh, or buttocks. If the patient is to receive frequent injections, it is best to alternate injection sites to reduce tissue irritation. After injection, the drug comes into the immediate vicinity of blood capillaries and permeates them by diffusion or filtration. The capillary wall is an example of a membrane that behaves as a lipid pore barrier, with lipid-soluble substances penetrating the membrane at rates varying with their oil–water partition coefficients. Lipid-insoluble (generally more water soluble) drugs penetrate the capillary membrane at rates that appear to be inversely related to their molecular size, with smaller molecules penetrating much more rapidly than larger ones. All substances, whether lipid soluble or not, cross the capillary membrane much more rapidly than other body membranes. The blood supply to the site of injection is an important factor in considering the rate of drug absorption; consequently, the closer capillaries are to the site of injection, the more prompt is the drug's entrance into the circulation. Also, the more the capillaries, the more surface area for absorption and the faster the rate of absorption. Some substances modify the rate of drug absorption from a subcutaneous site of injection. The addition of a vasoconstrictor to the injection formulation (or its prior injection) will generally diminish the rate of drug absorption by causing constriction of the blood vessels in the area of injection and thereby reducing blood flow and the capacity for absorption. This principle is used in the administration of local anesthetics by use of the vasoconstrictor epinephrine. Conversely, vasodilators may be used to enhance subcutaneous absorption by increasing blood flow to the area. Physical exercise can also influence the absorption of drug from an injection site. Diabetic patients who rotate subcutaneous injection sites and then do physical exercise such as jogging must realize that the onset of insulin activity may be influenced by the selected site of administration. Because of the movement of the leg and blood circulation to it during running, the absorption of insulin from a thigh injection site can be expected to be faster than from an abdominal injection site.

Intramuscular Injections

Intramuscular injections are performed deep into the skeletal muscles, generally the gluteal or lumbar muscles. The selected site is where the danger of hitting a nerve or blood vessel is minimal. Aqueous or oleaginous solutions or suspensions may be used intramuscularly. Certain drugs, because of their inherent low solubility, provide sustained drug action after an intramuscular injection. For instance, one deep intramuscular injection of a suspension of penicillin G benzathine results in effective blood levels of the drug for 7 to 10 days. The addition of the decanoate ester decreases the solubility of haloperidol and, consequently, extends haloperidol's t½ from 18 hours orally to 3 weeks, an advantage in antipsychotic drug therapy.

Drugs that are irritating to subcutaneous tissue are often administered intramuscularly. Also, greater volumes (2 to 5 mL) may be administered intramuscularly than subcutaneously. When a volume greater than 5 mL is to be injected, it is frequently administered in divided doses to two injection sites. Injection sites are best rotated when a patient is receiving repeated injections over time.

Intravenous Injections

In the intravenous administration of drugs, an aqueous solution is injected directly into the vein at a rate commensurate with efficiency, safety, comfort to the patient, and the desired duration of drug response. Drugs may be administered intravenously as a single, small-volume injection or as a large-volume slow intravenous drip infusion (as is

common following surgery). Intravenous injection allows the desired blood level of drug to be achieved in an optimal and quantitative manner. Intravenous injections are usually made into the veins of the forearm and are especially useful in emergencies when immediate drug response is desired. It is essential that the drug be maintained in solution after injection and not be precipitated within the circulatory system, an event that might produce emboli. Because of a fear of the development of pulmonary embolism, oleaginous vehicles are not usually intravenously administered. However, an intravenous fat emulsion is used for patients receiving parenteral nutrition whose caloric requirements cannot be met by glucose. It may be administered either through a peripheral vein or a central venous catheter at a distinct rate to help prevent untoward reactions.

Intradermal Injections

Intradermal injections are administered into the corium of the skin, usually in volumes of about 0.1 mL. Common sites for the injection are the arm and the back. The injections are frequently performed as diagnostic measures, as in tuberculin and allergy testing.

Epicutaneous Route

Drugs are administered topically, or applied to the skin, for their action at the site of application or for systemic drug effects.

Drug absorption via the skin is enhanced if the drug substance is in solution, if it has a favorable lipid–water partition coefficient, and if it is not an electrolyte. Drugs that are absorbed enter the skin by way of the pores, sweat glands, hair follicles, sebaceous glands, and other anatomic structures of the skin's surface. Because blood capillaries lie just below the epidermal cells, a drug that penetrates the skin and is able to traverse the capillary wall finds ready access to the general circulation.

Among the few drugs applied to the skin surface for percutaneous absorption and systemic action are nitroglycerin (antianginal), testosterone (male hormone), oxybutynin (overactive bladder), methylphenidate (attention deficit hyperactivity disorder), rivastigmine (dementia), nicotine (smoking cessation), estradiol (estrogenic hormone), clonidine (antihypertensive), and scopolamine (antinausea, anti–motion sickness). Each of these drugs is available for use in a transdermal delivery system fabricated as an adhesive disk or patch that slowly releases the medication for percutaneous absorption. Additionally, nitroglycerin is available in an ointment for application to the skin for systemic absorption. Nitroglycerin is used therapeutically for ischemic heart disease, with the transdermal dosage forms becoming increasingly popular because of the benefit in patient compliance through their long-acting (24 hours) characteristics. The nitroglycerin patch is generally applied to the arm or chest, preferably in a hair-free or shaven area. The transdermal scopolamine system is also in the form of a patch to be applied to the skin, in this case behind the ear, for the prevention of nausea and vomiting associated with motion sickness. The commercial product is applied several hours before need (as prior to an air or sea trip), where it releases its medication over 3 days. The concepts of transdermal therapeutic systems are discussed further in Chapter 11.

For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and as such are formulated to provide prolonged local contact with minimal absorption. Drugs applied to the skin for their local action include antiseptics, antifungal agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and protectants against environmental conditions, such as the effects of the sun, wind, pests, and chemical irritants. For these purposes, drugs are most commonly administered in the form of ointments and related semisolid preparations such as creams and pastes, as solid dry powders or aerosol sprays, or as liquid preparations such as solutions and lotions.

Pharmaceutically, ointments, creams, and pastes are semisolid preparations in which the drug is contained in a suitable base (ointment base), which is itself semisolid and either hydrophilic or hydrophobic. These

bases play an important role in the proper formulation of semisolid preparations, and there is no single base universally suitable as a carrier of all drug substances or for all therapeutic indications. The proper base for a drug must be determined individually to provide the desired drug release rate, staying qualities after application, and texture. Briefly, *ointments* are simple mixtures of drug substances in an ointment base, whereas *creams* are semisolid emulsions less viscid and lighter than ointments. Creams are considered to have greater esthetic appeal for their nongreasy character, ability to vanish into the skin upon rubbing, and ability to absorb serous discharges from skin lesions. *Pastes* contain more solid materials than do ointments and are therefore stiffer and less penetrating. Pastes are usually employed for their protective action. Thus, when protective rather than therapeutic action is desired, the formulation pharmacist will favor a paste, but when therapeutic action is required, he will prefer ointments and creams. Commercially, many therapeutic agents are prepared in both ointment and cream form and are dispensed and used according to the particular preference of the patient and the prescribing practitioner.

Medicinal powders are intimate mixtures of medicinal substances usually in an inert base such as talcum powder or starch. Depending on the particle size of the resulting blend, the powder will have varying dusting and covering capabilities. In any case, the particle should be small enough to ensure against grittiness and consequent skin irritation. Powders are most frequently applied topically to relieve such conditions as diaper rash, chafing, and athlete's foot.

When topical application is desired in liquid form other than solution, lotions are most frequently employed. *Lotions* are emulsions or suspensions generally in an aqueous vehicle, although certain solutions have been designated as lotions because of either their appearance or application. Lotions may be preferred over semisolid preparations because of their nongreasy character and their increased spreadability over large areas of skin.

Ocular, Oral, Otic, and Nasal Routes

Drugs are frequently applied topically to the eye, ear, and mucous membranes of the nose, usually as ointments, suspensions, and solutions. Ophthalmic solutions and suspensions are sterile aqueous preparations with other ingredients essential to the safety and comfort of the patient. Ophthalmic ointments must be sterile and free of grit. Innovative new delivery systems for ophthalmic drugs continue to be investigated. One dosage form, the Ocusert, is an elliptical unit designed for continuous release of pilocarpine following placement in the cul-de-sac of the eye. Also, case reports of the ability of soft contact lenses to absorb drug from the eye have spawned research on soft contact lenses impregnated with drug. Most nasal preparations are solutions or suspensions administered by drops or as a fine mist. Research is directed toward the feasibility of nasal administration of insulin for diabetes mellitus. Ear preparations are usually viscid so that they have prolonged contact with the affected area. They may be employed simply to soften ear wax, to relieve an earache, or to combat an ear infection. Eye, ear, and nose preparations usually are not used for systemic effects, and although ophthalmic and otic preparations are not usually absorbed to any great extent, nasal preparations *may* be absorbed, and systemic effects after the intranasal application of solution are fairly common.

Other Routes

The lungs provide an excellent absorbing surface for the administration of gases and for aerosol mists of very minute particles of liquids or solids. The gas is usually oxygen, and the drugs are the common general anesthetics administered to patients entering surgery. The rich capillary area of the alveoli of the lungs, which in a man covers nearly a thousand square feet, provides rapid absorption and drug effects comparable in speed with those following an intravenous injection. In the case of drug particles, their size largely determines the depth to which they penetrate the alveolar regions and their solubility,

the extent to which they are absorbed. After contact with the inner surface of the lungs, an insoluble drug particle is caught in the mucus and is moved up the pulmonary tree by ciliary action. Soluble drug particles that are approximately 0.5 to 1.0 mm in size reach the minute alveolar sacs and are most prompt and efficient in providing systemic effects. Particles smaller than 0.5 mm are expired to some extent, and thus, their absorption is not total but variable. Particles 1 to 10 mm effectively reach the terminal bronchioles and to some extent the alveolar ducts and are favored for local therapy. Therefore, in the pharmaceutical manufacture of aerosol sprays for inhalation therapy, the manufacturers not only must attain the proper drug particle size but also must ensure their uniformity for consistent penetration of the pulmonary tree and uniform effects.

In certain instances and for local effects, drugs are inserted into the vagina or the urethra. Drugs are usually presented to the vagina in tablet or other form, such as a suppository, ointment, emulsion foam, gel, or solution, and to the urethra as a suppository or solution. Systemic drug effects may result after vaginal or urethral application of drugs following absorption of the drug from the mucous membranes of these sites.

FATE OF DRUG AFTER ABSORPTION

After absorption into the general circulation from any route of administration, a drug may become bound to blood proteins and delayed in its passage into the surrounding tissues. Many drug substances are highly bound to blood protein and others minimally bound. For instance, in the bloodstream, naproxen is 99% bound to plasma proteins, penicillin G is 60% bound, amoxicillin is only 20% bound, and minoxidil is unbound.

The degree of drug binding to plasma proteins is usually expressed as a percentage or as a fraction (termed *alpha*, or a) of the bound concentration (C_b) to the total concentration (C_t), bound plus unbound (C_u) drug:

$$\alpha = \frac{C_b}{C_u + C_b} = \frac{C_b}{C_t}$$

Thus, if one knows two of the three terms in the equation, the third may be calculated. Drugs having an alpha value above 0.9 are considered highly bound (90%); drugs with an alpha value below 0.2 are considered to be minimally (20% or less) protein bound. Table 5.8 presents approximate serum protein–binding characteristics for representative drugs in the blood under conditions associated with usual therapy. The drug–protein complex, which is reversible, involves albumin, although globulins also participate in the binding of drugs, particularly some of the hormones. The binding of drugs to biologic materials entails the formation of relatively weak bonds (e.g., van der Waals, hydrogen, and ionic bonds). The binding capacity of blood proteins is limited, and once they are saturated, additional drug absorbed into the bloodstream remains unbound unless bound drug is released, creating a vacant site for another drug molecule to attach. Any unbound drug is free to leave the bloodstream for tissues or cellular sites within the body.

Bound drug is neither exposed to the body's detoxification (metabolism) processes nor is it filtered through the renal glomeruli. Bound drug is therefore referred to as the *inactive* portion in the blood, and unbound drug, with its ability to penetrate cells, is termed the *active* blood portion. The bound portion of drug serves as a reservoir or depot from which the drug is released as the free form when the level of free drug in the blood no longer is adequate to ensure protein saturation. The free drug may be only slowly released, which prolongs the drug's stay in the body. For this reason, a drug that is highly protein bound may remain in the body longer and require less frequent dosage than another drug that is only slightly protein bound and remains in the body for only a short period. Evidence suggests that the concentration of serum albumin decreases about 20% in the elderly. This may be clinically significant for drugs that bind strongly to albumin, for example, phenytoin, because if there is less albumin available to bind the drug, there will be a corresponding increase of the free drug in the body. Without a downward dosage adjustment in an elderly patient, there

could be an increased incidence of adverse effects.

A drug's binding to blood proteins may be affected by the simultaneous presence of another drug or drugs. The additional drug or drugs may produce effects or duration of action quite dissimilar to that found when each is administered alone. Salicylates, for instance, decrease the binding capacity of thyroxin, the thyroid hormone, to proteins. Through this action, the displaced drugs become less protein bound, and their activity (and toxicity) may be increased. The intensity of a drug's pharmacologic response is related to the ratio of the bound drug to free active drug and to the therapeutic index of the drug. Warfarin sodium, an anticoagulant, is 97% bound to plasma protein, leaving 3% in free form to exert its effect. If a second drug, such as naproxen, which is strongly bound to plasma proteins, is administered and results in only 90% of the warfarin sodium being bound, 10% of warfarin sodium will be in the free form. Thus, the blood level of the free warfarin sodium (3% to 10%) will triple and possibly result in serious toxicity. The displacement of drugs from plasma protein sites is typical in the elderly, who normally take numerous medicines. Coupled with the aforementioned decrease in serum protein through the aging process, the addition of a highly protein-bound drug to an elderly patient's treatment regimen may pose significant problems if the patient is not monitored carefully for signs of toxicity.

In the same manner as they are bound to blood proteins, drugs may become bound to specific components of certain cells. Thus, drugs are not distributed uniformly among all cells of the body, but rather tend to pass from the blood into the fluid bathing the tissues and may accumulate in certain cells according to their permeability and chemical and physical affinities. This affinity for certain body sites influences their action, for they may be brought into contact with reactive tissues (their *receptor sites*) or deposited in places where they are inactive. Many drugs, because of their affinity for and solubility in lipids, are deposited in fatty body tissue, creating a reservoir from which they are slowly released to other tissues.

Table 5.8 EXAMPLES OF DRUG BINDING TO PLASMA PROTEINS

DRUG	PERCENT BOUND
Naproxen (Naprosyn)	99
Carvedilol (Coreg)	98
Esomeprazole (Nexium)	97
Warfarin sodium (Coumadin)	97
Fluoxetine (Prozac)	95
Zolpidem (Ambien)	93
Duloxetine (Cymbalta)	90
Indomethacin (Indocin)	90
Rosuvastatin (Crestor)	88
Penicillin V (Veetids)	75
Nitroglycerin (Nitro-Bid)	60
Penicillin G potassium	60
Methotrexate	50
Methicillin (Staphcillin)	40
Ceftizoxime (Cefizox)	30
Ciprofloxacin (Cipro)	20–40
Digoxin (Lanoxin)	20–25
Amoxicillin (Amoxil)	20
Metronidazole (Flagyl)	20
Mercaptopurine (Purinethol)	19
Ranitidine (Zantac)	15
Gabapentin (Neurontin)	3
Lisinopril (Zestril)	0
Minoxidil (Loniten)	0

Approximate valuwes based on conditions usually associated with drug therapy.

Drug Metabolism or Biotransformation

Although some drugs are excreted from the body in their original form, many drugs undergo biotransformation prior to excretion. Biotransformation indicates the chemical changes to drugs within the body as they are metabolized and altered by various biochemical mechanisms. The biotransformation of a drug results in its conversion to one or more compounds that are more water soluble,

more ionized, less capable of binding to proteins of the plasma and tissues, less capable of being stored in fat tissue, and less able to penetrate cell membranes, and thereby less active pharmacologically. Because of its new characteristics, a drug so transformed is rendered less toxic and is more readily excreted. It is for this reason that biotransformation is also commonly called detoxification or inactivation. (However, sometimes the metabolites are more active than the parent compound; see *prodrugs*, following.)

The exact metabolic processes (pathways) by which drugs are transformed are an active area of biomedical research. Much work has been done with the processes of animal degradation of drugs, and in many instances, the biotransformation in the animal is thought to parallel that in man. Four principal chemical reactions are involved in the metabolism of drugs: oxidation, reduction, hydrolysis, and conjugation. Most oxidation reactions are catalyzed by enzymes (oxidases) bound to the endoplasmic reticulum, a tubular system in liver cells. Only a small fraction of drugs are metabolized by reduction, through the action of reductases in the gut and liver. Esterases in the liver participate in the hydrolytic breakdown of drugs containing ester groups and amides. Glucuronide conjugation is the most common pathway for drug metabolism, through combination of the drug with glucuronic acid, forming ionized compounds that are easily eliminated via the urine (7). Other metabolic processes, including methylation and acylation conjugation reactions, occur with certain drugs to foster elimination.

In recent years, much interest has been shown in the metabolites of drug biotransformation. Certain metabolites may be as active as or even more active pharmacologically than the original compound. Occasionally, an active drug is converted into an active metabolite, which must be excreted as such or undergo further biotransformation to an inactive metabolite, for example, amitriptyline to nortriptyline. In other instances of drug therapy, an inactive parent compound, referred to as a *prodrug*, may be converted to an active therapeutic agent by chemical transformation in the body. An example is the prodrug enalapril (Vasotec), which after oral administration is hydrolyzed to enalaprilat, an active angiotensin-converting enzyme inhibitor used in the treatment of hypertension. Enalaprilat itself is poorly absorbed when taken orally (and thus the prodrug) but may be administered intravenously in aqueous solution. The use of these active metabolites as original drugs is a new area of investigation and a vast reservoir of potential therapeutic agents.

Several examples of biotransformations occurring within the body are as follows:

(1) Acetaminophen (active) $\xrightarrow{\text{conjugation}}$ Acetaminophen glucuronide (inactive)

(2) Amoxapine (active) $\xrightarrow{\text{oxidation}}$ 8-hydroxy-amoxapine (inactive)

(3) Procainamide (active) $\xrightarrow{\text{hydrolysis}}$ *p*-Aminobenzoic acid (inactive)

(4) Nitroglycerin (active) $\xrightarrow{\text{reduction}}$ 1 – 2 and 1 – 3 dinitroglycerol (inactive)

Some parent compounds undergo full, partial, or no biotransformation following administration. Lisinopril (Zestril), for example, does not undergo metabolism and is excreted unchanged in the urine. On the other hand, verapamil (Calan) metabolizes to at least 12 metabolites, the most prevalent of which is norverapamil. Norverapamil has 20% of the cardiovascular activity of the parent compound. Diltiazem (Cardizem) is partially metabolized (about 20%) to desacetyl diltiazem, which has 10% to 20% of the coronary vasodilator activity of the parent compound. Indomethacin (Indocin) is metabolized in part to desmethyl, desbenzoyl, and desmethyl desbenzoyl metabolites. Propoxyphene napsylate (Darvon N) is metabolized to norpropoxyphene, which has less central nervous system depressant action than the parent compound but greater local anesthetic effects. Most metabolic transformations take place in the liver, with some drugs, including diltiazem and verapamil, undergoing extensive first-pass effects. Other

drugs, such as terazosin (Hytrin), undergo minimal first-pass metabolism. The excretion of both drug and metabolites takes place primarily but to varying degrees via the urine and feces. For example, indomethacin and its metabolites are excreted primarily (60%) in the urine, with the remainder in the feces, whereas terazosin and its metabolites are excreted largely (60%) through the feces and the remainder in the urine.

Several factors influence drug metabolism. For example, there are marked differences between *species* in pathways of hepatic metabolism of a given drug. Species differences make it extremely difficult to extrapolate from one species to another, as with laboratory animals to humans. Furthermore, there are many examples of *interindividual variations* in hepatic metabolism of drugs within one species. Genetic factors affect the basal activity of the drug-metabolizing enzyme systems. Thus, there can be marked intersubject variation in rates of metabolism. Because of this variation, a physician must individualize therapy to maximize the chances for a constructive therapeutic outcome with minimal toxicity. Studies in humans have demonstrated that these differences have occurred within the cytochrome P-450 genetic codes for a family of isoenzymes responsible for drug metabolism.

Age of the patient is another significant factor in drug metabolism. Although pharmacokinetic calculations have not been able to develop a specific correlative relationship with age, it is known that the ability to metabolize drugs is low at the extremes of the age scale, that is, among the elderly and neonates. Liver blood flow is reduced by aging at about 1% per year beginning around age 30 (8). This decreased blood flow to the liver reduces the capacity for hepatic drug metabolism and elimination. For example, the half-life of chlordiazepoxide increases from about 6 hours at age 20 to about 36 hours at age 80. Furthermore, an immature hepatic system disallows the effective metabolism of drugs by the newborn or premature infant. As mentioned earlier, the half-life of theophylline ranges from 14 to 58 hours in the premature infant to 2.5 to 5 hours in young children aged 1 to 4 whose liver enzyme systems are mature.

Diet has also been demonstrated to modify the metabolism of some drugs. For example, the conversion of an asthmatic patient from a high- to a low-protein diet will increase the half-life of theophylline. It has also been demonstrated that the production of polycyclic hydrocarbons by the charcoal broiling of beef enhances the hepatic metabolism and shortens the plasma half-life of theophylline. It is conceivable that this effect also occurs with drugs that are metabolized in similar fashion to theophylline. Diet type, including starvation and intake of certain vegetables (brussels sprouts, cabbage, broccoli), has been shown to influence the metabolism of certain drugs. Coadministration of large quantities of grapefruit juice (at least 1 quart daily) may result in increased plasma levels of some of the HMG-CoA reductase inhibitors and increase the patient's risk of myopathy. Consequently, concurrent use of grapefruit juice should be avoided. Finally, exposure to other drugs or chemicals, such as pesticides, alcohol, and nicotine, and the presence of disease states, such as hepatitis, have all demonstrated an influence on drug metabolism and consequently the pharmacokinetic profile of certain drugs.

Excretion of Drugs

The excretion of drugs and their metabolites terminates their activity and presence in the body. They may be eliminated by various routes, with the kidney playing the dominant role by eliminating drugs via the urine. Drug excretion in the feces is also important, especially for drugs that are poorly absorbed and remain in the gastrointestinal tract after oral administration. Exit through the bile is significant only when reabsorption from the gastrointestinal tract is minimal. The lungs provide the exit for many volatile drugs through the expired breath. The sweat glands, saliva, and milk play only minor roles in drug elimination. However, if a drug gains access to the milk of a mother during lactation, it can easily exert its effects in the nursing infant. Drugs that do enter breast

milk and may be passed on to nursing infants include theophylline, penicillin, reserpine, codeine, meperidine, barbiturates, diltiazem, and thiazide diuretics. It is generally good practice for the mother to abstain from taking medication until the infant is weaned. If she must take medication, she should abide by a dosage regimen and nursing schedule that permit her own therapy yet ensure the safety of her child. Not all drugs gain entrance into the milk; nevertheless, caution is advisable. A summary of drug safety in lactations, including biopharmaceutic parameters, calculation of infant exposure, and a listing of drugs and their risk assessment, may be found at the following Web site: http://www.medsafe.govt.nz/Profs/PUarticles/lactation.htm.

Manufacturers' package inserts contain product-specific information (usually in the section on precautions) on drug migration into breast milk.

The unnecessary use of medications during the early stages of pregnancy is likewise restricted by physicians, because certain drugs are known to cross the placental barrier and gain entrance to the tissues and blood of the fetus. Among the many drugs known to do so are all of the anesthetic gases, many barbiturates, sulfonamides, salicylates, and a number of other potent agents like quinine, meperidine, and morphine, the latter two being narcotic analgesics with great potential for addiction. In fact, it is fairly common for an infant to be born addicted because of the addiction of its mother and the passage of the drugs across the placental barrier.

The kidney, as the main organ for the elimination of drugs from the body, must be functioning adequately if drugs are to be efficiently eliminated. For instance, elimination of digoxin occurs largely through the kidney by first-order kinetics; that is, the quantity of digoxin eliminated at any time is proportional to the total body content. Renal excretion of digoxin is proportional to the glomerular filtration rate, which when normal results in a digoxin half-life that may range from 1.5 to 2 days. When the glomerular filtration rate is impaired or disrupted, however, as in an anuric patient, the elimination rate decreases. Consequently, the half-life of digoxin may be 4 to 6 days. Because of this prolongation of digoxin's half-life, the dosage of the drug must be decreased or the dosage interval prolonged. Otherwise, digoxin toxicity will occur. The degree of impairment can be estimated by measurements of glomerular filtration rates, most often by creatinine clearance (CrCL). Usually, however, this is not feasible, and the patient's serum creatinine value is used within appropriate pharmacokinetic equations to help determine a drug's dosage regimen.

Some drugs may be reabsorbed from the renal tubule even having been sent there for excretion. Because the rate of reabsorption is proportional to the concentration of drug in un-ionized form, it is possible to modify this rate by adjusting the pH of the urine. By acidifying the urine, as with the oral administration of ammonium chloride, or by alkalinizing it, as with the administration of sodium bicarbonate, one can increase or decrease the ionization of the drug and thereby alter its prospect of being reabsorbed. Alkalinization of the urine has been demonstrated to enhance the urinary excretion of weak acids such as salicylates, sulfonamides, and phenobarbital. The opposite effect can be achieved by acidifying the urine. Thus, the duration of a drug's stay within the body may be markedly altered by changing the pH of the urine. Some foods, such as cranberry juice, can also acidify the urine and may alter drug excretion rates.

The urinary excretion of drugs may also be retarded by the concurrent administration of agents capable of inhibiting their tubular secretion. A well-known example is the use of probenecid to inhibit the tubular secretion of various types of penicillin, thereby reducing the frequency of dosage administrations usually necessary to maintain adequate therapeutic blood levels of the antibiotic drug. In this particular instance, the elevation of penicillin blood levels, by whatever route the antibiotic is administered, to twofold and even fourfold levels has been demonstrated by adjuvant therapy with probenecid. The effects are completely reversible upon withdrawal of the probenecid from concomitant therapy.

The fecal excretion of drugs appears to lag behind the rate of urinary excretion, partly because a day or so elapses before the feces reach the rectum. Drugs administered orally for local activity within the gastrointestinal tract and not absorbed will be eliminated completely via the feces. Unless a drug is particularly irritating to the gastrointestinal tract, there is generally no urgency about removing unabsorbable drugs from the system by means other than normal defecation. Some drugs that are only partially absorbed after oral administration will naturally be partly eliminated through the rectum.

PHARMACOKINETIC PRINCIPLES

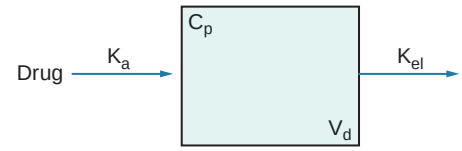
This section introduces the concept of pharmacokinetics and how it interrelates the various processes that take place when one administers a drug to a patient, that is, ADME. It is not intended to be comprehensive, and thus, for further information about the subject, the reader is referred to other appropriate literature.

A problem encountered when one needs to determine a more accurate dosage of a drug or a more meaningful interpretation of a biologic response to a dose is the inability to determine the drug concentration at the active site in the body. Consequently, the concept of compartmental analysis is used to determine what has become of the drug as a function of time from the moment it is administered until it is no longer in the body. Pharmacokinetic analysis uses mathematical models to simplify or simulate the disposition of the drug in the body. The idea is to begin with a simple model and then modify as necessary. The principal assumption is that the human body may be represented by one or more *compartments* or pools in which a drug resides in a dynamic state for a short time. A compartment is a hypothetical space bound by an unspecified membrane across which drugs are transferred (Fig. 5.12). The transfer of drugs into and out of this compartment is indicated by arrows that point in the direction of drug movement into or out of the compartment. The rate at which a drug is transferred throughout the system is designated by a symbol that usually represents an exponential rate constant. Typically, the letter K or k with numeric or alphanumeric subscripts is used.

Several assumptions are associated with modeling of drug behavior in the body. It is assumed that the volume of each compartment remains constant. Thus, an equation that describes the time course of the amount of drug in the compartment can be converted to an equation that depicts the time course of the drug concentration in the compartment by dividing both sides of the equation by the volume of the compartment. Second, it is assumed that once a drug enters the compartment, it is instantaneously and uniformly distributed throughout the entire compartment. Thus, it is assumed that a sampling of any one portion of the compartment will yield the drug concentration of the entire compartment.

In compartment models, it is assumed that drug passes freely into and out of compartments. Thus, these compartmental systems are known as open systems. Typically, drug transport between compartments follows first-order kinetics, wherein a constant fraction of drug is eliminated per unit of time and can be described by ordinary differential equations. In these linear systems, the time constants that describe the rate at which the plasma or blood concentration curve of a drug decays are independent of the dose, the volume of distribution, and the route of administration.

The simplest pharmacokinetic model is the single-compartment *open-model system*



Where:
C_p is the drug concentration in plasma
V_d is the volume of the compartment or volume of distribution

FIGURE 5.12 A one-compartment system.

(Fig. 5.12). This model depicts the body as one compartment characterized by a certain volume of distribution (V_d) that remains constant. Each drug has its own distinct volume of distribution, and this can be influenced by factors including age and disease status. In this scheme, a drug can be instantaneously introduced into the compartment, that is, via rapid intravenous administration, or gradually, as with oral administration. In the former case, it is assumed that the drug distributes immediately to tissues and instantly attains equilibrium. In the latter case, the drug is absorbed at a certain rate and is characterized by the absorption rate constant K_a. Finally, the drug is eliminated from the compartment at a certain rate that is characterized by an elimination rate constant, K_{el}.

It is relevant at this point to consider the *volume of distribution*, V_d, a proportionality constant that refers to the volume into which the total amount of drug in the body must be uniformly distributed to provide the concentration of drug actually measured in plasma or blood. This term can be misleading because it does not represent a specific body fluid or volume. It is influenced by the plasma protein binding and tissue binding of a drug. These then influence the distribution of the drug between plasma water, extracellular fluid, intracellular fluid, and total body water. Furthermore, because a drug can partition between fat and water according to its unique partition coefficient, this can also influence the volume of distribution. Because of these phenomena, pharmacokineticists find it convenient to describe drug distribution in terms of compartmental models.

To determine the rate of drug transfer into and out of the compartment, plasma, serum, or blood samples are drawn at predetermined times after the drug is administered and analyzed for drug concentration. Once a sufficient number of experimental data points are determined, these are plotted on semilogarithmic paper, and an attempt is made to fit the experimental points with a smooth curve. Figure 5.13 depicts the plasma concentration–time profile for a hypothetical drug following rapid intravenous injection of a bolus dose of the drug with instantaneous distribution. For drugs whose distribution follows first-order one-compartment pharmacokinetics, a plot of the logarithm of the concentration of drug in the plasma (or blood) versus time will yield a straight line. The equation that describes the plasma decay curve is

$$C_p = C_P^0 e^{-K_{el}t} \qquad \text{(Equation 5.1)}$$

where

Kel is the first-order rate of elimination of the drug from the body,

C_p is the concentration of the drug at a time equal to t, and

C_p^0 is the concentration of drug at time equal to zero, when all the drug administered has been absorbed but none has been removed from the body through elimination mechanisms, for example, metabolism and renal excretion.

The apparent first-order rate of elimination, K_{el}, is usually the sum of the rate constants of a number of individual processes, for example, metabolic transformation and renal excretion.

For the purpose of pharmacokinetic calculation, it is simpler to convert Equation 5.1 to natural logs:

$$\mathrm{Ln}C_p = \mathrm{Ln}C_p^0 - K_{el}(t) \qquad \text{(Equation 5.2)}$$

and then to log base$_{10}$:

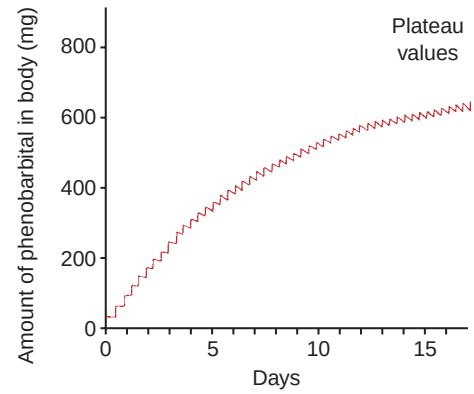


FIGURE 5.13 Plot of the plasma concentration–time data. (Adapted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 2nd Ed. Philadelphia, PA: Lea & Febiger, 1989.)

$$\text{Log } C_p = \text{Log } C_p^0 - K_{el}(t)/2.303$$

(Equation 5.3)

Equation 5.3 is then thought of in terms of the Y-intercept form:

$$Y = b + mX$$

$$\text{Log } C_p = \text{Log } C_P^0 - K_{el}/2.303(t)$$

and interpreted as such in the semilogarithmic plot illustrated in Figure 5.14. Most drugs administered orally can be adequately described using a one-compartment model, whereas drugs administered by rapid intravenous infusion are usually best described by a two-compartment or three-compartment model system.

Assuming that a drug's volume of distribution is constant within this system, the total amount of drug in the body (Q_b) can be calculated from the following equation:

$$Q_b = \left[C_P^0\right][V_d] \qquad \text{(Equation 5.4)}$$

Usually, C_p^0 is determined by extrapolating the drug concentration–time plot to time zero.

In this simple one-compartment system, it is assumed that the administered drug is confined to the plasma (or blood) and then excreted. Drugs that exhibit this behavior have small volumes of distribution. For example, a drug such as warfarin sodium, which is extensively bound to plasma albumin, will have a volume of distribution equivalent to that of plasma water, about 2.8 L in an average 70-kg adult. Some drugs, however, are initially distributed at somewhat different rates in various fluids and tissues. Consequently, these drugs' kinetic behavior can best be illustrated by considering an expansion of the one-compartment system to the *two-compartment model* (Fig. 5.15).

In the two-compartment system, a drug enters into and is instantaneously distributed throughout the central compartment. Its subsequent distribution into the second or peripheral compartment is slower. For simplicity, on the basis of blood perfusion and tissue–plasma partition coefficients for a given drug, various tissues and organs are considered together and designated either

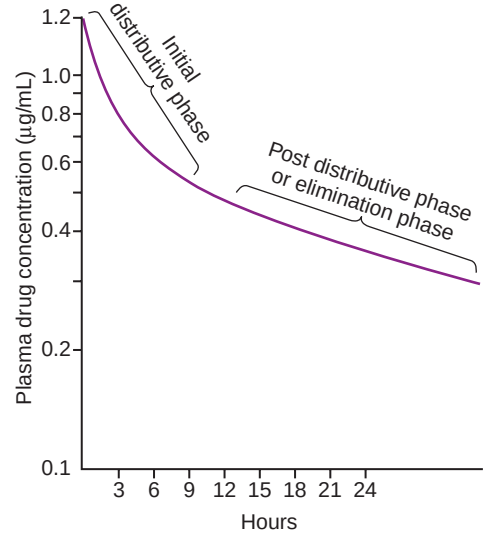
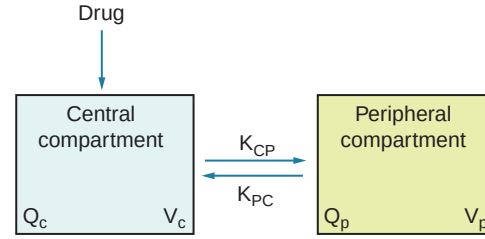


FIGURE 5.14 A semilogarithmic plot of plasma concentration versus time of an intravenous drug that follows first-order two-compartment pharmacokinetics.

central compartment or peripheral compartment. The central compartment is usually considered to include the blood, the extracellular space, and organs with good blood perfusion, such as the lungs, liver, kidneys, and heart. The peripheral compartment usually comprises tissues and organs that are poorly perfused by blood, such as the skin, bone, and fat.

Figure 5.16 depicts the plasma drug concentration–time plot for a rapidly administered intravenous dose of a hypothetical drug that exhibits kinetic behavior exemplifying a



Where:
Q_c = Quantity of drug in central compartment
V_c = Volume of the central compartment
Q_p = Quantity of drug in peripheral compartment
V_p = Volume of the peripheral compartment

FIGURE 5.15 A two-compartment system.

two-compartment system. Note the initial steep decline of the plasma drug concentration curve. This typifies the distribution of the drug from the central compartment to the peripheral compartment. During this phase, the drug concentration in the plasma will decrease more rapidly than in the postdistributive or elimination phase. Whether this distributive phase is apparent depends on the timing of the plasma samples, particularly in the time immediately following administration. A distributive phase can be very short, a few minutes, or last for hours and even days.

A semilogarithmic plot of the plasma concentration versus time after rapid intravenous injection of a drug best described by a two-compartment model system can often be resolved into two linear components. This procedure can be performed by the method of residuals (or feathering), shown in Figure 5.16. In this procedure, a straight line is fitted through the tail of the original curve and extrapolated to the Y-axis (the value obtained is B). A plot is then made of the absolute difference values of the original curve and the resultant extrapolated straight line. The slope of the feathered line (–a/2.303) and the extrapolated line (–b/2.303) and the intercepts, A and B, are determined. The following equation describes a two-compartment system:

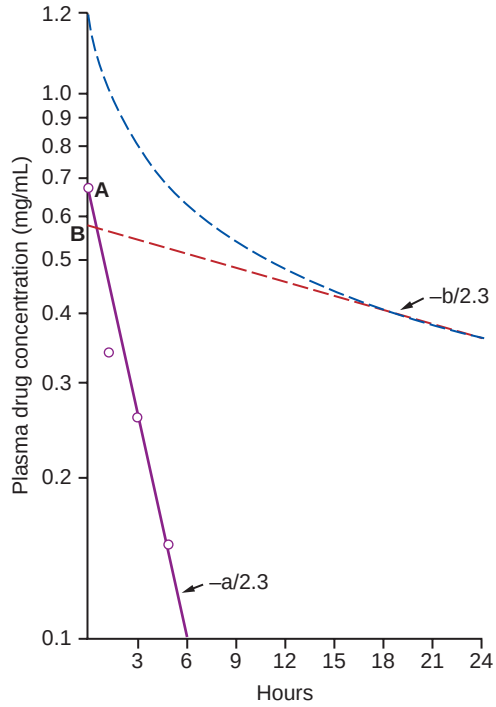


FIGURE 5.16 The logarithm of the drug concentration in plasma plotted versus time (*solid line*) after intravenous administration of a drug whose disposition can be described by a two-compartment model.

$$C_p = Ae^{-at} + Be^{-bt} \qquad \text{(Equation 5.5)}$$

This is a two-exponential equation that describes the two-compartment system. In this scheme, the slope of the line, –a/2.303, obtained from feathering yields the distributive rate of the drug. The slope of the terminal linear phase or elimination phase, –b/2.303, describes the rate of loss of the drug from the body and usually is considered to be a reflection of the metabolic processes and renal elimination from the body. Appropriate pharmacokinetic formulas allow the clinician to calculate the various volumes of distribution and rates of distribution and elimination for drugs whose pharmacokinetic behavior is exemplified by the two-compartment system.

Half-Life

The half-life ($t_{½}$) of a drug describes the time required for a drug's blood or plasma concentration to decrease by half. This fall in drug concentration is a reflection of metabolic processes and/or excretion. The biologic half-life of a drug in the blood may be determined graphically from a pharmacokinetic plot of a drug's blood concentration–time plot, typically after intravenous administration to a sample population. The amount of time required for the concentration of the drug to decrease by half is considered its half-life. The half-life can also be mathematically determined. Recall Equation 5.3 and rearrange the equation as follows:

$$\frac{K_{el}t}{2.303} = \text{Log } C_p^0 - \text{Log } C_p = \frac{\text{Log } C_p^0}{C_p} \qquad \text{(Equation 5.6)}$$

Then, if it assumed that C_p is equal to half of C_p^0,

$$\frac{K_{el}t}{2.303} = \frac{\text{Log}C_p^0}{0.5C_p^0} = \text{Log}2 \qquad \text{(Equation 5.7)}$$

Thus,

$$t_{1/2} = \frac{2.303\,\text{Log}\,2}{K_{el}} = \frac{0.693}{K_{el}} \qquad \text{(Equation 5.8)}$$

If this equation is rearranged, the half-life finds utility in the determination of drug elimination from the body, provided of course that the drug follows first-order kinetics. Rearranging the prior equation,

$$K_{el} = \frac{0.693}{t_{1/2}} \qquad \text{(Equation 5.9)}$$

First-order elimination rate constants are reported in time^{-1}, for example, minutes^{-1} or hours^{-1}. Thus, an elimination constant of a drug of 0.3 hour^{-1} indicates that 30% of the drug is eliminated per hour.

The half-life varies widely between drugs; for some, it may be a few minutes, whereas for others, it may be hours or even days (Table 5.9). Data on a drug's biologic half-life are useful in determining the most appropriate dosage regimen to achieve and maintain the desired blood level. These determinations usually result in recommended dosage schedules for a drug, such as every 4, 6, or 8 hours. Although these types of recommendations generally suit the requirements of most patients, they do not suit all patients. The most exceptional patients are those with reduced or impaired ability to metabolize or excrete drugs. These patients, most of whom have liver dysfunction or kidney disease, retain the administered drug in the blood or tissues for extended periods because of their decreased ability to eliminate the drug. The resulting extended biologic half-life of the drug generally necessitates an individualized dosage regimen calling for either less frequent administration than usual or the usual dosage schedule but a decrease in the amount of drug administered.

As mentioned previously, digoxin presents a good example of a drug having a half-life that is affected by the patient's pathologic condition. Digoxin is eliminated in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate. In subjects with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. In anuric patients (absence of urine formation), the half-life may be prolonged to 4 to 6 days. Theophylline's half-life also varies from population to population. In premature infants with immature liver enzyme systems in the cytochrome P-450 family, the half-life of theophylline ranges from 14 to 58 hours, whereas in children aged 1 to 4 whose liver enzyme systems are more mature, the theophylline half-life ranges from 2 to 5.5 hours. In adult nonsmokers, the half-life ranges from 6.1 to 12.8 hours, whereas in adult smokers, the average half-life of theophylline is 4.3 hours. The increase in theophylline clearance from the body among smokers is believed to be due to an induction of the hepatic metabolism of theophylline.

Table 5.9 SOME ELIMINATION HALF-LIFE VALUES

DRUG PRODUCT	ELIMINATION HALF-LIFE[a]
Amoxicillin (Amoxil)	1 h
Cimetidine (Tagamet)	2 h
Digoxin (Lanoxin)	1.5–2 d
Diltiazem (Cardizem)	2.5 h
Esomeprazole (Nexium)	1–1.5 h
Ibuprofen (Motrin)	1.8–2 h
Nitroglycerin	3 min
Phenytoin sodium (Dilantin)	7–29 h
Propoxyphene (Darvon)	6–12 h
Propranolol HCl (Inderal)	4 h
Ranitidine (Zantac)	2.5–3 h
Ropinirole (Requip)	6 h
Rosuvastatin (Crestor)	19 h
Tadalafil (Cialis)	17.5 h
Tobramycin sulfate (Nebcin)	2 h
Zolpidem tartrate (Ambien)	2.6 h

[a]Mean, average, or value ranges taken from product information found in *Physicians' Desk Reference*. 65th Ed. Montvale, NJ: Thompson PDR, 2011. Half-life values may vary with patient characteristics (e.g., age, liver or renal function, smoking habits), dose levels, and routes of administration.

The half-life of theophylline is decreased, and total body clearance is enhanced to such a degree in smokers that these individuals may actually require a 50% to 100% increase in theophylline dosage to produce effective therapeutic results. The time required to normalize the effect of smoking on theophylline metabolism in the body once the patient stops smoking may range from 3 months to 2 years. Because theophylline is metabolized in the liver, the half-life of theophylline will be extended in liver disease. For example, in one study of nine patients with decompensated cirrhosis, the average theophylline half-life was 32 hours.

The half-life of a drug in the bloodstream may also be affected by a change in the extent to which it is bound to blood protein or cellular components. Such a change in a drug's binding pattern may be brought about by the administration of a second drug having a greater affinity than the first drug for the same binding sites. The result is displacement of the first drug from these sites by the second drug and the sudden availability of free (unbound) drug, which may pass from the bloodstream to other body sites, including those concerned with its elimination. Displacement of one drug from its binding sites by another is generally viewed as an undesired event, since the amount of free drug resulting is greater than the level normally achieved during single-drug therapy and may result in untoward drug effects.

Concept of Clearance

The three main mechanisms by which a drug is removed or cleared from the body include (*a*) hepatic metabolism, that is, hepatic clearance, Cl_h, of a drug to either an active or inactive metabolite; (*b*) renal excretion, that is, renal clearance, Cl_r, of a drug unchanged in the urine; and (*c*) elimination of the drug into the bile and subsequently into the intestines for excretion in feces. An alternative way to express this removal or elimination from the body is to use total body clearance (Cl_B), which is defined as the fraction of the total volume of distribution that can be cleared per unit of time. Because most drugs undergo one or more of these processes, the total body clearance, Cl_B, of a drug is the sum of these clearances, usually hepatic, Cl_h, and renal, Cl_r. Clearance via the bile and feces is usually not significant for most drugs.

These processes of elimination work together, so a drug that is eliminated by renal excretion and hepatic biotransformation will have an overall rate of elimination. K_{el} is the sum of the renal excretion, k_u, and hepatic biotransformation, k_m. In the one-compartment model described earlier, total body clearance is the product of the volume of distribution, V_d, and the overall rate of elimination, K_{el}:

$$Cl_B = V_d \times k_{el} \qquad \text{(Equation 5.10)}$$

But recall that Kel equals 0.693/t½. If this is substituted in Equation 5.10 and the half-life, t½, solved for, the following equation is obtained:

$$t_{1/2} = \frac{0.693 V_d}{Cl_b} \qquad \text{(Equation 5.11)}$$

Total body clearance is a function of one or more processes, so if a drug is eliminated from the body through hepatic biotransformation and renal clearance, Equation 5.11 becomes

$$t_{1/2} = \frac{0.693 V_d}{(Cl_b + Cl_r)} \qquad \text{(Equation 5.12)}$$

Thus, a drug's half-life is directly proportional to the volume of distribution and inversely proportional to the total body clearance, which consists of hepatic and renal clearance. In infants and children, who exhibit larger volumes of distribution and have lower clearance values, most drugs have a longer half-life than in adults.

A decrease in the hepatic or renal clearance will prolong the half-life of a drug. This typically occurs in renal failure, and consequently, if one can estimate the percentage decrease in excretion due to renal failure, one can use Equation 5.11 to calculate the new half-life of the drug in the patient. Thus, an adjusted dosage regimen can be calculated to decrease the chance of drug toxicity.

Dosage Regimen Considerations

The previous chapter mentions factors that can influence the dosage of a drug. It is not easy to determine how much drug and how often to administer it for a desired therapeutic effect. There are two basic approaches to the development of dosage regimens. The first is the *empirical approach*, which entails administration of a drug in a certain quantity, noting the therapeutic response and modifying the amount and interval of dosage accordingly. Unfortunately, experience with administration of a drug usually starts with the first patient, and eventually, a sufficient number of patients receive the drug so that a fairly accurate prediction can be made. Besides the desired therapeutic effect, it is necessary to consider the occurrence and severity of side effects. Empirical therapy is usually employed when the drug concentration in serum or plasma does not reflect the concentration of drug at the receptor site in the body or the pharmacodynamic effect of the drug is not related (or correlated) with drug concentration at the receptor site. Empirical therapy is used for many anticancer drugs that demonstrate effects long after they have been excreted from the body. It is difficult to relate the serum level of these drugs with the desired therapeutic effect.

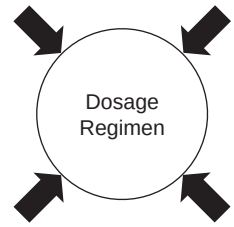
The second approach to the development of a dosage regimen is through the use of pharmacokinetics, or the *kinetic approach*. This approach is based on the assumption that the therapeutic and toxic effects of a drug are related to the amount of drug in the body or to the plasma (or serum) concentration of drug at the receptor site. Through careful pharmacokinetic evaluation of a drug's ADME after a single dose, the levels of drug attained from multiple dosing can be estimated. One can then determine the appropriateness of a dosage regimen to achieve a desired therapeutic concentration of drug in the body and evaluate the regimen according to therapeutic response.

Pharmacokinetics is but one of a number of factors that should be considered in the development of a dosage regimen. Table 5.10 illustrates a number of these. Certainly, an important factor is the inherent activity, that is, pharmacodynamics and toxicity. A second consideration is the pharmacokinetics of the drug, which are influenced by the

Table 5.10 FACTORS THAT DETERMINE A DOSAGE REGIMEN

ACTIVITY, TOXICITY

- Minimum therapeutic dose
- Toxic dose
- Therapeutic index
- Side effects
- Dose–response relationships



PHARMACOKINETICS

- Absorption
- Distribution
- Metabolism
- Excretion

CLINICAL FACTORS

Clinical State of Patient

- Age, weight, urine pH
- Condition being treated
- Existence of other disease states

Management of Therapy

- Multiple drug therapy
- Convenience of regimen
- Compliance of patient

OTHER FACTORS

- Tolerance–dependence
- Pharmacogenetics–idiosyncrasy
- Drug interactions
- Life style factors, for example, diet, recreational drug use

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dosage form. The third factor focuses upon the patient to whom the drug will be given and encompasses the clinical state of the patient and how the patient will be managed. Finally, atypical factors may influence the dosage regimen. Collectively, all of these factors influence the dosage regimen.

The regimen of a drug may simply involve a single dose, as with pinworm medication, or may call for multiple doses. In the latter instance, the objective of pharmacokinetic dosing is to design a regimen that will continually maintain a drug's therapeutic serum or plasma concentration within the therapeutic index, that is, above the MEC but below the MTC.

Frequently, drugs are administered one to four times per day, most often in a fixed dose, for example, 75 mg three times daily after meals. As mentioned earlier, after a drug is administered, its level within the body varies because of the influence of all of the processes, ADME. A drug will accumulate in the body when the dosing interval is less than the time needed for the body to eliminate a single dose. Figure 5.17 illustrates the plasma concentration for a drug given by intravenous administration and oral administration. The 50-mg dose of this drug was given at a dosing interval of 8 hours. The drug has an elimination half-life of 12 hours. As one can see, with continued dosing, the drug concentration reaches a *steady-state* or *plateau* concentration. At this limit, the amount of drug lost per interval is replenished when the drug is dosed again. Consequently, the concentration of drug in the plasma or serum fluctuates. Thus, for certain patient types, it is optimal to target dosing so that the plateau concentration resides within the therapeutic index of a drug to maintain a MEC. For example, the asthmatic patient maintained on theophylline must have a serum concentration between 10 and 20 mg/mL. Otherwise, the patient may be susceptible to an asthma attack. Thus, when dosing the asthmatic patient, it is preferable to give theophylline around the clock four times daily to sustain levels at least above the MEC. If this medicine is administered only every 4 hours during the waking hours, it is possible that the minimum concentration will fall below effective levels between the bedtime dose and the morning dose. Consequently, the patient may awaken in the middle of the night and have an asthma attack.

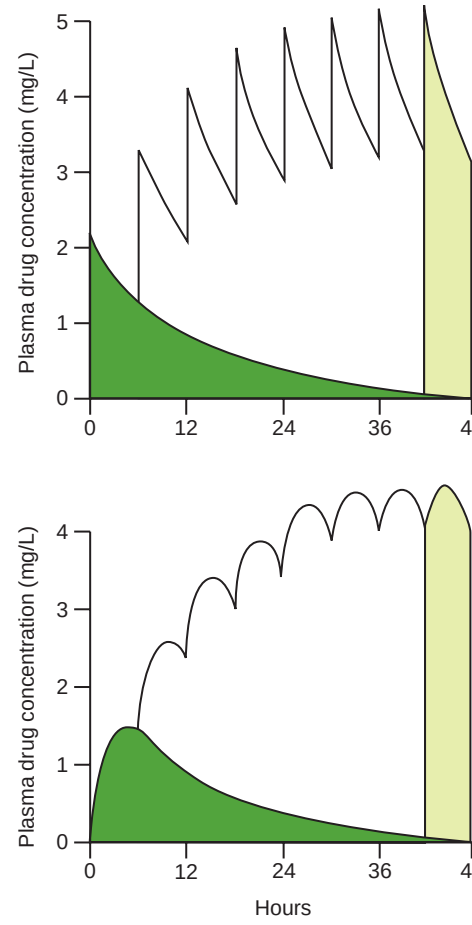

FIGURE 5.17 Plasma concentration of a drug given intravenously (*top*) and orally (*bottom*) on a fixed dose of 50 mg and fixed dosing interval of 8 hours. The half-life is 12 hours. The area under the plasma concentration–time curve during a dosing interval at steady state is equal to the total AUC for a single dose. The fluctuation of the concentration is diminished for oral administration (half-life of absorption is 1.4 hours), but the average steady-state concentration is the same as after intravenous administration, since f = 1. (Adapted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 3rd Ed. Baltimore, MD: Lippincott Williams & Wilkins, 1995.)

Patients can be monitored pharmacokinetically through appropriate plasma, serum, or blood samples, and some hospital

pharmacies have implemented pharmacokinetic dosing services. The intent is to maximize drug efficacy, minimize toxicity, and keep health care costs at a minimum. Thus, complications associated with overdose are controlled, and known drug interactions, such as between smoking and theophylline, can be accommodated. In these services, once the physician prescribes a certain amount of drug and monitors the clinical response, it is the pharmacist who coordinates the appropriate sample time to determine drug concentration in the appropriate body fluid. After the level of drug is attained, it is the pharmacist who interprets the result and consults with the physician regarding subsequent dosages.

Pharmacokinetic research has demonstrated that the determination of a patient's dosage regimen depends on numerous factors, and daily dose formulas exist for a number of drugs that must be administered on a routine maintenance schedule, for example, digoxin, procainamide, and theophylline. For certain drugs such as digoxin, which are not highly lipid soluble, it is preferable to use a patient's lean body weight (LBW) rather than total body weight (TBW) to provide a better estimate of the patient's volume of distribution. On the other hand, estimating a patient's CrCL for initial vancomycin dosing uses TBW according to Equation 5.13:

$$\text{CrCL (male) mL/min} = \frac{(140 - \text{age}) \times \text{TBW(kg)}}{72 \times \text{Scr} \times 0.82 \text{ for females}}$$

Subsequent doses then must be calculated based on obtaining a trough vancomycin level 30 minutes before the next scheduled dose. In addition, the dosing interval (in hours) is based upon the patient's calculated CrCL (9).

Alternatively, even though pharmacokinetic dosing formulas may exist, one must be cognizant that patient factors may be more relevant. For example, with the geriatric patient, it is advisable to begin drug therapy with the lowest possible dose and increase the dosage as necessary in small increments to optimize the patient's clinical response. Then the patient should be monitored for drug efficacy and reevaluated periodically. Examples of bioanalytical research laboratories are demonstrated in Figures 5.18 and 5.19.

FIGURE 5.18 Computed gas chromatography mass spectrometry used in bioanalytical studies. Consists of Hewlett Packard Gas Chromatograph (Model 5890 A) and VG Mass Spectrometer (Model UG 12–250). (Courtesy of Elan Corporation, plc.)

FIGURE 5.19 Assay of product samples using high-performance liquid chromatography. (Courtesy of Paddock Laboratories.)

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. List the partition coefficients for erythromycin and its related chemical entities and predict comparable effectiveness when administered in a topical dosage form.
2. Create a listing of five prodrugs used therapeutically and describe the rationale for the use of each prodrug.
3. Select a drug available in various chemical moieties that dictate varying parenteral dosage forms and describe the effect of chemical formula on its onset of activity, duration of activity, etc., of the drug.
4. Given a serum concentration–time curve for a specific drug, determine the peak height concentration, the time of the peak concentration, and the serum (or blood or plasma) area under the curve.
5. Given a blood concentration *versus* time plot, perform various pharmacokinetic calculations.
6. Given comparative bioavailability data and cost information for identical drug products from different manufacturers, select a product for the hospital formulary and provide a rationale for your decision.
7. Make a listing of drug products whose brand names include the term "elixir," but have little or no Alcohol USP in their formulations.

Individual Activities

1. Explain, with examples, how a drug's particle size influences its dissolution rate and solubility.
2. List four clinically available drugs that demonstrate either amorphous or crystalline forms, and describe the rationale for using a specific form for therapy.
3. Describe patient situations where one drug delivery approach would have advantages over another drug delivery approach.
4. Given a patient's data, calculate pharmacokinetic parameters.
5. Develop a listing of drugs dosed on peak and trough levels, and given patient data, demonstrate calculations for one such drug.
6. Given a patient case, select appropriate drug therapy, and determine an appropriate dosage regimen for the patient. Also, the selection of appropriate drug therapy should include flavor preference and discussion if a pediatric patient. Provide your rationale.

REFERENCES

1. Cogburn JN, Donovan MG, Schasteen CS. A model of human small intestinal absorptive cells 1: Transport barrier. Pharm Res 1991;8:210–216.
2. Christensen FN, et al. The use of gamma scintigraphy to follow the gastrointestinal transit of pharmaceutical formulations. J Pharm Pharmacol 1985;37:91–95.
3. Coupe AJ, Davis SS, Wilding IR. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. Pharm Res 1991;8:360–364.
4. Poole J. Curr Ther Res 1968;10:292–303.
5. Code of Federal Regulations, Title 21, Part 320. Bioavailability and Bioequivalence Requirements, 2012 (updated). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart. (Accessed October 5, 2012)
6. Chodos DJ, DiSanto AR. Basics of Bioavailability. Kalamazoo, MI: Upjohn, 1973.
7. Smith HJ. Process of drug handling by the body. Introduction to the Principles of Drug Design. 2nd Ed. London: Butterworth, 1988.
8. Cooper JW. Monitoring of drugs and hepatic status. Clinical Consult 1991;10(6):1991.
9. www.cumc.columbia.edu/dept/id/documents/vancomycindosingandmonitoringinadultpatients.pdf. (Accessed: July 16, 2008). The title is "Vancomycin dosing and monitoring in adults."