Introduction to Pharmacology

Pharmacologic agents are ubiquitous in today's society, and pharmacotherapeutics is an essential component of primary care practice. The four chapters in this section are dedicated to basic information about drugs. The chapter titled *Modern Pharmacology* reviews the clinical context that prescribing takes place in today, including regulation, taxonomy, and general use. *Principles of Pharmacology* describes the pillars in the foundation of pharmacology, including pharmacokinetics and pharmacodynamics. The chapter titled *Pharmacogenetics* introduces a 21st-century approach that will soon be an essential consideration prior to prescribing many drugs. This chapter reviews information about genetics that influence the clinical effects of pharmacologic agents The future may well encompass a genetic assessment for an individual prior to customized prescribing. The last chapter in this section, *Drug Toxicity*, addresses adverse effects of drugs in more detail, including toxic effects and poisonings associated even with commonly used agetns. All of the chapters in this section have clinical examples to illustrate the importance of the pharmacologic principles in practice.

1 Modern Pharmacology

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Chapter Glossary

Adverse drug event (ADE) Untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with the pharmacologic treatment.

Adverse drug reaction (ADR) Response to a drug that is noxious and unintended and that occurs at doses normally used for prophylaxis, diagnosis, or therapy.

Approved drug Substance that has been evaluated by the Food and Drug Administration (FDA) and allowed to be marketed as a drug in the United States.

Behind-the-counter (BTC) Descriptor for drugs that are sold without prescription, but that are subject to restrictions such as proof of identity because of potential risks. For example, pseudoephedrine is BTC because it may be used as an ingredient in the production of methamphetamine.

Black box warning Warning that appears on the package insert of a drug that notes harms associated with use of this drug. Black box warnings are mandated by the FDA and are often added to package inserts after postmarketing studies reveal unexpected adverse drug reactions or adverse drug events.

Brand name Trademarked name assigned to a drug by the manufacturer. Some brand names are similar to the generic name (e.g., pseudoephedrine/Sudafed); others suggest their indications for use (e.g., Tamiflu is indicated for treatment of influenza).

Breakthrough therapy/breakthrough drug Agent whose approval by the FDA is expedited after evidence shows that the drug, either alone or in combination with other treatments, provides superior outcomes for individuals with specific serious conditions or diseases.

Chemical name Name that describes the chemical composition of the agent. The chemical name is rarely used by prescribers and consumers.

Clinical trial Research study using human subjects to answer specific questions about new therapies, or new ways of using known treatments. Clinical trials are used to determine whether new drugs are both *safe* and *effective*.

Compounding Mixing or combining ingredients to produce a pharmaceutical agent.

Contraindication Situation in which an agent should *not* be used.

Controlled substances Pharmaceuticals listed in schedules found in U.S. Law 21 U.S.C. §802(32)(A). These drugs include both opiates and nonopiates, but generally all controlled substances have a high risk of addiction.

Counterfeit drugs Pharmaceuticals that are produced and sold in a deceptive manner so that they appear to be authentic drugs.

Designer drug Drug directed toward a specific biologic target that binds to and inhibits key molecules involved in a disease or pathologic event.

Direct-to-consumer (DTC) Advertisements for selected drugs placed in popular media and directed to the general public as opposed to being directed to providers.

Dispense (furnish) Process of giving a drug or drug prescription to a consumer.

Drug Chemical substance that brings about changes in a biologic system through its chemical action(s). Also called a *medication* or *pharmaceutical*.

Drug recall Removal of a pharmaceutical agent from the marketplace. It may be either voluntary or mandated by the FDA.

Effectiveness Ability of a drug or treatment to produce a result in real-life circumstances.

Food and Drug Administration (FDA) Regulatory body responsible for approving and monitoring most pharmaceuticals and devices marketed in the United States.

Formulary List of approved or available drugs. A formulary is often used by insurance companies to identify agents that will be reimbursed or paid for by the insurer.

Generally recognized as safe and effective (GRAS/E) Phrase used to describe why an agent has been determined to be safe to sell over the counter.

Generic name Formulation that contains the same active ingredients found in a brand-name formulation and is bioequivalent to that brand-name drug.

High-alert drug Pharmaceutical that is associated with significant harm if used in error.

Investigational new drug (IND) Designation for an agent that may be evaluated in clinical trials under regulation by the FDA.

Medication error Mishap that occurs during prescribing, transcribing, dispensing, administering, adhering to, or monitoring a drug.

Multiple-drug intake (MDI) Synonym for polypharmacy.

New drug application (NDA) Application through which a potential agent is registered as part of the FDA's drug approval process. For example, a company must file an NDA with the FDA to study a drug in clinical trials.

Off-label use Use or prescription of a drug for conditions other than those approved by the FDA.

Orphan drugs Agents that are prescribed for rare conditions and, therefore, have limited and infrequent use.

Over-the-counter (OTC) Pharmaceuticals sold without prescriptions; if some restrictions are placed on the drug's sale, then the OTC agent also may be called a behind-the-counter (BTC) drug.

Pharmacoeconomics Field of study that identifies, measures, and evaluates the costs of drug therapy to healthcare systems and society.

Polypharmacy Practice of treating individuals with multidrug regimens; this term generally is accepted to mean administration of five or more drugs. It may also be referred to as multiple-drug intake (MDI) or, in the case of lethal poisonings and overdoses, as combined-drug intoxication (CDI).

Precautions Situations listed on the package insert that can be associated with an adverse drug event (e.g., concomitant ingestion of alcohol with an agent; use of a contraceptive by women weighing more than 200 pounds). The evidence of association or the potential adverse drug event is not deemed important enough to contraindicate use of the agent or issue a black box warning.

Pregnancy categories FDA drug classification system to identify the fetal risks of drugs when used during pregnancy.

Prescriptive authority Privilege afforded by law to healthcare providers that allows them to order the dispensing of prescription medications.

Safety Plasma level or dose at which a drug's known adverse effects are not apparent.

Side effect Expected physiologic response unrelated to the desired drug effect.

Warnings FDA identification and dissemination of information about potential conditions associated with major adverse effects. Warnings include black box warnings, or serious information one step away from removal of the drug from the marketplace.

Society and Health

All societies have major concerns, both collectively and among individual members, about the maintenance of health and treatment of conditions or diseases. Over the millennia, a wide variety of interventions have been used for either or both of these objectives. Even today, interventions such as spiritual care, manipulation of body positions, variations in nutrition, and types of exercise remain the primary treatments for some conditions; are first-line interventions in many cultures; and are often are the topics of research studies. However, the use of pharmaceuticals has become one of the most—if not *the* most—common treatment for health conditions today.

Pharmacology and Drugs

Pharmacology is a word derived from the Greek word *pharmakon*, which means medicine or poison. Most sources define pharmacology more precisely as the study of how drugs interact with a living organism to produce a change in physiologic function. Any agent, substance, or medication that is used for medicinal purposes is a pharmaceutical.

Although there is general consensus on the definition of the word *pharmacology*, one of the great difficulties in the discussion of modern pharmacology is the existence of multiple meanings of the term *drug*. Within one context, *drug* connotes use of an illegal substance (e.g., cocaine)

and is associated with substance abuse. Not all drugs are illicit, however, and drugs such as marijuana that were previously illicit currently may be approved for medical use in some states. Prescriptive pharmaceuticals as well as **over-the-counter (OTC)** agents are also termed drugs. Nutritional supplements are viewed as drugs by most consumers, although they are not regulated as such in by the **Food and Drug Administration (FDA)**.[1] Therefore, it is wise to clarify the meaning of terms used. In this text, a **drug** is a chemical substance that brings about changes in a biologic system through its chemical action. The terms *pharmaceuticals, medications,* and *drugs* will be used interchangeably. Illicit or recreational drugs will be noted as such to promote clarity.

History of Pharmaceuticals

Details of the historical origins of the use of botanicals, herbals, or other types of medications are shrouded in the past. Early records suggest that traditional Chinese medicine practices included liberal use of such agents. From the Indian subcontinent, Ayurvedic medicine combined medications with surgical procedures as early as 1000 BC. Hippocrates, the great Greek physician, was also a herbologist, advocating multiple botanical treatments, many of which still can be found on the market today.

During the Middle Ages in Europe, some of the spices and herbs brought back from the Crusades were said to have attributes of magical healing. By the 1500s, apothecaries were found in various European towns. In the 1600s, botanists and herbalists, such as the Englishman Nicholas Culpeper, were codifying use of herbs and publishing findings and recommendations. Gradually, the use of botanicals became an expected intervention when health was threatened or disease was evident.

In the 1800s, a new industry was born with the advent of patent medicines and potions.[2] Ironically, patent medicines were not copyrighted, but rather were composed of secret ingredients under a trademarked name. Lydia Pinkham's Vegetable Compound included a number of herbs in alcohol.[3] Pinkham marketed the product to women for treatment of menstrual pain and disorders and accrued a personal fortune from widespread sales. The soft drink Coca-Cola was originally marketed as a nerve tonic patent medicine. Use of patent medicines was a logical strategy to treat common diseases in an era in which healthcare providers were unregulated and many provider-prescribed strategies had harmful effects (e.g., those associated with the liberal use of heavy metals). Most patent medicines were not harmful in regular doses, although their effectiveness could be subject to debate. Some older remedies continue to live in today's over-the-counter market, albeit with different ingredients, including Carter's Little Liver Pills, Luden's Cough Drops, and Fletcher's Castoria.

The nineteenth century was midwife to the birth of today's major pharmaceutical houses. Between 1830 and the turn of the twentieth century, the following groups began wholesale production of drugs: Schering and Merck in Germany; Hoffman-LaRoche in Switzerland; Burroughs Wellcome in England; and Abbot, Smith Kline, Parke-Davis, Eli Lilly, Squibb, and Upjohn in the United States. Other important companies such as Bayer (Germany), Ciba-Geigy and Sandoz (Switzerland), and Pfizer (United States) were first founded as producers of organic chemicals during the same time frame, and later moved into the area of pharmaceuticals.[4]

The Twentieth Century

If the nineteenth century was one of creation and growth of the modern pharmaceutical industry, the twentieth century was one of explosion and controversy. Pharmaceuticals became treatments for health promotion as well as treatments for disease. Vaccines were lauded as an example of primary prevention of disease. Immunizations, including the controversies regarding their current use, are discussed in detail in the *Immunizations* chapter.

During the 1900s, it became clear that pharmaceuticals could have adverse effects. Reports of adverse effects, allergic reactions, drug–drug interactions, and resistance to microbes began to populate the literature, especially in the last half of the century. Inadvertent or intentional overdoses involving prescription drugs became infamous because of the deaths of celebrities such as Marilyn Monroe, Elvis Presley, and Michael Jackson. The ready availability of medications with clinically significant **side effects** is a current topic in the pharmaceutical literature and popular press. Combining different agents has become such a common problem, it is referred to by some as **polypharmacy** or **multiple-drug intake (MDI)**.

Thus, it was predictable that regulation of pharmaceuticals came of age in the 1900s. This was the century in which laws were passed in the United States in an attempt to protect the public in a variety of areas.

The United States Food and Drug Administration

In the United States, the regulatory agency whose mission is to protect the public by assuring that drugs, biologic products,

medical devices, the national food supply, cosmetics, and products that emit radiation are safe, effective, and secure is the Food and Drug Administration (FDA). The U.S. Federal Food, Drug, and Cosmetic Act was passed in 1938, establishing the FDA as a governmental body regulating all aspects of pharmaceuticals. This act has undergone many modifications ranging from changes in minor rules to major revisions of the act itself, changes that continue today as Congress oversees the work of the FDA.

The origins of the FDA date back to 1906, with the passage of the Pure Food and Drug Act, also known as the Wiley Act. This legislation was designed to provide regulatory oversight to prevent manufacture, sale, and transportation of adulterated, misbranded, or poisonous foods, drugs, medicine, or liquors. In 1938, the Wiley Act was replaced with the Federal Food, Drug, and Cosmetic Act.

The Kefauver-Harris Amendment of 1962 was passed in response to the discovery of the teratogenic effects of thalidomide. This amendment put into place the requirement that drugs show evidence of **safety** and **effectiveness** before being approved for marketing in the United States. Evidence of safety and effectiveness is the essence of the FDA standards today.[5] Drug safety is paramount for the FDA. Included among the myriad activities of the FDA are monitoring drug claims, especially those advertised to consumers; establishing standards for drug testing; and awarding approval for new pharmaceuticals, as well as approval for the prescription medications that companies desire to move to over-the-counter status. The *Drug Toxicity* chapter discusses these activities in more detail.

In 1997, an amendment to the Federal Food, Drug, and Cosmetic Act was passed that established an open website registry that required drugs used for life-threatening conditions to be registered (www.ClinicalTrials.gov) for clinical trials. However, in other ways, the 1997 amendment eased FDA oversight of drugs. Drug approval could be based on one randomized controlled trial (RCT) and confirmatory evidence, a fast-track approval process was established whereby drug approval could be granted based on surrogate endpoints, and pharmaceutical companies were allowed to disseminate information about **off-label uses** of their drugs to healthcare providers.[6] Recent additions to the Federal Food, Drug, and Cosmetic Act include authorization for regulation of bioterrorism agents, requirements for enrollment into **clinical trials**, and expansion of FDA authority to assess postmarketing safety of drugs. This type of assessment is the purview of pharmacoepidemiology—the discipline that provides information about the health and cost outcomes of drugs, devices, and biologics after their approval for clinical use. Pharmacoepidemiology is defined as the study of the use of and effects of drugs in large numbers of people. Pharmacoepidemiology monitors reports of adverse effects, morbidity, or mortality following use of drugs after they are marketed. As a result of such monitoring, some drugs are withdrawn for use after being approved by the FDA.

After the 1999 publication of the Institute of Medicine's *To Err Is Human* report, prevention of **medication errors** took center stage in the efforts to provide safe health care.[7] Experts from many disciplines have promoted strategies that include methods for patient identification when a person is hospitalized; incorporation of "time-outs" during procedures, including those involving anesthesia; promotion of electronic prescribing to decrease the risk of misreading the drug name or the dose on handwritten prescriptions; recommendations to avoid sound-alike **brand names** (Box 1-1); simplification of packaging; and education of individuals so that they know their medications and can personally advocate for the correct administrations.

Box 1-1 High-Risk Sound-Alikes

The most common brand name for fosphenytoin, an antiepileptic drug, is *Cerebyx*. Cerebyx is an example of a drug that is considered to be a high-risk sound-alike due to its similarity to other frequently prescribed agents. Other pharmaceuticals that are similar to Cerebyx include Celebrex, a common brand of celecoxib, a nonsteroidal anti-inflammatory often used as a treatment for arthritis; Celexa (citalopram hydrobromide), an SSRI; and a botanic, huperzine A, now marketed under the brand name of Cerebra and suggested for treatment/prevention of Alzheimer's disease, although data are lacking on effectiveness.

Since these names are so similar, extra caution must be taken when caring for individuals who report taking these agents, as they, too, can become confused about which drug is being used. The FDA has a program within its organization, the Office of Surveillance and Epidemiology, formerly Office of Drug Safety, which periodically conducts meetings and publishes findings to promote clearer and unique naming options in an attempt to decrease accidental medication errors.

Table 1-1 The 2007 Amendments to the Federal Food, Drug, and Cosmetic Act

Amendment Provision	Description
Clinical trial registries expanded to include new drugs	All clinical trials evaluating any drug or biologic or medical device must be registered with www.ClinicalTrials.gov. The information on this website is available to the public, and the drug manufacturer is required to update information about the status of the clinical trial.
Required disclosure of study results	All clinical trials must disclose study results to the registry and results data bank section of www.ClinicalTrials.gov.
Postapproval safety studies may be required	In the past, postapproval studies were voluntary. Now, if the FDA has information about possible safety concerns, the agency can require that a postapproval study be conducted.
Safety labeling changes	The 2007 amendment gives the FDA authority to mandate a change to a drug label that describes safety information.
Risk evaluation and mitigation strategy (REMS)	The FDA may require that a drug manufacturer submit a REMS plan that specifies how a drug will be monitored to determine whether the benefits continue to outweigh the risks as the drug is more widely disseminated.
Technologies to ensure safety in the drug supply chain	The FDA is required to develop standards and methods to identify and validate effective technologies that will ensure the safety of the drug supply chain. These measures are intended to ensure that drugs marketed in the United States are free of contaminates, adulteration, or misbranding.

Abbreviations: FDA = Food and Drug Administration.

In 2006, the Institute of Medicine published a report titled *The Future of Drug Safety*. This report included 25 recommendations for improving the process of overseeing drug development from the preapproval process through postmarketing evaluations and strongly advocated that FDA authority be expanded and strengthened to protect the public from **adverse drug events (ADE)**.[8] Building on this work, the Food and Drug Administration Amendments Act of 2007 (H.R. 3580) expanded the FDA's authority in several ways (Table 1-1).

Today, the FDA has expanded authority to monitor and regulate the safety of marketed drug products by requiring drug manufacturers to conduct postapproval studies or clinical trials if the FDA becomes aware of new safety information. In addition, the FDA can require postapproval changes to drug labels that address safety issues such as the risk for **adverse drug reactions (ADR)**. The 2007 amendment produced several other major changes in pharmaceutical regulation, including giving the FDA authority to review **direct-to-consumer (DTC)** television advertisements prior to their dissemination; the FDA can now assign civil monetary penalties if such advertisements are determined to be false or misleading. More recent changes have focused on tobacco and the definition of **orphan drugs**.[9] The FDA has been attempting to label tobacco as a drug for purposes of regulation.[8-10]

This new ability to mandate postapproval changes to drug labels is well intended, albeit often difficult to implement. To allow informed decision making, comprehensive information must be available about the benefits and adverse effects of the medication in question. Knowledge of beneficial effects often is more likely to be available than knowledge of adverse effects. Most drug studies use an RCT methodology that is particularly useful to demonstrate if an intervention is beneficial, but RCTs are less useful for identifying rare adverse effects and not all publications report all ADEs.[11,12] RCTs tend to be small in terms of the number of participants; they are also limited to enrollees who are either healthy, as in the case of contraceptive studies, or to those who have a single diagnosis. In addition, they are conducted for a relatively short period of time. In reality, the effects of drugs women use are rarely completely evaluated in RCTs. Therefore, agents may come into the market, only to be removed within a few years as unexpected adverse drug reactions emerge when the drug is used by a larger population, including individuals who have additional disorders or who are taking additional medications. Large observational studies facilitate the identification of adverse drug reactions. Although they do not have the rigor of an RCT, their findings can be combined with the results of RCTs to help providers obtain more complete information about risks and benefits necessary for the person being informed.

The United States Pharmacopeia

The United States Pharmacopeia (USP) works closely with the FDA. The mission of the USP is to establish public standards to assure consumers of the quality, safety, and benefit of medicines and foods through a unique process of public involvement and use of volunteers. Unlike the FDA, which is a federal agency, the USP is a nongovernment, not-for-profit, public health organization. This organization is approximately a century older than the FDA. Indeed, by the end of the 1800s, all state boards of pharmacy had

mandated that pharmaceutical companies use the USP standards. USP standards as used when drugs are assessed for purity, potency, and consistency. Although the USP standards are U.S. based, they are recognized and used in more than 100 countries. USP standards are published in the *United States Pharmacopeia—National Formulary* and applied to prescription and over-the-counter medications. Should a dispute arise regarding a drug's purity or identity, the methods found in the USP for evaluation of purity, potency, assay/bioassay, and other properties would be the legally binding ones.

Although the development of standards and the verification of purity and quality are the most well known of USP's activities, this organization engages in several other activities. These additional functions include development of healthcare information that is unbiased about drugs; administration of the Medication Errors Reporting Program (MedMark), an online program for the reporting of medication errors and adverse drug effects; and support of a drug quality and information project to promote international drug safety.

Although the FDA is essential to pharmaceutical regulation and scrutiny, the sheer number of other organizations involved in aspects of drug development, use, and prescription illustrates the complexity involved in the use of pharmaceuticals today. The private sector, as exemplified by pharmaceutical companies and manufacturers of medical goods, is a major stakeholder in this activity. The USP belongs to the public sector, and is a nongovernmental organization. Other governmental bodies intimately involved with drugs in the United States include the Centers for Disease Control and Prevention (CDC), which publishes recommendations for treatments of disorders and diseases; the Drug Enforcement Administration (DEA), which regulates **controlled substances**; the Federal Communications Commission (FCC), which regulates advertising for over-the-counter drugs; and state governments, which control prescriptive authority for providers.

Categories of Drugs

The Naming of Drugs

Every drug has multiple names. Each agent has a **chemical name**, or a precise term describing it. The chemical name often is abbreviated or truncated into the **generic name**. Today, suffixes often are shared with other pharmaceuticals in the same drug category in an attempt to simplify relationships. For example, the names of angiotensin-converting enzyme (ACE) inhibitors used for hypertension tend to end in *pril*, such as captopril and lisinopril. In addition to chemical names and generic names, patented trade names and brand names are used for drugs. These brand names are the ones most frequently remembered by consumers due to advertising and skillful choices in assigning a brand name. For example, some brands specific for women include Evista, Evra, and Sarafem. Sometimes brand names sound alike, which may contribute to consumer confusion. For example, the brand Celebrex is an analgesic, whereas the sound-alike Celexa is an antidepressant. The various categories of drugs include over-the-counter, generic, orphan, and compounded agents.

Over-the-Counter Drugs

As opposed to drugs that require a legal prescription prior to purchase, over-the-counter (OTC) agents are pharmaceuticals that may be purchased by a consumer without a prescription. Originally, prescription drugs were available only at the counters of pharmacies or apothecaries. Over-the-counter drugs, in contrast, were found at the counters of general stores—hence the name. OTC agents are most commonly used for conditions that are considered minor and not an indication for medical consultation. Such products should not have significant adverse effects, need detailed drug monitoring, or have a major risk of addiction. Both OTC and prescription drugs are regulated by the FDA, although advertising of OTC agents is regulated by the FCC rather than the FDA. More than 80 drug categories of OTC agents exist, and millions of dollars are spent on these pharmaceuticals annually.

In the early 1970s, the FDA called together panels of experts to evaluate the OTC agents available at that time.[13] The FDA desired to reassure the public that all OTC drugs were both safe and effective. This was a major undertaking because more than 300,000 products were available as OTC products and the ingredients in them numbered more than 1000. Eventually it was decided that only the ingredients would be assessed. An OTC monograph system was devised so that the drugs determined to be **generally recognized as safe and effective (GRAS/E)** could remain on the market and not need to obtain a **new drug application (NDA)** for the purpose of being submitted to the FDA for approval. Few pharmaceutical companies choose to expend the time and financial commitment associated with filing an NDA. Therefore, most of the OTC products available today are well-established pharmaceuticals. All OTC agents are subject

to specific labeling regulations, including requirements governing their names, indications, dosing, **warnings**, and information for healthcare providers.

After a drug has been available by prescription and has an established record of safety, and usually when its patent is about to expire, the manufacturer may seek to obtain permission to move the agent to the OTC market. The last few decades have seen a number of pharmaceuticals that have moved from prescription-only to OTC status. Although the manufacturer ultimately may sell a drug for less money on the OTC market than by prescription, a greater volume of the drug is sold overall when the drug is OTC and has an opportunity to develop a brand following. Antisecretory antihistamines originally used for ulcer treatment and marketed for OTC treatment of heartburn (pyrosis) such as cimetidine (Tagamet) moved from prescription-only status to OTC in 1995. Other popular drugs that are now OTC include nonsedating antihistamines like loratadine (Claritin) and cetirizine hydrochloride (Zyrtec). Discussion has ensued regarding the possibility of more agents being switched, especially statins, because some other countries have already done so or are considering such a change.[9,14,15]

Because of either the length of time on the market and wide availability of the OTC agents or the scrutiny involved with prescription agents before they became OTC, few problems have been noted with OTC drugs. One notable exception was the FDA mandate in 2000 to withdraw phenylpropanolamine (PPA), a common ingredient in both cold remedies and weight loss agents. PPA was found to be associated with hemorrhagic stroke, and this risk is higher in women compared to men. In 2007, manufacturers voluntarily withdrew several OTC cough and cold remedies for infants after the FDA released information about both the ineffectiveness of the agents and the risk of overdose.

Another OTC agent, pseudoephedrine, led to a new variation of OTC drugs—that is, **behind-the-counter (BTC)** drugs. Pseudoephedrine remains an OTC agent. However, this drug can be added to other substances to produce methamphetamine for illicit use. Moving it from an easily accessible open shelf to a location behind the pharmacy counter allows a pharmacist or designee to obtain identification and record each purchase. The intention is that abuse could be tracked, yet consumers who legitimately wish to use the drug can continue to do so.

Generic versus Brand Drugs

Generic drugs are pharmaceuticals that contain the same active ingredients found in an original brand formulation. More than 60% of prescriptions are filled with generic drugs.[16,17] Generics must be demonstrated to be bioequivalent to the brand-name formulation; that is, they must be between 80% and 125% equal in bioavailability. These drugs usually emerge after patent protections for the original brands have expired, usually 7–12 years after first commercial production or 20 years after the first application for FDA consideration. Under the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act), an applicant desiring to market a generic agent must file an abbreviated new drug application (ANDA) with the FDA. Scientific materials that support the bioequivalence of the generic drug compared to the branded product are presented, and when the ANDA is approved, the **approved drug** is added to the FDA Approved Drug Products list (sometimes called the *Orange Book*) with an annotation to illustrate the equivalency.

In the majority of states, a pharmacist may substitute a generic drug for the equivalent brand-name product. Although generics are bioequivalent, some prescribers choose to note that no substitution is allowed; in such a case, the pharmacist must furnish the brand-name agent. This action is sometimes necessary because, although generic drugs and brand-name agents are bioequivalent, sometimes they have different effects in an individuals, secondary to minor changes in product ingredients such as fillers and binders or differences in individual metabolism.

Orphan Drugs

Occasionally there is a relatively rare medical condition (affecting fewer than 200,000 individuals) that can be treated by a pharmaceutical agent. The development and marketing of the drugs used to treat these rare conditions, called orphan drugs, may cost too much for these agents to be of interest to most pharmaceutical houses. Incentives are therefore provided to companies that develop and manufacture orphan drugs, including selected federal grants, as well as a 7-year period of exclusivity for selling the drug in the U.S. market.

Breakthrough Drugs

In 2012, the FDA Safety and Innovation Act was signed into law.[18] This act identified a new category of **breakthrough therapy**, encompassing agents colloquially called **breakthrough drugs**. These medications are used to treat individuals with serious or life-threatening conditions. Breakthrough drugs can be used alone or in combination with one or more other drugs. Some early evidence based

on clinically significant metrics that the drug is superior to current therapies is required to warrant this status. The advantage of drugs being classified into this category is that they are awarded an expedited review by the FDA, specifically receiving a decision on their approval within 60 days of the request.

Compounded Drugs

In years past, pharmacists mixed together pharmaceutical compounds instead of filling a prescription with pills sealed in blister packs. The process of mixing a pharmaceutical remedy, especially for a specific individual, is known as **compounding**. Although compounding remains uncommon today, the number of pharmacists practicing compounding appears to be growing. Some of the reasons for this growth are consumers' desire to avoid the inactive ingredients found in pills or creams that may be allergens (e.g., gluten) or to transform solid formulations into more easily swallowed liquids. Another reason for compounding is to produce bioidentical hormones, which are formulations of hormones that have varying potencies.

Compounding pharmacies generally are regulated by local jurisdictions, such as the states in which they are located, rather than by federal authorities. Traditional compounding pharmacies produce agents such as hormone therapy for a specific woman. However, today many compounding pharmacies produce quantities of a single agent such as steroids in sterile injectable forms and legally send them to other states. In 2012, one such pharmacy in the New England area inadvertently disseminated contaminated steroids to multiple sites in several states, which resulted in more than 700 individuals suffering harm and more than 50 persons dying.[19,20] This event fueled the argument that large compounding pharmacies are becoming indistinguishable from pharmaceutical companies, yet by calling themselves a "compounding pharmacy," they can avoid more rigorous FDA regulations. Based on that argument, proponents of tightening oversight of these pharmacies advocate that the compounds they produce should be evaluated in the same way that new drugs are assessed. To date, no regulatory changes regarding compounding pharmacies have been made.

High-Alert Drugs

High-alert drugs are pharmaceuticals associated with significant harm if they are used in error. Agents commonly labeled with this term include anticoagulants, adrenergic agents, chemotherapeutic drugs, and opiates. Oxytocin, for example, is a high-alert drug.[21] Designation of a drug as high alert does not indicate that errors are more likely with the medication; rather, it signals that when such errors occur, the results can be seriously injurious to the individual. Special strategies to reduce the risk of medication errors when high-alert drugs are used have been advocated, including consumer education about the drugs, use of auxiliary labels and electronic alerts, and use of redundancies such as double checks.[22]

Counterfeit Drugs

Counterfeit drugs are illegal agents that may be adulterated, past their expiration date, or mislabeled. Mislabeling includes having less or none of the expected active ingredient and/or having ingredients not listed on the label. Counterfeiting of drugs is a global problem, and one to which the United States is not immune.

Although a large number of medications—both branded and generic agents—have been found to be fake, it is likely that the majority of counterfeit drugs are lifestyle drugs (e.g., Viagra) that are advertised through the Internet. The FDA's Office of Criminal Investigation expends major time and energy attempting to protect the public from these counterfeit drugs, which are often shipped from other countries to the United States. Not only are many of these agents ineffective, but some of them contain harmful ingredients.[23,24]

Designer Drugs

New drugs have been developed to affect specific biologic targets. Some sources call these **designer drugs**, although confusion with this term may exist: In the drug abuse lexicon, the same descriptor is used to designate the combination of a variety of agents to create a new illicit or recreational drug. Designer drugs are toward a specific biologic target where they bind to and inhibit key molecules involved in a disease or pathologic event. For example, the selective estrogen receptor modulator raloxifene (Evista) is chemically similar to tamoxifen citrate (Nolvadex), but does not have the latter's risk for inducing endometrial cancer. Designer drugs are described in more detail in the *Pharmacogenetics and Pharmacogenomics* chapter.

Drug Development and Approval

Originally, drugs were developed largely based on empirical observations of the effects purported to occur after ingestion of plant substances. Today, many drugs are derived

synthetically. However, drugs can also be formed from constituents of plants or botanicals, animal derivations, and humans, for such agents as insulin. Often new drugs are developed using anecdotal information about the effects of older drugs. Some agents used for one disorder have been found to have side effects that are advantageous when those drugs are used as a treatment for another disorder. For example, antihistamines are FDA approved for treatment of motion sickness or insomnia, not because of their basic therapeutic effect to treat allergic reactions but because of their side effect as antinausea agents. Similarly, the drug terbutaline (Brethine) was originally developed as a treatment for asthma, but is also used as a uterine tocolytic because it interferes with uterine contractility.

Drug testing and approval are regulated at the federal level.[25] Figure 1-1 provides a visual overview of this process. The FDA has several centers, including the Center for Drug Evaluation and Research (CDER); it is through CDER that the FDA regulates the drug testing and approval processes. The following is a general description of how a new drug is studied, although some exceptions may occur.

An **investigational new drug (IND)** application is a legal method by which federal approval may be obtained to transport pharmaceuticals or medical devices to areas in which they may be used in clinical trials. Optimally, clinical trials are randomized, double blinded, and placebo controlled. Upon completion of the trials, the study results may be presented to the FDA in an NDA form with a request for approval. In the past, there has been criticism that companies might undertake multiple clinical trials to study one drug and release data only from those that successfully demonstrated effectiveness or safety. Today, clinical trials have to be registered with the FDA before data are obtained in an attempt to promote transparency.

Clinical Drug Trials

Several distinct phases of clinical testing are required for any NDA. Phase 1 trials are designed to determine the basic pharmacokinetics (i.e., how the drug behaves in the body with regard to absorption, metabolism, and excretion) of the new drug. When established drugs are being proposed for new indications, previous studies may be used for this purpose. Animal testing and in vitro models are still in active use. However, computer modeling and other technological modalities for evaluating the metabolism or toxicity of a drug have also been developed. Application of genomics, proteomics (the study of the structure and functions of proteins), and computational approaches now allow scientists to predict the metabolites of molecules. These techniques enable the drug developer to more accurately predict the pharmacodynamic (i.e., how the body responds to the drug with regard to duration of exposure and drug dose) activity of the drug and its metabolites, and integrate these predictions with human cell signaling and metabolic processes and networks. Toxicogenomic data can be included in this process.[26]

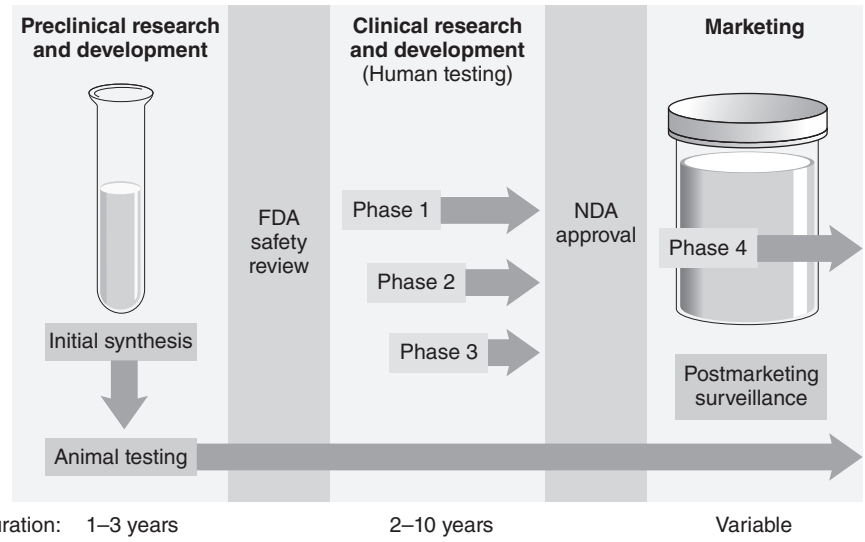

Figure 1-1 Steps required by the FDA for reviewing a new drug.

Source: Hanson GR, Venturelli PJ, Fleckenstein AE. *Drugs and Society.* 11th ed. Burlington, MA: Jones & Bartlett; 2012.[13]

Once a promising pharmaceutical agent has been identified, its toxic and therapeutic doses are determined.[27] Animal testing initially is performed to evaluate drug safety, including determination of the dose range that results in adverse or toxic side effects. Animal testing protocols typically use two or more species in an attempt to control for interspecies differences in pharmacokinetics. Animal testing is undertaken to determine the doses used in preliminary human testing, and its results may be described in the drug product labeling or human trial documents. Unfortunately, cross-species pharmacokinetics are not consistent, and the results of animal testing are not always predictive of human response to a pharmaceutical agent.

Dose–response relationships describe the required dose and frequency of dosing based on the therapeutic index for a drug in a specific population (such as pregnant women, neonates, or nonpregnant reproductive-age women). The therapeutic index is the dose range between the minimum therapeutic dose and the dose that initiates a toxic dose. Identification of the therapeutic index determines the potential therapeutic value and safety of a drug. Increasing the dose of a drug with a narrow therapeutic index (e.g., theophylline [Theo-Dur]) increases the probability of drug toxicity. Factors such as body mass index, metabolic rates, and genetics may all affect the therapeutic index for an individual.

Phase 1 clinical trials seek to determine the distribution, metabolism, and pharmacologic actions of drugs in humans; to determine the side effects associated with increasing doses; and to evaluate for evidence of effectiveness. Human participants are healthy individuals, usually adults of average weight and without chronic diseases. Persons younger than 18 years are excluded from most trials except those that are pediatric focused—a limitation for contraceptive studies because women in this age range frequently need and use contraceptive products.

Phase 2 clinical trials are conducted to evaluate the effectiveness of the drug for a particular indication or indications among individuals with the disease or condition under study, and to determine the common short-term side effects and risks. These studies usually have a small number of participants.

Phase 3 trials are undertaken after the smaller Phase 2 studies indicate the drug may be effective. Larger numbers of participants are involved in Phase 3 clinical trials, and risks and benefits are established through such studies. The basic information needed for drug labeling is determined during Phase 3. Collectively, Phases 1–3 are called preapproval studies.

Phase 4 trials are known as postmarketing studies. No matter how rigorous the Phase 1–3 studies are, wide postmarketing may reveal unexpected results. Untoward events or responses identified during the drug preapproval process are considered adverse drug reactions (a type of adverse drug event) when there is a reasonable possibility of association between the adverse event and the pharmaceutical agent. More recently, there has been an emphasis on the postmarking period because adverse events are more likely to be found in larger populations and within a real-life environment. For example, if a Phase 3 trial included 3000 participants, but a major adverse drug reaction associated with the drug occurs only once in 10,000 individuals, postmarketing may be the only venue in which this drug effect will be revealed. Also, drug–drug interactions may be first identified in postmarketing studies that include individuals who are taking other drugs as well as the one being evaluated. The 2007 FDA Amendment Act mandated increased reporting of drug adverse effects, and it is anticipated that additional attention will be paid to this area in the future. The *Drug Toxicity* chapter provides more detailed information on adverse drug reactions and events.

Regulation of Approved Pharmaceuticals

Legal Requirements for the Package Insert (Label)

Package inserts were first standardized in the late 1960s. One of the first package inserts written was for combination oral contraceptives, in which specific risks and benefits were required to be included. The FDA determines which information is to be provided in the package insert, and on occasion will mandate changes based on newer studies.

Although there is a standard format for the package insert, some manufacturers deviate from it slightly, such as by replacing some of the titles with lower-literacy versions. Among the required components are the brand and generic names of the drug; description of chemical structure, formulation, route of administration, and inactive ingredients; clinical pharmacology, usually containing a synopsis of the clinical trials; approved indications; **contraindications**; warnings, including serious side effects; **precautions**, especially for drug–drug interactions; adverse drug reactions, including those that might be considered minor side-effects; drug abuse and dependency potential;

overdose potential; recommended dose; and how the agent is supplied, including constraints for storage. Since 2006, package inserts also must include "Highlights," a section that summarizes risks and benefits; a table of contents; the date of initial approval; and contact information (web address and toll-free telephone number) to promote easier reporting of adverse effects.[28,29]

FDA Contraindications, Precautions, Warnings, and Other Actions

Precautions may appear on package inserts and are distinct from contraindications. A contraindication specifies who should not take the drug. Persons who are allergic to a drug have a contraindication to its use because adverse reactions are likely. However, precautions indicate that specific individuals who may be at a higher risk for an adverse drug reaction than the general population should use the drug carefully. For example, the transdermal contraceptive patch, marketed as Ortho Evra, has a precaution for women who weigh more than 90 kg (198 pounds).[30] This precaution exists because there is evidence that contraception is less effective among women who have a higher body mass index (BMI), although the strength of this association is difficult to assess from the original studies, because participation was limited to women who were of a healthy weight or at least no more than 35% heavier than the optimal weight. Therefore, currently data are not strong enough to mandate labeling weight of 90 kg or more a contraindication, but the precaution is included, which means the provider should review the evidence with a woman who weighs more than 90 kg and is considering using the contraceptive transdermal patch.

FDA warnings notify prescribers and the public about adverse effects that may be adverse drug reactions. After a drug is approved and marketed, the FDA continues to have a role in monitoring use of the drug. The manufacturer is legally required to review and report any adverse drug reaction to the FDA that is reported to the company. Unexpected serious reactions are to be reported within 15 days; other reactions may be reported on a quarterly basis as long as the drug is marketed. The FDA also solicits direct reports from consumers and providers through a program called MedWatch. This system includes an online voluntary reporting form, which can be completed on the FDA website. Based on reports received, the FDA may choose to issue a warning and require that it be added to or substituted for the existing package insert warnings. When warnings are issued, they are placed on the FDA website and publicized through press releases; they may also be explained in letters directly sent to prescribers and included in the package inserts.

On a postmarketing basis, drugs are used in real-life situations that include the possibility of potential drug–drug, drug–food, or drug–herb interactions.[31] Additional unexpected hazards may become evident via more research using the drug or via reports of adverse drug reactions noted by consumers. For example, in 1999, Merck and Company received approval to market rofecoxib (Vioxx), a nonsteroidal anti-inflammatory drug (NSAID). This agent did not induce gastrointestinal irritation, a side effect common with the other NSAIDs available at the time, but subsequent studies suggested rofecoxib was associated with an increased risk of heart attacks and strokes.[32] A flurry of editorials were published questioning details about the original clinical trials. One trial in particular, sponsored by Merck, was conducted with the intention of assessing rofecoxib (Vioxx) for the additional indication of prevention of colorectal polyps, but it was terminated prematurely when it became apparent that the relative risk for myocardial infarction and stroke was increased almost 100% among individuals using rofecoxib compared to those taking the placebo (relative risk [RR] = 1.92; 95% CI, 1.19–3.11; P = .008).[32] Although the FDA was in discussion with the manufacturer about the implications of these findings, Merck withdrew the drug from the marketplace, making any potential FDA warnings moot.

When a prescription drug is found to be associated with serious adverse reactions, including life-threatening risks, the FDA can issue its strongest warning, known as a **black box warning**. A black box warning is so named because a black border surrounds the text of the warning in both the package insert and on the FDA website/publications. An example of a black box warning is the one mandated by the FDA for medroxyprogesterone acetate in oil (Depo-Provera). In 2004, a black box warning was added to the label for this contraceptive agent, advising women and providers that there were sufficient data to identify a relationship between prolonged use of the drug and loss of bone density. The new recommendation contained within the black box stated that women should not use the agent for more than 2 years continuously unless other contraceptive methods were inadequate.

The most severe action that the FDA can take is to issue a **drug recall** order. Drug recalls or withdrawals from the market are almost exclusively secondary to the drug being determined to be unsafe; these removals can be either voluntary or mandatory.[33] A report in 2001 by the

U.S. General Accounting Office noted that the majority of drugs withdrawn between 1997 and 2001 had more pronounced adverse effects for women than men.[34] Some drugs may be withdrawn from the U.S. market, yet remain available in other countries.

Regulation of Direct-to-Consumer Advertising

Prior to 1997, the vast majority of pharmaceutical marketing in the United States consisted of educating healthcare professionals directly through visits by pharmaceutical representatives and exhibits at conferences, or indirectly through advertisements in journals. However, controversies about marketing existed even at that time. A 1992 study carried out by a group of experts using the FDA criteria of the time evaluated more than 100 drug ads and found that more than 40% contained misleading claims and 44% were deemed inadequate to be the sole source of information.[35]

Direct-to-consumer advertisements are often seen today. They are required to follow recently established FDA criteria because this federal agency has regulatory power over the content of advertising that addresses prescription drugs. Three types of DTC advertisements are allowed. The most common type is product claim advertisements, which include the drug's brand name, indications, risks, and benefits. This type of DTC must conform to FDA criteria. Help-seeking advertisements discuss the condition but do not name any particular drug and, therefore, are not regulated by the FDA. The third type, reminder advertisements simply list the brand name, dose, or cost. Because they do not make claims or discuss indications, such ads are also exempt from FDA regulation. Advertising for over-the-counter drugs is under the purview of the Federal Trade Commission.

DTC advertising initially was advocated as an attempt to better educate consumers and ultimately promote appropriate use of medications among consumers. A review of a decade of such advertising found that DTC communications were firmly entrenched in U.S. media, with the average American seeing an estimated 16 hours of these ads every year just on television.[36] Unfortunately, DTC advertising is also associated with problems such as overuse of medications, medicalization of common discomforts, and expenditures of more than $40 billion annually.[37] Over the years, the FDA has required selected ads to be withdrawn. For example, the manufacturer of terbinafine (Lamisil) had to change one of its ads that implied the drug was always a totally successful treatment for nail infection.

Prescriptive Authority

During the 1900s, **prescriptive authority** was afforded by law to physicians, veterinarians, dentists, and podiatrists in all states, and pharmacists were authorized to fill prescriptions and dispense drugs. In the last few decades, physician assistants, certified nurse-midwives, certified midwives, nurses in advanced practice, and psychologists have received full or limited prescriptive authority in most states. In addition, some other classes of prescribers have emerged. Pharmacists have presented claims that they can be safe prescribers and should be integral members of the healthcare team. The burgeoning array of psychoactive agents has led to some governmental agencies recognizing psychologists and other mental health professionals as prescribers.

Prescriptive authority is regulated by the state in which the prescriber works. Although physicians have no limits on the types of prescriptions that they can write, the prescriptive authority for other providers—such as podiatrists, certified nurse-midwives, and certified midwives—usually is limited to that person's professional scopes of practice. In some states, the prescriptive authority is delegated, indicating the authority is held by a prescribing physician and delegated to others, often a limited number of healthcare professionals.

Discussion has occurred regarding the state-based approach to prescriptive authority.[39] In the mid-1900s, it was logical to assume that a written prescription would be hand-carried to the local pharmacy, where it was filled. Today, it is common for a prescriber to electronically transmit a new prescription to a pharmacy, even if the pharmacy is just a few blocks away. That pharmacy, however, is likely to be a branch of a large conglomerate whose span of operations stretches across several states. Although the prescriber is authorized in one state, the individual may pick up the medication at a pharmacy branch located in another state. Moreover, the role of Internet-based pharmacies has raised legal issues regarding prescribing authority. U.S. pharmacies can operate online assuming the drugs they are dispensing are FDA approved and a legal prescription is available. Other Internet pharmacies are based outside the United States; they may not require a prescription and may illegally mail pharmaceuticals, including those that are not FDA approved, to individuals in the United States. Under these circumstances, such transport of drugs is considered illegal. These issues add to the debate about whether it is time for a federal prescriptive authority to be developed.

Regulation of Controlled Substances

Controlled substances are drugs, both opiates and nonopiates, that have a high risk of addiction. Controlled substances are regulated by the Drug and Enforcement Administration (DEA) of the U.S. federal government. These agents generally are categorized according to schedules (Table 1-2).[25] Prescribers of controlled substances must have legal state authority to prescribe and must obtain an identification number from the DEA for this purpose. Originally, prescribers were provided DEA numbers that began with the letter A; those numbers have been exhausted, so that now most of these identifiers start with the letter B. It is anticipated that the letter C will be used as the prefix in the near future. For physician assistants, nurses in advanced practice, midwives, and others, the DEA number begins with the letter M. The types of drugs that these healthcare professionals prescribe may be limited by a state according to state-devised schedules. A complex system to generate unique DEA numbers was developed in an attempt to identify forged prescriptions for controlled substances, but the equation can now be found on the Internet, and busy pharmacists have little time to do the necessary calculations. Nevertheless, this system persists.[39]

Table 1-2 Schedules for Controlled Substances

Schedule	Description	Example
I	The drug or other substance has a high potential for abuse. The drug or other substance has no currently accepted use in treatment in the United States. There is lack of accepted safety for use of the drugs or other substance under medical supervision.	Heroin
II	The drug or other substance has a high potential for abuse. The drug or other substance has a currently accepted medical use in treatment in the United States. Abuse of the drug or other substance may lead to severe psychological or physical dependence.	Methadone, morphine
III	The drug or other substance has less potential for abuse than the drugs or other substances in Schedules I and II. The drug or other substance has a currently accepted medical use in treatment in the United States. Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.	Products with < 90 mg of codeine per dose unit (Tylenol with codeine [Vicodin])
IV	The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III. The drug or other substance has a currently accepted medical use in treatment in the United States. Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.	Phenobarbital (Luminal)
V	The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV. The drug or other substance has a currently accepted medical use in treatment in the United States. Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.	Cough preparation containing < 200 mg of codeine per 100 mL or 100 g (Robitussin AC)

Source: United States Public Law, Title 21, Code of Federal Regulations (CFR) Part 1300 to 21 CFR §1308.[25]

The Role of the Pharmacist

During the Middle Ages, the role of the apothecary was well established. Such a healthcare professional was the forerunner of today's pharmacist. Apothecaries received prescriptions and filled them with the appropriate remedy. Many of the treatments required compounding. In turn, these providers developed the apothecary system of weights and measures, including the use of drams, scruples, and other terms that have since been largely replaced by the metric system. As their role evolved, most apothecaries entered the profession with a background in chemistry; hence they were sometimes called dispensing chemists.

To be legally recognized as a pharmacist in the United States today, an individual must have graduated from a recognized program and received a doctor of pharmacology (Pharm D) degree. Pharmacists increasingly work collaboratively in hospital settings and in some areas have received or are attempting to obtain a degree of prescriptive authority. Pharmacists fill prescriptions, **dispense** (or **furnish**) the drugs, and counsel the individuals obtaining the agent. Counseling is an important aspect of the pharmacist's role today; it includes advising individuals taking either prescription or nonprescription drugs or both, particularly regarding the way to safely take the agent(s), signs and symptoms of therapeutic as well as adverse effects, and the emerging body of evidence on drug–drug, drug–food, and/or drug–herb interactions.

The Cost of Drugs in Modern Society

The study of the costs and consequences of drug therapy for healthcare systems and society is called **pharmacoeconomics**. Development and marketing of a new drug is a complex and expensive process that generally requires years of research and development. Approximately 25 novel drugs are introduced each year, but not all are profitable. All manufacturers seek a blockbuster drug, or an agent that generates more than $1 billion in annual revenues. Pfizer had such an agent with its brand of atorvastatin (Lipitor): This pharmaceutical agent amassed more than $130 billion in revenues in the 14 years before its patent expired in 2011.[40]

Law described the use of pharmaceuticals in the modern world as part of the medicalization of society, or the belief that any condition, trivial or serious, can and should be treated with a drug instead of other interventions, especially nutrition and exercise.[41] In the United States, the cost of prescription and nonprescription drugs has increased substantially over the last 2 decades. Today, the United States is the largest market in the world for prescription drugs, accounting for as much as 75% of sales of the most popular agents and with 1 in 4 individuals using prescription agents.[42] The cost of drugs directly influences the fact that healthcare expenditures rise by more than 5% each year—a rate higher than inflation.[43]

The Role of Health Insurance Plans

Healthcare insurance also affects the marketing and use of pharmaceuticals. The first modern major U.S. commercial health plan was developed for teachers; it guaranteed hospital coverage and used a blue cross as its symbol—hence the Blue Cross plan for hospital-only insurance. Blue Shield plans emerged later to cover services delivered by physicians, and some of the hospital and physician coverage plans eventually merged to form combined Blue Cross Blue Shield plans.

Health insurance was primarily purchased by individuals until strict federal wage guidelines were put into place during World War II. At that time, it was determined that employers could use fringe benefits such as health insurance to attract employees (in lieu of offering higher wages), and such plans eventually became common elements in employee benefits packages. In the United States today, the majority of adults younger than 65 years have employer-sponsored health insurance, although that may change as healthcare exchanges become more widely available.[45]

Over the decades, healthcare coverage has expanded from catastrophic hospital care to include preventive care, ambulatory services, and, more recently, drug benefits. Drug benefits were added by commercial insurers in an attempt to curtail costs and add benefits for their subscribers. It has been estimated that in 1960, more than 95% of pharmaceuticals were paid for by individuals, whereas 30 years later, the majority were paid for by insurance plans; that share has increased with the expansion of Medicare coverage to include a drug benefit.[46]

Formularies

One popular method used by insurers to control pharmaceutical costs is a **formulary**. In the United States, each healthcare plan may have a different formulary, or list of drugs that it pays for. Often, pharmaceutical companies have negotiated favorable charges for drugs directly with the insurer in exchange for having their products listed on the formulary.

Some formularies are separated into cost-sharing tiers. When this arrangement is used, the top tier is usually composed of generic agents that are totally paid for by the insurer, without a consumer copayment being required. The other tiers contain more expensive agents and may require varying levels of copayments from the consumer. Some drugs may not be eligible for any reimbursement by the health insurance plan. A closed formulary allows only those drugs on the list to be prescribed and paid for by the insurer without an appeals process. In contrast, an open formulary places no limitations on which drugs the prescriber can chose to order.

Like traditional health insurance plans, Medicare and Medicaid as well as some large public or academic facilities attempt to control costs through the use of closed formularies. However, as an unintended consequence, it has been found that requiring copayments may decrease the use of medications, especially by individuals who have chronic conditions and who face high copayment charges for multiple medications.[47]

Medicare and Medicaid

Medicare and Medicaid are public insurance programs funded by either the federal government or a combination of the state and federal governments. Medicare primarily covers elderly individuals, while Medicaid is primarily geared toward insuring persons who demonstrate that they cannot pay for healthcare costs or obtain healthcare insurance. Medicare is completely a federal program; Medicaid is state managed.

A Medicare prescription drug plan (Medicare Part D) was enacted in 2003 and implemented in 2006. Private insurance companies, which in turn are reimbursed by the federal government, administer Medicare Part D. Approximately 2000 unique Part D plans exist, although numbers and types vary regionally. Concerns have been made about the complexity of this system, but early data suggest that Part D may decrease the numbers of individuals who forgo needed medications in an effort to save money.[48,49]

Under the Medicaid program, individuals usually are not assessed a copayment if the drug is Medicaid approved. Over-the-counter agents are not reimbursed for persons on Medicaid, although the generic equivalent written as a prescription may be covered.

Marketing Drugs

In recent years, the marketing of various pharmaceuticals to healthcare providers has provoked strong criticism. Some physicians have been given financial gifts in recognition of their willingness to prescribe specific drugs—a situation that creates a conflict of interest. In response to this phenomenon, a nonprofit group, No Free Lunch, was developed to encourage prescribers to be wary of marketing strategies from pharmaceutical groups that include free samples of drugs, drug-labeled paraphernalia, continuing education, and food.

In response to criticism of how brand-name drugs are marketed, the Pharmaceutical Research and Manufacturers of America (PhRMA) released a marketing guidance code.[50] For example, even pens and pads emblazoned with the names of the drugs are to be strictly limited or stopped; dinners or other activities for prescribers and family members are curtailed; and independent continuing education sponsored by pharmaceutical companies is supposed to be promoted separately from drug marketing. It remains to be seen how these changes will influence the prescribing habits of healthcare providers.

Drug Samples

Samples of pharmaceutical agents, usually prescription drugs, are commonly found in ambulatory facilities. Healthcare providers should be aware of whether they are legally allowed to dispense these samples. Although some professionals claim that sampling allows medically uninsured populations an alternative path to obtain access to necessary agents, studies have found that sampling is a method of marketing, encouraging individuals to continue on a specific pharmaceutical for the course of the condition or disease.[51]

Special Populations

Clinical Trials and Women

Until the 1990s, women of childbearing age frequently were excluded from clinical drug trials due to their potential for pregnancy and the related risk of inadvertent exposure of a fetus to the investigational drug. The disadvantage of this exclusion is that it means even commonly prescribed drugs may never have been evaluated for gender-related adverse effects or appropriate dosing for women. Yet, statistically, women have a higher incidence of adverse drug reactions than do men.[52-54]

Since the 1991 inception of the U.S. Office of Women's Health, researchers have been encouraged to include women as participants in clinical drug trials and to analyze trial data by gender. Inclusion of women as participants in clinical trials offers researchers the opportunity to evaluate gender-related differences that influence disease prevalence, presentation, and response to pharmacologic therapy. Analysis of these differences can provide insight into the biologic processes that contribute to these gender differences, and understanding these differences may lead to new directions in future research.

Pregnancy and the FDA

In 1980, the FDA published a description of five categories that ranked the risk of teratogenic effects of pharmaceutical agents to be used in drug labeling.[55] This list of five discrete **pregnancy categories**, A, B, C, D, and X, was unique to the United States. Other countries use a narrative approach to describe information available about use of drugs in pregnancy. Contrary to popular belief, the FDA did not assign specific drugs to these categories. Instead, the manufacturer reviewed the FDA categories and assigned a pregnancy category letter to the drugs marketed by that manufacturer.

The FDA Pregnancy Categories had several problems. Category C was the most problematic because it actually represented two separate concepts. An agent could be placed in Category C because there have been reports of teratogenicity in animals. For example, glucocorticosteroids were placed into this category because rabbits demonstrated embryotoxic and fetotoxic effects after exposure to these drugs, although no such findings have been reported in humans. However, a far more common reason than animal teratogenicity for classifying an agent into Category C is the second concept—namely, lack of

information about the drug's effects. Most drugs were placed into Category C for this reason, and it is because of this vagueness that the categorization system was problematic.

The categories could also mislead healthcare providers because teratogenic risk does not necessarily increase as the categories move from A to X. Pregnancy Categories C, D, and X are based on risks weighed against benefits, which means a particular drug labeled Category C may carry the same risks as a drug labeled Category X, yet have a C classification because it has more benefits. Category X was reserved for the few agents that are known teratogens for which alternative nonteratogenic agents exist. Acne is an example of a condition that is not life threatening, but the retinoids used to treat acne can cause lifelong congenital effects to the intrauterine conceptus and so should never be taken by pregnant women.

In 2008, a new system for the pregnancy and lactation section of drug labeling was proposed and in 2014, the FDA released a final amendment to the regulations governing content and format of the "Pregnancy" and "Nursing Mothers" subsections of the "Use in Specific Populations" section of labeling prescription drugs.[56] This rule requires removal of the letter pregnancy categories. The package inserts will now include three separate sections that provide information in a narrative format: "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential." Table 1-3 summarizes the new FDA labeling.

The goal of the new labeling is to provide information that will support counseling and the transfer of knowledge about the drug to the consumer.

Table 1-3 2014 Changes to FDA Drug Labeling for Pregnancy and Lactation

Category	Required Content
Pregnancy	***Pregnancy Registry subheading***: Existence of any pregnancy registries and contact information and instructions for how to enroll in pregnancy registries. ***Risk Summary subheading***: If the drug is absorbed systemically, content will include a summary of the risk for all developmental outcomes, using all available animal and human data. A statement that articulates the background risk will be included. ***Clinical Considerations subheading***: May also include dose adjustments for pregnancy, maternal adverse reactions, fetal adverse reactions, and the effect of the drug during labor and birth. ***Data subheading:*** Study type, exposure information (dose, duration, timing), fetal or neonatal adverse effects, number of subjects, and duration of study.
Lactation	***Risk Summary subheading:*** If the drug is absorbed systemically, the content will include data about the presence of the drug in human milk to the extent this information is available, effects of the drug on the breastfed child, and effects on breast milk production. ***Clinical Considerations subheading:*** Ways to minimize drug exposure in the breastfed child and information about monitoring or mitigating adverse reactions. The summary will include a risk and benefit statement. ***Data subheading:*** Study type, exposure information (dose, duration, timing), fetal or neonatal adverse effects, number of subjects and duration of study.
Females and Males of Reproductive Potential	This section is not required if none of the subheadings are applicable. When pregnancy testing or contraception are required or recommended before, during, or after drug therapy, or when there are human or animal data that suggest the drug has associated fertility effects, this information will be presented in subheadings "Pregnancy testing," "Contraception," and "Infertility."

Source: Modified from Food and Drug Administration. *Federal Regist*. 2014;79(233):72064-72103.[56]

Clinical Trials and the Elderly

Current rules regarding clinical drug trials necessitate that the published reports include the demographic characteristics of the subjects, including age, gender, and racial/ethnic backgrounds. Clearly, age is a major factor that must be involved in analysis because older individuals are more likely than younger persons to have a history of previous exposures to pharmaceuticals, multiple pathologic conditions, biologic variations in pharmacokinetics, and use of other agents (i.e., to be a polypharmacy user). Polypharmacy includes over-the-counter and herbal/botanical formulations. Use of multiple agents increases the risk of drug–drug, drug–herb, and drug–food interactions. Therefore, the elderly are not restricted from participation in clinical trials; indeed, they should be encouraged to enroll in such studies.

Rational Prescribing

Due to the complexity and seriousness involved in prescribing the appropriate agent for an individual, a rational approach has been advocated.[6,57] Several definitions exist for rational prescribing, as well as various examples. In general, rational prescribing includes four goals: (1) maximizing effectiveness of an agent; (2) minimizing side effects

and risks; (3) customizing the agent for an individual; and (4) minimizing cost.[47,58]

Customization includes consideration of an individual's lifestyle, insurance drug benefits (if any), and desires. For example, use of an injectable pharmaceutical may be a problem for a woman with severe arthritis in her hands. When prescribing a statin for a mature woman, it would be wise to ask if her partner is also taking a statin. If so, the prescriber should consider prescribing the same drug for the woman under the assumption that the couple may share these medications, even though all individuals are warned not to do so. The two individuals also may share knowledge about the drug and be more likely to remember the name and dosing if they take the same agent.

In addition to seeking the most inexpensive sales outlet for the agent and using drug benefits if available, a few other practical options exist that clinicians may employ to help individuals save money. Often a tablet containing twice the dose does not cost twice as much; that is, the provider may be able to educate an individual on how to split a tablet. This action is not possible for capsules, extended-release agents, or some other formulations. For those individuals with chronic conditions, a prescription for 90 days generally is less costly than three 30-day refills, and it often carries a lower payment for persons with drug benefits. When drugs move from prescription to over-the-counter status, it may be less expensive for the individual to maintain a prescription for the first few years when the manufacturer has no OTC generic option available, even though ultimately there is evidence that OTC switching can save the public money.[43] Lastly, individuals should be counseled to continue medications such as antimicrobials until the prescription is finished, and to be aware of when therapies may no longer be warranted so that they do not have to pay for refills of unnecessary drugs.

The prescriber should keep in mind that rational prescribing is PERSON centered. The acronym PERSON denotes pragmatics, effectiveness, route/dose, safety, options, and needs/desires. *Pragmatics* applies, for example, when prescribing a statin that is already used in the home. Homeless individuals have no access to refrigerators, so prescribing a drug for such a person with diabetes that requires a low temperature for storage is irrational. *Effectiveness* is essential. If an agent is not effective, then it should not be prescribed at all. The effect desired should be considered as well: Is the drug meant to be curative, to be prophylactic, or simply to reduce symptoms or act palliatively? Likewise, *route* and *dose* need to be considered. Some individuals are unable to swallow, for example, so they need transdermal, topical, or parental formulations.

Safety, like effectiveness, is an essential consideration. The potential adverse effects and contraindications must be weighed against the disease condition, whether present or potential. Medications for women in special populations (e.g., pregnancy and lactation) should be carefully considered. Interactions between the agent and other drugs, herbs, or foods need to be addressed. *Options* include consideration of other pharmaceutical agents as well as nonpharmaceutical therapies such as exercise and nutrition. Less costly generics should be considered if possible. Knowledge of the marketplace enables a prescriber to know when it is less expensive to prescribe a generic drug than an OTC agent, or to appreciate when agents are covered by drug benefits. *Needs and desires* of the individual also should be considered. Some women will accept a prescription for a suppository but never fill it because of personal distaste for the application procedure. A woman may request a scopolamine patch in preparation for a planned cruise or prefer a certain kind of packaging for ease of use.

Monitoring is an important additional component in rational prescribing. The response of the individual helps determine future treatments. For example, optimally a drug should result in a positive therapeutic response. However, adverse effects may dictate a modification of the drug regimen, and toxic effects may require its complete discontinuation.

Irrational prescribing is never intended, yet it often occurs because the U.S. healthcare system is both complex and overburdened. Currently, interprofessional education is advocated as a method of promoting rational prescribing for all providers.[59] Intentional engagement of the goals and approaches to rational prescribing is of value to modern society as a whole.

How to Write a Prescription

A standard prescription contains several components. It should include the name, credentials, and contact information for the prescriber; the name and identifying information for the person for whom the prescription is written; the superscription or Rx insignia (derived from an abbreviation for the Latin words meaning "recipe" or "take"); the inscription or generic name of the drug with dose; the subscription or directions to the individual filling

the prescription; the signature (from the Latin *signetur*, meaning "let it be labeled"), which details how the person for whom the drug is intended should use it; and the signed name of the authorized prescriber. Today, it is recommended that all prescriptions are written in English with no or minimal abbreviations. In particular, most Latin abbreviations should be avoided, as they often can be misinterpreted. For example, "qod" indicates every other day, but can be misread as "qid," resulting in eight administrations over a 48-hour period (as opposed to one administration over the same period). Some abbreviations exist in common usage and may continue to be seen, including in texts. These standard abbreviations include "po" (oral administration or by mouth); "bid," "tid," and "qid" (twice daily or three or four times daily, respectively); "prn" (as needed); as well as metric abbreviations such as "mg" and "mL" for milligrams and milliliters, respectively. Many facilities commonly maintain a list of acceptable abbreviations for charting as well as prescriptions. Box 1-2 lists recommendations to decrease medication errors when writing a prescription, and Figure 1-2 illustrates the components of a prescription.

Reduction of Medication Errors

In 1999, the U.S. Institute of Medicine released a study that estimated more than 90,000 individuals die in hospitals annually due to errors in the delivery of care.[7] Among these errors are many that are associated with pharmaceuticals, which are termed medication errors.

Although adverse effects have been estimated to occur with fewer than 0.5% of medication orders in hospitals, more than one-fourth of those that do occur are considered preventable.[7] Rates of adverse drug events in ambulatory facilities may even be higher. A suggested intervention to decrease medication errors is to use computerized ordering or electronic charting. Illegibility of a handwritten prescription increases the risk of a person receiving the wrong drug or dose. Electronic prescribing (e-prescribing) was recognized as a desirable goal in the 2003 Medicare Prescription Drug Improvement and Modernization Act, but rates of its implementation remain low.[60] The FDA has recognized that a myriad number of mobile apps exist, many of which provide information useful in avoiding medication errors, such as

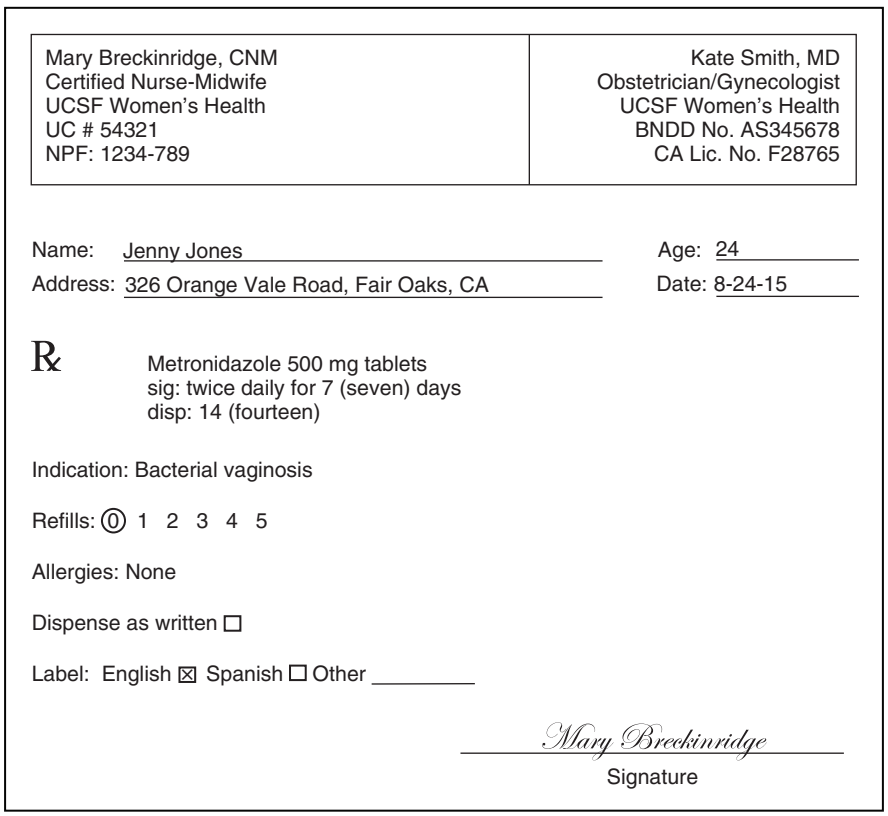

Figure 1-2 Sample prescription.

Box 1-2 Recommendations to Decrease Medication Errors When Writing a Prescription

Dos

Include numbers as both words and numerals (e.g., 60 [sixty] tablets).

Ensure clear writing, print in ink, or type the prescription.

Check for correct spelling (especially in an era of drugs with similar names).

Use English whenever possible instead of Latin.

State specific times (e.g., 8 A.M.) if possible.

Use a standard format, especially on preprinted blanks.

Use the most common formulation (e.g., 500 mg instead of 0.5 g).

Include a zero prefix with decimals less than 1 (e.g., 0.5 mg).

Use the abbreviation "mL" instead of "cc" because "mL" is less likely to be misread.

Don'ts

Do not use trailing zeros in decimals (e.g., 5.00).

Avoid unusual measurements such as teaspoons, tablespoons, pints, ounces, drams, grains, and minims.

Minimize vagueness (e.g., "prn"—at minimum, write "as needed for pain").

drug-to-drug interactions. To promote the development and use of quality apps for this purpose, the FDA issued nonbinding guidelines in 2013.[61]

Ethics and Prescribing Drugs

By definition, ethical dilemmas have no simple answers. Much of the discussion about ethical use of drugs concentrates on isolated topics such as pharmacotherapeutics, or use of a drug as a treatment for specific conditions. However, just as drugs have an important role in economics, they also have major ethical implications.[62] It is beyond the scope of this chapter to explore ethics and drug use in detail. However, the healthcare professional should consider how to personally approach a variety of issues, including prescribing for his or her own family; prescribing for oneself; selling nutritional supplements or other nonprescription items within the professional's office; use of placebos; support of selling agents overseas that are not marketed in the United States because of lack of effectiveness or risk of adverse effects; providing free samples of drugs; or acceptance of gifts from pharmaceutical companies, regardless of how minor the cost might be.[63]

Conclusion

Drugs are ubiquitous in modern society. Many medications have provided health, help, and hope for women. Unfortunately, some agents have also resulted in harm. Medicalization of conditions has often led women to seek pharmaceuticals as first-line treatments, even when other options may be equally effective or even safer. To promote the health of everyone in modern society, prescribing drugs should be conducted in a rational, legal, and ethical manner.

Resources

Organization	Description	Website
U.S. Food and Drug Administration (FDA)	The FDA is responsible for protecting public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines, and other biological products, as well as medical devices. The FDA is also responsible for the safety and security of dietary supplements and products that give off radiation. In addition, the FDA regulates tobacco products.	www.fda.gov
U.S. Immigration and Customs (counterfeit drugs)	Investigative arm of the Department of Homeland Security. This agency works to identify and prevent sale of counterfeit pharmaceuticals.	www.ice.gov
U.S. Department of Justice, Drug Enforcement Administration (DEA)	The mission of DEA's Office of Diversion Control is to prevent, detect, and investigate the diversion of controlled pharmaceuticals and listed chemicals from legitimate sources while ensuring an adequate and uninterrupted supply for legitimate medical, commercial, and scientific need.	www.deadiversion.usdoj.gov

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