Basic Concepts of Pharmacology

OBJECTIVES

After reading this chapter, you will be able to:

- Discern the meaning of pharmacology
- Identify drugs, their sources, and how they work
- Identify federal laws that regulate drugs and the agencies that administer those laws
- Understand the procedure for getting a new drug to market
- Understand the term “drug”
- Understand the difference between active and inert ingredients
- Identify several medications that have improved quality of life and increased life expectancy
- Identify natural, synthetic, synthesized, and semi-synthetic drugs
- Identify therapeutic, pharmacodynamic, diagnostic, prophylactic, and destructive agents
- Understand the use of National Drug Code (NDC) numbers
- Identify various commonly used pharmaceutical reference texts
- Identify receptors and their function in mechanisms of drug action
- Understand the general principles of pharmacokinetics and the importance of those principles in developing and testing drugs
- Identify the beneficial and harmful effects of drugs
- Identify common terms used to describe drug interactions

KEY TERMS

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Adulteration</th>
<th>Allergic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Affinity</td>
<td>Anaphylactic reaction</td>
</tr>
<tr>
<td>Addiction</td>
<td>Agonist</td>
<td>Antagonist</td>
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Technological advances made in the field of pharmacy have allowed for advances in the delivery of healthcare. Early practices of compounding to more recent, large-scale pharmaceutical-manufacturing operations have improved the synthesis and delivery of pharmaceuticals. Earlier scientific-research discoveries provided the foundations of these medical advances. As new drugs were developed, laws and regulations were put in place to protect the public. As the number of drugs available continues to grow, so does the information available to use them safely and properly. How and where to find this information and the drug references used by pharmacists and pharmacy technicians in the workplace will be explained.

**Pharmacology**

During the 19th century, Claude Bernard, a French physiologist, used the laboratory to determine the relationship between drugs and their sites of action within the body. He established pharmacology—the study of drugs and their properties and how they interact with the body—as a discipline of study.

*Pharmacology is the study of drugs and their properties and how they interact with the body.*

The **active ingredient** of a drug is responsible for the drug’s therapeutic effect. The active ingredient is the ingredient that produces the desired or intended effect. A drug may contain more than one active ingredient. Most drugs contain an active ingredient and one or several inert ingredients. An **inert ingredient**, also called an inactive ingredient, has little or no therapeutic value. These inert ingredients are generally
used to stabilize the active ingredient or to serve as a vehicle when making a solution, suspension, or topical preparation.

The active ingredient is responsible for a drug's therapeutic effect.

An inert ingredient has little or no therapeutic value.

**Drugs and Their Sources**

A **drug** is any substance used for the diagnosis, cure, treatment, or prevention of a disease or is intended to affect the structure or function of any living system. Drugs can be made from a variety of sources. They can be derived from sources such as plants, animals, minerals, or chemicals. Drugs can also be produced by recombinant DNA technology. A drug that is produced from recombinant DNA technology is referred to as a **biopharmaceutical**. Drugs that are derived from animals, plants, or minerals are classified as natural substances. Examples of drugs derived from plants include opium from the opium poppy, digoxin from foxglove, and colchicine from the cinchona tree. Drugs derived from animal sources include conjugated estrogen tablets and thyroxine. Drugs derived from minerals include iron salts, used to treat anemia.

**Drugs can be made from plant, animal, mineral, or chemical sources.**

**Drugs produced by recombinant DNA technology are called biopharmaceuticals.**

**Drugs derived from animals, plants, or minerals are classified as natural substances.**

Most drugs available on the market today are synthesized from naturally occurring chemicals. Drugs derived from these chemicals can be further categorized into synthetic, synthesized, or semi-synthetic drugs. A **synthetic drug** is a drug that is created artificially and that has a specific mechanism of action that results in a specific pharmacologic effect. Penicillin and the sulfa drugs are examples of synthetic drugs. Synthetic drugs are not created to mimic a naturally occurring drug. A **synthesized drug** is a drug created in the laboratory to mimic the pharmacologic actions of a naturally occurring drug. Methamphetamine is an example of a synthesized drug. A **semi-synthetic drug** is one that contains a combination of artificially created molecules and natural molecules. Amoxicillin and ampicillin are examples of semi-synthetic drugs.
These drugs are generally created to improve the properties of the naturally occurring substances or drugs.

**Drugs that are derived from chemicals are synthetic, synthesized, or semi-synthetic.**

Biogenetically engineered drugs are synthetic drugs with specific therapeutic effects that have been genetically engineered using recombinant **deoxyribonucleic acid (DNA)** technology. DNA is a complex, helically shaped molecule that carries the genetic code for each individual. DNA technology uses biology, chemistry, and immunology to create drugs that can alter the DNA code to prevent or treat diseases.

The classification of a drug is important because it places the drug into proper categories. Drugs can be classified according to their source, chemical structure, mechanism of action, or function.

**Drugs can be classified according to their source, chemical structure, mechanism of action, or function.**

### Drug Actions

Drugs exert various actions on body organs and systems. Often, the quantity of a drug or how well it binds to the target cell receptor will determine the action of a drug. A drug's mechanism of action also determines how and where it works in the body. How the body affects a drug over a period of time is also crucial to understanding drug actions and disease management with medications.

### Receptors

The human body maintains homeostasis by a system of control and feedback mechanisms. **Homeostasis** is the balance of the body with respect to fluid levels, pH, osmotic pressure, and concentrations of various substances. When the body’s own system of control and feedback mechanisms cannot maintain balance, drugs can be used to help the body restore and maintain homeostasis.

For the body to maintain homeostasis, cells must be able to communicate with each other. They do this primarily through the action of chemical messengers. These cells produce chemical substances that then diffuse throughout the extracellular fluid to reach the target cell. The chemical messenger recognizes the target cell and communicates with it via a specific protein molecule called a **receptor**, located on or near the surface of the cell. The messenger molecule binds to the receptor in much the same way as a key fits into a lock, thus allowing absorption to take place in a cell. This reaction produces the desired effect. These reactions take place naturally throughout the body. Only after the receptor makes a connection with the messenger will a reaction take place. Medications often mimic this natural mechanism.

**Cells communicate with each other through chemical messengers to maintain homeostasis.**

Different cells in the body contain different types of receptors, and only certain cells have the receptor that is the right fit for a particular chemical messenger. To properly bind to a particular receptor, the chemical messenger must have a chemical structure that is complementary to the receptor. This is referred to as **specificity**. The strength, or how tightly a drug binds to its receptor, is referred to as **affinity**.
Mechanisms of Action

A drug is administered to elicit a response in the body, either to prevent or manage a disease or to prevent or manage symptoms of a disease. The actions of the body on a drug over a period of time are described through pharmacokinetics. The effects a drug has on the body are described through pharmacodynamics. Drugs can act like chemical messengers and stimulate certain receptors, causing the human body to react in a specific way. Once the receptors are activated, they either trigger a particular response directly on the body or they trigger the release of hormones and/or other endogenous drugs in the body to stimulate a particular response.

Some drugs will bind to a particular receptor to elicit the same response as the body’s own chemical messenger. This type of drug is called an agonist because it stimulates and activates the receptors and enhances the natural reactions of the body.

A drug that binds to receptors to elicit the same response as the body’s own chemical messenger is called an agonist.

Other drugs block the action of the natural chemical messengers found in the body. This type of drug is called an antagonist. Antagonists have a similar affinity to the receptor sites and compete with the natural messenger for available receptor sites. When an antagonist binds to the receptor site, it prevents the naturally occurring chemical messenger from binding there, thus blocking the natural reaction of the body to the messenger.

A drug that competes for receptor sites and blocks the action of natural chemical messengers is called an antagonist.

Some drugs do not interact with receptors, but instead produce their effects by combining with specific molecules such as enzymes, which are substances that act as biochemical catalysts. Others produce their effects by embedding themselves in cell membranes.

Not all drugs are agonists and antagonists.

Understanding How an Agonist Works

Imagine for a moment the typical school custodian, carrying keys to fit the classroom and office locks for an entire high school. When the chemistry teacher locks himself out of his classroom, the custodian may try a number of keys before he finds the one that unlocks the door. Some keys will not fit in the lock, some may fit but not turn, but only one will fit in the lock and open the door. In this analogy, the keys represent an array of drugs. The lock on the door represents a specific drug receptor. The key that fits into the lock and opens the door represents an agonist. Keys that fit into the lock but do not open the door are like antagonists; not only will the keys not open the door, they also block other keys from entering the lock, thereby blocking an effective response. Keys that will not even fit in the lock represent drugs with no affinity for the specific receptor.
Pharmacokinetics

Pharmacokinetics, the study of how the body affects a drug over a period of time, enables scientists to develop dosage forms that are designed to produce a desired effect. Pharmacokinetics describes the effects that the body has on a drug. Each drug’s pharmacokinetics can be described by the following processes in the body:

- Absorption
- Distribution
- Metabolism
- Elimination

Understanding these processes and their effects on drugs is critical to the drug-development process and the understanding of drug actions in the body. They are often learned by using the mnemonic ADME, for Absorption, Distribution, Metabolism, and Elimination.

Pharmacokinetics describes the effect that the body has on a drug. It can be described by four processes: absorption, distribution, metabolism, and elimination.

Absorption

**Absorption** is the process by which a drug enters or passes through natural body barriers such as the skin, intestines, stomach, and blood-brain barrier and enters the bloodstream. How well the drug passes through these barriers depends on its route of administration, its solubility in blood or other bodily fluids, and other physical and chemical properties. It is one factor that determines how much of the drug is absorbed and, ultimately, its **efficacy**, or ability of the drug to produce a predictable effect in controlling or curing an illness in the body.

The route of administration can affect the rate and extent of absorption. Drugs administered in liquid solution are already dissolved, so they are absorbed more rapidly than those in solid dosage forms. Drugs administered intravenously do not require absorption because they are injected directly into the bloodstream. Drugs administered in solid dosage forms (tablets and capsules) require **disintegration** of the tablet or capsule and **dissolution** of the drug in the gastrointestinal tract, thereby slowing the rate of its absorption. Semi-solid dosage forms are also available for oral, vaginal, and rectal routes of administration. (You’ll learn more about these routes of administration later on.) Disintegration and dissolution depend on the physical properties of the dosage form and the physical and chemical properties of the drugs.

The majority of oral drugs are absorbed in the small intestine because of its large sur-
face area. The degree of movement of a drug within the gastrointestinal tract also affects absorption. The faster a drug gets to the small intestine, the quicker it is absorbed into the bloodstream.

**Drugs enter the bloodstream by a process called absorption.**

**Distribution**

After a drug is absorbed into the bloodstream, it is distributed to tissues, other body fluids, and ultimately to organs throughout the body. Not all organs are affected equally by drugs that are administered, however. This is because some areas of the body do not allow the drugs to infiltrate as quickly as other areas.

The most important rate-limiting factor for distribution of a drug is blood flow. Protein binding is another important factor related to drug distribution. Most drugs, to some extent, bind to proteins in the blood. The activity of a drug is directly proportional to the concentration of free drug in the bloodstream. Drug molecules that bind to protein in the blood are bound and unable to reach the intended site of action. Unbound, or free, drug particles are available to reach the site of action.

Disease states can affect protein binding. Drugs can also bind to proteins other than those in the blood, such as proteins in tissues. Drug particles that bind to proteins in tissues would also be unable to reach the desired site of action.

The blood-brain barrier is a natural system that functions to keep harmful chemicals from entering the cerebrospinal fluid (CSF) from the blood. Many drugs are not able to get to the central nervous system (CNS) because they are water soluble, while other medications may penetrate the blood-brain barrier and cause unwanted side effects.

The activity of a drug depends on the amount of free drug in the bloodstream.

**The most important rate-limiting factor for distribution of a drug is blood flow.**

**Metabolism**

Drug **metabolism** is the process of biochemical modification or degradation of a drug in the body. As the drug is distributed throughout the body, some of it is transferred to the liver, where it is metabolized. Metabolism changes the chemical structure of the drug to a more water-soluble form so that it can eventually be excreted by the kidneys. The byproduct or the substance into which the drug is converted when it is metabolized is called a **metabolite**. In some cases, the metabolite is the one responsible for the pharmacological effect. In other cases, the drug is metabolized to an inactive
substance or a less-toxic substance. The sequence by which a drug is converted to its metabolite is referred to as a metabolic pathway.

Some drugs can pass directly from the gastrointestinal tract to the liver. In these cases, the amount of active ingredient is reduced before it even enters the bloodstream. Other drugs are not metabolized in the liver at all and are excreted in the urine unchanged.

Different influences can affect the metabolism of a drug, including age, gender, diet, genetics, other diseases, and other drugs. Sometimes, when two or more drugs are administered together, one drug can decrease the metabolism of another drug by competitive or complete inhibition of the enzyme responsible for the metabolism of that drug. This results in an increased pharmacologic response to the other drug or toxicity. This process is referred to as inhibition. Other times, one drug can enhance the metabolism of another drug by inducing the enzyme responsible for the metabolism of the other drug, resulting in a decreased pharmacologic response to the other drug. This process is referred to as induction.

Metabolism changes the chemical structure of the drug so that it can eventually be excreted by the kidneys.

Age, gender, diet, concurrent diseases, and other drugs can affect the metabolism of a drug.

Elimination/Excretion

Elimination is the removal of the drug from the body. Excretion is usually associated with urination, but a drug can also be excreted in feces, sweat, breast milk, semen, or exhalation. Drugs that are not eliminated from the body properly can lead to toxicity.

Not all drugs are tested by the manufacturer for excretion into breast milk. A doctor must use his or her judgment when prescribing these drugs for patients who are breastfeeding.

Pharmacokinetic Properties

Understanding the pharmacokinetics of a particular drug enables researchers to determine how a drug should be administered to achieve an intended response while minimizing toxicity. For a drug to be effective, it must get to the site of action in concentrations large enough to allow the drug to exert its effect, but not so large that it produces toxicity. A basic understanding of pharmacokinetic principles is also necessary for the development and testing of drugs.

Bioavailability

Bioavailability is the degree to which or the proportion of the drug that is available to the site of action or target tissue to produce the desired effect. All drugs are metabolized in different ways and at different times. How much of the drug is actually available to produce the intended effect is an important consideration when deciding which drug to use and how often.

Drugs that are administered intravenously (IV) have a bioavailability of 100%. The bioavailability of drugs administered by other routes such as oral, topical, subcutaneous, or intramuscular injection varies. Some drugs pass directly from the gastrointestinal tract to the liver (first-pass effect), where they are metabolized before the active ingredient even enters the bloodstream, thereby reducing its bioavailability.
If a drug given orally undergoes considerable first-pass metabolism, its bioavailability will be decreased. In this case, drugs are often given in higher doses or by intravenous administration to counter this effect. Drugs administered intravenously bypass the first-pass effect because they are injected directly into the bloodstream. The proportion of drug that is available to the site of action is referred to as its bioavailability.

### Half-Life

**Half-life** ($t_{1/2}$) is the amount of time it takes the plasma concentration of the drug to decrease by 50%, or reach half of the original concentration. An easier way to think about half-life is that it is the amount of time it takes the body to metabolize and excrete one-half of the drug. For example, if a person takes a medication that has a half-life of five hours, that means in five hours, one-half of the drug will be eliminated from the bloodstream. Note that it takes about three to five half-lives to reach steady state with continuous dosing. A longer half-life means that the drug has a longer duration of action. The half-life of a drug is important because it enables you to calculate when the drug will be eliminated from the body, which helps determine the drug’s dosing interval. By knowing the half-life of a drug, you can avoid accumulation of the drug and toxicity.

Half-life is the amount of time it takes for the plasma concentration of the drug to decrease by 50%.

Different drugs have different half-lives.

### Therapeutic Window

Some drugs have a **therapeutic window**—that is, a range of serum concentrations at which the drug is most effective with minimal toxicity. When the amount of drug in the bloodstream elicits the desired response, the drug is said to be at the therapeutic level. If a drug is underdosed, it has little therapeutic benefit. If it is overdosed, it can lead to toxicity and death.

The therapeutic window of a drug tells you the range of serum concentrations at which the drug is most effective.

The length of time a drug is within the therapeutic window is referred to as its **duration of action**. To maintain serum concentrations within the therapeutic window, the patient should receive **maintenance doses** of the drug. In some cases, a **loading dose** is required to bring serum concentrations of the drug to a therapeutic level quickly. To determine the loading dose, it is important to know the volume of distribution of a drug. The **volume of distribution** tells you the relationship between the amount of drug in the bloodstream and the dose of the drug given.

Some drugs such as digoxin (Lanoxin) or carbamazepine (Tegretol) have a narrow therapeutic window. A narrow therapeutic window describes a situation in which there is very little difference between a drug’s therapeutic level and toxic level. These drugs require monitoring of serum concentrations to ensure that levels do not rise above (toxicity) or fall below (sub-therapeutic) the therapeutic window.
The duration of action of a drug tells you how long the serum concentrations remain within the therapeutic window.

A loading dose can bring serum concentrations of a drug to a therapeutic level quickly. Maintenance doses are needed to keep serum concentrations within the therapeutic window.

A dose-response curve defines the relationship between the dose of the drug and the response or effect of the drug at that dose. As the dose of the drug increases, the response to the drug also increases, until increases in the dose of some drugs have no further effect above a particular dosage level. When this happens, it is called a ceiling effect. Acetaminophen (Tylenol) is an example of a drug with a ceiling effect.

**Uses of Drugs**

Drugs can be classified according to their use or pharmacologic effect. Some medications may belong in more than one category.

A therapeutic agent is any drug that relieves symptoms of a disease, stops or delays disease, or maintains health. Examples of therapeutic agents include vitamins, analgesics, antibiotics, and antidepressants. A pharmacodynamic agent is any drug that alters bodily functions. Examples include drugs used to increase or decrease blood pressure, general anesthetics to cause loss of consciousness, and caffeine to keep us awake. A diagnostic agent is any drug used in the diagnosis or identification of a disease.

A pharmacodynamic agent alters body functions to elicit a desired response.

A Diagnostic agent is any drug that is used for diagnostic purposes.

A therapeutic agent maintains health, relieves symptoms, combats illness, or reverses the disease process.
Most diagnostic agents are chemicals that contain radioactive isotopes. An isotope is a form of a chemical element that contains the same number of protons as the regular element, but a different number of neutrons. Radioactive isotopes give off energy in the form of radiation, which can be used for diagnosis and treatment. One example of a radioactive isotope is iodine-131 ($^{131}\text{I}$).

A prophylactic agent is any drug that prevents a disease or illness from occurring. Examples of prophylactic agents include vaccines or antibiotics given for the prevention of disease. A destructive agent is a drug that destroys or kills abnormal and sometimes normal cells. Destructive agents can also kill bacteria, fungi, or viruses. Examples include penicillin, antineoplastic drugs, which are used to treat cancer, and radioactive iodine.

- A prophylactic agent is used to prevent an illness from occurring.
- A destructive agent destroys or kills abnormal or normal cells.

## Drug Effects

The pharmacokinetics of an individual drug provides insight into the possible effects, both therapeutic and adverse, of a drug. The reaction to a drug varies from person to person. Response to drug therapy must be monitored to ensure that the therapy produces the desired effect, while minimizing the chances of side effects.

**Therapeutic Effect**

A drug is given to produce a desired effect on the body, either to treat a disease or to relieve symptoms. This is referred to as a drug’s **therapeutic effect**. Sometimes drugs are administered to prevent the occurrence of an infection or disease. When a drug is administered in this fashion, its effect is referred to as **prophylaxis**. Drugs can have a local or systemic effect. When a drug has a **local effect**, the effect is confined to one area or organ of the body. An example of this would be local anesthesia, when an anesthetic medication is administered directly into one part of the part of the body, such as procaine (Novocain) being administered into the gums during a dental procedure. When a drug has a **systemic effect**, the effect is on the entire body. An example of a systemic drug is a chemotherapy agent used to treat cancer. It affects all the cells in the body, not just the cancer cells.

Vitamins are therapeutic agents that maintain health. Prophylactic agents such as vaccines prevent an illness or disease from occurring.
The desired effect that a drug produces is called a therapeutic effect.

The healthcare professional must assess each individual patient to determine appropriateness of therapy. When a drug is given according to its labeling and is known to be of benefit for a given disease, symptom, or condition, it is an indication for that drug. Even if a drug is indicated for a specific patient, the physician must weigh the benefits of the drug for that disease or condition with the risks to the patient. Often, a drug can be dangerous when used in certain situations. When a patient has a certain condition, disease, or symptom for which the drug should not be used, it is a contraindication for that drug. When a drug is contraindicated for a particular patient, it should not be prescribed for that patient.

An indication for a drug is the disease, symptom, or condition that may be treated by using the drug (FDA-approved use). When a drug is used off-label, it means that it is being prescribed for a purpose other than that indicated on its label (non-FDA approved use).

A contraindication for a drug is a disease, condition, or symptom for which the drug is not indicated or will cause harm.

Side Effects
A side effect is an unintended response to a drug. Examples of common side effects include nausea, diarrhea, vomiting, constipation, lethargy, and drowsiness. Side effects can vary in severity, ranging from mild to serious. Often, drugs are prescribed because of their side effects. Some drugs have been marketed for use in one disease because of the side effects noted while using the same drug for treatment of another disease. One example of this is sildenafil. Although it was originally developed to treat heart disease, it was noticed in trials to enhance penile erections. This resulted in the approval of the drug Viagra to treat erectile dysfunction.

A side effect is any unintended response to the drug. Common side effects include nausea, diarrhea, vomiting, lethargy, and drowsiness.

Allergic Reactions
An allergic reaction is a local or general response of the immune system to an antigen. An antigen is a molecule that stimulates an immune response. Allergic reactions can manifest in a variety of ways. The first response the body has to an allergen is usually little or no reaction. Upon subsequent exposure, the body remembers the antigen and responds with a more severe response. These responses can vary from mild in severe to life threatening. The reactions themselves could be immediate or delayed responses to the antigen. Histamine is the chemical your body releases when you are having an allergic reaction. Examples of ways that an allergic reaction could manifest include rash, hives (urticaria), itching (pruritis), wheals (red, blistered areas), fluid accumulation in tissues, sneezing, wheezing, and swelling. A severe allergic response to an allergen is called an anaphylactic reaction. It is an immediate, life-threatening reaction that involves respiratory distress (difficulty breathing) followed by shock. Often, the response to a drug is unrelated to the dose of that drug. This is called an idiosyncratic reaction.
Drug Dependence

**Drug dependence** means the body needs the drug to function normally, and that abruptly stopping the drug will lead to withdrawal symptoms. **Addiction** is the perceived need to use the drug to attain physical and psychological effects, despite it being dangerous. A common sign of drug addiction is lack of control. One can be dependent on a drug without being addicted to the drug.

**Physical dependence** to a drug occurs when physical symptoms of withdrawal, such as sweating, racing heart, and difficulty breathing, present when the use of the drug is stopped. **Psychological dependence** to a drug is when psychological symptoms, such as irritability, inability to sleep, or depression, occur when the use of the drug is stopped. Patients with drug dependence can experience physical dependence, psychological dependence, or both.

**Drug abuse** is any use of a drug for purposes other than that for which it was prescribed or in amounts other than that prescribed. Often, drug abuse can lead to drug addiction.

Tolerance

**Tolerance** is a decrease in the pharmacological response to a drug that occurs with continued administration. To overcome tolerance, the dosage or interval at which the drug is administered may need to be increased.

Drug Interaction

One drug can exert an effect on another drug. Food, alcohol, herbal preparations, vitamins, and nicotine can also interact with prescription and over-the-counter drugs. Drugs can interact with other drugs by inhibiting (decreasing the activity) or inducing (increasing the activity) the enzymes responsible for the metabolism of the other drug. Drugs can also have an additive effect on each other. That means the combined effect of both drugs is additive.

A common way in which foods or drugs interact is by a system of enzymes called cytochrome P450 (CYP). Grapefruit juice is one example of a food that inhibits a CYP450 isoenzyme found primarily in the intestines. Inhibition of CYP450 isoenzymes by grapefruit juice results in less of a drug undergoing first-pass metabolism, resulting in increased serum concentrations of the drug. For this reason, consumption of grapefruit and its juice are not recommended when taking certain drugs.

Following are some common drug interactions:

- **Additive**: The combined effect of both drugs is equivalent to the sum of the effects of each drug taken alone.
- **Antagonism**: One drug blocks the action of another drug.
- **Synergism**: The combined effect of both drugs is greater than the sum of the effects of each drug taken alone.
- **Potentiation**: One drug increases the potency of the other drug. The combined effect is greater than the sum of the effects of each drug taken alone.

**Drug Names**

The manufacturer of each drug assigns a chemical name, a generic name, and a brand name (also called a trade name) to each drug **Table 2.1**. The chemical name describes the chemical structure of the drug. The generic name is often a shortened version of the chemical name. It describes the drug without any indication to the name of the
manufacturer. The brand name is the name under which the manufacturer markets the drug and is the name that is found on the product’s official label. The brand name is protected by a patent; only the company that holds the patent has the right to market that product under that name. Different manufacturers are allowed to market the same generic drug under different brand names, or by simply using the generic name.

### Regulation of Drugs

The manufacturing, distributing, and dispensing of drugs is highly regulated. Federal and state laws and regulatory bodies ensure that drugs that are dispensed are safe and effective, and that they are dispensed in a regulated and controlled manner.

#### Federal Laws

Federal laws and subsequent amendments were established to set the standards of practice for pharmacy and to protect the public from the unregulated manufacturing, distribution, and dispensing of unsafe drugs. Regulatory bodies assist in the administration and enforcement of these laws to ensure the safe use of drugs. These agencies follow written rules or established guidelines to carry out federal or state laws. (Refer to Chapter 1 for more on regulatory bodies.)

The Pure Food and Drug Act of 1906, the first federal law regulating drugs, prevented the manufacture, sale, or distribution of inaccurately labeled food and drugs across state lines. It also required that labels not contain false information of a drug’s strength and purity.

**The Pure Food and Drug Act required labels to have accurate information regarding a drug’s strength and purity.**

The Federal Food, Drug, and Cosmetic Act (FD&C), which created the Food and Drug Administration (FDA), was passed in 1938 because the Pure Food and Drug Act was not worded strictly enough. The FDA is the oldest consumer-protection agency in the country. This act required all drug manufacturers to file a New Drug Application (NDA) to provide evidence of a drug’s safety when used as directed on the label before the drug could be approved for marketing. It also gave the FDA the authority to approve or deny NDAs and to conduct inspections of manufacturing facilities to ensure compliance with regulations. The manufacturer also had to ensure the purity, packaging, and strength of the medication. Pharmaceutical manufacturers were also
required to conduct animal studies and human clinical trials and to submit the results of these studies before approval of a new drug would be granted. Pharmaceutical manufacturers were also required to include patient package inserts (PPIs) and directions to the consumer.

All manufacturers of new drugs must file a New Drug Application (NDA) with the FDA to be approved for marketing.

This act also clarified and extended the definitions of adulterated drugs (adulteration deals with the preparation and storage of a medication) and misbranded drugs (misbranding is making false or exaggerated claims that can mislead a consumer). The act also defined the United States Pharmacopeia and the National Formulary as official compendia.

Misbranding is making false or exaggerated claims that can mislead a consumer.

Adulteration deals with the preparation and storage of a medication.

In 1951, the Durham-Humphrey Amendment added more instructions for pharmaceutical manufacturers and established clear criteria for the classification of prescription and nonprescription over-the-counter medications. It prohibited the dispensing of legend prescription drugs without a prescription and required each prescription medication to bear the following legend: “Caution: Federal Law prohibits dispensing without a prescription.”

The Drug-Approval Process

To receive approval for marketing, the FDA has regulations for the way a manufacturer researches and develops a new drug. It requires that all manufacturers or drug sponsors submit a New Drug Application (NDA) to provide evidence of a drug’s safety and efficacy, gathered through an intensive testing process in animals and humans. (Before any new drug can be tested in humans, the manufacturer must receive approval from the FDA.) The NDA will contain the results of these tests, the proposed labeling for the new drug, a description of the chemical composition of the drug, pharmacokinetic studies, and details of the manufacturing and packaging process. If the FDA determines that the new drug is indeed safe and effective when used according to the package labeling, it will be approved for marketing.

First, the drug is tested in the laboratory to assess its activity, potency, selectivity, and toxicity in animals. It is also tested for safety. If it meets all necessary criteria, the manufacturer or sponsor will develop a plan for testing the drug in humans. This plan is submitted to the FDA in the form of an Investigational New Drug (IND) application. The FDA reviews the IND application for assurance that the trials do not place humans at risk of harm. If the IND application, sometimes called an INDA, is approved by the FDA, clinical studies in humans can begin.

The FDA also plays an important role in guiding the design and conduct of clinical
Clinical trials of new drugs can be divided into four phases:

- **Phase I** trials are generally conducted by the manufacturer or sponsor to evaluate safety in small numbers of healthy volunteers (between 20 and 80 people). These studies also determine a safe dosage range and identify side effects. The data obtained in phase I trials are used to design future clinical studies.

- **Phase II** trials are often conducted by academicians on larger groups of patients (up to 300 people) who have the illness or disease the drug is intended to treat. These studies assess drug activity, dosing requirements, and efficacy, as well as safety. If the results of these trials are promising, phase III trials are conducted.

- **Phase III** trials are often conducted in hundreds or thousands of patients to provide a broader assessment of safety and efficacy of the drug at various doses. During this phase, the new drug is often compared to drugs that are already available on the market for the same disease or illness. If the new drug being investigated is promising after phase III trials, a manufacturer can submit an NDA to the FDA.

- **Phase IV** studies, also referred to as post-marketing studies, continue to test and monitor the safety of the drug after it has been approved for marketing by the FDA. These studies also identify safety issues associated with widespread and long-term use.

The NDA will contain the results of phase I–III clinical trials. If the FDA determines that the new drug is indeed safe and effective when used according to the package labeling, it will be approved for marketing.

On average, it takes 12 years for a drug to be approved. However, the FDA has instituted reforms that shorten the review process for drugs used to treat serious or life-threatening diseases. Applications are reviewed based on priority. Drugs that have the greatest potential benefit and those that offer a significant medical advantage over existing therapies are given priority.

The approval of a drug by the FDA is based on the information that is available at that time. The FDA determines that a drug is safe for approval by weighing the potential benefits of the new drug or therapy against its potential risks. Sometimes, safety issues can only be uncovered when the drug is being used by millions of people over a period of time. Although the FDA has an extensive drug-review process, some drugs make it to the market only to be removed or relabeled due to safety concerns. **Figure 2.4**
Pregnancy

Drugs are not actively tested on pregnant women, but clinical data is gathered from pregnant women taking medications. The FDA classifies all drugs by placing them into one of five pregnancy categories. These categories determine the level of risk to the fetus. The pregnancy categories are as follows:

- **A**: No risk to the fetus
- **B**: No evidence of risk to human fetuses
- **C**: Risk to the fetus cannot be ruled out
- **D**: Definite risk to the fetus
- **X**: Contraindicated—do not use

Some healthcare professionals may not feel comfortable asking a woman if she is pregnant. Even so, pregnancy categories should be considered whenever medication is dispensed to a woman of childbearing age. Pharmacists often need to ask women if they are pregnant or plan to become pregnant.

Post-marketing Surveillance

Post-marketing surveillance (phase IV studies) is important because it ensures the continual safety and quality of drugs that are already available on the market. These
studies also ensure that drugs that have already been approved that endanger public health are promptly removed from the market. Healthcare professionals and patients can report serious adverse reactions to the FDA’s Medical Products Reporting Program, called MedWatch.

Anyone can report serious adverse reactions to the FDA’s MedWatch Program, which can be found at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

Black-Box Warning

Some drugs that are on the market have what is termed a black-box warning on the package insert. A black-box warning warns the prescriber that this drug has been associated with some problems, but still is effective when used as directed. It is required on medications and other products that carry a high risk potential to the patient.

Thousands of drugs have black-box warnings.

Important Drug Discoveries

Advances in healthcare have been largely attributed to the discovery of drugs. These drugs have allowed for increases in life expectancy and improvements in the quality of life. Following are just a few examples of drug discoveries that have changed the way we maintain our health.

The Smallpox Vaccine

In 1796, Dr. Edward Jenner observed that milkmaids who caught the cowpox virus did not get smallpox. He realized that inoculation with one disease (cowpox) resulted in immunity to another disease (smallpox). Exposure to cowpox produced antibodies that had cross-immunity with smallpox. An antibody is a complex molecule that is made in response to the presence of an antigen or foreign substance. This theory—that inoculation with a specific pathogen prior to infection may prevent occurrence of a disease—formed the basis of the discovery of subsequent vaccines. A vaccine, such as for hepatitis B, influenza, or polio, is a substance that is given to stimulate
the immune system to produce antibodies to build immunity against a particular disease. Because of the smallpox vaccine, smallpox has been eradicated worldwide.

**Radioactive Drugs**

In the early 1900s, Madame Marie Curie developed methods for the separation of radium from radioactive residues in enough quantities to allow for the careful study of its therapeutic properties. She promoted the use of radium to alleviate the suffering of soldiers during World War I. The discovery of radioactivity formed the basis of nuclear imaging for the diagnosis and treatment of disease. Without this discovery, there would be no CAT scans or magnetic resonance imagings (MRIs). There would also be no radiation therapy for diseases such as cancer.

**Insulin**

In the 1920s, Sir Frederick Banting and his assistant, Charles Best, discovered insulin. Building upon previous research that showed a link between the pancreas and diabetes, they isolated and purified a substance they termed insulin. Prior to the discovery of insulin, diabetics had high rates of complications and death. This discovery has improved the quality of life and life expectancy for diabetic patients.

**Penicillin**

In 1928, Dr. Alexander Fleming and his colleagues discovered penicillin, the first antibiotic. Fleming noticed that some of his bacterial Petri dishes were contaminated with a fungus and that there was a zone around an invading fungus where the bacteria did not seem to grow. He isolated this substance from the invading fungus, identified it as an organism from the *Penicillium* genus, and named it penicillin. The discovery of this antibiotic saved many lives during World War II. Penicillin was mass-produced in 1945 and brought to the commercial market.

The discovery of penicillin has changed the world of modern medicine by introducing useful antibiotics for the prevention and treatment of bacterial infections. Although there are many antibiotics available, continued research is needed to overcome bacterial resistance.

Penicillin causes the most drug allergies. Update the patient’s allergy history profile when receiving a prescription for an antibiotic. Patients with a penicillin allergy may also have cross-sensitivity to other antibiotics.

**The Polio Vaccine**

Polio is a disease that attacks the central nervous system. Once a patient is infected, there is no cure for polio.
Treatment of symptoms involved the use of an iron lung, which artificially maintained respiration until the patient could breathe by himself. In 1933, Jonas Salk created a vaccine containing inactivated viruses from three kinds of polio strains from animal cultures. Using the chemical formalin, he killed the whole virus.

A few years later, Albert Sabin developed an oral form of the polio vaccine that contained a live but attenuated form of the virus (that is, the infectious part of the virus was inactive). In 1963, the oral vaccine became available for widespread use. Because of the polio vaccine, polio has been eradicated worldwide.

It is important to reassure patients of the benefits of routine vaccinations.

**National Drug Code**

The Drug Listing Act of 1972 mandated the assignment of a unique drug code to each medication after it is approved by the FDA. This code is known as the National Drug Code (NDC). It consists of 10 or 11 characters, divided into three segments that identify the manufacturer, medication and dosage form, and size and type of packaging. The first four or five digits (labeler code) identify the manufacturer or distributor of the drug. (Note that a manufacturer can have multiple manufacturer codes.) The next three or four digits (product code) identify the product, strength, and dosage form of the medication. The last two digits (package code) identify the packaging size and type. The NDC can be used to verify that a medication is correct when it is dispensed. When processing medications through insurance, the NDC must match what is being billed.

When a manufacturer discontinues a drug product, its product code may be reassigned to another drug product five years after the expiration date of the discontinued product or, if there is no expiration date, five years after the last shipment of the discontinued product into commercial distribution. Reuse of product codes may occur, under the specified conditions, regardless of the NDC, product code, and package code configuration used.

**References Used in Pharmacy**

Drug information reference texts are important tools available to pharmacists and pharmacy technicians. Various healthcare professionals constantly ask pharmacists questions about the use of medications. Knowing which reference book to choose and how to access this information is necessary to provide reliable and accurate information, save time, and avoid frustration.

Most drug references have a section on how to use the text. Being familiar with using these references will enable the technician to find the correct information. This section discusses only the most common references found in a pharmacy setting. Most references available to pharmacists and technicians also come in a variety of formats: text and online.
With the Internet, you can have instant access to an enormous amount of information. But because information posted on the Internet is not regulated, you should be wary of its accuracy. Always ascertain the sponsor of the site. Determine the source of information and whether its credentials are reliable. Websites of pharmacy organizations, of pharmacy associations, and at universities are good places to look for information.

**Approved Drug Products with Therapeutic Equivalence Evaluations: The FDA Orange Book**

The FDA Orange Book contains a list of all drugs approved for use by the FDA. It can be used to determine whether a generic drug or a drug with a different brand name and the same chemical composition is **bioequivalent**, meaning it can be safely substituted for the brand-name product. It lists the drug products that the FDA considers to be therapeutically equivalent to other pharmaceutical products. It also contains information on discontinued drugs and orphan drugs. It is published annually, but the online version is updated more frequently.

**Drug Facts and Comparisons**

*Drug Facts and Comparisons* provides quick and easy access and comparative tables for drug comparison. It contains information on product availability, formulations, dosages, indications, mechanisms of action, adverse effects, drug interactions, and patient information. It is available as a loose-leaf binder with monthly updates, a hardcover, a pocket guide, and online.

**United States Pharmacopeia–National Formulary (USP-NF)**

This reference is a combined edition of the United States Pharmacopeia and the National Formulary. It establishes the criteria and standards for pharmaceutical manufacturing when submitting a new drug application to the FDA and quality control and legal standards for drugs in the United States. It contains standards for medicines, dosage forms, drug substances, medical devices, and dietary supplements. The standards originate from sponsors who provide draft standards and supporting data to either create new or revise existing monographs and general chapters. USP's scientific staff and volunteer experts review this input, conduct laboratory tests (if necessary), and forward the new or revised monograph or general chapter to Pharmacopeial Forum (PF) for public review and comment. The public process helps to refine and finalize USP standards for publication as official text in the USP–NF. USP's expert committees, composed of volunteer scientists elected on the basis of their knowledge and expertise, approve USP–NF standards. It is available in hardcover, online with a subscription, or on CD-ROM.

The FDA Orange Book is used to determine whether a generic drug is bioequivalent to a brand-name product. A patient brings in a prescription for Tegretol with the instructions “Brand Medically Necessary.” Given the situation, the technician should prepare to dispense Tegretol rather than carbamazepine, which is the generic form of Tegretol. If the “dispense as written” or “brand medically necessary” comments are not on this prescription, the pharmacy technician may prepare to dispense carbamazepine, which is determined to be bioequivalent to Tegretol, the brand-name product, per the FDA Orange Book.

*Drug Facts and Comparisons* provides comparative tables and information on drug formulations, dosages, indications, mechanisms of action, adverse effects, drug interactions, and patient information.

The USP-NF establishes standards for pharmaceutical manufacturing and quality control and legal standards for drugs.
The PDR contains pictures that can be helpful in identifying unknown drugs by color, shape, or markings. It also contains contact information for manufacturers that have paid a fee to be included in this book.

**Physician’s Desk Reference (PDR)**

This book is a compilation of the patient package inserts (PPIs) from pharmaceutical manufacturers that have paid a fee to be included into the reference. It contains pictures of these drugs and can be helpful in identifying unknown drugs by color, shape, or markings. The PDR also contains contact information for these manufacturers. This book is used primarily by physicians and is updated annually. It is available in hardcover, on CD-ROM, and online.

The Drug Topics Red Book contains average and wholesale pricing for drugs.

**Drug Topics Red Book**

This book contains information on the average and wholesale prices of drugs. It also has charts for easy and quick referencing that provide information such as which drugs should not be crushed. It includes tables with dosing instructions converted into Spanish. This book is available in paperback and CD-ROM.

AHFS DI is useful in a hospital setting because it contains information on parenteral drugs.

**American Hospital Formulary Service Drug Information (AHFS DI)**

This reference is used primarily in hospitals. It contains drug monographs (mainly for parenteral administration, which means any route other than into the gastrointestinal tract). **Monographs** provide drug information, including approved and off-label uses, dosages, indications, adverse effects, drug interactions, mechanisms of action, pharmacology, pharmacokinetics, and stability. It is available in hardcover, CD-ROM, and online.

**Handbook of Nonprescription Drugs**

This reference is published by the American Pharmacists Association. It provides information and dosing information on nonprescription medications (OTCs), nutritional supplements, medical foods, and homeopathic medications. It is available in hardcover or as a textbook that can be downloaded.

Remington’s contains information on drug stability and compatibility.

**Remington’s Pharmaceutical Sciences: The Science and Practice of Pharmacy**

This reference contains particularly useful information on drug stability and compatibility. It also contains information on medication safety, immunology, disease-state management, specialization in pharmacy practice, and professional communication. It is available in hardcover with a companion CD-ROM.
**Trissel's Handbook on Injectable Drugs**
This reference is used in the hospital setting for information on parenteral agents, including administration, stability, and compatibility with other parenteral solutions and drugs. It is available in hardcover, CD-ROM, and via PDA.

**Goodman & Gilman’s The Pharmacological Basis of Therapeutics**
This reference contains information on pharmacokinetics and pharmacodynamics, membrane transporters and drug response, pharmacogenetics, and principles of therapeutics in all systems of the body.

**The Lawrence Review of Natural Products**
This reference is published by Facts and Comparisons, a division of Wolters Kluwer, and contains scientific information on herbal medications.

**Martindale’s The Complete Drug Reference**
This reference provides information on drugs in clinical use, investigational and herbal drugs, diagnostic agents, pesticides, coloring agents, preservatives, and noxious substances used worldwide. It is available in hardcover or CD-ROM.
**Chapter Summary**

- Drugs have allowed for increases in life expectancy and improvements in the quality of life.
- Pharmacology is the study of drugs and their actions on the body.
- Drugs are derived from sources such as animals, plants, minerals, chemicals, and recombinant DNA technology.
- The FDA sets regulations that require manufacturers to provide evidence of a drug’s safety and efficacy before it can be approved for marketing.
- Laws were established to set the standards of practice for pharmacy and to protect the public from the unregulated manufacturing, distribution, and dispensing of unsafe drugs.
- Regulatory bodies follow written rules or established guidelines to carry out federal or state laws.
- A drug’s active ingredient is responsible for the drug’s therapeutic effect. An inert ingredient, also called an inactive ingredient, has little or no therapeutic value.
- Drugs that are derived from chemicals can be further categorized as synthetic, synthesized, or semi-synthetic.
- Drugs can be categorized as therapeutic, pharmacodynamic, diagnostic, prophylactic, or diagnostic, depending on their use.
- Pharmacokinetics is the study of the effects the body has on a drug. The processes can be divided into absorption, distribution, metabolism, and elimination.
- Some drugs exert their action by binding to receptors on or within the body to mimic or block the action of chemical messengers, while others compete with another drug for its receptor.
- One drug can exert an effect on another drug. Food, alcohol, and nicotine can also interact with prescription and over-the-counter drugs.
- Drugs have therapeutic effects, adverse reactions, and side effects.
- Drug information reference texts are important tools available to pharmacists and pharmacy technicians.

**Learning Assessment Questions**

1. Which of the following books is created from patient package inserts (PPIs) from the manufacturers?
   - A. Drug Topics Red Book
   - B. USP-NF
   - C. PDR
   - D. Drug Facts and Comparisons

2. Which reference book is the best source for quickly comparing several medications?
   - A. Drug Facts and Comparisons
   - B. Handbook of Nonprescription Drugs
   - C. USP DI
   - D. PDR

3. Which reference book is the best source for finding information on the average and wholesale price of a drug?
   - A. Drug Topics Red Book
   - B. Handbook of Nonprescription Drugs
   - C. USP DI
   - D. Drug Facts and Comparisons

4. An active ingredient exerts which of the following?
   - A. The therapeutic effect
   - B. The placebo effect
   - C. The inert effect
   - D. No physiologic effect

5. Which of the following is a substance that is introduced into the body to produce immunity to disease?
   - A. An inert ingredient
   - B. A vaccine
   - C. An antibody
   - D. A radioactive isotope

6. A therapeutic agent does which of the following?
   - A. Maintains health
   - B. Relieves symptoms
   - C. Stops or delays the disease
   - D. All of the above
7. Iodine-131 (\(^{131}\text{I}\)) is an example of which of the following?
   A. Prophylactic agent
   B. Destructive agent
   C. Pharmacodynamic agent
   D. Diagnostic agent

8. Clinical trials can be divided into how many phases?
   A. Two phases
   B. Five phases
   C. Four phases
   D. Six phases

9. What are warning statements on the patient package insert that indicate a serious or even-life threatening adverse reaction from a drug called?
   A. Black-box warnings
   B. Indications for use
   C. Side effects
   D. Patient medication guides

10. Which of the following references would be helpful in determining if a generic drug is bioequivalent to a brand name drug?
    A. The FDA Orange Book
    B. PDR
    C. USP-NF
    D. Patient medication guides

11. Banting and Best are known for their discovery of what?
    A. Radiopharmaceuticals
    B. Insulin
    C. Polio vaccine
    D. Digoxin

12. The National Drug Code (NDC) does not identify which of the following?
    A. Product manufacturer
    B. Package size
    C. Package type
    D. Pregnancy category

13. A drug that has a pregnancy category X rating means it is which of the following?
    A. Safe for use only in the first-trimester
    B. Safe for use only in the second-trimester
    C. Safe for use only in the third-trimester
    D. Contraindicated for use in pregnancy

14. What is the study of how the body affects a drug over time?
    A. Pharmacology
    B. Pharmacokinetics
    C. Biology
    D. Pharmacotherapeutics

15. What is the most important rate-limiting factor for distribution of a drug?
    A. Blood flow
    B. Solubility
    C. Half-life
    D. Bioavailability

16. Pharmacokinetics is the study of which parameters of a drug?
    A. Absorption
    B. Distribution
    C. Elimination
    D. All of the above

17. Half-life is the time required for which of the following?
    A. 50% of the drug to be eliminated from the body
    B. 25% of the drug to be eliminated from the body
    C. 100% of the drug to be eliminated from the body
    D. 75% of the drug to be eliminated from the body

18. A severe allergic reaction is called an __________.
    A. Antigen
    B. Allergen
    C. Anaphylactic reaction
    D. Addiction
19. Healthcare professionals and patients can report serious adverse reactions to the FDA's Medical Products Reporting Program, also called which of the following?
A. MedReporting
B. MedWatch
C. FDA hotline
D. TIPs

20. The NDA will contain the results of which of the following?
A. Phase I–III clinical trials
B. Phase IV trials
C. Phase 0 trials
D. Phase 6 trials