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# Pharmacology

## EXAMINATION & BOARD REVIEW

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# Katzung & Trevor's Pharmacology Examination & Board Review

Eleventh Edition


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**Katzung & Trevor's Pharmacology: Examination & Board Review, Eleventh Edition**



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# Preface

This book is designed to help students review pharmacology and to prepare for both regular course examinations and board examinations. The eleventh edition has been revised to make such preparation as active and efficient as possible. As with earlier editions, rigorous standards of accuracy and currency have been maintained in keeping with the book's status as the companion to the *Basic & Clinical Pharmacology* textbook. This review book divides pharmacology into the topics used in most courses and textbooks. Major introductory chapters (eg, autonomic pharmacology and CNS pharmacology) are included for integration with relevant physiology and biochemistry. The chapter-based approach facilitates use of this book in conjunction with course notes or a larger text. We recommend several strategies to make reviewing more effective (**Appendix I** contains a summary of learning and test-taking strategies that most students find useful).

First, each chapter has a short discussion of the major concepts that underlie its basic principles or the specific drug group, accompanied by explanatory figures and tables. The figures are in full color and some are new to this edition. Students are advised to read the text thoroughly before they attempt to answer the study questions at the end of each chapter. If a concept is found to be difficult or confusing, the student is advised to consult a regular textbook such as *Basic & Clinical Pharmacology*, 13th edition.

Second, each drug-oriented chapter opens with an "**Overview**" that organizes the group of drugs visually in diagrammatic form. We recommend that students practice reproducing the overview diagram from memory.

Third, a list of **High Yield Terms to Learn** and their definitions is near the front of most chapters. Make sure that you are able to define those terms.

Fourth, many chapters include a "**Skill Keeper**" question that prompts the student to review previous material and to see links between related topics. We suggest that students try to answer Skill Keeper questions on their own before checking the answers that are provided at the end of the chapter.

Fifth, each of the sixty-one chapters contains up to ten **sample questions** followed by a set of answers with explanations. For most effective learning, you should take each set of sample questions as if it were a real examination. After you have answered every question, work through the answers. When you are analyzing the answers, make sure that you understand why each choice is either correct or incorrect.

Sixth, each chapter includes a **Checklist** of focused tasks that you should be able to do once you have finished the chapter.

Seventh, most chapters end with a **Summary Table** that lists the most important drugs and includes key information concerning their mechanisms of action, effects, clinical uses, pharmacokinetics, drug interactions, and toxicities.

Eighth, when preparing for a comprehensive examination, you should review the strategies described in **Appendix I** if you have not already done so. Then review the list of drugs in **Appendix II: Key Words for Key Drugs**. Students are also advised to check this appendix as they work through the chapters so they can begin to identify drugs out of the context of a chapter that reviews a restricted set of drugs.

Ninth, after you have worked your way through most or all of the chapters and have a good grasp of the Key Drugs, you should take the comprehensive examinations, each of 100 questions, presented in **Appendices III and IV**. These examinations are followed by a list of answers, each with a short explanation or rationale underlying the correct choice and the numbers of the chapters in which more information can be found if needed. We recommend that you take an entire examination or a block of questions as if it were a real examination: commit to answers for the whole set before you check the answers. As you work through the answers, make sure that you understand why each answer is either correct or incorrect. If you need to, return to the relevant chapters(s) to review the text that covers key concepts and facts that form the basis for the question.

We recommend that this book be used with a regular text. *Basic & Clinical Pharmacology*, 13th edition (McGraw-Hill, 2015), follows the chapter sequence used here. However, this review book is designed to complement any standard medical pharmacology text. The student who completes and understands *Pharmacology: Examination & Board Review* will greatly improve his or her performance and will have an excellent command of pharmacology.

Because it was developed in parallel with the textbook *Basic & Clinical Pharmacology*, this review book represents the authors' interpretations of chapters written by contributors to that text. We are grateful to those contributors, to our other

faculty colleagues, and to our students, who have taught us most of what we know about teaching.

We very much appreciate the invaluable contributions to this text afforded by the editorial team of Karen Edmonson, Rachel D'Annucci Henriquez, Shruti Awasthi, Harriet Lebowitz, and Michael Weitz. The authors also thank Katharine Katzung for her excellent proofreading contributions to this edition.

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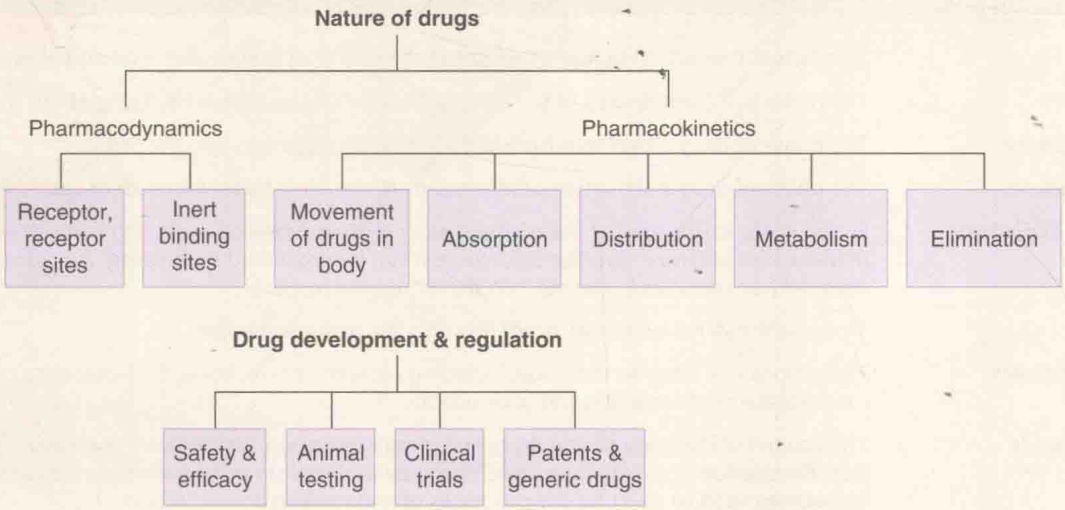
# Contents

# PART I BASIC PRINCIPLES

CHAPTER 1

# Introduction

**Pharmacology** is the body of knowledge concerned with the action of chemicals on biologic systems. **Medical pharmacology** is the area of pharmacology concerned with the use of chemicals in the prevention, diagnosis, and treatment of disease, especially in humans. **Toxicology** is the area of pharmacology concerned with the undesirable effects of chemicals on biologic systems. **Pharmacokinetics** describes the effects of the body on drugs, eg, absorption, excretion, etc. **Pharmacodynamics** denotes the actions of the drug on the body, such as mechanism of action and therapeutic and toxic effects. The first part of this chapter reviews the basic principles of pharmacokinetics and pharmacodynamics that will be applied in subsequent chapters. The second part of the chapter reviews the development and regulation of drugs.



# I. THE NATURE OF DRUGS

Drugs in common use include inorganic ions, nonpeptide organic molecules, small peptides and proteins, nucleic acids, lipids, and carbohydrates. Some are found in plants or animals, and others are partially or completely synthetic. Many drugs found in nature are **alkaloids,** which are molecules that have a basic pH in solution, usually as a result of amine groups in their structure. Many biologically important endogenous molecules and exogenous drugs are optically active; that is, they contain one or more asymmetric centers and can exist as enantiomers. The enantiomers of optically active drugs usually differ, sometimes more than 1000-fold, in their affinity for biologic receptor sites. Furthermore, such enantiomers may be metabolized at different rates in the body, with important clinical consequences.

### A. Size and Molecular Weight

Drugs vary in size from molecular weight (MW) 7 (lithium) to over MW 50,000 (thrombolytic enzymes, antibodies, other proteins). Most drugs, however, have MWs between 100 and 1000. Drugs smaller than MW 100 are rarely sufficiently selective in their actions, whereas drugs much larger than MW 1000 are often poorly absorbed and poorly distributed in the body. Most protein drugs ("**biologicals**") are commercially produced in cell, bacteria, or yeast cultures using recombinant DNA technology.

### B. Drug-Receptor Bonds

Drugs bind to receptors with a variety of chemical bonds. These include very strong covalent bonds (which usually result in irreversible action), somewhat weaker electrostatic bonds (eg, between a cation and an anion), and much weaker interactions (eg, hydrogen, van der Waals, and hydrophobic bonds).

# PHARMACODYNAMIC PRINCIPLES

### A. Receptors

Drug actions are mediated through the effects of drug ligand molecules on drug **receptors** in the body. Most receptors are large regulatory molecules that influence important biochemical processes (eg, enzymes involved in glucose metabolism) or physiologic processes (eg, ion channel receptors, neurotransmitter reuptake transporters, and ion transporters).

If drug-receptor binding results in activation of the receptor, the drug is termed an **agonist**; if inhibition results, the drug is considered an **antagonist**. Some drugs mimic *agonist* molecules by *inhibiting* metabolic enzymes, eg, acetylcholinesterase inhibitors. As suggested in Figure 1–1, a receptor molecule may have several binding sites. Quantitation of the effects of drug-receptor binding as a function of dose yields **dose-response curves** that provide information about the nature of the drug-receptor interaction. Dose-response phenomena are discussed in more detail in Chapter 2. A few drugs are enzymes themselves (eg, thrombolytic enzymes, pancreatic enzymes). These drugs do not act on endogenous receptors but on substrate molecules.

### B. Receptor and Inert Binding Sites

Because most ligand molecules are much smaller than their receptor molecules (discussed in the text that follows), specific regions of receptor molecules provide the local areas responsible for drug binding. Such areas are termed **receptor sites** or **recognition sites**. In addition, drugs bind to some nonregulatory molecules in the body without producing a discernible effect. Such binding sites are termed **inert binding sites**. In some compartments of the

## High-Yield Terms to Learn

| | |
|---|---|
| **Drugs** | Substances that act on biologic systems at the chemical (molecular) level and alter their functions |
| **Drug receptors** | The molecular components of the body with which drugs interact to bring about their effects |
| **Distribution phase** | The phase of drug movement from the site of administration into the tissues |
| **Elimination phase** | The phase of drug inactivation or removal from the body by metabolism or excretion |
| **Endocytosis, exocytosis** | Endocytosis: Absorption of material across a cell membrane by enclosing it in cell membrane material and pulling it into the cell, where it can be processed or released. Exocytosis: Expulsion of material from vesicles in the cell into the extracellular space |
| **Permeation** | Movement of a molecule (eg, drug) through the biologic medium |
| **Pharmacodynamics** | The actions of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic actions |
| **Pharmacokinetics** | The actions of the body on the drug, including absorption, distribution, metabolism, and elimination. Elimination of a drug may be achieved by metabolism or by excretion. *Biodisposition* is a term sometimes used to describe the processes of metabolism and excretion |
| **Transporter** | A specialized molecule, usually a protein, that carries a drug, transmitter, or other molecule across a membrane in which it is not permeable, eg, $Na^+/K^+$ ATPase, serotonin reuptake transporter, etc |
| **Mutagenic** | An effect on the inheritable characteristics of a cell or organism—a mutation in the DNA; usually tested in microorganisms with the Ames test |
| **Carcinogenic** | An effect of inducing malignant characteristics |
| **Teratogenic** | An effect on the in utero development of an organism resulting in abnormal structure or function; not generally heritable |

## High-Yield Terms to Learn (*continued*)

| | |
|---|---|
| **Placebo** | An inactive "dummy" medication made up to resemble the active investigational formulation as much as possible but lacking therapeutic effect |
| **Single-blind study** | A clinical trial in which the investigators—but not the subjects—know which subjects are receiving active drug and which are receiving placebos |
| **Double-blind study** | A clinical trial in which neither the subjects nor the investigators know which subjects are receiving placebos; the code is held by a third party |
| **IND** | Investigational New Drug Exemption; an application for FDA approval to carry out new drug trials in humans; requires animal data |
| **NDA** | New Drug Application; seeks FDA approval to market a new drug for ordinary clinical use; requires data from clinical trials as well as preclinical (animal) data |
| **Phases 1, 2, and 3 of clinical trials** | Three parts of a clinical trial that are usually carried out before submitting an NDA to the FDA |
| **Positive control** | A known standard therapy, to be used along with placebo, to evaluate the superiority or inferiority of a new drug in relation to the other drugs available |
| **Orphan drugs** | Drugs developed for diseases in which the expected number of patients is small. Some countries bestow certain commercial advantages on companies that develop drugs for uncommon diseases |

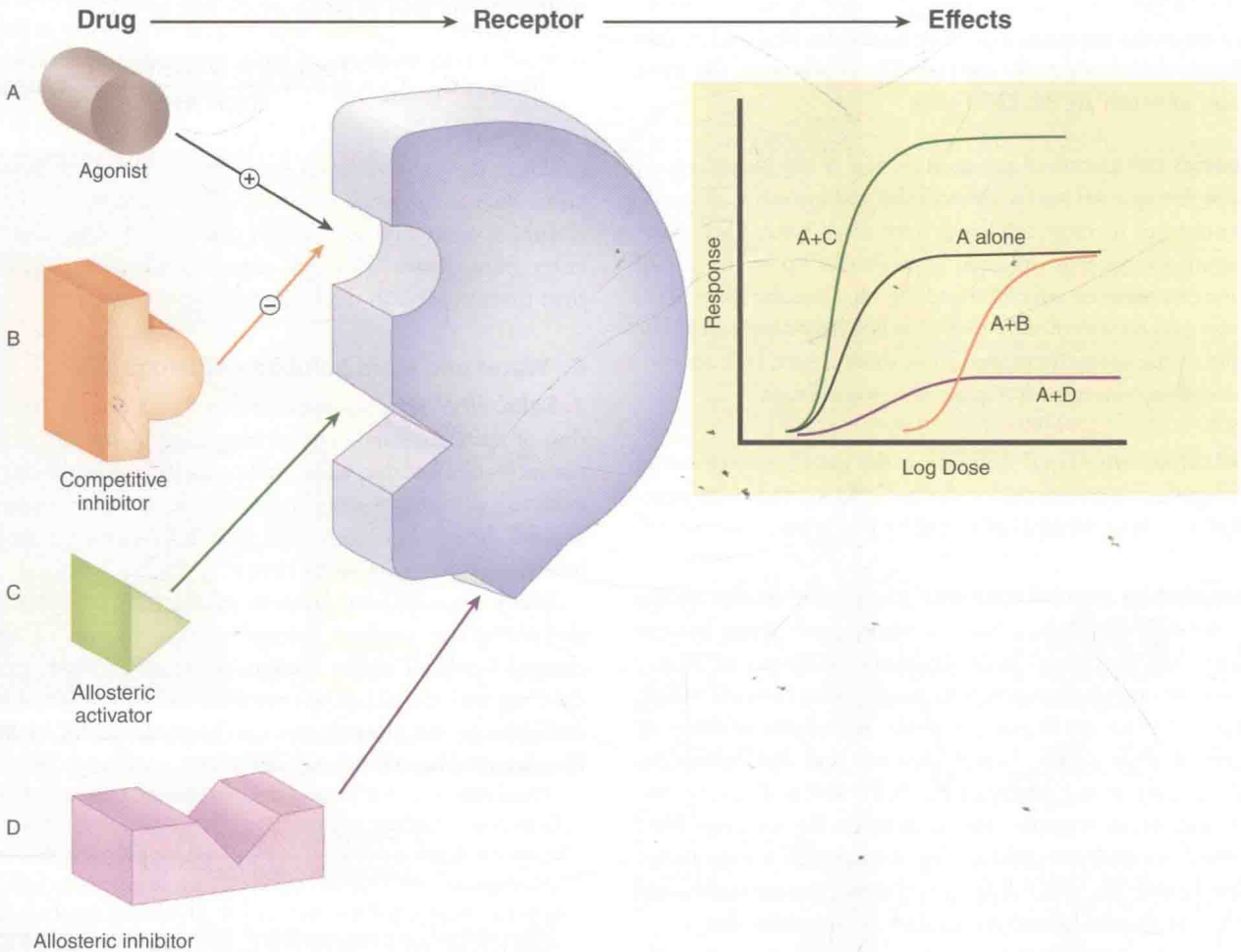



**FIGURE 1–1** Potential mechanisms of drug interaction with a receptor. Possible effects resulting from these interactions are diagrammed in the dose-response curves at the right. The traditional agonist (drug A)-receptor binding process results in the dose-response curve denoted "A alone." B is a pharmacologic antagonist drug that competes with the agonist for binding to the receptor site. The dose-response curve produced by increasing doses of A in the presence of a fixed concentration of B is indicated by the curve "A+B." Drugs C and D act at different sites on the receptor molecule; they are *allosteric* activators or inhibitors. Note that allosteric inhibitors do not compete with the agonist drug for binding to the receptor, and they may bind reversibly or irreversibly. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 1–3.)

body (eg, the plasma), inert binding sites play an important role in buffering the concentration of a drug because bound drug does not contribute directly to the concentration gradient that drives diffusion. **Albumin** and **orosomucoid** ($\alpha_1$-acid glycoprotein) are two important plasma proteins with significant drug-binding capacity.

## PHARMACOKINETIC PRINCIPLES

To produce useful therapeutic effects, most drugs must be absorbed, distributed, and eliminated. Pharmacokinetic principles make rational dosing possible by quantifying these processes.

### The Movement of Drugs in the Body

To reach its receptors and bring about a biologic effect, a drug molecule (eg, a benzodiazepine sedative) must travel from the site of administration (eg, the gastrointestinal tract) to the site of action (eg, the brain).

#### A. Permeation

Permeation is the movement of drug molecules into and within the biologic environment. It involves several processes, the most important of which are discussed next.

***1. Aqueous diffusion***—Aqueous diffusion is the movement of molecules through the watery extracellular and intracellular spaces. The membranes of most capillaries have small water-filled pores that permit the aqueous diffusion of molecules up to the size of small proteins between the blood and the extravascular space. This is a passive process governed by Fick's law (see later discussion). The capillaries in the brain, testes, and some other organs lack aqueous pores, and these tissues are less exposed to some drugs.

***2. Lipid diffusion***—Lipid diffusion is the passive movement of molecules through membranes and other lipid barriers. Like aqueous diffusion, this process is governed by Fick's law.

***3. Transport by special carriers***—Drugs that do not readily diffuse through membranes may be transported across barriers by mechanisms that carry similar endogenous substances. A very large number of such transporter molecules have been identified, and many of these are important in the movement of drugs or as targets of drug action. Unlike aqueous and lipid diffusion, carrier transport is not governed by Fick's law and is capacity-limited. Important examples are transporters for ions (eg, $Na^+/K^+$ ATPase), for neurotransmitters (eg, transporters for serotonin, norepinephrine), for metabolites (eg, glucose, amino acids), and for foreign molecules **(xenobiotics)** such as anticancer drugs.

After release, amine neurotransmitters (dopamine, norepinephrine, and serotonin) and some other transmitters are recycled into nerve endings by transport molecules. Selective inhibitors for these transporters often have clinical value; for example, several antidepressants act by inhibiting the transport of amine neurotransmitters back into the nerve endings from which they have been released.

***4. Endocytosis***—Endocytosis occurs through binding of the transported molecule to specialized components (receptors) on cell membranes, with subsequent internalization by infolding of that area of the membrane. The contents of the resulting intracellular vesicle are subsequently released into the cytoplasm of the cell. Endocytosis permits very large or very lipid-insoluble chemicals to enter cells. For example, large molecules such as proteins may cross cell membranes by endocytosis. Smaller, polar substances such as vitamin $B_{12}$ and iron combine with special proteins ($B_{12}$ with intrinsic factor and iron with transferrin), and the complexes enter cells by this mechanism. Because the substance to be transported must combine with a membrane receptor, endocytotic transport can be quite selective. **Exocytosis** is the reverse process, that is, the expulsion of material that is membrane-encapsulated inside the cell from the cell. Most neurotransmitters are released by exocytosis.

#### B. Fick's Law of Diffusion

Fick's law predicts the rate of movement of molecules across a barrier. The concentration gradient ($C_1 - C_2$) and permeability coefficient for the drug and the area and thickness of the barrier membrane are used to compute the rate as follows:

$$\text{Rate} = C_1 - C_2 \times \frac{\text{Permeability coefficient}}{\text{Thickness}} \times \text{Area} \qquad (1)$$

Thus, drug absorption is faster from organs with large surface areas, such as the small intestine, than from organs with smaller absorbing areas (the stomach). Furthermore, drug absorption is faster from organs with thin membrane barriers (eg, the lung) than from those with thick barriers (eg, the skin).

#### C. Water and Lipid Solubility of Drugs

***1. Solubility***—The aqueous solubility of a drug is often a function of the electrostatic charge (degree of ionization, polarity) of the molecule, because water molecules behave as dipoles and are attracted to charged drug molecules, forming an aqueous shell around them. Conversely, the lipid solubility of a molecule is inversely proportional to its charge.

Many drugs are weak bases or weak acids. For such molecules, the *pH of the medium* determines the fraction of molecules charged (ionized) versus uncharged (nonionized). If the $pK_a$ of the drug and the pH of the medium are known, the fraction of molecules in the ionized state can be predicted by means of the **Henderson-Hasselbalch** equation:

$$\log\left(\frac{\text{Protonated form}}{\text{Unprotonated form}}\right) = pK_a - pH \qquad (2)$$

"Protonated" means *associated with a proton* (a hydrogen ion); this form of the equation applies to both acids and bases.

***2. Ionization of weak acids and bases***—Weak bases are ionized—and therefore more polar and more water-soluble—when they are protonated. Weak acids are not ionized—and so are less water-soluble—when they are protonated.

The following equations summarize these points:

$$\underset{\text{protonated weak base (charged, more water-soluble)}}{RNH_3^+} \rightleftharpoons \underset{\text{Unprotonated weak base (uncharged, more lipid-soluble)}}{RNH_2} + \underset{\text{proton}}{H^+} \quad (3)$$

$$\underset{\text{protonated weak acid (uncharged, more lipid-soluble)}}{RCOOH} \rightleftharpoons \underset{\text{Unprotonated weak acid (charged, more water-soluble)}}{RCOO^-} + \underset{\text{proton}}{H^+} \quad (4)$$

The Henderson-Hasselbalch relationship is clinically important when it is necessary to estimate or alter the partition of drugs between compartments of differing pH. For example, most drugs are freely filtered at the glomerulus, but lipid-soluble drugs can be rapidly reabsorbed from the tubular urine. If a patient takes an overdose of a weak acid drug, for example, aspirin, the excretion of this drug is faster in alkaline urine. This is because a drug that is a weak acid dissociates to its charged, polar form in alkaline solution, and this form cannot readily diffuse from the renal tubule back into the blood; that is, the drug is trapped in the tubule. Conversely, excretion of a weak base (eg, pyrimethamine, amphetamine) is faster in acidic urine (Figure 1–2).

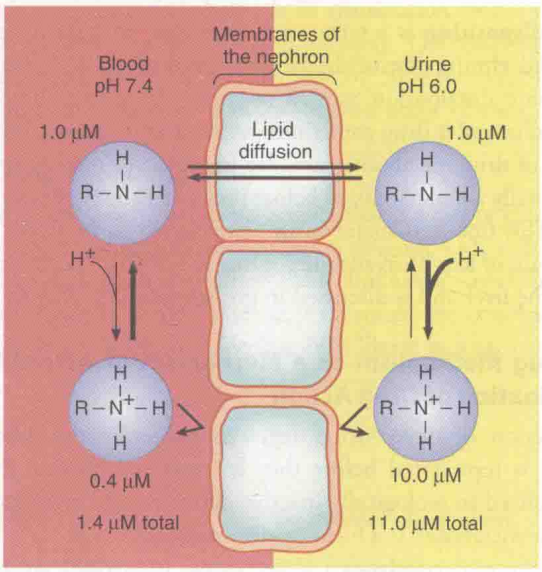



**FIGURE 1–2** The Henderson-Hasselbalch principle applied to drug excretion in the urine. Because the nonionized form diffuses readily across the lipid barriers of the nephron, this form may reach equal concentrations in the blood and urine; in contrast, the ionized form does not diffuse as readily. Protonation occurs within the blood and the urine according to the Henderson-Hasselbalch equation. Pyrimethamine, a weak base of $pK_a$ 7.0, is used in this example. At blood pH, only 0.4 μmol of the protonated species will be present for each 1.0 μmol of the unprotonated form. The total concentration in the blood will thus be 1.4 μmol/L if the concentration of the unprotonated form is 1.0 μmol/L. In the urine at pH 6.0, 10 μmol of the nondiffusible ionized form will be present for each 1.0 μmol of the unprotonated, diffusible form. Therefore, the total urine concentration (11 μmol/L) may be almost 8 times higher than the blood concentration.

## Absorption of Drugs

### A. Routes of Administration

Drugs usually enter the body at sites remote from the target tissue or organ and thus require transport by the circulation to the intended site of action. To enter the bloodstream, a drug must be absorbed from its site of administration (unless the drug has been injected directly into the vascular compartment). The rate and efficiency of absorption differ depending on a drug's route of administration. In fact, for some drugs, the amount absorbed may be only a small fraction of the dose administered when given by certain routes. The amount absorbed into the systemic circulation divided by the amount of drug administered constitutes its **bioavailability** by that route. Common routes of administration and some of their features are listed in Table 1–1.

**TABLE 1–1 Common routes of drug administration.**

| | |
|---|---|
| Oral (swallowed) | Offers maximal convenience; absorption is often slower. Subject to the **first-pass effect**, in which a significant amount of the agent is metabolized in the gut wall, portal circulation, and liver before it reaches the systemic circulation |
| Buccal and sublingual (not swallowed) | Direct absorption into the systemic venous circulation, bypassing the hepatic portal circuit and first-pass metabolism |
| Intravenous | Instantaneous and complete absorption (by definition, bioavailability is 100%). Potentially more dangerous |
| Intramuscular | Often faster and more complete (higher bioavailability) than with oral administration. Large volumes may be given if the drug is not too irritating. First-pass metabolism is avoided |
| Subcutaneous | Slower absorption than the intramuscular route. First-pass metabolism is avoided. |
| Rectal (suppository) | The rectal route offers partial avoidance of the first-pass effect. Larger amounts of drug and drugs with unpleasant tastes are better administered rectally than by the buccal or sublingual routes |
| Inhalation | Route offers delivery closest to respiratory tissues (eg, for asthma). Usually very rapid absorption (eg, for anesthetic gases) |
| Topical | The topical route includes application to the skin or to the mucous membrane of the eye, ear, nose, throat, airway, or vagina for *local* effect |
| Transdermal | The transdermal route involves application to the skin for *systemic* effect. Absorption usually occurs very slowly (because of the thickness of the skin), but the first-pass effect is avoided |

### B. Blood Flow

Blood flow influences absorption from intramuscular and subcutaneous sites and, in shock, from the gastrointestinal tract as well. High blood flow maintains a high drug depot-to-blood concentration gradient and thus facilitates absorption.

### C. Concentration

The concentration of drug at the site of administration is important in determining the concentration gradient relative to the blood as noted previously. As indicated by Fick's law (Equation 1), the concentration gradient is a major determinant of the rate of absorption. Drug concentration in the vehicle is particularly important in the absorption of drugs applied topically.

## Distribution of Drugs

### A. Determinants of Distribution

***1. Size of the organ***—The size of the organ determines the concentration gradient between blood and the organ. For example, skeletal muscle can take up a large *amount* of drug because the *concentration* in the muscle tissue remains low (and the blood-tissue gradient high) even after relatively large amounts of drug have been transferred; this occurs because skeletal muscle is a very large organ. In contrast, because the brain is smaller, distribution of a smaller amount of drug into it will raise the tissue concentration and reduce to zero the blood-tissue concentration gradient, preventing further uptake of drug unless it is actively transported.

***2. Blood flow***—Blood flow to the tissue is an important determinant of the *rate of uptake* of drug, although blood flow may not affect the *amount* of drug in the tissue at equilibrium. As a result, well-perfused tissues (eg, brain, heart, kidneys, and splanchnic organs) usually achieve high tissue concentrations sooner than poorly perfused tissues (eg, fat, bone).

***3. Solubility***—The solubility of a drug in tissue influences the concentration of the drug in the extracellular fluid surrounding the blood vessels. If the drug is very soluble in the cells, the concentration in the perivascular extracellular space will be lower and diffusion from the vessel into the extravascular tissue space will be facilitated. For example, some organs (such as the brain) have a high lipid content and thus dissolve a high concentration of lipid-soluble agents rapidly.

***4. Binding***—Binding of a drug to macromolecules in the blood or a tissue compartment tends to increase the drug's concentration in that compartment. For example, warfarin is strongly bound to plasma albumin, which restricts warfarin's diffusion out of the vascular compartment. Conversely, chloroquine is strongly bound to extravascular tissue proteins, which results in a marked reduction in the plasma concentration of chloroquine.

### B. Apparent Volume of Distribution and Physical Volumes

The apparent volume of distribution ($V_d$) is an important pharmacokinetic parameter that reflects the above determinants of the distribution of a drug in the body. $V_d$ relates the amount of drug in the body to the concentration in the plasma (Chapter 3). In contrast, the physical volumes of various body compartments are less important in pharmacokinetics (Table 1–2). However, obesity alters the ratios of total body water to body weight and fat to total body weight, and this may be important when using highly lipid-soluble drugs. A simple approximate rule for the aqueous compartments of the normal body is as follows: 40% of total body weight is intracellular water and 20% is extracellular water; thus, water constitutes approximately 60% of body weight.

**TABLE 1–2 Average values for some physical volumes within the adult human body.**

| Compartment | Volume (L/kg body weight) |
|---|---|
| Plasma | 0.04 |
| Blood | 0.08 |
| Extracellular water | 0.2 |
| Total body water | 0.6 |
| Fat | 0.2–0.35 |

## Metabolism of Drugs

Drug **disposition** is a term sometimes used to refer to metabolism and elimination of drugs. Some authorities use disposition to denote distribution as well as metabolism and elimination. Metabolism of a drug sometimes terminates its action, but other effects of drug metabolism are also important. Some drugs when given orally are metabolized before they enter the systemic circulation. This first-pass metabolism was referred to in Table 1–1 as one cause of low bioavailability. Drug metabolism occurs primarily in the liver and is discussed in greater detail in Chapter 4.

### A. Drug Metabolism as a Mechanism of Activation or Termination of Drug Action

The action of many drugs (eg, sympathomimetics, phenothiazines) is terminated before they are excreted because they are metabolized to biologically inactive derivatives. Conversion to an inactive metabolite is a form of **elimination**.

In contrast, **prodrugs** (eg, levodopa, minoxidil) are inactive as administered and must be metabolized in the body to become active. Many drugs are active as administered and have active metabolites as well (eg, morphine, some benzodiazepines).

### B. Drug Elimination Without Metabolism

Some drugs (eg, lithium, many others) are not modified by the body; they continue to act until they are excreted.

## Elimination of Drugs

Along with the dosage, the rate of elimination following the last dose (disappearance of the active molecules from the site of action, the bloodstream, and the body) determines the duration of action

for many drugs. Therefore, knowledge of the time course of concentration in plasma is important in predicting the intensity and duration of effect for most drugs. ***Note:*** Drug *elimination* is not the same as drug *excretion:* A drug may be eliminated by metabolism long before the modified molecules are excreted from the body. For most drugs and their metabolites, excretion is primarily by way of the kidney. Volatile anesthetic gases, a major exception, are excreted primarily by the lungs. For drugs with active metabolites (eg, diazepam), elimination of the parent molecule by metabolism is not synonymous with termination of action. For drugs that are not metabolized, excretion is the mode of elimination. A small number of drugs combine irreversibly with their receptors, so that disappearance from the bloodstream is not equivalent to cessation of drug action. These drugs may have a very prolonged action. For example, phenoxybenzamine, an irreversible inhibitor of α adrenoceptors, is eliminated from the bloodstream in less than 1 h after administration. The drug's action, however, lasts for 48 h, the time required for turnover of the receptors.

### A. First-Order Elimination

The term *first-order elimination* indicates that the rate of elimination is proportional to the concentration (ie, the higher the concentration, the greater the amount of drug eliminated per unit time). The result is that the drug's concentration in plasma decreases exponentially with time (Figure 1–3, left). Drugs with first-order elimination have a characteristic **half-life of elimination** that is constant regardless of the amount of drug in the body. The concentration of such a drug in the blood will decrease by 50% for every half-life. Most drugs in clinical use demonstrate first-order kinetics.

### B. Zero-Order Elimination

The term *zero-order elimination* implies that the rate of elimination is constant regardless of concentration (Figure 1–3, right). This occurs with drugs that saturate their elimination mechanisms at concentrations of clinical interest. As a result, the concentrations of these drugs in plasma decrease in a linear fashion over time. Such drugs do not have a constant half-life. This is typical of ethanol (over most of its plasma concentration range) and of phenytoin and aspirin at high therapeutic or toxic concentrations.

## Pharmacokinetic Models

### A. Multicompartment Distribution

After absorption into the circulation, many drugs undergo an early distribution phase followed by a slower elimination phase. Mathematically, this behavior can be simulated by means of a "two-compartment model" as shown in Figure 1–4. The two compartments consist of the blood and the extravascular tissues. (Note that each phase is associated with a characteristic half-life: $t_{1/2\alpha}$ for the first phase, $t_{1/2\beta}$ for the second phase. Note also that when concentration is plotted on a logarithmic axis, the elimination phase for a first-order drug is a straight line.)

### B. Other Distribution Models

A few drugs behave as if they were distributed to only 1 compartment (eg, if they are restricted to the vascular compartment). Others have more complex distributions that require more than 2 compartments for construction of accurate mathematical models.

# ■ II. DRUG DEVELOPMENT & REGULATION

The sale and use of drugs are regulated in almost all countries by governmental agencies. In the United States, regulation is by the **Food and Drug Administration (FDA).** New drugs are developed in industrial or academic laboratories. Before a new drug can be approved for regular therapeutic use in humans, a series of animal and experimental human studies **(clinical trials)** must be carried out.

New drugs may emerge from a variety of sources. Some are the result of identification of a new target for a disease.

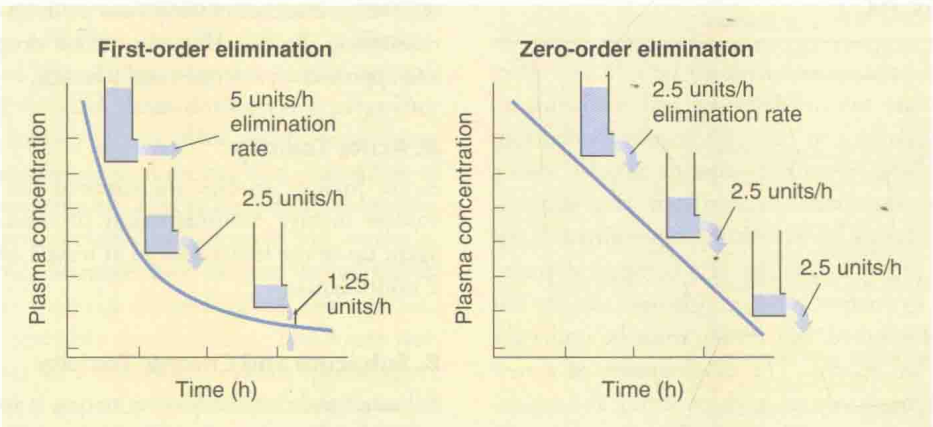



**FIGURE 1–3** Comparison of first-order and zero-order elimination. For drugs with first-order kinetics (left), rate of elimination (units per hour) is proportional to concentration; this is the more common process. In the case of zero-order elimination (right), the rate is constant and independent of concentration.

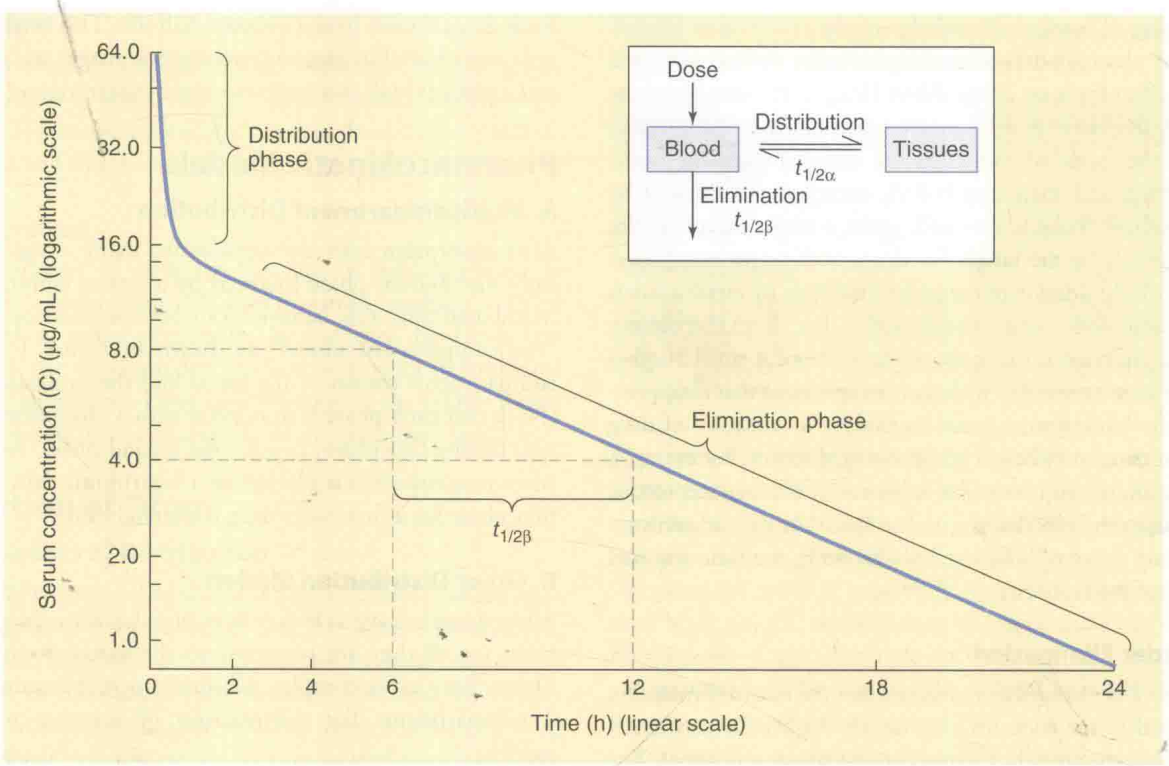



**FIGURE 1–4** Serum concentration-time curve after administration of a drug as an intravenous bolus. This drug follows first-order kinetics and appears to occupy two compartments. The initial curvilinear portion of the data represents the distribution phase, with drug equilibrating between the blood compartment and the tissue compartment. The linear portion of the curve represents drug elimination. The elimination half-life ($t_{1/2\beta}$) can be extracted graphically as shown by measuring the time between any two plasma concentration points on the elimination phase that differ by twofold. (See Chapter 3 for additional details.)

Rational molecular design or screening is then used to find a molecule that selectively alters the function of the target. New drugs may result from the screening of hundreds of compounds against model diseases in animals. In contrast, many (so-called "me-too" drugs) are the result of simple chemical alteration of the pharmacokinetic properties of the original prototype agent.

## SAFETY & EFFICACY

Because society expects prescription drugs to be safe and effective, governments regulate the development and marketing of new drugs. Current regulations in the USA require evidence of relative safety (derived from acute and subacute toxicity testing in animals) and probable therapeutic action (from the pharmacologic profile in animals) before human testing is permitted. Some information about the pharmacokinetics of a compound is also required before clinical evaluation is begun. Chronic toxicity test *results* are generally not required, but testing must be underway before human studies are started. The development of a new drug and its pathway through various levels of testing and regulation are illustrated in Figure 1–5. The cost of development of a new drug, including false starts and discarded molecules, is often greater than 500 million dollars.

## ANIMAL TESTING

The animal testing of a specific drug that is required before human studies can begin is a function of its proposed use and the urgency of the application. Thus, a drug proposed for occasional topical use requires less extensive testing than one destined for chronic systemic administration.

Because of the urgent need, anticancer drugs and anti-HIV drugs require less evidence of safety than do drugs used in treatment of less threatening diseases. Urgently needed drugs are often investigated and approved on an accelerated schedule.

### A. Acute Toxicity

Acute toxicity studies are required for all new drugs. These studies involve administration of incrementing doses of the agent up to the lethal level in at least 2 species (eg, 1 rodent and 1 nonrodent).

### B. Subacute and Chronic Toxicity

Subacute and chronic toxicity testing is required for most agents, especially those intended for chronic use. Tests are usually conducted for 2–4 weeks (subacute) and 6–24 months (chronic), in at least 2 species.

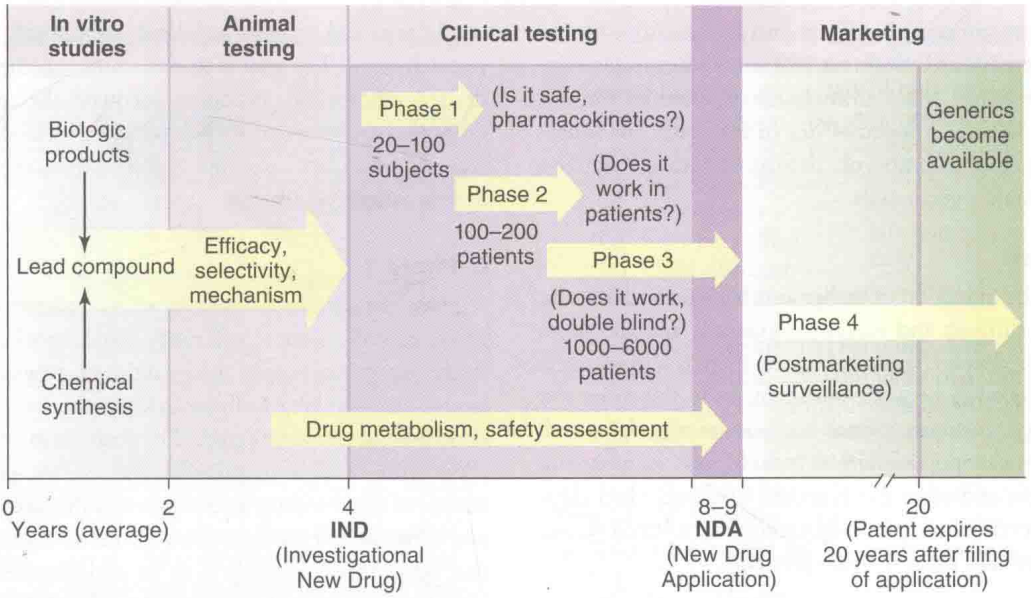



**FIGURE 1–5** The development and testing process required to bring a new drug to market in the United States. Some requirements may be different for drugs used in life-threatening diseases. (Reproduced, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 12th ed. McGraw-Hill, 2012: Fig. 5–1.)

## TYPES OF ANIMAL TESTS

### A. Pharmacologic Profile

The pharmacologic profile is a description of all the pharmacologic effects of a drug (eg, effects on cardiovascular function, gastrointestinal activity, respiration, hepatic and renal function, endocrine function, CNS). Both graded and quantal dose-response data are gathered.

### B. Reproductive Toxicity

Reproductive toxicity testing involves the study of the fertility effects of the candidate drug and its teratogenic and mutagenic toxicity. The FDA has used a 5-level descriptive scale to summarize information regarding the safety of drugs in pregnancy (Table 1–3). **Teratogenesis** can be defined as the induction of developmental defects in the somatic tissues of the fetus (eg, by exposure of the fetus to a chemical, infection, or radiation). Teratogenesis is studied by treating pregnant female animals of at least 2 species at selected times during early pregnancy when organogenesis is known to take place and by later examining the fetuses or neonates for abnormalities. Examples of drugs known to have teratogenic effects include thalidomide, isotretinoin, valproic acid, ethanol, glucocorticoids, warfarin, lithium, and androgens. **Mutagenesis** denotes induction of changes in the genetic material of animals of any age and therefore induction of heritable abnormalities. The **Ames test,** the standard in vitro test for mutagenicity, uses a special strain of salmonella bacteria that depends on specific nutrients in the culture medium. Loss of this dependence as a result of exposure to the test drug signals a mutation. Many carcinogens (eg, aflatoxin, cancer chemotherapeutic drugs, and other agents that

**TABLE 1–3 FDA ratings of drug safety in pregnancy.**

| Category | Description |
|---|---|
| A | Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote |
| B | Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters) |
| C | Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only when the potential benefit justifies the potential risk to the fetus |
| D | There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective) |
| X | Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant |

bind to DNA) have mutagenic effects and test positive in the Ames test. The **dominant lethal test** is an in vivo mutagenicity test carried out in mice. Male animals are exposed to the test substance before mating. Abnormalities in the results of subsequent mating (eg, loss of embryos, deformed fetuses) signal a mutation in the male's germ cells.

### C. Carcinogenesis

Carcinogenesis is the induction of malignant characteristics in cells. Carcinogenicity is difficult and expensive to study, and the Ames test is often used to screen chemicals because there is a moderately high degree of correlation between mutagenicity in the Ames test and carcinogenicity in some animal tests, as previously noted. Agents with known carcinogenic effects include coal tar, aflatoxin, dimethylnitrosamine and other nitrosamines, urethane, vinyl chloride, and the polycyclic aromatic hydrocarbons in tobacco smoke (eg, benzo[*a*]pyrene) and other tobacco products.

## CLINICAL TRIALS

Human testing of new drugs in the United States requires approval by institutional committees that monitor the ethical (informed consent, patient safety) and scientific aspects (study design, statistical power) of the proposed tests. Such testing also requires the prior approval by the FDA of an **Investigational New Drug Exemption application (IND)**, which is submitted by the manufacturer to the FDA (Figure 1–5). The IND includes all the preclinical data collected up to the time of submission and the detailed proposal for clinical trials. The major clinical testing process is usually divided into 3 phases that are carried out to provide information for a **New Drug Application (NDA)**. The NDA includes all the results of preclinical and clinical testing and constitutes the request for FDA approval of general marketing of the new agent for prescription use. A fourth phase of study (the surveillance phase) follows NDA approval. In particularly lethal conditions, the FDA may permit carefully monitored treatment of patients before phases 2 and 3 are completed.

### A. Phase 1

A phase 1 trial consists of careful evaluation of the dose-response relationship and the pharmacokinetics of the new drug in a small number of *normal* human volunteers (eg, 20–100). An exception is the phase 1 trials of cancer chemotherapeutic agents and other highly toxic drugs; these are carried out by administering the agents to volunteer patients with the target disease. In phase 1 studies, the acute effects of the agent are studied over a broad range of dosages, starting with one that produces no detectable effect and progressing to one that produces either a significant physiologic response or a very minor toxic effect.

### B. Phase 2

A phase 2 trial involves evaluation of a drug in a moderate number of *sick* patients (eg, 100–200) with the target disease. A placebo or positive control drug is included in a single-blind or double-blind design. The study is carried out under very carefully controlled conditions, and patients are closely monitored, often in a hospital research ward. The goal is to determine whether the agent has the desired efficacy (ie, produces adequate therapeutic response) at doses that are tolerated by sick patients. Detailed data are collected regarding the pharmacokinetics and pharmacodynamics of the drug in this patient population.

### C. Phase 3

A phase 3 trial usually involves many patients (eg, 1000–6000 or more, in many centers) and many clinicians who are using the drug in the manner proposed for its ultimate general use (eg, in outpatients). Such studies usually include placebo and positive controls in a double-blind crossover design. The goals are to explore further, under the conditions of the proposed clinical use, the spectrum of beneficial actions of the new drug, to compare it with placebo (negative control) and older therapy (positive control), and to discover toxicities, if any, that occur so infrequently as to be undetectable in phase 2 studies. Very large amounts of data are collected and these studies are usually very expensive. Unfortunately, relatively few phase 3 trials include the current standard of care as a positive control.

If the drug successfully completes phase 3, an NDA is submitted to the FDA. If the NDA is approved, the drug can be marketed and phase 4 begins.

### D. Phase 4

Phase 4 represents the postmarketing surveillance phase of evaluation, in which it is hoped that toxicities that occur very infrequently will be detected and reported early enough to prevent major therapeutic disasters. Manufacturers are required to inform the FDA at regular intervals of all reported untoward drug reactions. Unlike the first 3 phases, phase 4 has not been rigidly regulated by the FDA in the past. Because so many drugs have been found to be unacceptably toxic only after they have been marketed, there is considerable current interest in making phase 4 surveillance more consistent, effective, and informative.

## DRUG PATENTS & GENERIC DRUGS

A patent application is usually submitted around the time that a new drug enters animal testing (Figure 1–5). In the United States, approval of the patent and completion of the NDA approval process give the originator the right to market the drug without competition from other firms for a period of 10–14 years from the NDA approval date. After expiration of the patent, any company may apply to the FDA for permission to market a generic version of the same drug if they demonstrate that their generic drug molecule is **bioequivalent** (ie, meets certain requirements for content, purity, and bioavailability) to the original product.

## DRUG LEGISLATION

Many laws regulating drugs in the United States were passed during the 20th century. Refer to Table 1–4 for a partial list of this legislation.