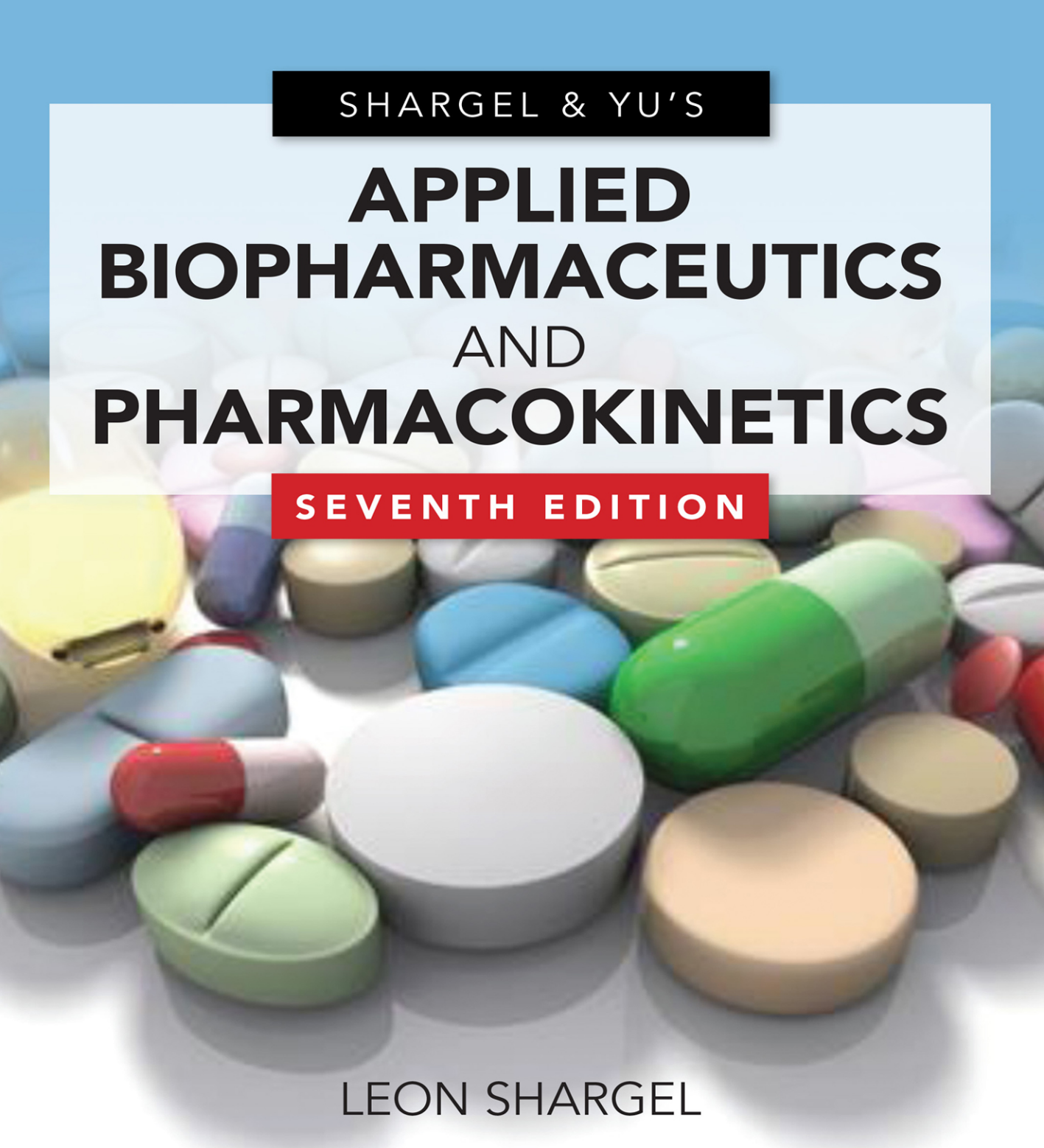
SHARGEL & YU'S

APPLIED BIOPHARMACEUTICS AND PHARMACOKINETICS

SEVENTH EDITION



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Applied Biopharmaceutics & Pharmacokinetics

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Applied Biopharmaceutics & Pharmacokinetics

Seventh Edition

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Preface

The publication of this seventh edition of *Applied Biopharmaceutics and Pharmacokinetics* represents over three decades in print. Since the introduction of classic pharmacokinetics in the first edition, the discipline has expanded and evolved greatly. The basic pharmacokinetic principles and biopharmaceutics now include pharmacogenetics, drug receptor theories, advances in membrane transports, and functional physiology. These advances are applied to the design of new active drug moieties, manufacture of novel drug products, and drug delivery systems. Biopharmaceutics and pharmacokinetics play a key role in the development of safer drug therapy in patients, allowing individualizing dosage regimens and improving therapeutic outcomes.

In planning for the seventh edition, we realized that we needed expertise for these areas. This seventh edition is our first edited textbook in which an expert with intimate knowledge and experience in the topic was selected as a contributor. We would like to acknowledge these experts for their precious time and effort. We are also grateful to our readers and colleagues for their helpful feedback and support throughout the years.

As editors of this edition, we kept the original objectives, starting with fundamentals followed by a holistic integrated approach that can be applied to practice (see scope and objectives in Preface to the first edition). This textbook provides the reader with a basic and practical understanding of the principles of biopharmaceutics and pharmacokinetics that can be applied to drug product development and drug therapy. Practice problems, clinical examples, frequently asked questions and learning questions are included in each chapter to demonstrate how these concepts relate to practical situations. This textbook remains unique in teaching basic concepts that may be applied to understanding complex issues associated with *in vivo* drug delivery that are essential for safe and efficacious drug therapy.

The primary audience is pharmacy students enrolled in pharmaceutical science courses in pharmacokinetics and biopharmaceutics. This text fulfills course work offered in separate or combined courses in these subjects. Secondary audiences for this textbook are research, technological and development scientists in pharmaceutics, biopharmaceutics, and pharmacokinetics.

This edition represents many significant changes from previous editions.

- The book is an edited textbook with the collaboration of many experts well known in biopharmaceutics, drug disposition, drug delivery systems, manufacturing, clinical pharmacology, clinical trials, and regulatory science.
- Many chapters have been expanded and updated to reflect current knowledge and application of biopharmaceutics and pharmacokinetics. Many new topics and updates are listed in Chapter 1.
- Practical examples and questions are included to encourage students to apply the principles in patient care and drug consultation situations.
- Learning questions and answers appear at the end of each chapter.
- Three new chapters have been added to this edition including, *Biostatistics* which provides introduction for popular topics such as risk concept, non-inferiority, and superiority concept in new drug evaluation, and *Application of Pharmacokinetics in Specific Populations* which discusses issues such as drug and patient related pharmacy

topics in during therapy in various patient populations, and *Biopharmaceutic Aspects of the Active Pharmaceutical Ingredient and Pharmaceutical Equivalence* which explains the synthesis, quality and physical/chemical properties of the active pharmaceutical ingredients affect the bioavailability of the drug from the drug product and clinical efficacy.

Leon Shargel
Andrew B.C. Yu

Preface to First Edition

The publication of the twelfth edition of this book is a testament to the vision and ideals of the original authors, Alfred Gilman and Louis Goodman, who, in 1941set forth the principles that have guided the book through eleven editions: to correlate pharmacology with related medical sciences, to reinterpret the actions and uses of drugs in light of advances in medicine and the basic biomedical sciences, to emphasize the applications of pharmacodynamics to therapeutics, and to create a book that will be useful to students of pharmacology and to physicians. These precepts continue to guide the current edition.

As with editions since the second, expert scholars have contributed individual chapters. A multiauthored book of this sort grows by accretion, posing challenges editors but also offering memorable pearls to the reader. Thus, portions of prior editions persist in the current edition, and I hasten to acknowledge the contributions of previous editors and authors, many of whom will see text that looks familiar. However, this edition differs noticeably from its immediate predecessors. Fifty new scientists, including a number from out-side. the U.S., have joined as contributors, and all chapters have been extensively updated. The focus on basic principles continues, with new chapters on drug invention, molecular mechanisms of drug action, drug toxicity and poisoning, principles of antimicrobial therapy and pharmacotherapy of obstetrical and gynecological disorders. Figures are in full color. The editors have continued to standardize the organization of chapters: thus, students should easily find the basic physiology, biochemistry, and pharmacology set forth in regular type; bullet points highlight important lists within the text; the clinician and expert will find details in extract type under clear headings.

Online features now supplement the printed edition. The entire text, updates, reviews of newly approved drugs, animations of drug action, and hyper links to relevant text in the prior edition are available on the Goodman & Gilman section of McGraw-Hill's websites, *AccessMedicine.com* and *AccessPharmacy.com*. An Image Bank CD accompanies the book and makes all tables and figures available for use in presentations.

The process of editing brings into view many remarkable facts, theories, and realizations. Three stand out: the invention of new classes of drugs has slowed to a trickle; therapeutics has barely begun to capitalize on the information from the human genome project; and, the development of resistance to antimicrobial agents, mainly through their overuse in medicine and agriculture, threatens to return us to the pre-antibiotic era. We have the capacity and ingenuity to correct these shortcomings.

Many, in addition to the contributors, deserve thanks for their work on this edition; they are acknowledged on an accompanying page. In addition, I am grateful to Professors Bruce Chabner (Harvard Medical School/Massachusetts General Hospital) and Björn Knollmann (Vanderbilt University Medical School) for agreeing to be associate editors of this edition at a late date, necessitated by the death of my colleague and friend Keith Parker in late 2008. Keith and I worked together on the eleventh edition and on planning this edition. In anticipation of the editorial work ahead, Keith submitted his chapters before anyone else and just a few weeks before his death; thus, he is well represented in this volume, which we dedicate to his memory.

Laurence L. Brunton

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Dr. Leon Shargel is a consultant for the pharmaceutical industry in biopharmaceutics and pharmacokinetics. Dr. Shargel has over 35 years experience in both academia and the pharmaceutical industry. He has been a member or chair of numerous national committees involved in state formulary issues, biopharmaceutics and bioequivalence issues, institutional review boards, and a member of the USP Biopharmaceutics Expert Committee. Dr. Shargel received a BS in pharmacy from the University of Maryland and a PhD in pharmacology from the George Washington University Medical Center. He is a registered pharmacist and has over 150 publications including several leading textbooks in pharmacy. He is a member of various professional societies, including the American Association Pharmaceutical Scientists (AAPS), American Pharmacists Association (APhA), and the American Society for Pharmacology and Experimental Therapeutics (ASPET).

Dr. Andrew Yu has over 30 years of experience in academia, government, and the pharmaceutical industry. Dr. Yu received a BS in pharmacy from Albany College of Pharmacy and a PhD in pharmacokinetics from the University of Connecticut. He is a registered pharmacist and has over 30 publications and a patent in novel drug delivery. He had lectured internationally on pharmaceutics, drug disposition, and drug delivery.

1 Introduction to Biopharmaceutics and Pharmacokinetics

Leon Shargel and Andrew B.C. Yu

Chapter Objectives

- Define drug product performance and biopharmaceutics.
- Describe how biopharmaceutics affects drug product performance.
- Define pharmacokinetics and describe how pharmacokinetics is related to pharmacodynamics and drug toxicity.
- Define the term clinical pharmacokinetics and explain how clinical pharmacokinetics may be used to develop dosage regimens for drugs in patients.
- Define pharmacokinetic model and list the assumptions that are used in developing a pharmacokinetic model.
- Explain how the prescribing information or approved labeling for a drug helps the practitioner to recommend an appropriate dosage regimen for a patient.

DRUG PRODUCT PERFORMANCE

Drugs are substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Drugs are given in a variety of dosage forms or *drug products* such as solids (tablets, capsules), semisolids (ointments, creams), liquids, suspensions, emulsions, etc, for systemic or local therapeutic activity. Drug products can be considered to be drug delivery systems that release and deliver drug to the site of action such that they produce the desired therapeutic effect. In addition, drug products are designed specifically to meet the patient's needs including palatability, convenience, and safety.

Drug product performance is defined as the release of the drug substance from the drug product either for local drug action or for drug absorption into the plasma for systemic therapeutic activity. Advances in pharmaceutical technology and manufacturing have focused on developing quality drug products that are safer, more effective, and more convenient for the patient.

BIOPHARMACEUTICS

Biopharmaceutics examines the interrelationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. The importance of the drug substance and the drug formulation on absorption, and *in vivo* distribution of the drug to the site of action, is described as a sequence of events that precede elicitation of a drug's therapeutic effect. A general scheme describing this dynamic relationship is illustrated in Fig. 1-1.

First, the drug in its dosage form is taken by the patient by an oral, intravenous, subcutaneous, transdermal, etc, route of administration. Next, the drug is released from the dosage form in a predictable and characterizable manner. Then, some fraction of the drug is absorbed from the site of administration into either the surrounding tissue for local action or into the body (as with oral dosage forms), or both. Finally, the drug reaches the site of action. A pharmacodynamic response results when the drug concentration at the site of

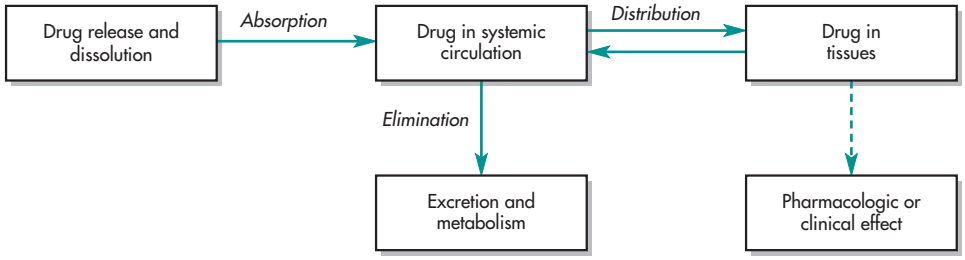

FIGURE 1-1 Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

action reaches or exceeds the *minimum effective concentration* (MEC). The suggested dosing regimen, including starting dose, maintenance dose, dosage form, and dosing interval, is determined in clinical trials to provide the drug concentrations that are therapeutically effective in most patients. This sequence of events is profoundly affected—in fact, sometimes orchestrated—by the design of the dosage form and the physicochemical properties of the drug.

Historically, pharmaceutical scientists have evaluated the relative drug availability to the body *in vivo* after giving a drug product by different routes to an animal or human, and then comparing specific pharmacologic, clinical, or possible toxic responses. For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level. In addition, the *bioavailability* (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug, even for the same route of administration. This difference in drug bioavailability may be manifested by observing the difference in the therapeutic effectiveness of the drug products. Thus, the nature of the drug molecule, the route of delivery, and the formulation of the dosage form can determine whether an administered drug is therapeutically effective, is toxic, or has no apparent effect at all.

The US Food and Drug Administration (FDA) approves all drug products to be marketed in the United States. The pharmaceutical manufacturers must perform extensive research and development prior to approval. The manufacturer of a new drug product must submit a *New Drug Application* (NDA) to the FDA, whereas a generic drug pharmaceutical manufacturer must submit an *Abbreviated New Drug Application* (ANDA). Both the new and generic drug product manufacturers must characterize their drug and drug product and demonstrate that the drug product performs appropriately before the products can become available to consumers in the United States.

Biopharmaceutics provides the scientific basis for drug product design and drug product development. Each step in the manufacturing process of a finished dosage form may potentially affect the release of the drug from the drug product and the availability of the drug at the site of action. The most important steps in the manufacturing process are termed *critical manufacturing variables*. Examples of biopharmaceutic considerations in drug product design are listed in Table 1-1. A detailed discussion of drug product design is found in Chapter 15. Knowledge of physiologic factors necessary for designing oral products is discussed in Chapter 14. Finally, drug product quality of drug substance (Chapter 17) and drug product testing is discussed in later chapters (18, 19, 20, and 21). It is important for a pharmacist to know that drug product selection from multisources could be confusing and needs a deep understanding of the testing procedures and manufacturing technology which is included in the chemistry, manufacturing, and control (CMC) of the product involved. The starting material (SM) used to make the API (active pharmaceutical ingredient), the processing method used during chemical synthesis, extraction, and the purification method can result in differences in the API that can then affect drug product performance (Chapter 17). Sometimes a by-product of the synthetic process, residual solvents, or impurities that remain may be harmful or may affect the product's physical or chemical stability. Increasingly, many drug sources are imported and the manufacturing of these products is regulated by codes or pharmacopeia in other countries. For example, drugs in Europe may be meeting EP (European Pharmacopeia) and since 2006,

TABLE 1-1 Biopharmaceutic Considerations in Drug Product Design

Items	Considerations
Therapeutic objective	Drug may be intended for rapid relief of symptoms, slow extended action given once per day, or longer for chronic use; some drug may be intended for local action or systemic action
Drug (active pharmaceutical ingredient, API)	Physical and chemical properties of API, including solubility, polymorphic form, particle size; impurities
Route of administration	Oral, topical, parenteral, transdermal, inhalation, etc
Drug dosage and dosage regimen	Large or small drug dose, frequency of doses, patient acceptance of drug product, patient compliance
Type of drug product	Orally disintegrating tablets, immediate release tablets, extended release tablets, transdermal, topical, parenteral, implant, etc
Excipients	Although very little pharmacodynamic activity, excipients may affect drug product performance including release of drug from drug product
Method of manufacture	Variables in manufacturing processes, including weighing accuracy, blending uniformity, release tests, and product sterility for parenterals

agreed uniform standards are harmonized in ICH guidances for Europe, Japan, and the United States. In the US, the USP-NF is the official compendia for drug quality standards.

Finally, the equipment used during manufacturing, processing, and packaging may alter important product attribute. Despite compliance with testing and regulatory guidance involved, the issues involving pharmaceutical equivalence, bioavailability, bioequivalence, and therapeutic equivalence often evolved by necessity. The implications are important regarding availability of quality drug product, avoidance of shortages, and maintaining an affordable high-quality drug products. The principles and issues with regard to multisource drug products are discussed in subsequent chapters:

Chapter 14	Physiologic Factors Related to Drug Absorption	How stomach emptying, GI residence time, and gastric window affect drug absorption
Chapter 15	Biopharmaceutic Considerations in Drug Product Design	How particle size, crystal form, solubility, dissolution, and ionization affect *in vivo* dissolution and absorption. Modifications of a product with excipient with regard to immediate or delayed action are discussed. Dissolution test methods and relation to *in vivo* performance
Chapter 16	Drug Product Performance, *In Vivo*: Bioavailability and Bioequivalence	Bioavailability and bioequivalence terms and regulations, test methods, and analysis examples. Protocol design and statistical analysis. Reasons for poor bioavailability. Bioavailability reference, generic substitution. PE, PA, BA/BE, API, RLD, TE SUPAC (Scale-up postapproval changes) regarding drug products. What type of changes will result in changes in BA, TE, or performances of drug products from a scientific and regulatory viewpoint
Chapter 17	Biopharmaceutic Aspects of the Active Pharmaceutical Ingredient and Pharmaceutical Equivalence	Physicochemical differences of the drug, API due to manufacturing and synthetic pathway. How to select API from multiple sources while meeting PE (pharmaceutical equivalence) and TE (therapeutic equivalence) requirement as defined in CFR. Examples of some drug failing TE while apparently meeting API requirements. Formulation factors and manufacturing method affecting PE and TE. How particle size and crystal form affect solubility and dissolution. How pharmaceutical equivalence affects therapeutic equivalence. Pharmaceutical alternatives. How physicochemical characteristics of API lead to pharmaceutical inequivalency
Chapter 18	Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy	Drug product quality and drug product performance Pharmaceutical development. Excipient effect on drug product performance. Quality control and quality assurance. Risk management Scale-up and postapproval changes (SUPAC) Product quality problems. Postmarketing surveillance

Thus, biopharmaceutics involves factors that influence (1) the design of the drug product, (2) stability of the drug within the drug product, (3) the manufacture of the drug product, (4) the release of the drug from the drug product, (5) the rate of dissolution/release of the drug at the absorption site, and (6) delivery of drug to the site of action, which may involve targeting the drug to a localized area (eg, colon for Crohn disease) for action or for systemic absorption of the drug.

Both the pharmacist and the pharmaceutical scientist must understand these complex relationships to objectively choose the most appropriate drug product for therapeutic success.

The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology. Studies in biopharmaceutics use both *in vitro* and *in vivo* methods. *In vitro* methods are procedures employing test apparatus and equipment without involving laboratory animals or humans. *In vivo* methods are more complex studies involving human subjects or laboratory animals. Some of these methods will be discussed in Chapter 15. These methods must be able to assess the impact of the physical and chemical properties of the drug, drug stability, and large-scale production of the drug and drug product on the biologic performance of the drug.

PHARMACOKINETICS

After a drug is released from its dosage form, the drug is absorbed into the surrounding tissue, the body, or both. The distribution through and elimination of the drug in the body varies for each patient but can be characterized using mathematical models and statistics. *Pharmacokinetics* is the science of the kinetics of drug absorption, distribution, and elimination (ie, metabolism and excretion). The description of drug distribution and elimination is often termed *drug disposition*. Characterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for individuals and groups of patients.

The study of pharmacokinetics involves both experimental and theoretical approaches. The experimental aspect of pharmacokinetics involves the development of biologic sampling techniques, analytical methods for the measurement of drugs and metabolites, and procedures that facilitate data collection and manipulation. The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration. The application of statistics is an integral part of pharmacokinetic studies. Statistical methods are used for pharmacokinetic parameter estimation and data interpretation ultimately for the purpose of designing and predicting optimal dosing regimens for individuals or groups of patients. Statistical methods are applied to pharmacokinetic models to determine data error and structural model deviations. Mathematics and computer techniques form the theoretical basis of many pharmacokinetic methods. Classical pharmacokinetics is a study of theoretical models focusing mostly on model development and parameterization.

PHARMACODYNAMICS

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body; this includes the mechanisms of drug action and the relationship between drug concentration and effect. A typical example of pharmacodynamics is how a drug interacts quantitatively with a drug receptor to produce a response (effect). Receptors are the molecules that interact with specific drugs to produce a pharmacological effect in the body.

The pharmacodynamic effect, sometimes referred to as the pharmacologic effect, can be therapeutic and/or cause toxicity. Often drugs have multiple effects including the desired therapeutic response as well as unwanted side effects. For many drugs, the pharmacodynamic effect is dose/drug concentration related; the higher the dose, the higher drug concentrations in the body and the more intense the pharmacodynamic effect up to a maximum effect. It is desirable that side effects and/or toxicity of drugs occurs at higher drug concentrations than the drug concentrations needed for the therapeutic effect. Unfortunately, unwanted side effects often occur concurrently with the therapeutic doses. The relationship between pharmacodynamics and pharmacokinetics is discussed in Chapter 21.

CLINICAL PHARMACOKINETICS

During the drug development process, large numbers of patients are enrolled in clinical trials to determine efficacy and optimum dosing regimens. Along with safety and efficacy data and other patient information, the FDA approves a label that becomes the package insert discussed in more detail later in this chapter. The approved labeling recommends the proper starting dosage regimens for the general patient population and may have additional recommendations for special populations of patients that need an adjusted dosage regimen (see Chapter 23). These recommended dosage regimens produce the desired pharmacologic response in the majority of the anticipated patient population. However, intra- and interindividual variations will frequently result in either a subtherapeutic (drug concentration below the MEC) or a toxic response (drug concentrations above the *minimum toxic concentration,* MTC), which may then require adjustment to the dosing regimen. *Clinical pharmacokinetics* is the application of pharmacokinetic methods to drug therapy in patient care. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations.

The study of clinical pharmacokinetics of drugs in disease states requires input from medical and pharmaceutical research. Table 1-2 is a list of 10 age adjusted rates of death from 10 leading causes of death in the United States in 2003. The influence of many diseases on drug disposition is not adequately studied. Age, gender, genetic, and ethnic differences can also result in pharmacokinetic differences that may affect the outcome of drug therapy (see Chapter 23). The study of pharmacokinetic differences of drugs in various population groups is termed *population pharmacokinetics* (Sheiner and Ludden, 1992; see Chapter 22). Application of Pharmacokinetics to Specific Populations, Chapter 23, will discuss many of the important pharmacokinetic considerations for dosing subjects due to age, weight, gender, renal, and hepatic disease differences. Despite advances in modeling and genetics, sometimes it is necessary to monitor the plasma drug concentration precisely in a patient for safety and multidrug dosing consideration. Clinical pharmacokinetics is also applied to *therapeutic drug monitoring* (TDM) for very potent drugs, such as those with a narrow therapeutic range, in order to optimize efficacy and to prevent any adverse toxicity. For these drugs, it is necessary to monitor the patient, either by monitoring plasma drug concentrations (eg, theophylline) or by monitoring a specific pharmacodynamic endpoint such as prothrombin clotting time (eg, warfarin). Pharmacokinetic and drug analysis services necessary for safe drug monitoring are generally provided by the *clinical pharmacokinetic service* (CPKS). Some drugs frequently monitored are the aminoglycosides and anticonvulsants. Other drugs closely monitored are those used in cancer chemotherapy, in order to minimize adverse side effects (Rodman and Evans, 1991).

TABLE 1-2 Ratio of Age-Adjusted Death Rates, by Male/Female Ratio from the 10 Leading Causes of Death* in the US, 2003

Disease	Rank	Male:Female
Disease of heart	1	1.5
Malignant neoplasms	2	1.5
Cerebrovascular diseases	3	4.0
Chronic lower respiration diseases	4	1.4
Accidents and others*	5	2.2
Diabetes mellitus	6	1.2
Pneumonia and influenza	7	1.4
Alzheimers	8	0.8
Nephrotis, nephrotic syndrome, and nephrosis	9	1.5
Septicemia	10	1.2

*Death due to adverse effects suffered as defined by CDC.

Source: National Vital Statistics Report Vol. 52, No. 3, 2003.

Labeling For Human Prescription Drug and Biological Products

In 2013, the FDA redesigned the format of the prescribing information necessary for safe and effective use of the drugs and biological products

(FDA Guidance for Industry, 2013). This design was developed to make information in prescription drug labeling easier for health care practitioners to access and read. The practitioner can use the prescribing information to make prescribing decisions. The labeling includes three sections:

- *Highlights of Prescribing Information (Highlights)*—contains selected information from the Full Prescribing Information (FPI) that health care practitioners most commonly reference and consider most important. In addition, highlights may contain any boxed warnings that give a concise summary of all of the risks described in the **Boxed Warning** section in the **FPI**.
- *Table of Contents (Contents)*—lists the sections and subsections of the FPI.
- *Full Prescribing Information (FPI*)—contains the detailed prescribing information necessary for safe and effective use of the drug.

An example of the Highlights of Prescribing Information and Table of Contents for Nexium (esomeprazole magnesium) delayed release capsules appears in Table 1-3B. The prescribing information sometimes referred to as the approved label or the package insert may be found at the FDA website, Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). Prescribing information is updated periodically as new information becomes available. The prescribing information contained in the label recommends dosage regimens for the average patient from data obtained from clinical trials. The indications and usage section are those indications that the FDA has approved and that have been shown to be effective in clinical trials. On occasion, a practitioner may want to prescribe the drug to a patient drug for a non-approved use or indication. The pharmacist must decide if there is sufficient evidence for dispensing the drug for a non-approved use (off-label indication). The decision to dispense a drug for a non-approved indication may be difficult and often made with consultation of other health professionals.

Clinical Pharmacology

Pharmacology is a science that generally deals with the study of drugs, including its mechanism, effects, and uses of drugs; broadly speaking, it includes pharmacognosy, pharmacokinetics, pharmacodynamics, pharmacotherapeutics, and toxicology. The application of pharmacology in clinical medicine including clinical trial is referred to as clinical pharmacology. For pharmacists and health professionals, it is important to know that NDA drug labels report many important study information under **Clinical Pharmacology** in Section 12 of the standard prescription label (Tables 1-3A and 1-3B).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

Question

Where is toxicology information found in the prescription label for a new drug? Can I find out if a drug is mutagenic under side-effect sections?

Answer

Nonclinical toxicology information is usefully in Section 13 under **Nonclinical Toxicology** if available. Mutagenic potential of a drug is usually reported under animal studies. It is unlikely that a drug with known humanly mutagenicity will be marketed, if so, it will be labeled with special warning. Black box warnings are usually used to give warnings to prescribers in Section 5 under Warnings and Precautions.

Pharmacogenetics

Pharmacogenetics is the study of drug effect including distribution and disposition due to genetic differences, which can affect individual responses to drugs, both in terms of therapeutic effect and adverse effects. A related field is pharmacogenomics, which emphasizes different aspects of genetic effect on drug response. This important discipline is discussed in Chapter 13. Pharmacogenetics is the main reason why many new drugs still have to be further studied after regulatory approval, that is, postapproval phase 4 studies. The clinical trials prior to drug approval are generally limited such that some side effects and special responses due to genetic differences may not be adequately known and labeled.

TABLE 1-3A Highlights of Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXIUM safely and effectively. See full prescribing information for NEXIUM.
NEXIUM (esomeprazole magnesium) delayed-release capsules, for oral use
NEXIUM (esomeprazole magnesium) for delayed-release oral suspension
Initial U.S. Approval: 1989 (omeprazole)

RECENT MAJOR CHANGES

Warnings and Precautions. Interactions with Diagnostic Investigations for Neuroendocrine Tumors (5.8) 03/2014

INDICATIONS AND USAGE

NEXIUM is a proton pump inhibitor indicated for the following:
- Treatment of gastroesophageal reflux disease (GERD) (1.1)
- Risk reduction of NSAID-associated gastric ulcer (1.2)
- *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (1.3)
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (1.4)

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Adults	20 mg or 40 mg	Once daily for 4 to 8 weeks
12 to 17 years	20 mg or 40 mg	Once daily for up to 8 weeks
1 to 11 years	10 mg or 20 mg	Once daily for up to 8 weeks
1 month to less than 1 year 2.5 mg, 5 mg or 10 mg (based on weight). Once daily, up to 6 weeks for erosive esophagitis (EE) due to acid-mediated GERD only.		
Risk Reduction of NSAID-Associated Gastric Ulcer		
	20 mg or 40 mg	Once daily for up to 6 months
***H. pylori* Eradication** (*Triple Therapy*):		
NEXIUM	40 mg	Once daily for 10 days
Amoxicillin	1000 mg	Twice daily for 10 days
Clarithromycin	500 mg	Twice daily for 10 days
Pathological Hypersecretory Conditions		
	40 mg	Twice daily
See full prescribing information for administration options (2)		
Patients with severe liver impairment do not exceed dose of 20 mg (2)		

DOSAGE FORMS AND STRENGTHS

- NEXIUM Delayed-Release Capsules: 20 mg and 40 mg (3)
- NEXIUM for Delayed-Release Oral Suspension: 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg (3)

CONTRAINDICATIONS

Patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred) (4)

(*Continued*)

TABLE 1-3A Highlights of Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules (Continued)

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

- Symptomatic response does not preclude the presence of gastric malignancy (5.1)
- Atrophic gastritis has been noted with long-term omeprazole therapy (5.2)
- PPI therapy may be associated with increased risk of *Clostriodium difficile*-associated diarrhea (5.3)
- Avoid concomitant use of NEXIUM with clopidogrel (5.4)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine (5.5)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.6)
- Avoid concomitant use of NEXIUM with St John's Wort or rifampin due to the potential reduction in esomeprazole levels (5.7,7.3)
- Interactions with diagnostic investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors (5.8,12.2)

ADVERSE REACTIONS

Most common adverse reactions (6.1):

- Adults (≥18 years) (incidence ≥1%) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth
- Pediatric (1 to 17 years) (incidence ≥2%) are headache, diarrhea, abdominal pain, nausea, and somnolence
- Pediatric (1 month to less than 1 year) (incidence 1%) are abdominal pain, regurgitation, tachypnea, and increased ALT

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- May affect plasma levels of antiretroviral drugs – use with atazanavir and nelfinavir is not recommended: if saquinavir is used with NEXIUM, monitor for toxicity and consider saquinavir dose reduction (7.1)
- May interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib, and digoxin) Patients treated with NEXIUM and digoxin may need to be monitored for digoxin toxicity. (7.2)
- Combined inhibitor of CYP 2C19 and 3A4 may raise esomeprazole levels (7.3)
- Clopidogrel: NEXIUM decreases exposure to the active metabolite of clopidogrel (7.3)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction (7.3)
- Tacrolimus: NEXIUM may increase serum levels of tacrolimus (7.5)
- Methotrexate: NEXIUM may increase serum levels of methotrexate (7.7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 03/2014

PRACTICAL FOCUS

Relationship of Drug Concentrations to Drug Response

The initiation of drug therapy starts with the manufacturer's recommended dosage regimen that includes the drug dose and frequency of doses (eg, 100 mg every 8 hours). Due to individual differences in the patient's genetic makeup (see Chapter 13 on pharmacogenetics) or pharmacokinetics, the recommended dosage regimen drug may not provide the desired therapeutic outcome. The measurement of plasma drug concentrations can confirm whether the drug dose was subtherapeutic due to the patient's individual pharmacokinetic profile (observed by low plasma drug concentrations) or was not responsive to drug therapy due to genetic difference in receptor response. In this case, the drug concentrations

TABLE 1-3B Contents for Full Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules

FULL PRESCRIBING INFORMATION: CONTENTS*
1. INDICATIONS AND USAGE
1.1 Treatment of Gastroesophageal Reflux Disease (GERD)
1.2 Risk Reduction of NSAID-Associated Gastric Ulcer
1.3 *H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
1.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
2. DOSAGE AND ADMINISTRATION
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
5.1 Concurrent Gastric Malignancy
5.2 Atrophic Gastritis
5.3 *Clostridium difficile* associated diarrhea
5.4 Interaction with Clopidogrel
5.5 Bone Fracture
5.6 Hypomagnesemia
5.7 Concomitant Use of NEXIUM with St John's Wort or rifampin
5.8 Interactions with Diagnostic Investigations for Neuroendocrine Tumors
5.9 Concomitant Use of NEXIUM with Methotrexate
6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7. DRUG INTERACTIONS
7.1 Interference with Antiretroviral Therapy
7.2 Drugs for Which Gastric pH Can Affect Bioavailability
7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways
7.4 Interactions with Investigations of Neuroendocrine Tumors
7.5 Tacrolimus
7.6 Combination Therapy with Clarithromycin
7.7 Methotrexate
8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10. OVERDOSAGE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14. CLINICAL STUDIES
14.1 Healing of Erosive Esophagitis
14.2 Symptomatic Gastroesophageal Reflux Disease (GERD)
14.3 Pediatric Gastroesophageal Reflux Disease (GERD)
14.4 Risk Reduction of NSAID-Associated Gastric Ulcer
14.5 *Helicobacter pylori (H. Pylon)* Eradication in Patients with Duodenal Ulcer Disease
14.6 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
16. HOW SUPPLIED/STORAGE AND HANDLING
17. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Source: FDA Guidance for Industry (February 2013).