



SHARGEL & YU'S

**APPLIED  
BIOPHARMACEUTICS  
AND  
PHARMACOKINETICS**

**SEVENTH EDITION**

LEON SHARGEL

ANDREW B.C. YU

**Mc  
Graw  
Hill**  
Education

# Applied Biopharmaceutics & Pharmacokinetics

Seventh Edition

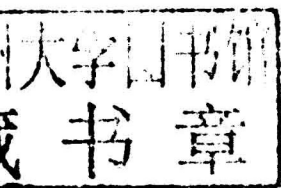
## EDITORS

### Leon Shargel, PhD, RPh

*Applied Biopharmaceutics, LLC  
Raleigh, North Carolina  
Affiliate Professor, School of Pharmacy  
Virginia Commonwealth University, Richmond, Virginia  
Adjunct Associate Professor, School of Pharmacy  
University of Maryland, Baltimore, Maryland*

### Andrew B.C. Yu, PhD, RPh

*Registered Pharmacist  
Gaithersburg, Maryland  
Formerly Associate Professor of Pharmaceutics  
Albany College of Pharmacy  
Albany, New York  
Formerly CDER, FDA  
Silver Spring, Maryland*



**Mc  
Graw  
Hill**  
Education

New York Chicago San Francisco Athens London Madrid Mexico City  
Milan New Delhi Singapore Sydney Toronto

## **Applied Biopharmaceutics & Pharmacokinetics, Seventh Edition**

Copyright © 2016 by McGraw-Hill Education. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

Previous editions copyright © 2012 by The McGraw-Hill Companies, Inc.; © 2005, 1999, 1993 by Appleton & Lange; © 1985, 1980 by Appleton-Century-Crofts.

1 2 3 4 5 6 7 8 9 0 DOC/DOC 20 19 18 17 16 15

ISBN 978-0-07-183093-5

MHID 0-07-183093-6

This book was set in Times LT Std by Cenveo® Publisher Services.

The editor was Regina Y. Brown

The production supervisor was Rick Ruzycka.

The production manager was Tanya Punj, Cenveo Publisher Services.

The design was by Elise Lansdon; the cover design was by Barsoom Design, with cover art © Gregor Schuster/Corbis.

RR Donnelley was printer and binder.

This book is printed on acid-free paper.

## **Library of Congress Cataloging-in-Publication Data**

Shargel, Leon, 1941- , author.

Applied biopharmaceutics & pharmacokinetics / Leon Shargel, Andrew B.C. Yu.—Seventh edition.

p. ; cm.

Applied biopharmaceutics and pharmacokinetics

Includes bibliographical references and index.

ISBN 978-0-07-183093-5 (hardcover : alk. paper)—ISBN 0-07-183093-6 (hardcover : alk. paper)

I. Yu, Andrew B. C., 1945- , author. II. Title. III. Title: Applied biopharmaceutics and pharmacokinetics.

[DNLM: 1. Biopharmaceutics. 2. Pharmacokinetics. 3. Drug Administration Routes. 4. Models, Chemical. QV 38] RM301.4

615.7—dc23

2015014810

McGraw-Hill books are available at special quantity discounts to use as premiums and sales promotions, or for use in corporate training programs. To contact a representative please e-mail us at [bulksales@mcgraw-hill.com](mailto:bulksales@mcgraw-hill.com).

# Applied Biopharmaceutics & Pharmacokinetics



## Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

# Contributors

S. Thomas Abraham, PhD  
Associate Professor  
Department of Pharmaceutical Sciences  
College of Pharmacy & Health Sciences  
Campbell University  
Buies Creek, North Carolina

Michael L. Adams, PharmD, PhD  
Associate Professor  
Department of Pharmaceutical Sciences  
College of Pharmacy & Health Sciences  
Campbell University  
Buies Creek, North Carolina

Antoine Al-Achi, PhD  
Associate Professor  
Campbell University  
College of Pharmacy & Health Sciences  
Buies Creek, North Carolina

Lily K. Cheung, PharmD  
Assistant Professor  
Department of Pharmacy Practice  
College of Pharmacy & Health Sciences  
Texas Southern University  
Houston, Texas

Diana Shu-Lian Chow, PhD  
Professor of Pharmaceutics  
Director  
Institute for Drug Education and Research (IDER)  
College of Pharmacy  
University of Houston  
Houston, Texas

Philippe Colucci, PhD  
Principal Scientist  
Learn and Confirm Inc.  
Sr. Laurent, QC, Canada

Dale P. Conner, Pharm.D.  
Director  
Office of Bioequivalence  
Office of Generic Drugs  
CDER, FDA  
Silver Spring, Maryland

Barbara M. Davit, PhD, JD  
Executive Director  
Biopharmaceutics  
Merck & Co.  
Kenilworth, New Jersey

Hong Ding, PhD  
Assistant Professor  
Department of Immunology  
Herbert Wertheim College of Medicine  
Florida International University  
Miami, Florida

John Z. Duan, PhD  
Master Reviewer  
Office of New Drug Products  
Office of Pharmaceutical Quality  
FDA/CDER  
Silver Spring, Maryland

Murray P. Ducharme, PharmD, FCCP, FCP  
 President and CEO  
 Learn and Confirm Inc.  
 Sr. Laurent, QC, Canada  
 Professeur Associé  
 Faculté de Pharmacie  
 University of Montreal, Canada  
 Visiting Professor  
 Faculty of Pharmacy  
 Rhodes University, South Africa

Mathangi Gopalakrishnan, MS, PhD  
 Research Assistant Professor  
 Center for Translational Medicine  
 School of Pharmacy  
 University of Maryland  
 Baltimore, Maryland

Phillip M. Gerk, PharmD, PhD  
 Associate Professor  
 Department of Pharmaceutics  
 Virginia Commonwealth University  
 MCV Campus  
 School of Pharmacy  
 Richmond, Virginia

Charles Herring, BSPharm, PharmD, BCPS, CPP  
 Associate Professor  
 Department of Pharmacy Practice  
 College of Pharmacy & Health Sciences  
 Campbell University  
 Clinical Pharmacist Practitioner  
 Adult Medicine Team  
 Downtown Health Plaza of Wake Forest Baptist  
 Health  
 Winston-Salem, North Carolina

Christine Yuen-Yi Hon, PharmD, BCOP  
 Clinical Pharmacology Reviewer  
 Division of Clinical Pharmacology III  
 Office of Clinical Pharmacology  
 Office of Translational Sciences  
 Center for Drug Evaluation and Research  
 Food and Drug Administration  
 Silver Spring, Maryland

Minerva A. Hughes, PhD, RAC (US)  
 Senior Pharmacologist  
 Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Silver Spring, Maryland

Manish Issar, PhD  
 Assistant Professor of Pharmacology  
 College of Osteopathic Medicine of the Pacific  
 Western University of Health Sciences  
 Pomona, California

Vipul Kumar, PhD  
 Senior Scientist I  
 Nonclinical Development Department  
 Cubist Pharmaceuticals Inc.  
 Lexington, Massachusetts

S.W. Johnny Lau, RPh, PhD  
 Senior Clinical Pharmacologist  
 Food and Drug Administration  
 Office of Clinical Pharmacology  
 Silver Spring, Maryland

David S.H. Lee, PharmD, PhD  
 Assistant Professor  
 Department of Pharmacy Practice  
 Oregon State University/Oregon Health and Science  
 University College of Pharmacy  
 Portland, Oregon

Patrick J Marroum, PhD  
 Director  
 Clinical Pharmacology and Pharmacometrics  
 AbbVie  
 North Chicago, Illinois

Shabnam N. Sani, PharmD, PhD  
 Assistant Professor  
 Department of Pharmaceutical and Administrative  
 Sciences  
 College of Pharmacy  
 Western New England University  
 Springfield, Massachusetts

Leon Shargel, PhD, RPh  
Manager and Founder  
Applied Biopharmaceutics, LLC  
Raleigh, North Carolina  
Affiliate Professor  
School of Pharmacy  
Virginia Commonwealth University  
Richmond, Virginia

Sandra Suarez Sharp, PhD  
Master Biopharmaceutics Reviewer/Biopharmaceutics  
Lead  
Office of New Drug Products/Division of  
Biopharmaceutics  
Office of Pharmaceutical Quality  
Food and Drug Administration  
Silver Spring, Maryland

Rodney Siwale, PhD, MS  
Assistant Professor  
Department of Pharmaceutical and Administrative  
Sciences  
College of Pharmacy  
Western New England University  
Springfield, Massachusetts

Changquan Calvin Sun, PhD  
Associate Professor of Pharmaceutics  
University of Minnesota  
Department of Pharmaceutics  
College of Pharmacy  
Minneapolis, Minnesota

He Sun, PhD  
President and CEO  
Tasly Pharmaceuticals Inc.  
Rockville, Maryland  
Professor and Chairman  
Department of Pharmaceutical Economics and Policy  
School of Pharmaceutical Science and Technology  
Tianjin University  
Tianjin, P. R. China

Vincent H. Tam, PharmD, BCPS (Infectious Diseases)  
Professor Department of Clinical Sciences and  
Administration  
University of Houston College of Pharmacy  
Texas Medical Center Campus  
Houston, Texas

Dr. Susanna Wu-Pong, PhD  
Associate Professor  
Director  
Pharmaceutical Sciences Graduate Program  
VCU School of Pharmacy  
Richmond, Virginia

Andrew B.C. Yu, PhD, RPh  
Registered Pharmacist  
Formerly senior reviewer, CDER, FDA  
Associate Pharmaceutics Professor  
Albany College of Pharmacy  
Albany, New York

Corinne Seng Yue, BPharm, MSc, PhD  
Principal Scientist  
Learn and Confirm Inc.  
Sr. Laurent, QC, Canada

Hong Zhao, PhD  
Clinical Pharmacology Master Reviewer  
Clinical Pharmacology Team Leader  
Office of Clinical Pharmacology (OCP)  
Office of Translational Sciences (OTS)  
Center for Drug Evaluation and Research (CDER)  
U.S. Food and Drug Administration (FDA)  
Silver Spring, Maryland

HaiAn Zheng, PhD  
Associate Professor  
Department of Pharmaceutical Sciences  
Albany College of Pharmacy and Health Sciences  
Albany, New York



# 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 pharmaceuticals, 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 1941 set 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 multi-authored 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

# About the Authors

**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 pharmaceuticals, drug disposition, and drug delivery.

# Contents

Contributors	xi
Preface	xv
Preface to First Edition	xvii

## 1. Introduction to Biopharmaceutics and Pharmacokinetics 1

Drug Product Performance	1
Biopharmaceutics	1
Pharmacokinetics	4
Pharmacodynamics	4
Clinical Pharmacokinetics	5
Practical Focus	8
Pharmacodynamics	10
Drug Exposure and Drug Response	10
Toxicokinetics and Clinical Toxicology	10
Measurement of Drug Concentrations	11
Basic Pharmacokinetics and Pharmacokinetic Models	15
Chapter Summary	21
Learning Questions	22
Answers	23
References	25
Bibliography	25

## 2. Mathematical Fundamentals in Pharmacokinetics 27

Calculus	27
Graphs	29
Practice Problem	31
Mathematical Expressions and Units	33
Units for Expressing Blood Concentrations	34
Measurement and Use of Significant Figures	34
Practice Problem	35
Practice Problem	36
Rates and Orders of Processes	40
Chapter Summary	42
Learning Questions	43
Answers	46
References	50

## 3. Biostatistics 51

Variables	51
Types of Data (Nonparametric Versus Parametric)	51
Distributions	52

Measures of Central Tendency	53
Measures of Variability	54
Hypothesis Testing	56
Statistically Versus Clinically Significant Differences	58
Statistical Inference Techniques in Hypothesis Testing for Parametric Data	59
Goodness of Fit	63
Statistical Inference Techniques for Hypothesis Testing With Nonparametric Data	63
Controlled Versus Noncontrolled Studies	66
Blinding	66
Confounding	66
Validity	67
Bioequivalence Studies	68
Evaluation of Risk for Clinical Studies	68
Chapter Summary	70
Learning Questions	70
Answers	72
References	73

## 4. One-Compartment Open Model: Intravenous Bolus Administration 75

Elimination Rate Constant	76
Apparent Volume of Distribution	77
Clearance	80
Clinical Application	85
Calculation of $k$ From Urinary Excretion Data	86
Practice Problem	87
Practice Problem	88
Clinical Application	89
Chapter Summary	90
Learning Questions	90
Answers	92
Reference	96
Bibliography	96

## 5. Multicompartment Models: Intravenous Bolus Administration 97

Two-Compartment Open Model	100
Clinical Application	105

Practice Problem	107
Practical Focus	107
Practice Problem	110
Practical Focus	113
Three-Compartment Open Model	114
Clinical Application	115
Clinical Application	116
Determination of Compartment Models	116
Practical Focus	117
Clinical Application	118
Practical Problem	120
Clinical Application	121
Practical Application	121
Clinical Application	122
Chapter Summary	123
Learning Questions	124
Answers	126
References	128
Bibliography	129

## 6. Intravenous Infusion 131

One-Compartment Model Drugs	131
Infusion Method for Calculating Patient Elimination Half-Life	135
Loading Dose Plus IV Infusion—One-Compartment Model	136
Practice Problems	138
Estimation of Drug Clearance and $V_D$ From Infusion Data	140
Intravenous Infusion of Two-Compartment Model Drugs	141
Practical Focus	142
Chapter Summary	144
Learning Questions	144
Answers	146
Reference	148
Bibliography	148

## 7. Drug Elimination, Clearance, and Renal Clearance 149

Drug Elimination	149
Drug Clearance	150
Clearance Models	152
The Kidney	157
Clinical Application	162
Practice Problems	163
Renal Clearance	163
Determination of Renal Clearance	168
Practice Problem	169
Practice Problem	169
Relationship of Clearance to Elimination Half-Life and Volume of Distribution	170
Chapter Summary	171
Learning Questions	171
Answers	172

References	175
Bibliography	175

## 8. Pharmacokinetics of Oral Absorption 177

Introduction	177
Basic Principles of Physiologically Based Absorption Kinetics (Bottom-Up Approach)	178
Absorption Kinetics (The Top-Down Approach)	182
Pharmacokinetics of Drug Absorption	182
Significance of Absorption Rate Constants	184
Zero-Order Absorption Model	184
Clinical Application—Transdermal Drug Delivery	185
First-Order Absorption Model	185
Practice Problem	191
Chapter Summary	199
Answers	200
Application Questions	202
References	203
Bibliography	204

## 9. Multiple-Dosage Regimens 205

Drug Accumulation	205
Clinical Example	209
Repetitive Intravenous Injections	210
Intermittent Intravenous Infusion	214
Clinical Example	216
Estimation of $k$ and $V_D$ of Aminoglycosides in Clinical Situations	217
Multiple-Oral-Dose Regimen	218
Loading Dose	219
Dosage Regimen Schedules	220
Clinical Example	222
Practice Problems	222
Chapter Summary	224
Learning Questions	225
Answers	226
References	228
Bibliography	228

## 10. Nonlinear Pharmacokinetics 229

Saturable Enzymatic Elimination Processes	231
Practice Problem	232
Practice Problem	233
Drug Elimination by Capacity-Limited Pharmacokinetics: One-Compartment Model, IV Bolus Injection	233
Practice Problems	235
Clinical Focus	242
Clinical Focus	243
Drugs Distributed as One-Compartment Model and Eliminated by Nonlinear Pharmacokinetics	243

Clinical Focus	244
Chronopharmacokinetics and Time-Dependent Pharmacokinetics	245
Clinical Focus	247
Bioavailability of Drugs That Follow Nonlinear Pharmacokinetics	247
Nonlinear Pharmacokinetics Due to Drug-Protein Binding	248
Potential Reasons for Unsuspected Nonlinearity	251
Dose-Dependent Pharmacokinetics	252
Clinical Example	253
Chapter Summary	254
Learning Questions	254
Answers	255
References	257
Bibliography	258

## 11. Physiologic Drug Distribution and Protein Binding 259

Physiologic Factors of Distribution	259
Clinical Focus	267
Apparent Volume Distribution	267
Practice Problem	270
Protein Binding of Drugs	273
Clinical Examples	275
Effect of Protein Binding on the Apparent Volume of Distribution	276
Practice Problem	279
Clinical Example	280
Relationship of Plasma Drug-Protein Binding to Distribution and Elimination	281
Clinical Examples	282
Clinical Example	284
Determinants of Protein Binding	285
Clinical Example	285
Kinetics of Protein Binding	286
Practical Focus	287
Determination of Binding Constants and Binding Sites by Graphic Methods	287
Clinical Significance of Drug-Protein Binding	290
Clinical Example	299
Clinical Example	300
Modeling Drug Distribution	301
Chapter Summary	302
Learning Questions	303
Answers	304
References	306
Bibliography	307

## 12. Drug Elimination and Hepatic Clearance 309

Route of Drug Administration and Extrahepatic Drug Metabolism	309
---------------------------------------------------------------	-----

Practical Focus	311
Hepatic Clearance	311
Extrahepatic Metabolism	312
Enzyme Kinetics—Michaelis-Menten Equation	313
Clinical Example	317
Practice Problem	319
Anatomy and Physiology of the Liver	321
Hepatic Enzymes Involved in the Biotransformation of Drugs	323
Drug Biotransformation Reactions	325
Pathways of Drug Biotransformation	326
Drug Interaction Example	331
Clinical Example	338
First-Pass Effects	338
Hepatic Clearance of a Protein-Bound Drug: Restrictive and Nonrestrictive Clearance From Binding	344
Biliary Excretion of Drugs	346
Clinical Example	348
Role of Transporters on Hepatic Clearance and Bioavailability	348
Chapter Summary	350
Learning Questions	350
Answers	352
References	354
Bibliography	355

## 13. Pharmacogenetics and Drug Metabolism 357

Genetic Polymorphisms	358
Cytochrome P-450 Isozymes	361
Phase II Enzymes	366
Transporters	367
Chapter Summary	368
Glossary	369
Abbreviations	369
References	370

## 14. Physiologic Factors Related to Drug Absorption 373

Drug Absorption and Design of a Drug Product	373
Route of Drug Administration	374
Nature of Cell Membranes	377
Passage of Drugs Across Cell Membranes	378
Drug Interactions in the Gastrointestinal Tract	389
Oral Drug Absorption	390
Oral Drug Absorption During Drug Product Development	401
Methods for Studying Factors That Affect Drug Absorption	402
Effect of Disease States on Drug Absorption	405
Miscellaneous Routes of Drug Administration	407

Chapter Summary	408
Learning Questions	409
Answers to Questions	410
References	411
Bibliography	414

## 15. Biopharmaceutic Considerations in Drug Product Design and *In Vitro* Drug Product Performance 415

Biopharmaceutic Factors and Rationale for Drug Product Design	416
Rate-Limiting Steps in Drug Absorption	418
Physicochemical Properties of the Drug	420
Formulation Factors Affecting Drug Product Performance	423
Drug Product Performance, <i>In Vitro</i> : Dissolution and Drug Release Testing	425
Compendial Methods of Dissolution	429
Alternative Methods of Dissolution Testing	431
Dissolution Profile Comparisons	434
Meeting Dissolution Requirements	436
Problems of Variable Control in Dissolution Testing	437
Performance of Drug Products: <i>In Vitro</i> – <i>In Vivo</i> Correlation	437
Approaches to Establish Clinically Relevant Drug Product Specifications	441
Drug Product Stability	445
Considerations in the Design of a Drug Product	446
Drug Product Considerations	450
Clinical Example	456
Chapter Summary	461
Learning Questions	462
Answers	462
References	463
Bibliography	466

## 16. Drug Product Performance, *In Vivo*: Bioavailability and Bioequivalence 469

Drug Product Performance	469
Purpose of Bioavailability and Bioequivalence Studies	471
Relative and Absolute Availability	472
Practice Problem	474
Methods for Assessing Bioavailability and Bioequivalence	475
<i>In Vivo</i> Measurement of Active Moiety or Moieties in Biological Fluids	475
Bioequivalence Studies Based on Pharmacodynamic Endpoints— <i>In Vivo</i> Pharmacodynamic (PD) Comparison	478
Bioequivalence Studies Based on Clinical Endpoints—Clinical Endpoint Study	479
<i>In Vitro</i> Studies	481

Other Approaches Deemed Acceptable (by the FDA)	482
Bioequivalence Studies Based on Multiple Endpoints	482
Bioequivalence Studies	482
Design and Evaluation of Bioequivalence Studies	484
Study Designs	490
Crossover Study Designs	491
Clinical Example	496
Clinical Example	496
Pharmacokinetic Evaluation of the Data	497
The Partial AUC in Bioequivalence Analysis	498
Examples of Partial AUC Analyses	499
Bioequivalence Examples	500
Study Submission and Drug Review Process	502
Waivers of <i>In Vivo</i> Bioequivalence Studies (Biowaivers)	503
The Biopharmaceutics Classification System (BCS)	507
Generic Biologics (Biosimilar Drug Products)	510
Clinical Significance of Bioequivalence Studies	511
Special Concerns in Bioavailability and Bioequivalence Studies	512
Generic Substitution	514
Glossary	517
Chapter Summary	520
Learning Questions	520
Answers	525
References	526

## 17. Biopharmaceutical Aspects of the Active Pharmaceutical Ingredient and Pharmaceutical Equivalence 529

Introduction	529
Pharmaceutical Alternatives	533
Practice Problem	534
Bioequivalence of Drugs With Multiple Indications	536
Formulation and Manufacturing Process Changes	536
Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules	536
Changes to an Approved NDA or ANDA	537
The Future of Pharmaceutical Equivalence and Therapeutic Equivalence	538
Biosimilar Drug Products	539
Historical Perspective	540
Chapter Summary	541
Learning Questions	541
Answers	542
References	542