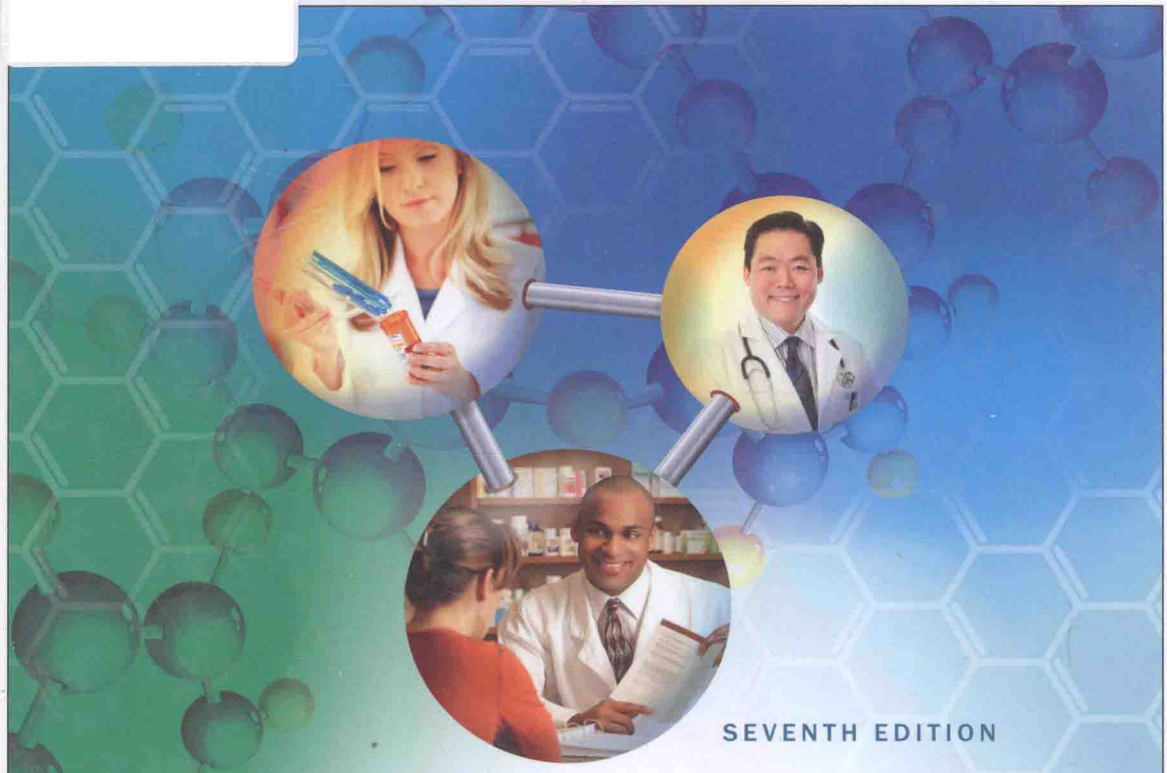
INTERNATIONAL EDITION

Not authorised for sale in United States, Canada, Australia and New Zealand



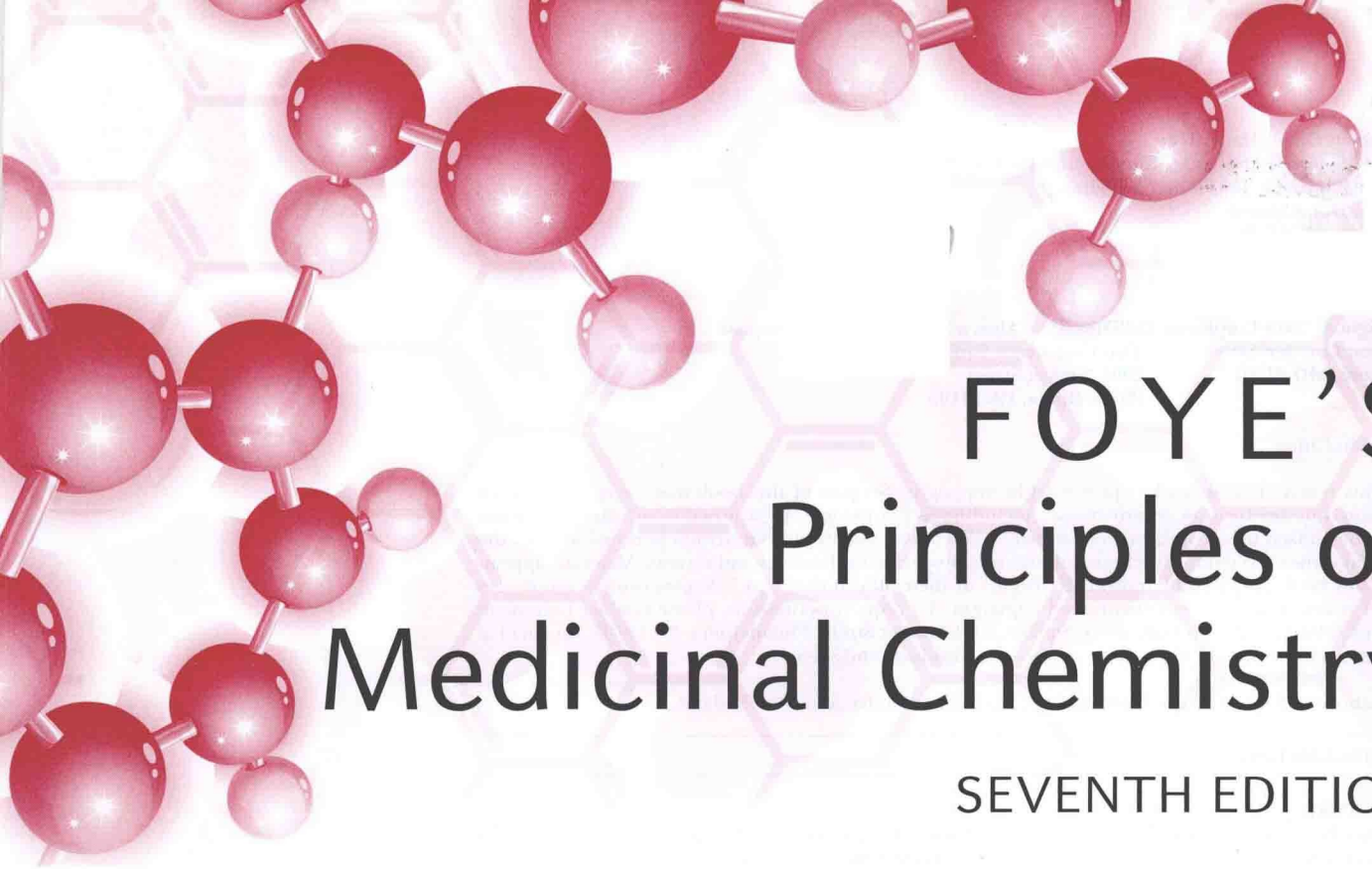
SEVENTH EDITION

Foye's Principles of Medicinal Chemistry

Thomas L. Lemke | David A. Williams
Victoria F. Roche | S. William Zito

Wolters Kluwer Health | Lippincott Williams & Wilkins

Wolters Kluwer Health | Lippincott Williams & Wilkins



FOYE'S Principles of Medicinal Chemistry

SEVENTH EDITION

Edited By

THOMAS L. LEMKE, PHD
Professor Emeritus
College of Pharmacy
University of Houston
Houston, Texas

DAVID A. WILLIAMS, PHD
Professor Emeritus of Chemistry
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Associate Editors

VICTORIA F. ROCHE, PHD
Professor of Pharmacy Sciences
School of Pharmacy and Health Professions
Creighton University
Omaha, Nebraska

S. WILLIAM ZITO, PHD
Professor Pharmaceutical Sciences
College of Pharmacy and Allied Health Professions
St. John's University
Jamaica, New York

Wolters Kluwer | Lippincott Williams & Wilkins
Health

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: David Troy
Product Managers: Andrea M. Klingler and Paula C. Williams
Marketing Manager: Joy Fischer-Williams
Designer: Doug Smock
Compositor: SPi Global

Seventh Edition

351 West Camden Street
Baltimore, MD 21201

Two Commerce Square
2001 Market Street
Philadelphia, PA 19103

Printed in China

ISBN 978-1-4511-7572-1

DISCLAIMER

Care has been taken to confirm the accuracy of the information present and to describe generally accepted practices. However, the authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. Application of this information in a particular situation remains the professional responsibility of the practitioner; the clinical treatments described and recommended may not be considered absolute and universal recommendations.

The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with the current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs and medical devices presented in this publication have Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the health care provider to ascertain the FDA status of each drug or device planned for use in their clinical practice.

To purchase additional copies of this book, call our customer service department at (800) 638-3030 or fax orders to (301) 223-2320. International customers should call (301) 223-2300.

Visit Lippincott Williams & Wilkins on the Internet: http://www.lww.com. Lippincott Williams & Wilkins customer service representatives are available from 8:30 am to 6:00 pm, EST.

9 8 7 6 5 4 3 2 1

RRS1112

FOYE'S Principles of Medicinal Chemistry

SEVENTH EDITION

This textbook is dedicated to our students and to our academic colleagues who mentor these students in the principles and applications of medicinal chemistry. The challenge for the student is to master the chemical, pharmacological, pharmaceutical and therapeutic aspects of the drug and utilize the knowledge of medicinal chemistry to effectively communicate with prescribing clinicians, nurses and other members of the health care team, as well as in discussing drug therapy with patients.

Thomas L. Lemke
David A. Williams
Victoria F. Roche
S. William Zito

Preface

As defined by IUPAC, medicinal chemistry is a chemistry-based discipline, involving aspects of the biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships (SAR), which is the relationship between chemical structure and pharmacological activity for a series of compounds.

As we look back 38 years to the first edition of *Foye's Principles of Medicinal Chemistry* and nearly 63 years to the first edition of Wilson and Gisvold's textbook, *Organic Chemistry in Pharmacy* (later renamed *Textbook of Organic Medicinal and Pharmaceutical Chemistry*), we can examine how the teaching of medicinal chemistry has evolved over the last half of the 20th century. Sixty years ago the approach to teaching drug classification was based on chemical functional groups; in the 1970s it was the relationship between chemical structure and pharmacological activity for a series of compounds, and today medicinal chemistry involves the integration of these principles with pharmacology, pharmaceutics, and therapeutics into a single multi-semester course called pharmacodynamics, pharmacotherapeutics, or another similar name. Drug discovery and development will always maintain its role in traditional drug therapy, but its application to pharmacogenomics may well become the treatment modality of the future. In drug discovery, toxicogenomics is used to improve the safety of drugs mandated by U.S. Food and Drug administration by studying the adverse/toxic effects of drugs in order to draw conclusions on the toxic and safety risk to patients. The scope of knowledge in organic chemistry, biochemistry, pharmacology, and therapeutics allows students to make generalizations connecting the physicochemical properties of small organic molecules and peptides to the receptor and biochemical properties of living systems.

Creating new drugs to combat disease is a complex process. The shape of a drug must be right to allow it to bind to a specific disease-related protein (i.e., receptor) and to work effectively. This shape is determined by the core framework of the molecule and the relative orientation of functional groups in three dimensional space. As a consequence, these generalizations, validated by repetitive examples, emerge in time as principles of drug discovery and drug mechanisms, principles that describe the structural relationships between diverse organic molecules and the biomolecular functions that predict their mechanisms toward controlling diseases.

Medicinal chemistry is central to modern drug discovery and development. For most of the 20th century, the majority of drugs were discovered either by identifying the active ingredient in traditional natural remedies, by rational drug design, or by serendipity. As we have moved into the 21st century, drug discovery has focused on drug targets and high-throughput screening of drug hits and computer-assessed drug design to fill its drug pipeline. Medicinal chemistry has advanced during the past several decades from not only synthesizing new compounds but to understanding the molecular basis of a disease and its control, identifying biomolecular targets implicated as disease-causing, and ultimately inventing specific compounds (called "hits") that block the biomolecules from progressing to an illness or stop the disease in its tracks. Medicinal chemists use structure-activity relationships to improve the "hits" into "lead candidates" by optimizing their selectivity against the specific target, reducing drug activity against non-targets, and ensuring appropriate pharmacokinetic properties involving drug distribution and clearance.

These are tough times for the drug industry, as companies are looking at diminishing pipelines of potential new drugs, growing competition from generic versions of their drugs and increasing pressure from regulatory agencies to ensure that products are both safe and more effective than existing drugs. With the completion of sequencing of the human genome there are now greater challenges facing the drug industry for applications of new technologies in discovery and development. The number of drug targets once considered to be less than 500, has doubled and is expected to increase tenfold. Diseases that were once thought to be caused by a single pathology are now known to have differing etiologies requiring highly specific medications. In order to maintain its pipeline of new drugs, the drug industry is integrating biopharmaceuticals, such as therapeutic antibodies (e.g., in the treatment of arthritis), along with small-molecule drugs. As the drug industry undergoes reform, drug companies are developing collaborations with academia for new sources of drug molecules.

The editors of this textbook are all medicinal chemists, and our approaches to editing this seventh edition of *Foye's Principles of Medicinal Chemistry* are influenced by our respective academic backgrounds. We believe that our collaboration on this textbook represents a melding of our perspectives that will provide new dimensions of appreciation and understanding for all students. In

addition we recognize the benefits of medicinal chemistry can only be valuable if the science can be translated into improving the quality of life of our patients. As a result it is essential that the student apply the chemistry of the drugs to their patients and we have attempted to bridge the gap between the science of drugs and the real life situations through the use of scenarios and case studies. Finally in editing this multi-authored book we have tried to promote a consistent style in the organization of the respective chapters.

ORGANIZATIONAL PHILOSOPHY

The organizational approach taken in this textbook builds from the principles of drug discovery, physicochemical properties of drug molecules, and ADMET (absorption-distribution-metabolism-excretion-toxicity) to their integration into therapeutic substances with application to patient care. Our challenge has been to provide a comprehensive description of drug discovery and pharmacodynamic agents in an introductory textbook. To address the increasing emphasis in U.S. pharmacy schools on integrating medicinal chemistry with pharmacology and clinical pharmacy and the creation of one-semester principle courses, we organized the book into four parts: Part I: Principles of Drug Discovery; Part II: Drug Receptors Affecting Neurotransmission and Enzymes as Catalytic Receptors; Part III: Pharmacodynamic Agents (with further subdivision into drugs affecting different physiologic systems); and Part IV: Disease State Management. Parts I and II are designed for a course focused on principles of drug discovery and Parts II through IV are relevant to integrated courses in medicinal chemistry/pharmacodynamics/pharmacotherapeutics.

WHAT IS NEW IN THIS EDITION

The pharmacist sits at the interface between the healthcare system and the patient. The pharmacist has the responsibility for improving the quality of life of the patient by assuring the appropriate use of pharmaceuticals. To do this appropriately, the pharmacist must bring together the basic sciences of chemistry, biology, biopharmaceutics and pharmacology with the clinical sciences. In an attempt to relate the importance of medicinal chemistry to the clinical sciences, each of the chapters in Part II, Pharmacodynamic Agents, through Part IV, Disease State Management, includes the following:

- **A clinical significance section:** At the beginning of most chapters, a practicing clinician has provided a statement of the clinical significance of medicinal chemistry to the particular therapeutic class of drugs.
- **A clinical scenario section:** At the beginning of the chapters in Part III and IV the clinician has provided a brief clinical scenario (mini-case) or real-life therapeutic problem related to the disease state under consideration. A solution to the case or problem appears at the end of the chapter along with the medicinal chemist's analysis of the solution. The intent of this section is to pose a problem at the beginning of the chapter to stimulate the student's thinking as he/she reads through the chapter and then bring the learning "full circle" with the clinician's and chemist's solution to the case/problem revealed once the entire chapter has been read.
- **A case study:** Each of the above chapters ends with a case study (see the "Introduction to Medicinal Chemistry Case Studies" section of this preface). As with previous editions of Foye's Principles of Medicinal Chemistry these cases are meant help the student evaluate their comprehension of the therapeutically relevant chemistry presented in the chapter and apply their understanding in a standardized format to solving the posed problem. All cases presented in this text underwent review by a practicing pharmacist to ensure clinical accuracy and relevance to contemporary practice.

In addition, the reader will find at the beginning of most chapters a list of drugs (presented by generic or chemical names) discussed in that chapter. Additionally, at the beginning of each chapter, one will find a list of the commonly used abbreviations in the chapter.

Several new chapters appear in the seventh edition, including Chapter 5, Membrane Drug Transporters; Chapter 16, Anesthetics: General and Local Anesthetics; Chapter 19, CNS Stimulants and Drugs of Abuse; and Chapter 42, Obesity and Nutrition. Lastly, a second color has been added to this edition to help emphasize particular points in the chapters. In most figures where drug metabolism occurs the point of metabolism is highlighted in red with coloration of the functionality which has been changed.

STUDENT AND INSTRUCTOR RESOURCES

Student Resources

A Student Resource Center at http://thePoint.lww.com/Lemke7e includes the following materials:

- Full Text Online
- Additional Case Studies
- Answers to Additional Case Studies
- Practice Quiz Questions
- Drug Updates
- U.S. Drug Regulation: An Overview

Instructor Resources

We understand the demand on an instructor's time. To facilitate and support your educational efforts, you will have access to Instructor Resources upon adoption of *Foye's Principles of Medicinal Chemistry, 7th edition.* An Instructor's Resource Center at http://thePoint.lww.com/Lemke7e includes the following:

- Full Text Online
- Image Bank
- Answers to In-Text Case Studies
- Angel/Blackboard/WebCT Course Cartridges
- U.S. Drug Regulation: An Overview

ACKNOWLEDGEMENTS

We are indebted to our talented and conscientious contributors, for without them this book would not exist. This includes chapter authors, clinicians who wrote both the clinical significance sections and scenarios, and to Victoria Roche and Sandy Zito for creation of the exciting and educational case studies. We also thank our respective academic institutions for the use of institutional resources and for the freedom to exercise the creative juices needed to bring new ideas to a textbook in medicinal chemistry.

We are grateful for the many people at Lippincott Williams & Wilkins who were there to answer questions, make corrections, and support us through their encouraging words. Many of those who shepherded this book through the complex process of publication worked behind the scene and are not known to us, but we specifically acknowledge Andrea M. Klingler and Paula Williams (Product Managers), and David Troy (Acquisitions Editor) for their kind and gentle prodding.

Finally, we want to acknowledge our respective spouses, Pat and Gail, who were supportive of this time-consuming labor of love. Untold hours were spent away from the family sitting in front of our computers in order to bring this project to fruition.

Thomas L. Lemke, PhD
David A. Williams, PhD

INTRODUCTION TO MEDICINAL CHEMISTRY CASE STUDIES

We are pleased to share our newest medicinal chemistry case studies with student and faculty users of *Foye's Principles of Medicinal Chemistry*. One case study is provided at the end of most chapters. This preface is written to explain their scope and purpose, and to help those who are unfamiliar with our technique of illustrating the therapeutic relevance of chemistry get the most out of the exercise.

Like the more familiar therapeutic case studies, medicinal chemistry case studies are clinical scenarios that present a patient in need of a pharmacist's expert intervention. The learner, most commonly in the role of the pharmacist, evaluates the patient's clinical and personal situation and makes a drug product selection from a limited number of therapeutic choices. However, in a medicinal chemistry case study, only the structures of the potential therapeutic candidates are given. To make their professional recommendation, students must conduct a thorough analysis of *key structure activity relationships (SAR)* in order to predict such things as relative potency, receptor selectivity, duration of action and potential for adverse reactions, and then apply the knowledge gained to meet the patient's therapeutic needs.

The therapeutic choices we offer in each case have been purposefully selected to allow students to review the therapeutically relevant chemistry of different classes of drugs used to treat a particular disease. We recognize that this approach might occasionally omit some compounds viewed by practitioners as drugs of choice within a class or the formulary entry at their practice sites. Faculty employing the cases as in-class or take-home assignments might alter the structural choices provided to meet their teaching and learning goals, and this is certainly acceptable. Regardless of how they are used, students working thoughtfully and scientifically through the cases will not only master chemical concepts and principles and reinforce basic SAR, but also learn how to actively use their unique knowledge of drug chemistry when thinking critically about patient care. This skill will be invaluable when, as practitioners, they are faced with a full gamut of therapeutic options to analyze in order to ensure the best therapeutic outcomes for their patients.

In short, here's what we hope students will gain by working our cases.

- Mastery of the important concepts needed to be successful in the medicinal chemistry component of the pharmacy curriculum;
- An ability to identify the relevance of drug chemistry to pharmacological action and therapeutic utility, and to discriminate between therapeutic options based on that understanding;
- An enhanced ability to think critically and scientifically about drug use;
- A commitment to caring about the impact of professional decisions on patients' quality of life;
- The ability to demonstrate the unique role of the pharmacist as the chemist of the health care team.

We hope you find these case studies both challenging and enjoyable, and we encourage you to use them as a springboard to more in-depth discussions with your faculty and/or colleagues about the role of chemistry in rational therapeutic decision-making.

Victoria F. Roche, PhD
S. William Zito, PhD

Contributors

Ali R. Banijamali, PhD
Ironwood Pharmaceuticals
Cambridge, MA

Raymond G. Booth, PhD
University of Florida
College of Pharmacy
Gainsville, FL

Ronald Borne, PhD
The University of Mississippi
School of Pharmacy
University, MS

Robert W. Brueggemeier, PhD
The Ohio State University
College of Pharmacy
Columbus, OH

James T. Dalton, PhD
The Ohio State University
College of Pharmacy
Columbus, OH

Małgorzata Dukat, PhD
Virginia Commonwealth University
School of Pharmacy
Richmond, VA

E. Kim Fifer, PhD
University of Arkansas for Medical Sciences
College of Pharmacy
Little Rock, AR

Elmer J. Gentry, PhD
Chicago State University
College of Pharmacy
Chicago, IL

Marc Gillespie, PhD
St. John's University
College of Pharmacy and Allied Health Professions
Queens, NY

Richard A. Glennon, PhD
Virginia Commonwealth University
School of Pharmacy
Richmond, VA

Robert K. Griffith, PhD
West Virginia University
School of Pharmacy
Morgantown, WV

Marc Harrold, PhD
Duquesne University
Mylan School of Pharmacy
Pittsburgh, PA

Peter J. Harvison, PhD
University of the Sciences in Philadelphia
Philadelphia College of Pharmacy
Philadelphia, PA

Sunil S. Jambhekar, PhD
Lake Erie College of Osteopathic Medicine
Bradenton, FL

David A. Johnson, PhD
Duquesne University
Mylan School of Pharmacy
Pittsburgh, PA

Stephen Kerr, PhD
Massachusetts College of Pharmacy and Health
School of Pharmacy
Boston, MA

Douglas Kinghorn, PhD
The Ohio State University
College of Pharmacy
Columbus, OH

James J. Knittel, PhD
Western New England College
School of Pharmacy
Springfield, MA

Vijaya L. Korlipara, PhD
St. John's University
College of Pharmacy and Allied Health Professions
Queens, NY

Barbara LeDuc, PhD
Massachusetts College of Pharmacy and Health
School of Pharmacy
Boston, MA

Thomas L. Lemke, PhD
University of Houston
College of Pharmacy
Houston, TX

Mark Levi, PhD
US Food & Drug Administration
National Center for Toxicological Research
Division of Neurotoxicology
Jefferson, AR

Matthias C. Lu, PhD
University of Illinois at Chicago
College of Pharmacy
Chicago, IL

Timothy Maher, PhD
Massachusetts College of Pharmacy and Health Sciences
School of Pharmacy
Boston, MA

Ahmed S. Mehanna, PhD
Massachusetts College of Pharmacy and Health Sciences
School of Pharmacy
Boston, MA

Duane D. Miller, PhD
The University of Tennessee
College of Pharmacy
Memphis, TN

Nader H. Moniri
Mercer University
College of Pharmacy and Health Sciences
Atlanta, GA

Marilyn Morris, PhD
University of Buffalo - SUNY
School of Pharmacy and Pharmaceutical Sciences
Buffalo, NY

Bridget L. Morse
University of Buffalo - SUNY
School of Pharmacy and Pharmaceutical Sciences
Buffalo, NY

Wendel L. Nelson, PhD
University of Washington
School of Pharmacy
Seattle, WA

John L. Neumeyer, PhD
Harvard Medical School
McLean Hospital
Belmont, MA

Gary O. Rankin, PhD
Marshall University
School of Medicine
Huntington, WV

Edward B. Roche, PhD
University of Nebraska
College of Pharmacy
Omaha, NE

Victoria F. Roche, PhD
Creighton University
School of Pharmacy and Health Professions
Omaha, NE

David A. Williams, PhD
Massachusetts College of Pharmacy and Health Sciences
School of Pharmacy
Boston, MA

Norman Wilson, BSc, PhD, CChem, FRSC
University of Edinburgh
Edinburgh, Scotland

Patrick M. Woster, PhD
Medical University of South Carolina
College of Pharmacy
Charleston, SC

Tanaji T. Talele, PhD
St. John's University
College of Pharmacy and Allied Health Professions
Queens, NY

Robin Zavod, PhD
Midwestern University, Chicago
College of Pharmacy
Chicago, IL

S. William Zito, PhD
St. John's University
College of Pharmacy and Allied Health Professios
Queens, NY

Clinical Scenario and Clinical Significance

Paul Arpino, RPh
Harvard Medical School
Department of Pharmacy
Massachusetts General Hospital
Boston, MA

Kim K. Birtcher, MS, PharmD, BCPS, CDE, CLS
University of Houston
College of Pharmacy
Houston, TX

Jennifer Campbell, PharmD
Creighton University
School of Pharmacy and Health Professions
Omaha, NE

Judy Cheng, PharmD
Massachusetts College of Pharmacy and Health Sciences
School of Pharmacy
Boston, MA

Elizabeth Coyle, PharmD
University of Houston
College of Pharmacy
Houston, TX

Joseph V. Etzel, PharmD
St. John's University
College of Pharmacy and Allied Health Professions
Queens, NY

Marc Gillepspie, PhD
St. John's University
College of Pharmacy and Allied Health Professions
Queens, NY

Michael Gonyeau, PharmD, BCPS
Northeastern University
School of Pharmacy
Boston, MA

David Hayes, PharmD
University of Houston
College of Pharmacy
Houston, TX

Elizabeth B. Hirsch, PharmD, BCPS
Northeastern University
School of Pharmacy
Boston, MA

Jill T. Johnson, PharmD, BCPS
University of Arkansas for Medical Sciences
College of Pharmacy
Little Rock, AR

Vijaya L. Korlipara, PhD
St. John's University
College of Pharmacy and Allied Health Professions
Queens, NY

Beverly Lukawski, PharmD
Creighton University
School of Pharmacy and Health Professions
Omaha, NE

Timothy Maher, PhD
Massachusetts College of Pharmacy and Health Sciences
School of Pharmacy
Boston, MA

Susan W. Miller, PharmD
Mercer University
College of Pharmacy and Health Sciences
Atlanta, GA

Kathryn Neill, PharmD
University of Arkansas for Medical Sciences
College of Pharmacy
Little Rock, AR

Kelly Nystrom, PharmD, BCOP
Creighton University
School of Pharmacy and Health Professions
Omaha, NE

Nancy Ordonez, PharmD
University of Houston
College of Pharmacy
Houston, TX

Anne Pace, PharmD
University of Arkansas for Medical Sciences
College of Pharmacy
Little Rock, AR

Nathan A. Painter, PharmD, CDE
University of California, San Diego
Skaggs School of Pharmacy and Pharmaceutical Science
La Jolla, CA

Thomas L. Rihn, PharmD
Duquesne University
School of Pharmacy
Pittsburgh, PA

Jeffrey T. Sherer, PharmD, MPH, BCPS, CGP
University of Houston
College of Pharmacy
Houston, TX

Douglas Slain, PharmD, BCPS
West Virginia University
College of Pharmacy
Morgantown, WV

Autumn Stewart, PharmD
Duquesne University
School of Pharmacy
Pittsburgh, PA

Tanaji T. Talele, PhD
St. John's University
College of Pharmacy and Allied Health Professions
Queens, NY

Mark D. Watanabe, PharmD, PhD, BCPP
Northeastern University
School of Pharmacy
Boston, MA

Reviewers

Michael Adams, PharmD, PhD
Assistant Professor
Pharmaceutical Sciences
Campbell University School of Pharmacy
Buies Creek, NC

Zhe-Sheng Chen, MD, PhD
Associate Professor
Pharmaceutical Science
St. John's University
Queens, NY

John Cooperwood, PhD
Associate Professor
Pharmaceutical Sciences
Florida Agricultural and Mechanical University College of Pharmacy
Tallahassee, FL

Matthew J. DellaVecchia, PhD
Assistant Professor of Pharmaceutical Sciences
Gregory School of Pharmacy
Palm Beach Atlantic University
Palm Beach, FL

Marc Harrold, PhD
Professor of Medicinal Chemistry
Mylan School of Pharmacy
Duquesne University
Pittsburgh, PA

Kennerly Patrick, PhD Med Chem
Professor
Pharmaceutical Sciences
Medical University of South Carolina
College of Pharmacy
Charleston, SC

Tanaji Talele, PhD
Associate Professor of Medicinal Chemistry
Department of Pharmaceutical Sciences
College of Pharmacy & Allied Health Professions
St. John's University
Queens, NY

Ganeshsingh Thakur, PhD
Center for Drug Discovery
Assistant Professor
Pharmaceutical Sciences
Northeastern University
Boston, MA

Constance Vance, PhD
Adjunct Assistant Professor
University of North Carolina at Chapel Hill
Chapel Hill, NC