

# Pharmacokinetics

Second Edition  
Revised and Expanded

Milo Gibaldi  
Donald Perrier



# **Pharmacokinetics**

## DRUGS AND THE PHARMACEUTICAL SCIENCES

*A Series of Textbooks and Monographs*

*Edited by*

**James Swarbrick**

*School of Pharmacy*

*University of North Carolina*

*Chapel Hill, North Carolina*

- Volume 1. PHARMACOKINETICS, *Milo Gibaldi and Donald Perrier (out of print)*
- Volume 2. GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICALS: A PLAN FOR TOTAL QUALITY CONTROL, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV (out of print)*
- Volume 3. MICROENCAPSULATION, *edited by J. R. Nixon (out of print)*
- Volume 4. DRUG METABOLISM: CHEMICAL AND BIOCHEMICAL ASPECTS, *Bernard Testa and Peter Jenner*
- Volume 5. NEW DRUGS: DISCOVERY AND DEVELOPMENT, *edited by Alan A. Rubin*
- Volume 6. SUSTAINED AND CONTROLLED RELEASE DRUG DELIVERY SYSTEMS, *edited by Joseph R. Robinson*
- Volume 7. MODERN PHARMACEUTICS, *edited by Gilbert S. Banker and Christopher T. Rhodes*
- Volume 8. PRESCRIPTION DRUGS IN SHORT SUPPLY: CASE HISTORIES, *Michael A. Schwartz*
- Volume 9. ACTIVATED CHARCOAL: ANTIDOTAL AND OTHER MEDICAL USES, *David O. Cooney*
- Volume 10. CONCEPTS IN DRUG METABOLISM (in two parts), *edited by Peter Jenner and Bernard Testa*
- Volume 11. PHARMACEUTICAL ANALYSIS: MODERN METHODS (in two parts), *edited by James W. Munson*
- Volume 12. TECHNIQUES OF SOLUBILIZATION OF DRUGS, *edited by Samuel H. Yalkowsky*
- Volume 13. ORPHAN DRUGS, *edited by Fred E. Karch*
- Volume 14. NOVEL DRUG DELIVERY SYSTEMS: FUNDAMENTALS, DEVELOPMENTAL CONCEPTS, BIOMEDICAL ASSESSMENTS, *Yie W. Chien*
- Volume 15. PHARMACOKINETICS, Second Edition, Revised and Expanded, *Milo Gibaldi and Donald Perrier*

*Other Volumes in Preparation*

# Pharmacokinetics

SECOND EDITION, REVISED AND EXPANDED

---

---

*Milo Gibaldi*

University of Washington  
School of Pharmacy  
Seattle, Washington

*Donald Perrier*

School of Pharmacy  
University of Arizona  
Tucson, Arizona

**informa**  
healthcare

---

New York London

Informa Healthcare USA, Inc.  
52 Vanderbilt Avenue  
New York, NY 10017

© 2007 by Informa Healthcare USA, Inc.  
Informa Healthcare is an Informa business

No claim to original U.S. Government works  
Printed in the United States of America on acid-free paper  
30 29 28 27 26 25 24 23 22 21

International Standard Book Number-10: 0-8247-1042-8 (Hardcover)  
International Standard Book Number-13: 978-0-8247-1042-2 (Hardcover)

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. A wide variety of references are listed. Reasonable efforts have been made to publish reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequences of their use.

No part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access [www.copyright.com](http://www.copyright.com) (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC) 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

**Visit the Informa Web site at  
[www.informa.com](http://www.informa.com)**

**and the Informa Healthcare Web site at  
[www.informahealthcare.com](http://www.informahealthcare.com)**

## Preface

Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion. It also concerns the relationship of these processes to the intensity and time course of pharmacologic (therapeutic and toxicologic) effects of drugs and chemicals. Pharmacokinetics is a quantitative study that requires a preexisting competence in mathematics at least through calculus. It is also a biologic study and can be very useful to the biomedical scientist.

At a fundamental level, pharmacokinetics is a tool to optimize the design of biological experiments with drugs and chemicals. All biologists would benefit from some knowledge of pharmacokinetics whenever they engage in data analysis. It has become increasingly important in the design and development of new drugs and in the reassessment of old drugs. Clinical applications of pharmacokinetics have resulted in improvements in drug utilization and direct benefits to patients.

There is consensus that the origin of pharmacokinetics can be traced to two papers entitled "Kinetics of distribution of substances administered to the body" written by Torsten Teorell and published in the *International Archives of Pharmacodynamics* in 1937. Since this unheralded beginning, the study of pharmacokinetics has matured rapidly; undoubtedly growth has been stimulated by major breakthroughs in analytical chemistry, which permit us to quantitatively detect minute concentrations of drugs and chemicals in exceedingly small volumes of biological fluids, in data processing, and by the brilliant insights of many scientists. Dost, Kruger-Theimer, Nelson, Wagner, Riegelman, and Levy are among those scientists and must be reserved a special place in the history of the development of pharmacokinetics.

Our goals in preparing this revision were similar to those that prompted us to undertake the initial effort. The need for revision was amply clear to us each time we looked at our files, bulging with research papers and commentaries on pharmacokinetic methods and

applications published since 1975. The buzz words today are clearance concepts, noncompartmental models, and physiologic pharmacokinetics. Again, we strived to present the material in an explicit and detailed manner. We continue to believe that *Pharmacokinetics* can be used in formal courses, for self-study, or for reference purposes.

We thank our colleagues for their work and publications, our staffs for their labors and support, and our families for their love and understanding.

Milo Gibaldi  
Donald Perrier



## Contents

Preface iii

1. One-Compartment Model 1
  - Intravenous Injection 2
  - Intravenous Infusion 27
  - First-Order Absorption 33
  - Apparent Zero-Order Absorption 40
  - References 42
2. Multicompartment Models 45
  - Intravenous Injection 48
  - Intravenous Infusion 63
  - First-Order Absorption 81
  - Determination of Pharmacokinetic Parameters 84
  - References 109
3. Multiple Dosing 113
  - Intravenous Administration 113
  - Intravenous Infusion 128
  - First-Order Absorption 132
  - Determination of Pharmacokinetic Parameters from Multiple-Dosing Data 143
  - References 143
4. Absorption Kinetics and Bioavailability 145
  - Absorption Rate 146
  - Extent of Absorption 167
  - Statistical Considerations in Comparative Bioavailability Studies 185
  - Sustained Release 188
  - References 195

5.	Apparent Volume of Distribution	199
	Relationship Between Volume of Distribution, Drug Binding and Elimination, and Anatomic Volume	200
	Tissue Binding	209
	Estimation of Apparent Volumes of Distribution	211
	References	218
6.	Kinetics of Pharmacologic Response	221
	Kinetics of Directly Reversible Pharmacologic Response	221
	Kinetics of Indirect Pharmacologic Response	245
	Kinetics of Irreversible Pharmacologic Response	254
	Appendix: Solutions for $C_S$ , $C_X$ , and $C_T$ for Cell Systems Sensitive to Drugs That are Cell Cycle Specific	265
	References	267
7.	Nonlinear Pharmacokinetics	271
	Michaelis-Menten Kinetics	271
	Some Pharmacokinetic Characteristics of Michaelis-Menten Processes	272
	In Vivo Estimation of $K_m$ and $V_m$	277
	Clearance, Half-Life, and Volume of Distribution	287
	Drug Concentration at Steady State	289
	Time to Steady State	290
	Area Under the Curve and Bioavailability	294
	Composition of Urinary Excretion Products	297
	Other Nonlinear Elimination Processes	301
	Enzyme Induction	303
	Nonlinear Binding	307
	Some Problems in Quantifying Nonlinear Pharmacokinetics	313
	References	315
8.	Clearance Concepts	319
	Organ Clearance	319
	Total Clearance	321
	Hepatic Clearance	322
	Hepatic Clearance and Drug Binding in Blood	327
	Drug Binding and Free Drug Concentration	330
	Half-Life, Intrinsic Clearance, and Binding	331
	First-Pass Effect	332
	Gut Wall Clearance	336
	Lung Clearance	338
	Renal Clearance	341
	Clearance Concepts Applied to Metabolites	344
	Physical Models of Organ Clearance	347
	Blood Clearance Versus Plasma Clearance	349
	References	351

- 9. **Physiological Pharmacokinetic Models** 355
  - Blood Flow Rate-Limited Models 358
  - Experimental Considerations 364
  - Blood Clearance 366
  - Lung Clearance 368
  - Apparent Volume of Distribution 369
  - Nonlinear Disposition 370
  - Membrane-Limited Models 372
  - Species Similarity and Scale-Up 375
  - References 382
  
- 10. **Application of Pharmacokinetic Principles** 385
  - Multiple Dosing 385
  - Dose Adjustments in Renal Failure 393
  - Hemodialysis 397
  - Methods for Determination of Individual Patient Parameters 401
  - References 405
  
- 11. **Noncompartmental Analysis Based on Statistical Moment Theory** 409
  - Statistical Moments 410
  - Bioavailability 411
  - Clearance 411
  - Half-Life 412
  - Absorption Kinetics 413
  - Apparent Volume of Distribution 413
  - Fraction Metabolized 414
  - Predicting Steady-State Concentrations 414
  - Predicting Time to Steady State 415
  - Conclusions 416
  - References 416
  
- Appendix A **Method of Laplace Transforms** 419
  - References 423
  
- Appendix B **Method for Solving Linear Mammillary Models** 425
  - References 431
  
- Appendix C **Method of Residuals** 433
  
- Appendix D **Estimation of Areas** 445
  - Reference 449
  
- Appendix E **Prediction of Drug Concentrations on Multiple Dosing Using the Principle of Superposition** 451
  - References 457

Appendix F Estimation of Rates	459
Reference	463
Appendix G Selective Derivations	465
Michaelis-Menten Equation	465
Time To Reach a Fraction of Steady State for a Drug Eliminated by Parallel First-Order and Capacity-Limited Processes	467
Reference	473
Appendix H Computer Programs	475
References	476
Author Index	479
Subject Index	489