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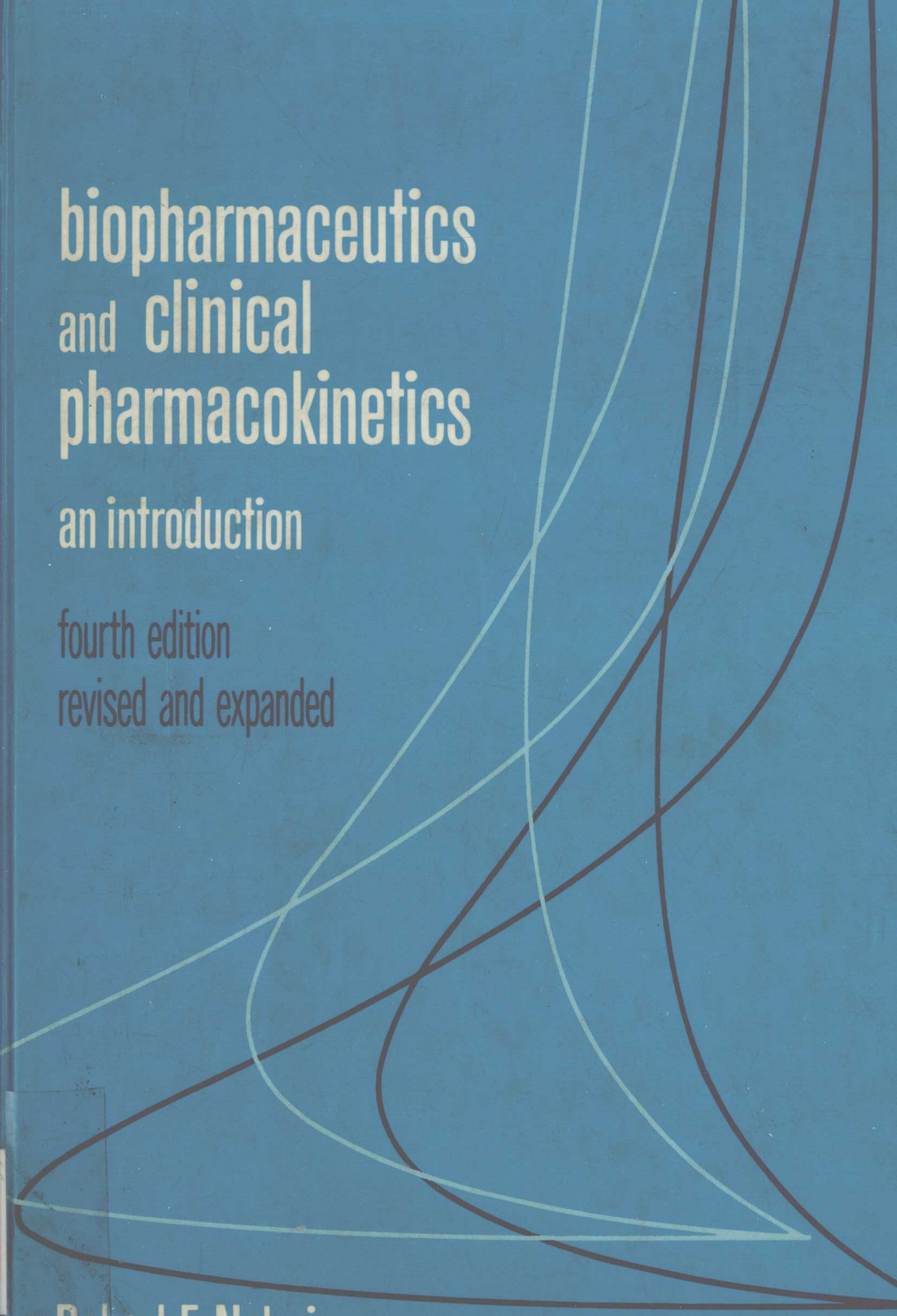
an introduction

fourth edition
revised and expanded



Robert E. Notari

Biopharmaceutics and Clinical Pharmacokinetics

AN INTRODUCTION

Fourth Edition, Revised and Expanded

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MARCEL DEKKER, INC. New York and Basel

Library of Congress Cataloging-in-Publication Data

Notari, Robert E.
Biopharmaceutics and clinical pharmacokinetics.

Includes bibliographies and index.
1. Biopharmaceutics. 2. Pharmacokinetics. I. Title.
[DNLM: 1. Biopharmaceutics. 2. Kinetics.
3. Pharmacology. QV 38 N899b]
RM301.4.N67 1987 615'.7 86-13548
ISBN 0-8247-7523-6

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Biopharmaceutics and Clinical Pharmacokinetics

To my parents

Preface to the Fourth Edition

Biopharmaceutics and pharmacokinetics are quantitative subjects. One cannot appreciate their meaning simply by reading about them any more than one could learn mathematics by reading descriptions of it. This text is designed to help the reader to discover their meaning through experience in the manner that a researcher would gain such insight. The experience is provided by analyzing data presented in problems. These problems are strategically placed to complement the descriptions of each concept, thus making this text a workbook. The format can best be regarded as a complete course, wherein the subjects are presented in sequence. The student is expected to interact by solving problems, but may, depending upon the level of past experiences, omit material. Based on this text a typical course outline might be:

I. Introduction and Overview
II. Kinetic Analysis of Data: Order and Rate Constants
III. Kinetics of Drug Transport Through Membranes
IV. Model-Independent versus Compartmental Model Pharmacokinetic Analyses
V. Biopharmaceutics in the Evaluation and Design of Drug Delivery Systems
VI. Dosage Regimen Design and Adjustment in Renal Failure
VII. Pharmacokinetic Evaluation and Design in Molecular Modification
VIII. Application of Pharmacokinetics to Drug Therapy

Presentation of these subjects is meant to form a logical chain. Chapter 1 gives an historical perspective, emphasizing the half-century lag period between the awareness of drug product quality and the concern for bioavailability. The kinetic analysis of data comprises Chapter 2, which teaches how to plot

data to treat first-order, zero-order, or Michaelis-Menten kinetics. Drug transport is addressed in Chapter 3, which extends kinetic analyses to active and passive transport, the influence of protein binding and pH, and data treatment involving asymptotic values. The calculation of pharmacokinetic parameters based on model-independent analyses is presented in Chapter 4. Because of widespread use of modeling in the literature, one-, two-, and three-compartment open-model methods, together with their limitations, are also presented. Biopharmaceutics is treated in Chapter 5, which stresses how the formulation can influence the drug plasma concentration time-course. It includes factors influencing absorption, clinical assessment of bioavailability, design of controlled-release devices, and clinical evaluations. Since these subjects entail analyses of drug plasma concentration time-courses, biopharmaceutics is intentionally placed after the pharmacokinetic chapter, which deals with the fate of a drug introduced into the blood. Dosage regimens are covered in Chapter 6, which presents the kinetic determination of size and frequency of dosing to achieve desired clinical endpoints, together with methods for individualizing regimens in disease states such as renal failure. The evaluation of molecular effects on pharmacokinetics is a unique aspect of this text. Chapter 7 discusses how the structure can influence the time-course of drug in the blood in contrast to the influence of the formulation. It is aimed at casting aside many common misconceptions regarding comparisons of pharmacokinetic data for prodrugs and closely related analogs; several classes of antibiotics are reviewed to illustrate these effects. Finally, Chapter 8 addresses how the patient can influence the pharmacokinetic behavior of the drug and what compensatory measures are appropriate. It begins with a survey of factors which may alter drug pharmacokinetics beyond what is therapeutically acceptable. The monitoring of drug plasma levels and dosage adjustments of five agents are then reviewed as examples wherein risk dictates individualization. The level of expertise gained by completing this sequence should allow the reader to understand the literature and to enter a higher-level course with a thorough appreciation for the significance of the subjects.

One of the primary changes made in this edition is the stress on model-independent pharmacokinetics. A section on classical pharmacokinetic modeling is included for completeness, but its limitations are also emphasized. In keeping with this goal, the symbols published by the Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology (1982) have been adopted (see the Appendix, p. 405). This system allows a single model-independent definition for terms which otherwise require separate symbols for each model. For a more detailed explanation, see Nomenclature (p. xix). Other notable changes include an increased number of problems, an expanded treatment of bioavailability, and a reduction in

the fundamentals of those kinetics which precede pharmacokinetics, so that the reader's preparatory time to reach the title subject is minimized. Logarithmic tables are deleted from this edition as it is assumed that pocket calculators have made them obsolete. The reader will find a calculator that will handle exponentials to base e is convenient in the dosage regimen calculations.

Any criticisms, suggestions, or questions would be most gratefully received by the author.

Robert E. Notari

Preface to the Third Edition

The first edition, written during the 1960s and published in 1971, noted that "The approaches discussed here may seem a bit too sophisticated and costly to the reader who has not previously come upon the concept of an individualized dosage regimen." This statement followed a discussion suggesting that "pharmacokinetics will make an ever increasing contribution to the rational clinical use of drugs . . ." The second edition (1975) contained "a new addition covering dosage regimen calculations in patients with normal renal function or with renal failure," together with an additional chapter on the pharmacokinetic aspects of molecular modification. The latter was described as "a field which is relatively undeveloped." These applications of pharmacokinetics were minor components in the second edition and absent from the first edition.

The immense progress in these two areas, clinical pharmacokinetics and pharmacokinetic drug design, has necessitated the writing of this third edition. They now occupy roughly one-half of this text. Chapters 5 and 7 are devoted to clinical pharmacokinetics. The application of pharmacokinetics to drug design and evaluation comprises Chapter 6, the longest in the text. Progress in the development of prodrugs represents a major portion of this expanded chapter.

I must reemphasize that the text is not intended as a review but rather an introduction. Development of concepts is the primary goal, and examples have been selected to illustrate them. Problem solving by the reader remains the *modus operandi* for comprehending the principles and their applications. As in previous editions, it is the author's hope that this text will provide a starting place for those who wish to pursue further study or who want only a simplified but quantitative appreciation of the field.

The many inquiries I have received over the years have proven invaluable in identifying areas for revision. I am most grateful to all those who have

graciously given helpful comment or asked for clarification; both provide insight that an author cannot attain for himself. I particularly wish to acknowledge Dr. Adam Danek, Dr. Jacek Bojarski, and Dr. Halina Krasowska, who stimulated the publication of the second edition in Poland (1978) and who translated the English edition into Polish. This experience provided great encouragement to me, and the questions surrounding the translation called attention to several ambiguities that have led to rewording in the third edition. The continued beautiful art work of Yvonne Holsinger and the excellent typing of Sue Sheffield are most sincerely appreciated.

I would be grateful to receive any comments or questions from readers of the third edition as I truly regard both as a service to the author.

Robert E. Notari

Preface to the Second Edition

The objectives of this book are identical to those of the first edition. It is a place to begin your studies—an introduction. Hopefully, it is both simple and accurate. And the agreement between reader and author has also remained constant. This is a workbook. If you are willing to work the problems, the principles should become meaningful to you by the process of discovery.

To that end the second edition has been modified to make it more self-sufficient. As each new principle is introduced, two types of problems are presented. Sample problems are completely solved so that you can diagnose your error when your answer is not correct (and assuming that mine is!). Practice problems are designed to test your ability to apply what you have learned. They are generally slightly more difficult.

The constancy of objectives is not a reflection of a lack of progress in the field or a lack of change between the editions. Indeed, the second edition is largely a new book. In accomplishing the updating and improving of the book, the author gratefully acknowledges the indispensable contributions of co-authors Joyce L. DeYoung (Chapters 2 and 3) and Raymond C. Anderson (Chapter 5).

Those who are familiar with the first edition will find it helpful to know what changes have been made. Chapter 2 and 3 have been completely rewritten and restyled. While they cover the same subject matter, the order of presentation is different. Chapter 2 now contains pharmacokinetic models and the basic kinetics required to understand them. For example, a beaker is still used to teach two-compartment model kinetics, but it is immediately followed by the analogous situation in pharmacokinetics. The basic kinetics are therefore kept minimal and limited to models with pharmacokinetic counterparts. Chapter 3 contains methods and discussions for calculating pharmacokinetic parameters. Among the notable changes is the expansion of the section dealing with the apparent volume of distribution. This has

been completely updated to include both discussion and equations regarding variation in calculated values obtained by different methods for multicompartmental drugs.

Chapter 4 has been expanded. It begins with a revised section on the interpretation of blood level curves and ends with a new addition covering dosage regimen calculations in patients with normal renal function or with renal failure. This latter area is one of the most widely recognized contributions of pharmacokinetic sciences to improved clinical therapy.

Chapter 5 is a new addition to the book. It is aimed at fostering both an understanding and an interest in the effects of molecular manipulation on pharmacokinetic parameters and the resultant pharmacologic impact. This is a field which is relatively undeveloped (as compared with studies on dosage-form effects) but which will be a key to future evaluation and development of new drugs.

The second edition is amply referenced. Each chapter provides sufficient citations for the interested reader to check on the validity or limitations of the subject matter presented or to become more familiar with a particular field.

Again, I would greatly appreciate receiving comments, criticisms, suggestions, opinions, or notifications of errors regarding any section of the book. A similar invitation in the preface to the first edition was accepted by several people, whose comments had a direct influence on the production of the second edition. While I cannot cite them all, I would particularly like to thank Dr. Adam Danek, Dr. Gerald E. Schumacher, Dr. Donald A. Zuck, and Dr. James W. Ayres for their helpful suggestions, encouraging comments, and poignant questions.

Robert E. Notari

Preface to the First Edition

This book is designed as an introductory text for use in formal courses or for self-study. It is aimed at both biomedical researchers and practitioners. The book assumes no prior knowledge of either kinetics or calculus on the part of the reader. Derivations are provided for those who are mathematically inclined. Those who are not may simply make use of the final or "working" equations. None of the subjects is beyond the level of comprehension of an advanced undergraduate with no calculus background. However, one must approach this book "actively," with graph paper and pencil in hand and with desire to learn well in mind. The material is presented in "building-block" fashion, and it is imperative that the user solve the examples and practice problems to have all of the pieces necessary to build a solid foundation. Topics are covered in a cumulative manner, and skipping a principle will almost certainly result in an inability to understand a subsequent topic fully. Although it is not a programmed text, it must be approached in the same fashion—as a workbook. Casual reading will not suffice.

One problem that faces those who develop an interest in learning biopharmaceutics and pharmacokinetics for the first time is how to get started. Byron once wrote, "Nothing is more difficult than a beginning." This is certainly true for the present subject. Most current references are not written at the basic introductory level. They assume that the reader has some level of sophistication in either calculus or kinetics or both. In addition they do not provide for active participation in the form of problem solving. A teacher wishing to develop a course would have to do so from the literature. Yet it is difficult to read the literature without a fundamental knowledge of the field. This book is meant to provide that knowledge for teachers, students, biomedical practitioners, and research scientists in medicinal chemistry, pharmacology, pharmacy, and other biomedical disciplines. Chapters 2 and 3 comprise the basic introductory materials, and Chapter 4 illustrates some

of the applications. An understanding of this text should provide sufficient introduction to the field to allow further reading of more complex applications in the literature.

During the past six years I have been teaching biopharmaceutics to senior students in the College of Pharmacy of The Ohio State University. The absence of a textbook for the course has presented a number of difficulties. Although assigned readings of review articles and selected chapters have proven helpful, they fail to provide the structural foundation that a textbook achieves. Students repeatedly failed to visualize the total structure of the subject material until the course was nearly complete in spite of the fact that detailed syllabi and other outlines were distributed each quarter. Students were generally accustomed to working with a required text which serves to define the course goals in much more detail and provides a means for reading ahead. Furthermore, when a student experienced difficulties in solving homework problems, there was no reference book to provide additional information over and above that found in the lecture notes. Problem sets had to be created, printed, and distributed in lieu of an available source such as a required text. There was no provision for additional practice problems for the student who felt the need for such experience.

As a result, the outlines, problem sets, graphic demonstrations, classroom handouts, short presentations of principles, etc., grew in both number and in size until some of the materials distributed to the class approached the size of a chapter or even a small book. Most of the contents of this text have evolved from the development of these undergraduate teaching aids. Some of the subject matter was added later to accommodate an intermediate level graduate course. All of the examples and practice problems have been worked many times over by undergraduate and graduate students alike. Over the past two years (and prior to its publication) the book has been successfully used as a required text in both undergraduate and graduate courses here at Ohio State.

It would be impossible to list the names of all those students whose comments and general interest served to stimulate the writing of this book as well as to influence its contents and mode of presentation. Certainly I must acknowledge the graduating classes of the College of Pharmacy of The Ohio State University from 1965 through 1971, who had the dubious honor of serving as "guinea pigs" for the development of this course. Sincere thanks for their patience and enthusiasm. It is with pleasure that I thank the graduate students and faculty who read the text and in some cases helped develop the problems and examples. Among them I wish especially to acknowledge the efforts of Miss Marilyn Lue Chin, Mrs. Joyce DeYoung, Imtiaz Chaudry, Raymond Anderson, and Dr. Richard H. Reuning. The physical appearance

of the text is a testimonial to the fine art work of Mrs. Yvonne Holsinger and the excellent typing of Miss Carol J. Lusk.

Finally, any comments, criticisms, suggestions, errors or improvements would be most gratefully received by the author.

Robert E. Notari

Nomenclature

Those who are familiar with the nomenclature system involving A, α, B, β may find it helpful to examine its relationship to the system used herein [1]. For a complete listing of symbols and their definitions, please see the Appendix (p. 405). It is a simple system wherein each exponential multiplier is given the same symbol, λ, subscripted sequentially until the final entry, which is always given the subscript z, i.e., λ_Z. Thus, the counterparts to the older systems are given by the following, where C is concentration in plasma following intravenous administration:

monoexponential

$$C = C_0 e^{-Kt}$$

$$C = C(0)e^{-\lambda_Z t}$$

biexponential

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

$$C = C_1 e^{-\lambda_1 t} + C_Z e^{-\lambda_Z t}$$

triexponential

$$C = Ae^{-\alpha t} + Be^{-\beta t} + Ge^{-\gamma t}$$

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_Z e^{-\lambda_Z t}$$

A model-independent definition for biological half-life is thus $t_{1/2} = 0.693/\lambda_Z$, which fits the mono-, bi-, and triexponential situation without having to rewrite the equation in terms of K, β, and γ. Similarly, clearance may be defined as $CL = \lambda_Z V_Z$, where V_Z is defined as (DOSE)/(AUC)(λ_Z). Both of these are model-independent definitions which apply to all three cases.

The remainder of the nomenclature is sufficiently similar to popularly employed systems to require no explanation. The primary change lies in the use of λ and the apparent volume of distribution, V_Z. These are based on

sufficient logic to make them easily acceptable on usage especially since they afford such convenience in making model-independent definitions.

REFERENCE

1. *Manual of Symbols, Equations and Definitions in Pharmacokinetics*, Committee for Pharmacokinetic Nomenclature, American College of Clinical Pharmacology, Philadelphia, Pennsylvania, 1982.