# Biopharmaceutics and Clinical Pharmacokinetics

Fourth Edition

Milo Gibaldi

# *Biopharmaceutics and Clinical Pharmacokinetics*

MILO GIBALDI, PH.D.

*Dean, School of Pharmacy*
*Associate Vice President,*
*Health Sciences*
*University of Washington*
*Seattle, Washington*

FOURTH EDITION



LEA & FEBIGER • Philadelphia • London • 1991

Lea & Febiger
200 Chester Field Parkway
Malvern, Pennsylvania 19355-9725
U.S.A.
(215) 251-2230
1-800-444-1785

Lea & Febiger (UK) Ltd.
145a Croydon Road
Beckenham, Kent BR3 3RB
U.K.

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

Gibaldi, Milo.
Biopharmaceutics and clinical pharmacokinetics / Milo Gibaldi.—4th ed.
p. cm.
Includes bibliographical references.
ISBN 0-8121-1346-2
1. Biopharmaceutics. 2. Pharmacokinetics. I. Title
[DNLM: 1. Biopharmaceutics. 2. Pharmacokinetics. QV 38 G437b]
RM301.4.G53 1990
615'.7—dc20
DNLM/DLC
for Library of Congress 90-5614
CIP

*First Edition, 1971*
Reprinted 1973, 1974, 1975
*Second Edition, 1977*
Reprinted 1978, 1979, 1982
*Third Edition, 1984*
Reprinted 1988
*Fourth Edition, 1991*
*First Spanish Edition, 1974*
*First Japanese Edition, 1976*
*Second Japanese Edition, 1981*
*Second Turkish Edition, 1981*



PRINTED IN THE UNITED STATES OF AMERICA

Print no.: 4 3 2 1

*To Florence and Ann*

# *Preface*

Biopharmaceutics is a major branch of the pharmaceutical sciences; it concerns the relationship between the physical and chemical properties of a drug in a dosage form and the pharmacologic, toxicologic, or clinical response observed after its administration. The study of biopharmaceutics has been extended beyond that of a descriptive discipline by the development of pharmacokinetics, which concerns the study and characterization of the time course of drug absorption, distribution, metabolism, and excretion, as well as the relationship of these processes to the intensity and time course of therapeutic and adverse effects of drugs. Pharmacokinetics involves the application of mathematics and biochemistry in a physiologic and pharmacologic context. The development of clinical pharmacokinetics is the culmination and logical outcome of advances in the areas of pharmacokinetics, clinical pharmacology, toxicology, analytic chemistry, biopharmaceutics, and therapeutics. Simply stated, clinical pharmacokinetics is a health sciences discipline that deals with the application of pharmacokinetics to the safe and effective therapeutic management of the individual patient.

At one time it was common to assume that the response to a drug was simply a function of intrinsic pharmacologic activity, to define potency in terms of a milligram per kilogram dose, and to compare the "potencies" of drugs with similar pharmacologic effects, without a proper frame of reference. Today, it is recognized that dose-response relationships are not the same after oral and parenteral administration of a drug or, in some cases, after different dosage forms of a drug.

It is now evident for most drugs that a more appropriate assessment of potency is realized by considering drug concentration-response rather than dose-response relationships. The concentration of a drug in the plasma depends on the rate and extent of absorption, which in turn is a function of the route of administration, of certain properties of the drug, and of the dosage form. Drug absorption may markedly affect the onset, intensity, and duration of biologic response.

The intrinsic activity of a drug is determined in reference to its biophase or receptor site concentration. For a reversibly acting drug the attainment and maintenance of some minimal concentration in the biophase dictate the onset and duration of biologic response. The maximum level of drug reached at the receptor site determines the intensity of response. To fully appreciate the complexities of a biologic response, one must take into account the distribution and elimination of a drug. The distribution of a drug from the blood to the various tissues and fluids of the body determines what levels are achieved in the biophase. Hence, distribution is an important factor in the onset and intensity of response and may sometimes play a role in the duration of response. Duration of effect, however, is usually related to the elimination rate of the drug from the body. Drug elimination involves renal and biliary excretion as well as biotransformation in the liver and other organs. These processes determine the persistence of drug levels in the biophase.

Clinicians have long appreciated that patient-to-patient variability in response to certain drugs is often great. In the past, these differences were all too frequently ascribed exclusively to individual "sensitivity" or "resistance." We now believe that most of these differences can be explained by intersubject variability in drug absorption, distribution, and elimination. The age, size, and sex of the patient, genetic and disease-related considerations, and concomitant drug therapy can influence these processes. An understanding of the causes of intersubject variability allows the possibility of developing individualized dosing regimens and of improving drug therapy.

Some knowledge of the principles of biopharmaceutics and clinical pharmacokinetics is essen-

tial for all health scientists and clinicians concerned with drug therapy. Competence in these principles and the ability to apply this knowledge in the patient setting are imperative for the pharmacist and clinical pharmacologist.

I acknowledge the contributions of scores of scientists and clinicians who are dedicated to the improvement of drug therapy. Without their work, this book could not begin. I am deeply indebted to my staff at the University of Washington for their unflagging support and to my colleagues in Seattle, Washington, Buffalo, New York, and throughout the pharmaceutical industry for the intellectual stimulation they have provided all these many years.

*Seattle, Washington* MILO GIBALDI