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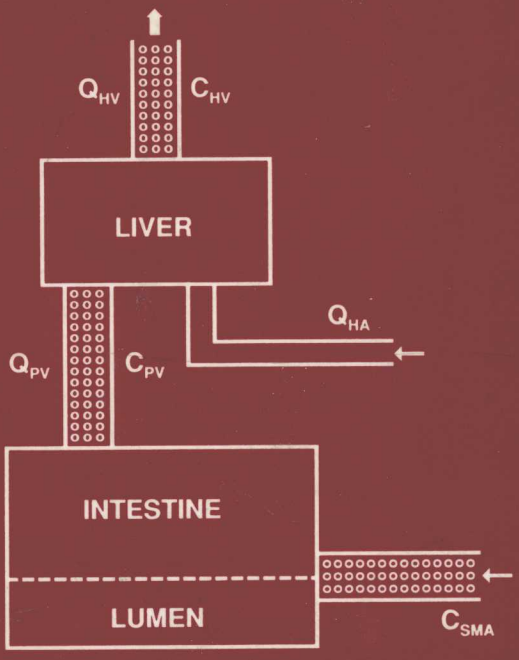
Pharmacokinetics

Regulatory - Industrial - Academic Perspectives

Second Edition



edited by
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Regulatory - Industrial - Academic Perspectives

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To Caroline, Christine, Clara, Graham, Luisa, and Stephen

Preface

The objective of this book is to present the latest concepts and developments in the area of pharmacokinetics from the perspective of those actively working in the regulatory, industrial, and academic environments. The first edition of the book was published in 1988. Since that time there have been considerable upheavals in the pharmaceutical industry. These have been associated with quantum scientific advances and achievements as well as continued globalization of pharmaceutical drug discovery and development on the one hand, and the challenges of cost containment and increasing regulatory demands on the other. These events continue to have a considerable impact on drug development and also on the critical role that pharmacokinetics and drug metabolism play in discovery and development and in drug therapy.

We felt it both timely and necessary to prepare this second edition in order to keep abreast of the changing roles and responsibilities of pharmacokinetics. This book is the result of that initiative. While the overall thrust of this second edition is similar to that of the first edition, a number of changes have been made. Although a strong component of classical pharmacokinetics and metabolism has been retained, there is greater emphasis on topics that are rapidly changing within the dynamic framework of the application of pharmacokinetic principles.

The first chapter addresses the central issue of good laboratory practice regulations, as applied to pharmacokinetics. This is followed by chapters on methods of assessing drug absorption, drug delivery systems, peptide and protein drug de-

livery, and membrane transport. Drug distribution is addressed in chapters on blood–brain barrier permeability, pharmacokinetic and pharmacodynamic relationships of drugs acting on the central nervous system, and quantitative whole-body autoradiography. Two chapters discuss recent advances in drug metabolism methodology and the use of hepatic in vitro systems as models for human drug metabolism. The latter part of the book focuses on drug development with chapters on the monolithic approach of integration of pharmacokinetics into development, nonclinical and clinical pharmacokinetics in drug discovery and development, and population pharmacokinetics and pharmacodynamics. The book concludes with regulatory perspectives of bioavailability and bioequivalence of oral controlled-release products, and statistical issues relating to bioavailability and bioequivalence studies.

Our intent in preparing this book has been to continue to present the latest concepts in the most rapidly changing areas in the broad discipline of pharmacokinetics. We have drawn from the expertise of authors who are active leaders in their respective fields, and have attempted to focus on areas that are undergoing the greatest change and are having the greatest influence on the many applications of pharmacokinetics and drug metabolism. We hope that this second edition of pharmacokinetics has achieved this objective. We are grateful for the generous contributions of our colleagues, who took the time from their busy schedules. We also thank Theresa Davis for her limitless administrative help and patience during the preparation of this book.

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Principles of the Good Laboratory Practice Regulations Applied to Pharmacokinetics

Dexter S. Goldman

Goldman Associates International, Inc., Rockville, Maryland

I. HISTORY AND INTENT OF THE REGULATIONS

A. 1970–1978

All individuals, and ''individuals'' is used in its broadest sense, within a social system are bound by regulations, spoken as well as unspoken. Within political units, organizations are bound by regulations, some of which may make good sense, others of which are used to exemplify and even drive social policy. In the 1970s in the United States the Food and Drug Administration (FDA), rocked by allegations and proof of misconduct and fraud within segments of the pesticide* and drug testing industry, used its authority under the Federal Food, Drug and Cosmetic Act (FFDCA) and the Public Health Service Act (PHSA) to propose regulations governing the conduct of nonclinical laboratory studies† [1] submitted to the FDA by manufacturers and other petitioners to demonstrate the safety and effectiveness of their products. Historically, the FDA never has had the resources to test or evaluate the safety and effectiveness of chemicals under its jurisdiction. Public policy was, therefore, to require manufacturers and petitioners to provide these data at their own expense; this policy continues to this day. The FDA prescribed the type and extent of such testing, reviewed the data submitted, and eventually either permitted distribution and sale of a regulated chemical or device or, lacking sufficient information, refused to allow distribution and sale.

Prior to 1978 the FDA had in place a program of small size that was used as an adjunct to desk audits and reviews of data supporting petitions for action. These on-site investigations were generally the result of questions raised during the review of data; that is, they were retrospective. The FDA had assumed that the nonclinical studies submitted were the result of the application of appropriate testing procedures by a testing facility. The change came in 1975 when FDA investigators showed that fraud and deception had entered the testing industry. FDA's point of view is best illustrated by an understated analysis of the problem that appeared in the preamble to the proposed rule on Good Laboratory Practice (GLP) regulations for nonclinical studies [2]:

> Recent FDA experiences have identified significant problems in the manner in which nonclinical laboratory studies are being performed. Deficiencies were found during inspections of the testing facilities of major pharmaceutical firms, inspections of several private contract testing facilities, and internal reviews of

*The toxicological properties of pesticides were tested since the FDA classified these chemicals as food additives and, accordingly, they were under its jurisdiction.

†''Nonclinical laboratory study'' means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.