

# Preclinical Development Handbook

ADME and Biopharmaceutical Properties

Edited by Shayne Cox Gad

# PRECLINICAL DEVELOPMENT HANDBOOK

## **ADME and Biopharmaceutical Properties**

SHAYNE COX GAD, PH.D., D.A.B.T.

Gad Consulting Services Cary, North Carolina



### PRECLINICAL DEVELOPMENT HANDBOOK

ADME and Biopharmaceutical Properties

# PRECLINICAL DEVELOPMENT HANDBOOK

## **ADME and Biopharmaceutical Properties**

SHAYNE COX GAD, PH.D., D.A.B.T.

Gad Consulting Services Cary, North Carolina



Copyright © 2008 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at http://www.wiley.com/go/permission.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

#### Library of Congress Cataloging-in-Publication Data is available.

ISBN: 978-0-470-24847-8

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

## CONTRIBUTORS

- Adegoke Adeniji, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, *Chemical and Physical Characterizations of Potential New Chemical Entity*
- Adeboye Adjare, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, *Chemical and Physical Characterizations of Potential New Chemical Entity*
- **Zvia Agur,** Institute for Medical Biomathematics (IMBM), Bene-Ataroth, Israel; Optimata Ltd., Ramat-Gan, Israel, *Mathematical Modeling as a New Approach for Improving the Efficacy/Toxicity Profile of Drugs: The Thrombocytopenia Case Study*
- Melvin E. Andersen, The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina, *Physiologically Based Pharmacokinetic Modeling*
- Joseph P. Balthasar, University of Buffalo, The State University of New York, Buffalo, New York, *Pharmacodynamics*
- Stelvio M. Bandiera, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada, *Cytochrome P450 Enzyme*
- **Ihor Bekersky,** Consultant, Antioch, Illinois, *Bioavailability and Bioequivalence Studies*
- **Marival Bermejo,** University of Valencia, Valencia, Spain, *How and Where Are Drugs Absorbed*?
- Jan H. Beumer, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, Mass Balance Studies
- **Prasad V. Bharatam,** National Institute of Pharamaceutical Education and Research (NIPER), Nagar, India, *Modeling and Informatics in Drug Design*

- **Deepa Bisht,** National JALMA Institute for Leprosy and Other Myobacterial Diseases, Agra, India, *Accumulation of Drugs in Tissues*
- Scott L. Childs, SSCI, Inc., West Lafayette, Indiana, Salt and Cocrystal Form Selection
- Harvel J. Clewell III, The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina, *Physiologically Based Pharmacokinetic Modeling*
- Brett A. Cowans, SSCI, Inc., West Lafayette, Indiana, Salt and Cocrystal Form Selection
- **Dipankar Das,** University of Alberta, Edmonton, Alberta, Canada, *Protein–Protein Interactions*
- **A. G. de Boer,** University of Leiden, Leiden, The Netherlands, *The Blood–Brain Barrier and Its Effect on Absorption and Distribution*
- Pankaj B. Desai, University of Cincinnati Medical Center, Cincinnati, Ohio, Data Analysis
- Merrill J. Egorin, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, *Mass Balance Studies*
- Julie L. Eiseman, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, *Mass Balance Studies*
- **Moran Elishmereni,** Institute for Medical Biomathematics (IMBM), Bene-Ataroth, Israel, *Mathematical Modeling as a New Approach for Improving the Efficacy/ Toxicity Profile of Drugs: The Thrombocytopenia Case Study*
- **Dora Farkas,** Tufts University School of Medicine, Boston, Massachusetts, *Mechanisms and Consequences of Drug–Drug Interactions*
- Sandrea M. Francis, National Institute of Pharamaceutical Education and Research (NIPER), Nagar, India, *Modeling and Informatics in Drug Design*
- Shayne Cox Gad, Gad Consulting Services, Cary, North Carolina, Regulatory Requirements for INDs/FIH (First in Human) Studies
- **P.J. Gaillard,** to-BBB Technologies BV, Leiden, The Netherlands, *The Blood–Brain Barrier and Its Effect on Absorption and Distribution*
- Srinivas Ganta, University of Auckland, Auckland, New Zealand, Permeability Assessment
- Sanjay Garg, University of Auckland, Auckland, New Zealand, Permeability Assessment
- **Isabel Gonzalez-Alvarez,** University of Valencia, Valencia, Spain, *How and Where Are Drugs Absorbed*?
- Eric M. Gorman, The University of Kansas, Lawrence, Kansas, Stability: Physical and Chemical
- Luis Granero, University of Valencia, Valencia, Spain, Absorption of Drugs after Oral Administration

- **David J. Greenblatt,** Tufts University School of Medicine, Boston, Massachusetts, Mechanisms and Consequences of Drug–Drug Interactions
- Ken Grime, AstraZeneca R&D Charnwood, Loughborough, United Kingdom, Utilization of In Vitro Cytochrome P450 Inhibition Data for Projecting Clinical Drug–Drug Interactions
- William L. Hayton, The Ohio State University, Columbus, Ohio, Allometric Scaling
- William W. Hope, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, *Experimental Design Considerations in Pharmacokinetics Studies*
- Eugene G. Hrycay, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada, *Cytochrome P450 Enzymes*
- Teh-Min Hu, National Defense Medical Center, Taipei, Taiwan, Allometric Scaling
- Subheet Jain, Punjabi University, Patiala, Punjab, India, Dissolution
- Izet M. Kapetanovic, NIH NCI Division of Cancer Prevention, Chemoprevention Agent Devleopment Research Group, Bethesda, Maryland, Analytical Chemistry Methods: Developments and Validation
- Kamaljit Kaur, University of Alberta, Edmonton, Alberta, Canada, Protein–Protein Interactions
- Jane R. Kenny, AstraZeneca R&D Charnwood, Loughborough, United Kingdom, Utilization of In Vitro Cytochrome P450 Inhibition Data for Projecting Clinical Drug–Drug Interactions
- Masood Khan, Covance Laboratories Inc., Immunochemistry Services, Chantilly, Virginia, *Method Development for Preclinical Bioanalytical Support*
- Smriti Khanna, National Institute of Pharamaceutical Education and Research (NIPER), Nagar, India, *Modeling and Informatics in Drug Design*
- Yuri Kheifetz, Institute for Medical Biomathematics (IMBM), Bene-Ataroth, Israel, Mathematical Modeling as a New Approach for Improving the Efficacy/ Toxicity Profile of Drugs: The Thrombocytopenia Case Study
- Yuri Kogan, Institute for Medical Biomathematics (IMBM), Bene-Ataroth, Israel, Mathematical Modeling as a New Approach for Improving the Efficacy/Toxicity Profile of Drugs: The Thrombocytopenia Case Study
- Niels Krebsfaenger, Schwarz Biosciences, Monheim, Germany, Species Comparison of Metabolism in Microsomes and Hepatocytes
- **Thierry Lave,** F. Hoffman-LaRoche Ltd., Basel, Switzerland, *Physiologically Based Pharmacokinetic Modeling*
- Albert P. Li, In Vitro ADMET Laboratories, Inc., Columbia, Maryland, In Vitro Evaluation of Metabolic Drug–Drug Interactions: Scientific Concepts and Practical Considerations

#### viii CONTRIBUTORS

- **Charles W. Locuson,** University of Minnesota, Minneapolis, Minnesota, *Metabolism Kinetics*
- Alexander V. Lyubimov, University of Illinois at Chicago, Chicago, Illinois, Analytical Chemistry Methods: Developments and Validation; Dosage Formulation; Bioavailability and Bioequivalence Studies
- **Dermot F. McGinnity,** AstraZeneca R&D Charnwood, Loughborough, United Kingdom, *Utilization of* In Vitro *Cytochrome P450 Inhibition Data for Projecting Clinical Drug–Drug Interactions*
- **Peter Meek,** University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, *Computer Techniques: Identifying Similarities Between Small Molecules*
- **Donald W. Miller,** University of Manitoba, Winnipeg, Manitoba, Canada, *Transporter Interactions in the ADME Pathway of Drugs*
- Mehran F. Moghaddam, Celegne, San Diego, California, *Metabolite Profiling and* Structural Identification
- Guillermo Moyna, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, Computer Techniques: Identifying Similarities Between Small Molecules
- Eric J. Munson, The University of Kansas, Lawrence, Kansas, Stability: Physical and Chemical
- Ann W. Newman, SSCI, Inc., West Lafayette, Indiana, Salt and Cocrystal Form Selection
- Mohammad Owais, Aligarh Muslim University, Aligarh, India, Accumulation of Drugs in Tissues
- Brian E. Padden, Schering-Plough Research Institute, Summit, New Jersey, Stability: Physical and Chemical
- Sree D. Panuganti, Purdue University, West Lafayette, Indiana, Drug Clearance
- Jayanth Panyam, University of Minnesota, Minneapolis, Minnesota, Distribution: Movement of Drugs through the Body
- **Yogesh Patil,** Wayne State University, Detroit, Michigan, *Distribution: Movement* of Drugs through the Body
- James W. Paxton, The University of Auckland, Auckland, New Zealand, Interrelationship between Pharmacokinetics and Metabolism
- **Olavi Pelkonen**, University of Oulu, Oulu, Finland, In Vitro *Metabolism in Preclini*cal Drug Development
- **Vidmantas Petraitis,** National Cancer Institute, National Institutes of Health, Bethesda, Maryland, *Experimental Design Considerations in Pharmacokinetics Studies*
- Ana Polache, University of Valencia, Valencia, Spain, Absorption of Drugs after Oral Administration

- Elizabeth R. Rayburn, University of Alabama at Birmingham, Birmingham, Alabama, Linkage Between Toxicology of Drugs and Metabolism
- Micaela B. Reddy, Roche Palo Alto LLC, Palo Alto, California, *Physiologically* Based Pharmacokinetic Modeling
- **Robert J. Riley,** AstraZeneca R&D Charnwood, Loughborough, United Kingdom, Utilization of In Vitro Cytochrome P450 Inhibition Data for Projecting Clinical Drug–Drug Interactions
- Sevim Rollas, Marmara University, Istanbul, Turkey, In Vivo Metabolism in Preclinical Drug Development
- Bharti Sapra, Punjabi University, Patiala, Punjab, India, Dissolution
- **Richard I. Shader,** Tufts University School of Medicine, Boston, Massachusetts, Mechanisms and Consequences of Drug–Drug Interactions
- **Dhaval Shah,** University of Buffalo, The State University of New York, Buffalo, New York, *Pharmacodynamics*
- **Puneet Sharma,** University of Auckland, Auckland, New Zealand, *Permeability* Assessment
- **Beom Soo Shin,** University of Buffalo, The State University of New York, Buffalo, New York, *Pharmacodynamics*
- Meir Shoham, Optimata Ltd., Ramat-Gan, Israel, Mathematical Modeling as a New Approach for Improving the Efficacy/Toxicity Profile of Drugs: The Thrombocy-topenia Case Study
- Mavanur R. Suresh, University of Alberta, Edmonton, Alberta, Canada, Protein-Protein Interactions
- Craig K. Svensson, Osmetech Molecular Diagnostics, Pasadena, California, Drug Clearance
- A. K. Tiwary, Punjabi University, Patiala, Punjab, India, Dissolution
- Ari Tolonen, Novamass Analytical Ltd., Oulu, Finland; University of Oulu, Oulu, Finland, In Vitro *Metabolism in Preclinical Drug Development*
- **Timothy S. Tracy,** University of Minnesota, Minneapolis, Minnesota, *Metabolism Kinetics*
- Miia Turpeinen, University of Oulu, Oulu, Finland, In Vitro Metabolism in Preclinical Drug Development
- Jouko Uusitalo, Novamass Analytical Ltd., Oulu, Finland, In Vitro Metabolism in Preclinical Drug Development
- Vladimir Vainstein, Institute for Medical Biomathematics (IMBM), Bene-Ataroth, Israel; Optimata Ltd., Ramat-Gan, Israel, *Mathematical Modeling as a New Approach for Improving the Efficacy/Toxicity Profile of Drugs: The Thrombocytopenia Case Study*

#### **x** CONTRIBUTORS

- Krishnamurthy Venkatesan, National JALMA Institute for Leprosy and Other Myobacterial Diseases, Agra, India, *Accumulation of Drugs in Tissues*
- Lisa L. von Moltke, Tufts University School of Medicine, Boston, Massachusetts, Mechanisms and Consequences of Drug–Drug Interactions
- Jayesh Vora, PRTM Management Consultants, Mountain View, California, Data Analysis
- **Thomas J. Walsh,** National Cancer Institute, National Institutes of Health, Bethesda, Maryland, *Experimental Design Considerations in Pharmacokinetics Studies*
- Naidong Weng, Johnson & Johnson Pharmaceutical Research & Development, Bioanalytical Department, Raritan, New Jersey, *Method Development for Preclinical Bioanalytical Support*
- **Randy Zauhar,** University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, *Computer Techniques: Identifying Similarities Between Small Molecules*
- **Ruiwen Zhang,** University of Alabama at Birmingham, Birmingham, Alabama, Linkage Between Toxicology of Drugs and Metabolism
- Yan Zhang, Drug Metabolism and Biopharmaceutics, Incyte Corporation, Wilmington, Delaware, *Transporter Interactions in the ADME Pathway of Drugs*
- Irit Ziv, Optimata Ltd., Ramat-Gan, Israel, Mathematical Modeling as a New Approach for Improving the Efficacy/Toxicity Profile of Drugs: The Thrombocytopenia Case Study

## CONTENTS

Preface		XV
1	<b>Modeling and Informatics in Drug Design</b> Prasad V. Bharatam, Smriti Khanna, and Sandrea M. Francis	1
2	<b>Computer Techniques: Identifying Similarities Between</b> <b>Small Molecules</b> <i>Peter Meek, Guillermo Moyna, and Randy Zauhar</i>	47
3	<b>Protein–Protein Interactions</b> Kamaljit Kaur, Dipankar Das, and Mavanur R. Suresh	87
4	<b>Method Development for Preclinical Bioanalytical Support</b> Masood Khan and Naidong Weng	117
5	<b>Analytical Chemistry Methods: Developments and Validation</b> <i>Izet M. Kapetanovic and Alexander V. Lyubimov</i>	151
6	<b>Chemical and Physical Characterizations of Potential New</b> <b>Chemical Entity</b> <i>Adegoke Adeniji and Adeboye Adejare</i>	211
7	<b>Permeability Assessment</b> Srinivas Ganta, Puneet Sharma, and Sanjay Garg	227
8	How and Where Are Drugs Absorbed? Marival Bermejo and Isabel Gonzalez-Alvarez	249
9	<b>Absorption of Drugs after Oral Administration</b> Luis Granero and Ana Polache	281

### xii CONTENTS

10	<b>Distribution: Movement of Drugs through the Body</b> Jayanth Panyam and Yogesh Patil	323
11	<b>The Blood–Brain Barrier and Its Effect on Absorption</b> <b>and Distribution</b> <i>A. G. de Boer and P. J. Gaillard</i>	353
12	<b>Transporter Interactions in the ADME Pathway of Drugs</b> Yan Zhang and Donald W. Miller	407
13	<b>Accumulation of Drugs in Tissues</b> Krishnamurthy Venkatesan, Deepa Bisht, and Mohammad Owais	429
14	Salt and Cocrystal Form Selection Ann W. Newman, Scott L. Childs, and Brett A. Cowans	455
15	<b>Dissolution</b> A.K. Tiwary, Bharti Sapra, and Subheet Jain	483
16	Stability: Physical and Chemical Eric M. Gorman, Brian E. Padden, and Eric J. Munson	545
17	<b>Dosage Formulation</b> Alexander V. Lyubimov	571
18	<b>Cytochrome P450 Enzymes</b> <i>Eugene G. Hrycay and Stelvio M. Bandiera</i>	627
19	Metabolism Kinetics Charles W. Locuson and Timothy S. Tracy	697
20	<b>Drug Clearance</b> Sree D. Panuganti and Craig K. Svensson	715
21	In Vitro Metabolism in Preclinical Drug Development Olavi Pelkonen, Ari Tolonen, Miia Turpeinen, and Jouko Uusitalo	743
22	<b>Utilization of</b> <i>In Vitro</i> <b>Cytochrome P450 Inhibition Data for</b> <b>Projecting Clinical Drug–Drug Interactions</b> <i>Jane R. Kenny, Dermot F. McGinnity, Ken Grime, and Robert J. Riley</i>	775
23	<i>In Vivo</i> Metabolism in Preclinical Drug Development Sevim Rollas	829
24	<i>In Vitro</i> Evaluation of Metabolic Drug–Drug Interactions: Scientific Concepts and Practical Considerations <i>Albert P. Li</i>	853
25	<b>Mechanisms and Consequences of Drug–Drug Interactions</b> Dora Farkas, Richard I. Shader, Lisa L. von Moltke, and David J. Greenblatt	879
26	<b>Species Comparison of Metabolism in Microsomes and Hepatocytes</b> <i>Niels Krebsfaenger</i>	919

	CONTENTS	xiii
27	Metabolite Profiling and Structural Identification Mehran F. Moghaddam	937
28	Linkage between Toxicology of Drugs and Metabolism Ruiwen Zhang and Elizabeth R. Rayburn	975
29	Allometric Scaling William L. Hayton and Teh-Min Hu	1009
30	Interrelationship between Pharmacokinetics and Metabolism James W. Paxton	1037
31	<b>Experimental Design Considerations in Pharmacokinetic Studies</b> William W. Hope, Vidmantas Petraitis, and Thomas J. Walsh	1059
32	<b>Bioavailability and Bioequivalence Studies</b> Alexander V. Lyubimov and Ihor Bekersky	1069
33	Mass Balance Studies Jan H. Beumer, Julie L. Eiseman, and Merrill J. Egorin	1103
34	<b>Pharmacodynamics</b> Beom Soo Shin, Dhaval Shah, and Joseph P. Balthasar	1133
35	<b>Physiologically Based Pharmacokinetic Modeling</b> <i>Harvey J. Clewell III, Micaela B. Reddy, Thierry Lave, and Melvin E. Andersen</i>	1167
36	Mathematical Modeling as a New Approach for Improving the Efficacy/Toxicity Profile of Drugs: The Thrombocytopenia Case Study Zvia Agur, Moran Elishmereni, Yuri Kogan, Yuri Kheifetz, Irit Ziv, Meir Shoham, and Vladimir Vainstein	1229
37	<b>Regulatory Requirements for INDs/FIH (First in Human) Studies</b> Shayne Cox Gad	1267
38	<b>Data Analysis</b> Jayesh Vora and Pankaj B. Desai	1309
Ind	Index	

## PREFACE

This *Preclinical Development Handbook: ADME and Biopharmaceutical Properties* continues and extends the objective behind the entire *Handbook* series: an attempt to achieve a through overview of the current and leading-edge nonclinical approaches to evaluating the pharmacokinetic and pharmacodynamic aspects of new molecular entity development for therapeutics. The 38 chapters cover the full range of approaches to understanding how new molecules are absorbed and distributed in model systems, have their biologic effects, and then are metabolized and excreted. Such evaluations provide the fundamental basis for making decisions as to the possibility and means of pursuing clinical development of such moieties. Better performance in this aspect of the new drug development process is one of the essential keys to both shortening and increasing the chance of success in developing new drugs.

The volume is unique in that it seeks to cover the entire range of available approaches to understanding the performance of a new molecular entity in as broad a manner as possible while not limiting itself to a superficial overview. Thanks to the persistent efforts of Mindy Myers and Gladys Mok, these 38 chapters, which are written by leading practitioners in each of these areas, provide coverage of the primary approaches to the problems of understanding the mechanisms that operate in *in vivo* systems to transfer a drug to its site of action and out.

I hope that this newest addition to our scientific banquet is satisfying and useful to all those practitioners working in or entering the field.