

THIRD EDITION

DRUGS

From Discovery to Approval



RICK NG

WILEY Blackwell

DRUGS

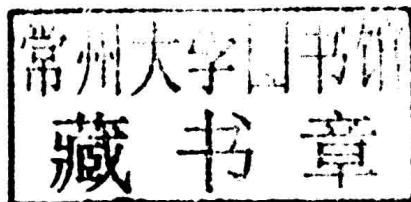
From Discovery to Approval

Third Edition

RICK NG, PhD, MBA

Trainer

National University of Singapore Academy of GxP Excellence (NUSAGE)
Singapore



WILEY Blackwell

Copyright © 2015 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/permissions>.

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 the 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:

Ng, Rick, author.

Drugs : from discovery to approval / Rick Ng. – Third edition.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-1-118-90727-6 (cloth)

I. Title.

[DNLM: 1. Drug Discovery. 2. Chemistry, Pharmaceutical. 3. Clinical Trials as Topic—methods. 4. Drug Approval—legislation & jurisprudence. 5. Drug Approval—methods. 6. Technology, Pharmaceutical.

QV 745]

RM301.25

615'.19—dc23

2014045567

Cover image: Laboratory Equipment Robot Arm working © 4X-image /iStockphoto;
Scientist taking a sample out of a petri dish using a pipette © DNY59 /iStockphoto;
DNA molecule © ermess /iStockphoto;
Medicine pills © AlexRaths /iStockphoto;
tablet pc, stethoscope and electrocardiogram © dolgachov /iStockphoto;
Close look © shironosov /iStockphoto; and
Chemical Formula © BlackJack3D /iStockphoto

Typeset in 10/12pt TimesTenLTStd by Laserwords Private Limited, Chennai, India.

Printed and bound in Malaysia by Vivar Printing Sdn Bhd

DRUGS

To
Cherry, Shaun and Ashleigh

PREFACE

In 2001, I decided to write a book about pharmaceuticals to cover the topics in drug discovery and development, manufacturing, and regulatory compliance. My intention is to have a book that is relevant, informative, and easy to read and understand. My target readership is the pharmaceutical professionals, healthcare students, and general public who wish to have practical information about pharmaceuticals. The result was this book – *Drugs: From Discovery to Approval*, first published in 2004 and then the second edition in 2009.

For this third edition, I have completely revised the contents to include the latest advances and developments. I have added new information and examples. There are now two case studies at the end of each chapter to provide more in-depth perspectives on current issues facing the pharmaceutical industry.

I am particularly grateful to Dr. Wayne Gordon, who read through the entire manuscript and provided many helpful suggestions. Dr. Loh Kean Chong and Dr. Dinesh Khokal have read through all the editions, and their contributions are very much appreciated. I also wish to thank Dr. Peter New and Mr. Chris Sweeney for their perceptive comments on different sections of this book. I am indebted to Mr. Ryan O’Connell, who meticulously checked through the manuscript and corrected the errors and inconsistencies.

I acknowledge the assistance of Ms. Mindy Okura-Marszycki (Senior Acquisitions Editor) and Ms. Stephanie Dollan (Editorial Assistant) from John Wiley and Sons, Inc. My thanks go to them for supporting this edition and arranging access to John Wiley’s database for my research and reference.

My family has given me unqualified support and encouragement throughout the time I spent writing and revising these three editions. I am thankful to my wife and children for believing in me and I dedicate this book to them.

RICK NG
March 2015

CONTENTS

PREFACE	xv
1 INTRODUCTION	1
1.1 Aim of this Book / 1	
1.2 An Overview of the Drug Discovery to Approval Process / 2	
1.3 The Pharmaceutical Industry / 6	
1.4 Economics of Drug Discovery and Development / 11	
1.5 Trends in Drug Discovery and Development / 13	
1.6 Case Study #1.1 / 15	
1.7 Case Study #1.2 / 17	
1.8 Summary of Important Points / 20	
1.9 Review Questions / 20	
1.10 Brief Answers and Explanations / 21	
1.11 Further Reading / 22	
2 DRUG DISCOVERY: TARGETS AND RECEPTORS	23
2.1 Drug Discovery Processes / 23	
2.2 Medical Needs / 24	
2.3 Target Identification / 26	
2.4 Target Validation / 33	
2.5 Drug Interactions with Targets or Receptors / 36	
2.6 Enzymes / 40	

- 2.7 Receptors and Signal Transduction / 42
- 2.8 Assay Development / 52
- 2.9 Case Study #2.1 / 52
- 2.10 Case Study #2.2 / 53
- 2.11 Summary of Important Points / 57
- 2.12 Review Questions / 57
- 2.13 Brief Answers and Explanations / 58
- 2.14 Further Reading / 58

3 DRUG DISCOVERY: SMALL MOLECULE DRUGS

61

- 3.1 Introduction / 61
- 3.2 Irrational Approach / 62
- 3.3 Rational Approach / 67
- 3.4 Antisense Approach / 85
- 3.5 RNA Interference Approach / 88
- 3.6 Chiral Drugs / 91
- 3.7 Closing Remarks / 92
- 3.8 Case Study #3.1 / 94
- 3.9 Case Study #3.2 / 96
- 3.10 Summary of Important Points / 98
- 3.11 Review Questions / 99
- 3.12 Brief Answers and Explanations / 99
- 3.13 Further Reading / 100

4 DRUG DISCOVERY: LARGE MOLECULE DRUGS

103

- 4.1 Introduction / 103
- 4.2 Vaccines / 105
- 4.3 Antibodies / 117
- 4.4 Cytokines / 128
- 4.5 Hormones / 134
- 4.6 Gene Therapy / 137
- 4.7 Stem Cells and Cell Therapy / 139
- 4.8 Case Study #4.1 / 141
- 4.9 Case Study #4.2 / 144
- 4.10 Summary of Important Points / 146
- 4.11 Review Questions / 147
- 4.12 Brief Answers and Explanations / 148
- 4.13 Further Reading / 148

5	DRUG DEVELOPMENT AND PRECLINICAL STUDIES	151
5.1	Introduction / 151	
5.2	Pharmacodynamics / 154	
5.3	Pharmacokinetics / 158	
5.4	Toxicology / 168	
5.5	Animal Tests, <i>In Vitro</i> Assays, and <i>In Silico</i> Methods / 172	
5.6	Formulations and Delivery Systems / 175	
5.7	Nanotechnology / 183	
5.8	Case Study #5.1 / 184	
5.9	Case Study #5.2 / 185	
5.10	Summary of Important Points / 187	
5.11	Review Questions / 188	
5.12	Brief Answers and Explanations / 188	
5.13	Further Reading / 189	
6	CLINICAL TRIALS	191
6.1	Definition of Clinical Trial / 191	
6.2	Ethical Considerations / 192	
6.3	Clinical Trials / 195	
6.4	Regulatory Requirements for Clinical Trials / 204	
6.5	Clinical Data Management / 215	
6.6	Role of Regulatory Authorities / 218	
6.7	Gene Therapy Clinical Trial / 218	
6.8	Adaptive Clinical Trial / 220	
6.9	Meta-Analysis / 221	
6.10	Case Study #6.1 / 222	
6.11	Case Study #6.2 / 226	
6.12	Summary of Important Points / 227	
6.13	Review Questions / 228	
6.14	Brief Answers and Explanations / 228	
6.15	Further Reading / 229	
7	REGULATORY AUTHORITIES	231
7.1	Role of Regulatory Authorities / 231	
7.2	US Food and Drug Administration / 233	
7.3	European Medicines Agency / 236	
7.4	Japan's Pharmaceuticals and Medical Devices Agency (PMDA) / 238	
7.5	China Food and Drug Administration / 240	

- 7.6 India's Central Drugs Standard Control Organization / 240
- 7.7 Australia's Therapeutic Goods Administration / 241
- 7.8 Canada's Health Canada / 243
- 7.9 Other Regulatory Authorities / 243
- 7.10 Authorities other than Drug Regulatory Agencies / 243
- 7.11 International Conference on Harmonization / 244
- 7.12 World Health Organization / 245
- 7.13 Pharmaceutical Inspection Cooperation Scheme / 246
- 7.14 Case Study # 7.1 / 246
- 7.15 Case Study # 7.2 / 249
- 7.16 Summary of Important Points / 250
- 7.17 Review Questions / 251
- 7.18 Brief Answers and Explanations / 251
- 7.19 Further Reading / 252

8 REGULATORY APPLICATIONS 253

- 8.1 Introduction / 253
- 8.2 United States / 254
- 8.3 European Union / 272
- 8.4 Japan / 280
- 8.5 China / 282
- 8.6 India / 287
- 8.7 Australia / 287
- 8.8 Canada / 287
- 8.9 Case Study #8.1 / 290
- 8.10 Case Study #8.2 / 292
- 8.11 Summary of Important Points / 294
- 8.12 Review Questions / 299
- 8.13 Brief Answers and Explanations / 299
- 8.14 Further Reading / 300

9 GOOD MANUFACTURING PRACTICE: REGULATORY REQUIREMENTS 301

- 9.1 Introduction / 301
- 9.2 United States / 302
- 9.3 Europe / 308
- 9.4 International Conference on Harmonization (ICH) / 309
- 9.5 Pharmaceutical Inspection Cooperation Scheme (PIC/S) / 311
- 9.6 Selected Core Elements of GMP / 312

- 9.7 Selected GMP Systems / 335
- 9.8 New cGMP Initiatives / 350
- 9.9 Case Study #9.1 / 352
- 9.10 Case Study #9.2 / 358
- 9.11 Summary of Important Points / 362
- 9.12 Review Questions / 363
- 9.13 Brief Answers and Explanations / 363
- 9.14 Further Reading / 364

10 GOOD MANUFACTURING PRACTICE: DRUG MANUFACTURING 367

- 10.1 Introduction / 367
- 10.2 GMP Manufacturing / 371
- 10.3 GMP Inspection / 372
- 10.4 Manufacture of Small Molecule APIs (Chemical Synthesis Methods) / 379
- 10.5 Manufacture of Large Molecule APIs (Recombinant DNA Methods) / 385
- 10.6 Finished Dosage Forms / 394
- 10.7 Product Quality Review / 398
- 10.8 Manufacturing Variations / 399
- 10.9 Case Study #10.1 / 400
- 10.10 Case Study #10.2 / 404
- 10.11 Summary of Important Points / 407
- 10.12 Review Questions / 408
- 10.13 Brief Answers and Explanations / 408
- 10.14 Further Reading / 408

11 FUTURE PERSPECTIVES 411

- 11.1 Past Advances and Future Challenges / 411
- 11.2 Small Molecule Pharmaceutical Drugs / 412
- 11.3 Large Molecule Biopharmaceutical Drugs / 414
- 11.4 Traditional Medicine / 414
- 11.5 Personalized Medicine / 419
- 11.6 Gene Therapy / 420
- 11.7 Cloning and Stem Cells / 420
- 11.8 Old Age Diseases and Aging / 423
- 11.9 Lifestyle Drugs / 423
- 11.10 Performance-Enhancing Drugs / 428
- 11.11 Chemical and Biological Terrorism / 428

11.12	Transgenic Animals and Plants /	432
11.13	Antibiotics Drug Resistance /	433
11.14	Regulatory Issues /	435
11.15	Intellectual Property Rights and Marketing Exclusivities /	437
11.16	Bioethics /	440
11.17	Concluding Remarks /	442
11.18	Case Study #11.1 /	445
11.19	Case Study #11.2 /	447
11.20	Further Reading /	449
APPENDIX 1	HISTORY OF DRUG DISCOVERY AND DEVELOPMENT	451
A1.1	Early History of Medicine /	451
A1.2	Drug Discovery and Development in the Middle Ages /	453
A1.3	Foundation of Current Drug Discovery and Development /	454
A1.4	Beginnings of Modern Pharmaceutical Industry /	454
A1.5	Evolution of Drug Products /	455
A1.6	Further Reading /	456
APPENDIX 2	CELLS, NUCLEIC ACIDS, GENES, AND PROTEINS	457
A2.1	Cells /	457
A2.2	Nucleic Acids /	460
A2.3	Genes and Proteins /	462
A2.4	Further Reading /	468
APPENDIX 3	SELECTED DRUGS AND THEIR MECHANISMS OF ACTION	469
APPENDIX 4	A DHFR PLASMID VECTOR	481
APPENDIX 5	VACCINE PRODUCTION METHODS	483
APPENDIX 6	VACCINES APPROVED BY FDA	485
APPENDIX 7	PHARMACOLOGY/TOXICOLOGY REVIEW FORMAT	489
APPENDIX 8	EXAMPLES OF GENERAL BIOMARKERS	495
APPENDIX 9	TOXICITY GRADING	499
APPENDIX 10	HEALTH SYSTEMS IN SELECTED COUNTRIES	505

ACRONYMS	509
GLOSSARY	515
INDEX	519

