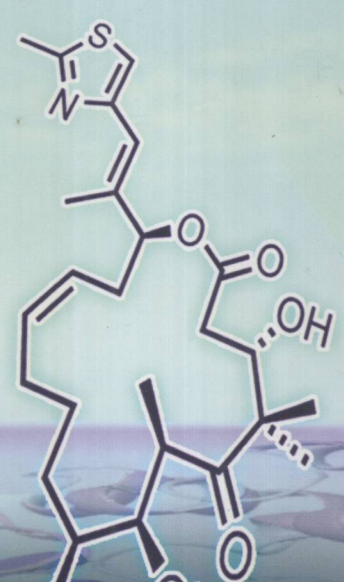


DRUG DISCOVERY AND DEVELOPMENT

VOLUME 1
Drug Discovery

Edited by
MUKUND S. CHORGHAD



From first principles to real-world applications — here is the first comprehensive guide to drug discovery and development

Modern drug discovery and development require the collaborative efforts of specialists in a broad array of scientific, technical, and business disciplines—from biochemistry to molecular biology, organic chemistry to medicinal chemistry, pharmacology to marketing. Yet surprisingly, until now, there were no authoritative references offering a complete, fully integrated picture of the process.

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- Includes chapters on combinatorial chemistry, molecular biology-based drug discovery, genomics, and chemogenomics

Drug Discovery and Development is an indispensable working resource for industrial chemists, biologists, biochemists, and executives who work in the pharmaceutical industry.

MUKUND S. CHORGHADÉ, PHD, is President of Chorghade Enterprises, Inc., a firm based in Natick, Massachusetts that provides consultations to major pharmaceutical companies on collaborations with worldwide academic, government, and industrial laboratories; European technology-based companies; process reengineering; and project management of technology transfer.

Cover Design: Michael Rutkowski

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ISBN 0-471-39848-9



9 780471 398486

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A JOHN WILEY & SONS, INC., PUBLICATION

“Epothilone” cover art by Doug Scard
www.sputniknewmedia.com

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

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Library of Congress Cataloging-in-Publication Data:

Drug discovery and development/edited by Mukund S. Chorghade.

p. cm.

Includes bibliographical references and index.

ISBN-13: 978-0-471-39848-6

ISBN-10: 0-471-39848-9 (cloth : v. 1)

1. Drug development. I. Chorghade, Mukund S. (Mukund Shankar)

[DNLM: 1. Drug Design. 2. Chemistry, Pharmaceutical—methods.

3. Drug Evaluation, Preclinical—methods. QV 744 D79334 2006]

RM301.25C488 2006

615'.19—dc22

2005021297

Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

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Volume 1: Drug Discovery

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**DRUG DISCOVERY
AND DEVELOPMENT**

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PREFACE

The pharmaceutical sector has traditionally been a vibrant, innovation-driven, and highly successful component of industry at large. In recent years, a confluence of spectacular advances in chemistry, molecular biology, genomics, and chemical technology and the cognate fields of spectroscopy, chromatography, and crystallography have led to the discovery and development of numerous novel therapeutic agents for the treatment of a wide spectrum of diseases. To facilitate this process, there has been a significant and noticeable effort aimed at improving the integration of discovery technologies, chemical outsourcing for route selection and delivery of active pharmaceutical ingredients, drug product formulations, clinical trials, and refined deployment of information technologies. Multidisciplinary and multifunctional teams focusing on lead generation and optimization have replaced the traditional, specialized research groups. To develop a drug from conception to commercialization, the biotechnology and biopharmaceutical industries (which have been highly entrepreneurial) have reached out and established global strategic partnerships with numerous companies.

Currently, there is no single book in the market that provides an overview of strategies, tactics, milestones, and benchmarks in the entire sequence of operations involved in discovering a drug and delivering it to the armamentarium of clinicians and medical practitioners. A large number of advanced texts dealing exclusively with medicinal chemistry have been published; process chemistry has not received the attention it deserves (the journal *Organic Process Research and Development* is a useful and overdue step in this direction). Strategic in licensing, virtual company interactions and related topics have hitherto not been chronicled in books on drug discovery. There is usually a great gulf between the medicinal and process chemists in industry; neither has the opportunity to delve into the disparate literature of the other. This book is designed to bridge this gap and provide greater understanding of the target areas.

Conversely, the book is not designed to be a treatise or an encyclopedia. Its scope precludes complete coverage of any defined area. Ideally, it is envisioned to be an advanced-level monograph with appeal to active researchers and investigators in the entire gamut of

operations comprising the drug discovery and development process. This two-volume text will be useful to a broad community of academic and industrial chemists. An overview of several recent developments is presented; this will make it valuable as a reference primer. The topics and the extent to which they are summarized are based on decisions by the editor and authors. Each contributor has achieved international distinction in the relevant fields.

The introductory chapter in the first volume, by Dr. Richard Pariza, delineates all the essential elements that comprise the development process, from the initial conception of a program to the successful marketing of a new drug. A time line for making critical decisions, conducting pivotal studies, and the approximate duration of different activities is described. The time line helps to put the entire developmental process into perspective for the reader and serves as a conceptual index that unifies all the contributions. Dr. Pariza elaborates on these concepts by describing some fascinating aspects of the work done on commercially successful analogs of erythromycin.

Professor Paul Erhardt describes the competition in the pharmaceutical industry to be “first to the market” in a chosen therapeutic area and the strategies currently being pursued. These include research in combinatorial chemistry, collaboration with biopharmaceutical and “virtual companies,” and strategies in the licensing of drug candidates, among others. Increasingly, the large pharmaceutical corporations have turned to the establishment of strategic links with small biotechnology and biopharmaceutical companies for in-licensing of drug candidates and enhancement of drug portfolios. The author takes a futuristic look at what medicinal chemistry is expected to be in the new millennium. Dr. Erhardt is chairman of the Division of Chemistry and Human Health of the International Union of Pure and Applied Chemistry; his insights gleaned from expertise and experience constitute a valuable lesson.

Professor Lester Mitscher, an internationally renowned academician and expert, and Professor Apurba Dutta take us through the next critical phase of the drug discovery process: detailed studies of the absorption, metabolism, and excretion of potential drug candidates. Such studies are of pivotal importance in determining the suitability of a new compound for further clinical evaluation. His chapter on contemporary drug discovery presents a broad overview of the successive steps in the progression of a drug from mind to marketplace.

Combinatorial chemistry has played a highly visible role in the drug discovery effort in several companies; numerous new companies have been set up to partner established companies in the discovery of new molecular entities. The strategic focus in this field is continually shifting; Dr. Ian Hughes reviews the state of the art with selected examples from his own research at GlaxoSmithKline. This is followed by an excellent exposition by Drs. Norton Peet and Hwa-Ok Kim regarding efficient design and development of parallel solution-phase synthesis. Specific examples of lead identification and optimization are presented.

Dr. János Fischer and Dr. Anikó Gere delve into the important area of the timing of analog research in medicinal chemistry. This work is a remarkable synthesis of knowledge of drugs and their functional congeners and has formed the basis of a major IUPAC project. Professor Camille Wermuth presents fascinating examples of specific new drugs being derived via the functionalization of old drugs. This approach uses the old drugs as new scaffolds and derives benefit from new molecules already having a propensity to be “drug-like.” Professor Wermuth has worked at the academia–industry interface for collaboration in drug discovery.

Drs. Susan Dana Jones and Peter Warren focus on the impact of proteomics on the discovery of drugs: newer methods for efficient, economical, and safer production, and the development of novel targets and assays for the application of traditional medicinal chemistry methods. A brief survey of novel therapeutic concepts such as gene therapy, antisense, transgenic animals, and pharmacogenomics that have opened new vistas in drug development are surveyed. The authors have familiarized readers with several newer biology-based technologies. Next, Professor Paul Erhardt introduces the concept of using drug metabolism databases during the drug discovery and development process.

Professor C. Robin Ganellin exemplifies the discovery of Tagamet using classical structure–activity relationships and modeling of pharmacophore receptors. This drug was the first “billion-dollar drug.” The research work by Sir James Black and Robin Ganellin has long been considered to be a tour de force in modern medicinal chemistry.

The art and science of medicinal chemistry is exemplified and epitomized clearly in the next few chapters. The exponents of the art are highly distinguished and prolific industrial researchers whose work spans the gamut of the therapeutic spectrum. Dr. Bruce Maryanoff brilliantly summarizes research into the discovery of potent nonpeptide vasopressin receptor antagonists. The work is a great tribute to the perseverance and persistence of researchers. Valuable insights are presented into the discovery process: A key idea is followed through despite initial adversity. Dr. Paul Feldman presents an informative case study on the discovery of Ultiva (remifentanyl). This is an ultrashort-acting analgesic used as an adjunct to anesthesia. Dr. Paul Feldman introduces the rationale for its discovery and discusses how remifentanyl fits into the anesthesia drug regimen. The desire to discover an ultrashort-acting analgesic, the group’s medicinal chemistry efforts, and the structure–activity relationships are discussed. The divergent syntheses of analogs and the final process route are described. Finally, the clinical trial data and clinical uses are incorporated in the chapter to give a complete picture of Ultiva. Drs. Karl Grozinger, John Proudfoot, and Karl Hargrave discuss the discovery and development of nevirapine. This drug was a key ingredient in our efforts to combat AIDS, and the success of the researchers is an object lesson in creativity and how various skills were brought to the forefront of research.

Drs. John Babich and William Eckelman present insights into the applications of nuclear imaging in drug discovery and development; the work is technologically complex and involves radiopharmaceuticals. An increasing number of biopharmaceutical companies are involved in this activity; readers will find this to be a new and exciting domain of expertise.

Drs. Pradeep Dhal, Chad Huval, and Randal Holmes–Farley take the reader into a new and somewhat unexplored area of polymer therapeutics. The exciting idea of using a polymer as an active pharmaceutical ingredient was introduced in the 1990s and led to the discovery of drugs such as Renagel and Welchol. A large-molecular-weight polymer when used as a drug manifests its action in the gastrointestinal tract by adsorbing and removing unwanted analytes. The drug is not systemically absorbed in the blood and therefore does not generate any hazardous metabolites or lead to any toxic effects. It is also unnecessary to do long-term toxicity tests. This leads to a significant acceleration of the time required to introduce a drug to meet unmet medical needs.

Professor Bhushan Patwardhan and his collaborators demonstrate the utility of botanical immunomodulators and chemoprotectants in cancer therapy. Much of this work has its genesis in the Indian medicine systems of ayurveda; this turns pharmacology “on its head.” It starts with plant extracts that have been used extensively in medicine in Asia and identifies the active ingredients from a complex mixture of ingredients. There is considerable

scientific debate and discussion about whether the active moieties exhibit their pharmacological action in tandem or singly.

A detailed introduction to the second volume will be presented in its preface; given here are glimpses of what is to come to whet the reader's appetite. Drs. G. N. Qazi and S. Taneja provide a unique perspective on the therapeutic action of bioactive molecules in medicinal plants. Their group has several years of experience in prospecting natural products in plants and following up with the isolation, characterization, and structure elucidation of natural products.

Professor Steven Ley and his collaborators at Cambridge University enlighten readers as to how natural products have served as inspiration for the discovery of new high-throughput chemical synthesis tools. A salient feature of this masterpiece is the creative use of polymer-supported reagents.

Drs. Braj and Vidya Lohray elaborate on the role of insulin sensitizers in emerging therapeutics. A noteworthy feature of this work is that it was done entirely in India and represents a fast-growing trend: the discovery of new chemical entities in that country.

Drs. Raymond McCague and Ian Lennon at Dowpharma next discuss the criteria for industrial readiness of chiral catalysis technology for the synthesis of pharmaceuticals. They exemplify how and why stereoselective reactions are invented for pharmaceutical researchers: The methodology is applicable in both the discovery and development phases of a drug in making analogs rapidly and by scalable transformations. Dr. Mukund Chorghade then introduces readers to the field of process chemistry: the quest for the elucidation of novel, cost-effective, and scalable routes for production of active pharmaceutical ingredients. The medicinal chemistry routes used in the past have often involved the use of cryogenic reactions, unstable intermediates, and hazardous or expensive reagents. A case study of the development of a process for an antiepileptic drug is presented; readers will also see how problems in the isolation, structure elucidation, and synthesis of metabolites were circumvented.

Drs. Mukund K. Gurjar, J. S. Yadav, G. V. M. Sharma, P. Radha Krishna, C.V. Ramana, Yatendra Kumar, Braj and Vidya Lohray, and Bipin Pandey have each made seminal contributions to process chemistry. They have invented commercial processes for key pharmaceuticals that have resulted in significant economies in cost and minimization of waste, and have engineered "green chemistry" and the development of eco-friendly processes. These scholars describe their work in the next few chapters with case studies of specific compounds. The work is an eloquent testimony to the collaboration and cooperation inherent in the strategic triad of academics institutions government, and industry. The work is applicable to the synthesis of both agricultural and fine chemicals.

Over the last few years, an increasing number of pharmaceutical and biopharmaceutical companies have resorted to outsourcing activities in chiral synthesis, process development, and manufacturing. Dr. Peter Pollack demonstrates this strategy, provides useful pointers about the do's and don'ts, and beautifully elaborates the risks and rewards inherent in outsourcing in the pharmaceutical industry.

Dr. Shrikant Kulkarni exemplifies solving regulatory problems via thorough investigations of processes and processing parameters. Dr. Peter Pollack delineates the fascinating impact of specialty chemicals on drug discovery and development, providing further illustration of the power and utility of outsourcing in drug manufacture.

Chemical engineering plays a central and pivotal role in scale-up operations. Dr. Andrei Zlota discusses chemical process scale-up tools, mixing calculations, statistical design of experiments, and automated laboratory reactors.

Dr. Richard Wife explains how some novel initiatives will lead to rescue of “lost chemistry and molecules,” how the net will make research results accessible to the entire chemical world, and how information sharing will lead to better and more efficient research. Thought-provoking and novel studies aimed at predicting compound stability are presented.

In the concluding chapter, Dr. Colin Scott describes some general principles and practices in drug development. A brief review is presented of the history of the requirements for clinical studies leading to the registration of a drug prior to being marketed. This is followed by a discussion of ethical issues related to clinical studies, the phases of drug development, and clinical trial design features. The support operations necessary for the initiation of clinical trials and optimization of results are described. Finally, a global development plan, accelerated development opportunities, international regulatory procedures, and postmarketing requirements are summarized.

There are few courses in academic chemistry departments that deal with drug discovery and development. Graduating students typically have scant exposure to the fascinating world of industrial chemistry. I am confident that the material will excite students interested in careers in the pharmaceutical industry. A salient feature of the book is the inclusion of several case studies that exemplify and epitomize the concepts detailed in each chapter. An instructor interested in developing a course in pharmaceutical chemistry will find the book useful as a teaching text for a one-semester course.

Dr. Raghunath A. Mashelkar, Director General of the Council of Scientific and Industrial Research, has stated: “Rapid paradigm shifts that are taking place in the world as it moves from superpower bipolarity to multipolarity, as industrial capitalism gives way to green capitalism and digital capitalism, as information technology creates netizens out of citizens, as the nations move from ‘independence’ to ‘interdependence,’ as national boundaries become notional, and as the concept of global citizenship gets evolved, will see a world full of new paradigms and new paradoxes; there is no doubt that the rapid advance of science and technology will directly fuel many of these. The global pharmaceutical and, in particular, the contract R&D organizations have seen a dramatic change in their capabilities and sophistication. International pharmaceutical companies should now be ideally poised to seek collaborations to bring innovative drugs to the consumers at an affordable price.”

Finally, I wish to thank my wife, Veena, my son, Rajeev, and my parents for their encouragement, emotional support, understanding, and love. They have helped immeasurably during this endeavor.

MUKUND S. CHORGHADE

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