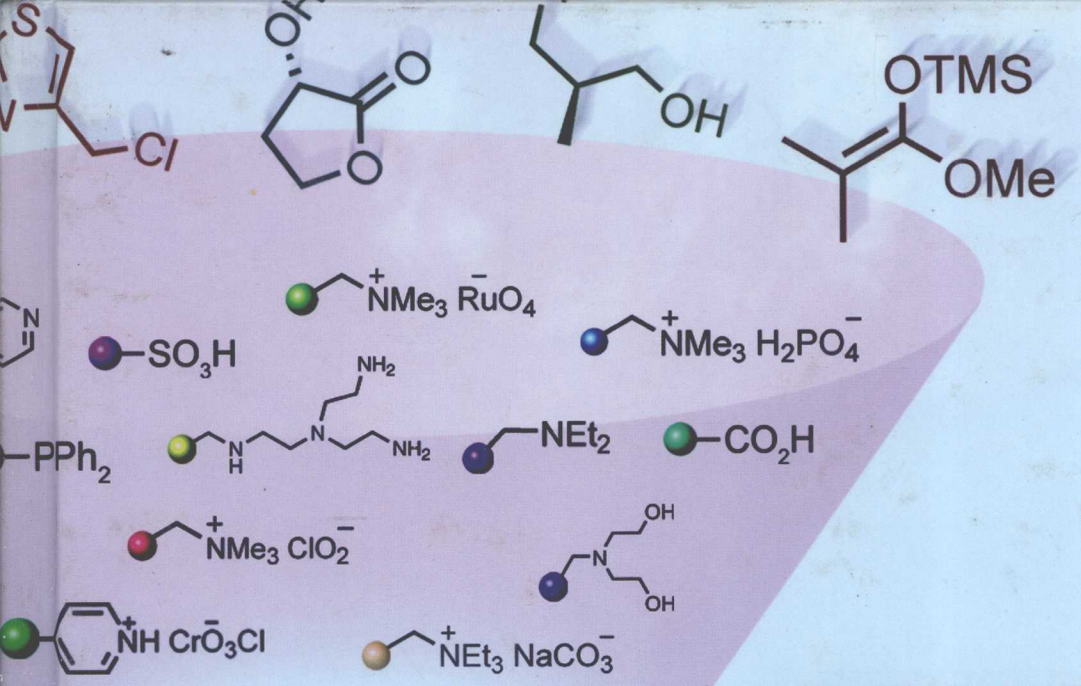
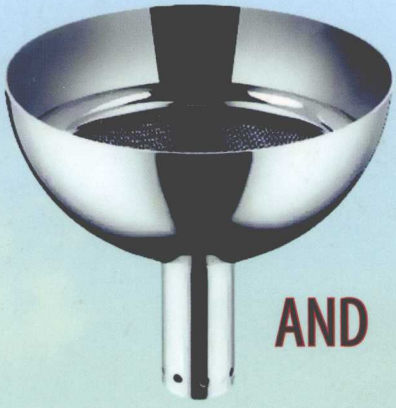
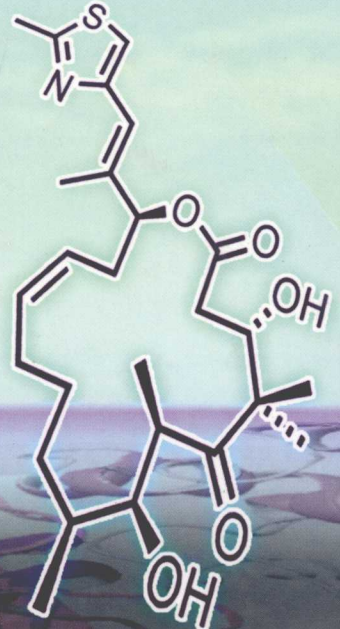


DRUG DISCOVERY AND DEVELOPMENT





VOLUME 2

Drug Development

Edited by
MUKUND S. CHORGHADE

DRUG DISCOVERY AND DEVELOPMENT

Volume 2: Drug Development

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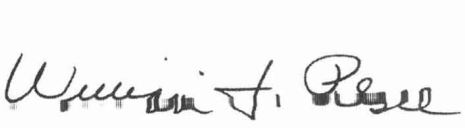

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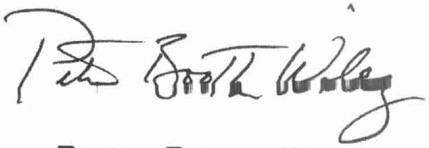

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PREFACE

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. 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.

This 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.

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 timeline 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 unifies all contributions.

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. The author takes a futuristic look at what medicinal chemistry is expected to be in the new millennium. Dr. Erhardt's 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.

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. Dr. Ian Hughes reviews the state of the art with selected examples from his own research at Glaxo Smith Kline. 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.

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. 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."

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. Dr. Paul Feldman presents an informative case study on the discovery of Ultiva (remifentanil). This is an ultrashort-acting analgesic used as an adjunct to anesthesia. Dr. Paul Feldman introduces the rationale for its discovery and discusses how remifentanil 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. 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 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.

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 gastro-intestinal tract by adsorbing and removing unwanted analytes.

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.

Volume 2 builds on the outstanding contributions by the authors of Volume 1. Drs. S. C. Taneja and G. N. Qazi 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. The traditional medicinal systems such as Indian and Chinese and those used by African tribes are treasure houses of traditional wisdom, and with the help of modern scientific methods they will continue to be the basis of development of new therapeutic agents. These authors discuss comprehensively how this knowledge can be coupled with diversity-oriented synthesis to discover new therapeutic agents.

Professor Steven Ley, BP 1702 Professor of Chemistry, 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. The natural world inspires us all—from artist and philosopher to biologist and chemist alike. In our quest for new knowledge, the exquisite and varied architectures of natural products provide a rich pallet for discovery. Synthesis chemists are drawn to these structures as testing grounds for synthetic strategies and for the development of new methods. But we are also drawn to advance the art of molecular assembly of some of nature's most enigmatic creations. However, more is accessible to the synthesis chemists' skills, they can modify natural materials to probe structure activity profiles; they can provide fragment molecules or related structural scaffolds through library generation. Only the synthesis chemist can go beyond the molecule, contemplating macromolecular assemblies and creating unnatural arrangements with awe-inspiring levels of molecular diversity, limited only by their imaginations. Described in this chapter is how methods of immobilizing reagents on polymeric supports or using scavenging agents and catch-and-release techniques can impact on natural product synthesis, and thereby create opportunities for structures mimicking naturally-occurring architectures.

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. This chapter specifically addresses chiral catalytic technologies. Chiral technology is an important focus given that many synthetic pharmaceutical candidates are chiral, will need to be produced in the single chiral isomer (enantiomer) form and some specialised *chiral* technology will be needed for the synthesis. Catalytic technologies are of particular interest for the superior economics when applied to the manufacture of intermediates to pharmaceutical agents, and particularly suited are methods of biocatalysis and chemocatalysis. Some of these methods find sufficiently frequent application that significant up-front technology investment is warranted, and there are enough projects on which to apply the technologies, to build up a still higher level of expertise.

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. Described is an interesting application of the technology of metalloporphyrins assisted metabolite prediction, estimation, quantitation and synthesis.

Drs. Mukund K. Gurjar, Mahendra Deshpande, J. S. Yadav, G. V. M. Sharma, P. Radha Krishna, C.V. Ramana, Punna Srinivas, Chepuri 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 academic institutions, government, and industry. The work is applicable to the synthesis of both agricultural and fine chemicals. Moreover, the work described has led to the establishment of successful contract research businesses.

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 post-marketing 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 super-power 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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