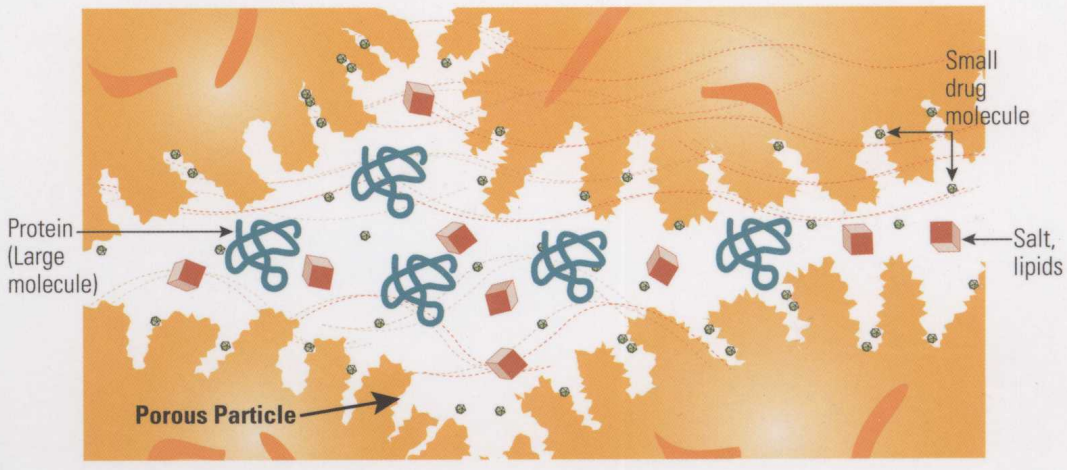
Early Drug Development

Strategies and Routes to First-in-Human Trials

Edited by *Mitchell N. Cayen*



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FOREWORD

From 1950 to the late 1990s, the global pharmaceutical industry was responsible for a series of advances that addressed major disease areas and led to significant improvements in public health and quality of life. In no particular order, these treatments may be exemplified by drugs (a) controlling blood pressure, and latter, blood cholesterol; (b) controlling gastric acid secretion; (c) controlling female fertility; and (d) progressively addressing major cancers, so that many tumor types are now treated as chronic diseases rather than terminal illnesses. The reader will be able to add many other examples to this list. Although these years were also marked by instances of patients harmed by drug treatments, most notably thalidomide in the early 1960s, the introduction of new therapies has revolutionized medical care for many people, created new personal freedoms, and is a major factor in the increase in life expectancy achieved in many countries over the past 50 or more years.

In recent years, the ability of the pharmaceutical industry to sustain this remarkable contribution has been challenged. Although we have seen a huge growth both in scientific understanding in the biomedical sciences and in the technical feasibility of many aspects of drug research and development, these advances have not been accompanied by corresponding increases in research productivity: put very simply, the research and development pipeline of new medicines has gotten blocked, so that fewer and fewer new agents reach the market each year. The reasons for this are many and varied. Making new compounds with interesting and therapeutically relevant biological activity is a challenge, but those that are produced lack other key features of usable drugs. In recent years it has proved very difficult indeed to develop such active compounds into novel medicines. The business model used by many pharmaceutical companies is not capable of infinite replication. The development of more "blockbuster" drugs, which have underpinned much of the growth seen from the mid-1970s onward, is now less and less likely in times when science seeks to stratify drug development and medicine seeks individualized therapies. The protection of intellectual

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property and the maximization of marketing exclusivity are now more important than ever and come under pressure from health care providers, who emphasize the need for low-cost generic prescribing as one means to address the escalation of costs. The regulatory environment in the early twenty-first century is both sophisticated and questioning in all jurisdictions and is supported by the very high expectations of the public in terms of both the efficacy and safety of new therapies. It is to be hoped that recent developments in this area, such as the U.S. Food and Drug Administration's Critical Path and the European Union's Innovative Medicines Initiative, will bear fruit, but there have been few successes thus far.

Against this background, this new volume provides an invaluable guide to the earliest and most critical stages of drug development, getting promising new chemicals into humans quickly, effectively, and safely, to provide information of maximum benefit for critical decision making. The Editor, who has a lifetime of experience in exactly this arena, has identified a series of key topics and matched them to well-qualified authors, resulting in an extremely helpful handbook to guide the experienced investigator and novice alike through what can all too easily be a mine field.

Drug development is simultaneously an art and a science. It depends on excellent science in all of the various chemical, biological, and clinical disciplines that contribute, but at present at least the coordination of the management of all of the resources required as well as critical and fully informed decision making is best regarded as an art. It is my view that this new volume represents a substantial contribution by providing an integrated approach to an area that has suffered from excessive fragmentation.

JOHN CALDWELL

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August 2009

PREFACE

During my career in the pharmaceutical industry in Canada and the United States, initially as a bench scientist and subsequently in managing departments in big pharma companies, and now as an industry consultant, I have never ceased to view the drug discovery and development paradigm with a combination of excitement, awe, wonder, and caution. There are many reasons for this mix of emotions. First, the discovery and development of successful medicines represent hugely complex challenges, with what seems to be a constantly shifting end zone. Our learning curve about the etiology and treatment of disease, coupled with the numerous changes in regulatory climate, help contribute, in my view, to make successful pharmaceutical development one of the most difficult of business enterprises. The second and probably more fundamental reason for these feelings is that the more I have learned over the years about how foreign compounds interface with living organisms, the more I realize that there is so much that I will never learn or understand. This is a sobering thought. Those of us who are in the business of developing medicines to treat human disease are doing the best we can to assure that we do not put patients at risk and that there is a high likelihood of therapeutic success. Given the complexity of the human body, the best we can hope for, based on all our advances over several millennia, is that successful therapeutics continue to morph from hit-and-miss to higher odds of positive outcomes in larger percentages of the target population. We still have a long way to go. It continues to amaze me that in most therapeutic areas, we have only reached the stage where we are merely alleviating disease symptoms rather than curing the actual disease.

It is therefore not surprising that the road to successful drug development has many twists, turns, and intersections, and that many travelers take different routes. It is critical to note that the path must eventually lead not to the submission of a new drug application (NDA), but to the attainment of an approvable NDA. The primary goal of this book is to describe those routes that have the greatest likelihood of a successful journey during the initial stages of the voyage

[i.e., up to the first-in-human (FIH) trial]. The authors who provide these perspectives have had decades of experience in both big and small pharma companies, biotechnology companies, contract research organizations, regulatory affairs, and various aspects of consulting. Each chapter focuses on a specific discipline that contributes to the late discovery and early development of new candidate drugs, and is designed to describe the state-of-the-science, challenges, strategies, and "how to" regarding study designs and data interpretation. Many basic concepts are described and explained. The text can be used as a primer for new investigators as well as a resource for the experienced. It should be noted that each author is presenting the topic from his or her viewpoint and perspectives and that for the most part, no one size fits all. Indeed, given the fact that no single discipline can stand on its own, there is some overlap between chapters, and the reader may therefore obtain different viewpoints on similar topics (e.g., safety assessment of metabolites in Chapters 2, 3, 8, and 9; the TGN1412 monoclonal antibody human toxicity issue in Chapters 10 and 12). For example, approaches will vary based on such factors as:

- Small-molecule versus biotherapeutic drug
- Route of drug administration
- Frequency of drug administration
- Target disease
- Corporate resources, goals, portfolio management, and competitive landscape

We decided early where on the drug development path to end this book, and that was in the planning (but not implementation) of an FIH study. However, the more difficult decision was deciding where to begin. For various reasons, including the fact that there are numerous excellent published treatises on the discovery process, we decided arbitrarily to start at the point where a new chemical entity (NCE) has been shown to possess pharmacological activity in an initial screen (hit-to-lead), and then proceed to the next step toward the process of selection as a candidate drug (lead optimization). Accordingly, there is extensive discussion of those disciplines and activities necessary to demonstrate that the FIH trial will have a high likelihood of success; these disciplines include toxicology, safety pharmacology, CMC (chemistry, manufacturing, and controls), ADME (absorption, distribution, metabolism, and excretion), pharmacokinetics and toxicokinetics, GLPs (good laboratory practices), bioanalysis, regulatory submissions, and related activities. It is emphasized that there is no such thing as the perfect drug candidate, whether from the efficacy or safety viewpoint; as Sir Harold Macmillan pointed out: "To be alive at all involves some risk."

One of my personal challenges when I begin consultation with a pharmaceutical company is to learn the lexicon which is the in-house language but which may not be readily transparent to new visitors. We have tried to be consistent within and have decided arbitrarily to use such terms as FIH [rather than FTIM

(first time in man)], NCE [rather than NME (new molecular entity) or NCD (new candidate drug)], and nonclinical (rather than preclinical, though both will be found).

I would like to thank Jonathan Rose at John Wiley & Sons for inviting me to put this book together and for his guidance during the process. I am very grateful to the authors of the various chapters for their dedication and patience, and for providing this project with their vast array of experience and expertise.

It is my joy to dedicate this book to my wife, Judy, who was instrumental in encouraging me to take on this project and whose love and support were absolutely invaluable during its course.

MITCHELL N. CAYEN

Bedminster, New Jersey
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CONTENTS

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