FORMULATION AND ANALYTICAL DEVELOPMENT FOR LOW-DOSE ORAL DRUG PRODUCTS

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JACK ZHENG
Pharmaceutical Sciences R&D, Lilly Research Labs, Eli Lilly and Company

A JOHN WILEY & SONS, INC., PUBLICATION

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Opportunities multiply as they are seized

—Sun Tsu

To my wonderful wife Lijuan and my talented children Karen and Allen for their love, encouragement, and support

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PREFACE

In November 2005, I co-chaired a symposium entitled "Analytical and Formulation Development Strategies, Challenges and Regulatory Considerations for Low-dose Drug Products" during the annual meeting of the American Association of Pharmaceutical Scientists. The goal of the symposium was to provide an overview on development of low-dose drug products from the perspective of pharmaceutical, analytical, and regulatory sciences, including formulation design, process development, analytical method development, and regulatory considerations. The presenters included Dr Norm Sesi from Eli Lilly and Company, Dr Ravi Harapanhalli from the U.S. Food and Drug Administration, Dr Mary am Ende from Pfizer Inc., and Dr Keith Hutchison from Capsugel, Division of Pfizer Inc. After the meeting, I was approached by John Wiley & Sons Inc. to discuss the publication of a book on analytical and formulation development of low-dose drug products. As a pharmaceutical scientist who has worked in product development for more than a decade, I know that product development scientists in the pharmaceutical industry and the graduate students in the pharmacy schools will benefit from a book that collects the existing knowledge, techniques, and strategies in development of low-dose drug products. After two years of diligent work, all contributors and the publisher, John Wiley& Sons Inc., have made the book available to our readers.

Formulation and Analytical Development for Low-Dose Oral Drug Products focuses on the key topics involved in the challenges and strategies in analytical, formulation, and regulatory perspectives for development of low-dose drug products. The book begins with eight chapters devoted to aspects of formulation and process

development of low-dose drug products, including theoretical consideration of particle size of drug substance, micronization and physical characterization of drug substance, control of excipients, and different manufacturing platform technologies. Chapter 2 provides an overview of challenges and strategies in formulation development of low-dose drug products. Chapters 4–7 are concerned with formulation and process development of low-dose drug products. Commonly used manufacturing platform technologies for low-dose drug products are discussed, such as high-shear wet granulation, fluid bed granulation, direct compression, and roller compaction. Chapters 3, 8, and 9 deal with drug substance, ranging from theoretical consideration of particle size according dose strengths, the methods for micronization of drug substance, and quality and functionality of pharmaceutical excipients.

Chapters 10–13 focus on challenges in analytical method development for low-dose drug products, including physical characterization of the micronized powder and the solid state of API in dosage forms. Analytical issues related to low-dose assay and impurities are discussed together with some specific case studies. Chapter 11 provides guidance on how to run appropriate dissolution testing so that meaningful data can be obtained. Chapter 14 provides a particularly interesting perspective on how pharmaceutical excipients should be controlled in the development of low-dose drug products and how an excipients library can help formulation scientists select appropriate excipients for better control of product quality. There is also a chapter specifically addressing practical concerns in the pharmaceutical industry with respect to cleaning verification of manufacturing equipment, illuminated by many examples.

The last section of the book is devoted to a few very important topics in development of low-dose drug products, including regulatory perspectives and containment technologies used in analytical laboratories and manufacturing plants. I hope that this combination of topics will enable the readers to obtain a broad overview on development of low-dose drug products.

I sincerely acknowledge the contributing authors of this book and thank them for their cooperation in the timely preparation of their specialized chapters, which allowed me to produce a book that reflects state-of-the-art thinking in analytical and formulation development of low-dose drug products. I would especially like to thank Drs Joe Zhou, Ralph Lipp, and Paul Collins for stepping in at the final hour and writing chapters on the fluid bed granulation technology and micronization of drug substance. Without these chapters, the book would have been incomplete. Also, I give my appreciation to Drs Gus Hartauer, Dave Maclaren, Ralph Lipp, Eugene Inman, Bret Huff, and Tom Verhoeven for their tremendous support and encouragement for my preparing this book. My sincerest thanks to Ms Karen Boleyn, a senior technical writer, for reviewing and making editorial corrections for several chapters in this book. Special thanks are expressed to Drs David Long, Tim Woznik, David Moeckly, Paul Sirois, James Wood, and Thirumala Kommuru for peer review of book chapters. Further, I would like to thank the editors at John Wiley and Sons Inc., in particular Jonathan Rose, for his accessibility and helpfulness

in all aspects of the book's production. Finally, I would like to thank my wife Lijuan (Susan) and my talented children, Karen (a Yalie) and Allen, for their love, understanding, and support in the time I have spent editing this book. Now I will have more time for them upon the completion of this project.

JACK ZHENG, PH.D.

Indianapolis, Indiana

FOREWORD

A few years ago, I sat in my office with Dr Jack Zheng as we discussed a technically challenging chemical stability issue we were having with a very-low-dose formulation of an early-phase clinical compound. There are unique challenges that a development team faces with low-dose compounds delivered orally; in effect, we agreed that it would be extremely useful to generate an internal guidance leveraging our collective in-house knowledge in this area. Jack not only acted on that idea, but has gone one better by recruiting a team of experienced scientists from multiple companies across the industry to author a book on this very topic.

At first glance, the thought of bringing forward a molecule with very low doses can have an appealing upside. One specific benefit is seen in reduced quantities of often very expensive active pharmaceutical ingredient (API) needed during the various stages of the development process, as well as impact on COPS. While this is definitely an advantage, this book clearly demonstrates that the hurdles present in developing a low-dose product can quickly offset that advantage. Time and expense can increase if the team does not robustly plan for and develop a formulation, manufacturing process, and analytical/API physical property control strategy to overcome those challenges. The most effective development plan in these cases arises from a multidisciplinary approach to bring to bear the best science and exploration of appropriate design space. This approach is reflected in the individual chapters of this book, where specific technical areas such as *in vitro* dissolution testing, physical transformation and containment techniques are discussed, but in the context of the ultimate goal of developing a commercial product.

The development of low-dose formulations is certainly not new to the pharmaceutical industry; one obvious example is the long-term clinical use of digoxin tablets. However, with the introduction of new technologies to identify molecular

targets and the use of high-throughput screening techniques to select structures with increased selectivity and activity toward a given target, the trend has been toward an ever-increasing amount of candidates dosed in the submilligram range. The increase in candidates meeting this definition of low-dose, along with the combination of increasing regulatory (e.g., impurity specifications) and technical requirements for such products, makes this book a valuable and timely contribution to pharmaceutical sciences.

Recent estimates have approached $1.2 billion for the cost of development of a new chemical entity into a commercial drug product (i.e., medicine). This book is a systematic, technical collection on this relevant topic than can help lead to a more effective and efficient drug development process. I consider it to be a welcome addition to the library of all drug product developers involved in bringing new therapies to patients.

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CHAPTER 1

AN OVERVIEW

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U.S. law defines a drug as any substance, other than a food or device, either (1) intended for use in the diagnosis, cure, relief, treatment, or prevention of disease or (2) intended to affect the structure or function of the body. The mission of pharmaceutical scientists is to continue developing safer and more effective new drugs to conquer various human diseases. However, successfully developing new medicines for patients requires significant collaboration of many interdisciplinary sciences, including:

- molecular biology;
- medicinal chemistry;
- pharmacology;
- toxicology;
- preformulation;
- formulation;
- clinical evaluation;
- synthetic chemistry;
- quality assurance/control;
- regulatory affairs;
- sales and marketing.

The objectives of formulation and analytical scientists are to develop new drug products for human use that are chemically and physically stable, bioavailable upon administration, manufacturable, cost-effective, elegant, and marketable.

Formulation and Analytical Development for Low-Dose Oral Drug Products. Edited by Jack Zheng

Pharmacologically, a drug should demonstrate its ability to:

- target the intended site or receptor (selectivity);
- remain attached to the receptor (affinity);
- show its effectiveness (efficacy);
- show its safety (adverse/side effects).

Ideally, a drug should be highly selective for its biological target, so that it has little or no effect on other physiological systems. The drug should also be very potent and effective, so that low doses of drug substance can be used, even for disorders that are difficult to treat. Finally, the drug should be administered orally, not only for patient compliance, but also for ease of production, distribution, and administration.

Drug product development is a process of transforming concept into reality. The process is not only science, but also art. After selecting a new drug candidate, drug development moves from preclinical studies to critical clinical investigation, and then to various stages of clinical and commercial product development. A drug candidate can become a drug product only when the compound is clinically efficacious and safe, and the developed product is bioavailable and stable, produces the desired pharmacological effects, and can be manufactured consistently with the identity, strength, quality, and purity it is represented to possess.

During development of an oral solid dosage form, dose strength is one of the critical product attributes that may have a significant impact on formulation and analytical development. Especially for a low-dose drug product, pharmaceutical scientists face great challenges in formulation, manufacture, analytical chemistry, and regulatory requirements.

This book addresses the challenges and strategies in developing low-dose oral solid drug products (i.e., less than 1 mg per dose unit), and aids development scientists in improving research and development productivity with a scientific and structured approach to product development. The information presented in the book is based on the extensive experience of the contributors, all of whom are actively working in the pharmaceutical industry and/or regulatory agency and have gained significant knowledge from their practical experience.

1.1 THE DRUG DISCOVERY AND DEVELOPMENT PROCESS

Drug discovery and development is a time-consuming and unpredictable process as well as an expensive venture. Today the average cost to research and develop each successful drug is estimated to be somewhere between $1.2 billion and $1.5 billion.[1] The whole adventure is highly innovative, highly risky, highly regulated, and highly technology- and information-intensive. Typically, it takes 10–15 years to develop a safe and effective new medicine from the early stage of discovery until the drug is available to treat patients.[2] This process, as illustrated in Fig. 1.1,

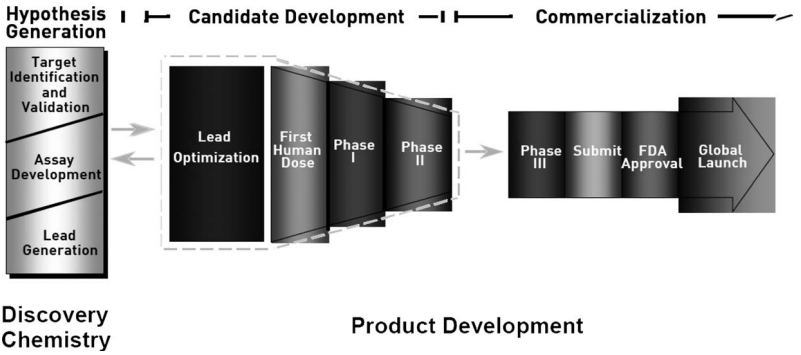

Figure 1.1 New drug discovery and development process. (See color insert.)

is normally divided into two key phases: discovery and development. During these phases, scientists have to:

- understand disease status, hypothesize "targets" that new drugs might be able to affect, and validate the targets;
- discover the molecule(s) to interact with the target hypothesized;
- assess the new compound (drug candidate) in the laboratory and clinic for safety and efficacy;
- develop the right drug product/dosage form for the intended use;
- gain regulatory approval and get the new drug into the hands of physicians and patients.

1.1.1 The Discovery Phase

Before discovering any new drug, scientists strive to understand the disease needing treatment and unravel the underlying cause of the condition. To do this, they investigate:

- how the genes are altered;
- how that alteration affects the proteins they encode;
- how those proteins interact with each other in living cells;
- how those affected cells change the specific tissue they are in;
- how the disease affects the patient.

This knowledge is the critical foundation for hunting a new medicine and treating the disease.

In 2001, scientists completed the sequencing of the human genome. They found that the genome of *Homo sapiens* consists of 24 distinct chromosomes (22 autosomal and the sex-determining X and Y chromosomes). There are approximately 3 billion

DNA base pairs containing an estimated 20,000–25,000 genes.[3,4] Each gene codes for a protein, and these proteins carry out all the functions of the human body, laying out how it grows and works. These genes and proteins can also be involved in disease. Hence, scientists are able to understand the inner workings of human disease at both the tissue level and the molecular level.

Once scientists understand the underlying cause of a disease, they can select a "target" for a potential new drug. A target is generally a single molecule, such as a gene or protein, which is involved in a particular disease state. Scientists call this earliest step in drug discovery "target identification."

After identifying a potential target, scientists must demonstrate that it actually is involved in the disease and that a drug can act on it. This process is called "target validation." Target validation is a crucial step in the drug discovery process that helps scientists minimize research paths that look promising, but that ultimately lead to dead ends. Target validation involves proving that DNA, RNA, or a protein molecule is directly involved in a disease process in vitro and in vivo, and that it can be a suitable target for a new therapeutic drug. Scientists use several methods to validate a target.

One type of target validation uses computer models. They are a fast, relatively cheap option for initial screening of both targets and potential drugs. The models usually focus on how the two types of candidate structures interact with each other.[5] Sense reversal is another route to target validation. It hinges on disrupting gene expression to reduce the amount of the corresponding protein, thereby identifying the physiological role of the target. Examples of this technique include gene knockouts, antisense technology, and RNA interference (RNAi).

One disadvantage of doing target validation at the genetic level, however, is that many genes produce several different protein isoforms that can have subtly different functions. Post-translational modifications can also give protein variations. To address these issues, a developing approach in target validation, proteomics, focuses on manipulating the activity of the potential target protein itself. Proteomics investigates and manipulates the protein make-up of a cell so it is easier to distinguish and target just one specific form of a protein.

In vivo target validation involves more complicated experiments in animal models of diseases.[5] However, animal models for certain diseases, such as psychiatric illnesses, are extremely difficult to develop. The alternative is to use gene knockouts, in which genes are deleted or disrupted to halt their expression in vivo. This can be a powerful method of predicting drug action. This method is based on the assumption that knocking out the gene for the potential target has the same effect as administering a highly specific inhibitor of the target protein in vivo. Once the target is validated, it can then be used for screening potential new drug candidates.

Scientists screen thousands of compounds (either by synthesizing or choosing from libraries) to find a molecule, or "lead compound," that may interact with the target to alter the disease course. De novo and high-throughput screening are methods commonly used to find a lead compound.[6,7] Promising lead candidates are called "hits." Hits go through a series of tests to provide an early assessment of the safety, efficacy, and pharmacokinetic properties.