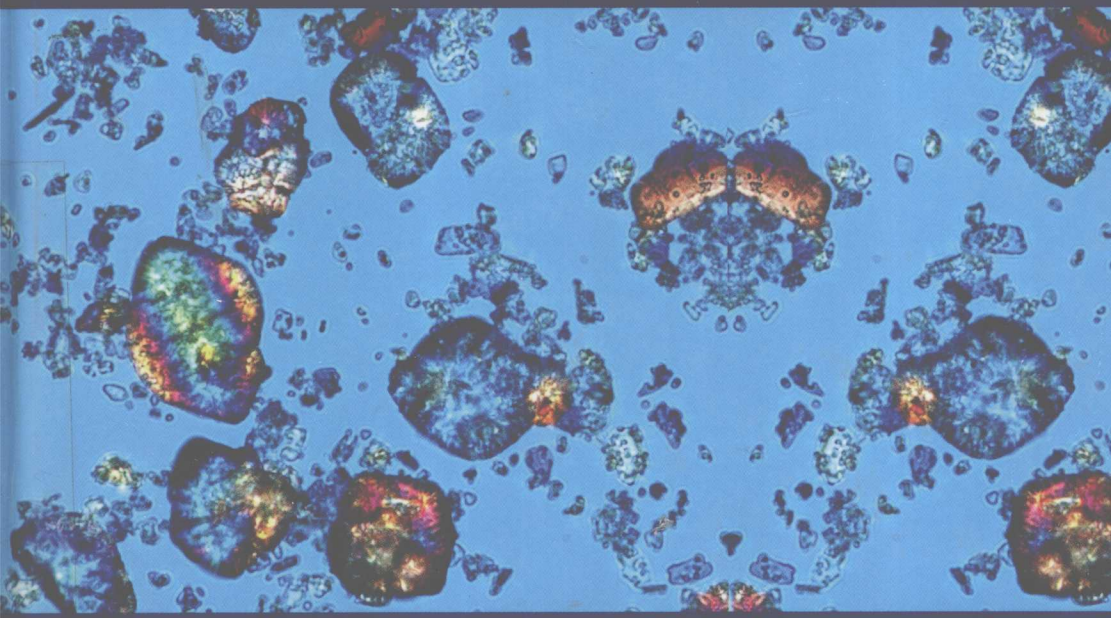
Formulation and Analytical Development for Low-Dose Oral Drug Products

Edited by *Jack Zheng*



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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

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.

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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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