Dose Finding in Drug Development

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Preface

This book emphasizes dose selection issues from a statistical point of view. It presents statistical applications in the design and analysis of dose–response studies. The importance of this subject can be found from the International Conference on Harmonization (ICH) E4 Guidance document.

Establishing the dose–response relationship is one of the most important activities in developing a new drug. A clinical development program for a new drug can be broadly divided into four phases – namely Phases I, II, III, and IV. Phase I clinical trials are designed to study the clinical pharmacology. Information obtained from these studies will help in designing Phase II studies. Dose–response relationships are usually studied in Phase II. Phase III clinical trials are large-scale, long-term studies. These studies serve to confirm findings from Phases I and II. Results obtained from Phases I, II, and III clinical trials would then be documented and submitted to regulatory agencies for drug approval. In the United States, reviewers from Food and Drug Administration (FDA) review these documents and make a decision to approve or to reject this New Drug Application (NDA). If the new drug is approved, then Phase IV studies can be started. Phase IV clinical trials are also known as postmarketing studies.

Phase II is the key phase to help find doses. At this point, dose-ranging studies and dose-finding studies are designed and carried out sequentially. These studies usually include several dose groups of the study drug, plus a placebo treatment group. Sometimes an active control treatment group may also be included. If the Phase II program is successful, then one or several doses will be considered for the Phase III clinical development. In certain life-threatening diseases, flexible-dose designs are desirable. Various proposals about design and analysis of these studies are available in the statistical and medical literature.

Statistics is an important science in drug development. Statistical methods can be applied to help with study design and data analysis for both preclinical and clinical studies. Evidences of drug efficacy and drug safety in human subjects are mainly established on the findings from randomized double-blind controlled clinical trials. Without statistics, there would be no such trials. Descriptive statistics are frequently used to help understand various characteristics of a drug. Inferential

statistics helps quantify probabilities of successes, risks in drug discovery and development, as well as variability around these probabilities. Statistics is also an important decision-making tool throughout the entire drug development process. In clinical trials of all phases, studies are designed using statistical principles. Clinical data are displayed and analyzed using statistical models.

This book introduces the drug development process and the design and analysis of clinical trials. Much of the material in the book is based on applications of statistical methods in the design and analysis of dose-response studies. In general, there are two major types of dose-response concerns in drug development—concerns regarding drugs developed for nonlife-threatening diseases and those for life-threatening diseases. Most of the drug development programs in the pharmaceutical industry and the ICH E4 consider issues of nonlife-threatening diseases. On the other hand, many of the NIH/NCI sponsored studies and some of the pharmaceutical industry-sponsored studies deal with life-threatening diseases. Statistical and medical concerns in designing and analyzing these two types of studies can be very different. In this book, both types of clinical trials will be covered to a certain depth.

Although the book is prepared primarily for statisticians and biostatisticians, it also serves as a useful reference to a variety of professionals working for the pharmaceutical industry. Nonetheless, other professions – pharmacokienticists, clinical scientists, clinical pharmacologists, pharmacists, project managers, pharmaceutical scientists, clinicians, programmers, data managers, regulatory specialists, and study report writers can also benefit from reading this book. This book can also be a good reference for professionals working in a drug regulatory environment, for example, the FDA. Scientists and reviewers from both U.S. and foreign drug regulatory agencies can benefit greatly from this book. In addition, statistical and medical professionals in academia may find this book helpful in understanding the drug development process, and the practical concerns in selecting doses for a new drug.

The purpose of this book is to introduce the dose-selection process in drug development. Although it includes many preclinical experiments, most of dose-finding activities occure during the Phase II/III clinical stage. Therefore, the emphasis of this book is mostly about design and analysis of Phase II/III dose–response clinical trials. Chapter 1 offers an overview of drug development process. Chapter 2 covers dose-finding in preclinical studies, and Chapter 3 details Phase I clinical trials. Chapters 4 to 8 discuss issues relating to design, and Chapters 9 to 13 discuss issues relating to analysis of dose–response clinical trials. Chapter 14 introduces power and sample size estimation for these studies. For readers who are interested in designs involving life-threatening diseases such as cancer, Chapters 4 and 5 provide a good overview from both the nonparametric and the parametric points. In planning dose–response trials, researchers are likely to find PK/PD and trial simulation useful tools to help with study design. Hence Chapters 6 to 8 cover these and other general design issues for Phase II studies. In data analysis of dose–response results, the two major approaches are modeling approaches and multiple comparisons. Chapters 9 and 10 cover the

modeling approach while Chapters 11 and 12 cover the multiple comparison methods. Chapter 13 discusses the analysis of categorical data in dose-finding clinical trials.

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Contents