

Preface

Clinical development of new drugs (or new biologics) can be broadly divided into four phases: Phases I, II, III, and IV. The first 3 phases are considered as “pre-marketing development,” and Phase IV is known as the “post-marketing” phase. For the pre-marketing clinical development programs, concerns for developing agents treating life-threatening diseases, such as cancer, are different from concerns for other indications. In oncology development programs for treating cancer patients, typical Phase I trials recruit cancer patients and escalate doses to help find the maximally tolerable dose (MTD). Then, this MTD is used in Phase II for proof of concept (PoC) and for Phase III confirmatory trials.

On the other hand, in most of the product candidates developed for the treatment of chronic diseases or non-life-threatening conditions, Phase I clinical trials recruit healthy normal volunteers, and the main objectives of Phase I are to understand the pharmacokinetics (PK) and to estimate MTD. Phase II clinical trials are designed to establish PoC and to estimate the efficacy dose range. After these exploratory phases (Phase I to explore PK and upper limit of dose range, Phase II to explore lower limit of dose range), Phase III uses large-scale confirmatory clinical trials with an objective to establish the longer-term efficacy and safety of this new candidate product. If the dose(s) studied in these Phase III trials demonstrate efficacy and safety, then these doses can be approved by regulatory agency for indicated patient population use. The focus of this book is on the Phase II development of medicinal products treating most non-life-threatening indications, oncology generally excluded (although some of the material may be relevant to oncology trials).

In practice, most of the new compounds or new biologics fail to become a successful medical intervention. Hence, an appropriate angle to view clinical development could be to think of it as a weeding out process. In other words, if a product candidate does not demonstrate clinical efficacy or safety, then this candidate should be stopped for further development. From this point of view, an efficient clinical development process should be such that if the candidate is a successful drug, then this drug should be made available for treating patients as soon as possible. On the contrary, if this candidate is not a successful agent, then it

should be stopped from further development as early as possible, in order to avoid unnecessary sponsor investment and resources.

The difficult question is how to achieve both objectives. We believe the most efficient process of new drug development should align with the concept of “design to stop.” Using this strategy, the project team uses every clinical trial to weed out the drug candidate under development. This is the most efficient way of ensuring an unsuccessful candidate to be stopped at the earliest stage. The natural question would then be “What about the successful candidates?” In fact, a good drug reveals its good properties under most simple designs. Across all the successful drugs on the market, most of them revealed their good efficacy and safety characteristics at very early stage of clinical development. In other words, with the “design to stop” strategy, it is very unlikely to weed out a very good product candidate.

For study drugs developed to treat a non-life-threatening condition, before it enters Phase II, it is not known whether this study drug can deliver the expected efficacy (because efficacy cannot be observed from healthy volunteers in Phase I). At the end of Phase II, a critical decision must be made as to whether to continue developing this test drug into Phase III, which implies an enormous amount of commitment in investment and resources. Given this background of medicinal product development, project team members need to know that among all of the product development processes, no other step could be more important and critical than Phase II.

The objective of this book is to clarify the importance of Phase II clinical development and also to lay out the key thinking process in designing and analyzing of each Phase II clinical study. With a clear understanding of the importance of Phase II, as well as how to face these challenges in new product development, readers will be able to design the most efficient Phase II clinical trials. As a product candidate moves into Phase II, these strategies will maximize the likelihood that a “not so good” candidate will be weeded out as early as possible and that the really good product can reach to the patients as soon as possible.

As a general note, the references for each chapter are at the end of the chapter so that the readers can readily refer to the chapter under discussion. Thus, each chapter is self-contained with respect to references. The first seven chapters focus on design of Phase II clinical trials, and then, Chaps. 8–10 discuss analysis of these clinical data. Finally, Chap. 11 covers a Bayesian approach, and Chap. 12 lays out Phase III trial considerations.

The entire content of this book is intended solely and strictly for educational and pedagogical purposes. The material herein expresses the views of the authors and does not in any way reflect the views of their employers or any other entity.

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