PRINCIPLES OF CLINICAL PHARMACOLOGY

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CHAPTER

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Design of Clinical Development Programs

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INTRODUCTION

This chapter provides an overview of the clinical drug development process, which includes the clinical proof of mechanism (POM), clinical proof of concept (POC), the characterization of clinical safety, the characterization clinical activity, and the generation of evidence of safety and effectiveness to support regulatory review and, ultimately, marketing approval. The clinical trials that are conducted to generate the safety and effectiveness database, to meet the regulatory standard of "evidence," are referred to as "confirming clinical trials." It is this understanding of the clinical effectiveness and safety of a new drug that provides the knowledge for informed decision-making regarding the clinical development, approval, marketing, prescribing, and proper use of a new drug. The clinical development process consists of (a) clinical trials for scientific development, (b) clinical trials for scientific regulatory purposes, and (c) clinical trials that are pharmacoeconomically motivated (1). This chapter covers the clinical drug development process with a focus on *critical decision points* and the use of the *learning and confirming* and the *label-driven question-based* approaches to designing, developing, and planning clinical development strategies.

This chapter is intended to provide the reader with a strategic overview of the manner in which an effective and efficient contemporary clinical development program is created. It is beyond the scope of a single chapter to be able to adequately cover all aspects of a clinical development program. More comprehensive overviews of the operational aspects of clinical plans and clinical trial design are provided by texts written by Spilker (2) and Friedman (3). For a comprehensive overview of clinical trial design and analysis, the reader is referred to *Studying a Study and Testing a Test* by Riegelman (4). Information about the new drug regulatory review process and how it relates to new drug development is presented in Chapter 34 and at the Center for Drug Evaluation and Research (CDER) Handbook web site (5). Another valuable resource for the design and conduct of clinical trials is a comprehensive glossary of clinical drug development terminology (6). In addition, the U.S. Food and Drug Administration (FDA) announced a Critical Path Initiative in 2004 and this provides insight into several areas of focus for streamlining the drug development process (7).

PHASES, SIZE, AND SCOPE OF CLINICAL DEVELOPMENT PROGRAMS

The FDA broadly defines *drugs* as those compounds that are synthesized and *biologics* as those that are produced by living organisms. However, for the purposes of this chapter, we will use the term "drug" to represent both drugs and biologics.

Global Development

Within the past decade, international guidelines and regulations have become more uniform through

the efforts of the International Conference on Harmonization (ICH) (8). The efforts of the ICH, which included participation of regulatory agencies, industry, and academia from the United States, Europe, and Japan, have resulted in a series of comprehensive ICH Guidances. These guidances address effectiveness (E), safety (S), and manufacturing (M), and develop a Common Technical Document.

Clinical Drug Development Phases

Traditionally, the clinical development process has been divided into four phases.

Phase I

As described in Chapter 31, Phase I includes first-in-human (FIH) trials to provide information about the safety (tolerability) and pharmacokinetics of a new drug. These trials are usually conducted in healthy volunteers unless the trials involve certain cytotoxic drugs such those used in cancer and HIV treatments. It should be noted that Phase I-type clinical pharmacology trials, such as those to study pharmacokinetics in special populations, can and do occur throughout the clinical drug development process (see Chapter 1, Figure 1.1).

Phase II

Phase II consists of small trials in individuals with the illness to be treated (usually trials of 24 to 300 persons). The goals of Phase II trials are to provide either a proof of mechanism or a proof of the hypothesized therapeutic concept, identify the patient population(s) in which the new drug appears to work, and determine an appropriate dose regimen for subsequent large-scale trials. Dose regimen includes the loading dose, maintenance dose, dose frequency, dose duration, and dose adjustments for special populations and for coadministration with other drugs.

Phase III

Phase III trials are trials conducted to confirm the effectiveness of a new drug in a broad patient population in order to establish clinical settings in which the drug works or does not work. These trials also are designed to provide an evaluation of the frequency and intensity of adverse drug events that are likely to be encountered in subsequent clinical use. These trials are large (250 to >1000 patients) so as to provide information that can reasonably be extrapolated to the general population. After successful completion of Phase III trials that meet U.S. requirements, the sponsor of the development program generally files a New Drug Application (NDA) or Biologics License Application (BLA) with the Food and Drug Administration. FDA approval of these applications is required before the product can be marketed in the United States. Similar procedures are in place in other countries (i.e., a Marketing Authorization Application in Europe and/or the equivalent regulatory submission in Japan and other parts of Asia); here the focus is primarily on U.S. regulatory review processes and requirements.

Phase IV

Phase IV trials are conducted as postmarketing efforts to further evaluate the characteristics of the new drug with regard to safety, efficacy, new indications for additional patient populations, and new formulations. Phase IV is generally used to characterize all post-NDA/BLA clinical development programs. However, some organizations use Phase IV to describe only FDA-requested clinical trials and use Phase V to describe internally motivated market expansion trials (e.g., new indications, new formulations, updated safety databases).

It is noteworthy that in an attempt to better characterize the types of information and knowledge that are developed during each phase, terms such as early-Phase II or late-Phase III (or Phase IIa and Phase IIIb, respectively) have crept into the clinical development lexicon. Although the traditional four phases are helpful in broadly defining a clinical drug development program, the use of these phases in a strict chronological sense or as milestones would be misleading. A strict chronological interpretation would infer that pharmacokinetic determinations are very limited and only occur in the early (Phase I) part of the clinical drug development process, and that Phase IV market expansion trials are started only after the new drug has been approved. Therefore, instead of thinking of drug development as a series of consecutive phases, it is preferable to think of the drug development process as a series of interactive knowledge-building efforts, like the expanding layers of an onion, that allow us to make cogent scientific drug development decisions.

Drug Development Time and Cost — A Changing Picture

Clinical drug development is a complex, expensive, and lengthy process that can be thought of as having several main objectives in support of the ultimate goal — marketing approval with the desired indications and claims. The average cost of bringing one new medicine to market cited by the Pharmaceutical

Research and Manufacturers of America (PhRMA) (9, 10) is $799 million, and a report by Bain & Company (11) estimates the cost for a new drug at $1.7 billion. These cost estimates take the following factors into consideration:

- The actual cost of the successful drug discovery and development programs.
- The cost of money [the financial return that would be realized if the money spent on research and development (R&D) were invested in long-term notes].
- The cost of unsuccessful discovery and development projects ("dry holes").

The actual "out-of-pocket" expense for a single new drug varies, depending on the number of indications, formulations, and study participants needed to obtain regulatory approval, but is probably in the neighborhood of $200 million to more than $300 million. It is noteworthy that if one divides the total R&D spent for the year 2004, ~$38.8 billion (12), by 34, the number of new molecular entities (NMEs) that were approved by the FDA during 2004 (13), one arrives at an estimate of ~$1.14 billion per NME. It also should be noted that since large pharmaceutical companies expend approximately one-half of their R&D funds on line extensions, the average cost per new drug approved for marketing may indeed approach an average cost of approximately $500–700 million, which, of course, includes funding for the 11 out of the 12 drugs that enter clinical trials but never achieve marketing approval (14).

Estimates for the cost per participant in a clinical trial range from less than $2,000/person for a short treatment, to as much as $15,000/person for lengthy or complex treatments. In addition to the clinical grants to investigators, the full clinical costs include development of the protocol and of the clinical investigators' brochure, clinical investigator meetings, monitoring and site visits, clinical data collection, data quality resolution, data management and analysis, and report preparation. If the clinical database needed to achieve approval requires 4,000 to 8,000 study participants, one can see how the cost of the clinical portion of drug development can quickly approach $150 million.

Clinical drug development requires the integration of many disciplines, including discovery research, nonclinical and clinical development, pharmacometrics, statistics and bioinformatics, regulatory science, and marketing to identify, evaluate, develop, and achieve regulatory approval for the successful marketing of new drugs.

In the recent past, the overall time from the initiation of a drug discovery program to regulatory approval was 10 to 15 years, but this has been reduced so that development timelines now range from 4 to 6 years. Much of the time and expense of drug development is related to the large numbers of individuals who need to be studied in clinical trials. Clinical development programs with large numbers of individuals are needed for therapies such as broad-spectrum antibiotics, which usually are developed for many indications. Similarly, large clinical programs are needed for a vaccine or flu treatment. In these cases the incidence of the disease is small and many individuals are needed to demonstrate a clinically significant difference in disease incidence between test-drug-treated and placebo-treated study participants. As a result, contemporary clinical development plans usually include a minimum of 1,500 participants, the ICH default minimum, and often exceed 6,000 participants.

The drivers that determine the size of a clinical development program include what is referred to as the "treatment effect size" and the intended level of differentiation that is being sought by the developer. The treatment effect is determined by the underlying population event rate and the expected event rate in the treated population (3). The level of differentiation impacts the trial size in that if developers want to provide evidence that their drug is as safe as an already marketed drug that has an adverse event rate in the range of 4%, it has been estimated that an 80,000-patient trial would be need to provide convincing evidence that the new drug is "equivalent" with regard to the incidence of the adverse event being studied. Likewise, there have been recent occurrences in which the incidence of certain adverse events for an already marketed drug was in the range of 30–40% and the developer of a new drug wanted to demonstrate that the new drug had an adverse event rate of one-half that of the already marketed drug. Although convincing evidence of a clinically significant decrease in the adverse event rate might be generated with 250–500 patients, it may require much larger trials to demonstrate that the new drug has the same level of effectiveness as the existing drug ("noninferiority" of the new drug). Otherwise, the argument could be made that the new drug may be safer, but may also be less effective (e.g., 50% safer, but also 50% less effective).

Although the cost of drug development is likely to remain high, contemporary drug development technologies, the availability of high-quality contract research organizations (CROs) for the outsourcing of key efforts, and the emergence of online clinical trial data collection and management ("e-R&D") have reduced the average time from drug discovery to NDA/BLA submission to a new benchmark of

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