CHAPTER 2

Introduction to Regulated Clinical Trials

I. INTRODUCTION

Clinical trials are classified as Phase I, Phase II, and Phase III clinical trials. The goals of these trials are to acquire data on safety and efficacy, to receive regulatory approval for the relevant drug or medical device, and to provide safe and effective treatments for the relevant disease or condition. Regulatory approval is granted by agencies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan (1). Phase I clinical trials are distinguished as being the initial trials conducted on human subjects. Phase I trials are sometimes called "first-in-human studies" (2) or "first-in-man studies" (3).

Before any drug is used in humans, it must be designed (or discovered), tested in animals, and characterized. Drugs are characterized by their purity, stability to storage, toxicity in animals, pharmacokinetics (PK) in animals, and efficacy in animals. In the United States, an Investigational New Drug (IND) application must be submitted to the FDA in order to gain approval for initiating clinical trials (4). The IND summarizes data on the chemistry and stability of the active drug substance, studies using in vitro methods such as studies with cultured cells, data on toxicity and efficacy acquired from animal studies, and any available data on humans. The term "clinical data" only refers to data from studies on human subjects (not to data from animal studies).

The main goals of a Phase I clinical trial are to assess safety and to determine an effective dose suitable for subsequent Phase II trials. In clinical trials on anti-cancer drugs, Phase I trials are often configured to determine the minimal dose that can cause significant toxicity. From this particular dose, it is often assumed that the dose is that which will be most effective against the cancer. In other words, the most appropriate dose is that which is just below a dose that produces unacceptable toxicity. But this method is not used to arrive at the dose used in clinical trials for diseases that are not cancers.

Phase I clinical trials begin by administering a small dose of the study drug to a group of three or more patients. Subsequently, cohorts of patients receive increasing doses, first by 100%, then 66%, 50%, 40%, and 33%, a progression that is loosely based

[1] Sihna G. Japan works to shorten "drug lag," boost trials of new drugs. *J Natl Cancer Inst*. 2010;102:148–151.
[2] European Medicines Agency (EMEA). Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (July 2007).
[3] Castle G, Marshall C. CHMP guideline on reducing risk in first-in-man trials: how will it affect your research. Informa UK, Ltd. Oct. 2007; 20–22.
[4] Tamimi NA, Ellis P. Drug development: from concept to marketing! *Nephron Clin Pract*. 2009;113:c125–1231.

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