CHAPTER 24

Drug Safety

I. INTRODUCTION

The term *pharmacovigilance* refers to the process of identifying and responding to drug safety issues, where this process occurs during clinical trials as well as after regulatory approval (1). Drug safety data are collected or "captured" during the course of clinical trials intended for regulatory approval, as well as after approval (2).

The goals of Phase I clinical trials include determining drug safety, characterizing the drug's pharmacokinetic (PK) and pharmacodynamic (PD) properties, and acquiring information useful for arriving at the most optimal dose for Phase II and Phase III clinical trials. Information on optimal dose encompasses the amount of drug to be administered, route of administration, and timing of doses. The main goals of Phase II and III clinical trials are to acquire information on both safety and efficacy.

Safety is determined by capturing adverse events (AEs), and then determining which AEs result from the disease, which AEs likely arise from the drug, and which AEs are irrelevant to the disease or to the drug. Adverse events encompass all unfavorable events, including those caused by the drug, those caused by the disease being treated, and those resulting from causes that appear irrelevant to the drug or disease, such as automobile accidents. The subset of AEs that are caused by any given drug is called *adverse drug reactions.*

Adverse events may be observed and captured by the clinician or, alternatively, by the study subject. Adverse events, and other information on the disease and drug that are captured by the study subject, are called patient-reported outcomes (PROs) (3).

Generally, regulatory approval is a function of both efficacy and safety. But extra emphasis may be placed on safety in a type of trial design called a non-inferiority clinical trial. In this type of trial, the basis of approval can be more a function of improved safety, and less a function (or not at all a function) of improved efficacy. According to the European Medicines Agency (EMA), "a noninferiority trial aims to demonstrate that the test product is not worse than the comparator by more than a pre-specified, small amount" (4). In comments on non-inferiority trials, Pocock (5) observed that

[1] Talbot JC, Nilsson BS. Pharmacovigilance in the pharmaceutical industry. *Br J Clin Pharmacol*. 1998;45:427–431.
[2] Scharf O, Colevas AD. Adverse event reporting in publications compared with sponsor database for cancer clinical trials. *J Clin Oncol*. 2006;24:3933–3938.
[3] U.S. Dept. of Health and Human Services. Food and Drug Administration. Guidance for Industry. Patient-reported outcome measures: use in medical product development to support labeling claims. December 2009 (43 pages).
[4] European Medicines Agency. Guideline on the choice of the non-inferiority margin. 2005 (11 pages).
[5] Pocock SJ. The pros and cons of noninferiority trials. *Fundam Clin Pharmacol*. 2003;17:483–490.

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