phase is primarily to elucidate the PD characteristics of the agent and their impact upon the therapeutic activity (8). Therefore, the determination of the PK profile of the drug and/or the metabolites in animals as a guide to these characteristics in humans is critical. Additionally, the development and use of biomarkers in animal models are strongly recommended because these can demonstrate early signals of efficacy and toxicity in humans (9–14).

In this chapter, some real drug development cases will be introduced, in which the preclinical database was adequately utilized to provide drug developers with supportive, and sometimes critical, evidence necessary to design efficient and informative clinical development programs, thereby facilitating final regulatory approvals. These examples will be followed by a brief discussion on the implication of using the preclinical database in a specific drug development setting.

1. UTILIZING THE PRECLINICAL DATABASE TO SELECT HUMAN DOSE

The selection of dose for the first-time-in-man (FTIM) study is one of the most important and difficult decisions to be made when entering the clinical phase of drug development. The dose for the FTIM study has to be small enough to not to cause harm to the subjects, but, at the same time, a starting dose that is too small must be avoided since it will increase the time needed to reach the maximum tolerated dose (MTD) or the clinically efficacious dose. Many methods to determine the safe human dose have been introduced with mixed results (15–17).

1.1. Determination of Starting Dose: a Regulatory Agency's View

The US Food and Drug Administration (FDA) released the Draft Guidance for Industry and Reviewers for Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers ("Draft Dose Guidance" hereafter) in December, 2002, outlining a standardized process for deriving the maximum recommended starting dose (MRSD) for adult healthy volunteers for first in human clinical trials of new molecular entities (18). The Draft Dose Guidance defined the MRSD as the highest initial dose in a clinical trial that is predicted to cause no adverse reactions in adult healthy volunteers.

The process for selecting the MRSD is summarized in Fig. 1. The MRSD is selected after the determination of the no observed adverse effect levels (NOAELs), based upon the analysis of toxicity data from preclinical animal studies. Although only the NOAEL is used in the first step of the algorithm, other data (exposure/toxicity relationships, pharmacologic data, or prior clinical experience with related drugs) will affect the choice of the most appropriate species, scaling, and safety factors in later steps.