2. WHAT IS A MODEL AND WHY DO WE DO WE MAKE THEM?

A system is a collection of interacting objects. A car, a computer, and a living organism each represent different types of systems. A model is any representation of a system that accounts for the properties of the system. Certainly, many classes of models exist. One that comes immediately to mind is a scale model wherein some physical object is re-created and scaled to a size that is more convenient for viewing, e.g., an architect's design of new building. In pharmacokinetic–pharmacodynamic modeling, the models are mathematical and statistical in nature, and they attempt to characterize the relationship between dose and some dependent variable. A pharmacokinetic model describes the relationship between dose and drug concentration, usually in plasma or serum, while the pharmacodynamic model relates drug concentration to efficacy, adverse events, or outcome. A pharmacokinetic–pharmacodynamic model integrates dose to response and the role of such models in drug development is the subject of a guidance issued by the Food and Drug Administration (4).

Modeling, especially quantitative modeling based on mathematics and statistics, serves many useful purposes. One is that it characterizes and summarizes a set of data into a cohesive structure. For example, given a set of concentration–time data, a pharmacokinetic model summarizes the data into a few simple parameters; for example, clearance—a parameter that relates concentration to rate of change in concentration. Second, and most importantly, is that modeling may allow predictions to be made, a process that is referred to as simulation. Conditional on a pharmacokinetic model structure and parameter values or population distributions, predictions can be made regarding changes in dose frequency or total dose administered. Given a pharmacokinetic–pharmacodynamic model, predictions on outcome or safety can be made regarding projected changes in dose, dose frequency, or changes in the parameters that describe the system, such as the expected increase in exposure if renal clearance were decreased in patients with renal failure. The ability to predict makes simulation a very important tool in drug development, since further product development can then proceed in a rational manner; the converse of this would be to have to do study after study to answer important questions that arise during the drug development process, without being able to integrate answers to the questions in a coherent, testable whole.

3. WHAT CONDITIONS ARE NECESSARY FOR THE PRECLINICAL MODEL TO BE VALID IN HUMANS?

Most of the literature that advocates an increased role of pharmacokinetic–pharmacodynamic modeling in the drug development process has focused on developing models early in *clinical* development and then using these