adverse effects in humans (usually very well, but there are notable lapses; for example, giving false positives and false negatives) and an understanding of what initial clinical trials are intended to do. Though an "approved" IND grants one entry into limited evaluations of drug effects in humans, flexibility in the execution and analysis of these studies offers a significant opportunity to also investigate efficacy [5].

Once past the discovery and initial lead or candidate selection stages, each aspect of development becomes more tightly connected with the other aspects of the development of a compound, particularly the potential clinical aspects. These interconnections are coordinated by project management systems. Many times during the early years of the development process, biological evaluation of efficacy and safety constitutes the rate-limiting step—it is, in the language of project management, on the critical path.

Another way in which pharmaceutical development varies from toxicology as practiced in other industries is that it is a much more multidisciplinary and integrated process. This particularly stands out in the incorporation of the evaluation of ADME (absorption, distribution, metabolism, and excretion) aspects in the safety evaluation process. These pharmacokinetic/metabolism (PKM) aspects are evaluated for each of the animal model species utilized to predict the safety of a potential drug prior to evaluation in humans. Frequently, in vitro characterizations of metabolism for model (or potential model) species and humans are performed to allow optimal model selection and understanding of findings. This allows for an early appreciation of both the potential bioavailability of active drug moieties and the relative predictive values of the various biological models. Such data early on are also very useful (in fact, sometimes essential) in setting does levels for later animal studies and in projecting safe dose levels for clinical use. Unlike the case in most other realms of development of biologically active molecules, one is not limited to extrapolating the relationships between administered dose and systemic effects. Rather, one has significant information on systemic levels of the therapeutic moiety—typically, total area under the curve (AUC), peak plasma levels (C_{max}), and plasma half-lives, at a minimum.

2 SCREENS: THEIR USE AND INTERPRETATION IN DRUG DISCOVERY

Much (perhaps even most) of what is performed in safety assessment can be considered screening—trying to determine if some effect is or is not (to an acceptable level of confidence) present [6]. The general concepts of such screens are familiar to toxicologists in the pharmaceutical industry because the approach is a major part of the activities of the pharmacologists involved in the discovery of new compounds. But the principles underlying screening are not generally well recognized or understood. And such understanding is essential to the proper use, design, and analysis of screens [7, 8]. Screens are