candidate is worthy of further development or should be terminated from the development pipeline.

A thorough understanding of any nonhuman model is fundamentally important so that drug-related outcomes can be separated from normal, endogenous variability or other processes unrelated to the drug. Rodents, canines, and nonhuman primates have become common preclinical models not always because of their strong direct relevance to potential human outcome but because of the established understanding of these animals and their underlying physiology (2–4).

In the following chapters, preclinical drug development will be reviewed in a sequence consistent with current rational and efficient practices. The reader will be introduced to animal models, species selection and will then proceed to chapters on definitive pharmacokinetic, pharmacodynamic and toxicology evaluations. Other important chapters describe formulation impacts, alternative technologies, and the relationship between preclinical findings and the clinical setting.

Looking into the future, the scientist who is engaged in preclinical drug development will more than ever factor innovation into the balance of risk vs. benefit (5,6). Even after rigorous preclinical and clinical evaluation, the potential for drug toxicity can be profound. For example, US drug R&D expenditures for 1995 were $15.2 billion and had nearly doubled to $30.5 billion in 2001. Yet, in the US alone over 100,000 patients die each year as a result of drug side effects (7,8). Furthermore, an additional two million patients require hospitalization or extension of existing hospitalization each year to treat drug side effects. While current preclinical safety assessments generally identify drug candidates with systematic toxicity potential, they remain insensitive to nonsystematic toxicity or to conditions that increase risk of known toxicity.

Weighing a drug's intrinsic toxicity relative to potential clinical benefit, those people conducting preclinical development become the messengers bearing safety margins and insight on early clinical development. There are limitations on how safe and efficacious a drug candidate can be made based on formulation, route of administration, and dose regimen. Hence, the most opportunity for achieving success lies with drug candidate selection. This is common sense but not often appreciated. Intelligent drug candidate selection incorporates knowledge of a molecule's (i) absorption, distribution, and metabolism properties, (ii) binding affinity to the intended pharmacologic receptor(s) and (iii) toxicity potential. Indeed, a 10-fold reduction in binding affinity may be more than offset by a bioavailability that has been improved by only 2–3 fold since increasing bioavailability reduces variability in absorption. For example, a drug with just 10% bioavailability has intrinsically poor absorption properties that may include poor solubility, dissolution rate, permeability or metabolic instability such as 1st pass metabolism. Consequently, dose-to-dose bioavailability may