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The Scope of Preclinical Drug Development: An Introduction and Framework

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The science of preclinical drug development is a risk-based exercise that extrapolates nonhuman safety and efficacy information to a potential human outcome. In fact, the preclinical development program for nearly every drug is an exercise in predicting clinical results with little data to support the use of the animal model under study. In the end, human studies validate the nonhuman models. Yet, understanding preclinical drug response—pharmacologic and toxic—with respect to dose, frequency, and route enables the clinical scientist to initiate and continue human trials under rational and ethical conditions. Those conditions include a starting dose and dose frequency that is at the highest region of a no effect level, a safe dose escalation scheme that permits differentiation of response as a function of drug exposure and an understanding of when potential toxicity may outweigh potential additional pharmacologic benefit (Fig. 1). Of similar significance but often under-appreciated is an understanding of pharmacokinetic and response variability—sources, type, and magnitude. So, while we report and often predict mean effect, there is rarely an average patient who will receive a drug. Consequently, most patients who receive a drug within a labeled dose regimen will not respond with an average pharmacologic response; nor, will most patients develop an average syndrome of adverse events. Rather, it is often vast diverse populations of individuals