dose frequencies, or distribution of drug into tissues is likely to generate data with little predictive value.

In parallel, recent advances in identifying and quantifying gene expression and signaling processes permit mechanistic insight into drug activity and toxicity (17,18). Validation of new in vitro methods for toxicity assessment will further reduce animal use and increase the likelihood of a molecule entering clinical trials (19,20).

In summary, the understanding of preclinical drug disposition—distribution, metabolism, excretion—coupled with an understanding of cell or tissue specific activity/toxicity completes the knowledge base for a drug candidate to move into and through clinical evaluation. This understanding is achieved by generation of a clinical strategy that is then used to draft the initial preclinical plan.

Few, if any, preclinical plans remain intact throughout their lifespan. It should be anticipated that as studies are completed and observations are confirmed, ongoing and future studies are likely to require modification.

Throughout all development programs, it is imperative that the preclinical scientist assesses each study prior to implementation. What questions must be answered by the study? Do those questions warrant animal use or can more ethical in vitro methods be utilized. Does the proposed study have a high likelihood of answering those questions? If so, will the answers affect the subsequent clinical development? No study should ever be conducted unless there is clarity in the study goals and clarity in the expectations on how much risk is being eliminated from the clinical program by conducting the study.

The preclinical scientist is charged with advancing lead candidates into and through clinical development. This is achieved by reducing risk in the decision-making process for all clinic-related questions. While clinical risk is low, if not nonexistent, prior to human trials the cost of risk becomes substantial as the drug candidate moves into larger human trials and into more complex populations.

A scientifically sound preclinical program permits efficient, safe clinical development. The absence of such a program will promote poor decision-making and potentially serious clinical consequences. In this era of the public demanding better and safer medications both faster and at less cost, the preclinical scientist oversees a vital responsibility.

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