range between 5% and 20% (and likely more). Inevitably this 4-fold fluctuation gives rise to subtherapeutic or toxic target tissue concentrations in some or all of the patient population and will likely lead to treatment failure. It is intuitive that variability in serum drug concentrations has less magnitude when absorption approaches 100%. In turn, it can be anticipated that as intrinsic bioavailability increases, the impact of food, age, and other factors on absorption will decrease. Clearly, in the quest for more potent and target-specific drugs, a similar effort must be exerted to achieve greatest bioavailability.

With respect to screening for drug clearance, numerous validated technologies are available to assess the potential for metabolism and likely routes of elimination (9–11). Greater utilization of human recombinant enzymes, cells, and tissues will accelerate our insight into appropriate selection of lead candidates for preclinical and clinical development. Likewise, isolated perfused organs can provide valuable insight into potential sites and mechanisms for drug metabolism and excretion.

Together, these technologies offer significant value in generating rank order information on lead drug candidates. In addition, they provide an early understanding of potential variables that may impact absorption or elimination.

With a lead drug candidate in hand an immediate understanding of drug disposition and elimination is demanded. Tissue accumulation, sequestration, and metabolism strongly influence the profile of pharmacologic effect and also give early warning on sites of potential toxicity.

Most promising in the advancement of pharmacokinetics and toxicology are the technologies that enable greater quantitative information to be gained on drug disposition and toxicity while using fewer animals. Advanced physiological-based pharmacokinetics (PBPK) and mixed effects modeling offer insight into drug disposition that can provide immediate value to the toxicologist and can also be extrapolated to potential human exposure (12,13).

Mahmood and Balian (14) and others (15) have published extensively on interspecies scaling techniques. The prediction of drug distribution volume, clearance, and half-life provides a rational basis for prospective preclinical and clinical study designs. While providing significant value to the development team these predictions also carry uncertainty and the scientist using the information must respect that caveat. Profound differences in anatomy and physiology between the preclinical species and humans can challenge the relevance of allometric scaling and, for that matter, all preclinical work. While rats have a lifespan that will not likely exceed 5 years, the lifespan of a human can often exceed 90 years. While rats have heart rates of $\sim$360 beats per minute, the human heart rate is $\sim$65 beats per minute. Respiratory metabolism, measured as O_2 consumption, is $\sim$0.84 and 0.20 mL/hr/g in rats and humans, respectively. Similarly, there are also substantial differences in various organ blood flows, relative organ weights, and tissue architectures (16). Simple cross-species extrapolation of doses,