- If the exponent of the simple allometric equation lies between 0.71 and 1.0, a prediction based upon the simple allometric equation will substantially overestimate the predicted clearance. In this situation, accounting for differences in maximum life span potential (MLP) appears to improve the fit. For this situation, *CL* would be estimated as follows:

$$CL = a(MLP \times CL)^b / MLP \text{ of humans}$$

  where $MLP = 185.4\ (BW)^{0.636}\ (W)^{-0.225}$, BW = brain weight, MLP of humans $= 8.18 \times 10^5$.
- If the exponent of the simple allometric equation is greater than 1.0, the product of *CL* and *BW* can be used to predict human *CL* with reasonable accuracy. For this situation, *CL* would be estimated as follows:

$$CL \times BW = aW^b.$$

- In cases where $b > 1.3$ or < 0.55, neither of these three methods could adequately predict the *CL* of humans.

Under experimental conditions where drug pharmacokinetics can be examined across a wide spectrum of animal species, there is the luxury of being able to examine residual errors in order to determine the covariates that optimize the fit of the regression line. In so doing, the investigator can minimize the error in predicted vs. observed parameter values in humans [e.g., (170)]. However, what happens when one attempts to estimate a human equivalent dose (HED) on the basis of the NOAEL associated with the animal species of interest? In that situation, the fundamental objective is to ensure that the dose administered will result in negligible toxicity. This point brings us back to the debate described in the beginning of this section: is it more appropriate to scale to the power of 0.75 or 0.67? To that end, the use of an exponent of 0.75 rather than 0.67 will result in a far larger estimated starting dose in humans (e.g., a nearly 2-fold greater estimate when scaled on the basis of data derived from smaller rodent species, such as mice). Accordingly, the use of 0.75 could result in a higher and potentially more dangerous starting dose in humans. For this reason, the HED calculation is often based upon b=0.67 (150), thereby increasing the probability that the drug will be safe when administered for the first time in healthy human volunteers.

7. CONCLUDING THOUGHTS

While this chapter focused on animal models, comparative anatomy and physiology, and the extrapolation of preclinical data to humans, a far more complex question is whether or not preclinical data can also predict