

humans (which are nose and mouth breathers) vs. rats (which are obligate nose breathers).

- The number of daughter generations of the air passage in humans is 35, while there are fewer than 25 generations in the rat.
- The total lung volume of rats is only 10% that of humans.

Furthermore, in contrast to convention, the species most closely resembling humans with regard to respiratory system structure and function are the horse and donkey.

In general, when using multiple species for assessing the risk of drug toxicity in humans, the probability of an inappropriate conclusion is generally low (43). Boxenbaum and DiLea (44) estimated these risks in an effort to predict the likelihood of a serious adverse event when a drug is administered as a first-time dose to healthy human subjects:

- Sum of observed occasions when rat and other non-primate species exhibited a “good” or “fair” model for human drug toxicity = 0.92.
- Frequency of an adverse event that is predicted incorrectly = 8% of total tests. This may be attributable to an adverse reaction seen in animals that does not occur in humans, or an adverse event in humans that was not predicted in animal studies.
- Assuming a 5% risk of failure to predict an adverse event in humans and given the safety factors built into the estimate of the first-time dose in humans, of that 5% risk, only 1% of those events is serious. Accordingly, the risk of a serious adverse event associated with studies involving first-time dose in humans = $0.05 \times 0.01 = 0.0005$. In other words, in only 0.05% of the times do we anticipate that an unexpected serious adverse event will occur when a drug is administered for the first time to human subjects when there is an appropriate and adequate preclinical toxicity profile on which the assumptions are based.

During a workshop of the International Life Science Institute in which the toxicity of pharmaceuticals in humans and laboratory animals was compared (45), it was concluded that an interspecies difference in parent drug exposure was an unlikely cause for differences in adverse reactions. Rather, interspecies differences in target tissue response and drug metabolism were concluded to be the more likely reason for many of these discrepancies.

5. INTERSPECIES PHARMACOKINETIC DIFFERENCES

5.1. Drug Absorption

A host of physiological variables may contribute to interspecies differences in drug absorption and bioavailability. These variables include drug product