

and is said to have predictive validity. Consider, for example, schizophrenia. Determining whether or not an animal is suffering from schizophrenia is not generally possible due to the significant communication barrier. In addition, the mechanisms through which this condition develops are poorly understood at the best. Despite these gaps in scientific knowledge, there are several *in vivo* models available for the study of schizophrenia, most of which depend upon the administration of drugs that exacerbate or induce symptoms in humans.¹⁶

SPECIES SELECTION

In considering which species to use for a particular *in vivo* study, it is important to be aware of the limitations of each possible choice. *In vivo* efficacy experiments are key decision points in the life of a program, as they are often viewed as proof of concept experiments. Failure of an *in vivo* experiment can lead to termination of a program, especially if the therapeutic target is novel (e.g., no marketed drugs using the proposed mechanism of action). It is, therefore, absolutely critical that the species employed gives the best correlation possible with the human condition or disease.

Non-human primates are, of course, the closest animal to humans overall, but they are rarely used in animal trials. There are very few non-human primates available for study, and non-human primates are both difficult and expensive to maintain. Their large size also directly impacts compound supply issues, as potential therapeutics are most often dosed on a milligram per kilogram basis. Larger animals require larger amounts of compounds, further driving up the expense of non-human primate studies. Additional ethical considerations also come into play. Non-human primates are typically used only when no other option is available.

Smaller species such as rats, mice, and dogs are far more common choices for *in vivo* experiments. Each species has its pluses and minuses, but the most important aspect in species selection is ensuring that the selected animal model correlates with the human condition. A rat model of atrial arrhythmia, for example, may be easier to work with than a more sophisticated model that employs beagles. If, however, the rat model does not correlate with the human condition, the data provided in running the rat model will have very little value in a drug discovery and development program. Although the beagle model may be more difficult and time-consuming, it is the appropriate choice as it will provide insight into the utility of a potential therapeutic agent in humans, whereas the rat model will not. It is critical to keep the end goal in mind when selecting the species for an *in vivo* experiment. It is also worth noting that PK studies (described in Chapter 6) should be performed in the same species as planned for the pharmacodynamics experiments.