concentration and pharmacodynamics. Also, the greater the number of assumptions that go into a model, the more likely it is that some of these assumptions are wrong or hard to convincingly support. It is hard to overstate the importance of justifying any and all assumptions embedded in a pharmacokinetic–pharmacodynamic model. The impact of possible inaccuracies must be persuasively assessed before a model will be accepted as credible.

Even if a well-defined relationship between drug concentration and effect is established in animals, there is no guarantee the relationship will hold in humans. We all understand that nonhuman animal species and humans are different at many levels, so making the extrapolation from animals to man becomes a leap of faith implying that animals and man are more similar than dissimilar. The more dissimilar the pharmacology/physiology between the animal species and humans, the more tenuous the extrapolation. Hence, the physiology of the system under study should be understood and species differences must be identified and corrected for during the extrapolation process. Information already independently established and part of the scientific body of peer-reviewed literature can be proactively used to support it, for example through targeted collaboration with academic institutions. From within a drug development company, lead compounds that have previously had a pharmacokinetic-pharmacodynamic model established preclinically, and then tested and validated in humans provide a great help in this regard. This provides some experience in the validity of the model and extrapolation, should the lead compound fail and back-up compounds having the same mechanism of action have to be created or resurrected from pipeline purgatory.

4. CASE STUDIES

The remainder of this chapter will deal with case studies where pharmacokinetic–pharmacodynamic models established preclinically were used to help guide clinical development or answer key development questions that could not be addressed in humans.

4.1. Case Study 1: *Modeling the EEG Effect of Drugs Affecting the Central Nervous System*

Meindert Danhof at the Center for Bio-Pharmaceutical Sciences at the University of Leiden in The Netherlands has been one of the leading proponents of preclinical pharmacokinetic–pharmacodynamic modeling as a means to accelerate drug development through the use of rational dose selection, so it seems natural to review some of his research first. Most of this body of research has revolved around the use of the electroencephalograph (EEG) as a tool to provide relevant biomarkers for agents affecting the central