CASE STUDY 9 (*Continued*)

where D_{50} is the dose that produces a 50% decrease in relative bioavailability, n is the shape factor, Food is a binary dummy variable indicating whether the dose was taken without (=0) or with food (=1), and θ_{Food} is the estimable parameter associated with a food effect.

During the model selection process, Model 1 (Equation 5.1) was found to best describe the food effect on apomine's $F1$.

Modeling of absorption process of apomine: A simple first-order absorption model might not be applicable in this case. Thus, several absorption models were tested during model development process, including

- First-order absorption model with or without lag time
- Time-dependent absorption using a change-point model with or without lag time (Higaki et al., 2001)
- Time-dependent absorption using a Bateman function model with or without lag time (Higaki et al., 2001)
- Zero-order absorption
- Simultaneous first- (with and without lag time) and zero-order absorption
- First-order absorption (with and without lag time) treated as a mixture model

Of all the absorption models tested, the last absorption model (first-order model where the absorption rate constant and lag time were treated as a mixture model) fitted the data best. In 97% of the subjects, the population-estimated absorption rate constant was 1.77 h^{-1} with a lag time of 0.821 h, and in the remaining 3% of the subjects, the population-estimated absorption rate constant was 0.361 h^{-1} without a lag time (Bonate et al., 2004).

Besides the population-based pharmacokinetic modeling approach described in Case Study 9, recently, several other mechanistic modeling approaches have been used in describing and predicting absorption processes. For example, physiologically based pharmacokinetics (PBPK) modeling using commercially available software applications such as GastroPlus™ and SimCYP® have seen their increasing popularity in assisting formulation design and absorption optimization.

CONCLUSIONS

Drugs with very low aqueous solubility usually have sizeable inter- and/or intrasubject variability in their pharmacokinetics, which makes the study design and conduct of Phase I studies very challenging, makes the assessments of dose–response and exposure–response relationships more difficult, and makes the dose recommendation and optimization less feasible for NDA and product labeling.

Water-insoluble drugs usually have high propensity for drug interactions at absorption level, such as food interaction, interactions with GI prokinetic agents, effect of alteration in gastric pH with concomitant use of gastric pH modulating agents, especially if these drugs also have narrow therapeutic windows. Such hurdles and risks should be taken into consideration when a clinical drug development plan is put together. A risk/benefit reality check should be done at each critical stage gate, and if the risks are deemed too large, a tough call for termination of the program should be made. Early attention to absorption properties and close collaboration and communication between the Clinical Pharmacologists and Pharmaceutical Development scientists are crucial to ensure that the impact of formulation changes to address absorption challenges may not adversely affect the development timeline.

Owing to the inherent limitations of such drugs, more caution needs to be exercised and more resources may be warranted to make a sound assessment of their safety and efficacy profiles.