Application of PBPK Modeling in Drug Development

Physiologically Based Pharmacokinetic (PBPK) Modeling is an emerging mathematical modeling technique utilizing a complex network of organ compartments to mechanistically describe the Absorption, Distribution, Metabolism and Elimination (ADME) of pharmaceutical compounds. In PBPK modeling, the body is represented as a set of different compartments corresponding to the organs of a body. These compartments are connected by blood flow to form a network that allows a compound to travel from one compartment to the other in a "physiologically" relevant manner, thus mimicking the time course of a drug in the body. By accurately defining the characteristics of these compartments and the transfer of compounds between them, a PK scientist can accurately simulate the pharmacokinetics of a compound.

Traditional PK compartmental methods combine different body organs into one, two or three compartments to fit the clinical data and describe the pharmacokinetics of a compound. On the other hand, PBPK modeling differs itself from other traditional modeling techniques by relying on a "bottom-up" approach in which first principles, such the physiochemical properties of compounds coupled with the physiological and anatomical parameters of the body, form the building blocks of the model that mechanistically describes the pharmacokinetics of a compound.

The mechanistic nature of PBPK modeling allows for a robust predictive capability with limited clinical data. Since clinical data is primarily used only for validation of a PBPK model, not only can preliminary predictions be made before access to clinical data, but also fewer costly clinical studies may need to be conducted. The mechanistic nature of the model further allows for a high level of versatility. For example, parameters of a well characterized PBPK model in a healthy human can be modified to reflect disease conditions to accurately describe changes in the pharmacokinetics of a compound in different disease states. Similarly, the availability of databases containing the anatomic and physiologic differences across different populations (e.g., pediatric, elderly, obese, pregnant, renal or hepatic impaired) makes it possible to predict the differences in pharmacokinetics of a compound across these populations.

Drug-drug interaction (DDI) is another application where PBPK modeling has proven useful. In-vitro data for protein binding and enzyme/transporter kinetic parameters are incorporated in PBPK models. Thus, models can be used to evaluate the change in exposure of a drug due to enzyme or transporter mediated DDI.

As PBPK models are highly mechanistic and use physiological parameters from all organs, drug concentration-time profiles can be predicted for every organ, thus providing predictions for tissue levels of a drug. Another important application of PBPK modeling is its utility in scaling exposure from animal subjects to humans to inform the dose in First-in-Human studies. PBPK also is widely used to extrapolate dosing from adult to pediatric populations to aid in safe and efficient planning of pediatric clinical trials. Historically, allometric scaling has been the primary method for such activities.

However, methods such as allometry are purely empirical and are inherently non-mechanistic. These methods do not consider variability outside of body weight, often resulting in inaccurate predictions. In contrast, the mechanistic nature of PBPK modeling allows the model to incorporate variability in enzyme and transporter expression levels during scaling, thus achieving higher accuracy with lower error.

Contact the Synteract pharmacometrics team to learn how we can help with your Drug Development program using PBPK modeling and simulation services.