PBPK Modeling

Chairs: Avijit Ghosh, Janssen Research & Development and Tristan Maurer, Pfizer

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PBPK Model Guided Drug Development and Labeling Optimization

The application of physiologically based pharmacokinetic (PBPK) modeling has developed rapidly within the pharmaceutical industry, ranging from drug discovery to FIH studies to drug approval. This presentation will provide an overview of typical PBPK modeling applications that are used preclinically or clinically for internal decision-making, mechanistic understanding of clinical observations and to influence regulatory decisions. Three case examples are discussed in detail to demonstrate the diversity of PBPK modeling applications in guiding drug development. Specifically, these three examples will highlight (1) best practice/workflow for the development of complex models, using efavirenz as an example; 2) the utility of PBPK modeling to make *a priori* prediction of DDIs involving combination therapies which are often utilized in an oncology setting, using paclitaxel as an example; 3) the utility of PBPK modeling to optimize drug labeling, using eliglustat as an example. Lastly, challenges and future opportunities for the application of PBPK models are discussed.

Rui Li, Pfizer

A systems platform to predict pharmacokinetics of liver transporter substrates

Different from highly permeable small molecules, the pharmacokinetics of liver transporters substrates is determined by the activity of hepatobiliary transporters and their interplay with passive diffusion as well as hepatic metabolism, leading to difficulties in applying more traditional pharmacokinetic prediction approaches. We have developed a systems pharmacokinetic platform based on a physiological based pharmacokinetic (PBPK) model which may provide a more credible way to make predictions for transporter substrates. The model is parameterized by hepatic active

uptake, passive diffusion, biliary, and metabolic clearances derived from multiple in vitro assays currently available at the earliest, preclinical stages of pharmaceutical research. Additional empirical vitro-to-in vivo scaling parameters are derived through a non-numerical global optimization method which simultaneously leverages extant clinical data in order to arrive at unique and unified scaling factors which would otherwise not be determinable. The result is a novel "middle-out" approach which leverages statistical system parameter estimation within the context of a fixed physiological/mechanistic framework. This approach provides a reasonable, self-consistent description of the clinical IV plasma PK of 12 structurally diverse OATP transporter substrates along with parameters necessary to infer exposure in the liver. With additional in vitro data, this platform also predicts the impact of OATP polymorphism and cirrhosis on the pharmacokinetics.

Speaker Xiling Jiang

Minimal Physiologically-Based Pharmacokinetic (mPBPK) Model for a Monoclonal Antibody against Interleukin-6 in Mice with Collagen-Induced Arthritis

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Therapeutic monoclonal antibodies (mAb) targeting soluble inflammatory cytokines exert their pharmacological effects in rheumatoid arthritis through binding and neutralizing free cytokines in target tissue sites. Therefore suppression of free cytokines in such sites directly relates to the magnitude of therapeutic response. Although the interrelationships between mAb and cytokines have been examined in the systemic circulation, less is known about the interaction of mAb and cytokines in inflamed joints. In the present study, the interplay between the mAb, CNTO 345, and its target IL-6 in serum as well as ankle joint synovial fluid were characterized in collagen-induced arthritic (CIA) mice. A minimal physiologically-based pharmacokinetic (mPBPK) model with target-

mediated drug disposition (TMDD) features in serum and ankle joint synovial fluid has been developed for the assessment of the TMDD dynamics of CNTO 345 and IL-6. Our model indicates that TMDD kinetics in ankle joints differ greatly from that in serum. The differences can be attributed to the limited tissue distribution of CNTO 345 in ankle joint synovial fluid, the significant rise of the IL-6 baseline in ankle joint synovial fluid in comparison with serum, and the relative time-scales of elimination rates between CNTO 345, free IL-6 and CNTO 345-IL-6 complex in serum and ankle joint synovial fluid.