PBPK application: From academic research to routine use in drug development and regulation

Ping Zhao

Bill and Melinda Gates Foundation, USA

Physiologically-based pharmacokinetic (PBPK) models include drug-specific and physiology-specific components. This feature allows simultaneous evaluation of the effects of multiple patient factors on pharmacokinetics and pharmacodynamics of a drug in humans. The last decade observed exponential increase in the use of PBPK to address drug development questions. Today, global regulatory bodies are routinely reviewing PBPK analyses submitted by drug sponsors. Among the US FDA, EMA and Japan's PMDA, discussions are ongoing with regard to recommendations on determining adequacy of a PBPK analysis. In 2016, FDA and EMA published first draft guidance and guideline on format and content of PBPK analyses submitted for review. Confidence of using PBPK varies depending on the predictive performance for an intended use. Predictive performance is generally established in the area of predicting enzyme based drug-drug interaction potential for investigational drug as victims. Under certain conditions, PBPK-simulated interaction magnitude is considered adequate by regulators to replace a dedicated clinical interaction trial. Simulated results have been included in product labels in the US, EU, and Japan. Confidence in using PBPK to predict drug PK in other areas are emerging. It continues to be challenging to predict PK in a specific population (e.g., pediatrics, patients with renal or hepatic impairment) using PBPK.