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Conducting Virtual Trials Using PBPK To Drive More Precise Label Claims

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Precision dosing—the right dose, for the right patient, at the right time—is crucial to providing patients with the safest and most effective medications. To make the dream of precision dosing a reality requires new approaches in drug development. Historically, our knowledge about a drug has been gathered empirically through discovery and pre-clinical studies, clinical studies, and post-marketing surveillance. Clinical trials reveal the "average response" to a drug. Yet, individual patients can respond quite differently to drugs due to their genetics, physiology, and ethnicity. Extreme drug responses are a problem — both for the patient and the pharmaceutical industry developing the drug. Furthermore, patients frequently take multiple medications concurrently. This raises their risk of drug-drug interactions (DDIs). Yet, it's impossible to study all potential clinical scenarios.

Biosimulation technology is revolutionizing the way in which the pharmaceutical industry does business and how the regulators are reviewing new drug approvals. Biosimulation leverages both empirical analysis of clinical data and mechanistic *in silico* approaches. The latter approach encompasses both *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based pharmacokinetic modeling and simulation (PBPK M&S).

PBPK Modeling Comes Of Age

PBPK modeling is a systems biology approach to drug development that is rapidly being leveraged by both drug companies and global regulators. This approach includes models within models that describe drug disposition in specific organs such as the brain, liver, gut, and kidney.

PBPK models consider drug-dependent pharmacological and physiochemical factors, as well as drug-independent intrinsic and extrinsic factors that impact drug disposition. Intrinsic factors include pregnancy status, race, age, gender, disease, genetics, and potential organ dysfunction. Extrinsic factors can encompass environment, smoking status, diet, alcohol use, and the presence of concurrent medications.

In addition, PBPK models incorporate genetic variability that can impact drug exposure. For example, genetic polymorphisms in cytochrome P450 2D6 (CYP2D6) can cause variability in drug metabolism. As a result, patients can be ultra-rapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs) or poor metabolizers (PMs) of the drug. A patient's metabolizer status can exacerbate or ameliorate the magnitude of a DDI. By combining *in vitro* information with systems parameters, PBPK helps answer questions based on population variability.

Regulatory Agencies Embrace The Use Of PBPK Model

In recent years, regulatory agencies have embraced PBPK models for informing decisions in drug development. In late 2013, the U.S. Food and Drug Administration (FDA) drug and biologic advisory committee met to discuss DDIs. On the subject of predicting DDIs, it stated that, "Because it would be impossible to conduct *in vivo* drug interaction studies for every potential drug interaction, some interactions

are predicted based on other data, including *in vitro* studies, extrapolation from *in vivo* studies, or *in silico* analyses, e.g., PBPK modeling."[1]

In 2015, both FDA and the European Medicines Authority published position papers affirming the many benefits of PBPK.[2,3] In the FDA paper, Dr. Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER) division, said, "Modeling [PBPK] work performed thus far at CDER has contributed tremendously to overall drug development in terms of safety and efficacy, which ultimately results in patients' benefits."

A simple Phase 1 two-way crossover DDI study can cost around $500,000. Thus, using PBPK to predict the risk of DDIs can save significant time and money by reducing the number of studies, especially for difficult-to-test populations such as oncology, pediatric, and rare disease patients. This tool also helps meet the ethical imperative to minimize the risks that clinical trials can pose to subjects.

Successful Use Of PBPK For Virtual DDI Trials

Eliglustat for Gaucher disease provides an example of how PBPK can inform drug development and guide clinical practice. Gaucher disease is a lysosomal storage disorder caused by a hereditary deficiency in the enzyme glucocerebrosidase, which affects 6,000 people in the U.S. Without this enzyme, the lipid glucocerebroside accumulates in cells and certain organs. The sequelae of Gaucher disease include liver and spleen enlargement, low red blood cell counts (anemia), low blood platelet counts, and bone problems.

Eliglustat is metabolized primarily by CYP2D6, and to a lesser extent by CYP3A4. It is also an inhibitor of CYP2D6 and both a substrate and inhibitor of P-gp. PBPK M&S was used extensively to understand and quantify the impact of CYP2D6 metabolizer status and concomitant medication on eliglustat exposure—as well as the effect that eliglustat has on other drugs—and guide the specific dose adjustment recommendations and labeling language.[4] Simulations using PBPK models were able to inform dosing recommendations written on the drug label and predict 12 DDI scenarios involving CYP2D6 EM, IM, and PM patients.[4]

Eliglustat (Cerdelga, Genzyme) was recently approved by the FDA for the long-term treatment of adults with Gaucher disease (type 1) who are EMs, IMs, or PMs of CYP2D6.[5] The PBPK models also predicted that patients who are UMs are unlikely to achieve adequate concentrations for a therapeutic effect. Eliglustat also received orphan drug designation from the FDA.[5] This designation provides the sponsor with additional years of marketing exclusivity.

A Glimpse Into The Future Impact Of PBPK M&S

While most regulatory submissions with a PBPK component are using the approach to assess DDIs, there is a growing use for pediatric, organ impairment, pharmacogenomic, and absorption applications.[6] As PBPK M&S becomes an increasingly accepted part of the drug development process, regulators no longer use it just to ask questions that could be answered by a clinical study. PBPK M&S is becoming an important tool for answering 'what if' questions of experimentally—or ethically—intractable clinical scenarios and placing us firmly on the road toward our goal of precision dosing.

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