CERTARA

Simcyp

Simcyp Consultancy: Bespoke PBPK Modeling and Simulation

In recent years, regulators have embraced physiologically-based pharmacokinetic (PBPK) modeling and simulation to inform drug discovery and development. This approach has supported label claims in more than twenty cases, driving down R&D costs and timelines, and increasing the likelihood of both clinical trial and regulatory success.

The Simcyp Simulator: Trusted by industry, regulators, and academia

Certara's Simcyp Simulator PBPK modeling and simulation platform links *in vitro* data to *in vivo* absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetic/pharmacodynamic (PK/PD) outcomes to explore potential clinical complexities prior to human studies and support decision-making in drug development. It can simulate pharmacokinetics in virtual patient populations to identify patients at extreme risk.

Most of the top-40 pharmaceutical companies (including all of the top 10), along with the major regulatory bodies (FDA, EMA, PMDA) are members of the Simcyp Consortium, which uses the Simcyp Simulator to select the most appropriate drug doses, design optimal clinical trials, evaluate new drug formulations, and predict drug-drug interactions (DDIs) and PK outcomes in clinical populations.

Using PBPK for drug development has moved from being an academic nicety to a regulatory necessity. The Simcyp Consultancy supports the growing interest within smaller pharmaceutical companies in leveraging PBPK for testing ideas and hypotheses without requiring training staff to use the Simcyp Simulator.

PBPK Data Analysis and Interpretation Consultancy Services

In addition to licensing the Simcyp Simulator, Certara offers consultancy services on all aspects of drug ADME and PK/PD data analysis and interpretation. Using a client's data, our Simcyp consultancy scientists can advise the design of PBPK models and deliver independent analysis, interpretation, and reports. This service is ideally suited to those clients who do not have the resources, time, or need to use our simulation technology directly.

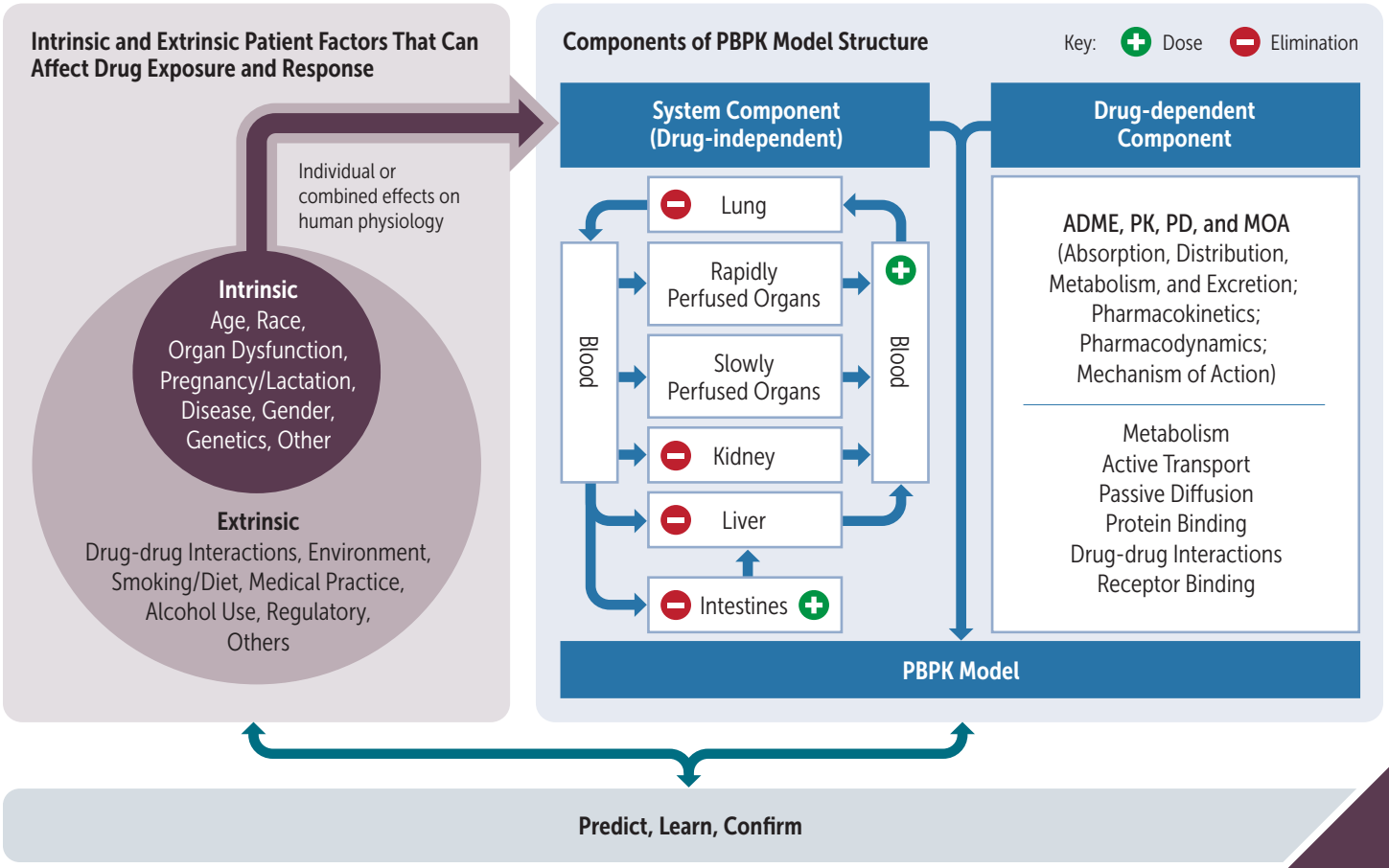
Benefits of Leveraging PBPK

- **Manage drug-drug interactions (DDI):** Unmanageable DDIs have led to the withdrawal of numerous drugs from the market. Many DDIs involve inhibition and/or induction of drug metabolizing enzymes. Consequently, predicting metabolically-based drug-drug interactions (mDDI) early in the drug development process is essential. The sophisticated population-based PBPK models within the Simcyp Simulator allow investigation of mDDIs due to competitive enzyme inhibition, mechanism-based inhibition, enzyme induction, and polypharmacy.
- **Accelerate formulation development:** An IVIVC (*in vitro-in vivo* correlation) describes the relationship between the *in vitro* properties of a dosage form and the *in vivo* responses. They can assist in quality control during manufacturing and selecting appropriate formulations. Unlike conventional IVIVC, PBPK, mechanistic IVIVC deconvolution models estimate *in vivo*

drug dissolution profiles while separately accounting for permeation, GI transit, and first pass elimination. This can allow more robust and transparent IVIVCs to be established against *in vitro* dissolution, and not the rate of systemic input. The Simcyp Simulator's Advanced Dissolution Absorption and Metabolism (ADAM) model can be used for mechanistic IVIVC.

- **Inform dosing for special populations:** The FDA requires that clinical studies be conducted in certain special populations (patients with renal or hepatic impairment, pregnant women, pediatrics, and patients taking concomitant drugs). However, other populations are also worth considering: different ethnic groups, obese and morbidly obese patients, post-bariatric surgery patients, etc. Randomized clinical trials only assess a fraction of potential PK/PD variability. By contrast, *in silico* studies using PBPK models can test a virtually unlimited set of "what if?" scenarios.

Application of PBPK Modeling and Simulation to Evaluate the Effect of Various Factors on Drug Exposure and Response



Adapted from Figure 1 (Zhao, Zhang et al. 2011)

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.

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