CERTARA

Simcyp

Simcyp Simulator

The Standard for Population-based Pharmacokinetic Modeling and Simulation

The Simcyp Population-based Simulator streamlines drug development through the modeling and simulation of pharmacokinetics (PK) and pharmacodynamics (PD) in virtual populations

The Simcyp Simulator is the pharmaceutical industry's most sophisticated physiologically-based pharmacokinetic (PBPK) platform for determining first-in-human dosing, optimizing clinical study design, evaluating new drug formulations, and predicting drug-drug interactions (DDIs). PBPK models describe the behavior of drugs in different body tissues. Each tissue is considered to be a physiological compartment. The concentration of the drug in each compartment is determined by combining systems data, drug data, and trial design information. The systems data includes demographic, physiological, and biochemical data for the individuals in the study population. The drug data consist of its physicochemical properties, its binding characteristics, and information on its metabolism, solubility, and formulation. The trial design information comprises the dose, administration route, dosing schedule, and co-administered drugs.

The Simulator includes a unique set of genetic, physiological and epidemiological databases that facilitate simulating virtual populations with different demographics and ethnicities. This enables predicting drug behavior in virtual patient populations instead of a virtual reference man, allowing individuals at extreme risk to be identified.

Developed and used by the leaders in mechanistic modeling

Since 2001, the Simcyp Consortium has served as a collaborative research center for PBPK and mechanistic modeling. Today, most of the top-40 biopharmaceutical companies (including all top ten) are Simcyp Consortium members. In addition to its industry members, leading academic institutions from around the globe, and key regulatory bodies, including the US Food and Drug Administration (FDA), European Medicines Agency, and Japanese Pharmaceuticals and Medical Devices Agency are Consortium affiliates. Consortium Members gain access to the latest version of the Simcyp Simulator, guide its ongoing development, and benefit from Simcyp experts' advice, training, and educational programs. A testament to the proven value that the Simcyp Simulator delivers is seen in the hundreds of peer-reviewed papers citing its use for drug development, toxicology and other key scientific areas. Further, the Simcyp Simulator has been used to inform 50 novel drug applications, including more than 200 label claims made without the need for clinical trials.

Leveraging the Simcyp Simulator v18 brings many benefits to pharmaceutical organizations:

- Optimize drug labels: In recent years, it was used by clients to inform more than 200 label claims for new drug approvals from the FDA.
- Gain access to leading-edge R&D: The Simcyp Simulator is the result of years of collaboration with a Consortium that includes leading pharma companies, academia, and major regulatory bodies.
- Decrease risk of adverse effects: Conduct virtual clinical trials in difficult to study vulnerable populations such as pediatric patients, pregnant women, and patients with impaired organ function.

Simcyp Simulator Version 18: New features

Simcyp Simulator version 18 introduces new features designed to support the delivery of safer, more effective medications including advanced food staggering and tumor models for optimizing trial design and dose selection.

New Tumor Models

Some of the most intractable oncology drug development challenges, such as improving survival rates for ovarian and pancreatic cancer sufferers, are due to the drug not successfully reaching the target site in the tumor. Anti-cancer drugs' capacity to treat solid tumors depends upon their plasma PK and their ability to reach their pharmacological target in the malignant tumor.

Version 18 of the Simcyp Simulator helps to quantify how much drug is getting to the target site within the tumor. The Simulator's permeability-limited tumor models now combine knowledge of the tumor composition with the drug's physicochemical properties to simulate the distribution of small molecule drugs or biologics.

These drug distribution models can also be combined with other tumor growth models, allowing a drug's concentration in the tumor and the resulting tumor growth or inhibition to be factored in. The Simcyp Simulator can model the impact of a single drug or a combination therapy on the tumor. It can also simulate target-mediated drug disposition in tumor for biologics.

The Simcyp Simulator contains 19 virtual populations for simulating drug performance via bridging, including a cancer patient population that has been leveraged for numerous drug programs.

Enhanced ADAM Model to Predict Back-conversion of Metabolites in the Gut Lumen

In some cases, the drug metabolite can be converted back to the parent drug in the gut lumen. Therefore, it is important to consider the kinetics of both parent drugs and their metabolites—which could be DDI victims or perpetrators—when evaluating safety risk during drug development. The Simcyp Simulator's Advanced Dissolution, Absorption and Metabolism (ADAM) model, which simulates drug disposition in the gut, has been enhanced to simulate back-conversion of metabolites in the gut lumen.

Many important medications are pro-drugs, i.e., the primary "metabolite" of a pro-drug is the pharmacologically active moiety rather than the parent compound (pro-drug). DDIs mediated by drug metabolites formed by gut bacteria can and have caused serious adverse events, including death. For example, sorivudine had to be withdrawn from the market within 40 days of approval due to lethal gut lumen (microbiota)-driven metabolic DDI with tegafur.

Updates to ADAM permit simultaneous modeling of the inter-conversion of parent compound to metabolite, entero-hepatic re-circulation, and efflux to the gut lumen, as well as metabolism- and/or transporter-mediated DDIs in the gut.

Expansion of Trial Design to Allow Food and Fluid Staggering

Drug-food effects can pose a serious safety issue and are an important element on the drug label. Therefore, regulators expect sponsors to understand a new compound's drug-food effects. If drug-food effects are determined not to be an issue, it removes a burden from patients and is one less factor that sponsors have to control in their clinical studies.

To help investigate and determine the optimal time for patients to consume food and fluids with their medication, the Simcyp Simulator now offers a "food-staggering" simulation capability. This allows clinical trials to be designed with independent drug dosing, meal, and fluid intake times in addition to the existing "fed" and "fasted" options. Several new Simcyp Simulator models ensure the relevant physiological parameters are adjusted as patients transition between fasted-fed and fed-fasted states. These additions include a new dynamic bile salts model, an improved fluid volumes dynamics model, and time-dependent intestinal and stomach pH models. As the fat content of a meal can also impact drug disposition, the Simcyp Simulator now also includes the FDA's "High fat diet based gastric pH model." These advances enable sponsors to model more real-life scenarios.

Mechanistic Absorption Models

Certara, in partnership with the University of Leuven in Belgium, is working under an FDA Office of Generic Drugs grant to further develop and qualify the PBPK modeling and simulation framework that enables the Simcyp Simulator to simulate and predict the behavior of supersaturating orally-dosed drug products in the human gastro-intestinal tract. As part of this development, the ADAM oral absorption model has been expanded significantly with the addition of a particle population balance (PPB) model. The new model enables simulating two different solid states of a drug to be handled simultaneously, including precipitation to a solid state different to that of the dosage form, precipitation to two solid states simultaneously, and modeling of formulations where there has been partial solid state conversion during storage. A nucleation model has also been incorporated, which is run as a competing process with particle growth, including growth of never-dissolved particles from the dosage form.

New Reverse Translation Tool (RTT)

Many of the input parameters for the Simcyp Simulator are derived from in vitro experiments. However, sometimes the requisite in-vitro data are not available, but clinical data are. The Simcyp Simulator now has a sophisticated mechanistic "Reverse Translation Tool" built to complement the retrograde model allowing researchers to take an in vivo value, such as an observed clearance, and work backwards to determine the original in vitro values. Further, an iterative approach is developed to calculate UGT-mediated intrinsic clearances in both liver and kidneys. The new tool offers more flexibility in study populations and selection between Extensive Metabolizers (EM) and other population phenotypes. The retrograde model, which was originally developed to create pediatric PBPK models, has been used to extrapolate data to other patient populations.

Expanded Compound Library

Certara has continued to expand its compound database; it is committed to providing compound qualification summaries for every new compound released as well as providing updated summaries for the existing compounds. These documents provide background on compound parameters and demonstrate the Simcyp Simulator's ability to mimic clinical studies. They are used by sponsors to support regulatory interactions with health authorities.

Access to continuing education and support

We are dedicated to your success with the Simcyp Simulator. Our educational programs include:

- Simcyp Workshops comprised of lectures—delivered by PK/PD experts—interspersed with interactive workshops and hands-on exercises centered on practical examples of model-informed approaches. Delegates work in small groups with an expert tutor.
- The Simcyp on-site education program provides bespoke Simulator-training at the client's site. The program caters to small groups of scientists with specific training requests and support, through to larger workshop-style sessions which will be tailored to your requirements.
- Simcyp online educational videos focus on various aspects of Simcyp Science and provide demos and practical tips for using the Simcyp Population-based Simulator. The material serves as a refresher for experienced users as well as being suitable for new users, or those who wish to become familiar with recently implemented features.

Compatible software

The Cardiac Safety Simulator (CSS) is an independent standalone product to investigate cardiotoxicity and generate simulated ECG traces; for further details please see the CSS brochure.

The SIVA Toolkit is a user-friendly standalone platform, designed to assist scientists with analyzing complex *in vitro* studies using whole cells, tissue samples and solid dosage forms to assess the metabolism, transport and dissolution/solubility of drugs; for further details please refer to the Simcyp In Vitro Analysis Toolkit (SIVA) brochure.

Ready to experience the power of the Simcyp Simulator?

Contact us at sales@certara.com to learn more about how you can use the Simcyp Simulator to get real answers from virtual populations.

References

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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.

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