CERTARA | SIMCYP

Simcyp™ PBPK Simulator

The Standard for Population-based Physiologically Based Modeling and Simulation

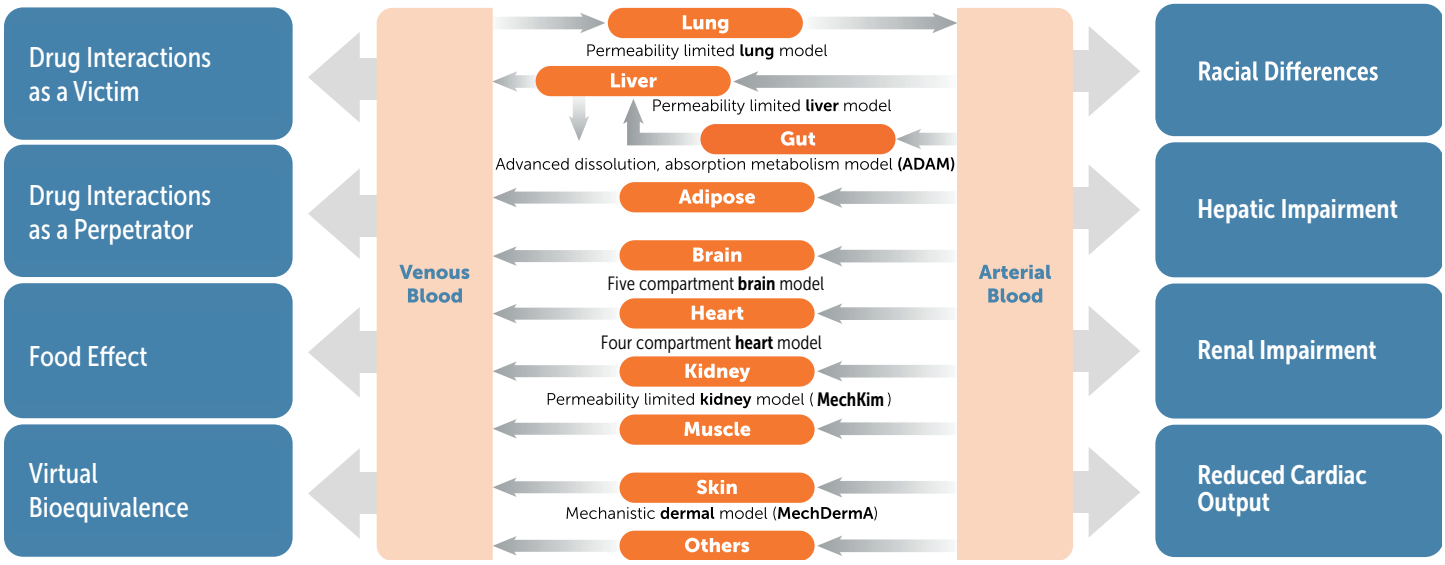
Updated with Version 22 Capabilities

Predict drug performance from virtual populations

The Simcyp Simulator is the pharmaceutical industry's most sophisticated physiologically based pharmacokinetics (PBPK) platform for determining first-in-human dosing, optimizing clinical study design, evaluating new drug formulations, setting the dose in untested populations, performing virtual bioequivalence analyses, and predicting drug-drug interactions (DDIs). Simcyp is being applied to small molecules, biologics, ADCs, generics, and new modality drugs.

- The Simulator includes extensive libraries on demographics, developmental physiology and the ontogeny of drug elimination pathways;
- An unmatched body of science, the Simulator includes 10 advanced mechanistic organs, 29 sub-populations, and 115+ compound files for use by member companies;
- Predicts *in vivo* pharmacokinetic exposure and pharmacodynamic effects based on *in vitro* data

Simcyp PBPK models describe the behavior of drugs in relevant body tissues and organs. Each organ may be described by one or several physiological compartments. The concentration of the drug in each compartment is determined by combining systems data, drug data, and trial design information. The Simulator includes a unique set of genetic, physiological and epidemiological databases that facilitate simulating virtual populations with different demographics, ethnicities, and disease states.



The Simcyp Simulator has the most advanced organ-specific PBPK models, driving use across innumerable applications from discovery to post-marketing

The Simcyp Simulator is used across the drug development cycle:

- Early PK prediction, FIH dosing
- Compound due diligence/risk analysis
- Drug-drug interaction simulations – perpetrator and victim
- Absorption modelling – formulation effects/bioequivalence, food effect
- Dosing for special populations – pediatrics, elderly, organ impairment, disease conditions, ethnic differences
- Evaluation of the impacts of extrinsic factors such as smoking and alcohol on drug performance.
- Novel routes of administration – dermal, inhalation, long-acting injectable
- Biologics – mAbs, ADCs, other proteins, cytokine mediated DDIs
- Virtual bioequivalence and formulations for complex generics

Trusted by industry, academic and regulatory leaders

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 11 regulatory bodies, including the US Food and Drug Administration, are affiliates of the Consortium.

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. Hundreds of peer-reviewed papers rely on the Simcyp Simulator, demonstrating its impact in drug development, clinical pharmacology, toxicology and other key scientific areas. Beyond the Consortium, the Simcyp consulting team performs hundreds of projects on behalf of large and small companies, at different stages across the development cycle, as they progress toward regulatory approval.

Most important, the Simcyp Simulator has been used to inform > 90+ novel drug applications, with > 300 label claims achieved virtually, in lieu of performing clinical trials.

In addition to joining the Simcyp Consortium there are a variety of other options for gaining access to our technology. A small-to-medium enterprise (SME) version of Simcyp is available for purchase. In 2022, we were proud to announce the release of Simcyp Discovery, a PBPK platform developed specifically for researchers in early drug development.

Simcyp Simulator Version 22: Key New Features

Each year, new features and capabilities are added to the Simcyp Simulator to enhance its utility in informing decision-making throughout the drug development process from discovery to post-marketing. These feature enhancements are prioritized based in part on guidance from our scientific advisory board and consortium members, but also in recognition of trends in the regulatory and pharmaceutical R&D landscapes. Here are some of the new features in Version 22 that are particularly relevant to recent market trends:

Expansion of Compound Library

Expedites assessment of DDIs for a wider variety of therapeutic compounds

A major application of the Simcyp Simulator is the prediction of DDIs based on in vitro data. As of December 2022, over 300 DDI label claims had been approved by the FDA based on Simcyp simulations in lieu of human clinical trials. These successes were made possible at least in part by Simcyp's extensive library of compound files. Compound files allow users to simulate key characteristics that are unique to the drug(s) of interest such as physicochemical properties, metabolizing enzymes, tissue binding, etc. Each compound file is extensively documented and validated in order for both sponsors and regulators to have confidence in the predictions of the Simcyp Simulator. We update our compound library on an ongoing basis in order to accommodate newly approved therapies, new knowledge about established therapies, and regulatory guidelines. In Version 22 of the Simcyp Simulator, we have added 14 new compound files, bringing the total available in our library to 115.

Additional Populations

Allows simulation of the increasingly diverse North American patient populations

In April of 2022, the US FDA released a new draft guidance to industry encouraging sponsors to expand recruitment of participants from underrepresented racial and ethnic populations in the U.S. into clinical trials. In response to this recommendation, four North American populations have been added to the Simcyp Simulator: White, African American, Asian and Latino/Hispanic. In addition, an elderly Chinese population has also been added in Version 22, and the population files for obese and morbidly obese have been updated to more accurately reflect the latest information on these subjects. All told, the Simcyp Simulator now offers the capability to simulate 29 distinct populations, including regional populations (ie China and Japan), patients with disease (ie cirrhosis and cancer) or organ impairment, pregnant and lactating women, and pediatric populations, including pre-term neonates.

> "The U.S. population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health"
>
> *- FDA Commissioner Robert M. Califf, M.D.*

Enhancement of Subcutaneous Dosing Capabilities

Improves bioavailability predictions after sub-cutaneous dosing

The importance of subcutaneous (SC) drug delivery devices continues to exhibit robust growth, especially for large molecule (biologic) therapies. The SC route of administration offers several advantages over intra-venous (IV) and intra-muscular (IM) administrations. SC injections generally exhibit prolonged absorption into the blood stream, similar to IM injections, but require considerably less force. In contrast to IV administrations, with proper training, patients can self-administer SC doses, thereby minimizing the need for doctor visits. With the enhancements made for Version 22, the Simcyp Simulator better supports simulating human PK resulting from SC doses of both small molecules and biologics at multiple injection sites (arm, abdomen, back, and thigh). In addition, SC absorption parameters may now be automatically estimated to fit observed data.

> "The global subcutaneous drug delivery devices market size was valued at USD 21.2 billion in 2019 and is expected to grow at a compound annual growth rate (CAGR) of 10.4% from 2020 to 2027."
>
> *- Grand View Research*

Improved Flexibility in Simultaneous Fitting

Facilitates integration of data from multiple sources

PBPK models are generally based on a plurality of informational sources. For example, in order to robustly estimate some model parameters, it may be necessary to simultaneously fit PK data from humans and multiple animal species. In Version 22, we now offer this capability. In addition, users may now estimate parameters across multiple clinical trials and Simcyp workspaces, and appropriately adjust for data below the lower limit of quantitation (BQL).

Additional feature enhancements in Simcyp Version 22:

- Pediatric Populations. Pharmacologically speaking, children are not small adults, and dose adjustments made based solely on body size often lead to under- or over-dosing in pediatric patients. At Simcyp, we remain committed to continually enhancing our technology to better serve the needs of pediatric populations. In Version 22, we have further improved our models of pediatric physiology, including the gastro-intestinal (GI) tract. We have also expanded our pediatric biologics model, and intensively qualified our models for CYP3A4 DDI perpetrators in pediatric populations.
- Pregnancy and Lactation. The Simcyp Simulator supports predicting maternal and fetal PK throughout the entire gestational cycle, including lactation. Expectant and lactating mothers often require medications for chronic and acute conditions. Ensuring that drug exposures are both therapeutic for the mother and safe for the child are a major challenge when treating this population. In Version 22, we have enhanced our pregnancy models to account for maternal ontogeny with regard to gestational-related changes in the abundance of metabolizing enzymes and transporters. We have also improved our models for the feto-placental interface, and expanded the set of parameters affecting fetal exposures that may be estimated. Finally, our lactation model has been updated to allow post-partum age, infant weight, milk intake, and other parameters to be accounted for when predicting infant PK.

- Dermal Absorption. Simcyp Simulator has offered a dermal simulator that was developed in partnership with the USFDA Office of Generics since 2014. Our dermal simulator (MechDermA) enables drug developers to demonstrate virtual bioequivalence (BE) using PBPK, thus reducing or eliminating the need for in vivo BE clinical trials. Recently, Simcyp MechDermA was used in the approval of a generic topical formulation of diclofenac 1%, in lieu of a BE study. In Version 22, we expanded our MechDermA module to include new skin types, application sites, and to predict environmental drug exposures.
- Long Acting Injectable (LAI) module. A mechanistic model has been developed in Simcyp Version 22 for polymer-based LAI formulations. The LAI module may be used to account for complex processes such as fluid influx into the implant, autocatalytic hydrolysis, and aqueous dissolution of small oligomers and monomers. The model can simulate and predict both In Vitro Release Tests (IVRT) and human in vivo implant performance.
- Virtual Bioequivalence (VBE) module. Several new features have been added to Simcyp's VBE module in Version 22, including the ability to determine study power and the clinically relevant dissolution safe space. In addition, the VBE module now supports the intravaginal and rectal routes of administration, and simulation of within-subject variability for several physiological parameters affecting oral absorption
- In-Vitro to In-Vivo Extrapolation (IVIVE) for Transporters. We have made several enhancements designed to improve prediction of in vivo PK for transporter substrates based on in vitro data. Our Mechanistic Kidney Model (MechKiM) has been updated to account for absolute transporter abundances, drug precipitation in the urine, and electrochemical gradient driven transporters. In addition, several other physiologic parameters governing renal function have been updated.
- Mechanism-Based Inhibition (MBI) of Metabolism. Mechanism-based inhibition, is an irreversible form of enzyme inhibition that occurs when an enzyme binds a substrate analog and forms an irreversible complex with it through a covalent bond during the normal catalysis reaction. Our models for MBI have now been expanded to include the slope function (Kinact/Kapp) and to allow the effect of multiple competitive inhibitors on the extent of MBI to be considered.
- Oral Absorption. A standalone excipient model has been added to model the effect of excipients such as cyclodextrin and micelle-forming surfactants on the oral absorption of API. Excipient displacement interactions between Substrate and Inhibitor 1 can also be modelled. In addition, a model for excipient concentration-dependent modification of gut wall passive permeability is now available to capture permeation enhancer effects on API absorption.

Regulators around the world have encouraged PBPK in a range of applications and guidance. Most recent examples include:

- US FDA final guidance *for both in vitro and clinical DDI*
- US FDA draft guidance *on DDI for therapeutic proteins*
- US FDA draft guidance *on pediatrics and neonatal studies*
- US FDA draft guidance *on PK in renally-impaired patients*
- US FDA final guidance *on PBPK analyses-format and content*
- US FDA draft guidance *on PBPK for biopharmaceutics use for oral drugs*
- US FDA FDARA *implementation guidance for pediatric studies of molecularly targeted oncology drugs:*
- US FDA draft guidance *of gastric pH dependent drug interactions with acid-reducing agents*
- EMA (Europe) *guidance on DDI*
- PMDA (Japan) *guidance on DDI*
- NMPA (China) *guidance on DDI*
- *ICH (International) guidance on DDI (M12)*
- *ICH guidance on pediatric extrapolation (E11A)*

These agencies are also actively seeking applications for expanded use of PBPK in special populations, complex drug formulations and complex generics for demonstrating bioequivalence.

Simcyp-supported FDA-approved novel drugs

ONCOLOGY	Agios — Tibsovo *(ivosidenib)*	Genentech — Cotellic *(cobimetinib)*	Novartis — Rydapt *(midostaurin)*
	Amgen — Blincyto *(blinatumomab)*	Genentech — Polivy *(polatuzumab vedotin-piiq)*	Novartis — Tabrecta *(capmatinib)*
	Amgen — Lumakras *(sotorasib)*	Genentech — Rozlytrek *(entrectinib)*	Novartis — Zykadia *(ceritinib)*
	Ariad — Alunbrig *(brigatinib)*	Incyte — Pemazyre *(pemigatinib)*	Novartis — Jakavi *(ruxolitinib)*
	Ariad (Takeda) — Iclusig *(ponatinib)*	Janssen — Balversa *(erdafitinib)*	Pfizer — Bosulif *(bosutinib)*
	AstraZeneca — Calquence *(acalabrutinib)*	Janssen — Erleada *(apalutamide)*	Pfizer — Lorbrena *(lorlatinib)*
	AstraZeneca — Lynparza *(olaparib)*	Lilly — Retevmo *(selpercatinib)*	Pharmacyclics — Imbruvica *(ibrutinib)*
	AstraZeneca — Tagrisso *(osimertinib)*	Lilly — Verzenio *(abemaciclib)*	Sanofi — Jevtana *(cabazitaxel)*
	Beigene — Brukinsa *(zanubrutinib)*	Loxo Oncology — Vitrakvi *(larotrectinib)*	Seattle Genetics — Tukysa *(tucatinib)*
	BluePrint Medicines — Ayvakit *(avapritinib)*	Mirati — Krazati *(adagrasib)*	Spectrum — Beleodaq *(belinostat)*
	Celgene — Inrebic *(fedratinib hydrochloride)*	Novartis — Farydak *(panobinostat)*	Takeda — Exkivity *(mobocertinib)*
	Daiichi Sankyo — Turalio *(pexidartinib)*	Novartis — Kisqali *(ribociclib succinate)*	Taiho — Lytgobi *(futibatinib)*
	Eisai — Lenvima *(lenvatinib)*	Novartis — Scemblix *(asciminib)*	Verastem — Copiktra *(duvelisib)*
	EMD Serono — Tepmetko *(tepotinib hydrochloride)*	Novartis — Odomzo *(sonidegib)*	
	Genentech — Alecensa *(alectinib)*	Novartis — Vijoice *(alpelisib)*	
RARE DISEASE	AkaRx (Eisai) — Doptelet *(avatrombopag maleate)*	Intercept — Ocaliva *(obeticholic acid)*	PTC Therapeutics — Emflaza *(deflazacort)*
	AstraZeneca — Koselugo *(selumetinib)*	Kadmon — Rezurock *(belumosudil)*	Sanofi Genzyme — Cerdelga *(eliglustat tartrate)*
	Aurinia — Lupkynis *(voclosporin)*	Merck — Welireg *(belzutifan)*	Vertex — Symdeko *(tezacaftor/ivacaftor)*
	Genentech — Enspryng *(satralizumab)*	Mirum — Livmarli *(maralixibat)*	Vertex — Trikafta *(elexacaftor/ivacaftor/tezacaftor)*
	Genentech — Evrysdi *(risdiplam)*	Mitsubishi Tanabe — Dysval *(Valbenazyne)*	
	Global Blood Therapeutics — Oxbryta *(voxelotor)*	Novartis — Isturisa *(osilodrostat)*	
CENTRAL NERVOUS SYSTEM	AbbVie — Rinvoq *(upadacitinib)*	Eisai — Dayvigo *(lemborexant)*	Lilly — Reyvow *(lasmiditan succinate)*
	AbbVie — Qulipta *(atogepant)*	Idorsia — Quviviq *(daridorexant)*	Novartis — Mayzent *(siponimod fumaric acid)*
	Alkermes — Aristada *(aripiprazole lauroxil)*	Janssen — Ponvory *(ponesimod)*	UCB — Briviact *(brivaracetam)*
	Alkermes — Lybalvi *(olanzapine/samidorphan)*	Kyowa Kirin — Nourianz *(istradefylline)*	
INFECTIOUS DISEASE	Gilead — Veklury *(remdesivir)*	Merck — Prevymis *(letermovir)*	Tibotec — Edurant *(rilpivirine)*
	Janssen — Olysio *(simeprevir)*	Nabriva — Xenleta *(lefamulin acetate)*	ViiV — Cabenuva Kit *(cabotegravir, rilpivirine)*
	Merck — Pifeltro *(doravirine)*	Novartis — Egaten *(triclabendazole)*	
GASTROENTEROLOGY	AstraZeneca — Movantik *(naloxegol)*	Phathom — Voquezna Triple Pak	Shire — Motegrity *(prucalopride)*
	Helsinn — Akynzeo *(fosnetupitant/palonosetron)*	Shionogi — Symproic *(naldemedine)*	
CARDIOVASCULAR	Actelion (J & J) — Opsumit *(macitentan)*	BMS — Camzyos *(mavacamten)*	Pfizer — Revatio *(sildenafil)*
	Bayer (and Merck) — Verquvo *(vericiguat)*	Johnson & Johnson — Xarelto *(rivaroxaban)*	
OTHER	AbbVie — Orilissa *(elagolix)*	Janssen — Invokana *(canagliflozin)*	Merck — Steglatro *(ertugliflozin)*
	Agios — Pyrukynd *(mitapivat)*	Lilly — Olumiant *(baricitinib)*	Peloton/Merck — Welireg *(belzutifan)*
	Galderma — Aklief *(trifarotene)*	Lilly — Mounjaro *(tirzepadide)*	Takeda — Livtencity *(maribavir)*

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Simcyp PBPK has been used to support > 90+ novel drugs in a range of therapeutic areas and across regulatory pathways including breakthrough, priority, fast track, and orphan

About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions and regulatory agencies across 62 countries.

For more information, visit **www.certara.com**.