

Simcyp™ PBPK Simulator

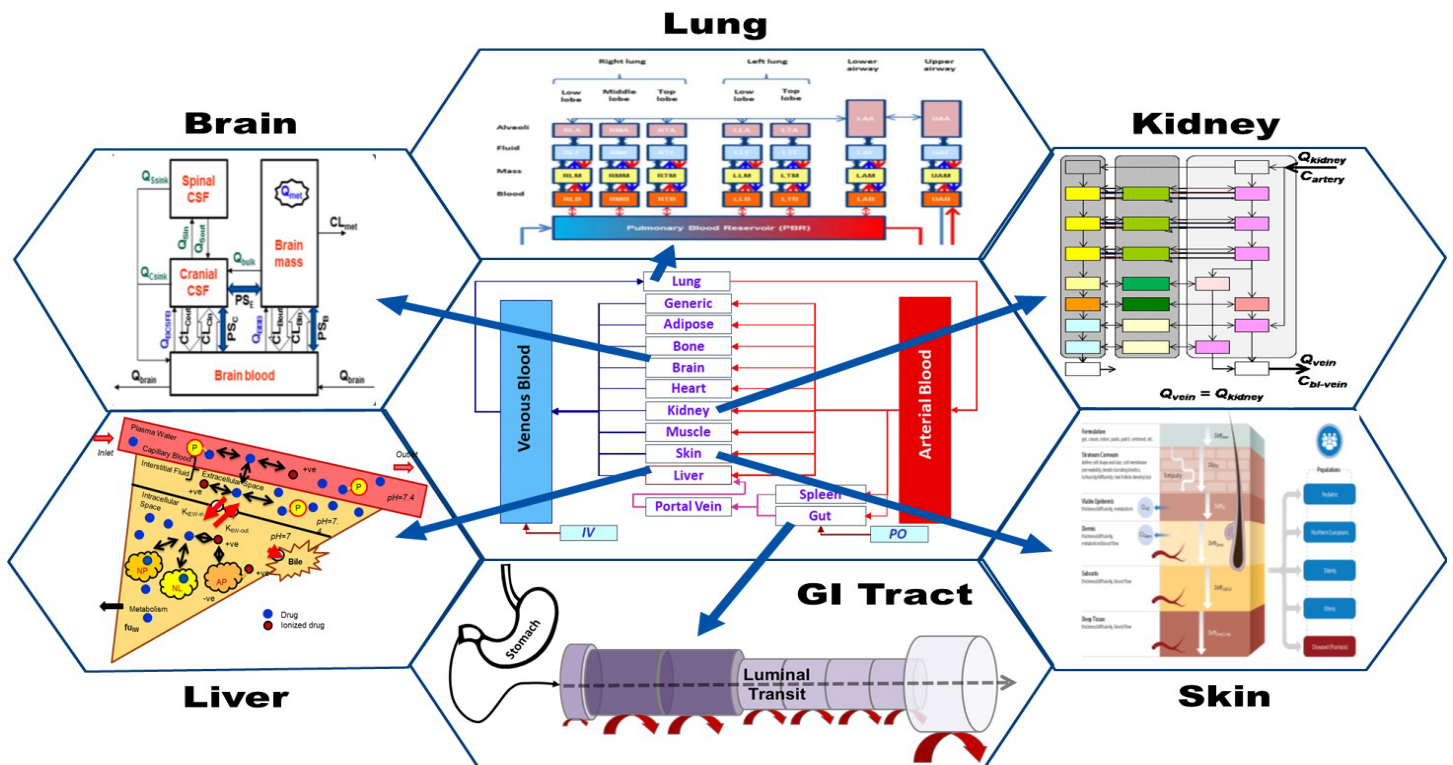
The Standard for Population-based Physiologically Based Modeling and Simulation
Updated with Version 21 Capabilities

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 with 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, 25 sub-populations, and 100+ compound files for use by member companies;
- Links *in vitro* data to *in vivo* absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetic / pharmacodynamic (PK/PD) outcomes to explore clinical scenarios and support drug development decisions;

Simcyp PBPK models describe the behavior of drugs in different body tissues, with each tissue considered a physiological compartment. 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 and ethnicities.



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 drug performance from extrinsic factors – smoking, alcohol
- Novel routes of administration – dermal, inhalation, long-acting injectable
- Biologics – mAbs, ADCs, other proteins, cytokine mediated DDIs
- Virtual bioequivalence and formulations for complex generics

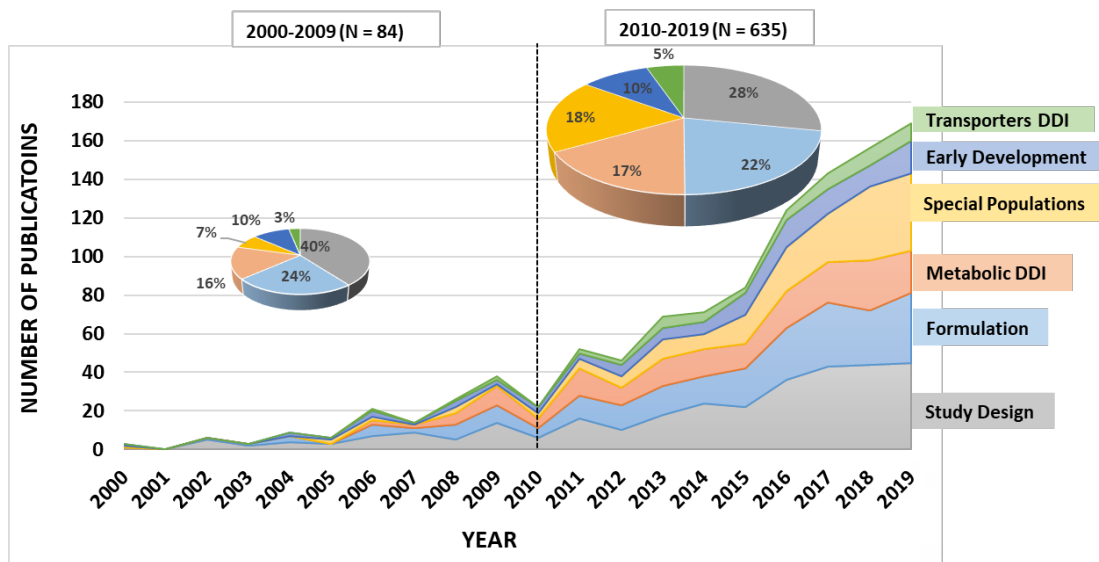
Trusted by industry, academic and regulatory leaders

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 > 85 novel drug applications, with > 250 label claims achieved virtually, in lieu of performing clinical trials.

A range of licensing options are available for the Simcyp Simulator, including joining the Consortium. The most recent version of the Simulator is used by our expert PBPK consultants for drug-specific projects.



Applications of successful use of PBPK are growing in both number and impact

In the past five years, the proportional use of PBPK has been increasing in areas of special populations and formulation development

Eman El-Khateeb, et al, "Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; in-depth analysis of applications, organizations, and platforms," Biopharm Drug Disp., Nov 2020

Simcyp Simulator Version 21: Key New Features

Each year, new features and capabilities are added to the Simcyp Simulator. The Simulator is used for: small molecule and biologic drugs, development of new drug modalities, new molecular entities and generics, discovery through post-marketing, and for optimizing different modes of administration. The Simcyp Simulator is available via licensure and is used by our expert consulting team on specific products, programs and other sponsor needs. New and expanded capabilities in Simcyp version 21 are as follows:

Simcyp Animal Simulators (Rat, Mouse, Dog & Monkey)

Seamless transition from animal to human, enabling fitting across multiple species

Simcyp Animal is used to identify key data requirements and refine the design of subsequent experiments. It can increase confidence in in vitro-in vivo extrapolation (IVIVE) before moving to human simulations and allows comparison of human and animal data without reliance on simple allometric scaling.

New to version 21 is the inter-species compound file transfer, which facilitates replication of compound file parameters across species, maximizing the use of combined data. Also new is a cross-species fitting tool that enables simultaneous fitting of small molecules parameters across all animal simulators, estimating the best value for each selected parameter. Finally, the structural and functional streamlining of the human brain model, in line with the animal simulators, including absolute abundance scaling and incorporation of relevant abundance and scalar literature data.

Hepatic and renal impaired populations

Aligned with new FDA guidance, Simcyp's renal and cirrhosis models are expanded to support dosing and labelling decisions

Per FDA's 2020 guidance, "drug development programs should include an early characterization of the expected effect of impaired renal function on a drug's PK, with the goal of enabling the inclusion of this population in late-phase trials by allowing appropriate prospective dosage adjustment. This information can be obtained with PBPK."

In Simcyp v 21, the renal and cirrhosis impairment populations were updated. The cirrhosis populations now include changes to non-CYP enzymes (UGTs, CES and FMOs) and also changes to hepatic transporter expression. A new mild renal impairment population was added, along with further demographic updates of the renal impairment populations, delivering three options to modellers - severe, moderate and mild.

Expansion of Genotype Library

Advancing pharmacogenomics with additional phenotypes and genotypes to assess drug activation, dosing and drug interactions

Genomic information is used to study individual responses to drugs, such that when a gene variant is associated with a particular drug response in a patient, there is the potential for making clinical decisions based on genetics by adjusting the dosage or choosing a different drug, for example.

A sizeable library of phenotypes and genotypes have been developed for the Simcyp Simulator over the past several years. This year, we have added and updated 12 of these, providing relative and absolute abundances with associated variability of several enzymes (including CYP2A6, CYP2B6, CYP2C9, CYP2C18, CYP2C19, CYP2J2, UGT1A1, UGT1A3). The focus of these updates was principally relating to incorporation of further data in healthy White, Chinese and Japanese populations. In addition, there is now a second Intermediate Metaboliser phenotype option, "IM2", for CYP450s and improvements to the genotype and CYP allelic enzyme kinetic usability and outputs in the simulator.

Expansion of Compound Library

Automates ability to perform DDI on a range of new compounds, including progestins, thus aligning with FDA's recent oral contraception guidance document

Well-documented, tested, validated and reusable compound files allow modelers and regulators to have confidence in the prediction of the Simcyp Simulator. With the addition of the new compound files listed below, the Simcyp Simulator has almost 110 validated compound master files. Of note is the addition of the progestins, which allow modelers to assess the impact of DDIs with oral contraceptives, per November, 2020 FDA Guidance.

With guidance from the Simcyp Consortium members, and after assessment of literature data, seven new compound models have been added to the compounds library for atezolizumab, buprenorphine, drospirenone, flurbiprofen, montelukast, pioglitazone and siponimod. In addition, seven compound files have been made available as research files in the compound repository on the Simcyp Members' Area for clopidogrel and its acyl-glucuronide metabolite, dasabuvir, glyburide, levonogestrel, maraviroc, rivaroxaban and tenofovir. The currently available library file for itraconazole has been updated to incorporate inhibition of P-gp and the interaction parameters have been refined for trimethoprim.

Additional features in Simcyp v21:


- **Determining and reporting the mass balance for various pathways.** For each pathway involved in drug elimination, this capability provides another layer of verification of the PBPK model.
- **A documentation tool for model development.** This tool allows the modeller to record changes in model parameters so that differences between file versions can be easily compared and reported at the compound, population and workspace levels. A set of modules allowing users to do a range of tasks automatically, for example generating workspaces has been added.
- **Pediatric module** – A pediatric oncology population was added to the Simulator, along with updated ontogeny profiles and increased range of automated pediatric options.
- **Pregnancy/lactation module** – Addition of gestational-dependent functions to the fetal PBPK model along with predictive models for trans-placental prediction.
- **Biologics module** – Simcyp v 20 combined models for monoclonal antibodies, antibody fragments, ADCs and bi-specifics with other proteins and peptides in one multidimensional module. V 21 adds to this by expanding the distribution model for lymph nodes. These capabilities are within the adult and pediatric biologics modules.
- **Oral absorption module** – In v 21, Simcyp updated the GI and permeability modules, along with the particle population balance model to improve prediction of complex formulations.
- **Virtual bioequivalence (VBE)** – In v 20, Simcyp introduced a new VBE module that leverages in vitro data and in silico modeling in lieu of running an in vivo comparative clinical bioequivalence endpoint study. In v 21 of the VBE module, statistical calculations for bioequivalence for crossover non replicate, partial replicate, full replicate and parallel study designs were implemented. Additionally, the Simulator enables the determine of VBE in pediatrics.

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

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 (<i>Ivosidenib</i>)	Genentech	Alecensa (<i>Alectinib</i>)	Novartis	Odomzo (<i>Sonidegib</i>)
	Amgen	Blinicyto (<i>Blinatumomab</i>)	Genentech	Cotellic (<i>Cobimetinib</i>)	Novartis	Piqray (<i>Alpelisib</i>)
	Ariad	Alunbrig (<i>Brigatinib</i>)	Genentech	Polivy (<i>Polatuzumab vedotin-PIIQ</i>)	Novartis	Rydapt (<i>Midostaurin</i>)
	Ariad (Takeda)	Iclusig (<i>Ponatinib</i>)	Genentech	Rozlytrek (<i>Entrectinib</i>)	Novartis	Tabrecta (<i>Capmatinib</i>)
	AstraZeneca	Calquence (<i>Acalabrutinib</i>)	Incyte	Pemazyre (<i>Pemigatinib</i>)	Novartis	Zykadia (<i>Certinib</i>)
	AstraZeneca	Lynparza (<i>Olaparib</i>)	Janssen	Balversa (<i>Erdafitinib</i>)	Pfizer	Bosulif (<i>Bosutinib</i>)
	AstraZeneca	Tagrisso (<i>Osimertinib</i>)	Janssen	Erleada (<i>Apalutamide</i>)	Pfizer	Lorbrena (<i>Lorlatinib</i>)
	Beigene	Brukina (<i>Zanubrutinib</i>)	Lilly	Retevmo (<i>Selpercatinib</i>)	Pharmacyclics	Imbruvica (<i>Ibrutinib</i>)
	BluePrint Medicines	Ayvakit (<i>Avapritinib</i>)	Lilly	Verzenio (<i>Abemaciclib</i>)	Sanofi	Jevtana (<i>Cabazitaxel</i>)
	Celgene	Inrebic (<i>Fedratinib hydrochloride</i>)	Loxo Oncology	Vitrakvi (<i>Larotrectinib</i>)	Seattle Genetics	Tukysa (<i>Tukatanib</i>)
	Daiichi Sankyo	Turalio (<i>Pexidartinib</i>)	Novartis	Farydak (<i>Panobinostat</i>)	Spectrum	Beleodaq (<i>Belinostat</i>)
	Eisai	Lenvima (<i>Lenvatinib</i>)	Novartis	Kisqali (<i>Ribociclib succinate</i>)	Takeda	Exkivity (<i>Mobocertinib</i>)
	EMD Serono	Tepmetko (<i>Tepotinib Hydrochloride</i>)	Novartis	Scemlix (<i>Asciminib</i>)	Verastem	Copiktra (<i>Duvelisib</i>)
	 RARE DISEASE	AkaRx (Eisai)	Doptelet (<i>Avatrombopag maleate</i>)	Global Blood Therapeutics	Oxbryta (<i>Voxelotor</i>)	Novartis
AstraZeneca		Koselugo (<i>Selumetinib</i>)	Intercept	Ocaliva (<i>Obeticholic acid</i>)	PTC Therapeutics	Emlaza (<i>Deflazacort</i>)
Auriana		Lupkynis (<i>Voslosporin</i>)	Kadman	Rezurock (<i>Belumosudil</i>)	Sanofi Genzyme	Cerdelga (<i>Eliuglstat tartrate</i>)
Genentech		Enspryng (<i>Satralizumab</i>)	Merck	Wellireg (<i>Belzutifan</i>)	Vertex	Symdeko (<i>Tezacaftor/ivacaftor</i>)
Genentech		Evrysdi (<i>Risdiplam</i>)	Miramis	Livarti (<i>Maralixibat</i>)	Vertex	Trikafta (<i>Elxacaftor/ivacaftor/tezacaftor</i>)
 CENTRAL NERVOUS SYSTEM	AbbVie	Rinvoq (<i>Upadacitinib</i>)	Eisai	Dayvigo (<i>Lemborexant</i>)	Lilly	Reyvow (<i>Lasmiditan succinate</i>)
	AbbVie	Qulipta (<i>Atogepant</i>)	GW Research	Epidiolex (<i>Cannabidiol</i>)	Novartis	Mayzent (<i>Siponimod fumaric acid</i>)
	Alkermes	Aristada (<i>Aripiprazole lauroxil</i>)	Janssen	Ponvory (<i>Ponesimod</i>)	UCB	Briavict (<i>Brivaracetam</i>)
	Alkermes	Lybalvi (<i>Olanzapine; Samidorphan</i>)	Kyowa Kirin	Nourianz (<i>Istradefylline</i>)		
 INFECTIOUS DISEASE	Gilead	Remdesivir (<i>Veklury</i>)	Merck	Prevymis (<i>Letermovir</i>)	Tibotec	Edurant (<i>Rilpivirine</i>)
	GSK	Dectova (<i>Zanamivir</i>)	Nabriva	Xenita (<i>Lefamulin acetate</i>)	VIIV	Cabenuva Kit (<i>Cabotegravir, Rilpivirine</i>)
	Janssen	Olysio (<i>Simeprevir</i>)	Novartis	Egaten (<i>Triclabendazole</i>)	VIIV	Vocabria (<i>Cabotegravir Sodium</i>)
	Merck	Pifeltro (<i>Doravirine</i>)				
 GASTROENTEROLOGY	AstraZeneca	Movantik (<i>Naloxegol</i>)	Shionogi	Symproic (<i>Naldemedine</i>)	Shire	Motegrity (<i>Prucalopride</i>)
	Helsinn	Akynzeo (<i>Fosnetupitant/paloesetrom</i>)				
 CARDIOVASCULAR	Actelion (J & J)	Opsumit (<i>Macitentan</i>)	Johnson & Johnson	Xarelto (<i>Rivaroxaban</i>)	Pfizer	Revatio (<i>Sildenafil</i>)
 OTHER	AbbVie	Orilissa (<i>Elagolix</i>)	Janssen	Invokana (<i>Canagliflozin</i>)	Merck	Steglatro (<i>Ertugliflozin</i>)
	Galderma	Aklief (<i>Trifarotene</i>)	Lilly	Olumiant (<i>Baricitinib</i>)	Pfizer	Revatio (<i>Sildenafil</i>)

Simcyp PBPK has been used to support >85 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 and technology to transform traditional drug discovery and development. Its clients include more than 1,650 global biopharmaceutical companies, leading academic institutions, and key regulatory agencies across 61 countries.

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