CERTARA | SIMCYP

Simcyp™ PBPK Simulator

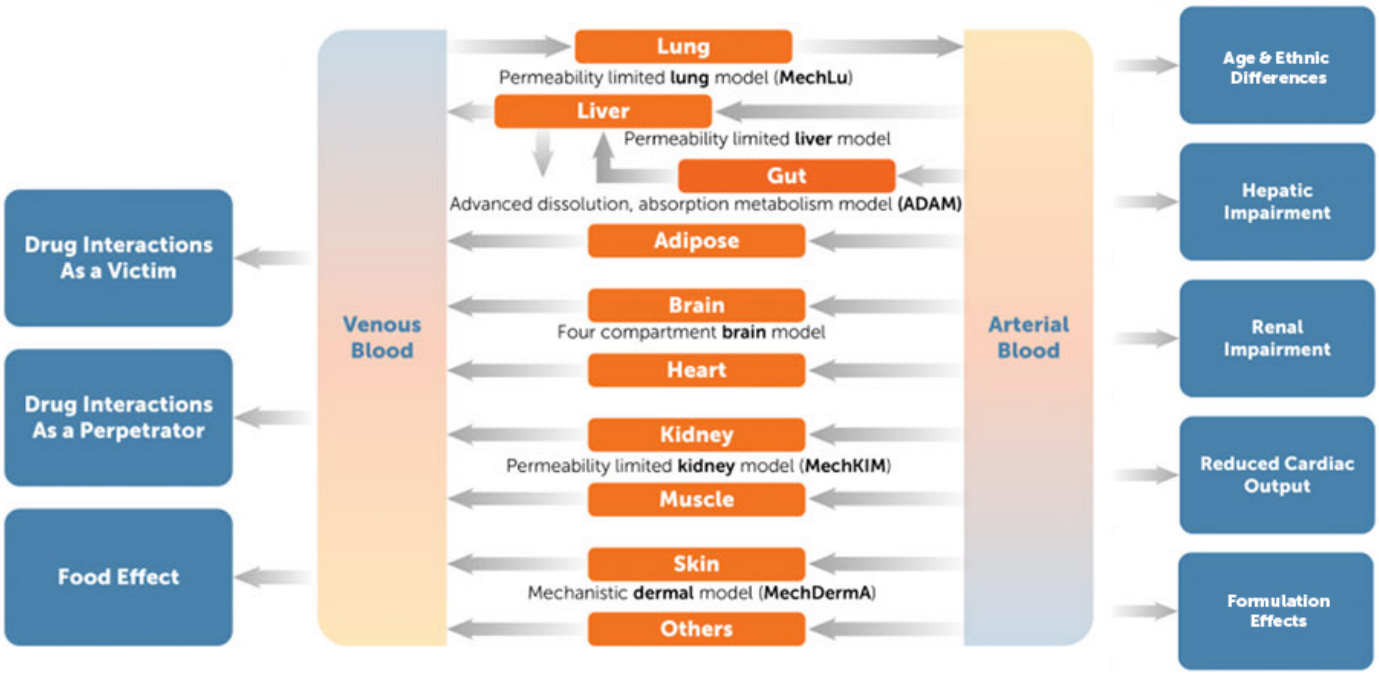
The Standard for Population-based Physiologically Based Modeling and Simulation

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.



One model, innumerable applications using the Simcyp Simulator

The Simcyp Simulator is used across the drug development cycle:

- For early pharmacokinetic determination of first-in-human dosing and to answer other translational questions;
- Leveraged to support strategic decision-making, the Simulator provides valuable information for designing clinical trials, to reduce trial size and complexity and to obtain clinical trial waivers;
- The Simulator quantitatively evaluates and predicts drug-drug interactions (DDIs) involving drug-metabolizing enzymes and membrane transporters, to evaluate PK variability as a function of ethnicity, organ impairment, and pharmacogenomics;
- It predicts dosing recommendations for different populations of patients, including pediatrics, geriatrics, ethnicities, organ impairment, and population bridging.

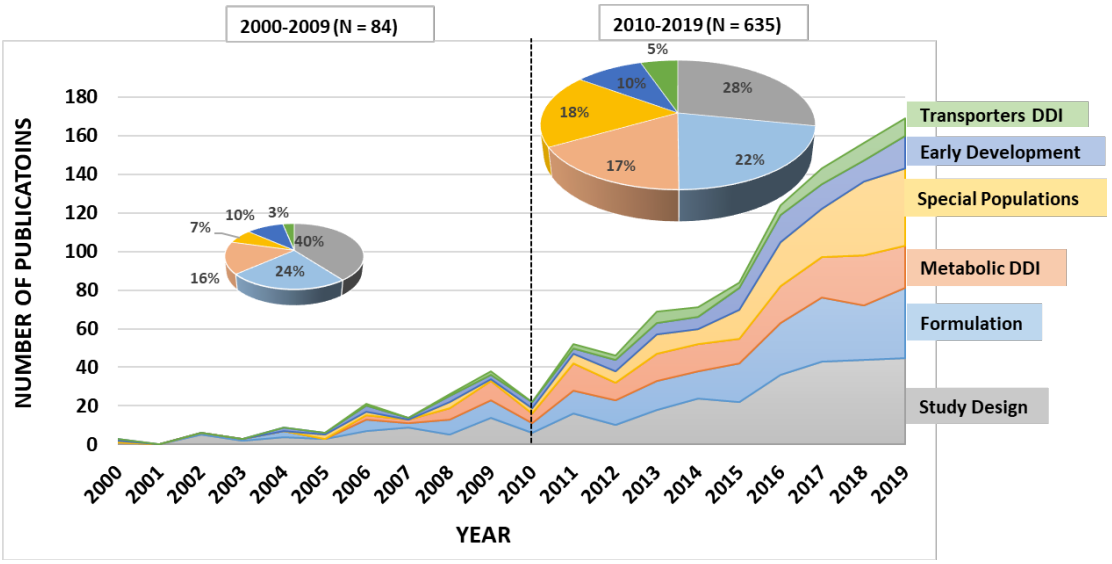
Trusted by industry, academic and regulatory leaders

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 >75 novel drug applications, with >200 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

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 20: 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. Additional capabilities in version 20 are as follows:

Transporters

Incorporating Transporters Induction Capability and Assessing their Potential Impacts on Prediction Accuracy of CYP3A4 Inducers

Functionality for modelling the induction or suppression of transporters has been incorporated to allow the prediction of clinical drug-drug interactions (DDIs) mediated by such mechanisms. The key feature is the ability to model the induction or suppression of transporters in the intestine, liver, and kidney in a dynamic manner, using the appropriate driving inducer or suppressor concentration in each organ and the level of the transporter at a given time over the duration of the simulation. Data for the turnover rate constant of P-gp and OATP1B1 have been collated from the literature and incorporated within the Simulator.

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

PBPK models in Animal Simulators are expanded and brought in-line with the Human Simulator

Additions to the animal models include improvements of the distribution models for all species, implementation of a 5-compartment brain model with associated scaling and transporter data, and the inclusion of allometry calculators for clearance and volume of distribution.

The permeability-limited brain models in all Animal Simulators have been extended and harmonized to use absolute abundance scaling of transporters at the blood-brain barrier (BBB). The Advanced Dissolution Absorption and Metabolism (ADAM) models in the Dog and Monkey Simulators now have the capability to input a disintegration profile for immediate-release dosage forms.

Expansion of the Biologics Modules

Additional flexibility to model protein conjugates, Fc fusion protein, bispecifics for non-mAbs and antibody fragments along with mAbs, ADCs and other proteins and peptides

Previous Biologics models for “Monoclonal Antibody/Antibody Drug Conjugate/Bispecific Antibodies” and “Other Therapeutic Proteins or Peptides” have been consolidated into a single Biologics model with unified screen design and outputs. This offers improved capability to model a range of different biologics modalities.

Further expansions include:

- Extension of the target shedding model to both minimal and full PBPK models for proteins and protein conjugates.
- Updating the tissue FcRn concentration and endosomal volume values using the published human tissue FcRn expression.
- A two-endosomal-compartment FcRn binding model has been developed to integrate pH-dependent FcRn binding. Both 1:1 and 2:1 FcRn binding stoichiometry are available for selection.

The Biologics module (non-conjugate) can be licensed and used independently of the small molecule Simulator.

Implementing a Multi-Compartment Liver with DDI Capability

Improved prediction of compounds that have hepatic blood flow limited clearance

A Permeability-limited Multi-Compartment Liver (PerMCL) model can now be incorporated within the full PBPK framework for compounds at Substrate, Substrate Primary Metabolite 1 and Inhibitor 1 positions with full support of DDI functionalities. The structure allows PerMCL to approximate the behavior of the dispersion model and can potentially improve DDI predictions for highly extracted substrates. The PerMCL model supports all types of enzyme and transporter DDI simulations, including competitive inhibition, mechanism-based inhibition (for CYP450 enzymes only), induction and suppression.

Expanding the IVIVC Module Capabilities

Increasing the capabilities to describe the relationship between an in-vitro property of a dosage form and an in-vivo response

The *In Vitro In Vivo* Correlation (IVIVC) module is significantly expanded to include:

- Immediate release dosage forms, using the diffusion layer model (DLM) to consider formulation-specific parameters such as particle size distribution, disintegration and precipitation parameters,
- monolith, enteric-coated and complex release profiles (e.g. Double Weibull and Pulse profiles) dosage forms for deconvolution,
- fed state simulation,
- fitting individual PK profiles for IVIVC, instead of mean profiles, considering covariates in deconvolution,
- virtual population simulation, instead of only average person,
- multiple dosing and simulating doses other than those used to establish IVIVC.

Expansion of the Compound Library and their Performance Verification

Simcyp Simulator now has ~100 compound files for modeling projects, including an expansive suite of oncology drugs

With guidance from the Simcyp Consortium members, and after extensive assessment of literature data, nine new compound models have been added to the Simcyp Simulator compounds library. New compound models have been developed for Atorvastatin, Cinacalcet, Dexamethasone, Esomeprazole, Ibrutinib, Lansoprazole, Mirabegron, Nebivolol and Ondansetron. In addition, Adefovir, Benzylpenicillin, Chlorzoxazone, and Pitavastatin compound models have been developed and made available through the compound repository in the Simcyp Members' Area. The currently available compound models for Erythromycin, Imipramine and Ritonavir have been refined.

Pediatrics / Pregnancy

The Simcyp Simulator addresses the need for dosing recommendations for these fragile populations, which are generally excluded from clinical trials and drug labeling

A new pediatric population, Sim-Chinese pediatrics, has been introduced to the Pediatric Simulator. The segregated transit time model (ADAM feature) has been opened up in the all Sim-pediatric populations. A new option for the selection of CYP3A4 ontogeny is now available to allow the selection of either the Simcyp default or modified Upreti and Walstrome ontogeny profiles.

Lactation Module

Drug prescribing for lactating mothers, challenged by ethical and limited sample size constraints, are now addressed via the Simcyp Simulator

A new mechanistic lactation module was developed and incorporated in the Simulator allowing prediction of drug secretion into milk in lactating women. The module can be used in either of the minimal or full PBPK models and provides equations to predict the Milk-to-Plasma (M/P) ratio. The model takes into account milk's volume, composition and pH, and the breasts transporters can be incorporated in the model. Risk factors, for example, the relative infant daily dose (RID) using the daily milk intake are determined as well.

The new lactation module is an add-on module to the Simulator and requires its own license.

Absorption Applications

The Advanced Dissolution, Absorption, and Metabolism (ADAM) model is a population-based mechanistic absorption modeling framework within the Simcyp Simulator

An extensive review of some aspects of intestinal anatomy, including small intestinal regional radii and length, plicae circulares scalars and regional blood flow, has been undertaken. The 'New Intestinal Anatomy' has been evaluated against a database of compounds with available in vivo fa, and on this basis the Simulator performs significantly better than the previous physiology (analysis to be published in due course). Other developments include feature and performance improvements to the M-ADAM model, improvements to the salt model in terms of driving the creation of supersaturation, addition of new user-friendly tools for the Particle Size Distribution, and the addition of Double Weibull and Pulse profile options to CR/MR model.

Virtual Bioequivalence

Use of the Simcyp Simulator, leveraging in vitro data and in silico modeling in lieu of running an in vivo comparative clinical bioequivalence endpoint study

V20 will feature an expanded and completely rebuilt Virtual Bioequivalence (VBE) module. This is a versatile user-friendly module to conduct virtual BE studies. The tool allows simulating various VBE studies for oral and dermally applied drugs. Both crossover and parallel trial designs can be simulated. In addition, a custom BE design option is also available which users can use to define up to four sequences and four periods in each sequence. Depending upon the crossover study design (standard crossover trial design or partial or full replicate crossover trial design), each simulated individual, randomly picked up from a desired population, receives both Reference and Test formulations. Therefore, simulations will be performed for each individual in different period. Both intra- inter-individual variability can be defined for a selection of desired model parameters.

The new VBE module is an add-on module to the Simulator and requires its own license.

Dermal/Skin Project

Expansion of the Simcyp MPML MechDermA model to simulate pre-clinical experimentation

A new in vitro permeation testing (IVPT) module uses the MPML MechDermA model to simulate absorption of drug through ex vivo skin, a common pre-clinical experiment. The new module facilitates fitting model parameters to IVPT receptor profiles, the optimized parameters can then directly be transferred back to the main Simulator. Outputs for the MPML MechDermA model have been updated and expanded, as has the ability to handle permeation enhancers. Parameter estimation and sensitivity analysis are now available for local skin concentrations. The ability to apply drug topically to two body sites simultaneously within the same individual has been added, allowing simulation of more complex dosing scenarios.

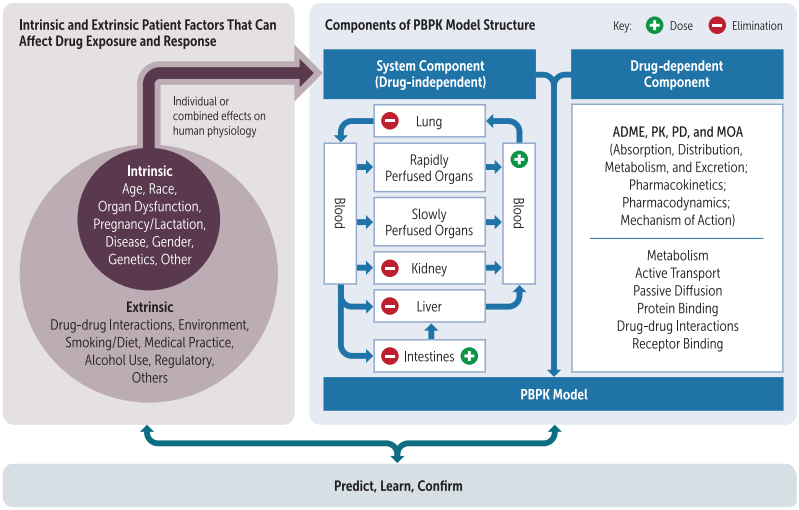
The new IPVT module is an add-on module to the Simulator and requires its own license.

Long-Acting Injectable (LAI) Simulator

Model for designing new formulations, repurposing existing drugs and evaluating potential for long acting injectable drug delivery

A mechanistic model for the subcutaneous administration of solid, in situ gel-forming, and microsphere poly-lactic co-glycolic acid (PLGA) implants will be available within the new long-acting injectables (LAI) module within the Simulator. We account for numerous critical quality attributes (CQAs) for PLGA formulations - such as monomer ratio, molecular weight distribution, porosity, etc. - through a mixture of compartmental, probabilistic, and statistical modelling and have tested this rigorously upon the existing literature data. Accordingly, we have provided both an in vivo simulation option and an in vitro release testing (IVRT) module capable of accounting for a multitude of bi-polymeric formulations and physiologies.

The new LAI module is an add-on module to the Simulator and requires its own license.



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

The Simcyp approach: Combine *in vitro-in vivo* extrapolation (IVIVE) and PBPK approaches in virtual individuals to predict drug concentration and effect

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Simcyp-supported FDA-approved novel drugs

Oncology | Rare Disease | CNS | Infectious Disease | Cardiovascular | Gastroenterology | Other

Agios	Tibsovo (*Ivosidenib*)	**Genentech**	Polivay (*Polatuzumab Vedotin-PIIQ*)	**Novartis**	Kisqali (*Ribociclib succinate*)
Amgen	Blincyto (*Blinatumomab*)	**Genentech**	Alecensa (*Alectinib*)	**Novartis**	Farydak (*Panobinostat*)
Ariad	Alunbrig (*Brigatinib*)	**Genentech**	Rozlytrek (*Entrectinib*)	**Novartis**	Rydapt (*Midostaurin*)
Ariad (Takeda)	Iclusig (*Ponatinib*)	**Incyte**	Pemazyre (*Pemigatinib*)	**Novartis**	Tabrecta (*Capmatinib*)
AstraZeneca	Calquence (*Acalabrutinib*)	**Janssen**	Erleada (*Apalutamide*)	**Pfizer**	Bosulif (Bosutinib)
AstraZeneca	Lynparza (*Olaparib*)	**Janssen**	Balversa (*Erdafitinib*)	**Pfizer**	Lorbrena (*Lorlatinib*)
AstraZeneca	Tagrisso (*Osimertinib*)	**Lilly**	Retevmo (*Selpercatinib*)	**Pharmacyclics**	Imbruvica (*Ibrutinib*)
Beigene	Brukinsa (*Zanubrutinib*)	**Lilly**	Verzenio (*Abemaciclib*)	**Sanofi**	Jevtana (*Cabazitaxel*)
BluePrint Medicines	Ayvakit (*Avapritmib*)	**Loxo Oncology**	Vitrakvi (*Larotrectinib*)	**Seattle Genetics**	Tukysa (*Tukatanib*)
Celgene	Inrebic (*Fedratinib Hydrochloride*)	**Novartis**	Zykadia (*Certinib*)	**Spectrum**	Beleodaq (*Belinostat*)
Eisai	Lenvima (*Lenvatinib*)	**Novartis**	Piqray (*Alpelisib*)	**Turalio**	Daiichi Sankyo (*Pexidartinib*)
Genentech	Cotellic (*Cobimetinib*)	**Novartis**	Odomzo (*Sonidegib*)	**Verastem**	Copiktra (*Duvelisib*)

Akarx	Doptelet (*Avatrombopag maleate*)	**Global Blood Therapeutics**	Oxbryta (*Voxelotor*)	**Sanofi Genzyme**	Cerdelga (*Eliglustat Tartrate*)
AstraZeneca	Koselugo (*Selumetinib*)	**Intercept**	Oclavia (*Obeticholic acid*)	**Vertex**	Symdeko (*Tezacaftor/ivacaftor*)
Genentech	Enspryng (*Satralizumab*)	**Novartis (Recordi)**	Isturida (*Osilodrostat*)	**Vertex**	Trikafta (*ELEXACAFTOR, IVACAFTOR, TEZACAFTOR; IVACAFTOR*)
Genentech	Evrysdi (*Risdiplam*)	**PTC Therapeutics**	Emflaza (*Deflazacort*)		

Alkermes	Aristada (*Aripiprazole*)	**Lilly**	Rayvow (*Lasmiditan Succinate*)	**UCB**	Briviact (*Brivaracetam*)
Eisai	Dayvigo (*Lemborexant*)	**Novartis**	Mayzent (*Siponimod Fumaric Acid*)		
GW Research	Epidiolex (*Cannabidiol*)	**Kyowa Kirin**	Nourianz (*Istradefylline*)		

Gilead	Remdesivir (*Veklury*)	**Merck**	Prevymis (*Letermovir*)	**Novartis**	Egaten (*TRICLABENDAZOLE*)
GSK	Dectora (*Zanamivir*)	**Merck**	Pifeltro (*Doravirine*)	**Tibotec**	Edurant (*Rilpivirine*)
Janssen	Olysio (*Simeprevir*)	**Nabriva**	Zenita (*Lefamulin Acetate*)		

Actelion (J & J)	Opsumit (*Macitentan*)	**Johnson & Johnson**	Xarelto (*Rivaroxaban*)	**Pfizer**	Revatio (*Sildenafi*)
Actelion (J & J)	Uptravi (*Selexipeg*)				

AstraZeneca	Movantik (*Naloxegol*)	**Shionogi**	Symproic (*Naldemedine*)	**Shire**	Motegrity (*Prucalopride*)
Helsinn	Akynzeo (*fosnetupitant/palonosetron*)				

AbbVie	Orilissa (*Elagolix*)	**Janssen**	Invokana (*Canagliflozin*)	**Merck**	Steglatro (*Ertugliflozin*)
AbbVie	Rinvoq (*Upadacitinib*)	**Lilly**	Olumiant (*Baricitinib*)	**Pfizer**	Revatio (*Sildenafil*)
Galderma	Aklief (*Trifarotene*)				

Simcyp PBPK has been used to support >75 novel drugs in a range of therapeutic areas and across regulatory pathways including breakthrough, priority, fast track, and orphan

About Certara

At Certara, we accelerate medicines to patients, partnering with life science innovators. Together we advance modern drug development with biosimulation, regulatory science, and market access solutions.

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