CERTARA®

# Simcyp™ PBPK Simulator

*The Standard for Population-based Physiologically Based Modeling and Simulation*

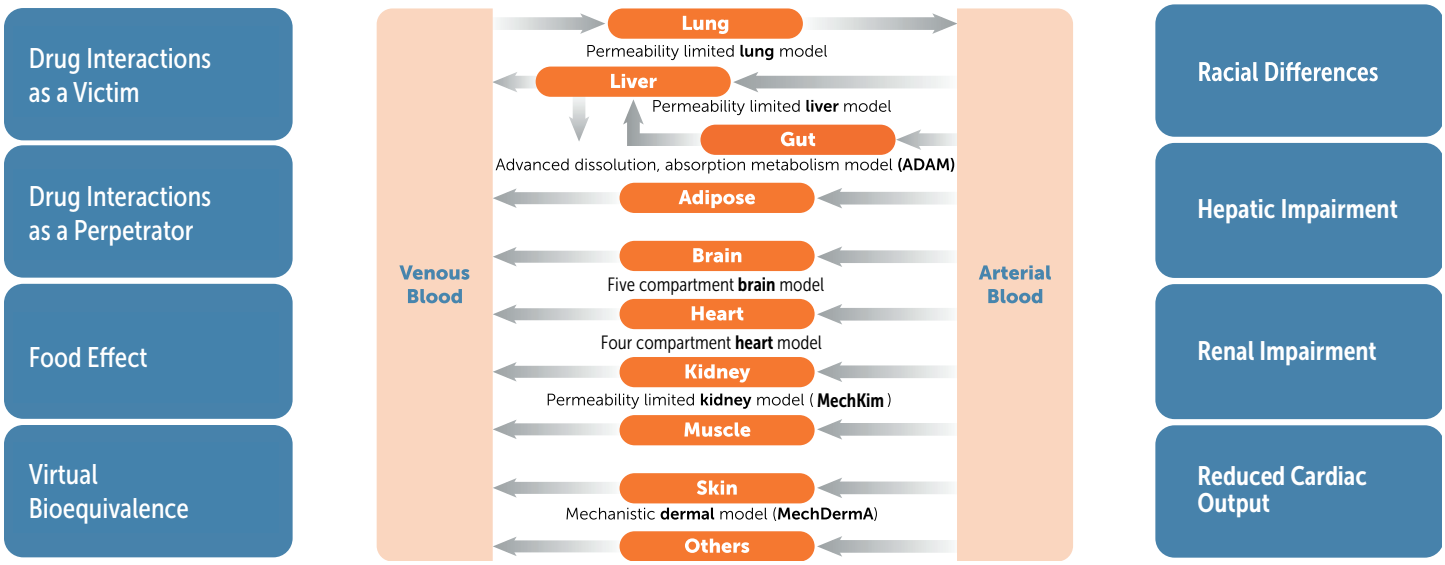
*Updated with Version 23 Capabilities*

## 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
- The Simcyp Simulator has been used in the FDA approval of >110 novel drugs

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, oligonucleotides, and siRNA
- 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. In addition to its 35+ 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.

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 are based on the on the Simcyp Simulator, demonstrating its impact in drug development, clinical pharmacology, toxicology and other key scientific areas. Additionally, 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 110+ novel drug applications, with > 375 label claims achieved virtually, in lieu of performing clinical trials.

Smaller companies can gain access to the Simulator via licensing or consulting services, without needing to join the Consortium. Simcyp has also released two new software products: Simcyp Discovery and Simcyp Biopharmaceutics.

## Simcyp Simulator Version 23

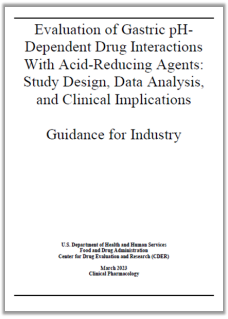
Each year, new features and capabilities are added to the Simcyp Simulator to enhance its utility in informing decision-making throughout the drug development process from discovery to post-marketing. These feature enhancements are prioritized based in part on guidance from our scientific advisory board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

## Aligning/informing/advancing regulatory guidance with Simcyp PBPK

In 2023, several new regulatory guidance documents were finalized that include recommendations for using PBPK to support drug development. The Simcyp R&D team, working with the consortium of Simcyp users has developed new PBPK models and compound files to address the questions and recommendations in these guidance documents. These capabilities are included in V23 of the Simulator.

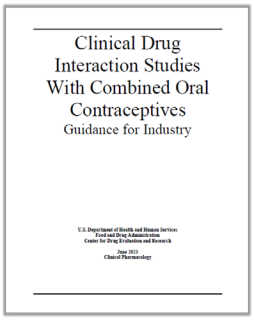
***Effect of Gastric pH-Dependent DDI with Acid Reducing Agents (ARAs)***

PBPK modelling has been recognized by the FDA as an alternative approach to clinical trials for the evaluation of DDIs mediated by gastric pH changes (pH-dependent DDIs). As ARAs are often taken to combat the side effects of oncology drugs, new functionality has been added to readily model the gastric pH-elevating effect of ARAs (e.g., proton pump inhibitors and H2-receptor antagonists) and the subsequent impact on the oral absorption of victim drugs. This functionality, expands the Simulator's capability to assess pH-dependent DDIs and can also be used to assess mitigation strategies such as dose staggering or formulation changes.


Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

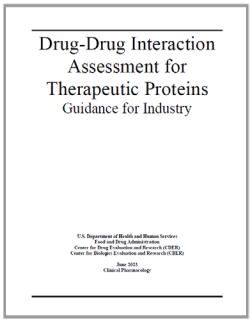
Guidance for Industry

### *DDI with Combined Oral Contraceptives (COC)*


Clinical Drug Interaction Studies With Combined Oral Contraceptives
Guidance for Industry

Per the US FDA, COCs, containing a progestin and an estrogen were used by 22% of all contraception users in 2016. 45% of those users take at least one other prescription drug, and 12% take at least three. DDIs between COCs and other drugs can adversely impact efficacy and/or safety such as unintended pregnancy, breakthrough bleeding, and the potential for venous thromboembolisms (VTEs). As many investigational drugs are co-prescribed with COCs after approval, the guidance recommends that the DDI potential between an investigational drug and COCs be evaluated during drug development and communicated in the labeling. The relevant compound files have been prepared for the Simulator to perform these analyses *in silico.*

### *DDI for Therapeutic Proteins (TPs)*


Drug-Drug Interaction Assessment for Therapeutic Proteins
Guidance for Industry

Collaborating for this new guidance, US FDA's CDER and CBER divisions recommends a systematic, risk-based approach to determine the need for DDI studies for TPs. A new Simulator enhancement enables mechanistic modelling of DDIs between TPs (i.e., cytokine and cytokine modulators) and small molecule drugs, particularly addressing DDIs stemming from altered levels of proinflammatory cytokines that modulate CYP enzyme expression. A new compound position named 'TP-Modulator' has been added to act as a perpetrator in interactions with small molecule drugs, either by inducing or suppressing CYP enzymes. This allows for the consideration of interactions among the cytokine modulator, endogenous cytokine, and cytokine receptor, leading to changes of CYP activity and, consequently, the metabolism of CYP substrate drugs. Additionally, building upon our existing comprehensive small molecule drug DDI network, the update facilitates the handling of more complex scenarios involving multiple small molecule victims and perpetrators.

## Biomarker-informed PBPK modeling for early DDI risk assessment

Endogenous substrates have been identified as potential biomarkers for predicting changes in drug transport and metabolism function, capable of indicating DDI risk for drug candidates in early development. To enable the assessment of DDI risk *in silico*, a new compound position that handles distinct endogenous biomarker (EB) file types has been added to the Simulator. Aligned with other compound slots available, the Endogenous Biomarker slot has the capacity to mutually interact with any other active small molecule moiety in the Simulator, therefore offering flexibility for the endogenous biomarker to participate as a 'victim' or 'perpetrator' in a virtual DDI study.

## Simcyp for New Modalities

### *Biologics*

While best known for its capabilities in small molecule modeling, the Simcyp Simulator has been steadily enhancing its technology for simulating pharmacokinetics of large molecules (see below). With the ability to model monoclonal antibodies, protein conjugates, Fc-fusion proteins, bi-specifics, and other proteins and peptides, and the interplay of small and large molecule for antibody drug conjugates (ADCs), V23 adds the capability to model two new molecule types—antisense oligonucleotides (ASO; ss-DNA) and silencing RNA (siRNA). A full PBPK model was developed, allowing the user to set the target of the simulated oligonucleotide drug in any of the 14 included compartments.

## Simcyp Biologics is used to answer many pivotal scientific questions:

- *FIH PK prediction, dose selection and optimization*
- *Extrapolation to special populations, such as pediatric and renal impairment*
- *Target selection/validation by linking PK to pharmacology*
- *The impact of half-life extension approaches on PK and PD*
- *Disposition and DDI for protein-small molecule conjugates (ADC), combined with small molecule simulator*
- *DDIs resulting from cytokine modulation*
- *Tumor penetration of proteins*
- *Target shedding and the impact on target tissue and tumor receptor occupancy*
- *The disposition of bi-specific binding proteins*
- *Receptor occupancy in specific tissues and linking to PD models*
- *Link to QSP models to investigate issues such as immunogenicity*

***Long acting injectables (LAI)***

The Simulator has been advancing in response to the growth on new modes of administration, including dermal, inhalation, ocular and injectables. In addition to its PLGA module, a new mechanistic model has been incorporated within V23 that simulates human pharmacokinetics of suspension-based long-acting injectable products. The model accounts for the product's critical quality attributes and physiological changes at the local absorption site resulting from the interaction of suspension particles with the local site physiology. Furthermore, the new model allows the simulation of two different formulations of the same molecule simultaneously. The model can also handle prodrugs.

## Expansion of Oral Absorption Models

Expanding our start-of-the-art Advanced Dissolution Absorption Metabolism (ADAM) model a semi-mechanistic pH-sensitive model for handling IVIVE of dissolution of CR/MR formulations is incorporated. Further, to better capture absorption from nanoparticle formulations a new particle drift model is developed and incorporated within the ADAM model. To improve simulation speed, an alternative model to the Particle Population Balance (PPB) particle handling model, called the Modified Mass Balance Only (MBO) model, is added giving identical results. Other additions include improved tools for handling solubility inputs, pH-dependent API stability in the gut lumen and pH-dependent dissolution (DLM) scalars.

## Other additional features in v23

- *New and expanded compound files*
  - *Simulator now has more than 120 individual and verified files*
- *Pediatric simulator*
  - *Advanced absorption model*
  - *Population verification: Japanese, Chinese, Oncology pediatrics*
- *Dermal*
  - *Formulation toolbox enhancements*
- *Pregnancy/Lactation models*
  - *Incorporating several postpartum-age dependent physiological parameters*
  - *Expansion of transplacental permeability prediction options*
- *Virtual Bioequivalence Module (VBE)*
  - *Automated Critical Quality Attributes (CQA) safe space determination for various parameters*
  - *VBE for local concentrations (oral and dermal)*
  - *VBE for inhalation route of administration*

# Simcyp-supported FDA-approved novel drugs

| | | | | |
|---|---|---|---|---|
| ONCOLOGY | AbbVie Venclexta *(venetoclax)* | EMD Serono Tepmetko *(tepotinib hydrochloride)* | Novartis Vijoice *(alpelisib)* |
| | Agios Tibsovo *(ivosidenib)* | Genentech Alecensa *(alectinib)* | Novartis Rydapt *(midostaurin)* |
| | Amgen Blincyto *(blinatumomab)* | Genentech Cotellic *(cobimetinib)* | Novartis Tabrecta *(capmatinib)* |
| | Amgen Lumakras *(sotorasib)* | Genentech Gavreto® *(pralsetinib)* | Novartis Zykadia *(ceritinib)* |
| | Ariad Alunbrig *(brigatinib)* | Genentech Polivy *(polatuzumab vedotin-piiq)* | Novartis Jakavi *(ruxolitinib)* |
| | Ariad (Takeda) Iclusig *(ponatinib)* | Genentech Rozlytrek *(entrectinib)* | Pfizer Daurismo *(glasdegib)* |
| | AstraZeneca Calquence *(acalabrutinib)* | Incyte Pemazyre *(pemigatinib)* | Pfizer Ibrance® *(palbociclib)* |
| | AstraZeneca Lynparza *(olaparib)* | Janssen Balversa *(erdafitinib)* | Pfizer Bosulif *(bosutinib)* |
| | AstraZeneca Tagrisso *(osimertinib)* | Janssen Erleada *(apalutamide)* | Pfizer Lorbrena *(lorlatinib)* |
| | AstraZeneca Truqap® *(capivaserib)* | Lilly Retevmo *(selpercatinib)* | Pharmacyclics Imbruvica *(ibrutinib)* |
| | Beigene Brukinsa *(zanubrutinib)* | Lilly Verzenio *(abemaciclib)* | Puma Nerlynx® *(neratinib)* |
| | Biohaven Nurtec *(rimegepant)* | Loxo Jaypirca *(pirtobrutinib)* | Sanofi Jevtana *(cabazitaxel)* |
| | BluePrint Medicines Ayvakit *(avapritinib)* | Loxo Oncology Vitrakvi *(larotrectinib)* | Seattle Genetics Tukysa *(tucatinib)* |
| | Celgene Inrebic *(fedratinib hydrochloride)* | Menarini/Stemline Orserdu *(elacestranto)* | Spectrum Beleodaq *(belinostat)* |
| | Daiichi Sankyo Turalio *(pexidartinib)* | Mirati Krazati *(adagrasib)* | Springworks Ogsiveo® *(nirogancent)* |
| | Daiichi Sankyo Ezharmia *(valmetostat tosilate)* | Novartis Farydak *(panobinostat)* | Takeda Exkivity *(mobocertinib)* |
| | Daiichi Sankyo Vanflyta® *(quizartinib dihydrochloride)* | Novartis Kisqali *(ribociclib succinate)* | Takeda Fruzaqla® *(fruquintinib )* |
| | Deciphera Qinlock *(ripretinib)* | Novartis Scemblix *(asciminib)* | Taiho Lytgobi *(futibatinib)* |
| | Eisai Lenvima *(lenvatinib)* | Novartis Odomzo *(sonidegib)* | Verastem Copiktra *(duvelisib)* |
| RARE DISEASE | Agios Pyrukynd *(mitapivat)* | Intercept Ocaliva *(obeticholic acid)* | Peloton/Merck Welireg *(belzutifan)* |
| | AkaRx (Eisai) Doptelet *(avatrombopag maleate)* | Ipsen Sohonus® *(palovarotene)* | PTC Therapeutics Emflaza *(deflazacort)* |
| | AstraZeneca Koselugo *(selumetinib)* | Kadmon Rezurock *(belumosudil)* | Sanofi Genzyme Cerdelga *(eliglustat tartrate)* |
| | Aurinia Lupkynis *(voclosporin)* | Merck Welireg *(belzutifan)* | Travere Filspari *(sparsentan)* |
| | Genentech Enspryng *(satralizumab)* | Mirum Livmarli *(maralixibat)* | Vertex Symdeko *(tezacaftor/ivacaftor)* |
| | Genentech Evrysdi *(risdiplam)* | Mitsubishi Tanabe Dysval *(Valbenazine)* | Vertex Trikafta *(elexacaftor/ivacaftor/tezacaftor)* |
| | 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)* | Pfizer Zavzpret *(zavegepant)* |
| | Alkermes Lybalvi *(olanzapine/samidorphan)* | Kyowa Kirin Nourianz *(istradefylline)* | UCB Briviact *(brivaracetam)* |
| INFECTIOUS DISEASE | Gilead Vexlury *(remdesivir)* | Merck Prevymis *(letermovir)* | Pfizer Paxlovid® *(nirmatrelvir, ritonavir)* |
| | Gilead Veklury (*remdesivir*) | Nabriva Xenleta *(lefamulin acetate)* | Tibotec Edurant *(rilpivirine)* |
| | Janssen Olysio *(simeprevir)* | Novartis Egaten *(triclabendazole)* | ViiV Cabenuva Kit *(cabotegravir/rilpivirine)* |
| | Merck Pifeltro *(doravirine)* | | |
| GASTROENTEROLOGY | AstraZeneca Farxigo *(dapaglifoxin)* | Phathom Voquezna TriplePak (*vonoprazan/amoxicillin/clarithromycin*) | Shire Motegrity *(prucalopride)* |
| | AstraZeneca Movantik *(naloxegol)* | Shionogi Symproic *(naldemedine)* | |
| | Helsinn Akynzeo *(fosnetupitant/palonosetron)* | | |
| CARDIOVASCULAR | Actelion (J & J) Opsumit *(macitentan)* | Johnson & Johnson Xarelto *(rivaroxaban)* | |
| | BMS Camzyos *(mavacamten)* | Pfizer Revatio *(sildenafil)* | |
| ENDOCRINE | AbbVie Orilissa *(elagolix)* | Janssen Invokana *(canagliflozin)* | Merck Steglatro *(ertugliflozin)* |
| | Astellas Veozah® *(fezolinetant)* | Lilly Olumiant *(baricitinib)* | |
| | Esperion Nexetol *(bempedoic acid)* | Lilly Mounjaro *(tirzepatide)* | |
| OTHER | Galderma Aklief *(trifarotene)* | Takeda Livtencity *(maribavir)* | |

**Updated March. 2024**

**Simcyp PBPK has been used to support > 110+ 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.

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