CERTARA | SIMCYP

Simcyp PBPK Consulting Services

Drug development decision-making from virtual populations: Proven • Cost-effective • Efficient

The past two decades have witnessed transformative changes in model-informed drug development, specifically the embracing of physiologically-based pharmacokinetic (PBPK) modeling to inform drug discovery and development. Simcyp PBPK has led the way, supporting the development of 70+ novel drugs, driving down R&D costs and timelines, eliminating the need for 200+ *in vivo* clinical studies, and increasing the likelihood of clinical trial and regulatory success.

Simcyp-supported FDA approved novel drugs

ONCOLOGY

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

RARE DISEASE

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

CNS

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

INFECTIOUS DISEASE

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

CARDIOVASCULAR

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

GASTROENTEROLOGY

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

OTHER

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

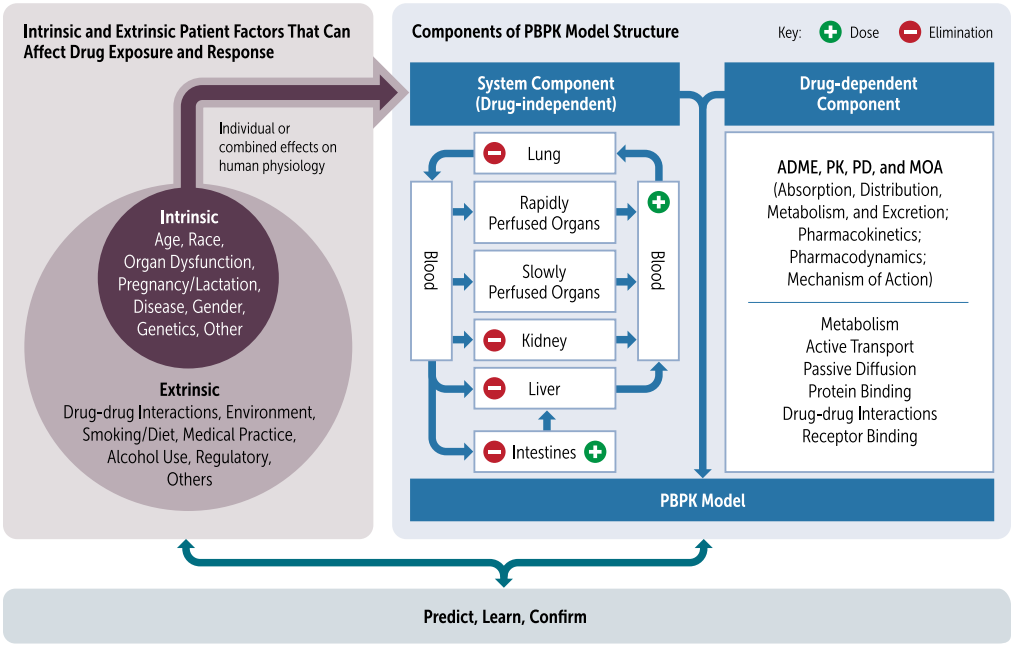
Simcyp PBPK has been used to support >70 novel drugs in a range of therapeutic areas and across regulatory pathways including breakthrough, priority, fast track, and orphan

The Simcyp Simulator: Trusted by industry, regulators, and academia

Certara's Simcyp Simulator PBPK modeling and simulation platform links *in vitro* data to *in vivo* absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetic/pharmacodynamic (PK/PD) outcomes to explore potential clinical questions prior to human studies, and to support decision-making across the drug discovery and development cycle.

Most of the top-40 pharmaceutical companies, along with the major regulatory bodies (FDA, EMA, PMDA) are members of the Simcyp Consortium. These companies use the Simcyp Simulator to predict human PK/dose, design optimal clinical trials, evaluate new drug formulations, predict drug-drug interactions (DDIs) and predict PK outcomes in different clinical populations. That same technology is available via our consulting services, where our PBPK modeling experts provide modeling, simulation and regulatory guidance to answer a range of drug discovery and development questions.

The Simcyp Simulator at work



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

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
- 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 benefits across the drug development cycle

PBPK is used throughout the drug life cycle to support decisions on whether, when, and how to conduct certain clinical pharmacology studies and to support dosing recommendations for product labeling. Used to support strategic decision-making, Simcyp PBPK provides valuable information for designing clinical trials and to obtain clinical trial waivers. Importantly, PBPK helps answer a myriad of "what if" questions about drug performance, dosing and alternate populations that could not be answered without lengthy, expensive and often challenging clinical studies.

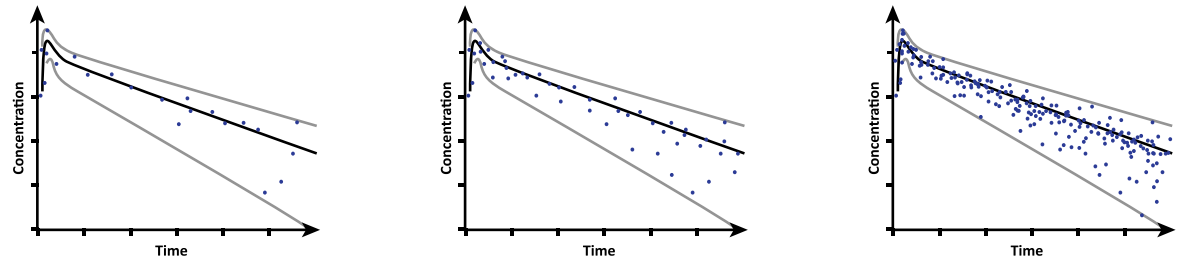
Example projects include:

- 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
- Early PK prediction, FIH dosing

Simcyp – the Gold Standard

The undisputed leader in using modeling & simulation for drug-drug-interaction analyses, Simcyp is the gold standard for PBPK regulatory approval

Simcyp benefits across the drug discovery and development cycle



Pre-Clinical

- Animal to human extrapolation
- Early formulation assessment
- FIH dose projection
- Early DDI risk assessment

Early Clinical (Healthy Volunteers)

- FIH single/ multiple ascending
- Dose exposure
- DDI (perpetrator and victim) modelling
- Absorption (food effect and formulation) modelling

Late Clinical (Patient Data)

- DDI (perpetrator and victim) modelling
- Pediatric and special population modelling
- Organ impairment modelling
- Label claims in lieu of clinical study

Simcyp PBPK delivers tangible benefits across the development cycle, informing clinical trial design, answering scientific questions, extrapolating to untested populations, and to obtain clinical trial waivers

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A history of achievement: Simcyp technology leadership

The undisputed leader in using modeling & simulation for drug-drug-interaction analyses, Simcyp is the gold standard for PBPK regulatory approval. Simcyp has enabled the first and only virtual bioequivalence approval for a complex generic drug. Simcyp has supported the approval of drugs under orphan, first-in-class, breakthrough and priority review applications. Simcyp provides models for pregnancy through pediatrics, bridging across ethnicities, and determining dose in the elderly, hepatic and renally impaired populations. Simcyp is also used to develop new formulations, including complex delivery methods such as dermal and long-acting injectable drugs.

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**.