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 80+ novel drugs, driving down R&D costs and timelines, 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 *(Bosutunib)*
	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)*
	Pharmacyclics	PImbruvica *(Ibrutinib)*	Beigene	Brukinsa *(Zanubrutinib)*	Genentech	Rozlytrek *(Entrectinib)*
	EMD Serono	Tepmetko *(Tepotinib Hydrochloride)*				
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)*
	Intercept	Ocaliva *(Obeticholic acid)*	Novartis	Isturisa *(Osilodrostat)*	AstraZeneca	Koselugo *(Selumetinig)*
	Genentech	Enspryng *(Satralizumab)*	Genentech	Evrysdi *(Risdiplam)*		
Central Nervous System	Alkermes	Aristada *(Aripiprazole)*	GW Research	Epidiolex *(Cannabidiol)*	Kyowa Kirin	Nourianz *(Istradefylline)*
	Eisai	Dayvigo *(Lemborexant)*	Novartis	Mayzent *(Siponimod fumaric acid)*	UCB	Briviact *(Brivaracetam)*
	Lilly	Reyvow *(Lasmiditan succinate)*	AbbVie	Rinvoq *(Upadacitinib)*		
Infectious Disease	GSK	Dectova *(Zanamivir)*	Janssen	Olysio *(Simeprevir)*	Novartis	Egaten *(Triclabendazole)*
	Merck	Prevymis *(Letermovir)*	Nabriva	Zenita *(Lefamulin acetate)*	Tibotec	Edurant *(Rilpivirine)*
	Merck	Pifeltro *(Doravirine)*	Gilead	Remdesivir *(Veklury)*	VIIV	Vocabria *(Cabotegravir Sodium)*
	VIIV	Cabenuva Kit *(Cabotegravir, Rilipivirine)*				
Cardiovascular	Johnson & Johnson	Xarelto *(Rivaroxaban)*	Actelion (J & J)	Opsumit *(Macitentan)*	Actelion (J & J)	Uptravi *(Selexipeg)*
	Pfizer	Revatio *(Sidenafi)*				
Gastroenterology	Shionogi	Symproic *(Naldemedine)*	AstraZeneca	Movantik *(Naloxegol)*	Helsinn	Akynzeo *(Fosnetupitant/palosetrom)*
	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 80+ novel drugs in a range of therapeutic areas and across regulatory pathways including breakthrough, priority, fast track, and orphan

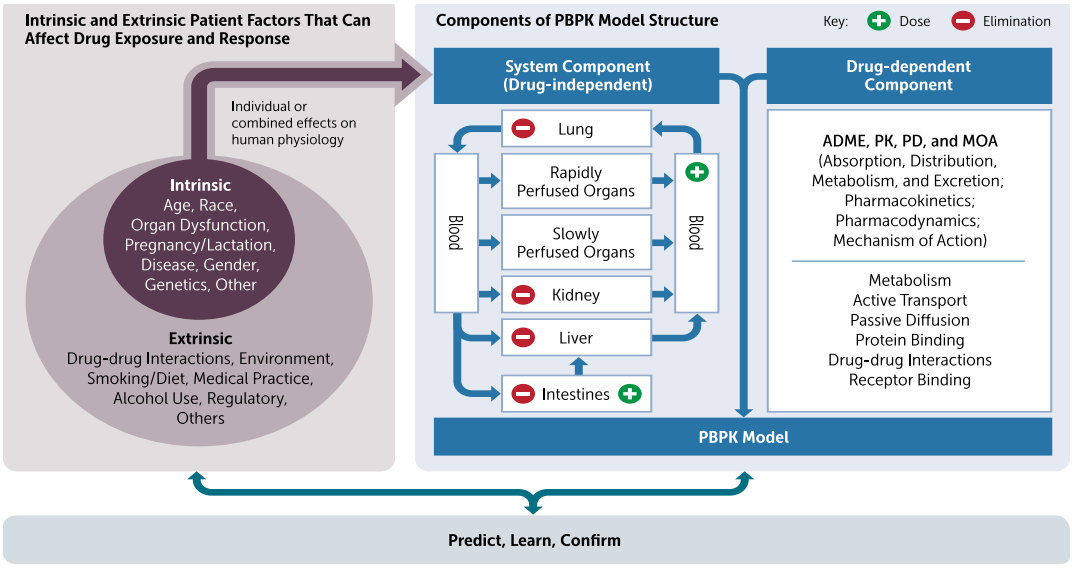
The Simcyp Simulator: Trusted by Industry, Regulators, and Academia

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 vs complexities prior to human studies, and to support decision-making across the drug 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 development questions. The Simcyp consulting team is the largest and most experienced group of PBPK scientists available, working with companies from first-in-human translation through regulatory approval, on both small molecules and biologics.

The Simcyp Simulator at work



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, logistically challenging clinical studies.

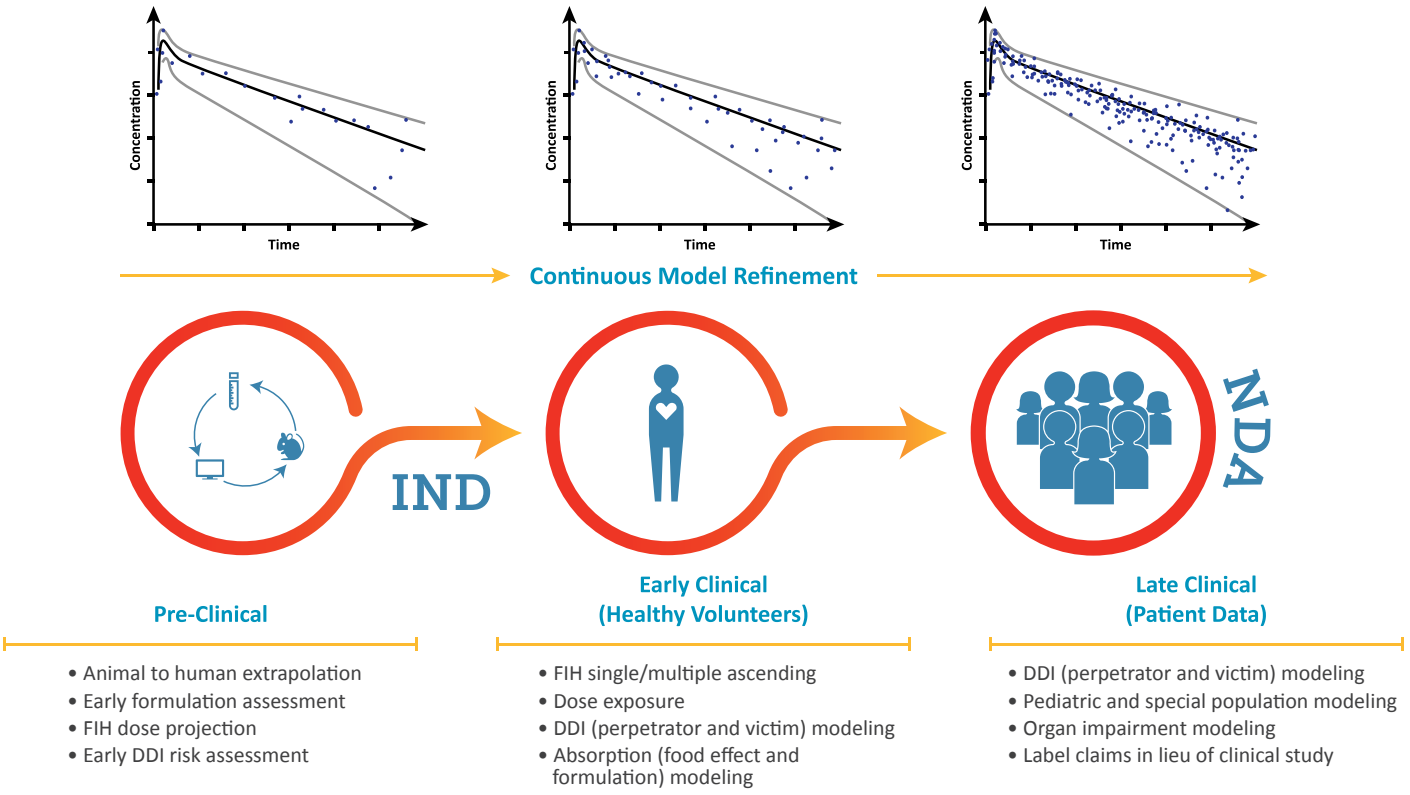
Example projects include:

- Drug-drug interaction simulations – perpetrator and victim
- Absorption modeling – 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 has the largest and most experienced team of PBPK scientists ready to support projects via expert consulting services.

Simcyp benefits across the drug discovery and development cycle



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. And, Simcyp is used to develop new formulations, including complex delivery methods such as dermal and long-acting injectable drugs.

About Certara

Certara accelerates medicines using biosimulation software and technology to transform traditional drug discovery and development. Its clients include 1,650 global biopharmaceutical companies, leading academic institutions, and key regulatory agencies across 61 countries.

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