CERTARA

Simcyp

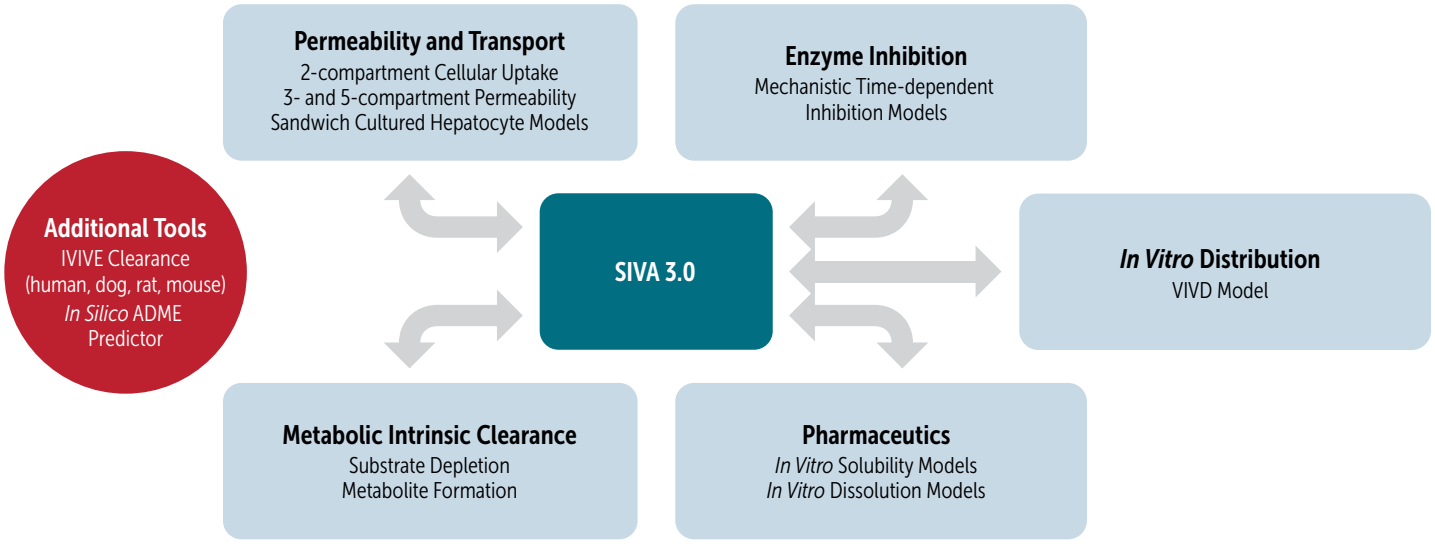
SIVA Toolkit v3

Simcyp *In Vitro* Analysis Toolkit

The SIVA Toolkit is a user-friendly platform, specifically designed to assist scientists with the analysis of complex *in vitro* studies using whole cells, tissue samples, and solid dosage forms to assess the exposure, metabolism, transport, and dissolution/solubility of drugs. SIVA combines the latest model-based data analysis approaches with powerful optimization algorithms in a sophisticated statistical environment.

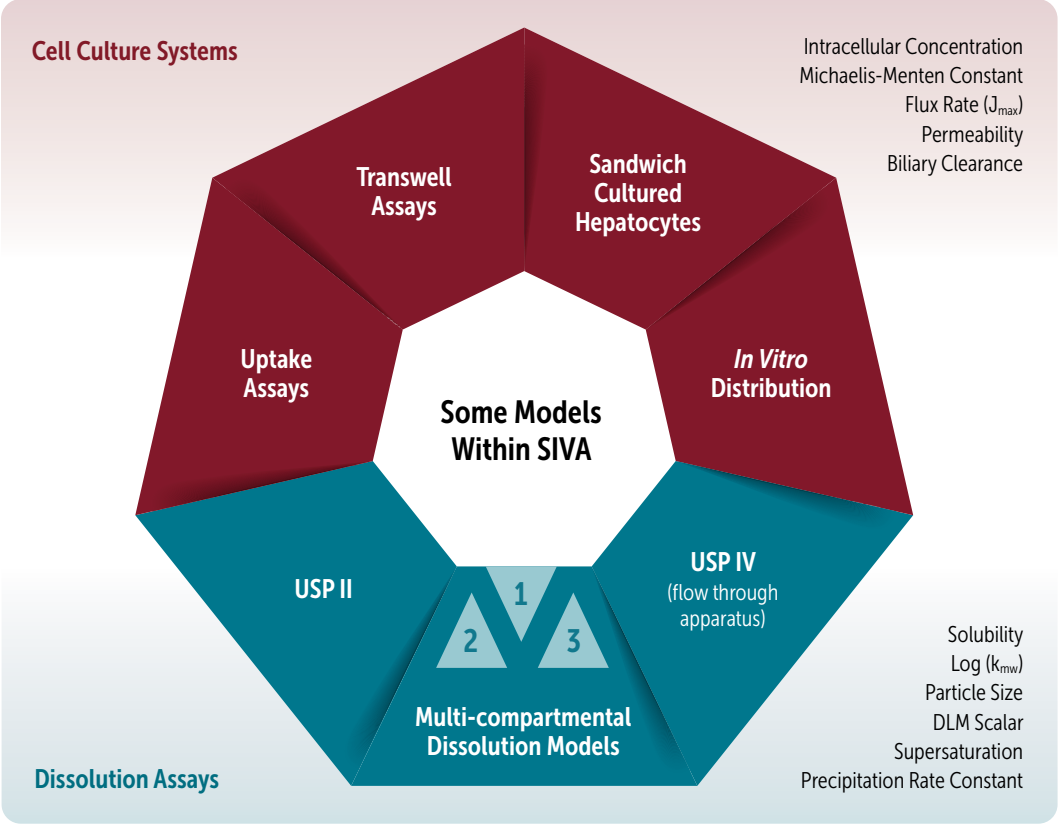
Analysis of *in vitro* data from whole cell systems and dissolution studies is complex, challenging, and time consuming, yet accurate data analysis and informed data interpretation early in the drug development process is crucial. Existing tools have mainly been developed for broader data analysis and not specifically designed for *in vitro* systems, do not readily support analysis via state-of-the-art models, and do not automatically incorporate statistical rigor, which are key elements to the successful prediction of *in vivo* behavior with physiologically-based pharmacokinetic (PBPK) models or efficiently implementing regulatory decision trees.

Key Elements Within the SIVA Toolkit



Key Features

- Specialized tool for drug discovery and development scientists
- Pre-defined library of models for *in vitro* assays used to assess various PK and dosage form related properties of candidate drugs
- Easy to use, user-friendly interface
- Simultaneous modeling of multiple experiments (improved confidence in estimates)
- Incorporation of statistical rigor via goodness of fit measurements and diagnostic plots
- Automated IVIVE enables integration of *in vitro* metabolic clearance data and physiological scaling factors for extrapolation of hepatic clearance for multiple species (human, dog, rat, mouse)
- Predicting ADME parameters using *in silico* models (eg, fraction of unbound drug in plasma, blood-to-plasma ratio)
- Prediction of intracellular operating concentrations driving qualitative and quantitative *in vitro* endpoints



The SIVA toolkit contains a pre-defined library of models for analysing *in vitro* data in the following key areas:

Metabolic Intrinsic Clearance: Provides linear and nonlinear models for estimating metabolic intrinsic clearance and enzyme kinetic parameters with automated IVIVE functionality for extrapolation of hepatic clearance in multiple species (human, dog, rat, mouse).

Permeability and Transport: Provides specific structural models to incorporate *in vitro* data generated using cellular uptake and permeability/transport assays (eg, suspended/cultured hepatocytes, Caco-2, MDCK cell lines). These models can be useful to estimate specific transporter kinetics describing uptake, efflux and metabolism, including the interplay of these multiple dynamic processes.

Mechanistic Enzyme Inhibition: Provides the ability to apply mechanistic models to the analysis of time-dependent enzyme inhibition studies. The mechanistic experimental protocol (MEP) is intended to simultaneously model several standard experiments in order to characterize time-dependent inhibition alongside competitive inhibition and metabolism of the inhibitor. The progress curve analysis (PCA) model is designed to account for the same processes but within the format of a progress curve experiment.

Dissolution: Provides mechanistic models of *in vitro* dissolution experiments permitting estimation of the fundamental parameters required for *in vivo* simulation of the dissolution of solid dosage forms. Included are a fluid dynamics model to account for stirring rate and a particle surface pH model to account for the impact of buffer species on dissolution of ionizable drugs (weak acids in this version). Library files defining the composition of widely used media such as FaSSIF, FeSSIF and simpler buffer systems are also provided.

Drug Solubility: Provides a framework within which to model aqueous as well as bio-relevant solubility permitting estimation of pKa(s), intrinsic solubility, bile micelle:water partition coefficient and related parameters of active pharmaceutical ingredients.

Virtual *In Vitro* Distribution: Provides a steady-state model for the prediction of intracellular concentrations that drive monitored *in vitro* endpoints in monolayer cell cultures. The model accounts for distribution considering differential ionisation, partitioning into the headspace air above culture media, binding to serum lipids and proteins in media, binding to plastic culture-ware, distribution into cells, and subcellular distribution into organelles (lysosomes and mitochondria). Prediction of real operating concentrations informs the translation of *in vitro* dose response to *in vivo*.

The SIVA Toolkit is a standalone product that can be purchased independent of the Simcyp Simulator.

Features in SIVA Toolkit v3

Models for Permeability/Transport

- 2-compartment Cellular Uptake (+/- Metabolism and Electrochemical Gradient Driven (EGD) Transport)
- 3- and 5-compartment Membrane Permeability (with dynamic sampling/replacement)
- Sandwich Cultured Hepatocyte Assays

Models for Metabolic Intrinsic Clearance

- Substrate Depletion
- Metabolite Formation

Models for Enzymes Inhibition

- Mechanistic Experimental Protocol
- Progress Curve Analysis

Automated IVIVE of Hepatic Clearance

The *In Silico* ADME Prediction Toolbox

- Plasma Protein Binding
- Nonspecific Microsomal Binding
- Blood-to-Plasma Ratio
- Hepatic Scaling Factors

Models for Formulation Dissolution Studies

- Modeling of dissolution rate in USP II, USP IV, and uDiss Apparatus
- Modeling of fluid hydrodynamics, including viscosity effects
- Modeling impact of buffer
- Ability to model disintegration
- Library of commonly used dissolution media
- Modeling Serial Dilution experiments
- Modeling supersaturation and precipitation kinetics in Multi-compartment Transfer systems and Two-phase Dissolution (with Serial Dilution) systems
- Estimate parameters/IVIVE scalars for *in vivo* simulations with the Simcyp Simulator
- Direct compatibility of the SIVA Dissolution module with the Simcyp Simulator

Models for Drug Solubility Studies

- Solubility modeling of neutral, acids, bases and ampholytes
- pH- Solubility profile modeling using Henderson-Hasselbalch equations
- Bio-relevant solubility modeling (FaSSIF, FeSSIF, etc.)
- Modeling impact of surfactant other than bile salt concentration on API solubility

***In Vitro* Distribution**

- Models monolayer cell culture system
- Prediction of *in vitro* distribution at steady-state
- Prediction of intracellular and intraorganelle concentrations

System Requirements: Windows

The SIVA Toolkit will run on PC hardware using any of the following:

- Microsoft Vista
- Microsoft Windows 7
- Microsoft Windows 8

Examples of *in vitro* assays and dissolution tests for which mathematical models are available within the SIVA Toolkit

- Cellular Uptake (eg, suspended hepatocytes)
- Transwell Assays (eg, Caco-2, MDCK, LLC-PK1)
- Cellular Uptake and Biliary Clearance (eg, sandwich cultured hepatocytes)
- USP II Dissolution Apparatus
- Up to 3 Vessel Transfer Model with dynamic media composition changes
- USP IV Dissolution Apparatus
- USP II Biphasic dissolution experiments
- Serial Dilution dissolution experiments

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

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