CERTARA

Simcyp

Simcyp Simulator

The Standard for Population-based Pharmacokinetic Modeling and Simulation

The Simcyp Population-based Simulator streamlines drug development through the modeling and simulation of pharmacokinetics (PK) and pharmacodynamics (PD) in virtual populations. The Simcyp Simulator is the pharmaceutical industry's most sophisticated platform for the prediction of drug-drug interactions and PK outcomes in clinical populations

PBPK model for antibody drug conjugates

Implementation of a physiologically-based pharmacokinetics (PBPK) model for antibody drug conjugates (ADCs) to facilitate modeling, characterization and simulation studies of pre-clinical ADCs and drug-drug interaction in a more mechanistic manner. For this purpose both large molecules (ie, antibodies) and small molecules (ie, cytotoxic drugs) have been modeled simultaneously based on an integrated PBPK approach. The model also includes target mediated drug disposition models in the plasma, lymph node, tissue and the tumor.

Enhancement of transporter capabilities

The Permeability-limited Liver (PerL) model has been expanded, allowing *in vitro-in vivo* extrapolation (IVIVE) of active drug transport on the basis of the absolute abundance of drug transporters in the liver and the ability to account for drug ionization in passive permeability. The library of specific and user-defined hepatic transporters has been expanded. Further, the liver transporters abundance values based on meta-analysis of recently published proteomic data are added to the population library.

Development of the Simcyp monkey

Development of the Simcyp monkey model to allow the prediction of drug PK in monkey. The model is based upon physiological data for cynomolgus macaques. However where data are lacking, or meta-analysis indicates no significant difference between the species, a combination of rhesus and cynomolgus data has been used. The model has similar functionality as of the Simcyp dog, including elimination by enzyme kinetics (liver and gut), inclusion of the liver and gut transporters, addition of parameter estimation, 15 CYP and transporter phenotypes.

Version 15 Features

- PBPK model for antibody drug conjugates
- Enhancement of transporter capabilities
- Development of the Simcyp Monkey
- Esterase metabolism
- Pharmaceutical capabilities
- Introduction of the M-ADAM (multiple-layer gut wall within ADAM model)
- Introduction of the pediatric biologics model
- Animal PBPK-PD developments
- Parameter estimation and ASA expansions
- Development of the lung model
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Esterase metabolism

Expansion of non-CYP metabolism to include esterase (ES) enzymes, specifically carboxylesterase (CES) metabolism of ester pro-drugs in the liver, gut and kidney. A metabolite can be formed and simulated via CES or plasma esterase enzymes. Further, an ontogeny function is implemented to incorporate the developmental change in esterase abundance during pediatric development.

Pharmaceutical capabilities

Addition to ADAM of regional and global diffusion layer model (DLM) scalars which can be estimated either from *in vitro* experiments using the SIVA Toolkit or from within the Simcyp Simulator; these scalars are intended to permit adjustment of the DLM to account for factors such as particle shape, for example. A new ADAM precipitation model has been added (Model 2) which includes lag time and has compatibility with the SIVA Toolkit Transfer Model. It is also now possible to enter regional as well as globally applied precipitation parameters. Parallel development of the SIVA Toolkit means that the next release will include models for USP IV flow-through systems (closed and open), media change experiments, transfer experiments, and two-phase systems. For immediate-release formulations it is now possible to enter a disintegration profile that can be estimated from *in vitro* experiments, this will soon be available using the SIVA Toolkit (R2). The Controlled/Modified Release Formulation options have been expanded to enable either a release profile or a dissolution profile to be specified for monoliths or dispersible formulations.

Introduction of the M-ADAM (multi-layer gut wall within ADAM) model

The multi-layer gut wall within the ADAM (M-ADAM) model is developed which incorporates (i) an unstirred boundary layer (UBL) for oral absorption from luminal fluid to enterocyte; (ii) a permeability-limited basolateral membrane between the enterocyte and the intestinal interstitial fluid (ISF); (iii) lymphatic absorption from the intestinal ISF to systemic circulation. The M-ADAM model allows full functionality for the uptake and efflux transporters in the basolateral membrane of the enterocyte. The model is now capable of modeling drug concentrations within the UBL, enterocyte compartments to be used as the driving force for drug permeation (passive and active), transporter drug-drug interactions (DDI) at both the apical and basolateral membranes and disposition within the ISF, while retaining the capacity to predict enterocyte concentrations for metabolic and efflux transporter DDI.

Introduction of the pediatric biologics model

The pediatric module is expanded to allow simulation of biologics. The pediatric biologics model incorporates age-related changes in system parameters, such as IgG, lymph volume, lymph flow, IgE, etc. Additional features to the pediatric model include flexibility in defining the population age, weight, height relationships, and entering a value for the fluid intake with formulation.

Animal PBPK-PD developments

Expansion of the dog model includes the following five enhancements: (i) updating the enzyme and transporter phenotype frequency allowing the simulation of extensive and poor metabolizers and transporters in beagle dogs; (ii) expansion of the model to include additional enzymes (CYP1a2, CYP2c21, CYP2d15, CYP2e21, CYP3a26) in the liver and gut; (iii) addition of population variability for non-oral absorption parameters such as hepatic scaling factors (HPGL and MPPGL); (iv) ability to modify tissue volumes based on 'tissue percent'; (v) the tissue composition data has been updated to reflect beagle tissue composition based on recently published literature data.

Expansions to the rat and mouse models includes the following four enhancements: (i) addition of S9 IVIVE for both the liver and gut; (ii) new functionality for esterase metabolism incorporating two labeled esterase enzymes (ES-User1, ES-User2) with recombinant, microsomal or S9 inputs in the liver and gut; (iii) inclusion of plasma esterase functionality allowing the metabolism in plasma and plasma metabolite formation; (iv) update to intestinal microsomal metabolism IVIVE to unify the correction factor approach between scraping and elution inputs based on the intestinal scaling factor preparation method.

Parameter estimation and ASA expansions

Expansion of the parameter expansion input sheet to allow fitting models to the observed data for the amount of substrate, inhibitor and metabolite in urine or their concentrations in any organ. The option to overlay observed data onto an ASA profile output and addition of unit conversions for output profiles is now offered in the sensitivity analysis profile outputs.

Development of the lung model

A multiple-compartment permeability-limited lung model has been added to the Simcyp Simulator. This model allows drug disposition to the respiratory system after systemic administration to be modeled and accounts for both passive and active disposition in various part of the lungs. This work was funded by a grant from the Critical Path Initiative and the Bill and Melinda Gates fund.

Simcyp command line console

Simcyp now comes bundled with a command line console that will run workspace simulations, or generate a population from the command line, without visual screens or popup messages: outputs are all in comma separated table files and the default output selection may be adjusted via explicit 'include' or 'exclude' requests listed in a configuration file.

Compatible software

The Cardiac Safety Simulator (CSS) was released by Simcyp as an independent standalone product in July 2013 to investigate cardiotoxicity and generate simulated ECG traces; for further details please see the CSS datasheet.

The SIVA Toolkit is a user-friendly standalone 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 metabolism, transport and dissolution/solubility of drugs.

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BR May 2016 v2 082216