CERTARA

Simcyp

Simcyp Simulator Version 17 Features

The Simcyp Population-based Simulator streamlines drug development through the modeling and simulation of pharmacokinetics and pharmacodynamics in virtual populations.

The Simulator is the pharmaceutical industry's most sophisticated platform for the prediction of drug-drug interactions and pharmacokinetic outcomes in clinical populations.

Expansion of Compounds Qualification Library

As a continuation of previous efforts for providing compound qualification summaries to assist clients with their regulatory interactions, a range of summaries for compounds in Version 16 have been produced and updates uploaded into the Simcyp members area.

New compound files were developed for the metabolites 5-HydroxyMethylTolterodine, Norfluoxetine (CYP2D6 Ki and CYP2C19 and CYP3A4 Ki, K_{app} and K_{inact} included) and Norverapamil (CYP3A4, CYP3A5 K_{app} and K_{inact} and P-gp Ki values included).

Refinements were made to the following substrates: Nifedipine, Tolterodine, 5-HydroxyMethyl Tolterodine, Imipramine and Desipramine. Further, the following inhibitors were refined: Cimetidine, Fluconazole, Quinidine, Ciprofloxacin, Fluoxetine, Norfluoxetine, Verapamil, and Norverapamil.

Expansion of Gut Transporters and IVIVE Techniques in the ADAM/M-ADAM Models

An additional 14 gut transporters have been added to the Advanced Dissolution, Absorption and Metabolism (ADAM) and Multi-layer ADAM (M-ADAM) models. The user now has the capacity to incorporate a non-specific assay binding term (fu_{inc}) to correct transporter kinetics input into the model. The current gut scaling transporters to *in vivo* uses a Relative Expression Factor (scalar) and employs a relative region-specific transporter expression to the gut segments in ADAM/M-ADAM, once normalised to the jejunum I. There is now a new scaling option via the absolute transporter expression (pmol) for each gut segment in each individual by selecting the Inter-System Extrapolation Factor for Transporters (ISEF,T) approach. A requirement of using the ISEF,T approach is that the absolute abundance of a transporter(s) should be quantified for your cell monolayer and the kinetic parameters (J_{max} or $C_{Lint,T}$) should be corrected for the transporter abundance.

A comprehensive meta-analysis of gut transporter abundances is also conducted and the outcome is incorporated in the population library.

Version 17 Features

- Expansion of compounds qualification library
- Expansion of gut transporters and IVIVE techniques in the ADAM/M-ADAM models
- Expansion of pharmacodynamics to the animal simulators
- Expansion of compounds library
- Expansion of populations library
- Incorporation of enzymes inter-correlations in virtual populations
- Expansion of the pediatric module
- Multi-phase multi-layer (MPML) mechanistic dermal (MechDermA) model (FDA grant)
- Incorportaion of feto-placenta module within rodent simulators
- Additional developments to the animal simulators

Expansion of Pharmacodynamics to the Animal Simulators

The ability to model a pharmacodynamic (PD) response driven by the simulated (total or unbound) concentration, or amount of drug in different compartments/tissues of the PBPK model, has been implemented as part of the Version 17 development of the Animal Simulators. The PD response can be modeled for small molecules and their primary metabolites as well as for therapeutic proteins where available. In addition to the concentration profile, various summarized (pharmacokinetics) PK parameters including AUC, C_{max} and concentration at a specified time are available to drive the PD response. Prior to the direct input of a PK parameter to drive the PD response, the option of using an effect compartment model (Keo; delay compartment) is also available. Built-in PD models available include four direct response models, viz. (i) Linear, (ii) Power function, (iii) Simple E_{max}, and (iv) Sigmoid E_{max} (Hill function). The option to link the PD response output from a direct response model to an indirect response model is also available for the four commonly used indirect response models, viz. (i) Inhibition of production of response, (ii) Inhibition of loss of response, (iii) Stimulation of production of response, and (iv) Stimulation of loss of response. Apart from the standard direct response and indirect response models, the ability to write user custom models via the Lua interface is also available as an additional option. Automated sensitivity analysis and parameter estimation from clinical PD response tools are also available for all built-in PD model parameters.

Expansion of Compounds Library

New compound files for Celecoxib (CYP2C9 substrate), Ethinylestradiol (CYP3A4, CYP2C9, CYP2C8, CYP1A2 and UGT1A1 substrate) and Valsartan (OATP1B1, OATP1B3, MRP2 and CYP2C9 substrate) have been included in this version of the Simulator. Additionally, in conjunction with the development of the Cancer generic oncology population, Docetaxel (CYP3A substrate), Methotrexate (OAT3, MRP substrate; Mech KiM) and Paclitaxel (CYP2C8, CYP3A4 and PgP substrate) oncology compound files have been developed and made available through the compound repository in the Simcyp Members' Area. Compound qualification summaries, verifying performance in Version 16 of the Simulator, for each of the developed files are available in the Simcyp Members' Area.

Expansion of Populations Library

A new Cancer population as a generic population template for modeling PBPK in oncology, incorporating changes in demographics, blood plasma binding proteins, as well as changes in hepatic transporter abundances, has been added to the Simulator. The Japanese population has been updated to incorporate recent demographic information, as well as CYP abundances. The severe renal impairment population (RenalGFR_less_30) has been updated to include the increases in α1-acid glycoprotein which are clinically observed. The option to incorporate a user-defined GFR relationship using the Lua interface is also included. The age distribution was also updated to incorporate any custom distributions.

A new trial design feature using the Excel PE template plug-in was also incorporated to expand usability and allow the user to specify covariates for a given trial to be simulated in multiple trials.

Incorporation of Enzymes Inter-Correlations in Virtual Populations

Assigning individuals' enzyme abundance values can have a significant impact on the PK/PD (parameters and profiles) variability predictions when generating virtual populations. So far, due to lack of information, Monte Carlo sampling was used to assign these enzyme abundances. However, recently, data have become available to determine and incorporate enzyme abundance inter-correlations.

The methodology and a new framework have been provided to allow incorporation of the inter-correlations in absolute abundance values between up to a total of 13 CYP450 hepatic enzymes. Based on the currently available proteomic data in the literature, the default correlation structure using the Cholesky decomposition method is determined and provided in a new user interface. Users can modify or import alternative inter-correlations data along with the desired mean and maximum values to incorporate in virtual population simulations.

Expansion of the Pediatric Module

Transporter ontogeny functions for major hepatic and intestinal transporters are incorporated in the Pediatric Simulator. Equations defining system parameters, such as haematocrit, plasma binding proteins, cardiac output, blood flows, and compositions for all tissues are now available on the screen, and users can modify them if they choose to. Users can now directly define changes in the fraction of drug unbound with age. The fluid intake as the formulation volume with both drug substrate and inhibitor can now be defined independently, enabling more accurate input of study design information.

A new Preterm Population has been added to the Simulator, which enables the prediction of PBPK/PD in the preterm infant from 28 Post Menstrual Age (PMA) until one month after birth. The population is linked to the full PBPK model for small molecules and linked to all metabolizing enzyme functionalities and hepatic transporters. The time-varying physiology feature of the Pediatric and Pregnancy modules is also expanded to include the Preterm Population.

Multi-phase Multi-layer (MPML) Mechanistic Dermal (MechDermA) Model (FDA Grant)

As part of a multi-year grant project from the US FDA GDUFAR funding, the features of the MPML model were further expanded. A vehicle evaporation model has been added to the MPML-MechDermA to take into account the effect of vehicle evaporation on dermal drug absorption from topical formulations. An empirical lag time parameter has been introduced to simulate the lag time in absorption. Additional deep tissue compartments such as subcutis and muscle have been incorporated with associated physiology for all eight anatomical locations to simulate the direct diffusion of the drug from the site of dermal application into the deep tissues. All viable tissue compartments of the model are now connected to the Pharmacodynamics (PD) modules of the Simcyp Simulator to simulate the local PD response after topical application. A mechanistic model and associated physiology have also been added to simulate drug absorption through psoriatic skin.

Furthermore, a range of fully flexible pediatric skin ontogeny functions and the default ontogeny parameters derived from meta-analysis of literature data to allow the impact of age related changes in dermal drug absorption were both added. Also, data collation and meta-analysis was carried out for Asian and Elderly skin physiology parameters, and the corresponding population files were expanded to allow simulations of such ethnicity and age effect on dermal absorption. Gender effect was also incorporated in skin physiology where data were available.

Incorporation of Feto-placenta Module within Rodent Simulators

A new Feto-placenta module is incorporated within the full PBPK models of the Rodent simulators, facilitating investigation of drugs disposition in fetus and amniotic fluid while passing through placental membrane. Fetal elimination and renal clearance, as well as uptake and efflux transport across various barriers, can be incorporated.

Additional Developments to the Animal Simulators

As part of Version 17 developments, several expansions and revisions have been implemented in the Animal simulators. Primarily, the 'Formulation' tab in the Absorption section has been rearranged in order to accommodate new features and streamline the simulator interface as per the Human simulator. A scalar for dissolution rate has been implemented (DLM scalar) in all the Animal simulators, which enables the user to fit or scale the predicted rate of dissolution uniformly or individually in all segments of the GI tract. Similarly, the absorption rate scalar has also been introduced into the permeability section of the absorption models so as to provide more flexibility on the absorption rate of the drug in different segments of the GI tract of all Animal simulators. An improvised supersaturation and precipitation model has been added to the Rat and Dog simulators, known as Model 2, similar to the Human simulator. The original precipitation model is now known as Model 1. Users are encouraged to apply Model 2 for simulating the supersaturation/precipitation behaviour of their drug, instead of Model 1 as it represents a more realistic intra-luminal situation as compared to Model 1, which was known to be particularly severe.

About Certara

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