CERTARA

Simcyp

Simcyp Simulator Version 16 Features

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.

Expansion of Distribution Models

In order to consider the contribution of ion permeability across the cell membrane on drug distribution into tissues, a non-unity, unbound, unionized, concentration ratio between intracellular and extracellular water ($Kp_{uu,uu}$) has been introduced. For this purpose the steady-state Fick-Nernst-Planck equations have been added to the classical Rogers & Rowland method (Method 2 in the Simcyp Simulator) to predict tissue: plasma partition coefficients and thus volume of distribution (V_{ss}). This new method (Method 3: Method 2 + ion membrane permeability) can have a significant impact on V_{ss} prediction for strong bases with a $pKa \geq 7$ where negative cell membrane potential enhances the permeability of positively charged ions thus concentrating them in intracellular water. This new method has shown negligible impact on V_{ss} prediction for acidic compounds.

Within the framework of the new V_{ss} prediction method, to represent of the lysosome or any other organelle, a subcellular compartment is incorporated within the intracellular space, enabling users to explore the contribution of ion-trapping semi-mechanistically.

As part of the project, the prediction equations used in Method 2 and Method 3 for weak bases and strong bases have been unified.

Based on the experimental BP for neutral or acidic compounds, where the V_{ss} is often over-predicted by Method 2 or Method 3 (possibly due to the uncertainty in the $logP_{o:w}$ used), a lipid binding scalar can be estimated and applied to Kp prediction. Additionally, a new equation has been incorporated in the simulator to predict $logP_{vo:w}$ from $logP_{o:w}$.

Expansion of Pediatrics Module

The pediatric module library interface has been expanded with the addition of a Renal Function tab where either the default GFR or a user-defined Lua model can be selected. The ontogeny screen has been extensively reorganized and expanded to allow user-input of intestinal and hepatic (sinusoidal

Version 16 Features

- Expansion of distribution models
- Parameter estimation and ASA expansions
- Consolidation of the absorption physiological population databases
- Expansion of induction capabilities
- Expansion of outputs and reporting
- Development of the Simcyp Monkey PBPK model–phase 2 (biologics)
- Expansion of pediatrics module
- Pharmacodynamic feedback
- Further development of the lung model (c-path collaboration)
- Multi-phase and multi-layer (MPML) skin model (FDA grant)

and canalicular) transporter as well as Cytosolic enzyme ontogeny. The pediatric biologics module also allows user-defined IgG CLcat and Systemic clearance ontogeny profiles for large molecules.

Parameter Estimation and ASA Expansions

The Parameter Estimation Excel input sheet has been restructured to allow options for entering dosing for all inhibitors in addition to the substrate dose and for up to two routes of administration for each individual and compound. Additional dependent variables (DVs) are also available to be selected in the input sheet for primary metabolite 2, inhibitors 2 and 3, inhibitor metabolite, amount of substrate in the urine in presence of the inhibitor, amount of inhibitor 1 metabolite in the urine, and also the following three DVs for fitting the ADC models: total antibody, conjugated antibody and conjugated drug.

After running Parameter Estimation there is now an option to determine confidence intervals for both the estimated parameters and predicted profiles. Visual predictive checks can also be generated and added to the outputs. Details of the dosing used will also be reported within both the PE Excel outputs and the results after running a simulation from the PE screen.

Given the importance of the fraction of metabolism (fm) in prediction of drug-drug interaction accuracy, the Automated Sensitivity Analysis (ASA) module has been expanded to run for either the fm of the substrate or the renal contribution to elimination (fe). This option is available in addition to the current standard sensitivity analysis. When activating the ASA screen the fm and fe values of all elimination contributions are listed for the population representative of the selected population. Only one fm/fe value can be selected for sensitivity analysis and no other screen parameters can also be selected. After running ASA for fm/fe, any of the summary parameter or profile outputs that can be selected for the existing standard sensitivity analysis, can also be selected for comparison with the fm/fe values. In addition to the existing outputs there is also Cmax ratio and substrate profiles in the presence of the inhibitors available for both standard ASA and ASA of fm/fe.

Development of the Simcyp Monkey PBPK Model – Phase 2 (Biologics)

As a follow-up to the V15 development of the Simcyp Monkey Simulator, models and databases to allow the prediction and simulation of pharmacokinetics of protein molecules (monoclonal antibodies and other peptides/proteins) have been developed and implemented. The models are 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, cynomolgus and human data has been used. The monkey biologics model has similar functionality to the Simcyp Human Therapeutic Protein models allowing subcutaneous absorption, distribution, elimination and various target-mediated drug disposition to be modelled.

Further Development of the Lung Model (C-Path collaboration)

The permeability-limited lung model is expanded to include a multiple-compartment granuloma model consisting of macrophage, interstitial fluid, caseum and blood. The macrophage number, and therefore the granuloma size, dynamically changes following the crosstalk of various cytokines, bacteria, B-cells and T-cells within the immunological system implemented using Lua scripting. The lung and granuloma model is expanded to all parent compounds (including the substrate and 3 inhibitors) in the simulator Therefore, the Full-PBPK models are extended to Inhibitor 2 and Inhibitor 3. All systemic DDIs mediated by CYPs, UGTs, esterases and/or transporters within the liver, kidney and/or gut are simulated simultaneously within full PBPK models.

Expansion of Induction Capabilities

For CYPs, the performance of the model has been investigated using relevant clinical examples (with prototype inducers and sensitive victims), and verified models with optimized/calibrated induction parameters are provided to predict the induction potential for CYP2C9 and CYP2B6.

Functionality for modelling the induction of UGTs has been incorporated allowing the prediction of clinical drug-drug interactions (DDIs) mediated via the induction of UGTs.

Furthermore, additional options (Additive and Multiplicative) have been provided to handle DDIs when multiple inducers or suppressors of enzymes are co-administered. These options provide greater flexibility to investigate the net DDI effect following concomitant administration of inducers/suppressors of enzymes. Also, the current induction interface has been improved for more flexibility.

Multi-Phase Multi-Layer (MPML) Skin Model (FDA Grant)

As part of a multi-year grant project from US FDA GDUFAR funding, we have developed a mechanistic model of dermal drug absorption that would allow virtual bioequivalence assessment to compare two different formulations (eg, cream vs gel) or the same formulation type with different attributes (eg, pH or viscosity of formulation base).

A dynamic, multi-phase and multi-layer (MPML) mechanistic dermal absorption model (MechDermA) has been introduced in V16 that models longitudinal diffusion and distribution processes considering skin physiology-related parameters (ie, tortuosity of the diffusion pathway, keratin adsorption kinetics, stratum corneum (SC) hydration state, hair follicular transport, pH at the skin surface and within the SC layers, etc.) and drug/formulation-specific parameters (i.e., formulation type, ionization at the skin surface, lipophilicity, vehicle viscosity, etc.). In V16, an extensive database for the adult healthy Caucasian skin physiology is provided. In V17, it is planned that the paediatric, geriatric and Asian populations will be added to the healthy adult population. It is also the aim to provide psoriasis skin characteristics to simulate dermal drug absorption in disease states and the ability to model excipient and vehicle effects on drug liberation and skin permeation.

Pharmacodynamics Feedback

The custom pharmacodynamic (PD) Lua scripting module has been expanded, providing feedback of a PD response resulting in a change in gastric acid pH over time in the PBPK model simulation. This enables the simulation of the potential interaction between drugs and formulations with pH-dependent solubility and acid reducing agents. The effect of such changes on drug dissolution and absorption are dynamically accounted for over the whole simulation duration.

Expansion of Outputs and Reporting

Enhancement of the outputs to Excel include additional options such as: (i) for statistical analysis of simulation results: output of geometric mean and 90% confidence intervals for AUC, Cmax and their interaction ratios, output of median and geometric mean plasma concentration profiles, addition of summary statistics tables to all physiological data output sheets and (ii) to improve the format of graphs: output of semi- log concentration profiles, time in units of days, report style format.

New outputs for time variant fm for a PK profiles simulation and the steady state fractional contribution of uptake transporters and passive permeability to uptake from the systemic circulation for the permeability- limited liver model and mechanistic kidney models.

A powerful Simcyp Report Assistant tool has also been implemented as a Word plugin to facilitate the integration of outputs generated by Simcyp into a report. Features include the option to insert an automatically generated table of inputs for a compound, plasma concentration profiles and summary tables of pharmacokinetic parameters (eg, AUC, Cmax, t1/2, Cmin and their interaction ratios) presented for each trial and the total simulated population. Example report templates and sample method text are also provided as Word documents for use in generating a PBPK model report.

The option to output simulation results to a database has been added, This feature stores all time-based profiles, individualised population and compound data and certain calculated values (eg, AUC) and is required for use with the Simcyp Report Assistant. The database output can also be used to import previous simulation results and create the standard Excel output at a later date. This is particularly useful for slow running simulations.

Consolidation of the Absorption Physiological Population Databases

There are multiple enhancements and flexibilities added to the oral absorption models in V16. The single biggest addition is the Segregated Transit Model to the ADAM (Advanced Dissolution, Absorption and Metabolism) model. As part of the V16 wish list project we reviewed the GI tract transit time data from the literature; several thousand data points and more than 100 clinical study arms were used to derive the transit time data for stomach, small intestine and colon. The data clearly suggest that monolithic tablets, pellets, particles and fluid transit at different rates in GI tract. Also the relative transit rates of those entities can be different in different regions of GI tract (stomach, small intestine and colon).

There is also an impact of prandial state on transit through the stomach and small intestine while colon transit is strongly gender-dependent. Hence, a user-friendly and detailed segregated transit time model is implemented in V16. Moreover, there is also flexibility to select if only the ascending colon is responsible for colonic absorption or drug absorption is occurring throughout the colon.

In addition, the ability to model metabolism in the colon is incorporated in V16 with available enzyme abundance data from the literature. A mechanistic model to account for the impact of food viscosity on the rate of dissolution is also added where a meta-analysis of luminal viscosity in the fasted condition is obtained from the literature, and in fed conditions the viscosity of a meal is diluted over timebased on the existing fluid dynamics model. In V16, a static dilution effect is incorporated where the food viscosity reduces as the contents move distally from segment to segment. However, a fully dynamic model is ready for implementation in V17.

A number of usability options were added which facilitate mechanistic enhancements in future. A full review of the fluid dynamics model has been undertaken and will be implemented in V17 as some aspects such as effect of osmolarity on fluid secretion/absorption require further investigation. In V16 the ability to modify the basal fluid volumes of the GI tract is provided. Fed stomach pH can now be modified and visualised by the user on the population screen. The facility to incorporate user-defined absorption scale factors is provided in V16. The mechanistic model to calculate the pH at the surface of dissolving particle was introduced in V14 for acidic drugs. In V16, a facility to incorporate user-defined surface pH for any dissolving drug is provided where effect of luminal environment, excipients, etc., can be simulated if such information is available from experiments or independent calculations. Finally, where precipitation has been predicted by the simulator, users are now warned of this in the Excel outputs and users are directed to take appropriate action.

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