Version Comparison and Performance Verification of library compounds within the Simcyp Simulator

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Introduction

A new version of the Simcyp Simulator is released every year in order to accommodate new mathematical models and new scientific data collated to update population and compound databases. Rigorous testing as well as version comparisons of pharmacokinetic (PK) parameters and drug-drug interaction (DDI) parameters is required to allow quality assurance between versions of the Simcyp Simulator and as performance verification of the released library files (population and compounds).

Objectives

- To give a summarised version comparison between V16R1 and V17B64 using the V17 updated Japanese population library as an example.
- To give an overview of the performance verification for the 74 compound PBPK models (70 compounds) available within the Simcyp Simulator database (V17).

Methods

In V17 of the Simcyp Simulator the Japanese population has been updated after a review of available physiological data. The age distribution in the population has been modified using a new mathematical feature in V17 that was not available within V16, hence the age-distribution in the V16 and 17 populations are different.

For all simulations the Sim-Japanese Simcyp Population database was used with the following setting: age range 20 to 50 years and 50% of the population were female. To include individuals with a wide range of values for key physiological parameters, *i.e.* phenotype with high CV and low population frequency, a population of 1000 subjects was used. A simulation of 20 trials x 50 subjects was simulated for each Simcyp (Sim- and SV-) compound.

For each compound the performance of the simulated PK profile, *i.e.* clearance, t_{max}, c_{max}, AUC, V_{ss}, and drug-drug interaction parameters , *i.e.* AUC ratio and C_{max} ratio, was compared. For substrate compounds verification of the compounds fm was demonstrated and for inhibitor files inhibition/induction parameters were verified. The following best practise approaches were used in this exercise:

- ❑ Where possible verification was conducted with studies not used for building the files. If there is no other possibility this needs to be stated clearly.
- ❑ A matrix approach was used where possible with at least 3 independent studies used for performance verification.
- ❑ Each pathway/enzyme/transporter should have independent verification if possible
- ❑ Verification of the file for all pathways/enzymes/transporters should be done with the same file *i.e.* not making changes from scenario to scenario

Results / Discussion

Currently 84 compound summaries have been written (Figure 1), comparing over 200 clinical studies for PK verification and over 80 for DDI verification (Figure 2). For each study simulated concentration-time profiles are performed with matched population characteristics (*e.g.,* age, gender, phenotype).

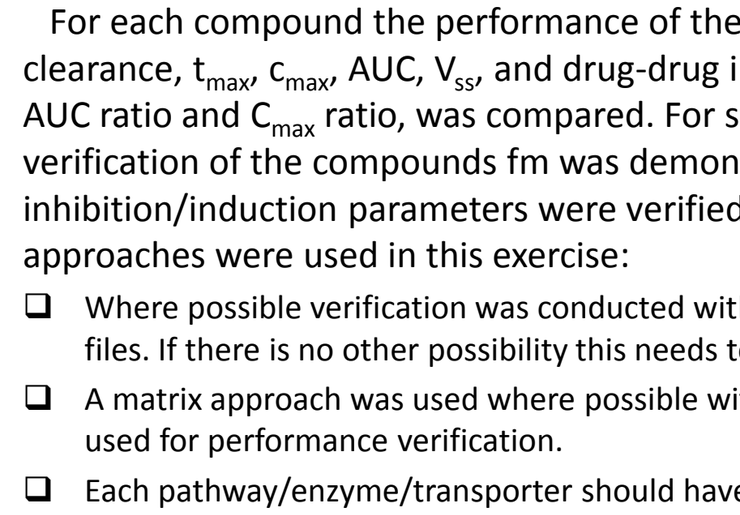

Figure 3 – Number of summaries completed and available to consortium members. In 2016/2017 'compound summary preparation' was part of the WishList #1 project.

In general, sufficient subjects should be simulated to recover population variability of key parameters and it is good practice to verify that the crucial input CV values (*e.g.* of the CYP pathway investigated) are propagated in the sample size of the simulated population.

Results / Discussion cont.

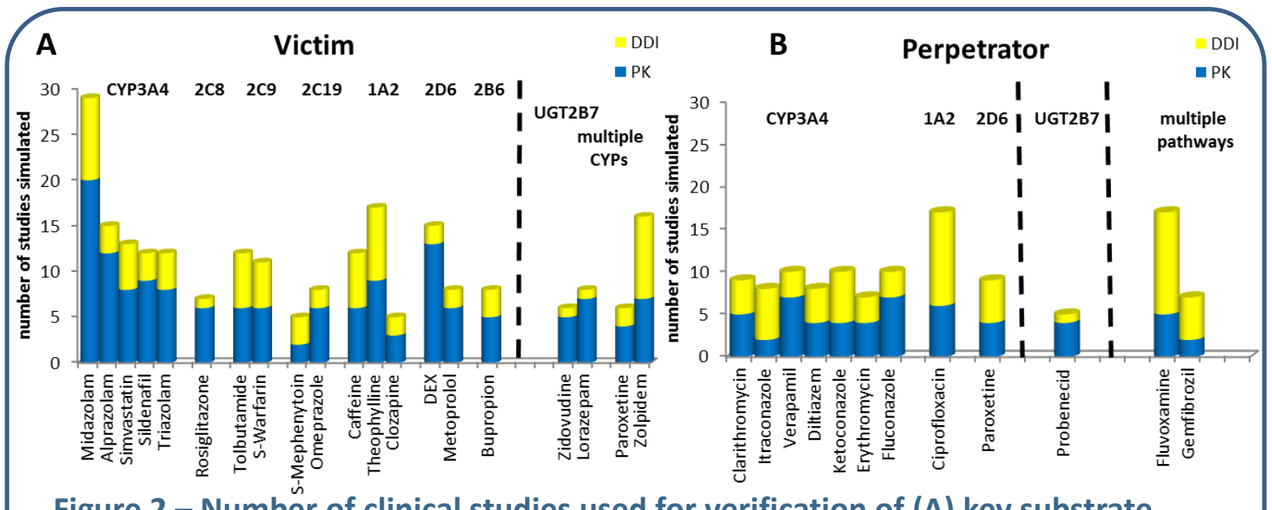

Figure 2 – Number of clinical studies used for verification of (A) key substrate and (B) key inhibitor files.

While for some enzymes sufficient substrate (fm 0.96 – 0.09) and inhibitor files (potent, moderate and poor; selective and broad) are available (CYP3A, Figure 3A) for others this may not be the case. Similarly for substrates it is often not possible to perform verification with selective inhibitors for minor pathways (Figure 3B).

Comparisons to observed data need to be performed carefully, considering analytical issues (*e.g.* dextromethorphan, parent drug *vs.* parent + conjugates, blood or plasma concentration), but also the time of the measurements ($AUC_{0\text{-}24h}$, $AUC_{0\text{-}Inf}$).

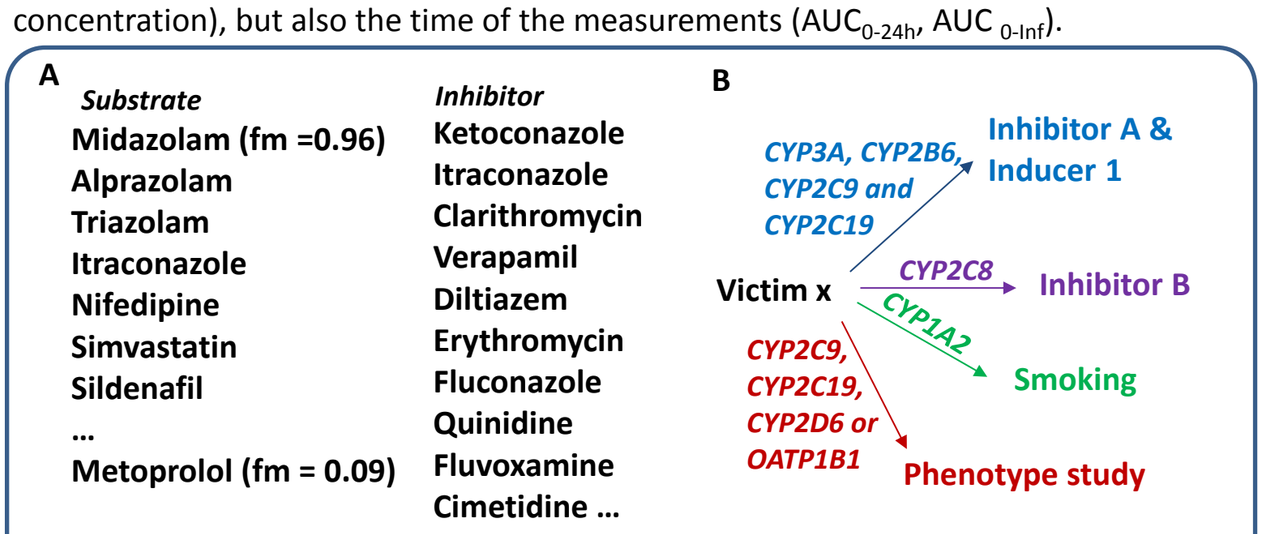

Figure 3 – (A) details on the substrate/inhibitor for the CYP3A4 matrix (B) detail on a substrate compound with multiple pathways

The library files within the Simcyp Simulator are verified with the models selected in the saved file, *i.e.* full PBPK and ADAM in solution. However, all compound files can be run in combination. *A victim utilizing the ADAM model can be combined with a perpetrator using the first order absorption model. A victim using a full-PBPK model can be combined with a perpetrator using the minimal PBPK. Therefore, it is not necessary to develop a compound as a minimal as well as a full PBPK model, however to utilize some more advanced models like the permeability-limited liver (PerL) model or the mechanistic kidney model (Mech KiM) it is necessary to use a full PBPK model that accounts for ionization and a reliable determination of the driving concentration at the transporter binding site. Some files within the Simcyp database have been verified as first order and ADAM files, e.g. probenecid and nifedipine (V17). The default file will be the file requiring the least computational power.*

Diagnostic plots for simulated CL_{iv}, CL_{po}, fa, F_G,F_H and V_{ss} in the PK-Parameter setting and $t_{max,}$ c_{max}, AUC and CL (Dose/AUC) in the PK-Profiles setting are always compared between versions. Figure 4 gives an example of the c_{max} comparison between version V16R1 and V17B64 for the updated V17 Japanese population.

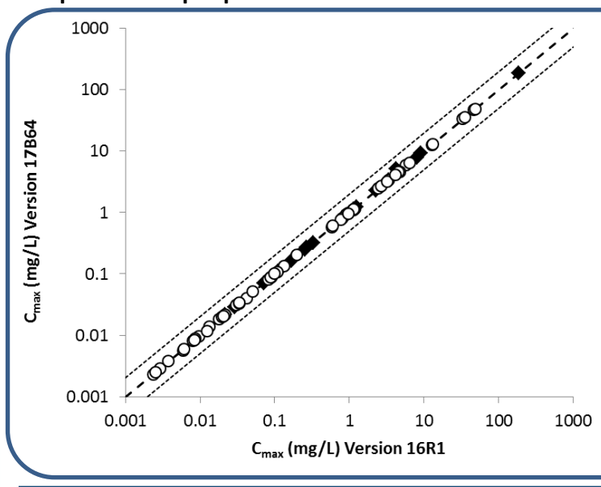

Figure 4 - Mean simulated C_{max} for the 20 Sim- (black squares) and 54 SV-compound files (white circles) using the Simcyp Simulator Version 16 Release 1 or Version 17 Build 64 in the Sim-Japanese population. The dashed line represents unity and the dotted lines represent a 2-fold difference.

Conclusion

- Version Comparisons should be based on a relevant size of population and reflect relevant updates in the model as well as the input parameters.
- 84 performance verification documents for victim and perpetrator files (52 compounds plus 8 metabolites) are currently available and freely shared with the consortium members.