RESPONSE DOCUMENT

INITIAL QUALIFICATION PROCEDURE –
EXTENSION TO THIRD LIST OF ISSUES –
SIMCYP SIMULATOR AND REQUEST FOR ADDITIONAL INFORMATION FROM SIMCYP
ITEMS 1 & 5

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Third List of Issues – additional information

ITEM 1

Simcyp Good Practice Manual: Please summarise in a table the required conditions for a new drug to ensure Simcyp prediction performance consistent with the qualification performance in each COU1-3.

RESPONSE: We have provided 3 tables below, one for each COU. Although the content of the 3 tables is similar, there are subtle differences that are relevant to each COU. We have stated that *in vitro* (industry standard) and clinical data are required but have focused more on the model development and verification steps than providing details of assay requirements for individual *in vitro* parameters.

In terms of what reflects a good/accurate fit, it is difficult to say. As we have indicated many times, an offset of 1.5-fold may be acceptable for one drug but not for another especially if multiple parameters are being optimised. Therefore, we have tried to indicate how we would do the model development step by step. We don't think this is the appropriate place to include a statement on the therapeutic window, but this should be stated when referencing the tables.

Do you foresee cases where the Simcyp compound and inhibitors would need to be further optimized when applying the Simcyp Simulator for DDI prediction and how will this affect the qualified predictive performance?

RESPONSE: Given that the compound files have been tested against an array of substrates (range in sensitivity) and inhibitors (range of strength) we don't anticipate that there should be any need for further optimisation. Even for CYP enzymes where smaller datasets are available, the performance of the compound files has been reasonably good.

	COU1: Data requirements and good practice steps for development and verification of a PBPK model for a new drug
COU 1	**The Simcyp Simulator (V19 R1) can be used to predict the effects of weak and moderate CYP inhibitors on the exposure of a drug administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a strong CYP inhibitor has been conducted (and used to verify the fmCYP).**
In vitro data	Physicochemical properties, solubility data (for complex absorption), permeability data, plasma protein and blood binding, *in vitro* metabolism data (including reaction phenotyping) and inhibition data (if relevant) are required and should be generated using industry standard protocols. Metabolism and inhibition data should be corrected for non-specific microsomal binding (measured or predicted) at the relevant microsomal protein concentration (final incubation concentration).
Clinical data	Pharmacokinetic studies including single (SD) and multiple dosing (MD) in healthy subjects over a range of doses under fasting conditions are required. A clinical study with a strong CYP inhibitor is also required.
Simulations	To ensure that the characteristics of the virtual subjects are matched closely to those of the subjects in the clinical studies, age range, ethnicity and sex ratios should be replicated in at least 10 simulated trials based on the number of subjects in each clinical trial. In addition, the dosage regimens used in the clinical studies should be replicated.
Model development	Initially, simulations based on *in vitro* data alone should be performed to determine whether the predicted PK parameters and concentration-time profiles are consistent with clinical datasets (SD and MD). If available, model development should be performed initially using intravenous data with a focus on the distribution (D) and elimination (E) parameters. Thereafter, absorption (A) related parameters (permeability and solubility) should be introduced into the PBPK model to predict PK parameters and plasma concentration-time profiles following oral administration. Model selection for ADE processes will be dependent on the characteristics of the compound itself.

	At each stage, optimisation of relevant parameters should be performed using clinical data, if necessary, to ensure accurate recovery of observed data (PK parameters and the shape of the concentration-time profile). For example, metabolic intrinsic clearance data should be scaled to accurately capture clearance. The volume of distribution may also need to be optimised via the Kp scalar to accurately predict the observed value if IV data are available.
DDI	After accurate recovery of the PK parameters and concentration-time profiles, the clinical DDI should be simulated using the Simcyp Simulator file for the strong inhibitor. The model for the strong CYP inhibitor should be verified for the dosage regimen used in the clinical study, especially if there is non-linearity associated with the disposition of the drug. If the degree of interaction is not predicted accurately, the contribution of the primary CYP enzyme (fmCYP) involved in the metabolism should be optimised to capture the observed DDI with the strong CYP inhibitor. Ideally, both predicted changes in C_{max} and AUC should be captured by the model.
Model verification	If available, independent datasets (not used for optimisation) should be used to verify the performance of the model with respect to single and multiple dosing and the DDI (fmCYP).
Model application	At this point, the model is considered to be verified and can be used for assessment of the effects of moderate and weak inhibitors (Simcyp Simulator files) of the CYP under investigation on the exposure of the new drug.

	COU2: Data requirements and good practice steps for development and verification of a PBPK model for a new drug
COU 2	**The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated inhibitory effect of a drug on the exposure of other CYP substrates administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the competitive inhibition effect in vivo).**
In vitro data	Physicochemical properties, solubility data (for complex absorption), permeability data, plasma protein and blood binding, *in vitro* metabolism data (including reaction phenotyping) and inhibition data are required and should be generated using industry standard

Clinical data	protocols. Metabolism and inhibition data should be corrected for non-specific microsomal binding (measured or predicted) at the relevant microsomal protein concentration (final incubation concentration). Pharmacokinetic studies including single (SD) and multiple dosing (MD) in healthy subjects over a range of doses under fasting conditions are required.
Simulations	To ensure that the characteristics of the virtual subjects are matched closely to those of the subjects in the clinical studies, age range, ethnicity and sex ratios should be replicated in at least 10 simulated trials based on the number of subjects in each clinical trial. In addition, the dosage regimens used in the clinical studies should be replicated.
Model development	Initially, simulations based on *in vitro* data alone should be performed to determine whether the predicted PK parameters and concentration-time profiles are consistent with clinical datasets (SD and MD). If available, model development should be performed initially using intravenous data with a focus on the distribution (D) and elimination (E) parameters. Thereafter, absorption (A) related parameters (permeability and solubility) should be introduced into the PBPK model to predict PK parameters and plasma concentration-time profiles following oral administration. Model selection for ADE processes will be dependent on the characteristics of the compound itself. At each stage, optimisation of relevant parameters should be performed using clinical data, if necessary, to ensure accurate recovery of observed data (PK parameters and the shape of the concentration-time profile). For example, metabolic intrinsic clearance data should be scaled to accurately capture clearance. The volume of distribution may also need to be optimised via the Kp scalar to accurately predict the observed value if IV data are available.
DDI	After accurate recovery of the PK parameters and concentration-time profiles, the DDI should be simulated using the Simcyp Simulator file for the sensitive CYP substrate used in the clinical DDI. The model for the sensitive CYP substrate should be verified for the dosage regimen used in the clinical study, especially if there is non-linearity associated with the disposition of the drug.

	If the degree of interaction is not predicted accurately, the *in-vitro* determined Ki value for the new drug should be optimised to capture the observed DDI with the sensitive CYP substrate. Ideally, both predicted changes in C_{max} and AUC should be captured by the model.
Model verification	If available, independent datasets (not used for optimisation) should be used to verify the performance of the model with respect to single and multiple dosing and the DDI (Ki).
Model application	At this point, the model is considered to be verified and can be used for assessment of the effects of the new drug on less sensitive substrates (Simcyp Simulator files) of the CYP under investigation.

	COU3: Data requirements and good practice steps for development and verification of a PBPK model for a new drug
COU 3	**The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated MBI effect of a drug on the exposure of other CYP substrates administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the MBI effect in vivo).**
In vitro data	Physicochemical properties, solubility data (for complex absorption), permeability data, plasma protein and blood binding, *in vitro* metabolism data (including reaction phenotyping) and inhibition data are required and should be generated using industry standard protocols. Metabolism and inhibition data should be corrected for non-specific microsomal binding (measured or predicted) at the relevant microsomal protein concentration (final incubation concentration).
Clinical data	Pharmacokinetic studies including single (SD) and multiple dosing (MD) in healthy subjects over a range of doses under fasting conditions are required.
Simulations	To ensure that the characteristics of the virtual subjects are matched closely to those of the subjects in the clinical studies, age range, ethnicity and sex ratios should be replicated in at least 10 simulated trials based on the number of subjects in each clinical trial. In addition, the dosage regimens used in the clinical studies should be replicated.
Model development	Initially, simulations based on *in vitro* data alone should be performed to determine whether the predicted PK parameters and concentration-time profiles are consistent with clinical datasets (SD and MD).

	If available, model development should be performed initially using intravenous data with a focus on the distribution (D) and elimination (E) parameters. Thereafter, absorption (A) related parameters (permeability and solubility) should be introduced into the PBPK model to predict PK parameters and plasma concentration-time profiles following oral administration. Model selection for ADE processes will be dependent on the characteristics of the compound itself. At each stage, optimisation of relevant parameters should be performed using clinical data, if necessary, to ensure accurate recovery of observed data (PK parameters and the shape of the concentration-time profile). For example, metabolic intrinsic clearance data should be scaled to accurately capture clearance. The volume of distribution may also need to be optimised via the Kp scalar to accurately predict the observed value if IV data are available.
DDI	After accurate recovery of the PK parameters and concentration-time profiles, the DDI should be simulated using the Simcyp file for the sensitive CYP substrate used in the clinical DDI. The model for the sensitive CYP substrate should be verified for the dosage regimen used in the clinical study, especially if there is non-linearity associated with the disposition of the drug. If the degree of interaction is not predicted accurately, the in-vitro determined k_{inact} value for the new drug should be optimised to capture the observed DDI with the sensitive CYP substrate. Ideally, both predicted changes in C_{max} and AUC should be captured by the model. If autoinhibition is relevant for the new drug, MD data should also be used to optimise the inactivation parameters.
Model verification	If available, independent datasets (not used for optimisation) should be used to verify the performance of the model with respect to single and multiple dosing and the DDI (k_{inact} or K_I).
Model application	At this point, the model is considered to be verified and can be used for assessment of the effects of the new drug on less sensitive substrates (Simcyp Simulator files) of the CYP under investigation.

ITEM 5

Update the compound files with:

- ***Literature references on the source of all parameters that have been optimized, to facilitate assessment of the adequacy of the compound files, and enable an easy cross-check that the studies used for optimization have not been used for evaluation of model performance.***
- ***In addition, the tables with observed and simulated AUC and Cmax-ratios presented in each compound file should be updated to include the studies in the qualification dataset.***
- ***In the tables with observed and simulated AUC and Cmax-ratios presented in each compound file the studies used for optimization should be clearly indicated, or preferably be placed under a separate heading to clarify that these datasets were used to build the interaction model and that the predictions shown in that part of the table are not independent.***
- ***For all PK-curves (data points and predicted curves) shown in the compound files, it should be clarified whether the study data shown in the plots come from studies used to optimise the drug parameters or not. Optimally, data from independent studies should be shown.***
- ***Please initially submit the updated file for a single compound (e.g. Fluvoxamine) to ensure that the information and format meet the Agency's expectations before expanding to all compound files.***

RESPONSE: We have provided a compound file summary "FEB2025-V19_Fluvoxamine-summary" for your review. We have tried to ensure that each of the above conditions have been met. We have the following specific comments:

- In the compound file summary, prior to presentation of the predicted versus observed DDIs, there are separate sections for absorption, distribution and elimination (ADE). Within each section, if any optimisation has been performed to capture the concentration-time profiles, this has been described and the source reference has been provided.
- In the table of input parameters (Table 11), the source has been cited and it is clearly indicated which of the ADE parameters have been optimised and the relevant ADE section describing this has been indicated.

- Where possible, we have tried to show predicted versus observed profiles based on clinical studies that were not used for optimisation of any parameters.
- None of the studies that were used to optimise the ADE parameters (and hence the profiles) overlapped with the clinical DDI studies.
- For the interaction parameters of fluvoxamine (CYP Ki values), a single DDI study was used to optimise the CYP1A2 Ki value (Culm Merdek et al., 2005). This is clearly stated in the DDI tables (Tables 1 and 2) and indicated in the table of input parameters (Table 11). This study was not included in the DDI qualification matrix.
- For the other enzymes, meta-analyses of available *in vitro* Ki values were performed. The resultant Ki values were reduced by 10-fold; this scalar was derived in the clinical study by Yao et al. (2001) to account for the differential between the performance of *in vitro* and *in vivo* Ki values. The above is indicated in the text and Table 11. This study was not used to assess the performance of fluvoxamine for DDI studies involving CYP2C9, CYP2C19, CYP2D6 or CYP3A4 i.e. it is not part of the DDI qualification matrix for these enzymes (Tables, 3,4,5,6,7,8,9,10).
- For each enzyme, all of the studies that were included in the qualification matrix have now been included in the respective DDI tables.