1 August 2025
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Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft Qualification Opinion for Simcyp Simulator

Comments from:

Name of organisation or individual
1. Novartis Europharm Limited
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1. General comments

General statement

The Agency acknowledges and appreciates the comments provided. As a general clarification, the objective of this qualification is not to serve as a comprehensive regulatory guidance or a good practice document for PBPK modelling in DDI predictions. Rather, it aims to characterize the predictive performance of Simcyp V19 within Contexts of Use (CoU) 1, 2, and 3, and within a specifically defined qualification design space, as outlined by the in-scope and out-of-scope criteria, compound files and good practice recommendations. Consequently, while several comments are highly relevant to the broader application of PBPK in DDI prediction, they fall outside the actionable scope of this qualification document. Such topics may be considered in future qualification procedures or addressed on a case-by-case basis during regulatory submissions.

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
58-73	2	Given the specific scope of the qualification document, using the Simcyp software V19R1, CYP-mediated competitive inhibition and mechanism-based inhibition via select CYP enzymes, in Caucasian healthy subjects in the fasted state, please consider elaborating on the applicability of the qualification document, expectations, and the suggested good practices if the specific clinical scenario falls outside the qualification space.	No change. The qualification design space is clearly defined by the in scope and out of scope list.
60-63	2	The document refers to a Northern European Caucasian population for simulations. It would be beneficial to expand on the applicability of the model beyond the Northern European Caucasian population or clarify limitations in	No change. The qualification design space is clearly defined by the in scope and out of scope list.

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
		extrapolating to other populations within the simulator.	
65	2	Prediction of average GMR for AUC and Cmax are mentioned within scope. Please consider preferably adding or providing an explanation on why Tmax and half-life (t_half) were not included in the qualification.	No change. Please refer to the general statement at the beginning of this document.
79-80	2	This software qualification describes very specific CoU where unbound concentrations of portal vein are used as the driving force in gut interactions (first-order oral absorption models). Please clarify whether the Simcyp models built using mechanistic absorption models (i.e., ADAM and M-ADAM), which use enterocyte concentrations in the interaction predictions are out of the scope of this qualification.	Specified that enterocyte concentrations are used in the case of ADAM model. Please refer to the general statement at the beginning of this document.
199-201 (table 1)	2	As mentioned under the Drug model development sub-heading - "Usually, AUC and Cmax of predicted values after single and multiple doses are expected to be within 1.25 of the observed values." Please consider loosening the acceptance criterion in certain contexts to 2-fold, given the appropriate justification and intended use of the model.	No change. Please refer to the general statement at the beginning of this document.
199-201 (table 1)	2	As mentioned under the Model optimisation or DDI prediction sub-heading - "Optimization of	No change. Please refer to the general statement at the beginning of this document.

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
		the fm for one enzyme impacts the fm for the other enzymes. If fm needs to be optimised, for DDI prediction sub-heading that fm should preferably be validated with a DDI study for another CYP enzyme." Please consider elaborating on the requirement depending on the context of use to validate each individual fm using alternative approaches (e.g., IVIVE, sensitivity analysis), other than through a DDI study.	
199-201 (table 1)	2	Mentioned under the Model optimisation for DDI prediction sub-heading - "Consequences for the Ki values of the other CYP enzymes should be discussed." This happens quite often when a Ki is optimized for an enzyme but not necessarily the impact is evaluated for other enzymes, please provide your views on applying sensitivity analysis to help resolve this concern.	Added that sensitivity analyses may resolve this issue.
379-380	2	Please consider providing a summary of the discussed shortcomings of the proposed performance metrics and acceptance criteria by the applicant during the March '24 SAWP meeting for reference.	No change. The shortcoming of the proposed performance metrics and acceptance criteria are discussed in the scientific discussion and in the annexes.
462-472	2	Please confirm the accessibility to links provided for Annexes 2 and 3.	No change. Links are working.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
Line 66	1	**Comment**: According to the Context Of Use, induction is not in scope of the qualification. **Proposed change (**if any): Add "Enzyme Induction" to the "Out of Scope" list.	This is made more explicit in the out-of-scope list.
Line 66	1	**Comment:** While cytochrome P450 (CYP) enzymes continue to develop throughout childhood, the extent of their potential decline in activity among older adults remains poorly understood. Given the importance of accurately quantifying enzyme abundance and activity to assess drug interaction potential, establishing clear guidance on the appropriate age ranges for such assessments would be beneficial. **Proposed change (if any):** Proposal to specify age-range and weight-range for which the qualification applies.	Adult population was specified in the scope list.
Line 66	1	**Comment**: CYP phenotyping has been mentioned but not specifically addressed in the assessment of the framework. Also, CYP2C9 is mentioned by not specific genotypes.	Added: The phenotypic classification of subjects for polymorphic CYP enzymes in the DDI qualification matrix is unclear. No statements can be made on the performance of the platform to predict DDIs in specific CYP phenotypic groups.

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
		Proposed change (if any): Proposal to specify if any CYP phenotypes are in scope. Also specify if any recommendations for handling CYP2C9 genotypes.	
Page 8, Table 1, Drug model development	1	**Comment:** In addition to mass balance study, Data from FIH SAD/MAD may also inform renal clearance. **Proposed change (if any):** Data from the mass balance study may inform renal clearance and in vivo fm for the various enzymes. Additionally, Data from FIH SAD/MAD may also inform renal clearance.	No change. It is already mentioned that Optimisation of relevant drug model parameters can be performed using clinical data, if necessary, to ensure accurate recovery of observed data (PK parameters and the shape of the concentration-time profile).
Line 30	1	**Comment:** Text mistake correction. **Proposed change (if any):** Replace without repetition: "To predict the average CYP-mediated MBI effect."	Corrected.
Line 189	1	**Comment**: Enzyme induction is out of scope of this qualification opinion. **Proposed change (if any):** State clearly that qualification does not cover induction (not only complex DDIs like inhibition/induction).	This was further specified in the out-of-scope list.

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
Page 8, Table 1, Drug model development	1	**Comment:** Good practice for model development is not directly related to platform qualification. Recommendations given in Draft qualification opinion are more detailed than in the EMA Guideline on the reporting of PBPK modeling and simulation. **Proposed change (if any):** We would welcome a specification on whether expectation to have predicted AUC and Cmax within 1.25 of the observed data applies only as recommendation during model building/optimization or is it as well expected performance for model verification when used for regulatory purpose. This requirement is not reflected in the EMA Guideline on the reporting of PBPK modeling and simulation.	No change. Please refer to the general statement at the beginning of this document.
Page 8, Table 1, Model optimization for DDI	1	**Comment:** Building on from above comment on Table 1. **Proposed change (if any):** We would welcome the specification of whether stringent requirement of AUC and/or Cmax Observed/predicted ratio ≤ 1.25 applies only as recommendation for Simcyp model optimization. This requirement is not reflected in the EMA Guideline on the reporting of PBPK modeling and simulation.	No change. Please refer to the general statement at the beginning of this document.

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
Line 65	1	**Comment:** proposed correction. **Proposed change (if any):** Prediction of ~~average~~ GMR for AUC and Cmax.	Corrected
Line 128	1	**Comment:** An aligned terminology would be welcomed throughout the manuscript. **Proposed change (if any):** Figure 1. Credible interval for ~~true~~ observed ~~AUCGMR~~ GMR AUC vs predicted ~~AUCGMR~~ GMR AUC	Corrected
Page 8, Table 1	1	**Comment:** use of endogenous biomarker is not mentioned. **Proposed change (if any):** Add in the "Out of scope" (page 3).	No change. It is evident that no endogenous biomarkers have been evaluated in this analysis.
Page 8, Table 1, Model optimization for DDi prediction	1	**Comment:** Use of Guest criteria limits to evaluate the prediction of interactions is not mentioned (Guest et al., 2011). **Proposed change (if any):** Suggestion to clarify the use of Guest criteria within specified COU.	No change. Please refer to the general statement at the beginning of this document.

Line number(s) of the relevant text	Stakeholder number	General comment (if any)	Outcome (if applicable)
Page 8, Table 1 Model optimization for DDi prediction	1	**Comment:** COU3, use of parameter sensitivity analysis (PSA) is not mentioned if KI and kinact need to be optimized	No change. Please refer to the general statement at the beginning of this document.
Page 8, Table 1 Model optimization for DDi prediction	1	**Comment:** IN COU3, it is not clear why only optimization of Kinact is recommended as a first step and not KI. For KI optimization DDI data from various dosing regimens are required, however clinical DDI studies are done using one dosing regimen. **Proposed change (if any):** Suggestion to clarify how optimization of Kinact and KI can be performed taking into consideration standard clinical DDI studies design.	The text was updated. Please refer to the general statement at the beginning of this document.