Response Document

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We have replied to each of your comments below to indicate how we have addressed the comment and where the relevant information can be found.

The EMA team has the following comments you may wish to implement to improve the dossier

Context of use

Please specify which substrates, inhibitors, populations, DDIs are in the scope of each context of use, i.e clarify that the context of use refers to healthy subjects, oral DDI studies under fasted conditions. Also it should be clear that no complex interactions are included in the qualification e.g. enzymes/transporters and inhibitor/inducer. Are there any additional characteristics that need to be prespecified to define the space where the CoU applies?

Response: The COU have been updated accordingly in the revised Briefing Document.

It is understood that the 4th CoU is to use PBPK to waive a DDI study. Please update the wording accordingly. Specify more the conditions for this context of use. E.g. what do you mean that the change in exposure and the inhibitory potency of the drug fall in the range of the qualification dataset? What parameters should be used in the sensitivity analysis and what range should be tested to conclude that indeed no interaction is to be expected? Are these conditions enough to waive a clinical DDI study?

Response: The COU has been revised accordingly in the revised Briefing Document.

Consider applying the credibility matrix to the different CoUs proposed: https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12669

Version control

The qualification is version specific, but the QT is open to discuss the DDI matrix, methods, requirements and process to qualify new versions in the future.

Response: Thank you for providing this information.

Selection of DDI matrix

Provide the rationale as why these substrates, inhibitors and in vivo DDI studies have been selected e.g. there are many more DDI studies with caffeine and fluvoxamine.

For some of the CYP enzymes there seem very few substrates and inhibitors. In particular, the applicant should clarify the low number of TDI inhibitors for all enzymes except CYP3A4.

The EMA PBPK guideline does not only recommend a larger number of substrates and inhibitors but also substrates with varying fractions metabolised.

Response: One of the biggest issues we had was finding enough relevant substrates and inhibitors for all enzymes. Even though a large number of studies are often identified in the UOW DIDB, when you start drilling down and looking at the individual studies and the substrate/inhibitor pairs that can be used to form a matrix, it is not always possible. For example, there are a large number of CYP2C8 studies but when you look at the published studies, only gemfibrozil or trimethoprim have been used against relevant substrates. This means that if the clinical study is used to verify the fmCYP2C8 it can no longer be used for verification. Thus, taking the UOW at face value without carefully going through it is not always appropriate.

Table 3. AUC_i/AUC values obtained from the literature

	AUC_i/AUC[a]						
Inhibitor (mg/day)	CER	FLV	MTK	PIO	REP	ROS	references
Cimetidine (1000-1200 mg)	1.0				1.2		[c]
Gemfibrozil (1200 mg)[b]	5.6	1.1	4.5	3.3	7.7	2.3	[d]
Itraconazole (100-200 mg)	1.3	0.9		1.1	1.4		[e]
Montelukast (10 mg)				1.0	1.0	1.0	[f]
Telithromycin (800 mg)			1.0		1.8		[g]
Trimethoprim (320-400 mg)				1.4	1.6	1.4	[h]

[a]Abbreviations: Cerivastatin (CER); Fluvastatin (FLV); Montelukast (MTK); Pioglitazone (PIO); Repaglinide (REP); Rosiglitazone (ROS)
[b] Gemfibrozil glucuronide is a time-dependent inactivator of CYP2C8
[c] (Muck et al., 1997; Hatorp and Thomsen, 2000)
[d] (Spence et al., 1995; Backman et al., 2002; Niemi et al., 2003a; Niemi et al., 2003b; Niemi et al., 2004a; Deng et al., 2005; Jaakkola et al., 2005; Tornio et al., 2008a; Karonen et al., 2010)
[e] (Kivisto et al., 1998; Mazzu et al., 2000; Niemi et al., 2003b; Jaakkola et al., 2005)
[f] (Jaakkola et al., 2006; Kajosaari et al., 2006; Kim et al., 2007)
[g] (Kajosaari et al., 2006)
[h] (Niemi et al., 2004a; Niemi et al., 2004b; Hruska et al., 2005; Tornio et al., 2008b)

For the qualification datasets It is also important not only to have positive DDIs but also have enough 'negative' DDI studies. So that an overview can be made for true negatives, false negatives, true positives, and false positives.

Response: We have provided a report based on a preliminary analysis for the negative CYP DDIS that was put together over the past few weeks. It provides an overview of the true negatives, false negatives, true positives, and false positives.

Please provide a summary of (i) the datasets extracted from the University of Washington Drug Interaction DataBase (incl. literature references), (ii) the (parts of the) datasets from the UoW DIDB that were used for fine-tuning the compound libraries and (iii) the (parts of the) datasets from the UoW DIDB that were used for evaluating the predictive performance (and hence are included in de DDI matrix).

The Applicant during the preparatory meeting indicated that they will include more information on the DDI matrix selection process.

Response: We have provided a slide deck indicating how the DDI matrix was derived. This has also been discussed in more detail in the briefing document. We have also provided relevant UOW DIDB searches that were performed.

Request for additional information

Please provide the full text literature references.

Response: We have provided all references for the DDI studies.

Upload workspaces for the different simulation scenarios.

Response: We have provided all of the workspaces.

Please provide access to equations for mathematical model structure verification (e.g. in matlab). Visual overview/figure of model structure would be helpful. Especially for ADAM model and permeability limited liver model (in case the latter is used). *During the preparatory meeting there was a debate on whether the code should be made available in some format. This will be confirmed during the qualification. In any case the equations are available in the literature, and full text references will be provided.*

Response: We have provided code in Matlab that allows access to DDI simulations. This can be found in the Folder named "Code" that will be uploaded to sharepoint.

@Upload the DDI matrix datasets from the university of Washington used for model qualification.

Upload the scripts used for the evaluation of predictive performance of Simcyp in a format/framework that allows EMA to re-run the analysis conducted by SimCyp.

Response: We have provided all excel files that will allow you to repeat the analysis.

Clinical DDI studies may have been used to optimize model parameters for some of the chosen inhibitors (e.g. Ki, Kinact) and substrates (e.g. fm), and subsequently verified using an independent clinical study if available. For each compound file where a parameter optimization was implemented, please provide information on if independent clinical studies were available (and if so, how many), along with appropriate tables and figures of the independent verification.

Response: Please see UOW slide deck and the briefing document that has been updated to provide details on this.

In many instances chosen pairs of inhibitors and substrates are not reflecting solely drug-drug interaction taking place via one single CYP enzyme. Instead, interaction can occur simultaneously via multiple enzymes and/or transporters. For example, interaction between clarithromycin (perpetrator) and repaglinide (victim) is presented by the Applicant as an example of CYP3A4 inhibition, while clarithromycin is also known as an OATP1B1/3 clinical inhibitor (FDA clinical inhibitor) and repaglinide as a clinical substrate of OATP1B1/3 (FDA clinical substrate). The same problem might be relevant for enzyme inhibitors affecting P-gp simultaneously. Therefore, the Applicant should present a tabular overview of all chosen pairs of inhibitors + substrates from the selected DDI studies, which should also include information about all reported additional interaction mechanisms for each pair of substances. Moreover, it should also be specified in the same table whether these additional interaction mechanisms were taken into account (i.e., implemented in the Simcyp simulator V19 R1) for the purpose of the present platform qualification.

Response: We have now included this table in Appendix 4 of the briefing document.