RESPONSE DOCUMENT

SIMCYP V19 MODEL-BASED BIAS AND UNCERTAINTY ANALYSES FOR *AUC* AND C_{max}, FINAL MODEL

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Introduction

This report documents the results of the final model of bias and imprecision applied to the Certara Simcyp Simulator®. A conceptual representation of the model is shown in Figure 1. It uses a mix of stratification (by inhibition mechanism) and hierarchical modelling (for between-subject variability), see Figure 2 for a graph of its assumed statistical dependencies. As a reminder, see Figure 19 in the Appendix for the directed acrylic graph representation of the initial submitted model (model A, "EMA m201.stan"). This final model, which we hereafter call "model F", is in a sense minimal. It has been coded using the *R* package RStan (the corresponding scripts are given in Appendix). Its exact structure is detailed in the next sub-section.

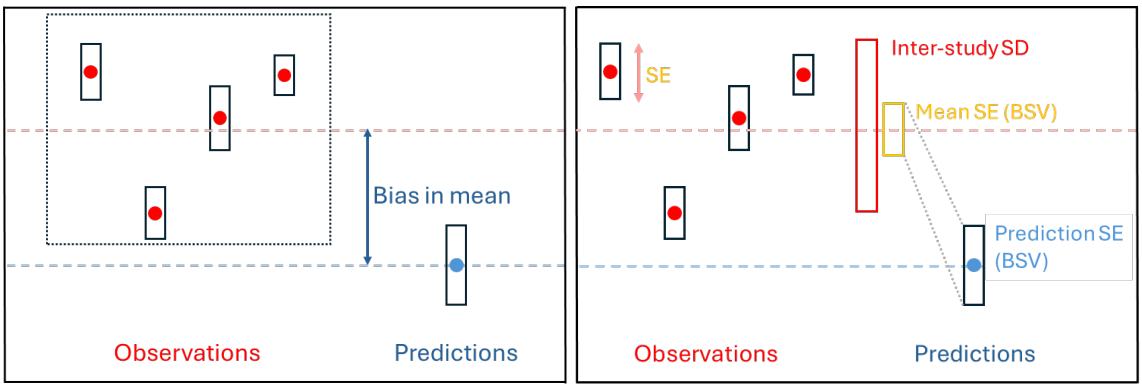

Figure 1: Schematic representation of the conceptual model. Left: Mean bias between observed and predicted geometric mean ratios. Right: The different variabilities and uncertainties studied; Observed and predicted between-subject variance (BSV) may differ by a factor to estimate (BSV bias); Inter-study variability can also be estimated, and it lumps in fact inter-study variability and potential prediction imprecision.

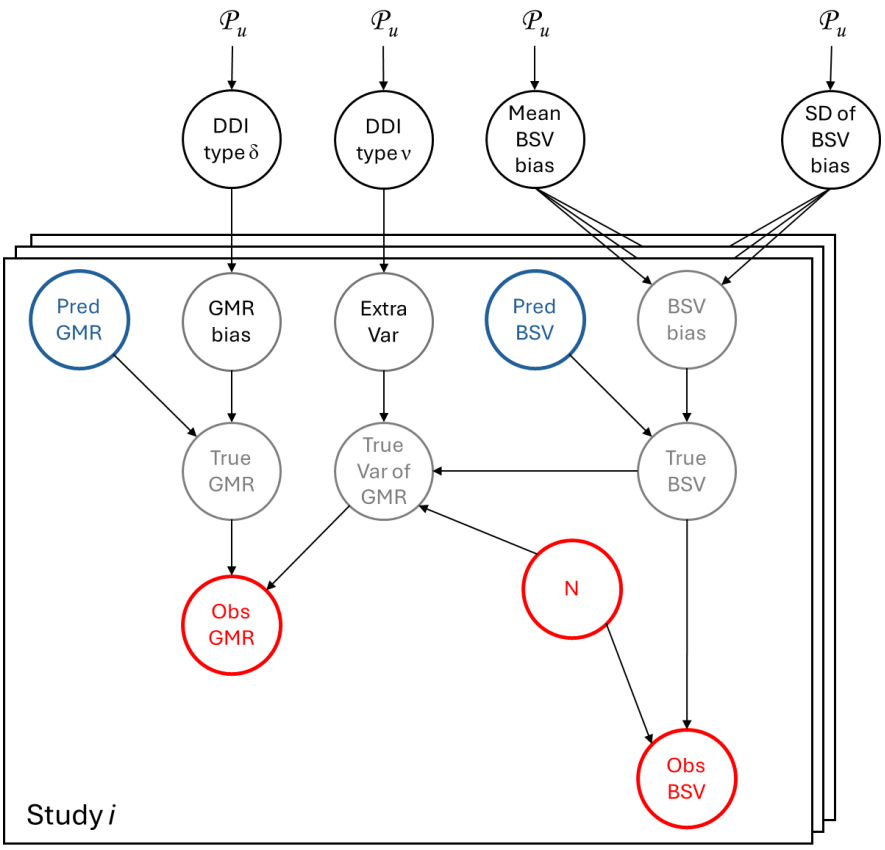

Figure 2: Directed acyclic graph representations of the final model F dependencies between variables and parameters. Literature data are in red; Simcyp® predictions in blue; Latent variables in grey; Estimands in black.

Final statistical bias and imprecision model (model F)

The GMR observed in study i (out of $N_{studies}$) is assumed to be lognormally distributed around a true GMR ($logGMR_i$, in log-space), with true standard deviation $\sigma_{GMR,i}$ (in log-space):

$$GMR_{i,obs} \sim \mathcal{LN}\left(logGMR_i, \sigma_{GMR,i}\right) \tag{1}$$

The true GMR is assumed equal to the Simcyp-predicted value, $GMR_{i,pred}$, corrected by a study-specific bias $\beta_{GMR,i}$:

$$logGMR_i = \log\left(GMR_{i,pred}\right) + \beta_{GMR,i} \tag{2}$$

The bias for study i depends on the type of interaction occurring (competitive *vs*. mechanism-based):

$$\begin{aligned} \beta_{GMR,i} &= \delta_{GMR,1} \text{ if } \mathbb{I}_{inh_i} = 1 \\ \beta_{GMR,i} &= \delta_{GMR,2} \text{ if } \mathbb{I}_{inh_i} = 2 \end{aligned} \tag{3}$$

Parameters $\delta_{GMR,1}$ and $\delta_{GMR,2}$ measure respectively the bias affecting predictions of competitive inhibition DDI studies or mechanism-based inhibition DDI studies. $\mathbb{I}_{inh_i}$ is an indicator function taking the value 1 if study *i* examined a competitive inhibition, and the value 2 in the case of a mechanism-based inhibition.

The true variance in log-space of $GMR_{i,obs}$, $\sigma^2_{GMR,i}$, is assumed to be equal to the sum of between-study variance, $\sigma^2_{stu,i}$ (which is assumed to depend on the type of interaction occurring), and a sampling variance equal to the true between-subject variance $\sigma^2_{sub,i}$, scaled by $N_{sub,i}$, the number of subjects in study *i*:

$$\sigma^2_{GMR,i} = \sigma^2_{stu,i} + \frac{\sigma^2_{sub,i}}{N_{sub,i}} \tag{4}$$

Between-study variance, $\sigma^2_{stu,i}$ is computed as:

$$\begin{aligned} \sigma^2_{stu,i} &= \nu_{stu,1} \text{ if } \mathbb{I}_{inh_i} = 1 \\ \sigma^2_{stu,i} &= \nu_{stu,2} \text{ if } \mathbb{I}_{inh_i} = 2 \end{aligned} \tag{5}$$

Parameters $\nu_{stu,1}$ and $\nu_{stu,2}$ measure respectively the bias affecting predictions of competitive inhibition DDI studies or mechanism-based inhibition DDI studies. $\mathbb{I}_{inh_i}$ is the same indicator function as above in Eq. 3.

Note that between-study variances, $\sigma^2_{stu,i}$, may include a component due to Simcyp's imprecision in predictions, but this component is not separately estimable.

The true between-subject variance in log-space for study *i* was assumed to be equal to the Simcyp-predicted between-subject variance (in log-space), corrected for potential variance bias, $\beta_{BSV,i}$:

$$\sigma^2_{sub,i} = \sigma^2_{sub,i,pred} \times \exp\left(\beta_{BSV,i}\right) \tag{6}$$

Here also, a hierarchical specification for $\beta_{BSV,i}$ allows for information sharing in BSV predictions bias estimates:

$$\beta_{BSV,i} \sim \mathcal{N}\left(\mu_{\beta BSV}, {\sigma_{\beta BSV}}^2\right) \tag{7}$$

The observed between-subject variance (in log-space) for study *i* is part of the data and assumed to be distributed according to the following gamma distribution, specified through shape and rate parameters k_i and τ_i respectively:

$$\sigma^2_{sub,i,obs} = \left[log\left(GSD_{i,obs}\right)\right]^2 \sim G\ (k_i, \tau_i) \tag{8}$$

$$k_i = N_{sub,i}/2 \tag{9}$$

$$\tau_i = k_i/\sigma^2_{sub,i} \quad (10)$$

The priors for parameters $\delta_{GMR,1}$ and $\delta_{GMR,2}$, are both normal:

$$\delta_{GMR,1} \sim \mathcal{N}(0,1) \quad (11)$$

$$\delta_{GMR,2} \sim \mathcal{N}(0,1) \quad (12)$$

The priors for the parameters of the BSV prediction bias, $\mu_{\beta BSV}$ and $\sigma_{\beta BSV}$, are respectively normal and truncated Cauchy:

$$\mu_{\beta BSV} \sim \mathcal{N}(0,1) \quad (13)$$

$$\sigma_{\beta BSV} \sim C(0,1)\ [0,\infty[\quad (14)$$

The priors for parameters $\nu_{stu,1}$ and $\nu_{stu,2}$ are both Cauchy, truncated to positive values:

$$\nu_{stu,1} \sim C(0,1)\ [0,\infty[\quad (15)$$

$$\nu_{stu,2} \sim C(0,1)\ [0,\infty[\quad (16)$$

Methods and software

Inference for model F was performed on all the data using Hamiltonian Markov chain Monte Carlo (HMCMC) simulations with the *R* package *RStan*. All post-processing and plotting was done in *R* [1].

AUC analyses

Data

We used the file "Processed full DB 08.csv". It was created using 252 clinical DDI studies involving CYP1A2, 2D6, 2C8, 2C9, 2C19, and CYP3A4, identified using the CDID (formerly UOW database). Simulations were run using the actual clinical study design and the demographics of the individuals (n) recruited into the clinical study. Ten virtual trials of n subjects were run for each simulation (20 trials when a small number of subjects was used). Thus, two sets of data were considered in this analysis: the GMRs and associated population SDs reported in the scientific literature, and the corresponding parameters generated as outputs by the Simcyp Simulator.

Published study results

The sources of the data have been reported in the updated analysis submitted in December, 2023. From the published reports involving six CYP enzymes, 46 victim drugs and 30 perpetrator drugs, we extracted the following information:

- The name of the victim drug and the route of administration (oral or IV).
- The name of the inhibitor drug, classification as a weak, moderate, or strong inhibitor and the route of administration (oral or IV).
- The type of inhibition: either competitive (CI) or mechanism-based inhibition (MBI).
- The total number of study subjects for which GMRs were reported in the clinical study.
- Whether the reported GMR was a ratio of the means (RoM) or the mean of individual ratios (MoR).
- One or several of the following: arithmetic mean of the ratios, geometric mean of the ratios (that is, GMR), upper and lower confidence interval bounds of the geometric mean, confidence interval coverage (90% or 95%), SD of the individual ratios, standard error of the arithmetic mean of the ratios.

Those data were preprocessed as follows (see "Data processing script" in Appendix):

- When the standard deviation of the individual ratios was missing, we used the geometric mean of the ratios and its confidence limits to compute it. We also computed the geometric SD of the ratios and their arithmetic mean.
- We then removed the 32 studies for which the arithmetic mean of ratios or their SD were still missing at that stage.
- We computed, using arithmetic means and SDs, the geometric SDs of ratios still missing at that stage.
- Finally, we computed, using arithmetic means and geometric SDs, the GMR still missing at that stage.

There remained 220 studies for which the GMR and the geometric SD of individual ratios were available. These were used in the model, together with the numbers of subjects.

Simcyp predictions

For each of the above reported studies, there was a corresponding set of data from the Simcyp simulations: the arithmetic mean, the SD, and the geometric means of individual ratios, together with the number of simulated subjects. The Simcyp simulations were performed using a cross-

over design and 10 or 20 times (when a small number of subjects was used in the clinical study) the number of subjects used in the reported studies. Therefore, we can consider the predictions to be much more precise than the reported values (see the updated analysis submitted in December 2023). The simulation results were preprocessed as follows (see "Data processing script" in the Appendix):

- We computed, using the arithmetic mean of individual ratios and their SD, the geometric SD of the predicted individual ratios.
- We checked that all the above computed geometric SDs were not null.

Model F goodness of fit graphs for AUC

Model F goodness of fit (Figure 3) is quite reasonable and much improved compared to the raw data and predictions, particularly for the between subject-variability. Bias correction by model F then improves the fit of the predictions to the data. Figure 4 shows goodness of fit stratified by inhibitor strength for model F, while Figure 5 shows goodness of fit with weak and moderate inhibitors grouped together. Figure 6 shows goodness of fit stratified by type of inhibition for model F. Across all stratifications, model F exhibits robust and consistent performance, effectively capturing raw data irrespective of the inhibitor strength or the type of inhibition.

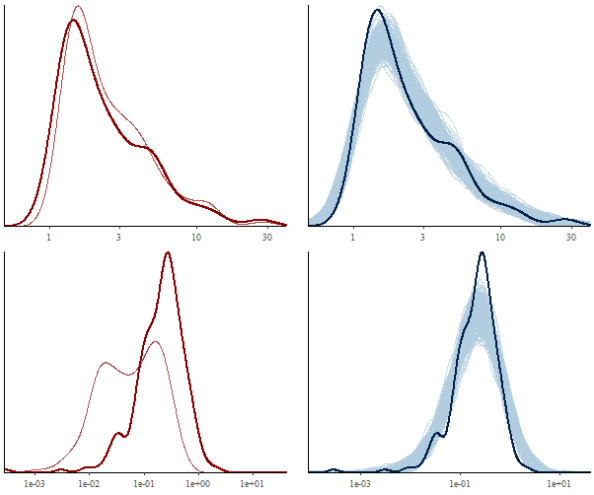

Figure 3: Fit of observed (dark lines) geometric ratios (top row) and between-subject variability in individual ratios (bottom row) with raw Simcyp predictions (left column) or posterior bias model predictions simulated using the parameters joint posterior distribution for model F (right column).

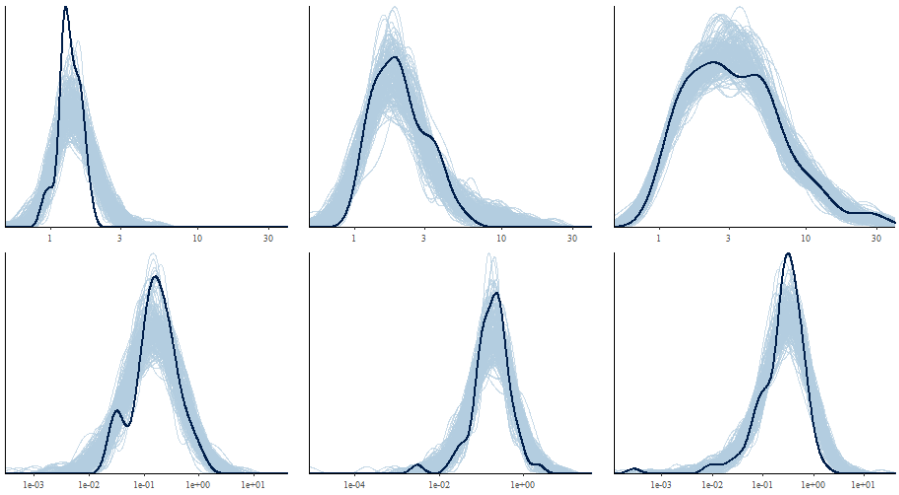

Figure 4: Fit of model F posterior bias predictions in the case of weak, moderate, and strong inhibitors (left, middle, right panes, respectively) to observed (dark lines) geometric ratios (top row of each pane) and between-subject variability in individual ratios (bottom row of each pane).

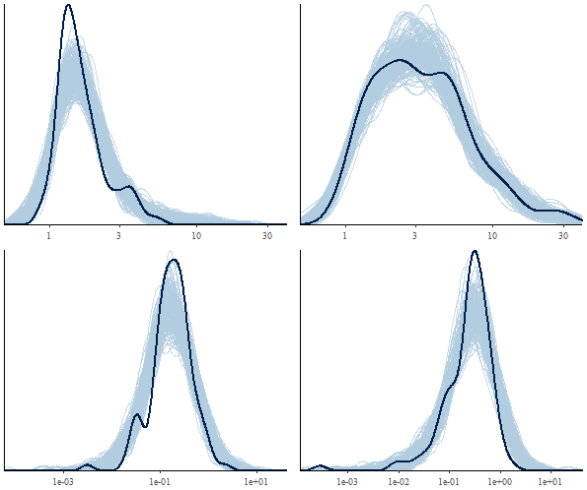

Figure 5: Fit of model F posterior bias predictions in the case of weak *or* moderate inhibitors (left column), and strong inhibitors (right column) to observed (dark lines) geometric ratios (top row of each pane) and between-subject variability in individual ratios (bottom row of each pane).

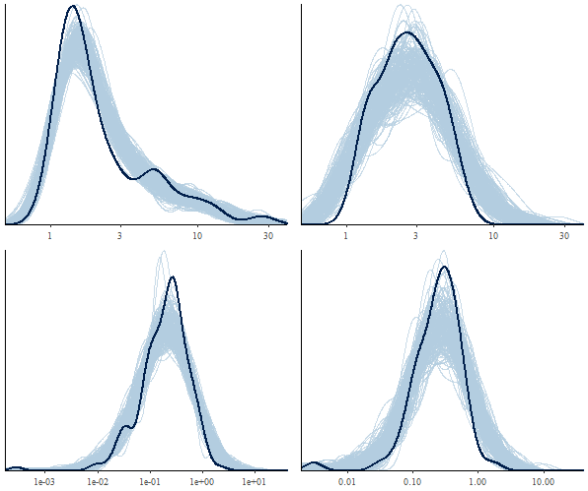

Figure 6: Fit of model F posterior bias predictions in the case of CI (left column) and MBI (right colum) to observed (dark lines) geometric ratios (top row of each pane) and between-subject variability in individual ratios (bottom row of each pane).

Model F parameter estimates for AUC

Table 1 gives the means and SDs of the parameters' marginal posterior distributions for model F. Mean GMR biases range from about -6% (for competitive inhibition) to -4% (for mechanism-based inhibition). On average, Simcyp over-predicts slightly the effect of DDIs. Those estimates are reasonably well-identified.

Between-study variances (on the log-scale) range from 0.032 (for CI) to 0.063 (for MBI); this corresponds to CVs ranging from 18% to 25% on the natural scale. Remember that this is an upper limit of Simcyp imprecision.

The mean bias in between-subject variability is about a factor 2 (that is, the ratio between observed and predicted between-subject CV is $\sqrt{\exp\,(1.41)} = 2.02$) according to model F, with a large variability across studies.

Overall, model F allows for pooling of information (this is obvious given its structure) and it yields estimates quite homogeneous and precise. This is particularly true in the case of between-subject variability bias, which should be better estimated in model F.

Table 1: Statistical summaries of the posterior distributions of the main parameters in model F.

Parameter	**Model F**	
	Mean	SD
Mean GMR biases		
CI	-0.0568	0.0192
MBI	-0.0413	0.0404
Between-study variances		
CI	0.0321	0.0069
MBI	0.0628	0.0191
BSV* bias mean	1.4050	0.0955
BSV* bias SD	1.2889	0.0737

* BSV: Between-subject variance.

Model F posterior predictive plots for AUC

Several predictive plots generated using the above model-based discrepancy analysis can be used to help drug development. Such plots are presented below for model F.

Credibility interval vs predicted GMR

The above meta-analysis model can be used to understand how uncertainty affects future DDI predictions for CYP inhibition for regulatory decision-making.

Figure 7 displays 90% credibility intervals for GMRs (*i.e.*, fold-changes) according to model F, by type of inhibition. Posterior samples of GMR bias and between-study variability were used to sample a log-normal distribution, as per the scripts provided by EMA (see Appendix for a table with the data used). The results are relatively consistent with predictions of GMRs for mechanism-based inhibition having a larger uncertainty (by a very small margin) than predictions for GMRs for competitive inhibition. For instance, at a predicted *AUC* GMR of 1.5, model F predicts a 90% credibility interval of [1.06; 1.91] for competitive inhibition and [0.95; 2.18] for mechanism-based inhibition.

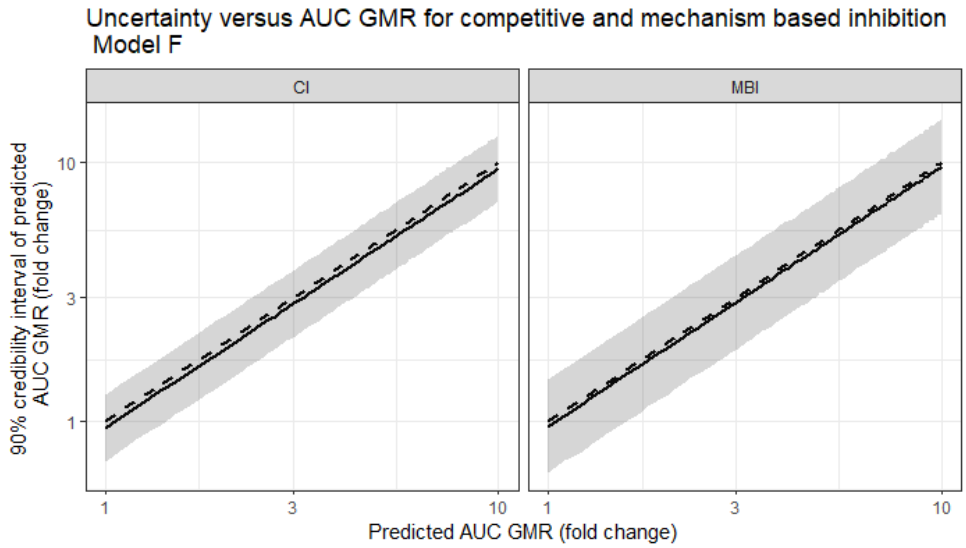

Figure 7: Model F-generated credibility intervals of predicted GMR values *vs*. those values for competitive inhibition (left pane) or mechanism-based inhibition (right pane). The x-axis values represent hypothetical GMR point estimates predicted by model F. The grey shaded area is the 90% credibility intervals of the predicted GMRs, the solid line is the median of the predicted GMRs, and the dashed line is the identity line.

Predicted GMR for hypothetical CYP substrates

EMA suggested that the above displays could be extended to include information about therapeutic range. Figure 8 shows the results obtained for a hypothetical scenario in which:

- A CYP substrate is being developed for which there is an adequate PBPK model.
- The therapeutic index is known for the drug in question and was hypothetically set to 0.5 to 2-fold compared to the expected geometric mean exposure at the therapeutic dose.
- A hypothetical DDI is predicted using the Simcyp® Simulator following concomitant administration with CYP inhibitor. The type of inhibition is considered. Model F posteriors were used, as above, to predict GMR uncertainty.

Using the same example as above with a predicted GMR of 1.5, Figure 8 overlays the 90% credibility interval of the GMR for competitive inhibition and mechanism-based inhibition on the therapeutic window. In the case of mechanism-based inhibition, a portion of the 90% credibility interval extends beyond the therapeutic range.

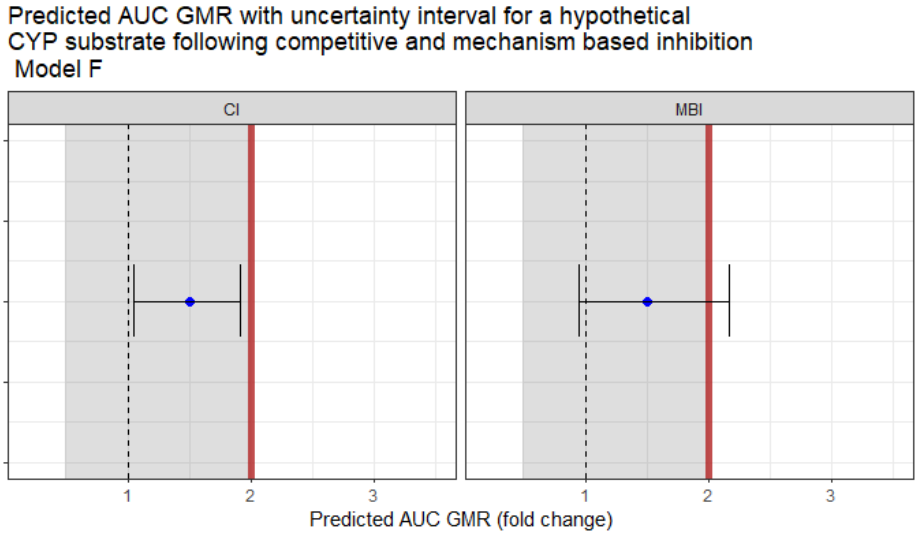

Figure 8: Model F-predicted GMR following CYP inhibition for a hypothetical CYP substrate in the case of competitive inhibition (left pane) or mechanism-based inhibition (right pane). The grey shaded area represents the therapeutic window. The red vertical line indicates its upper limit. The dashed vertical line indicates a predicted GMR without CYP inhibition. The blue dot represents the point estimate of the GMR predicted by the Simcyp® platform. The error bar gives the 90% credibility interval associated with the predicted GMR.

Probability of exceeding a therapeutic index *vs.* predicted GMR

The above displays were further processed to give the probability (estimated according to model F) of exceeding the therapeutic window when several hypothetical therapeutic windows are considered, as shown in Figure 9 for both competitive and mechanism-based inhibition. As illustrated in the figures above, the greater variability in the *AUC* GMR predictions for mechanism-based inhibition leads to exceeding the upper boundary of the therapeutic window at lower predicted *AUC* GMR values compared to competitive inhibition.

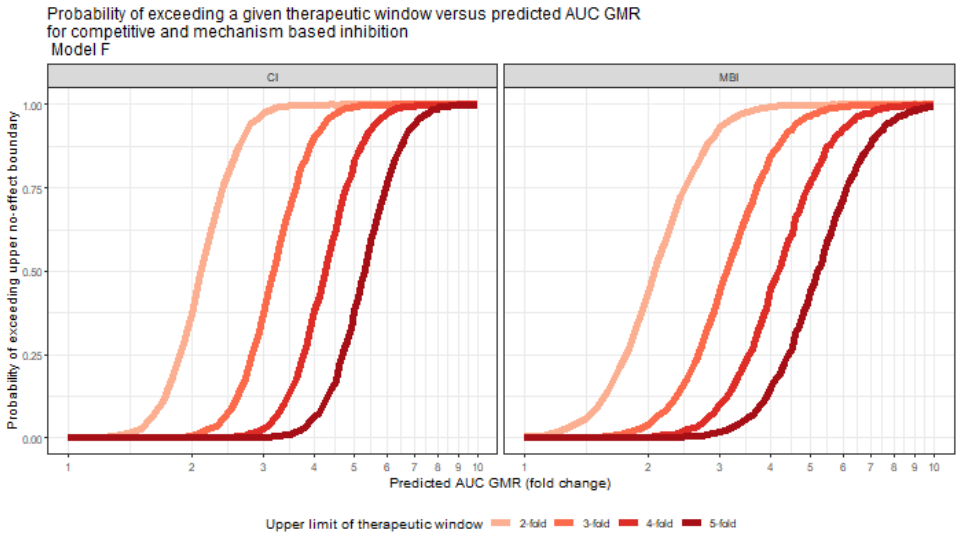

Figure 9: Probability, according to model F, of exceeding upper limit of the therapeutic index *vs*. predicted GMR for competitive inhibition (left pane) or mechanism-based inhibition (right pane). The predicted GMRs on the x-axis were predicted using Simcyp®. Results for hypothetical therapeutic index upper limits of 2-, 3-, 4- and 5-fold are displayed.

Maximum predicted GMR for less than 5% risk of exceeding a therapeutic index

The above analysis can be expanded to determine the predicted GMR that would lead to a 5% probability of exceeding the upper limit of a therapeutic window, as shown in Figure 10. The threshold of 5% is a preliminary proposal of EMA. For a two-fold upper limit of the therapeutic window (same example as above), the maximum predicted *AUC* GMR for <5% risk of exceeding the upper limit is predicted at 1.5 for competitive inhibition and 1.3 for mechanism-based inhibition.

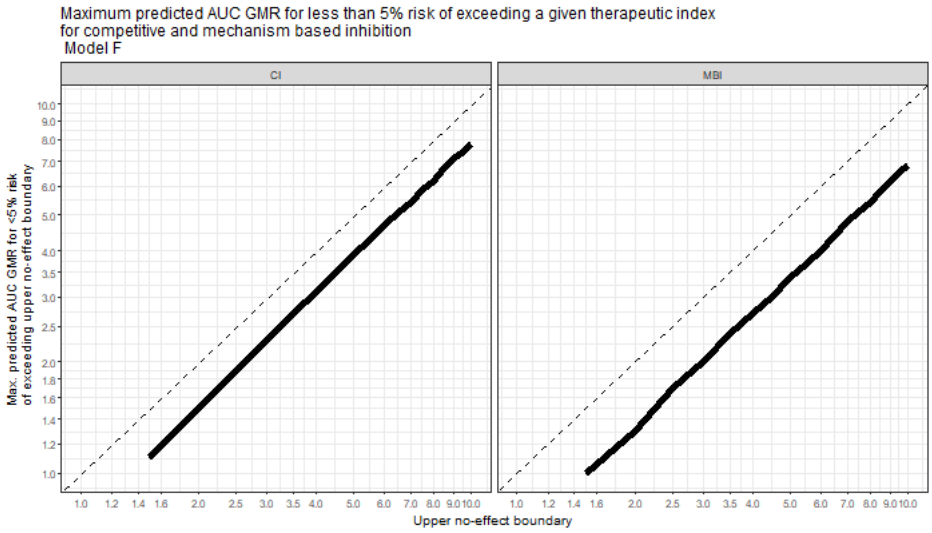

Figure 10: Maximum predicted GMR for <5% risk of exceeding the upper limit of a therapeutic index for competitive inhibition (left pane) or mechanism-based inhibition (right pane). The y-axis shows the maximum GMR predicted by Simcyp® with <5% risk of exceeding the upper limit of therapeutic index given the uncertainty obtained from model F analysis. The x-axis is the upper limit of the therapeutic index.

C_{max} analyses

The previous analyses focused on the Simcyp Simulator's bias and imprecision in predicting *AUC* ratios in the case of DDI simulations. This set of analyses focuses on bias and imprecision in predicting C_{max} ratios. It is well known that C_{max} and *AUC* are correlated measures of drug exposure. We therefore expect that exactly the same bias and imprecision model (model F) can be used for both parameters; only the database needs to be changed. We also expect similar estimates of bias and imprecision.

Data

For creating the file "Processed Cmax DB 01.csv", 189 clinical DDI studies involving CYP1A2, 2D6, 2C8, 2C9, 2C19, and CYP3A4 and reporting either C_{max} with and without inhibition, and/or C_{max} ratios, were identified using the CDID (formerly UOW database). As for *AUC*, simulations were run using the actual clinical study design and the demographics of the individuals (*n*) recruited into the clinical study. Ten virtual trials of *n* subjects were run for each simulation (20 trials when a small number of subjects was used). Thus, two sets of data were considered in this analysis: the GMRs and associated population SDs reported in the scientific literature, and the corresponding parameters generated as outputs by the Simcyp Simulator.

Published study results

The sources of the data have been reported in the updated analysis submitted in December, 2024. From the published reports we extracted, as for *AUC*, the following information:

- The name of the victim drug and the route of administration (oral or IV).
- The name of the inhibitor drug, classification as a weak, moderate, or strong inhibitor and the route of administration (oral or IV).
- The type of inhibition: either competitive (CI) or mechanism-based inhibition (MBI).
- The total number of study subjects for which GMRs were reported or could be calculated in the clinical study.
- Whether the reported GMR was a ratio of the means (RoM) or the mean of individual ratios (MoR).
- One or several of the following: arithmetic mean of the ratios, geometric mean of the ratios (that is, GMR), upper and lower confidence interval bounds of the geometric mean, confidence interval coverage (90% or 95%), SD of the individual ratios, standard error of the arithmetic mean of the ratios.

Those data were preprocessed as for *AUC*:

- When the standard deviation of the individual ratios was missing, we used the geometric mean of the ratios and its confidence limits to compute it. We also computed the geometric SD of the ratios and their arithmetic mean.
- We then removed the 28 studies for which the arithmetic mean of ratios or their SD were still missing at that stage.
- We computed, using arithmetic means and SDs, the geometric SDs of ratios still missing at that stage.
- Finally, we computed, using arithmetic means and geometric SDs, the GMR still missing at that stage.

There remained 160 studies for which the GMR and the geometric SD of individual ratios were available. These were used in the model, together with the numbers of subjects.

Simcyp predictions

For each of the above reported studies, there was a corresponding set of data from the Simcyp simulations: the arithmetic mean, the SD, and the geometric means of individual ratios, together with the number of simulated subjects. The Simcyp simulations were performed using a cross-

over design and 10 or 20 times (when a small number of subjects was used in the clinical study) the number of subjects used in the reported studies. Therefore, we can consider the predictions to be much more precise than the reported values (see the updated analysis submitted in December 2023). The simulation results were preprocessed as follows (see "Data processing script" in the Appendix):

- We computed, using the arithmetic mean of individual ratios and their SD, the geometric SD of the predicted individual ratios.
- We checked that all the above computed geometric SDs were not null.

Model F goodness of fit graphs for C_{max}

Model F goodness of fit (Figure 11) is quite reasonable and much improved compared to the raw data and predictions, particularly for the between-subject variability. Figure 12 shows goodness of fit stratified by inhibitor strength for model F, while Figure 13 shows goodness of fit with weak and moderate inhibitors grouped together. Figure 14 shows goodness of fit stratified by type of inhibition for model F. Across all stratifications, model F exhibits robust and consistent performance, effectively capturing raw data irrespective of the inhibitor strength or the type of inhibition.

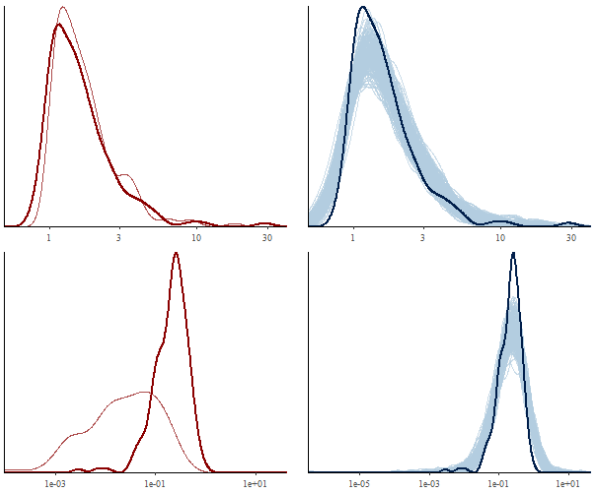

Figure 11: Fit of observed (dark lines) geometric ratios (top row) and between-subject variability in individual ratios (bottom row) with raw Simcyp predictions (left column) or posterior bias model predictions simulated using the parameters joint posterior distribution for model F (right column).

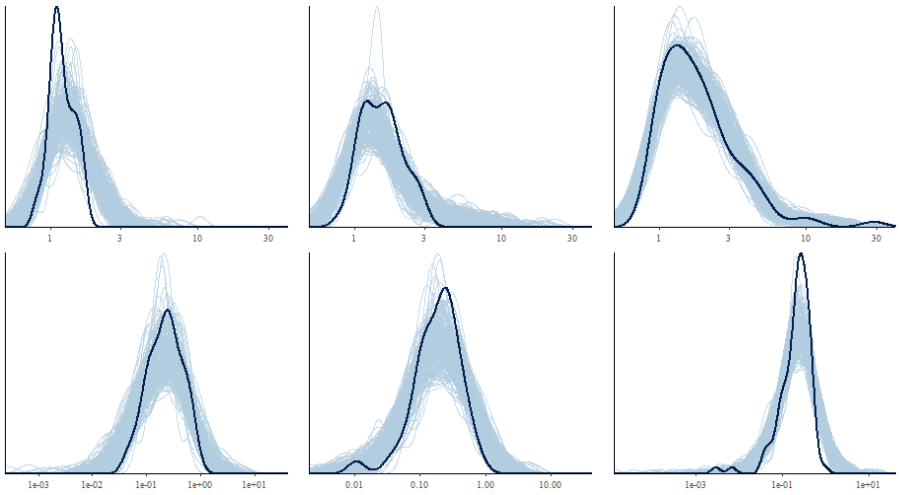

Figure 12: Fit of model F posterior bias predictions in the case of weak, moderate, and strong inhibitors (left, middle, right panes, respectively) to observed (dark lines) geometric ratios (top row of each pane) and between-subject variability in individual ratios (bottom row of each pane).

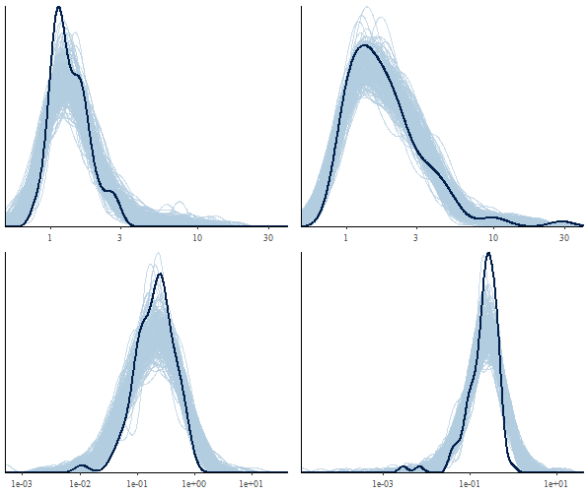

Figure 13: Fit of model F posterior bias predictions in the case of weak *or* moderate inhibitors (left column), and strong inhibitors (right column) to observed (dark lines) geometric ratios (top row of each pane) and between-subject variability in individual ratios (bottom row of each pane).

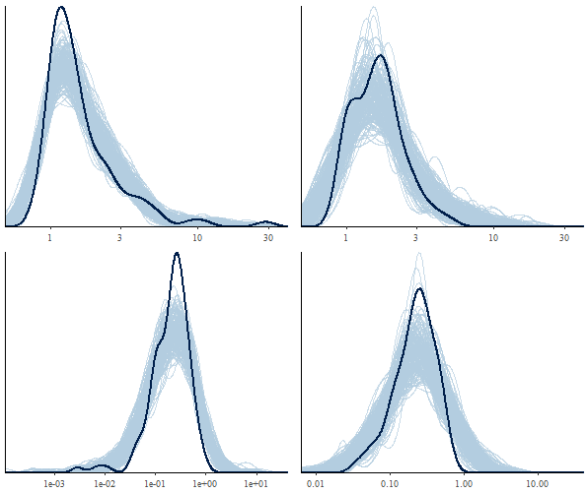

Figure 14: Fit of model F posterior bias predictions in the case of CI (left column) and MBI (right colum) to observed (dark lines) geometric ratios (top row of each pane) and between-subject variability in individual ratios (bottom row of each pane).

Model F parameter estimates for C_{max}

Table 2 gives the means and SDs of the parameters' marginal posterior distributions for model F. Mean GMR biases range from about -6% (for mechanism-based inhibition) to -4% (for competitive inhibition). On average, Simcyp over-predicts slightly the effect of DDIs. Those estimates are reasonably well-identified.

Between-study variances (on the log-scale) range from 0.035 (for CI) to 0.092 (for MBI); this corresponds to CVs ranging from 19% to 31% on the natural scale. Remember that this is an upper limit of Simcyp imprecision.

The mean bias in between-subject variability is about a factor 3 (that is, the ratio between observed and predicted between-subject CV is $\sqrt{\exp(2.29)} = 3.14$) according to model F, with a large variability across studies.

Overall, model F allows for pooling of information (this is obvious given its structure) and it yields estimates quite homogeneous and precise. This is particularly true in the case of between-subject variability bias, which should be better estimated in model F.

Table 2: Statistical summaries of the posterior distributions of the main parameters in model F.

Parameter	Model F	
	Mean	SD
Mean GMR biases		
CI	-0.0427	0.0236
MBI	-0.0606	0.0485
Between-study variances		
CI	0.0350	0.0083
MBI	0.0919	0.0258
BSV* bias mean	2.2851	0.1246
BSV* bias SD	1.4715	0.0910

* BSV: Between-subject variance.

Model F posterior predictive plots for C_{max}

Several predictive plots generated using the above model-based discrepancy analysis can be used to help drug development. Such plots are presented below for model F.

Credibility interval vs predicted GMR

The above meta-analysis model can be used to understand how uncertainty affects future DDI predictions for CYP inhibition for regulatory decision-making.

Figure 15 displays 90% credibility intervals for GMRs (*i.e.*, fold-changes) according to model F, by type of inhibition. Posterior samples of GMR bias and between-study variability were used to sample a log-normal distribution, as per the scripts provided by EMA (see Appendix for a table with the data used). The results are relatively consistent with predictions of C_{max} GMRs for mechanism-based inhibition having a larger uncertainty (by a very small margin) than predictions of GMRs for competitive inhibition. For instance, at a predicted C_{max} GMR of 1.5, model F predicts a 90% credibility interval of [1.05; 1.94] for competitive inhibition and [0.84; 2.35] for mechanism-based inhibition.

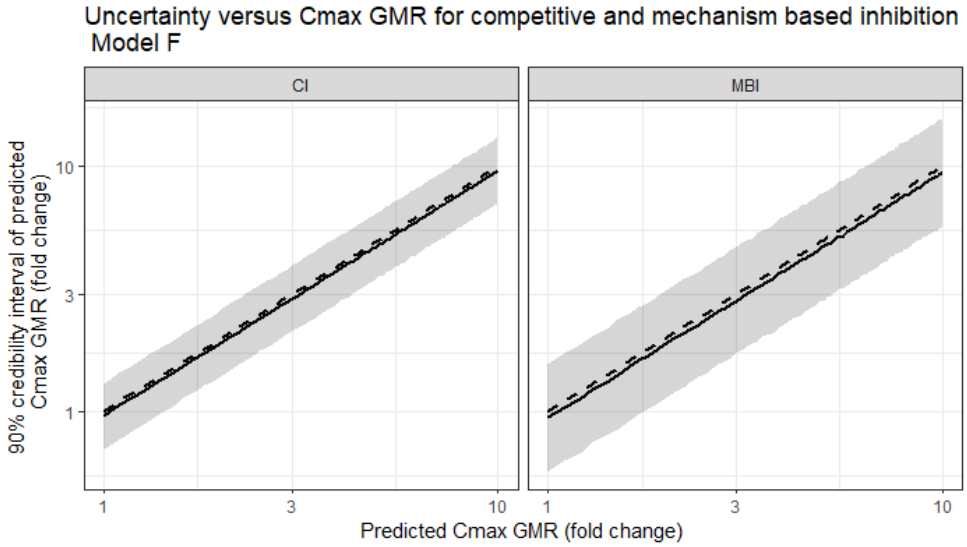

Figure 15: Model F-generated credibility intervals of predicted GMR values *vs*. those values for competitive inhibition (left pane) or mechanism-based inhibition (right pane). The x-axis values represent hypothetical GMR point estimates predicted by model F. The grey shaded area is the 90% credibility intervals of the predicted GMRs, the solid line is the median of the predicted GMRs, and the dashed line is the identity line.

Predicted GMR for hypothetical CYP substrates

EMA suggested that the above displays could be extended to include information about therapeutic range. Figure 16 shows the results obtained for a hypothetical scenario in which:

- A CYP substrate is being developed for which there is an adequate PBPK model.
- The therapeutic index is known for the drug in question and was hypothetically set to 0.5 to 2-fold compared to the expected geometric mean exposure at the therapeutic dose.
- A hypothetical DDI is predicted using the Simcyp® Simulator following concomitant administration with CYP inhibitor. The type of inhibition is considered. Model F posteriors were used, as above, to predict GMR uncertainty.

Using the same example as above with a predicted C_{max} GMR of 1.5, Figure 16 overlays the 90% credibility interval of the GMR for competitive inhibition and mechanism-based inhibition on the therapeutic window. In the case of mechanism-based inhibition, a portion of the 90% credibility interval extends beyond the therapeutic range whereas the 90% credibility interval lays inside the therapeutic window for competitive inhibition.

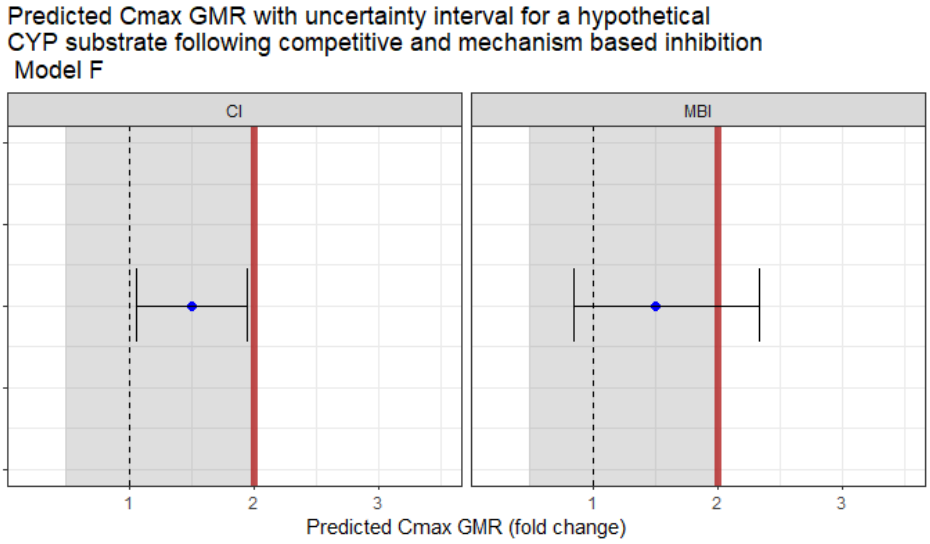

Figure 16: Model F-predicted GMR following CYP inhibition for a hypothetical CYP substrate in the case of competitive inhibition (left pane) or mechanism-based inhibition (right pane). The grey shaded area represents the therapeutic window. The red vertical line indicates its upper limit. The dashed vertical line indicates a predicted GMR without CYP inhibition. The blue dot represents the point estimate of the GMR predicted by the Simcyp® platform. The error bar gives the 90% credibility interval associated with the predicted GMR.

Probability of exceeding a therapeutic index *vs.* predicted GMR

The above displays were further processed to give the probability (estimated according to model F) of exceeding the therapeutic window when several hypothetical therapeutic windows are considered, as shown in Figure 17 for both competitive and mechanism-based inhibition. As illustrated in the figures above, the greater variability in the C_{max} GMR predictions for mechanism-based inhibition leads to exceeding the upper boundary of the therapeutic window at lower predicted C_{max} GMR values compared to competitive inhibition.

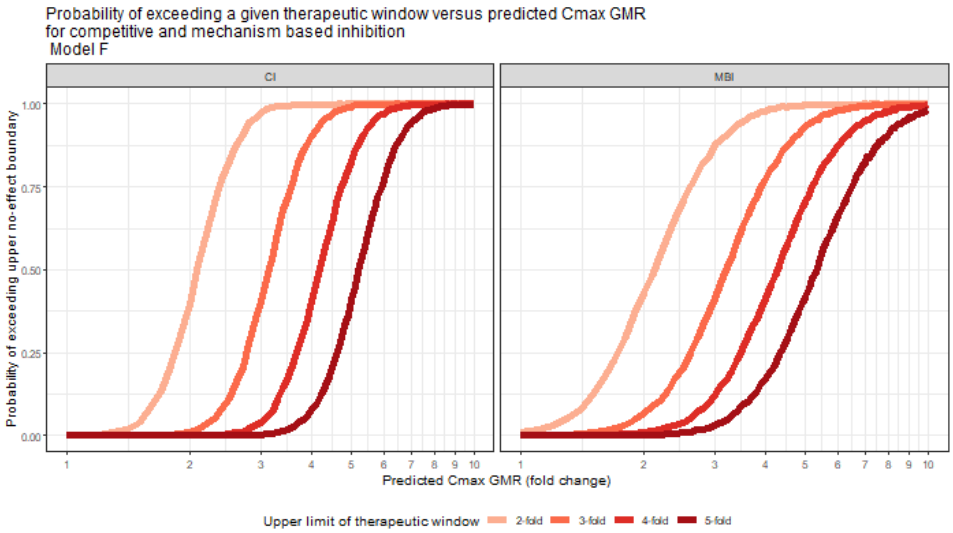

Figure 17: Probability, according to model F, of exceeding upper limit of the therapeutic index *vs*. predicted GMR for competitive inhibition (left pane) or mechanism-based inhibition (right pane). The predicted GMRs on the x-axis were predicted using Simcyp®. Results for hypothetical therapeutic index upper limits of 2-, 3-, 4- and 5-fold are displayed.

Maximum predicted GMR for less than 5% risk of exceeding a therapeutic index

The above analysis can be expanded to determine the predicted GMR that would lead to a 5% probability of exceeding the upper limit of a therapeutic window, as shown in Figure 18. The threshold of 5% is a preliminary proposal of EMA. For a two-fold upper limit of the therapeutic window (same example as above), the maximum predicted C_{max} GMR for <5% risk of exceeding the upper limit is predicted at 1.5 for competitive inhibition and 1.2 for mechanism-based inhibition.

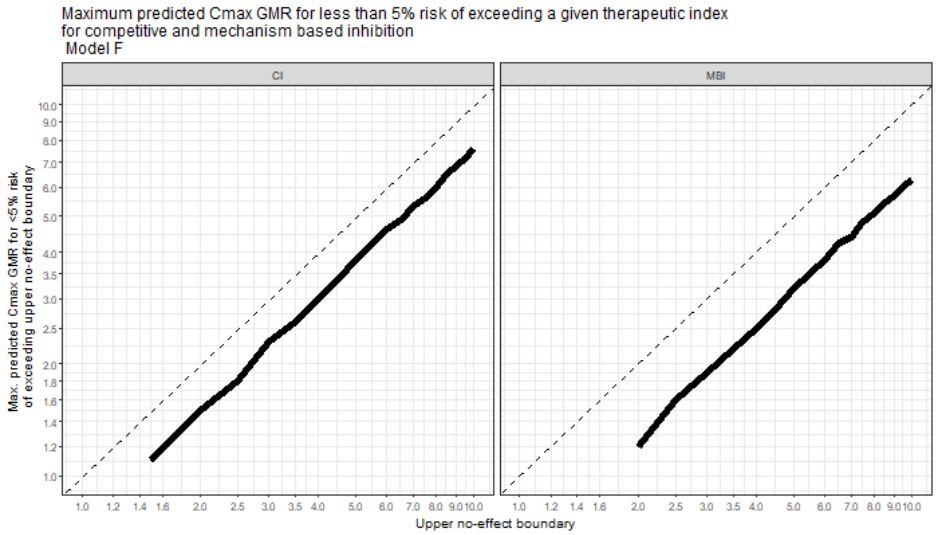

Figure 18: Maximum predicted GMR for <5% risk of exceeding the upper limit of a therapeutic index for competitive inhibition (left pane) or mechanism-based inhibition (right pane). The y-axis shows the maximum GMR predicted by Simcyp® with <5% risk of exceeding the upper limit of therapeutic index given the uncertainty obtained from model F analysis. The x-axis is the upper limit of the therapeutic index.

Conclusions

We have analyzed a model to investigate the Simcyp Simulator's (V19) bias and imprecision in predicting *AUC* and C_{max} ratios. It can be concluded that:

- The overall estimates of Simcyp bias and imprecision for *AUC* and C_{max} GMRs are low, robust and in line with each other, as expected by virtue of the known and understandable correlation between C_{max} and *AUC* (they are different statistics, one extreme, the other average, of the same concentration profile).
- Model F, which accounts for type of inhibition mechanism, is well identifiable and points to a small effect of inhibition type on bias and imprecision.
- Simcyp imprecision in *AUC* GMR predictions is *at most* 18% to 25% and in C_{max} GMR predictions is *at most* 19% to 31%.
- The mean bias in between-subject variability for *AUC* is about a factor 2, while for C_{max} is about a factor 3. This is an area where model-based assessment is strongly affected by data quality.

References

1. R Development Core Team. R: A Language and Environment for Statistical Computing, http://www.R-project.org. Vienna, Austria: R Foundation for Statistical Computing; 2013.

Appendix

Initial model (model A) DAG representation

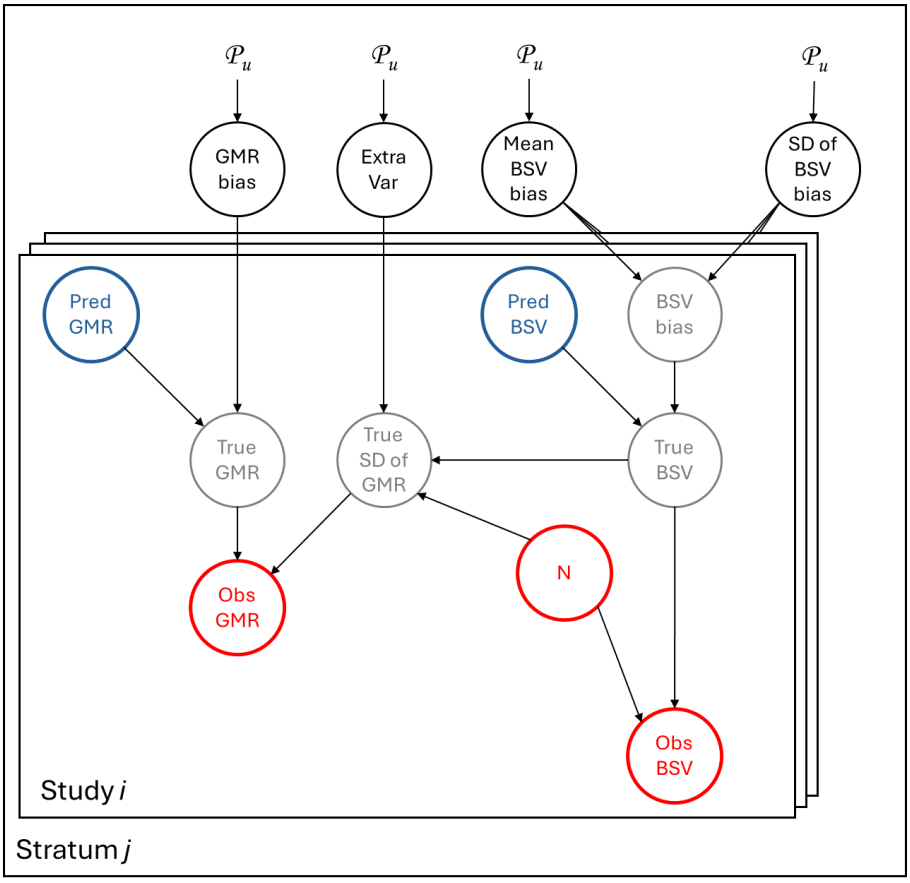

Figure 19: Directed acyclic graph representations of the final model A dependencies between variables and parameters. Literature data are in red; Simcyp® predictions in blue; Latent variables in grey; Estimands in black.

Model F code ("EMA agnostic m205.stan")

```
// R-code for fitting Bayesian meta-regression model
// SAWP model in Stan, CYP agnostic ("EMA agnostic m205.stan")

// m200: model B
// m201: model A (original Simcyp)
// m202: model C (B + weak and moderate inhibitor strength as linear covariate)
// m203: model D (C + strong inhibitors)
// m204: model E (D + nonlinear strength effect)
// m205: model F (B without CYPs category)

// ------------------
data {
  int<lower=0> N;
  int<lower=0> L;
  int NSub[N];
  int TIN[N];
  vector[N] Obs_BSV_of_ratio;
  vector[N] Obs_ratio;
  vector[N] BSV_simcyp_pred;
```

```
  vector[N] simcyp_ratio;
}

// ------------------
parameters {
  vector[L]          ratio_bias_TIN; // type changed compared to model B (m200)
  real               mean_BSV_bias;
  real<lower=0>      log_sd_BSV_bias;
  vector<lower=0>[L] extra_var_TIN;  // type changed compared to model B (m200)
  vector[N]          BSV_bias_std;
}

// ------------------
transformed parameters {
  vector[N] mean_bias;
  vector[N] log_corrected_ratio;
  vector[N] BSV_bias;
  vector[N] true_BSV_of_ratio;
  vector[N] shape;
  vector[N] scale;
  vector[N] rate;
  vector[N] extra_var_of_ratio;
  vector[N] total_var_of_ratio;
  vector[N] total_SD_of_ratio;

  for (n in 1:N){
    mean_bias[n] = ratio_bias_TIN[TIN[n]]; // no CYP indicator

    log_corrected_ratio[n] = log(simcyp_ratio[n]) + mean_bias[n];

    BSV_bias[n] = mean_BSV_bias + BSV_bias_std[n] * log_sd_BSV_bias;

    true_BSV_of_ratio[n] = exp(log(BSV_simcyp_pred[n]) + BSV_bias[n]);

    shape[n] = NSub[n]/2;  // alpha in STAN
    scale[n] = true_BSV_of_ratio[n]/shape[n];
    rate[n]  = 1/scale[n]; // beta in STAN

    extra_var_of_ratio[n] = extra_var_TIN[TIN[n]]; // no CYP indicator

    total_var_of_ratio[n] = true_BSV_of_ratio[n]/NSub[n] +
                            extra_var_of_ratio[n];

    total_SD_of_ratio[n] = sqrt(total_var_of_ratio[n]);
  }
}

// ------------------
model {
  // adaptive priors (describing the random effects distributions)
  BSV_bias_std ~ normal(0,1);

  // hyper-priors (describing the priors for the parameters for the
  // random effects distributions)
  mean_BSV_bias   ~ normal(0, 1);
  log_sd_BSV_bias ~ cauchy(0, 1);

  // regular priors
  ratio_bias_TIN ~ normal(0, 1);
  extra_var_TIN  ~ cauchy(0, 1); // was normal in model B

  // likelihood definition
  Obs_BSV_of_ratio ~ gamma(shape, rate);
  Obs_ratio ~ lognormal(log_corrected_ratio, total_SD_of_ratio);
}

// ------------------
generated quantities {
```

```
  array[N] real predBSV = gamma_rng(shape, rate);
  array[N] real predR   = lognormal_rng(log_corrected_ratio,
                                        total_SD_of_ratio);

// array[N] real predBSV2 = gamma_rng(shape*1000, 1000/scale);
// array[N] real predR2   = lognormal_rng(log_corrected_ratio,
//                           sqrt(extra_var_of_ratio));

  vector[N] log_lik;
  for (n in 1:N) {
    log_lik[n] = gamma_lpdf(Obs_BSV_of_ratio[n] | shape[n], rate[n]) +
                 lognormal_lpdf(Obs_ratio[n] | log_corrected_ratio[n],
                                               total_SD_of_ratio[n]);
  }
}

// End.
```

Data processing script

```
## Process database, cleaning and completing it
##============================================================================

## read the data
## =============
DDI.data = read.csv("Full DB 08.csv") # check the rounding!!!!
str(DDI.data)
dim(DDI.data) # 252,19
head(DDI.data)

## process the data to complete missing information
## ================================================
## Add a column of original study number
orig_num = 1:dim(DDI.data)[1]
DDI.data = cbind(DDI.data, orig_num)
head(DDI.data)
dim(DDI.data) # 252,20

## Add a column of observation geometric SD
Obs_GSD = rep(NA, dim(DDI.data)[1])
DDI.data = cbind(DDI.data, Obs_GSD)
head(DDI.data)
dim(DDI.data) # 252,21

## Checking: number of simulated subjects is 10 or 20 times trial size...
plot(DDI.data$Obs_Nsub, DDI.data$Pred_Nsub)
## 1/(DDI.data$Obs_Nsub / DDI.data$Pred_Nsub)

## For the lines which have missing observation arithmetic SD, use the
## observed geometric mean and CI limits to compute it. Compute also GSD and
## arithmetic mean:
to.process = which(is.na(DDI.data$Obs_SD))
for (i in to.process) {
  if (!(is.na(DDI.data$Obs_GeoM[i]) |
        is.na(DDI.data$Obs_CI_lower[i]) |
        is.na(DDI.data$Obs_CI_upper[i]))) { # if we have what we need...
    log.mean = log(DDI.data$Obs_GeoM[i])
    log.SD   = sqrt(DDI.data$Obs_Nsubjects[i]) *
               (log(DDI.data$Obs_CI_upper[i]) -
                log(DDI.data$Obs_CI_lower[i])) /
                (2 * qnorm(1 - (1 - DDI.data$CI_coverage[i]/100)/2))
    DDI.data$Obs_GSD[i] = exp(log.SD)
    DDI.data$Obs_SD[i]  = sqrt((exp(log.SD^2) - 1) *
                               exp(2 * log.mean + log.SD^2))
    DDI.data$Obs_Mean[i]= exp(log.mean + (log.SD^2) / 2)
  }
```

```
}
## Check
par(mfrow = c(2,2))
mycol = rep("black", dim(DDI.data)[1])
mycol[to.process] = "red"
plot(DDI.data$Obs_SD,   las=1, log="y", col=mycol)
plot(DDI.data$Obs_Mean, las=1, log="y", col=mycol)
plot(DDI.data$Obs_SD/DDI.data$Obs_Mean, las=1, log="y", col=mycol,
     ylab="Obs CV")
plot(DDI.data$Obs_GSD, las=1, log="y", col=mycol)

## nothing weird besides a very small SD and corresponding CV (2 subjects only)

## Plot the raw observed and predicted CVs
pdf("Plots raw pred and obs between-subject CVs.pdf")
plot(rep(0.3, dim(DDI.data)[1]),
     DDI.data$Obs_SD/DDI.data$Obs_Mean, xaxt="n", log="y",
     xlab="", ylab="", las=1, type="n",
     xlim=c(0,2), main="No data treatment")
x1 = 0.5
x2 = 1.5
## draw lines joining corresponding pred and obs
for (i in 1:dim(DDI.data)[1]) {
  lines(c(x1, x2), col="grey",
        c(DDI.data$Pred_SD[i] / DDI.data$Pred_Mean[i],
          DDI.data$Obs_SD[i]  / DDI.data$Obs_Mean[i]))
}
## draw the points
pred.CV = DDI.data$Pred_SD / DDI.data$Pred_Mean
points(rep(x1, dim(DDI.data)[1]), pred.CV, col="violet")
obs.CV  = DDI.data$Obs_SD  / DDI.data$Obs_Mean
points(rep(x2, dim(DDI.data)[1]), obs.CV,  col="black")
## draw the means
lines(c(x1-0.1, x1+0.1), rep(mean(pred.CV), 2), col="violet", lwd=2)
text(x1-0.2, mean(pred.CV)+0.02, lab="M", col="violet")
lines(c(x2-0.1, x2+0.1), rep(mean(obs.CV, na.rm=T), 2), col="black",  lwd=2)
text(x2+0.2, mean(obs.CV, na.rm=T)+0.05,  lab="M", col="black")
## draw the trimmed means
lines(c(x1-0.1, x1+0.1), rep(mean(pred.CV, trim=0.1), 2), col="red", lwd=1)
text(x1-0.2, mean(pred.CV)+0.02, lab="M", col="violet")
lines(c(x2-0.1, x2+0.1), rep(mean(obs.CV, trim=0.1, na.rm=T), 2),
      col="red",  lwd=1)
text(x2+0.2, mean(obs.CV, na.rm=T)+0.05,  lab="M", col="black")
legend(0, 3,
       c(paste("trimmed mean =",
               format(mean(pred.CV, trim=0.1), dig=2)),
         paste("trimmed mean =",
               format(mean(obs.CV, trim=0.1, na.rm=T), dig=2))),
       text.col=c("violet", "black"), pch="-", col="red")
## draw the geometric means
lines(c(x1-0.1, x1+0.1), rep(exp(mean(log(pred.CV))), 2),
      col="violet", lty=2, lwd=2)
text(x1-0.2, exp(mean(log(pred.CV))), lab="GM", col="violet")
lines(c(x2-0.1, x2+0.1), rep(exp(mean(log(obs.CV), na.rm=T)), 2),
      col="black",  lty=2, lwd=2)
text(x2+0.2, exp(mean(log(obs.CV), na.rm=T)),  lab="GM", col="black")
## add x axis
axis(1, at=c(x1, x2), lab=c("Predicted CV", "Observed CV"), cex=0.6)
dev.off()

## Plot the raw ratios of CVs
hist((obs.CV / pred.CV), 30)
ar.mean = mean(obs.CV / pred.CV, na.rm=T)
abline(v=ar.mean)
geo.mean = 10^mean(log10(obs.CV / pred.CV), na.rm=T)
abline(v=geo.mean)
## on a log-scale
pdf("Histogram of CV ratios.pdf")
```

```
hist(log10(obs.CV / pred.CV), 30, xaxt="n", main="Histogram of CV ratios",
     las=1, xlab="Ratios observed CV / predicted CV")
axis(1, at=seq(-1, 1, 1), lab=10^seq(-1, 1, 1))
mean(obs.CV / pred.CV, na.rm=T)
## abline(v=log10(ar.mean))
10^mean(log10(obs.CV / pred.CV), na.rm=T)
## abline(v=log10(geo.mean))
legend(-1, 40,
       c(paste("mean =",
               format(ar.mean, dig=3)),
         paste("geometric mean =",
               format(geo.mean, dig=3))),
       text.col=c("violet", "black"), pch="", col="red")
dev.off()

## Weed out lines without arithmetic mean or SD at this stage
to.remove = which(is.na(DDI.data$Obs_Mean) | is.na(DDI.data$Obs_SD))
removed.data = DDI.data[to.remove,]
DDI.data = DDI.data[-to.remove,] # all observed arithmetic SD available
dim(DDI.data) # 220,21

## We need all observed geometric SDs; if missing, compute them
## from arithmetic means and SDs:
to.process = which(is.na(DDI.data$Obs_GSD))
for (i in to.process) {
  DDI.data$Obs_GSD[i] = exp(sqrt(log(DDI.data$Obs_SD[i]^2 /
                                     DDI.data$Obs_Mean[i]^2 + 1)))
}
## Check
par(mfrow = c(1,1))
mycol = rep("black", dim(DDI.data)[1])
mycol[to.process] = "red"
plot(DDI.data$Obs_GSD, las=1, log="y", col=mycol)
dim(DDI.data) # 220,21

## We need all observed geometric means; if missing, compute them
## from arithmetic means and geometric SDs:
to.process = which(is.na(DDI.data$Obs_GeoM))
for (i in to.process) {
  DDI.data$Obs_GeoMean[i] = exp(log(DDI.data$Obs_Mean[i]) -
                                log(DDI.data$Obs_GSD[i])^2 / 2)
}
## Check
mycol = rep("black", dim(DDI.data)[1])
mycol[to.process] = "red"
plot(DDI.data$Obs_GeoM, las=1, log="y", col=mycol)
dim(DDI.data) # 220,21

## We need prediction geometric SDs; compute them from
## arithmetic means and SDs:
Pred_GSD = exp(sqrt(log(DDI.data$Pred_SD^2 / DDI.data$Pred_Mean^2 + 1)))
DDI.data = cbind(DDI.data, Pred_GSD)
## need to extend the columns of the removed data for compatibility
Pred_GSD = rep(NA, dim(removed.data)[1])
removed.data = cbind(removed.data, Pred_GSD)
dim(removed.data) # 32,22

## Check
par(mfrow = c(1,2))
## plot(DDI.data$Obs_SD,  DDI.data$Pred_SD,  las=1, log="")
plot(DDI.data$Obs_GeoMean, DDI.data$Pred_GeoMean, las=1, log="xy")
abline(0,1)
plot(DDI.data$Obs_GSD, DDI.data$Pred_GSD, las=1, log="") # clearly two groups
abline(0,1)

## Remove the studies with null prediction variance
to.remove = which(DDI.data$Pred_GSD == 1 )
if (length(to.remove) != 0) {
```

```
  removed.data = rbind(removed.data, DDI.data[to.remove,])
  DDI.data = DDI.data[-to.remove,]
}
dim(DDI.data)      # 220,22
dim(removed.data) # 32,22

## Save the database at this stage
write.csv(DDI.data, file="Processed full DB 08.csv", row.names=F)
write.csv(removed.data, file="Discarded from DB 08.csv", row.names=F)
## DDI.data = read.csv(file="Processed full DB 06.csv")

## How many studies do we have for each CYP?
dim(DDI.data)
table(DDI.data$CYP)
table(DDI.data$CYP[which(DDI.data$CI_MBI == "CI")])
table(DDI.data$CYP[which(DDI.data$CI_MBI != "CI")])

table(DDI.data$Substrate)
table(DDI.data$Inhibitor)

table(DDI.data$CYP)
table(DDI.data$CYP[which(DDI.data$Inhibitor_type == "weak")])
table(DDI.data$CYP[which(DDI.data$Inhibitor_type == "moderate")])
table(DDI.data$CYP[which(DDI.data$Inhibitor_type == "strong")])

## End.
```

Table of data for Figure 7 for AUC *GMRs*

Predicted GMR_{AUC}	90% credible interval for true GMR_{AUC}	
	CI	MBI
1.0	[0.7; 1.26]	[0.634; 1.45]
1.1	[0.775; 1.4]	[0.706; 1.61]
1.2	[0.848; 1.53]	[0.756; 1.74]
1.3	[0.915; 1.64]	[0.818; 1.87]
1.4	[0.98; 1.78]	[0.891; 2.04]
1.5	[1.06; 1.91]	[0.952; 2.18]
1.6	[1.12; 2.03]	[1.01; 2.31]
1.7	[1.19; 2.15]	[1.07; 2.48]
1.8	[1.26; 2.28]	[1.14; 2.63]
1.9	[1.34; 2.43]	[1.2; 2.78]
2.0	[1.4; 2.54]	[1.26; 2.9]
2.1	[1.47; 2.66]	[1.34; 3.05]
2.2	[1.54; 2.79]	[1.39; 3.21]
2.3	[1.61; 2.95]	[1.46; 3.35]
2.4	[1.69; 3.05]	[1.52; 3.5]
2.5	[1.74; 3.18]	[1.58; 3.65]
2.6	[1.83; 3.32]	[1.64; 3.83]
2.7	[1.9; 3.43]	[1.71; 3.97]
2.8	[1.98; 3.54]	[1.76; 4.08]
2.9	[2.04; 3.68]	[1.84; 4.24]
3.0	[2.11; 3.82]	[1.89; 4.36]
3.1	[2.18; 3.94]	[1.96; 4.51]
3.2	[2.26; 4.09]	[2.02; 4.63]
3.3	[2.32; 4.18]	[2.07; 4.75]
3.4	[2.39; 4.3]	[2.15; 4.94]
3.5	[2.45; 4.44]	[2.23; 5.1]
3.6	[2.54; 4.57]	[2.26; 5.23]
3.7	[2.61; 4.68]	[2.33; 5.37]
3.8	[2.67; 4.84]	[2.42; 5.49]
3.9	[2.75; 4.98]	[2.47; 5.71]
4.0	[2.83; 5.07]	[2.54; 5.87]
4.1	[2.88; 5.22]	[2.59; 5.96]
4.2	[2.95; 5.33]	[2.67; 6.05]
4.3	[3.02; 5.46]	[2.72; 6.19]
4.4	[3.09; 5.58]	[2.8; 6.4]
4.5	[3.17; 5.73]	[2.83; 6.53]
4.6	[3.24; 5.82]	[2.89; 6.61]
4.7	[3.29; 5.98]	[2.96; 6.83]
4.8	[3.38; 6.09]	[3.02; 6.95]
4.9	[3.44; 6.25]	[3.11; 7.07]
5.0	[3.53; 6.36]	[3.13; 7.28]
5.1	[3.59; 6.45]	[3.22; 7.43]
5.2	[3.65; 6.59]	[3.29; 7.65]
5.3	[3.73; 6.72]	[3.35; 7.65]
5.4	[3.81; 6.88]	[3.41; 7.88]
5.5	[3.86; 6.98]	[3.48; 7.98]
5.6	[3.93; 7.17]	[3.53; 8.18]
5.7	[3.99; 7.21]	[3.59; 8.29]
5.8	[4.07; 7.38]	[3.68; 8.39]
5.9	[4.18; 7.47]	[3.73; 8.55]
6.0	[4.24; 7.58]	[3.82; 8.64]
6.1	[4.27; 7.73]	[3.9; 8.83]
6.2	[4.36; 7.88]	[3.93; 9.01]
6.3	[4.43; 7.98]	[4.01; 9.13]
6.4	[4.48; 8.13]	[4.04; 9.35]
6.5	[4.57; 8.21]	[4.11; 9.41]
6.6	[4.62; 8.29]	[4.21; 9.6]
6.7	[4.7; 8.5]	[4.27; 9.7]
6.8	[4.78; 8.61]	[4.3; 9.89]
6.9	[4.86; 8.8]	[4.34; 10]
7.0	[4.94; 8.89]	[4.43; 10.2]
7.1	[4.99; 9]	[4.48; 10.2]
7.2	[5.07; 9.12]	[4.54; 10.4]
7.3	[5.17; 9.26]	[4.64; 10.7]
7.4	[5.23; 9.48]	[4.71; 10.8]
7.5	[5.3; 9.49]	[4.79; 11]
7.6	[5.31; 9.69]	[4.79; 11]
7.7	[5.42; 9.75]	[4.9; 11.2]
7.8	[5.5; 9.88]	[4.91; 11.4]
7.9	[5.56; 10.1]	[4.97; 11.5]
8.0	[5.63; 10.2]	[5.06; 11.6]
8.1	[5.7; 10.3]	[5.11; 11.8]
8.2	[5.75; 10.5]	[5.19; 12]
8.3	[5.81; 10.5]	[5.23; 12]
8.4	[5.88; 10.7]	[5.32; 12.2]
8.5	[5.95; 10.8]	[5.39; 12.3]
8.6	[6.03; 10.9]	[5.4; 12.5]
8.7	[6.05; 11]	[5.51; 12.6]
8.8	[6.21; 11.2]	[5.55; 12.8]
8.9	[6.24; 11.3]	[5.59; 12.8]
9.0	[6.32; 11.5]	[5.71; 13.1]
9.1	[6.38; 11.5]	[5.8; 13.2]
9.2	[6.44; 11.6]	[5.82; 13.3]
9.3	[6.51; 11.8]	[5.92; 13.7]
9.4	[6.59; 12]	[6; 13.7]
9.5	[6.66; 12.1]	[5.94; 13.8]
9.6	[6.75; 12.2]	[6.16; 13.9]
9.7	[6.83; 12.2]	[6.06; 14.1]
9.8	[6.91; 12.4]	[6.21; 14.3]
9.9	[6.96; 12.5]	[6.25; 14.4]
10.0	[7.02; 12.8]	[6.24; 14.6]

Table of data for Figure 15 for C_{max} GMRs

Predicted GMR_{Cmax}	90% credible interval for true GMR_{Cmax}		Predicted GMR_{Cmax}	90% credible interval for true GMR_{Cmax}	
	CI	MBI		CI	MBI
1.0	[0.699; 1.3]	[0.567; 1.56]	5.6	[3.9; 7.34]	[3.15; 8.66]
1.1	[0.769; 1.44]	[0.628; 1.72]	5.7	[3.99; 7.43]	[3.26; 8.86]
1.2	[0.842; 1.56]	[0.676; 1.87]	5.8	[4.06; 7.6]	[3.29; 8.94]
1.3	[0.912; 1.69]	[0.748; 2.01]	5.9	[4.14; 7.71]	[3.36; 9.17]
1.4	[0.986; 1.82]	[0.791; 2.17]	6.0	[4.24; 7.84]	[3.41; 9.28]
1.5	[1.05; 1.94]	[0.844; 2.35]	6.1	[4.26; 7.93]	[3.43; 9.55]
1.6	[1.13; 2.08]	[0.909; 2.5]	6.2	[4.34; 8.09]	[3.55; 9.7]
1.7	[1.19; 2.22]	[0.966; 2.64]	6.3	[4.43; 8.24]	[3.58; 9.72]
1.8	[1.27; 2.34]	[1.02; 2.77]	6.4	[4.5; 8.37]	[3.6; 9.95]
1.9	[1.33; 2.47]	[1.08; 2.96]	6.5	[4.58; 8.51]	[3.69; 10.1]
2.0	[1.4; 2.61]	[1.14; 3.11]	6.6	[4.66; 8.59]	[3.73; 10.3]
2.1	[1.48; 2.76]	[1.19; 3.26]	6.7	[4.67; 8.71]	[3.8; 10.4]
2.2	[1.55; 2.88]	[1.24; 3.45]	6.8	[4.78; 8.88]	[3.86; 10.6]
2.3	[1.61; 3.03]	[1.3; 3.55]	6.9	[4.86; 9.01]	[3.91; 10.7]
2.4	[1.68; 3.14]	[1.38; 3.69]	7.0	[4.9; 9.13]	[3.99; 10.9]
2.5	[1.76; 3.29]	[1.42; 3.88]	7.1	[5; 9.25]	[4.05; 11]
2.6	[1.82; 3.42]	[1.48; 4.03]	7.2	[5.06; 9.36]	[4.06; 11.2]
2.7	[1.89; 3.5]	[1.54; 4.19]	7.3	[5.08; 9.53]	[4.15; 11.4]
2.8	[1.96; 3.65]	[1.6; 4.31]	7.4	[5.18; 9.64]	[4.25; 11.5]
2.9	[2.04; 3.75]	[1.64; 4.57]	7.5	[5.23; 9.71]	[4.24; 11.5]
3.0	[2.13; 3.95]	[1.71; 4.66]	7.6	[5.34; 9.9]	[4.36; 11.8]
3.1	[2.18; 4.05]	[1.77; 4.86]	7.7	[5.39; 10.1]	[4.36; 12.1]
3.2	[2.23; 4.19]	[1.84; 4.99]	7.8	[5.49; 10.1]	[4.43; 12.3]
3.3	[2.3; 4.3]	[1.9; 5.06]	7.9	[5.58; 10.3]	[4.46; 12.3]
3.4	[2.38; 4.44]	[1.92; 5.34]	8.0	[5.6; 10.4]	[4.55; 12.5]
3.5	[2.46; 4.59]	[2.03; 5.49]	8.1	[5.69; 10.6]	[4.56; 12.5]
3.6	[2.53; 4.71]	[2.04; 5.53]	8.2	[5.77; 10.8]	[4.66; 12.8]
3.7	[2.6; 4.83]	[2.07; 5.7]	8.3	[5.82; 10.8]	[4.68; 12.9]
3.8	[2.67; 4.98]	[2.14; 5.91]	8.4	[5.88; 11]	[4.8; 13]
3.9	[2.74; 5.1]	[2.21; 6.12]	8.5	[5.99; 11.1]	[4.85; 13.3]
4.0	[2.82; 5.23]	[2.28; 6.23]	8.6	[6.01; 11.2]	[4.93; 13.3]
4.1	[2.88; 5.32]	[2.34; 6.38]	8.7	[6.18; 11.3]	[4.97; 13.5]
4.2	[2.93; 5.46]	[2.41; 6.53]	8.8	[6.18; 11.4]	[4.99; 13.7]
4.3	[3.02; 5.61]	[2.43; 6.69]	8.9	[6.25; 11.5]	[5.11; 13.8]
4.4	[3.1; 5.77]	[2.46; 6.9]	9.0	[6.35; 11.8]	[5.15; 14.2]
4.5	[3.16; 5.87]	[2.57; 6.95]	9.1	[6.41; 11.9]	[5.12; 14]
4.6	[3.22; 6.01]	[2.63; 7.18]	9.2	[6.46; 12]	[5.23; 14.4]
4.7	[3.31; 6.18]	[2.65; 7.3]	9.3	[6.58; 12.1]	[5.28; 14.6]
4.8	[3.38; 6.24]	[2.72; 7.48]	9.4	[6.58; 12.3]	[5.3; 14.6]
4.9	[3.47; 6.37]	[2.81; 7.64]	9.5	[6.63; 12.4]	[5.4; 14.8]
5.0	[3.54; 6.51]	[2.8; 7.8]	9.6	[6.71; 12.5]	[5.44; 15.1]
5.1	[3.55; 6.66]	[2.9; 7.88]	9.7	[6.82; 12.6]	[5.43; 15.1]
5.2	[3.68; 6.82]	[2.94; 8.06]	9.8	[6.94; 12.8]	[5.56; 15.4]
5.3	[3.74; 6.91]	[3.03; 8.23]	9.9	[6.93; 12.9]	[5.61; 15.4]
5.4	[3.78; 7.07]	[3.07; 8.4]	10.0	[7.01; 13.1]	[5.68; 15.7]
5.5	[3.87; 7.18]	[3.13; 8.62]			