Assessing Cross-Version Simcyp Simulator Prediction Performance Using a Bioequivalence Framework to Support EMA Qualification

Masoud Jamei, Céline Brochot, Pauline Bogdanovich, Sibylle Neuhoff, Oliver Hatley, Iain Gardner, Karen R. Yeo
Certara UK Limited, Sheffield, UK
Masoud.Jamei@certara.com

Simcyp Simulator V20-V24 DDI Performance Predictions for the EMA Qualification Matrix are Equivalent to those of the Qualified V19.

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Background and Objective

The Simcyp Physiologically Based Pharmacokinetic (PBPK) Simulator V19 was qualified for predicting drug-drug interactions for 6 CYP enzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5) for three contexts of use (CoU) cases by the European Medicine Agency (EMA) in 2025 [1]. Since the qualification process was started, several subsequent versions of the Simcyp Simulator have been released. Given V19 qualification, it is imperative that new versions of the Simulator can demonstrate consistency with the qualified version.
The EMA Qualification states that 'Every time a new Simcyp version is used in regulatory submissions a *de novo* justification of assumptions and methods for uncertainty quantification may not be needed if it is demonstrated that the CoU, Qualification matrix and scope complies with the V19 qualification space.' Although it is stated that a *de novo* justification may not be needed, the acceptance criteria for compliance with the V19 qualification space is not specified. Therefore, the question becomes – what metrics will best evaluate the predictive performance of subsequent versions when compared against those of V19?
The typical prediction performance criteria e.g. Average Fold Error (AFE) or Absolute Average Fold Error (AAFE) can be used however these assessments may not reflect potential variability changes from one version to another.

Methods

In order to tackle this issue, we propose testing the equivalence of the Simcyp predictions for the AUC and Cmax ratios obtained using the subsequent versions of the Simcyp Simulator (V20 to V24) against the V19 predictions using Two One-Sided Tests (TOST), as is conducted in typical bioequivalence (BE) assessments.

In this assessment the V19 results are considered the 'reference set' and the V20-V24 results are treated as 'test sets'. If the BE tests are passed, indicating that each version is 'equivalent' to the 'reference' version (V19), it would seem appropriate to consider that all 'equivalent' versions are also qualified for the same CoUs.

Results

The same qualification matrix of 220 studies for AUC Geometric Mean Ratio (GMR) and 159 studies for Cmax GMR were simulated in (V20 to V24) and the results are shown in tables and figures below.

Table 1 – The predicted AUC ratios across V19-V24.

Version	N	Mean	Median
V19	220	3.534	2.114
V20	220	3.459	2.169
V21	220	3.478	2.095
V22	220	3.521	2.097
V23	220	3.578	2.131
V24	220	3.513	2.158

Table 2 – The predicted Cmax ratios across V19-V24.

Version	N	Mean	Median
V19	159	2.123	1.560
V20	159	2.083	1.531
V21	159	2.092	1.540
V22	159	2.086	1.510
V23	159	2.102	1.546
V24	159	2.117	1.582

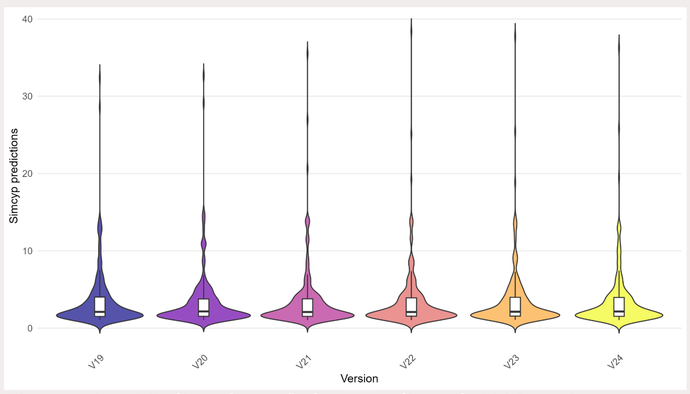

Figure 1 – Violin plot of the predicted AUC ratios across V19-V24.

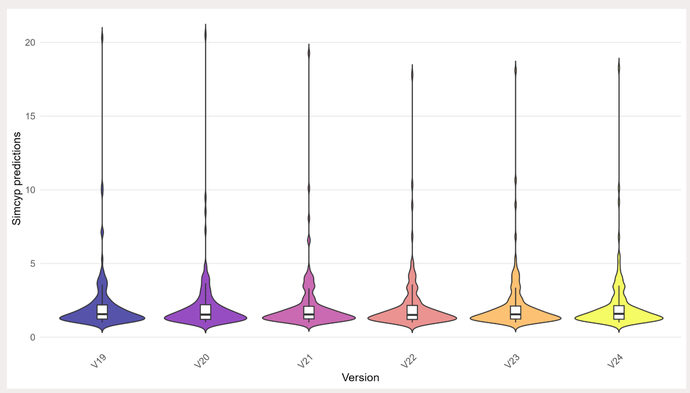

Figure 2 – Violin plot of the predicted Cmax ratios across V19-V24.

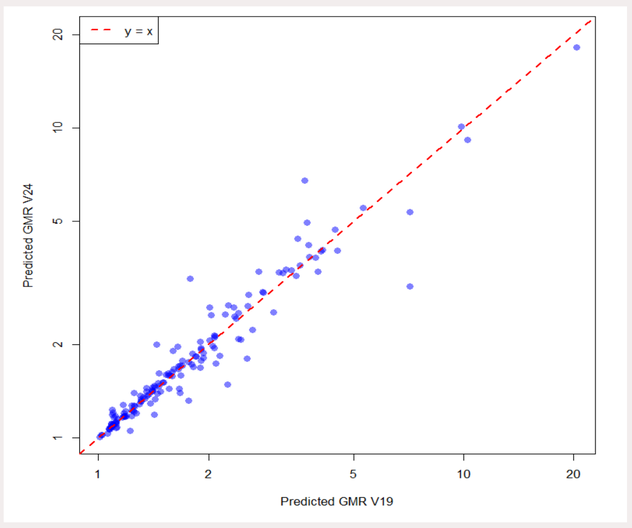

Figure 3 – The scatter plot for the predicted AUC Geometric Mean Ratio comparing V19 and V24.

The simulation results from V20 to V24 (test results) were compared against those of V19 (reference results) assessing equivalence within (80% - 125%) range using Two One-Sided Tests (TOST) for $\alpha = 0.05$ significance level. The equivalence is concluded if both one-sided tests are rejected ($p < 0.05$) and the 90% CI is within the equivalence margin.

The BE assessment results across all compared versions (V20 to V24) demonstrate that all versions' predictions are equivalent to V19 predictions and the p-values were below 0.001 and the 90% Confidence Intervals were well within 80%-125% range.

Discussion

Every year a new version of the Simcyp Simulator is released where current features and databases are expanded and/or updated based on the latest scientific advancements. Due to these changes a new version of the Simulator may not produce identical results to the previous version. To assess the performance of subsequent versions of the EMA qualified V19, the simulation results of V20 to V24 of the Simcyp Simulator using the same dataset were compared against those of V19 using TOST. The results showed that all versions are equivalent producing consistent results.

References

[1] EMA website visited on 20th Feb 2026; Opinions and letters of support on the qualification of novel methodologies for medicine development | European Medicines Agency (EMA)

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