Qualification of the Simcyp platform: Inter-Version Qualification Bridging

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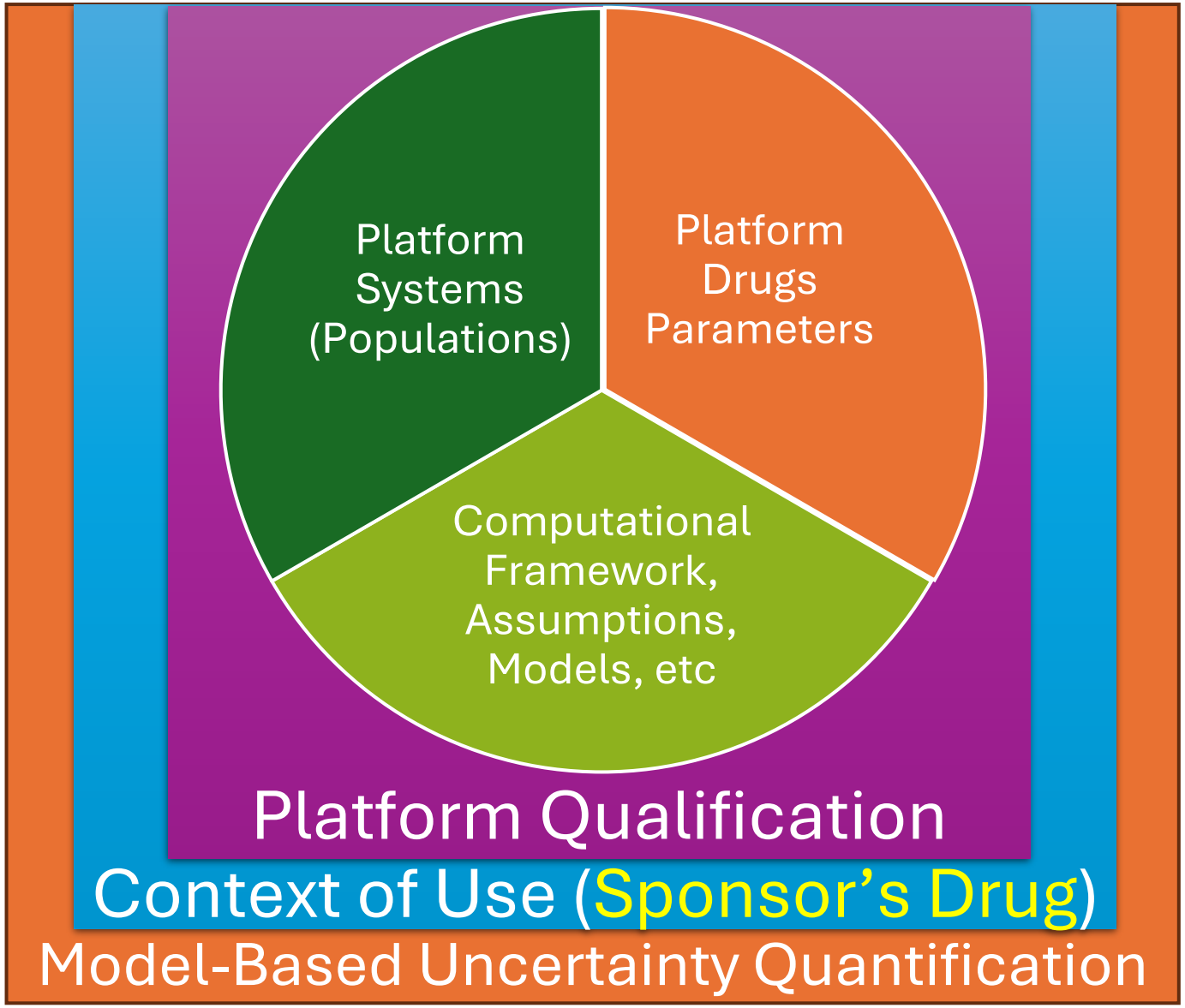
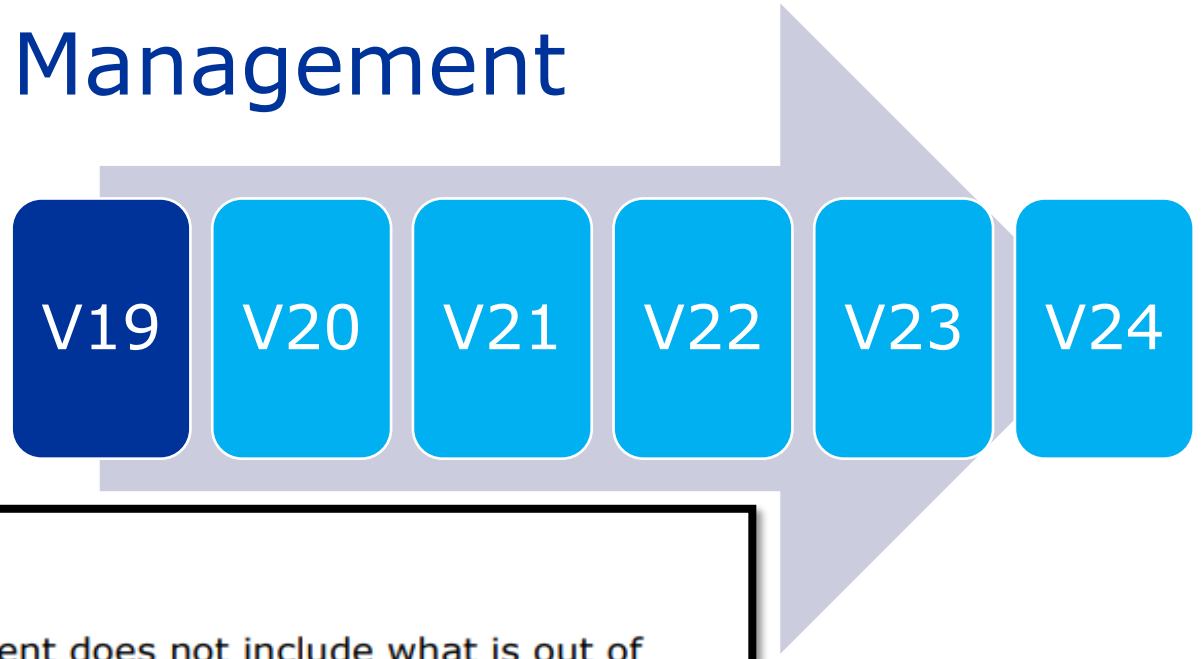
Elements and Scope of Platform Qualification

- Intended for ‘high impact’ regulatory scenarios, e.g. *in lieu* of clinical studies
- Uncertainty quantification only includes *external* (test, unseen, or independent) datasets; different from typical PopPK analysis
- M15 doesn’t seem to be concerned with ‘platform qualification’



Simcyp Simulator Life Cycle Management

Do we need to go through the same full qualification process for each new version?



Lifecycle management

The qualification is valid for Simcyp V19R1. Lifecycle management does not include what is out of scope for V19 and does not fall within the qualified COU.

The performance defined in this Qualification does not automatically apply to newer versions of the Simcyp PBPK platform. Every time a new Simcyp version is used in regulatory submissions a de novo justification of the 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. However, the new version DDI prediction may require updated results, e.g. updated uncertainty quantification analysis and graphs (see scripts and methodology outlined for the qualification of V19). Assessors should ensure that the new version and applications falls within the scope of the lifecycle management defined here. The recommendations for good practices, reporting and assessment may then be applicable to the assessment of newer versions.

Qualification Opinion for Simcyp Simulator

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Requirements for Inter-Version Qualification Bridging

- Transparency and Correctness
- Quality Assurance
- Traceability
- Reproducibility

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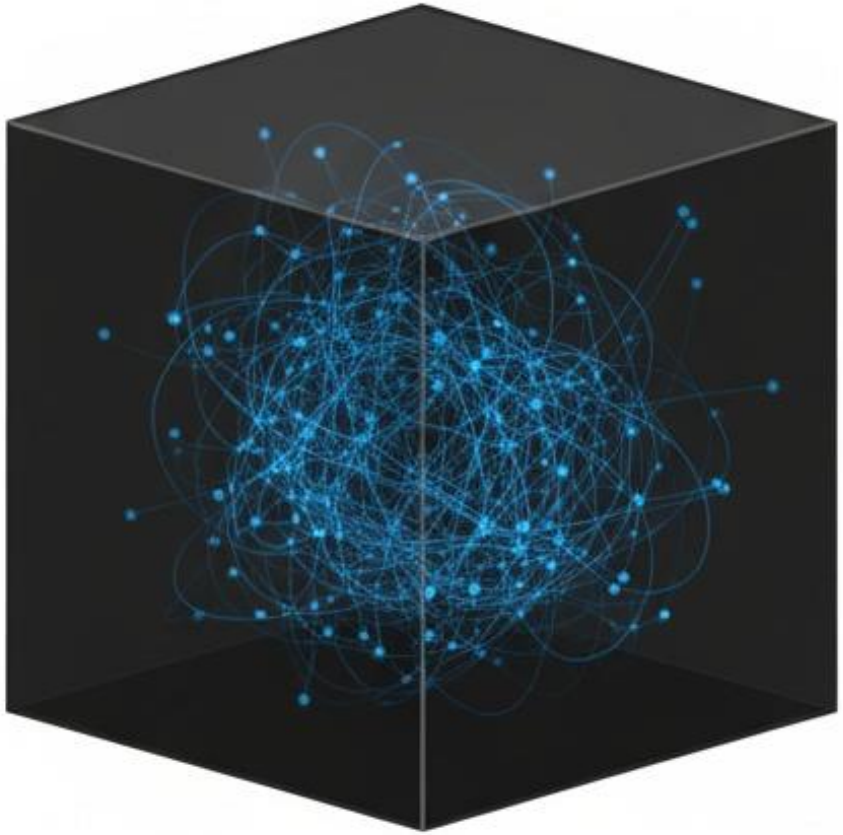
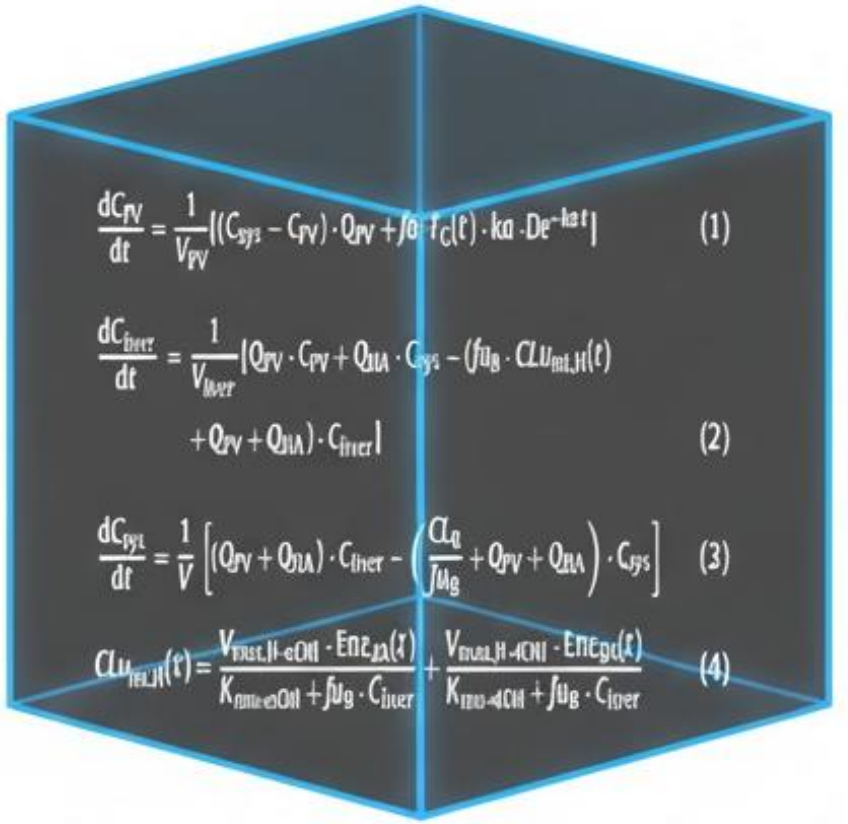
Black Box *vs* Glass Box!

AI Generated Image using Google's Nano Banana

The Glass Box approach is essential for Transparency, Quality Assurance, Traceability, and Reproducibility!





$$\frac{dC_{PV}}{dt} = \frac{1}{V_{PV}}\left[(C_{sys} - C_{PV}) \cdot Q_{PV} + fa \cdot F_C(t) \cdot ka \cdot De^{-kat}\right] \quad (1)$$

$$\frac{dC_{liver}}{dt} = \frac{1}{V_{liver}}\left[Q_{PV} \cdot C_{PV} + Q_{HA} \cdot C_{sys} - (fu_B \cdot CLu_{int,H}(t) + Q_{PV} + Q_{HA}) \cdot C_{liver}\right] \quad (2)$$

$$\frac{dC_{sys}}{dt} = \frac{1}{V}\left[(Q_{PV} + Q_{HA}) \cdot C_{liver} - \left(\frac{CL_R}{fu_B} + Q_{PV} + Q_{HA}\right) \cdot C_{sys}\right] \quad (3)$$

$$CLu_{int,H}(t) = \frac{V_{first,H-eCYP} \cdot Emax_{3A}(t)}{K_{first-eCYP} + fu_B \cdot C_{liver}} + \frac{V_{rest,H-rCYP} \cdot Emax_{3A}(t)}{K_{rest-rCYP} + fu_B \cdot C_{liver}} \quad (4)$$

[Physiologically based mechanistic modelling to predict complex drug–drug interactions involving simultaneous competitive and time-dependent enzyme inhibition by parent compound and its metabolite in both liver and gut—The effect of diltiazem on the time-course of exposure to triazolam - ScienceDirect]

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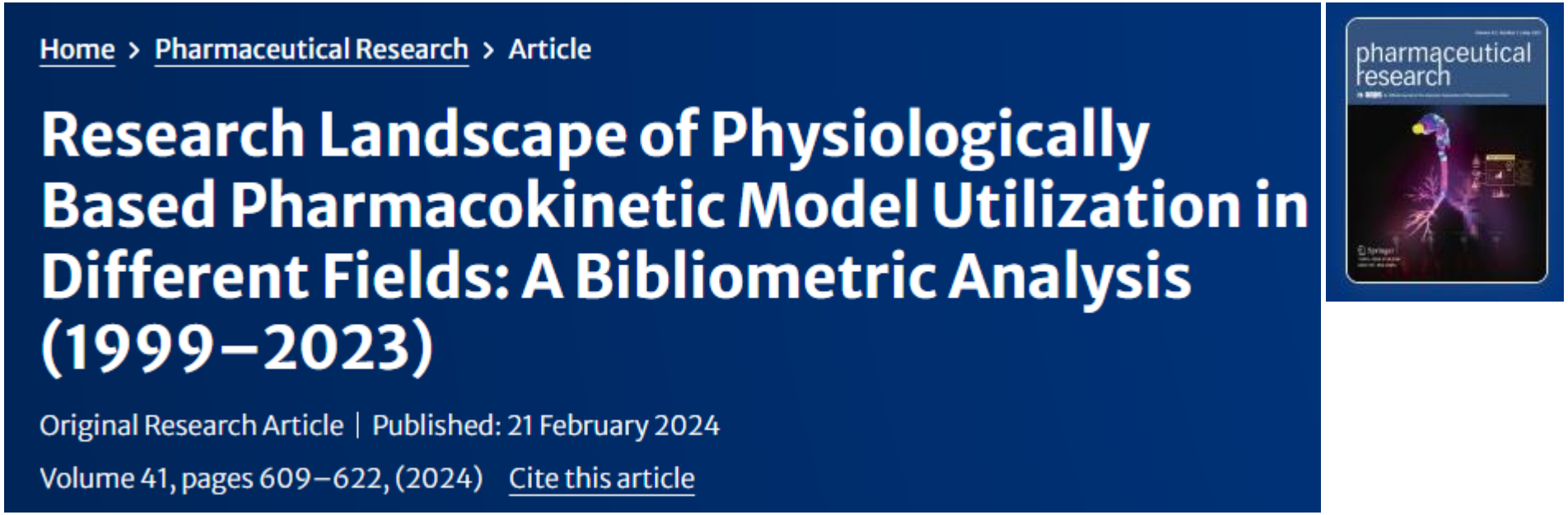
Open Science, Transparency and Peer Review



Xin Wang, Jiangfan Wu, Hongjiang Ye, Xiaofang Zhao & Shenyin Zhu

- https://doi.org/10.1007/s11095-024-03676-4

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Contribution to the Science of PBPK Modelling!

Rank	Countries	Counts	Centrality	Institutions	Counts	Centrality	Authors	Counts
1	USA	2179	0.82	US EPA	209	0.22	Rostami-hodjegan A	113
2	England	567	0.43	US FDA	174	0.1	Chewell HJ	107
3	Germany	347	0.36	University of Manchester	170	0.15	Andersen ME	97
4	P R China	249	0.07	Certara UK Ltd	124	0.06	Jamei M	66
5	Japan	239	0.19	SUNY Buffalo	119	0.12	Parrott N	64
6	Netherlands	223	0.15	University of Montreal	109	0.12	Yamazaki H	54
7	Canada	215	0.2	Simcyp Ltd	95	0.04	Haddad S	48
8	Switzerland	188	0.15	Pfizer Inc	86	0.04	Johnson TN	48
9	France	180	0.25	Genentech Inc	86	0.03	Sugiyama Y	48
10	Belgium	138	0.17	AstraZeneca	82	0.03	Krishnan K	47

- https://doi.org/10.1007/s11095-024-03676-4

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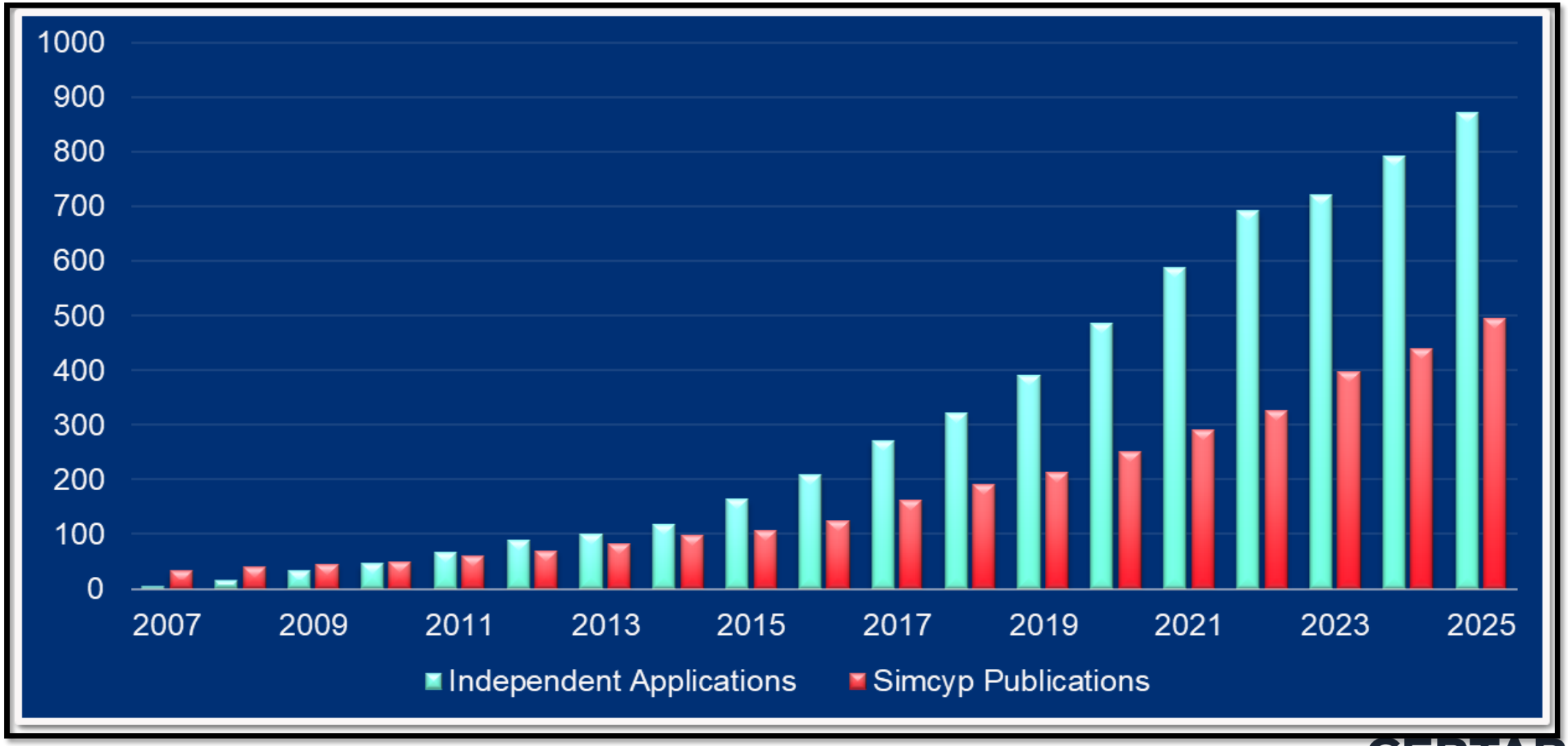
Trend of Publications by Simcyp and Independent Researchers



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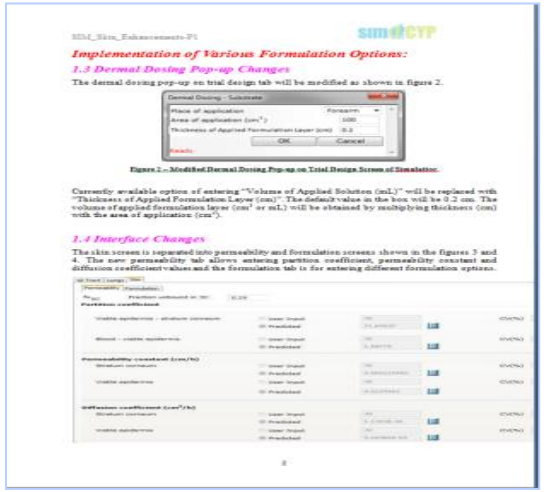
The Simcyp Simulator is developed within a tightly controlled framework

The Simcyp suite of products have been recommended for ISO 27001 certification!

Science/Design



Approval

Software Verification

Azure DevOps

Gate Keeper

MathWorks

Data, sources, Meta-Analysis

Approval

Simcyp Data Management System (SDM)

A Mature Quality Assurance Framework

[The Simcyp Population Based Simulator: Architecture, Implementation, and Quality Assurance | In Silico Pharmacology]

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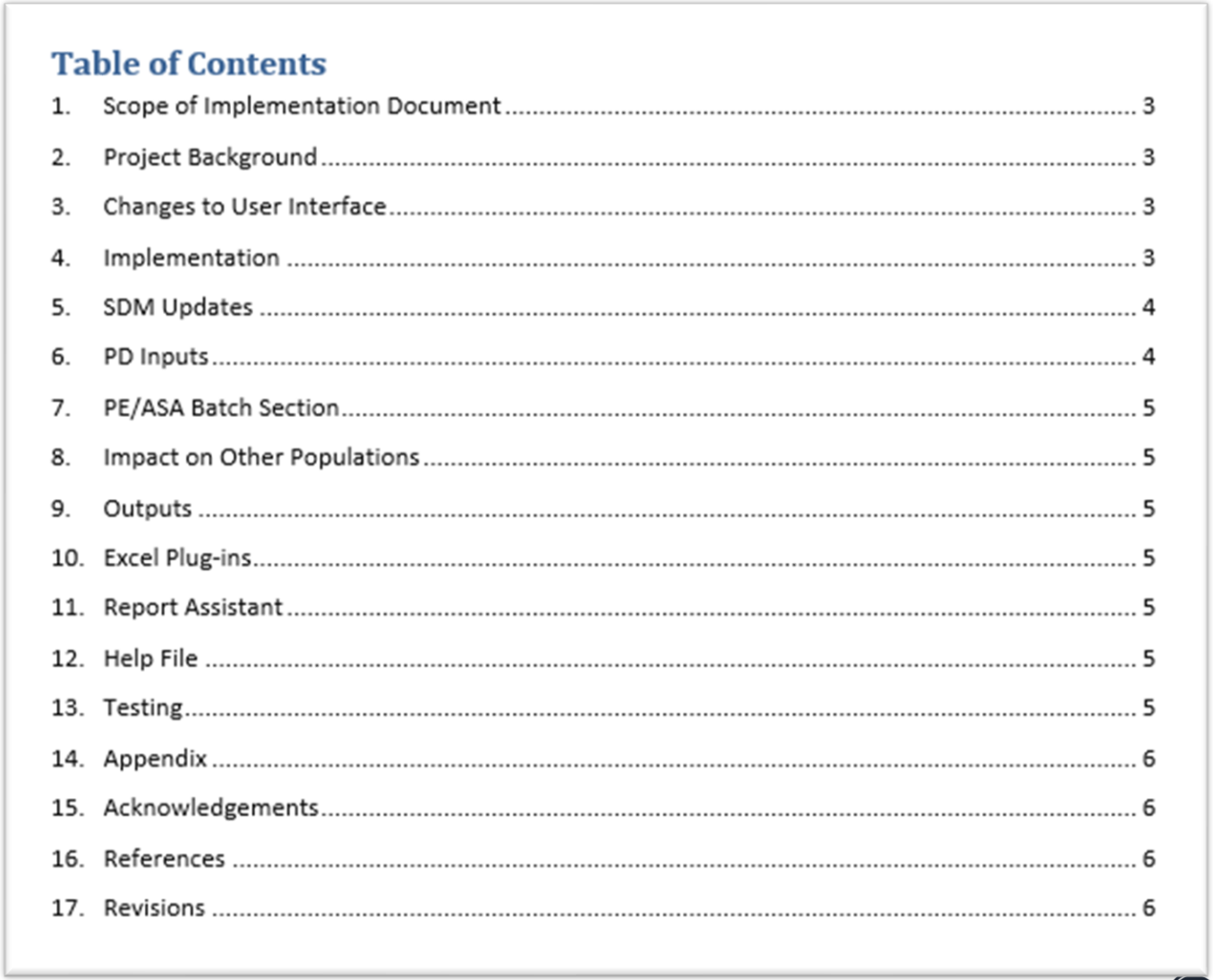
Implementation Documents

Implementation documents are the blueprint for updating, changing and introducing new functions, data, capabilities.
They cover the scientific and design aspects, prepared and reviewed by scientists and reviewed and approved by supervisors.



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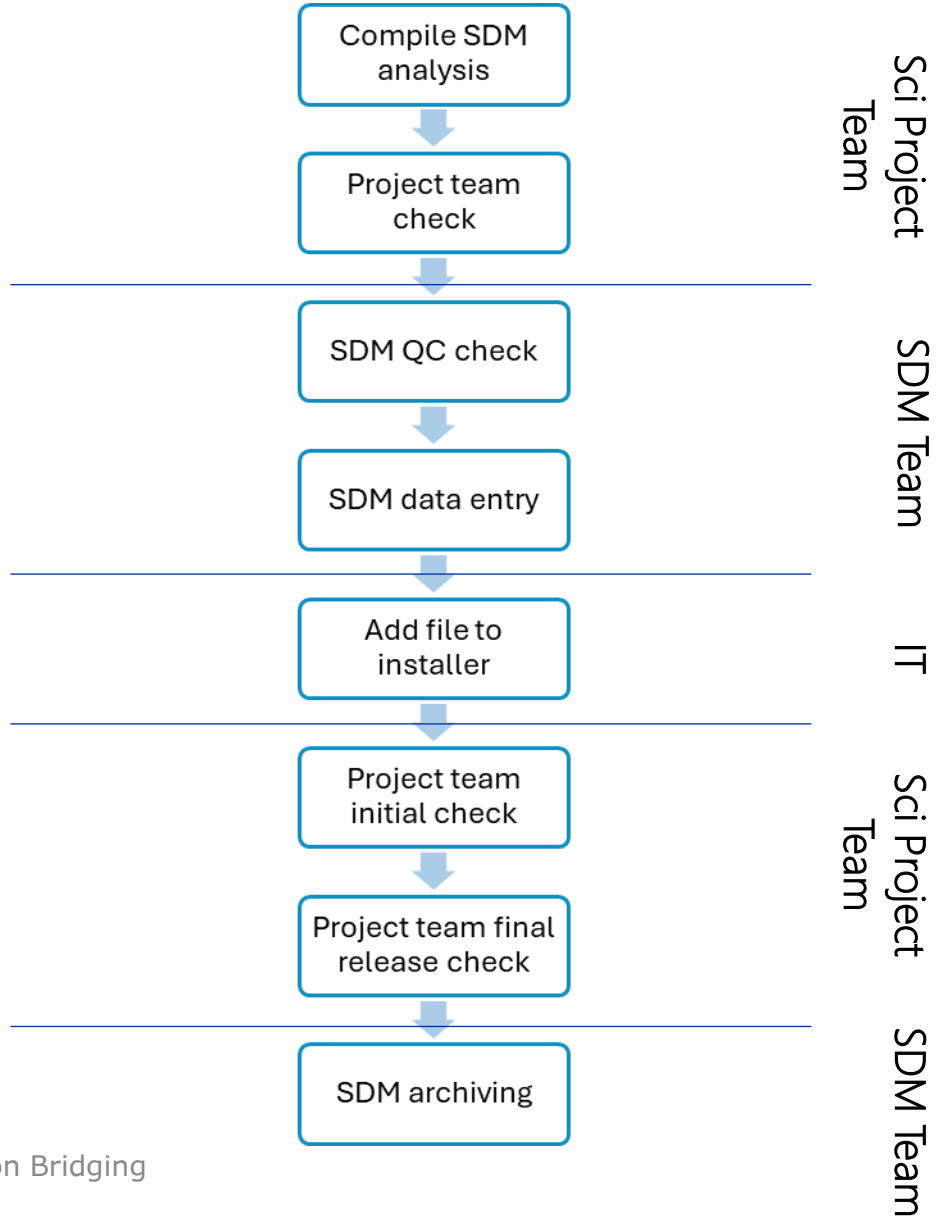
The Simcyp Data Management System (SDM) Workflow

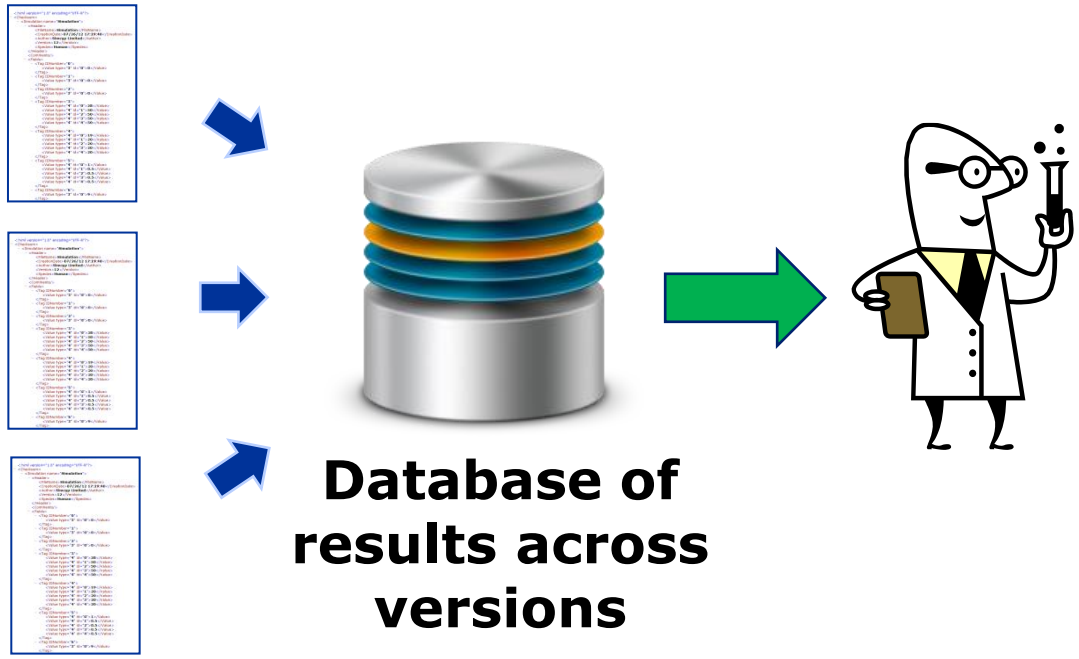
The steps are built into Azure DevOps, to trace, monitor and approve all steps.



Automated/Scientists/Testers (60+); Reproducibility and Verification

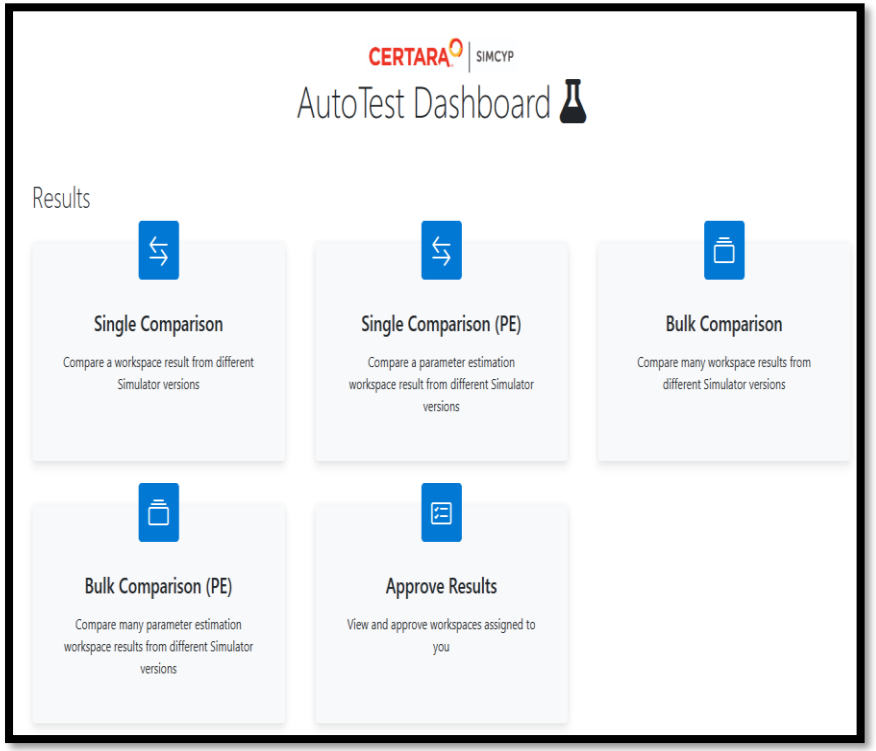
During the course of each version development (>1000 builds) the Simulator is continuously tested against various scenarios (>6000) for verification and regression against previous versions and identifying deviations.

Workspaces (1000s)



Database of results across versions

Updated and expanded after each version



Test Portal

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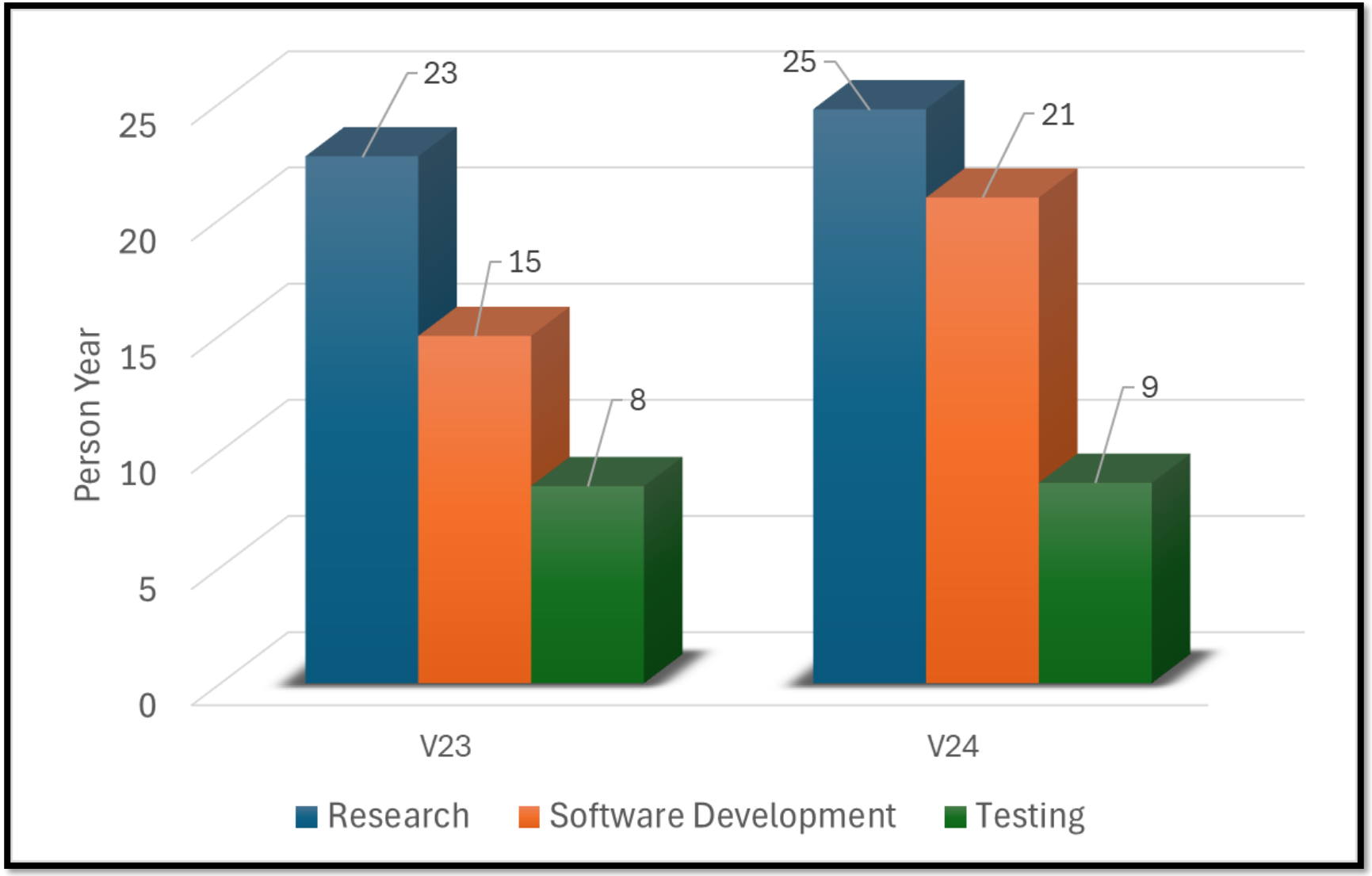
R&D Efforts Gone into Simcyp Simulator V23 and V24



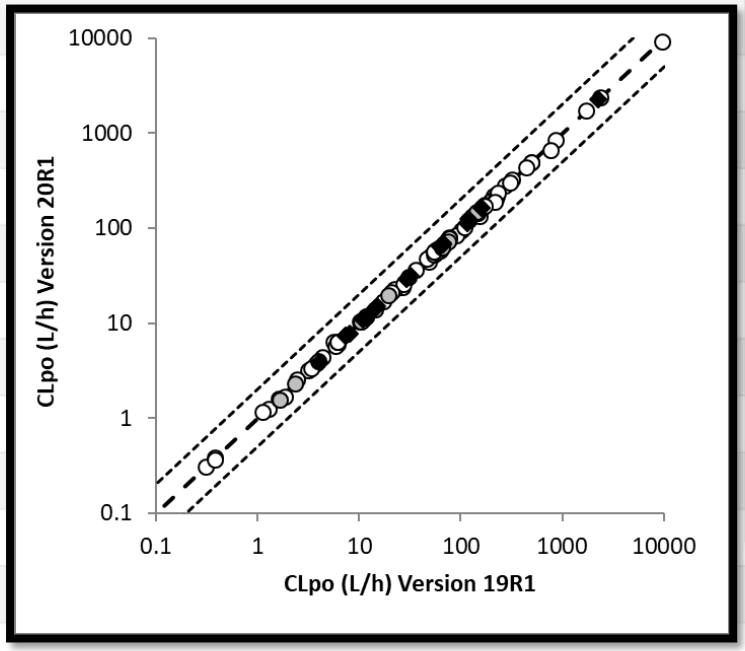
Version Comparisons Reports on ‘Simcyp Members Area’

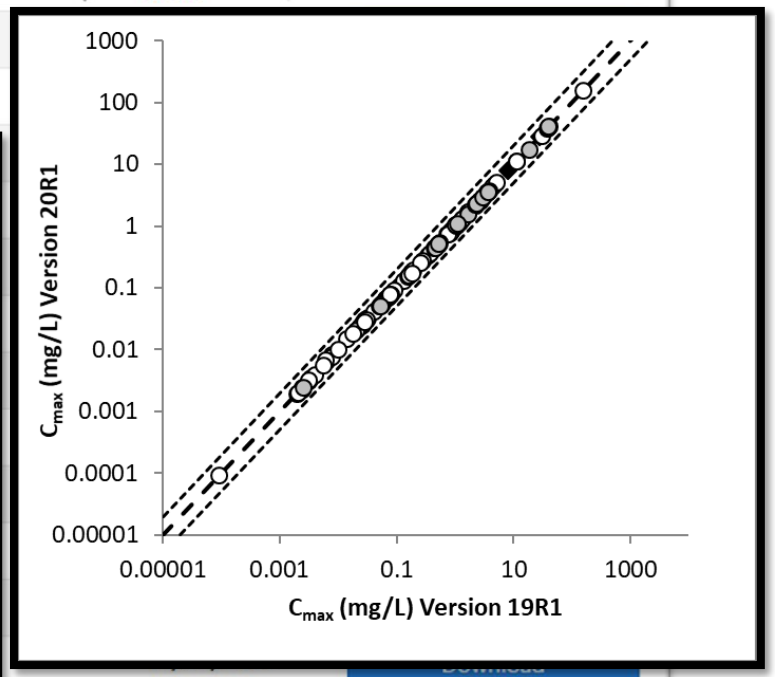
Simcyp Version Comparisons

The Version Comparison repository contains version-to-version comparison documentation of the Sim- and SV- files. The aim is to compare the overall compound file performance relative to the previous version. For updates and changes to a specific compound file, please refer to the **Simcyp Library Files** section and the **Appendix** in the **Simcyp User Guide**.

Show per page 25 Search Search...

File Name	Date	
V23R1_V24R1_VersionComparison_64bit		
V22R1_V23R2_VersionComparison_64bit		
V22R1_V23R1_VersionComparison_64bit		
V21R1_V22R1_VersionComparison_64bit		
V20R1_V21R1_VersionComparison_64bit		
V19R1_V20R1_VersionComparison_64bit		
V18R2_V19R1_VersionComparison_64bit		
V17R1_V18R2_VersionComparison_64bit		
V17R1_V18R1_VersionComparison_64bit		
V16R1_V17R1_VersionComparison_64bit		
V15R1_V16R1_VersionComparison_64bit		
V14R1_V15R1_VersionComparison_64bit		
V14R1_V15R1_VersionComparison_32bit	11/25/2022	Download
V13R2_V14R1_VersionComparison	11/25/2022	Download





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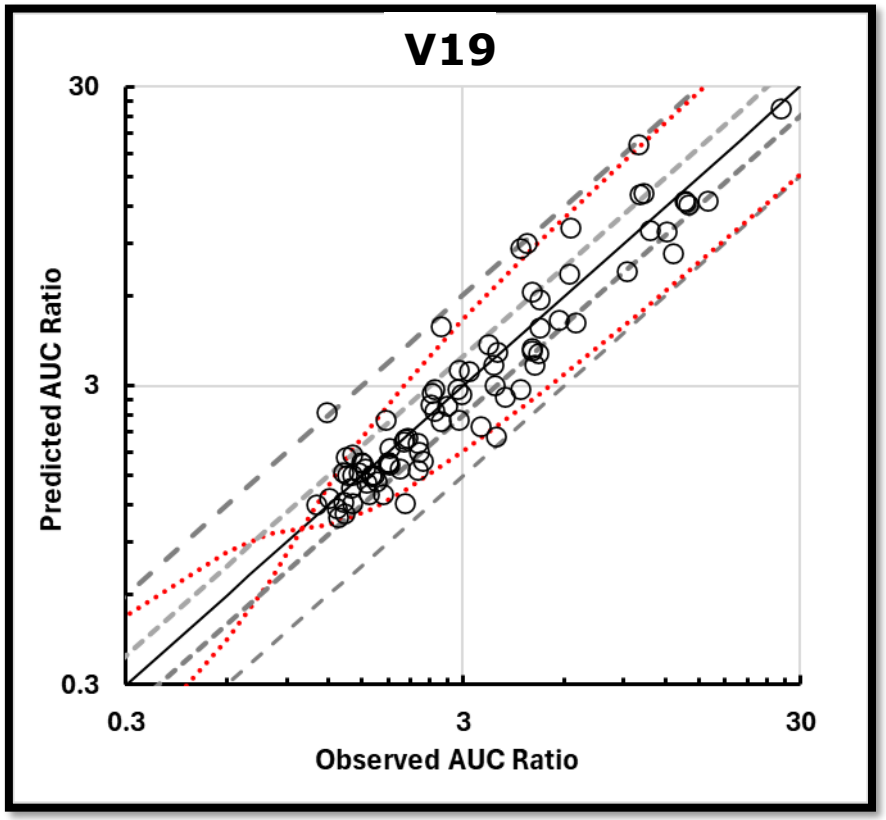
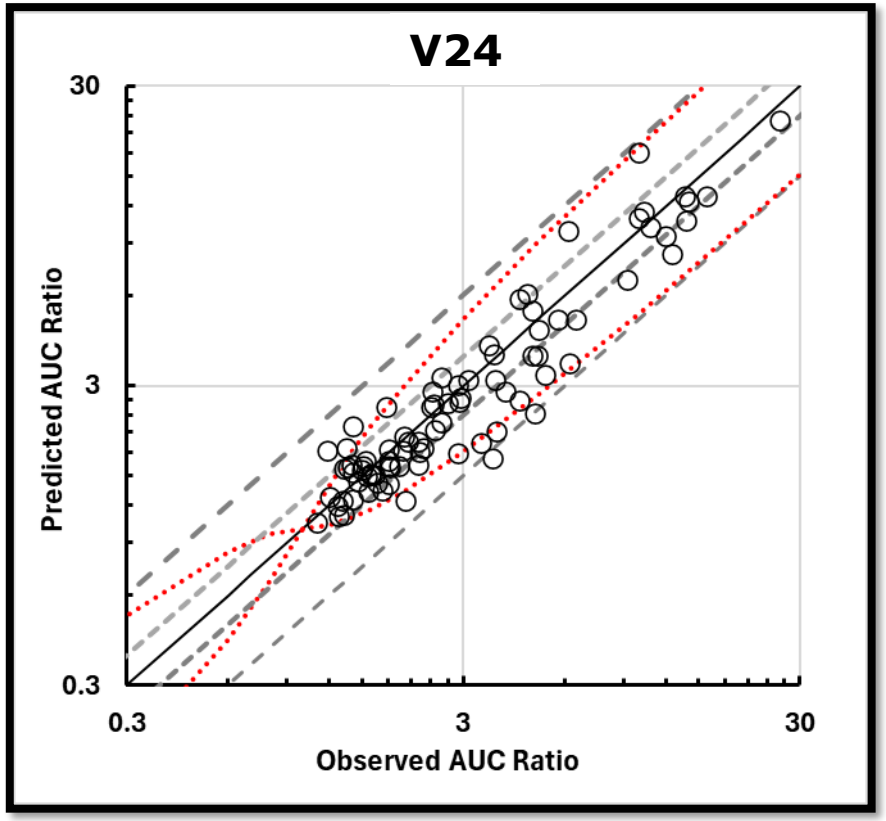
AUC Ratio Comparison (V19 vs V24) for CYP3A4 Matrix (**preliminary**)





AUC Ratio	**V19**	**V24**
AFE (bias)	0.98	0.93
AAFE (precision)	1.21	1.23
Number Studies	92	92

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Conclusions

- For inter-version qualification bridging transparency, quality assurance, traceability and reproducibility are essential.
- New version prediction performance uncertainty quantification can be done by the software developers.
- Alternatively, the analysis can be done withing each submission (as per current EMA PBPK qualification guidance).

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Acknowledgment

The Simcyp Team and Consortium Members

Thank you

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