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Simcyp

Qualification of the Simcyp platform for the intended purposes

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EMA workshop, London, UK
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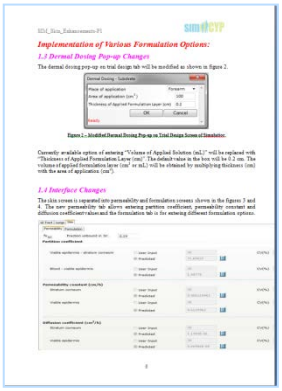
How do we qualify the Simcyp Simulator for intended purposes?

The Simcyp platform qualification is a *process* implemented within a quality assurance by design framework.

Science

Software



Approval

Verification

Gate keeper

Approval

Data, sources / Meta-Analysis

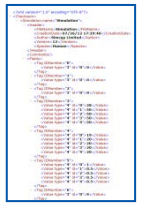
Simcyp Data Management System (SDM)

Quality Assurance Framework

Automated/Scientists (40+) regression/verification analysis

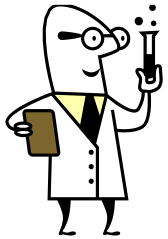
During the course of each version development (up to 100 builds) the Simulator is continuously tested against a subset of workspaces ~50 and periodically tested against a full set of workspaces ~500 for verification and regression against previous versions and identifying deviations.

Multiple Workspaces (100s)



Updated and expanded after each version

Database of results across versions



Test Portal

Automated and scientists (40+) testing

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Transparency and independent scrutiny

Continues publication of algorithms and models including detailed equations, compound and population models, as well as, active interaction with peers and experts expedite qualification.

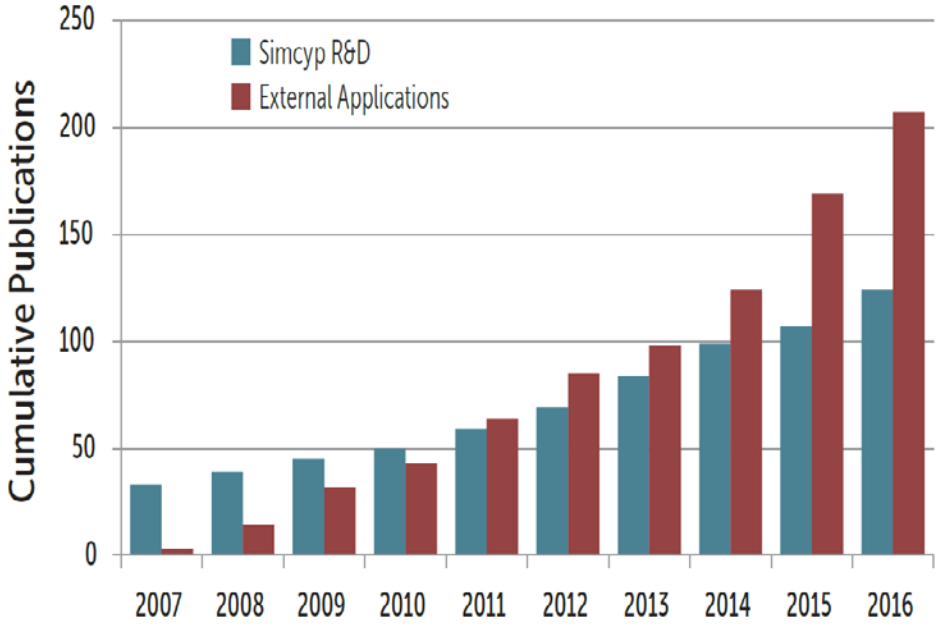
Free academic licenses

Research only: 69

Teaching only: 122

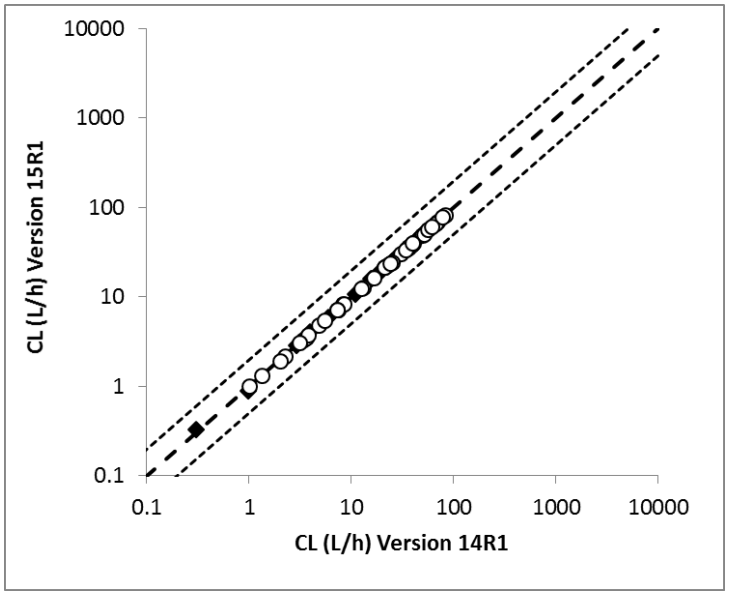
Teaching and research: 1329

Total: 1520

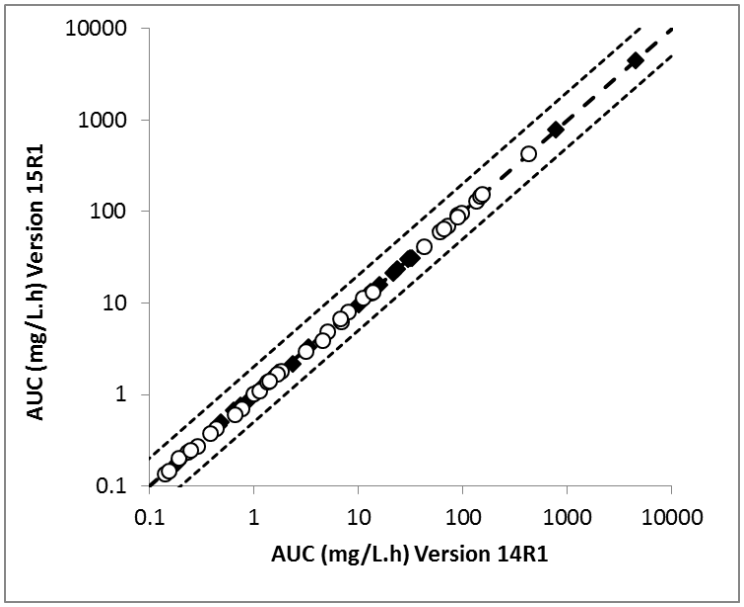


Cumulative peer-reviewed publications

Across version comparisons available to consortium/regulatory scientists



Static parameters



Dynamic parameters

The Version Comparison repository contains version-to-version comparison documentation of the compounds. The aim is to compare the overall compound file performance relative to the previous version.

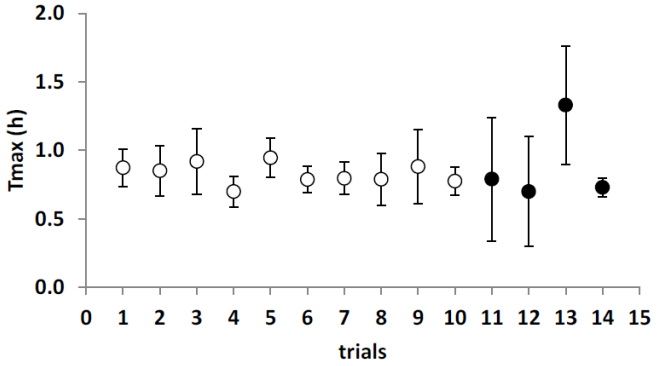
	Download	Size	Updated
	V13R2_V14R1_VersionComparison.pdf	0.44 MB	23/07/2015
	V14R1_V15R1_VersionComparison_32bit.pdf	0.46 MB	07/12/2015
	V14R1_V15R1_VersionComparison_64bit.pdf	0.45 MB	07/12/2015

Qualification of compounds/populations

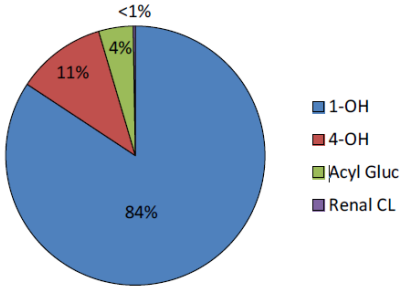
We've been posting summaries on Simcyp members area accessible to consortium/regulatory scientists.

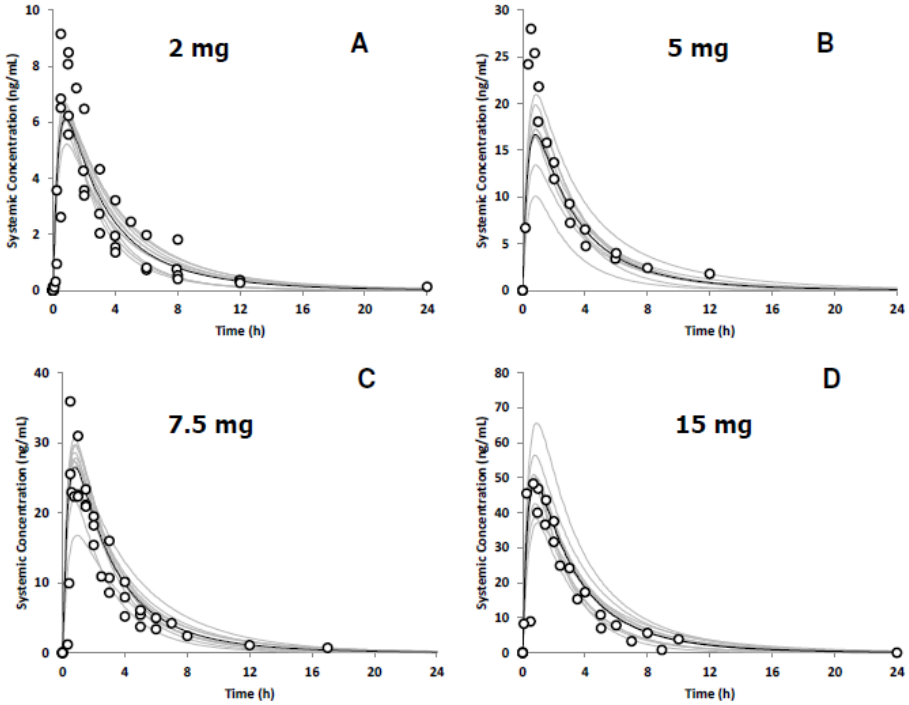
Model Summary

Absorption	1st order absorption	User inputs for fa and ka
Distribution	Minimal PBPK	User input for V_{ss}
Elimination	Enzyme kinetics	Recombinant data for CYP3A4 and CYP3A5; renal clearance from clinical studies



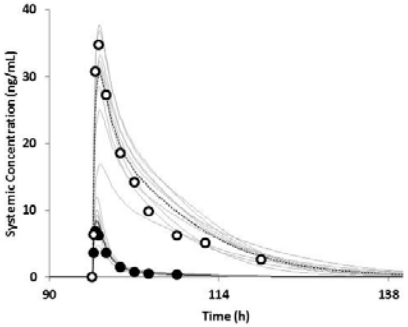
Key PK parameters including t_{max}, C_{max}, V_{ss}, CL, CL_{PO}





Qualification against a range of observed datasets

Victim compounds: Verification of fm among other parameters



DDIs of specific CYP inhibitors

	Observed		Predicted	
	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
Fluconazole + Midazolam po	2.30	3.79	1.92 (1.72 - 2.21)	3.16 (2.65 - 3.75)
Ketoconazole + Midazolam po	4.24	15.1	3.67 (3.06 – 4.68)	12.74 (10.71 - 14.85)
Ketoconazole + Midazolam iv		4.80		4.56 (3.61 – 5.53)

CYP3A4

	Observed		Predicted	
	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
Quinidine + Dextromethorphan	6.10	6.34	3.77 (2.85 – 4.38)	5.02 (3.75 – 5.63)
Quinidine + Dextromethorphan	4.38	7.31	3.90 (3.62 – 4.22)	5.38 (5.04 – 5.83)

CYP2D6

	Observed		Predicted	
	C_{max} ratio	AUC ratio	C_{max} ratio	AUC ratio
Fluvoxamine + caffeine	1.46	13.71	1.31 (1.18 – 1.53)	11.10 (7.82 – 14.69)
Ciprofloxacin + caffeine	1.07	1.17	1.08 (1.07 – 1.11)	1.20 (1.13 – 1.27)

CYP1A2

Also, looking into site of metabolism/interaction (liver vs gut) whenever possible e.g. midazolam.

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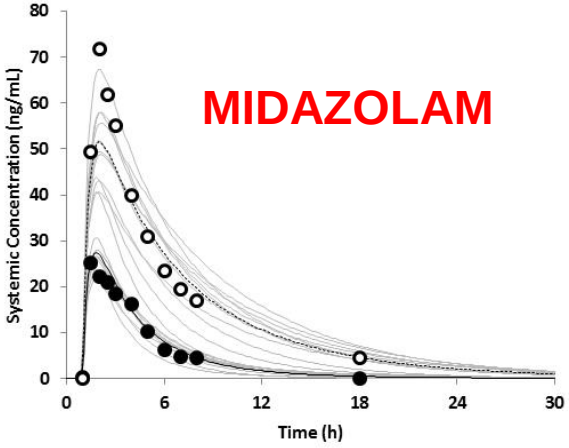
Perpetrator compound qualification

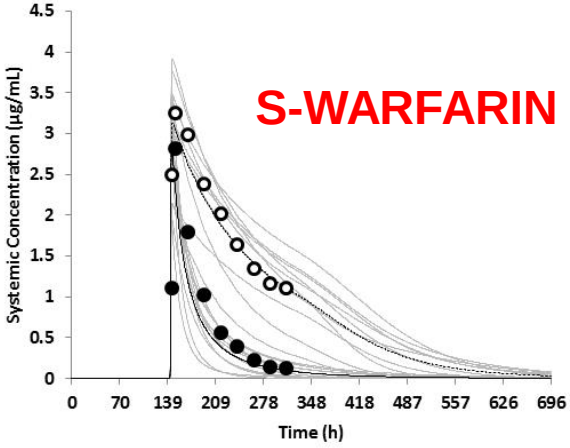
FLUCONAZOLE

Inhibitor of CYP3A4: Inhibitor of CYP2C9: Inhibitor of UGT2B7

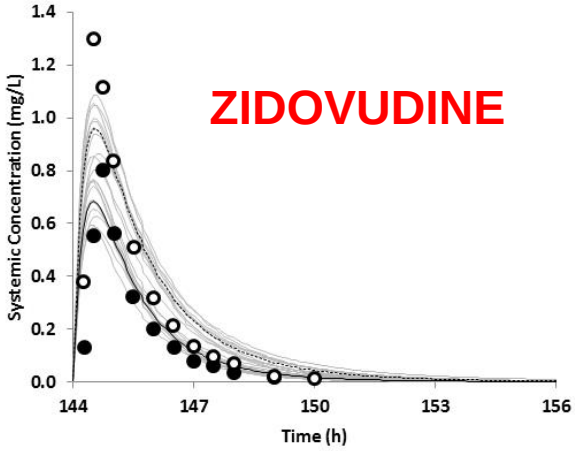
DDI with CYP3A4



DDI with CYP2C9



DDI with UGT2B7



Parameter	Ratio C_{max}	Ratio AUC
Mean	1.36	1.70
Trial 1	1.28	1.62
Trial 2	1.38	1.75
Trial 6	1.32	1.65
Trial 7	1.38	1.74
Trial 8	1.35	1.68
Trial 9	1.40	1.81
Trial 10	1.39	1.75
Observed	1.47	1.63

TRIAZOLAM

2C9 substrate	Fluconazole dose	Observed AUC ratio	Mean Predicted AUC ratio (trial range)
Tolbutamide	150mg SD	1.90	1.38 (1.34 -1.40)
Tolbutamide			– 1.68)
Phenytoin			- 1.56)
Phenytoin	200mg QD	1.88	1.41 (1.33 - 1.52)

TOLBUTAMIDE
PHENYTOIN

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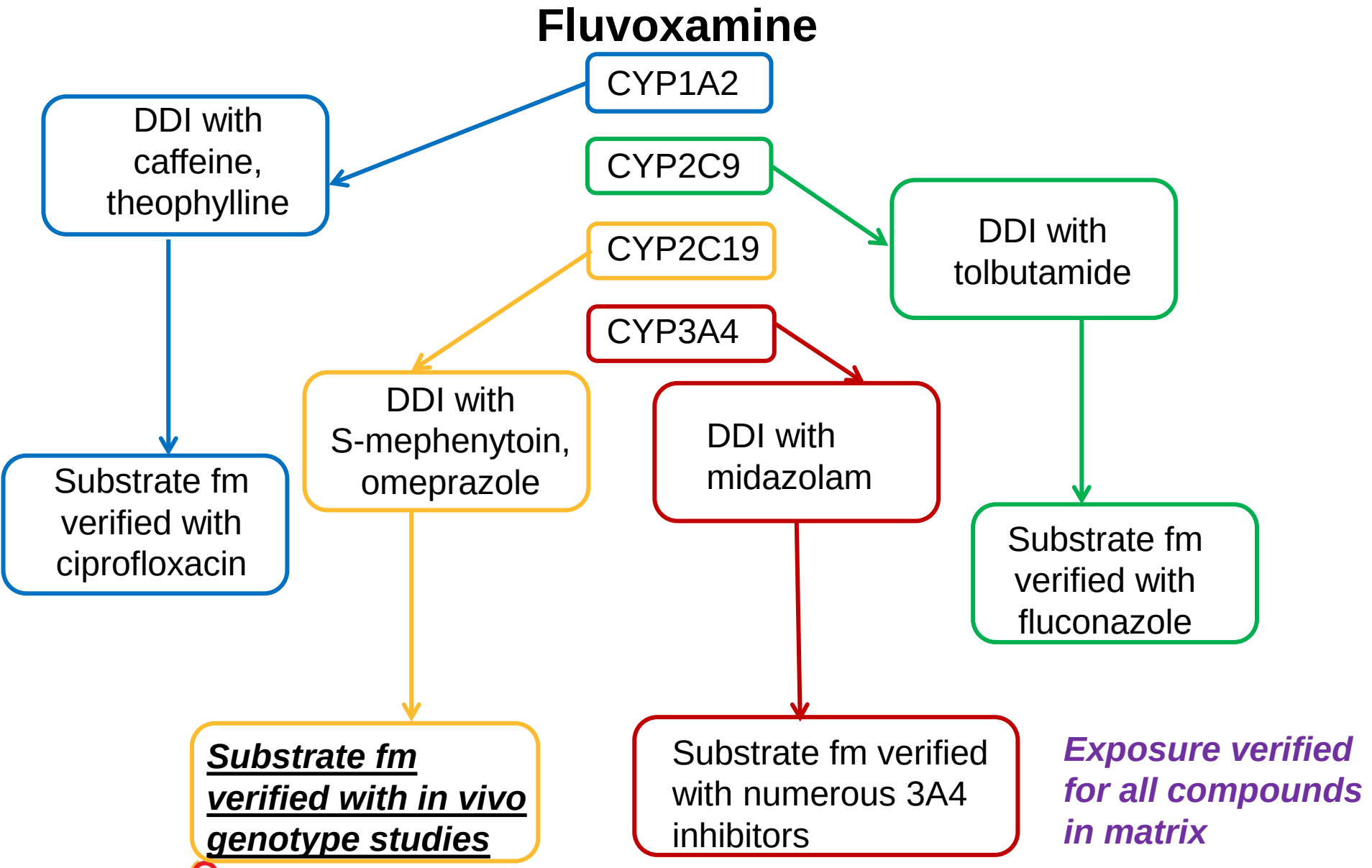
Matrix approach for perpetrators qualification



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Qualification processes/datasets

The three practical qualification processes seem to be adequate. However, the qualification by “learned societies” may need clarification.

Qualification datasets for site of inhibition can be challenging while alternative solutions, e.g. accurate prediction of AUC may indicate the model reliability.

Line 236:
“Again, the qualification will only be valid for situations covered by the qualification dataset, e.g. only for the specific enzyme(s), ***site of inhibition (e.g., liver, intestine)*** and the type of background data (including pharmacokinetic data, the system parameters and the population used) on which the simulations were based.

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In a constructive way - what changes would you propose?

"Accurate prediction" is mentioned but isn't defined?

Line 417:
"Sensitivity analysis should be performed for ***all parameters that are likely to markedly*** influence the outcome of the simulated pharmacokinetics and/or the model application."

The use of sensitivity analysis should be targeted/specific to parameters which are uncertain and/or specific assumptions made.

We know, for example, changing tissue blood flows and organ sizes will change the PK profile but is this a useful/necessary exercise?

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In a constructive way - what changes would you propose?

Line 399:
“Consideration should be given to whether there are parameters in the model that are ***correlated*** and if there is uncertainty in the value of ***more than one*** of the parameters. In the case that an ***identifiability issue is suspected*** additional in vitro or clinical data may be required to increase certainty in the parameters. A description on how ***any identifiability issues*** have been handled should be given. ”

In a mechanistic PBPK model, almost all parameters are (and have to be) correlated. Further, given the structure of population based PBPK models, there are many cases where identifiability can be an issue. Identifiability issues only in certain cases need investigation.

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Thank you for your attention!