PREPARATION MEETING: QUALIFICATION OF THE SIMCYP SIMULATOR (V19 R1) FOR PREDICTION OF DDIS INVOLVING CYP-MEDIATED INHIBITION

Initial Qualification Procedure Case EMA/SA/0000102776

Agenda

- Introductions
- Scope of qualification
- Context of use statements
- Supporting documentation
- Quality assurance procedures

Scope of Qualification

- Certara UK Ltd is seeking the EMA qualification opinion on the suitability of the Simcyp Simulator, as a tool to predict CYP-mediated DDIs of victim and perpetrator drugs involving inhibition following oral and IV administration.

- Specifically, Certara UK Ltd is considering this approach as a candidate for novel methodology qualification and is seeking the EMA opinion on the use of the Simcyp Simulator (V19 R1) as a tool to address the intended purpose as proposed in the context of use (COU) statements for high impact decisions, as per the draft EMA guideline document.

Context of Use Statements (1)

- **The Simcyp Simulator (V19 R1) can be used to predict:**
  - **the effects of weak and moderate CYP inhibitors on the exposure of a drug when a clinical study with a strong CYP inhibitor has been conducted (and used to verify the fmCYP).**
  - **the CYP-mediated inhibitory effect of a drug on the exposure of other CYP substrates when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the competitive inhibition effect *in vivo*).**
  - **the CYP-mediated MBI effect of a drug on the exposure of other CYP substrates when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the MBI effect *in vivo*).**

Context of Use Statements (2)

- For scenarios where no clinical studies have been conducted, the Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated inhibitory effect of a drug on the exposure of relevant CYP substrates (V19 files) if the predicted change in exposure of the substrate (because of competitive or MBI) falls in the range of the qualification dataset and in addition, the inhibitory potency of the drug falls in the range of the qualification dataset.
- Sensitivity analyses on relevant parameters (range based on uncertainty associated with measurement) should be conducted to assess the risk of predicting a false negative.

Context of Use – Drugs as Victims

Question of interest:

How should an investigational new drug (IND) which is metabolised by CYP3A4 (for example) be dosed when co-administered with corresponding CYP3A4 inhibitors?

Context of use:

The Simcyp Simulator (V19) can be used to predict the effects of weak and moderate CYP3A4 inhibitors (V19 files) on the exposure of the IND when a clinical study with a strong CYP3A4 inhibitor has been conducted (and used to verify the fmCYP3A4).

NOTE: No clinical DDI studies are proposed with weak and moderate CYP3A4 inhibitors.

Context of Use – Drugs as Perpetrators

Question of interest:

How should CYP3A4 drugs (for example) that are comedications be dosed when co-administered with an investigational new drug (IND) that is a CYP3A4 inhibitor?

Context of use (Scenario 1):

The Simcyp Simulator (V19) can be used to predict the CYP3A4-mediated inhibitory effect of an IND on the exposure of other CYP3A4 substrates (V19 files) when a clinical study with a sensitive CYP3A4 substrate has been conducted (and used to verify the inhibitory effect in vivo).

NOTE: No clinical DDI studies are proposed with CYP3A4 comedications.

Context of Use – Drugs as Perpetrators

Question of interest:

How should CYP3A4 drugs (for example) be dosed when co-administered with an investigational new drug (IND) that is a CYP3A4 inhibitor?

Context of use (Scenario 2):

The Simcyp Simulator (V19) can be used to predict the CYP3A4-mediated inhibitory effect of an IND on the exposure of CYP3A4 substrates (V19 files.

Sensitivity analyses on relevant parameters (range based on uncertainty associated with measurement) should be conducted to assess the risk of predicting a false negative.

NOTE: No clinical DDI studies are proposed with CYP3A4 drugs.

Supporting Documentation

Towards Qualification - CYP Inhibition

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ARTICLE

Prediction of CYP-mediated DDIs involving inhibition: Approaches to address the requirements for system qualification of the Simcyp Simulator

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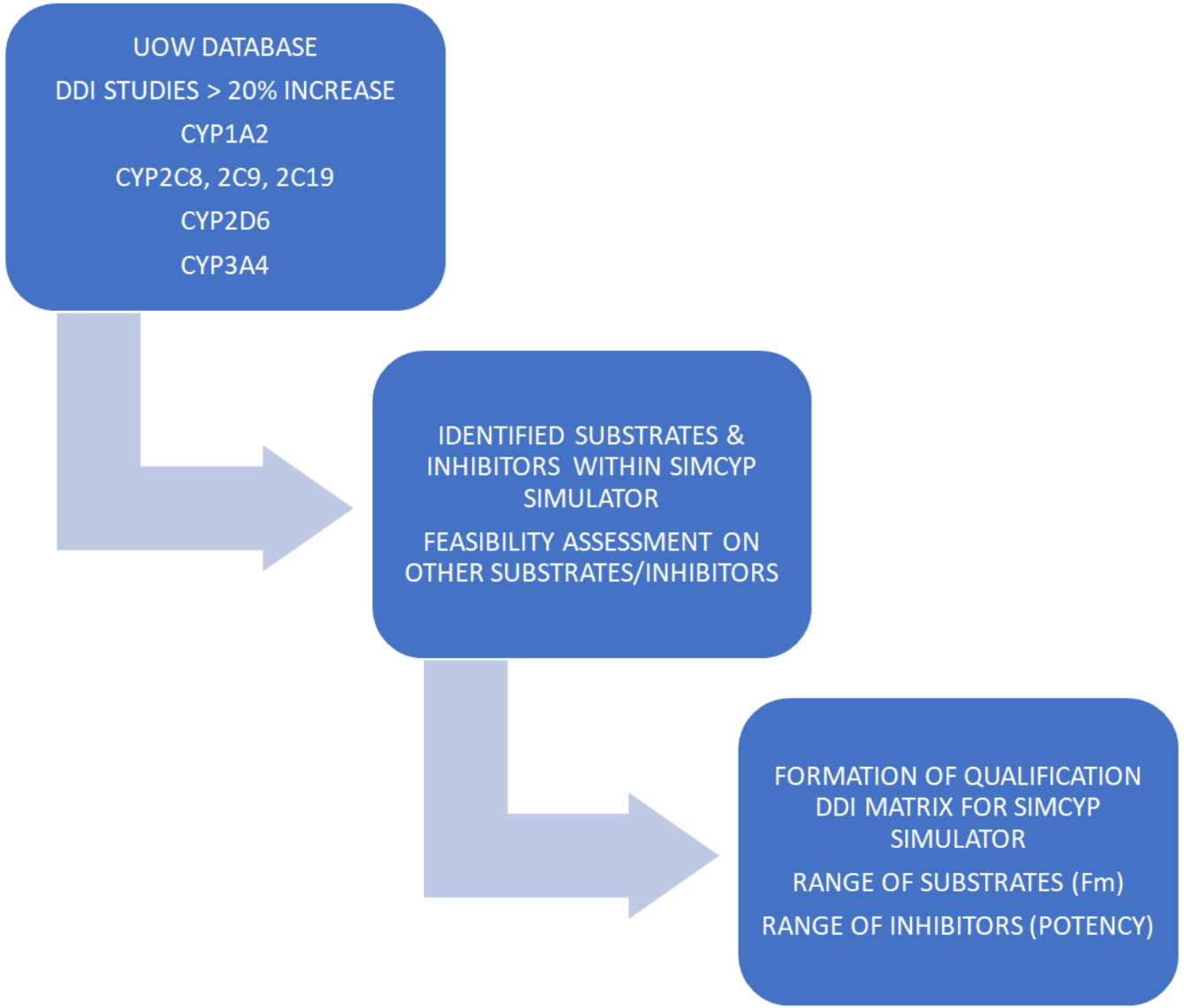
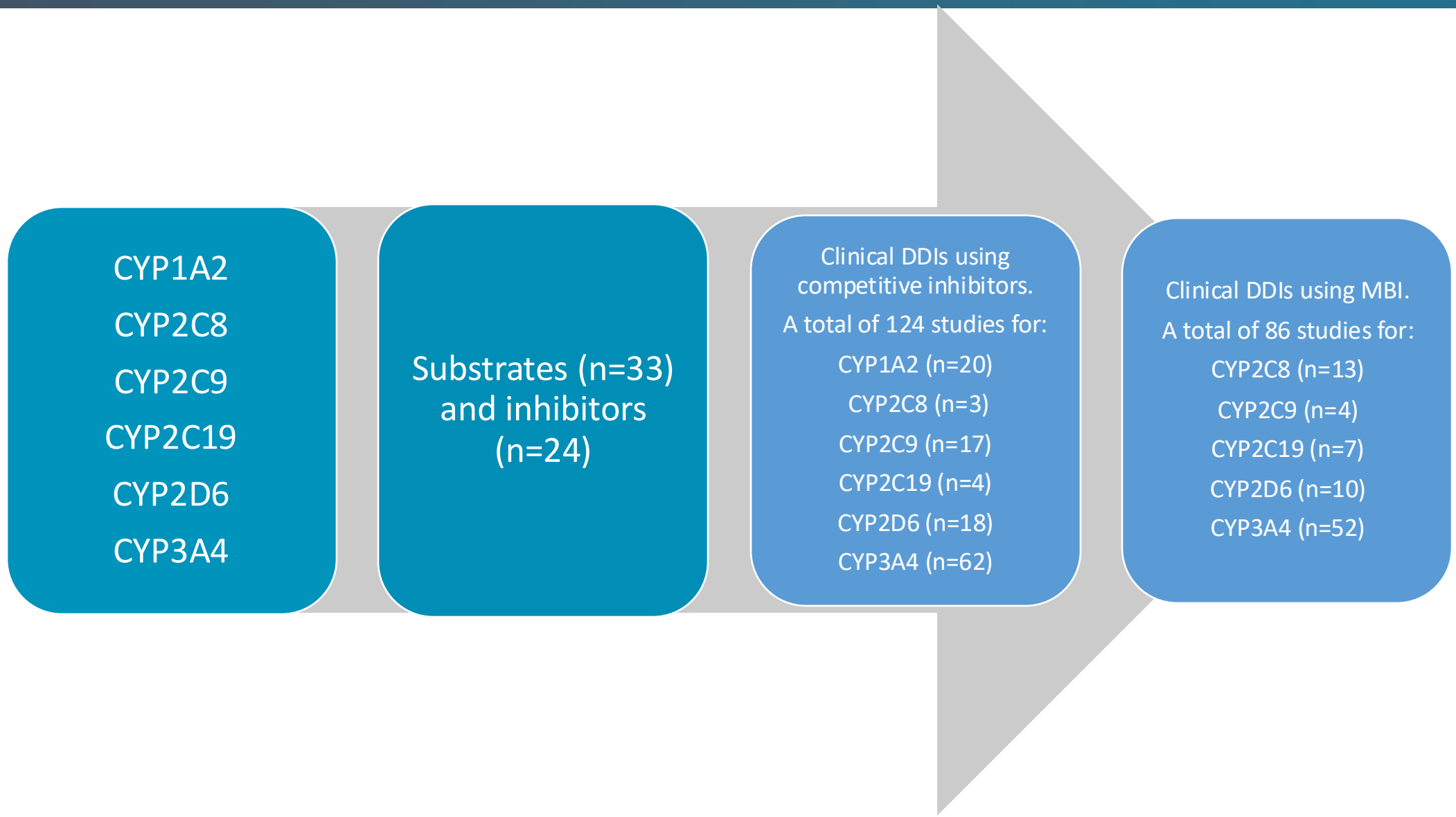
CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A

COMPETITIVE INHIBITION & MBI

Workflow Used to Derive DDI Qualification Matrix



Qualification DDI Matrix

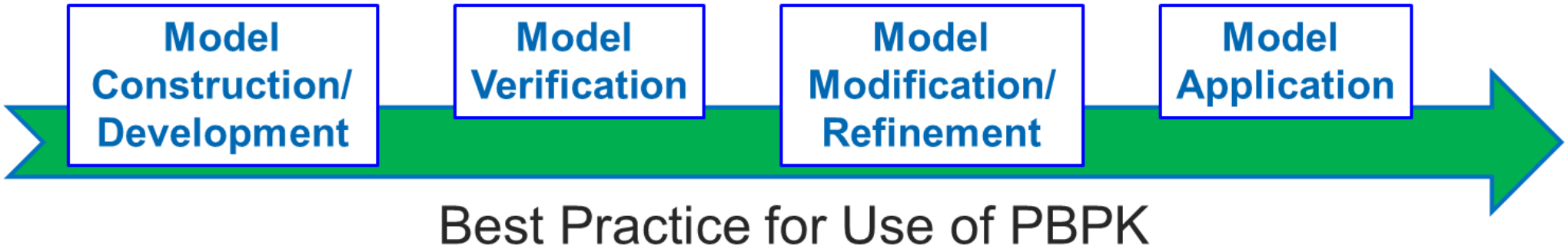


Substrate Characteristics

Enzyme	Substrate	fm%	Fg	F
CYP1A2	Caffeine	97.9	1	0.81
	Theophylline	75.8	1	0.83
	Tizanidine	96.6	1	0.16
CYP2C19	S-Mephenytoin	85.8	0.89	0.34
	Omeprazole	77.9	0.96	0.5
	Imipramine*	38.31	1	0.38
CYP2C8	Amiodarone	32.2	0.73	0.38
	Repaglinide	66.1	0.92	0.76
	Rosiglitazone	56.1	1	0.93
CYP2C9	Celecoxib	83.5	0.77	0.51
	Flurbiprofen	81.9	0.96	0.92
	Phenytoin	73.1	1	0.79
	S-Warfarin	98.4	0.99	0.86
	Tolbutamide	96.8	0.99	0.84
CYP2D6	Atomoxetine	78.6	0.91	0.61
	Desipramine	81.8	0.95	0.44
	Dextromethorphan	87.7	0.9	0.21
	Metoprolol	73.9	0.97	0.45
	Nebivolol	85.7	0.92	0.17
	Tolterodine	82.7	0.99	0.29

CYP3A4/5	Alfentanil	91.8	0.54	0.34
	Alprazolam	71	1	0.83
	Amiodarone	47.1	0.73	0.38
	Aprepitant	85.2	0.6	0.48
	Atazanavir	80.2	0.94	0.36
	Clarithromycin	73.6	0.85	0.51
	Dexamethasone	86.1	0.99	0.76
	Ibrutinib	95	0.4	0.04
	Midazolam	96.2	0.6	0.29
	Nifedipine	99.8	0.67	0.42
	Quinidine	71.7	0.95	0.66
	Rifabutin	66	0.14	0.11
	Repaglinide	33.7	0.92	0.76
	Sildenafil	86	0.67	0.38
	Simvastatin	88.7	0.12	0.04
	Triazolam	97.1	0.74	0.51
	Zolpidem	48.2	0.95	0.79

Development of Substrate and Inhibitor Files



Compound File Summaries

CERTARA® | SIMCYP

Compound Name: Midazolam

Property	Value
Compound type:	Substrate
Prefix:	Sim
Species:	Human
File data last updated:	V19 compound ADAM absorption option Km updated for CYP3A5 formation of 4-OH UGT data changed to HLM
Population used for verification:	Sim-Healthy Volunteer

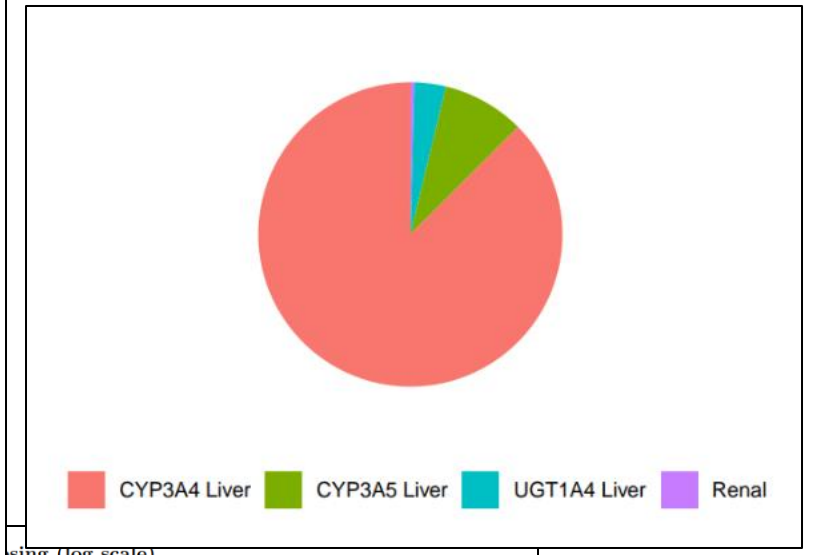
Simcyp Version this document relates to: V19r1

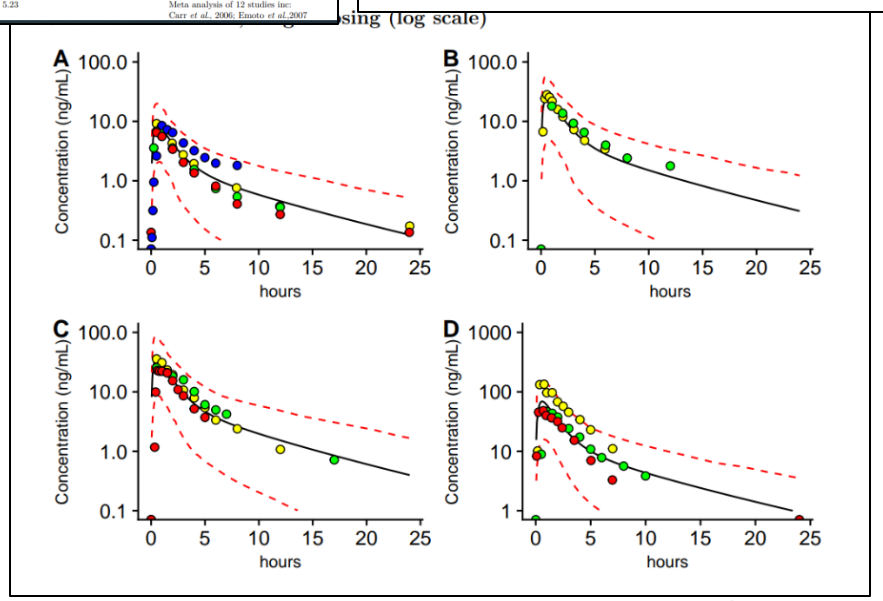
Prepared: April 2021

The Sim-Midazolam model within the Simcyp Compound Database has been developed as a probe substrate of CYP3A4.

Table 4 Input parameters for **SIM-Midazolam**

Parameter	Value	Method/Reference
Molecular weight (g/mol)	325.8	Pubchem
Log P	3.53	Calculated in ALOGPS 2.1
Compound Type	Monoprotic base	Simcyp data archive
pKa	6.0	Simcyp data archive
B/P	0.603	Meta analysis of 4 studies including (Allonen *et al.*, 1981; Heizmann *et al.*, 1983)
fu	0.032	(Greenblatt *et al.*, 1984; Vinik *et al.*,1983; Thummel *et al.*,1996)
Main binding protein	Human serum albumin	(Boman, 1973)
fa	1	Assumed
ka (1/h)	3	(Allonen *et al.*, 1981)
fu_{gut}	1	Default
Q_{gut} (L/h)	16.184	
Distribution Model	Minimal PBPk model	
Vss (L/kg)	0.88	(Kupferschmidt *et al.*, 1995)
Kin (1/h)	0.2	Derived from (Kupferschmidt *et al.*, 1995)
Kout (1/h)	0.25	Derived from (Kupferschmidt *et al.*, 1995)
V_{SAC} (L/kg)	0.23	Derived from (Kupferschmidt *et al.*, 1995)
Metabolism	Enzyme kinetics	
Enzyme	CYP3A4	
Pathway	1-OH	
V_{max} (pmol/min/pmol)	5.23	Meta analysis of 12 studies inc: Carr *et al.*, 2006; Emoto *et al.*,2007





Version 19 – DDI Analysis

UOW search Strategy

Files

Feasibility analysis findings

Analysis	Files for Analysis	Documentation for Simcyp

• **Qualification DDI matrix**
• **CYP1A2, CYP2D6 CYP2C8,9,19 CYP3A4**
• **Victims (n=34) and perpetrators (n=24)**
• **Competitive inhibition (n=124 studies)**
• **MBI (n=86 studies)**
	• Excel file for analysis
	• **Workspaces for each study design**
	• Outputs for each study design
	• **Table of clinical study design and observed results**
	• **References for the clinical studies**
		• References for model code – DDI
		• **Compound file summaries:**
		  • **indicating source of input parameters**
		  • **verification as victim or perpetrator (profiles and PK)**

Items in red will be provided.

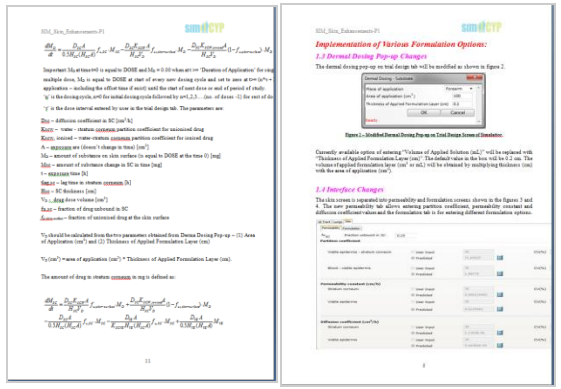
Items in bold black have been provided.

Quality Assurance Procedures

Simulator Expansion/Modification Processes

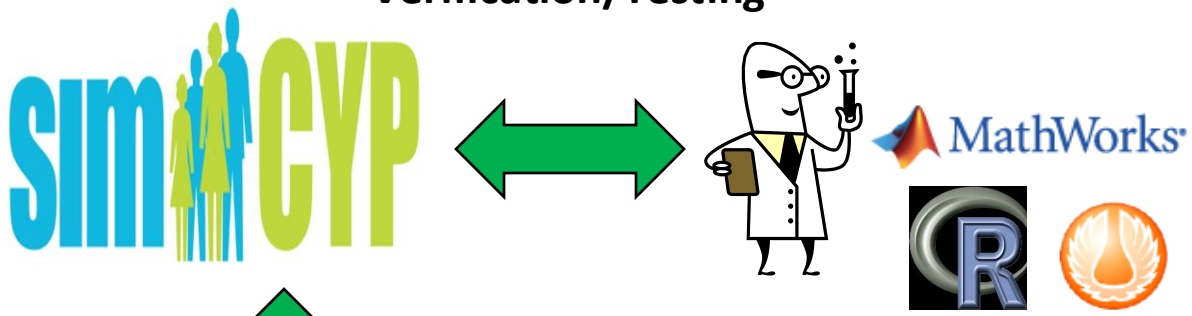
The Simcyp platform is developed and maintained under a robust Quality Assurance framework governed by various Standard Operating Procedures.

Fully Documented Scientific and Software Design



Approval

Verification/Testing



Gate keeper

Data, sources / Meta-Analysis

Approval

Simcyp Data Management System (SDM)

Quality Assurance Framework

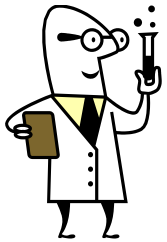
Automated/Scientists/Testers (50+) regression/verification analysis

During the course of each version development (up to 300 builds) the Simulator is continuously tested against a subset of workspaces ~ 100 and regularly tested against a full set of workspaces ~4000 for verification and regression against previous versions and identifying deviations.

Multiple Workspaces (1000s)

Updated and expanded after each version

Database of results across versions



Test Portal

Automated, scientists, testers (50+) testing

Version Comparison Report

After each release a report documenting the Simulator performance of compounds library against the previous version is provided in Simcyp Members Area. This includes AUC, C_{max}, T_{max}, CL_{iv}, CL_{po}, fa f_G, f_H, and V_{ss}.

Diagnostic plots - Dynamic simulations

The solid line represents the line of unity and the dashed lines a 2-fold difference in the following plots.

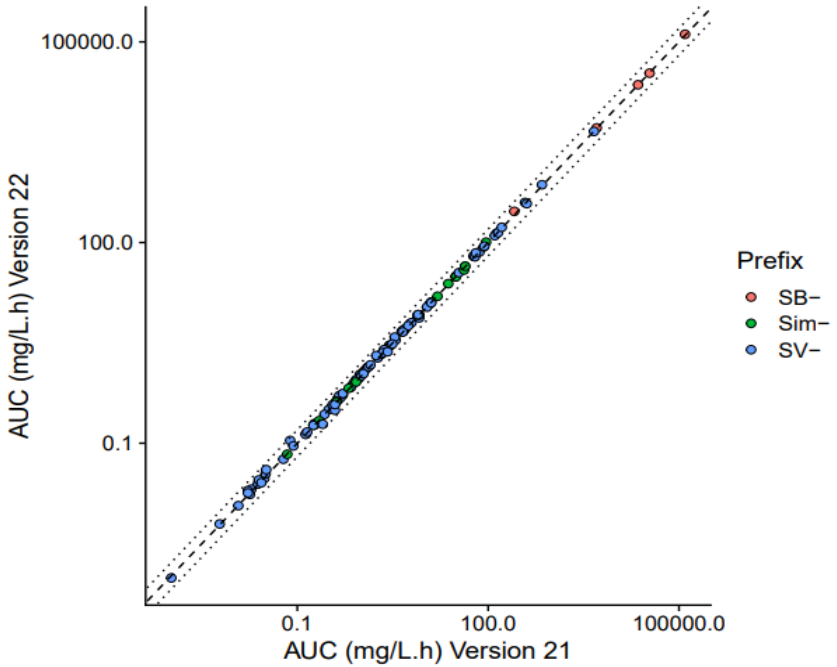


Figure 1. Mean simulated AUC (mg/L*h) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

Deviations

The table below shows the relative difference in pharmacokinetic parameters for the SV and Sim Compound files when they are run in V22 and V21. Results are presented as a percentage with 100% meaning no difference in the results for that compound between V22 and V21.

	PKPD Parameters						PKPD Profiles			
Name	**CLiv**	**CLpo**	**Fa**	**Fg**	**Fh**	**Vss**	**Cmax**	**Tmax**	**AUC**	**Dose/AUC**
Alfentanil	101	98	101	98	101	101	102	116	96	100
Alprazolam	100	103	99	100	100	101	97	99	101	103
Atazanavir	102	169	98	66	102	47	105	87	100	101
Atomoxetine	95	90	99	101	103	98	104	101	106	91
Atomoxetine-PM	97	99	99	100	100	98	100	100	101	99
Atorvastatin	101	102	105	92	102	102	124	68	95	104

An example of calculations documentation – Static DDI

4. Implementation

	Work item type	Title	Description	Acceptance criteria	Priority
1	User Story	Calculation of $R_{2,ICH}$	On Basic (Cut-off) Models → Mechanism Based Inhibition screen, algorithm for calculating $R_{2,ICH}$ (Figure 3)	To convert on-screen I_{max} (mg/L) ($I_{max,\ on\text{-}screen}$) to I_{max} (µM): $I_{max}(\mu M) = \frac{I_{max,on-screen}}{MW} * 1000$ Where "Imax,on-screen" is the Imax in mg/L shown on-screen as an inhibitor input parameter $k_{obs,h,ICH}(1/h) = \frac{k_{inact}*5*I_{max}*fup}{K_{app}*fu_{inc}+5*I_{max}*fup}$ $I_{gut}(\mu M) = \frac{\left(\frac{Dose}{MW}\right)}{0.25} \times 1000$ $R_{2,ICH} = \frac{k_{obs,h,ICH}+k_{deg,h,ICH}}{k_{deg,h,ICH}}$ Where $k_{deg,h,ICH}$ is the hepatic enzyme turnover values for the specific enzymes selected by the user on this screen. The values are to be taken from the entries on the *System Parameters* tab (Figure 7). The value in the 'ICH column' is used for the calculation. Calculation of R_2 and $R_{2,gut}$ are not affected. The $k_{deg,h}$ and $k_{deg,g}$ values in the 'Simcyp column' are used for the R_2 and $R_{2,gut}$ calculation. If $R_{2,ICH}$ >= 1.25 display red cross and ***'Interaction above threshold'*** next to the $R_{2,ICH}$ box. Else display green tick and ***'Interaction below threshold'***.	1
				If R_2 >= 1.25 display red cross and ***'Interaction above threshold'*** next to the R_2 box. Else display green tick and ***'Interaction below threshold'***. If $R_{2,gut}$ >= 1.25 display red cross and ***'Interaction above threshold'*** next to the R_2 box. Else display green tick and ***'Interaction below threshold'***.	

An example of calculations documentation – Transporters

In the case of user selection of the ISEF,T approach and $CL_{int,T}$, the intrinsic transporter clearance ($CL_{int,T,in\ vitro,i}$ (µL/min/pmol transporter) from an *in vitro* activity experiment for any of the transporter functionalities i.e., $CL_{out\text{-}uc\text{-}pt}$ → Apical Efflux, $CL_{out\text{-}cb\text{-}pt}$ → Basal Efflux, $CL_{in\text{-}uc\text{-}pt}$ → Apical Uptake and $CL_{in\text{-}cb\text{-}pt}$ → Basal Uptake, is scaled according to **Equation 6** for the whole proximal tubule clearance (all 3 segments). Note that for **Equation 6**, rather than specifying the clearance functionality as the result (left side of equation) we use $CLu_{int,T,i}$ (L/h) as it represents all functionalities.

The following equations should be applied to ALL transporters in MechKiM according to their localisation and functionality.

Units of parameters in the following equations: The majority of parameters units are already defined above, but those that are distinct for the ISEF,T equations are provided as follows: $CL_{int,T,in\ vitro,i}$ in µL/min/pmol transporter; *In vitro* derived maximal flux capacity $J_{max,in\ vitro,i}$ in pmol/min/pmol transporter, the transporter isoform protein abundance in the kidney, $Abundance_{K,i}$ in pmol/million PTC (mean provided on Population>Kidney screen (**Figure 3**), the Inter-System Extrapolation factor for Transporter ISEF, T is unit-less.

$$CLu_{inT,i}\left(\frac{L}{h}\right) = \left(\frac{CL_{int,T,in\ vitro,i}}{fu_{inc}}\right) \cdot SF_1 \cdot ISEF,T \cdot Abundance_{K,i} \cdot PTCPGK \cdot Kidney\ Weight \cdot 60.10^{-6} \qquad \textbf{Equation 6}$$

Equation 6 the product of the sum of the 3 proximal tubule regions and the respective scaling factors calculated based on the relative abundance of the transporter in each segment $SF_{2\text{-}pt1}$, $SF_{2\text{-}pt2}$, and $SF_{2\text{-}pt3}$, hence the following corrections are applied (as is currently the case for REF-based scaling). This should be applied to all functionalities so link the corrections in **Equation 7 - Equation 9** to $CL_{out\text{-}uc\text{-}pt}$, $CL_{out\text{-}cb\text{-}pt}$, $CL_{in\text{-}uc\text{-}pt}$, $CL_{in\text{-}cb\text{-}pt}$. Although not novel, **Equation 7 - Equation 9** are provided as this is the first instance such corrections are applied to an ISEF,T algorithm.

$$CLu_{inT,i-pt1}\left(\frac{L}{h}\right) = CLu_{inT,i} \cdot SF_{2-pt1} \qquad \textbf{Equation 7}$$

$$CLu_{inT,i-pt1}\left(\frac{L}{h}\right) = CLu_{inT,i} \cdot SF_{2-pt2} \qquad \textbf{Equation 8}$$

$$CLu_{inT,i-pt1}\left(\frac{L}{h}\right) = CLu_{inT,i} \cdot SF_{2-pt3} \qquad \textbf{Equation 9}$$

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