RESPONSE DOCUMENT
APRIL 9, 2025

ITEMS 1, 2, 3, 4 AND 6
FROM EMAIL DATED:
APRIL 2, 2025

CONTACT: **KAREN ROWLAND YEO**
SENIOR VICE-PRESIDENT
CERTARA UK LTD
LEVEL 2-ACERO
1 CONCOURSE WAY
SHEFFIELD S1 2BJ
UK

EMAIL: KAREN.YEO@CERTARA.COM

EMA ADDITIONAL REQUESTS FOR QUALIFICATION OPINION:

Additional requests for qualification opinion

1. Proposal for version control.

2. Proposal for providing substrate and inhibitor files at submission.

3. Evolution of DDI qualification matrix in a flow chart. This should also refer to the DB versions used in the Bayesian analysis.

4. Evolution of substrate and inhibitor files included in the qualification ideally using a flow chart.

5. Rerun the analyses and create graphs using the model proposed in the last discussion with Pieter (CYP agnostic).

6. Upload an example for substrate and inhibitor file which will be published.

ITEM 1: PROPOSAL FOR VERSION CONTROL

Additional requests for qualification opinion

The qualification analysis relates to V19R1 of the Simcyp Simulator. Version 24R1 has just been released, and we are now developing V25. A significant amount of work would be required to repeat the analysis for V20, V21, V22, V23 and V24. Before describing our strategy for bridging across the versions, it is important to note the following:

- Typically, when going from version to version, additional compounds or new modules are added (wish list items voted for by the Consortium Members on an annual basis). Please see Table 1 below to indicate specific wish list items that were included for V20-V24.
- Changes to existing code are rarely made unless an issue has been reported after release.
- Similarly, changes to existing data (compound file or system parameters) would only occur if a significant update had been identified in the literature or more data had become available to indicate that the performance of a compound could be enhanced.
- In the latter case, changes across versions are reported on the front of the compound file summaries (see submitted compound file summaries) that are provided for each version. Furthermore, these changes are also stated in a dedicated table for each version in the Appendix of the helpfile of the Simcyp Simulator.
- Below, in Tables 2 and 3, we indicate whether compound files used in the qualification DDI matrix were included as official files in V19 and or/V20 of the Simcyp Simulator. Furthermore, we indicate if any parameters were changed across the 2 versions. The intent is to demonstrate that only a few changes occur from version to version.

Prior to each release of the Simcyp Simulator, an automated version-to-version comparison is performed. Typically, PK parameters generated from simulations of V19 compound files in the V19 platform would be compared directly against those generated for V20 compound files in the V20 platform. Any significant deviations are interrogated to determine whether the findings were expected based on changes that had been introduced to the code, system parameters or compound file data. Explanations for any differences are then specified on the version comparison document.

- We have submitted the following version comparisons to demonstrate this:
    - V19R1 *versus* V20R1
    - V20R1 *versus* V21R1
    - V21R1 *versus* V22R1
    - V22R1 *versus* V23R1

Typically, there is a delay for uptake of a newly released version (V24R1) by our Consortium Members. Thus, we recommend bridging across versions V19R1 and V23R1 i.e. repeating all the simulations (DDI qualification matrix) and the Bayesian analysis for V23R1. At this point, if there are no significant differences (V19R1 *versus* V23R1) in the results of the predicted *versus* observed PK parameters (DDI qualification matrix) and the Bayesian analysis, then this analysis alongside the version comparison documents should be sufficient to demonstrate consistency across the versions.

Table 1: Wishlist items across Versions (20-24)

No.	Wishlist items for V20
1	• **Expansion of the compound library and their performance verification**
2	• **Expansion of Simcyp Animal Simulators' capabilities**
3	• **Incorporating transporters induction capability and assessing their potential impacts on prediction accuracy of CYP3A4 inducers**
4	• **Further expansion of the biologics modules**
5	• **Implementing a multiple liver compartment model with DDI capability**
6	• **Expanding the IVIVC module capabilities**
No.	Wishlist items for V21
1	• **The animal models should be equivalent to the human models in terms of complexity, functionality and ease of use. Priority decided by sub-voting.**
2	• **Further qualification of hepatic and renal impaired populations to improve predictive performance. Priority decided by sub-voting.**
3	• **Developing a model developments documentation tool.**
4	• **Updating and expanding population library databases on genotypes frequencies for CYPs, UGTs and transporters (e.g. CYP2B6 *1/*1 and *6 / *6 inclusion of UM, IMs, UGT1A9, UGT1A3, CYP2C19) and their corresponding abundances (from literature).**
5	• **Expansion of the compound library and their performance verification. The priority will be decided by sub-voting.**
6	• **Determining and reporting the mass balance for each pathway involved in elimination and excretion of drugs.**
No.	Wishlist items for V22
1	• **New and Upgraded Compound Files**
2	• **Further expansion of Transporters IVIVE**
3	• **Improvements in MBI Prediction and the interplay between MBI and Induction**
4	• **Sub-cutaneous dosing for Biologics and Small Molecules**
5	• **Simultaneous fitting of different scenarios using PE in Human Simulator**
6	• **Expansion of Available Populations**
No.	Wishlist items for V23
1	• **Expansion of the Oral Absorption Models**

2	• **Transporter Activity Biomarkers**
3	• **New and Updated Compound Files**
4	• **Incorporate pH-DDI Interactions to Simulator**
5	• **Drug Biologic Interactions**
6	• **PBPK Modelling of New Modalities**
No.	Wishlist items for V24
1	• **Expansion of the Oral Absorption Models**
2	• **Verification and Documentation of Transporter-mediated DDIs**
3	• **Expanding TMDD Models and Biologics module**
4	• **Develop new and upgraded Compound Files**
5	• **Expansion of Trial Design features**
6	• **Add non-linear binding to full PBPK model**

Table 2: Substrates

No.	Compound – Substrate file	Parameter	V19	V20	Comments
1	Alfentanil				No changes
2	Alprazolam				No changes
3	Aprepitant				File in neither version released
4	Atazanavir				No changes (as inhibitor included)
5	Atomoxetine				No changes
6	Caffeine				No changes
7	Carbamazepine				No changes (as inhibitor included)
8	Celecoxib				No changes
9	Clarithromycin				No changes (as inhibitor included)
10	Desipramine				No changes
11	Dexamethasone				Released in V20
12	Dextromethorphan				No changes
13	Duloxetine				File in neither version released
14	Flurbiprofen				File in neither version released
15	Ibrutinib				File in neither version released
16	Imipramine	Ka	0.45	0.8	Optimised to capture clinical profiles
		T_{max}	0.45	0.8	Revised to capture T_{max}
		V_{ss} CV (%)	30	20	Revised to capture variability
		2-OH CYP1A2 V_{max} (pmol/min/pmol)	2.6	1.6	Elimination parameters were determined using a retrograde approach and then refined based on fm data available for formation of desipramine. The retrograde CL_{int} was then used to back calculate V_{max} values using *in vitro* Km values.
		2-OH CYP2C19 V_{max} (pmol/min/pmol)	56.8	237.2	
		2-OH CYP2D6 V_{max} (pmol/min/pmol)	22.6	5.6	
		N-Desmethyl CYP1A2 V_{max} (pmol/min/pmol)	16.9	105.8	
		N-Desmethyl CYP2C19 V_{max} (pmol/min/pmol)	119.2	175	
		N-Desmethyl CYP2D6 V_{max} (pmol/min/pmol)	13.3	204.8	
		UGT1A4 V_{max} (pmol/min/mg)	292.5	136.78	

17	Lansoprazole				Released in V20
18	Metoprolol				No changes
19	Midazolam				No changes
20	Mirabegron				Released in V20 (as inhibitor included)
21	Montelukast				File in neither version released
22	Nebivolol				Released in V20
23	Nifedipine				No changes
24	Olanzapine				File in neither version released
25	Omeprazole				No changes
26	Paroxetine				No changes (as inhibitor included)
27	Phenytoin				No changes (as inhibitor included)
28	Pioglitazone				File in neither version released
29	Propranolol				File in neither version released
30	Quinidine				No changes
31	Repaglinide				No changes
32	Rifabutin				No changes (as perpetrator included)
33	Rosiglitazone				No changes
34	Sildenafil				No changes
35	Simvastatin				No changes
36	S-Mephenytoin				No changes
37	S-Warfarin				No changes
38	Theophylline				No changes
39	Tizanidine				File in neither version released
40	Tolbutamide				No changes
41	Tolterodine				No changes
42	Triazolam				No changes
43	Tucatinib				File in neither version released
44	Verapamil				No changes (as inhibitor included)
45	Voriconazole				File in neither version released
46	Zolpidem				No changes

Table 2: Inhibitors

No.	Compound – Inhibitor file	Parameter	V19	V20	Comments
1	Amiodarone				File in neither version released
	Mono-desethyl Amiodarone				File in neither version released
2	Atazanavir				No changes
3	Bupropion				No changes
	OH-Bupropion				No changes
4	Cimetidine				No changes for the release files for the EMA qualification Ki values for CYP3A4 reduced to 11 µM, and Ki values for CYP1A2 (4.58 µM) and CYP2C19 (8.22 µM) added.
5	Cinacalcet				Released in V20

6	Ciprofloxacin				No changes
7	Clarithromycin				No changes
8	Clopidogrel				File in neither version released
	Clopidogrel acyl glucuronide				File in neither version released
9	Diltiazem				No changes
	Desmethyl-Diltiazem				No changes
10	Duloxetine				File in neither version released
11	Erythromycin - EC	CYP3A4 K_I (µM)	82	32.8	Refined based on Meta-Analysis
		CYP3A Kapp (µM)	23.2	17.64	
		CYP3A4 K_{inact} (1/h)	2.25	0.8	
	Erythromycin	fa	1	0.60	Where Erythromycin is not dosed as EC formulation alternative file can be used with refined absorption parameters
		Ka (1/h)	3.58	0.52	
12	Fluconazole				No changes
13	Fluoxetine				No changes
	Nor-Fluoxetine				No changes
14	Fluvoxamine				No changes
15	Gemfibrozil				No changes
	Gemfibrozil 1-O-β Glucuronide				No changes
16	Itraconazole				No changes
17	Ketoconazole				No changes
18	Mirabegron				Released in V20
19	Omeprazole				No changes
20	Paroxetine				No changes
21	Propranolol				File in neither version released
22	Quinidine				No changes
23	Sulphaphenazole				No changes
24	Ticlopidine				No changes
25	Trimethoprim				No changes
26	Tucatinib				File in neither version released
27	Verapamil				No changes
	Norverapamil				No changes
28	Voriconazole				File in neither version released

ITEM 2: PROPOSAL FOR PROVIDING SUBSTRATE AND INHIBITOR COMPOUND FILE SUMMARIES AT SUBMISSION

Additional requests for qualification opinion

A. Our version specific compound file summaries are made available to all our Consortium Members (CM) via our secure Members Area. Typically, if a CM is going to include PBPK as part of their regulatory submission, they will download the relevant compound file summaries and include them. We will ensure that we communicate with them to state that this is a requirement for any future submissions.

In addition, it would be good if the EMA could clarify (in the opinion) their expectation of having sponsors include them, as part of their PBPK submissions.

B. Please also note that we have updated all the compound file summaries based on the feedback from the SAWP to reflect the following:

- DIDB (UOW) criteria
- Optimised parameters
- More details about input parameters
- Clarification of clearance routes that are considered or inhibitory mechanism

C. Below we indicate whether the substrates/inhibitors used in the qualification matrix were subsequently included in later versions. In some cases, the compound files were not included as official files mainly because there may not be sufficient interest in the files (as a comedication or index substrate/inhibitor). As you can appreciate, supporting a large number of files across versions can be a significant workload and therefore, the focus is typically compound files that would be routinely used during drug development, consistent with regulatory recommendations.

Indeed, it should be noted that some of the compound files were only included in the analysis to make the qualification matrix more diverse in terms of inhibitor strength and sensitivity. Therefore, it is unlikely that a number of the compound files will be used for prediction of DDI liability in regulatory submissions.

In some cases, we have prepared V19R1 summaries for these additional compounds. In other cases, if the files could be reproduced from publications and there was sufficient verification, we felt that citation of the relevant publication would suffice.

Substrate	Name	Enzyme	Version
Substrate	Alfentanil	CYP3A4	19
Substrate	Alprazolam	CYP3A4	19
Substrate	Aprepitant	CYP3A4	**No**

Substrate	Atazanavir	CYP3A4	19 (Inh)
Substrate	Atomoxetine	CYP2D6	19
Substrate	Caffeine	CYP1A2	19
Substrate	Carbamazepine	CYP3A4	19 (Inh)
Substrate	Celecoxib	CYP2C9	19
Substrate	Clarithromycin	CYP3A4	19 (Inh)
Substrate	Desipramine	CYP2D6	19
Substrate	Dexamethasone	CYP3A4	20
Substrate	Dextromethorphan	CYP2D6	19
Substrate	Duloxetine	CYP1A2	23
Substrate	Flurbiprofen	CYP2C9	21
Substrate	Ibrutinib	CYP3A4	21
Substrate	Imipramine	CYP2C19	19**
Substrate	Lansoprazole	CYP2C19	20
Substrate	Metoprolol	CYP2D6	19
Substrate	Midazolam	CYP3A4	19
Substrate	Mirabegron	CYP3A4	20 (Inh)
Substrate	Montelukast	CYP2C8	21
Substrate	Nebivolol	CYP2D6	20
Substrate	Nifedipine	CYP3A4	19
Substrate	Olanzapine	CYP1A2	**No**
Substrate	Omeprazole	CYP2C19	19
Substrate	Paroxetine	CYP2D6	19 (Inh)
Substrate	Phenytoin	CYP2C9	19 (Inh)
Substrate	Pioglitazone	CYP2C8	21
Substrate	Propranolol	CYP2D6	**No**
Substrate	Quinidine	CYP3A4	19
Substrate	Repaglinide	CYP2C8	19
Substrate	Repaglinide	CYP3A4	19
Substrate	Rifabutin	CYP3A4	19 (Inh)
Substrate	Rosiglitazone	CYP2C8	19
Substrate	Sildenafil	CYP3A4	19
Substrate	Simvastatin	CYP3A4	19
Substrate	S-Mephenytoin	CYP2C19	19
Substrate	S-Warfarin	CYP2C9	19
Substrate	Theophylline	CYP1A2	19
Substrate	Tizanidine	CYP1A2	**No**
Substrate	Tolbutamide	CYP2C9	19
Substrate	Tolterodine	CYP2D6	19
Substrate	Triazolam	CYP3A4	19
Substrate	Tucatinib	CYP2C8	**No**
Substrate	Verapamil	CYP3A4	19 (Inh)
Substrate	Voriconazole	CYP2C19	22

Additional requests for qualification opinion

Substrate	Zolpidem	CYP3A4	19

Inhibitor	**Name**	**Enzyme**	**Version**
Inhibitor	Amiodarone	CYP2C9	24
Inhibitor	Amiodarone	CYP3A4	24
Inhibitor	Atazanavir	CYP3A4	19
Inhibitor	Bupropion	CYP2D6	19
Inhibitor	Cimetidine	CYP1A2	**No**
Inhibitor	Cimetidine	CYP2C19	**No**
Inhibitor	Cimetidine	CYP2D6	19
Inhibitor	Cimetidine	CYP3A4	19*
Inhibitor	Cinacalcet	CYP2D6	20
Inhibitor	Ciprofloxacin	CYP1A2	19
Inhibitor	Clarithromycin	CYP3A4	19
Inhibitor	Clopidogrel	CYP2C8	**No**
Inhibitor	Clopidogrel acyl glucuronide	CYP2C8	**No**
Inhibitor	Desmethyl-diltiazem	CYP3A4	19
Inhibitor	Diltiazem	CYP3A4	19
Inhibitor	Duloxetine	CYP2D6	23
Inhibitor	Erythromycin	CYP3A4	19**
Inhibitor	Fluconazole	CYP2C9	19
Inhibitor	Fluconazole	CYP2C19	19
Inhibitor	Fluconazole	CYP3A4	19
Inhibitor	Fluoxetine	CYP2C19	19
Inhibitor	Fluoxetine	CYP2D6	19
Inhibitor	Fluoxetine	CYP3A4	19
Inhibitor	Fluvoxamine	CYP1A2	19
Inhibitor	Fluvoxamine	CYP2C9	19
Inhibitor	Fluvoxamine	CYP2C19	19
Inhibitor	Fluvoxamine	CYP2D6	19
Inhibitor	Fluvoxamine	CYP3A4	19
Inhibitor	Gemfibrozil	CYP2C8	19
Inhibitor	Gemfibrozil glucuronide	CYP2C8	19
Inhibitor	Hydroxy-bupropion	CYP2D6	19
Inhibitor	Hydroxy-itraconazole	CYP3A4	19
Inhibitor	Itraconazole	CYP3A4	19
Inhibitor	Ketoconazole	CYP3A4	19
Inhibitor	Mirabegron	CYP2D6	20
Inhibitor	Mono Desethyl Amiodarone	CYP2C9	24
Inhibitor	Nor-fluoxetine	CYP2C19	19

Inhibitor	Nor-fluoxetine	CYP2D6	19
Inhibitor	Nor-fluoxetine	CYP3A4	19
Inhibitor	Nor-verapamil	CYP3A4	19
Inhibitor	Omeprazole	CYP2C19	19
Inhibitor	Paroxetine	CYP2D6	19
Inhibitor	Propranolol	CYP1A2	**No**
Inhibitor	Quinidine	CYP2D6	19
Inhibitor	Sulphaphenazole	CYP2C9	19
Inhibitor	Ticlopidine	CYP2C19	19
Inhibitor	Trimethoprim	CYP2C8	19
Inhibitor	Tucatinib	CYP2C8	**No**
Inhibitor	Verapamil	CYP3A4	19
Inhibitor	Voriconazole	CYP2C19	22

ITEMS 3 AND 4. EVOLUTION OF DDI QUALIFICATION MATRIX AND SUBSTRATE AND INHIBITOR FILES INCLUDED IN THE QUALIFICATION

A power point presentation has been provided indicating the development and composition of the DDI qualification matrix since the initial submission. We have indicated how/why the 220 studies for the final database (Bayesian analysis) were selected from the 246 studies used in the final qualification DDI matrix.

We included several flow diagrams that indicate the development and composition of the matrix.

Below, we provide tables indicating which substrates/inhibitors were included in the different versions of the qualification matrix.

Table: Substrates used in the qualification matrix

Substrates	Enzyme	13-Mar-23	16-Dec-24	13-Mar-23	16-Dec-24
Caffeine	CYP1A2	YES	YES	1	1
Duloxetine	CYP1A2	NO	YES		2
Olanzapine	CYP1A2	NO	YES		3
Theophylline	CYP1A2	YES	YES	2	4
Tizanidine	CYP1A2	YES	YES	3	5
Imipramine	CYP2C19	YES	YES	4	6
Lansoprazole	CYP2C19	NO	YES		7
Omeprazole	CYP2C19	YES	YES	5	8
S-Mephenytoin	CYP2C19	YES	YES	6	9
Voriconazole	CYP2C19	NO	YES		10
Montelukast	CYP2C8	NO	YES		11
Pioglitazone	CYP2C8	NO	YES		12
Repaglinide	CYP2C8	YES	YES	7	13
Rosiglitazone	CYP2C8	YES	YES	8	14
Tucatinib	CYP2C8	NO	YES		15
Celecoxib	CYP2C9	YES	YES	9	16
Flurbiprofen	CYP2C9	YES	YES	10	17
Phenytoin	CYP2C9	YES	YES	11	18
S-Warfarin	CYP2C9	YES	YES	12	19
Tolbutamide	CYP2C9	YES	YES	13	20
Atomoxetine	CYP2D6	YES	YES	14	21
Desipramine	CYP2D6	YES	YES	15	22
Dextromethorphan	CYP2D6	YES	YES	16	23
Metoprolol	CYP2D6	YES	YES	17	24
Nebivolol	CYP2D6	YES	YES	18	25
Paroxetine	CYP2D6	NO	YES		26

Propranolol	CYP2D6	NO	YES		27
Tolterodine	CYP2D6	YES	YES	19	28
Alfentanil	CYP3A4	YES	YES	20	29
Alprazolam	CYP3A4	YES	YES	21	30
Aprepitant	CYP3A4	YES	YES	22	31
Atazanavir	CYP3A4	YES	YES	23	32
Carbamazepine	CYP3A4	NO	YES		33
Clarithromycin	CYP3A4	YES	YES	24	34
Dexamethasone	CYP3A4	YES	YES	25	35
Ibrutinib	CYP3A4	YES	YES	26	36
Midazolam	CYP3A4	YES	YES	27	37
Mirabegron	CYP3A4	NO	YES		38
Nifedipine	CYP3A4	YES	YES	28	39
Quinidine	CYP3A4	YES	YES	29	40
Repaglinide	CYP3A4	YES	YES	7	13
Rifabutin	CYP3A4	YES	YES	30	41
Sildenafil	CYP3A4	YES	YES	31	42
Simvastatin	CYP3A4	YES	YES	32	43
Triazolam	CYP3A4	YES	YES	33	44
Verapamil	CYP3A4	NO	YES		45
Zolpidem	CYP3A4	YES	YES	34	46

Table: Inhibitors used in the qualification matrix

Perpetrator	Enzyme	13-Mar-23	16-Dec-24	13-Mar-23	16-Dec-24
Cimetidine	CYP1A2	NO	YES		4
Ciprofloxacin	CYP1A2	YES	YES	6	6
Fluvoxamine	CYP1A2	YES	YES	13	14
Propranolol	CYP1A2	NO	YES		22
Cimetidine	CYP2C19	NO	YES		4
Fluconazole	CYP2C19	YES	YES	11	12
Fluoxetine	CYP2C19	YES	YES	12	13
Fluvoxamine	CYP2C19	YES	YES	13	14
Nor-fluoxetine	CYP2C19	YES	YES	12	13
Omeprazole	CYP2C19	NO	YES		20
Ticlopidine	CYP2C19	YES	YES	23	25
Voriconazole	CYP2C19	NO	YES		28
Clopidogrel	CYP2C8	NO	YES		8
Clopidogrel acyl glucuronide	CYP2C8	NO	YES		8
Gemfibrozil	CYP2C8	YES	YES	14	15
Gemfibrozil glucuronide	CYP2C8	YES	YES	14	15
Trimethoprim	CYP2C8	YES	YES	24	26
Tucatinib	CYP2C8	NO	YES		27

Amiodarone	CYP2C9	YES	YES	1	1
Fluconazole	CYP2C9	YES	YES	11	12
Fluvoxamine	CYP2C9	YES	YES	13	14
Mono Desethyl Amiodarone	CYP2C9	YES	YES	1	1
Sulphaphenazole	CYP2C9	YES	YES	22	24
Bupropion	CYP2D6	YES	YES	3	3
Cimetidine	CYP2D6	NO	YES	4	4
Cinacalcet	CYP2D6	YES	YES	5	5
Duloxetine	CYP2D6	NO	YES		10
Fluoxetine	CYP2D6	YES	YES	12	13
Fluvoxamine	CYP2D6	YES	YES	13	14
Hydroxy-bupropion	CYP2D6	YES	YES	3	3
Mirabegron	CYP2D6	NO	YES		18
Nor-fluoxetine	CYP2D6	YES	YES	12	13
Paroxetine	CYP2D6	YES	YES	18	21
Quinidine	CYP2D6	YES	YES	19	23
Amiodarone	CYP3A4	YES	YES	1	1
Atazanavir	CYP3A4	YES	YES	2	2
Cimetidine	CYP3A4	YES	YES	4	4
Clarithromycin	CYP3A4	YES	YES	7	7
Cyclosporine	CYP3A4	YES	NO	8	
Desmethyl-diltiazem	CYP3A4	YES	YES	9	9
Diltiazem	CYP3A4	YES	YES	9	9
Erythromycin	CYP3A4	YES	YES	10	11
Fluconazole	CYP3A4	YES	YES	11	12
Fluoxetine	CYP3A4	YES	YES	12	13
Fluvoxamine	CYP3A4	YES	YES	13	14
Hydroxy-itraconazole	CYP3A4	YES	YES	15	16
Itraconazole	CYP3A4	YES	YES	15	16
Ketoconazole	CYP3A4	YES	YES	16	17
Nor-fluoxetine	CYP3A4	YES	YES	12	13
Nor-verapamil	CYP3A4	YES	YES	17	19
Rifampicin	CYP3A4	YES	NO	20	
Ritonavir	CYP3A4	YES	NO	21	
Verapamil	CYP3A4	YES	YES	17	19
Aprepitant	CYP3A4	YES	NO	25	

ITEM 6: UPLOAD AN EXAMPLE FOR SUBSTRATE AND INHIBITOR FILE WHICH WILL BE PUBLISHED.

We have provided 3 compound file summaries:

1. Midazolam as a substrate file – we chose this because it is obviously used routinely in drug development and is a well characterized file
2. Fluvoxamine as an inhibitor file – we chose this because again it is used routinely as a strong inhibitor
3. Cimetidine as an inhibitor file – this file is quite complex and has multiple aspects. The key thing we wanted to display was the ability to assess the differential weak inhibitory effects on a number of CYP enzymes.

PREVIOUSLY REQUESTED ITEM

Although not listed in the email dated April 2, 2025, we were previously asked to provide Forest Plots – we have generated these for each CYP per mechanism.