CERTARA®

SAWP DISCUSSION MEETING

QUALIFICATION PROCEDURE - SIMCYP SIMULATOR V19

MARCH 6, 2024

Attendees from Certara UK Ltd

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Dialling in from the UK

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List of EMA Issues to be Discussed

EMA Issues 1 (Issues related to pooling data across CYPS for the purpose of qualification)

EMA Issues 2,5,6,7 (Issues related to model predictive performance including quantifying and reporting model uncertainty)

EMA Issues 3,4,8 (Issues related to acceptance criteria)

3 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 administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a strong CYP inhibitor has been conducted (and used to verify the fmCYP).
2. The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated inhibitory effect of a drug on the exposure of other CYP substrates administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the competitive inhibition effect in vivo).
3. The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated MBI effect of a drug on the exposure of other CYP substrates administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the MBI effect in vivo).

EMA Issue 1 – Pooling of Data Across Enzymes (1)

- *4 contexts of use (CoU) are defined; however, the analyses are not submitted per CoU. The CoUs are defined mechanistically while analyses were shown per enzyme for all 3 CoU together or for all enzymes combined per mechanism of inhibition. Discuss whether pooling of the DDI data for the various CYP enzymes is appropriate for each CoU and whether DDI data for the two mechanisms of inhibition can be combined per enzyme. Consider in this discussion that a rank order approach may be considered for hepatic reversible inhibition but not for MBI (ICH-M12), the location of inhibition (only hepatic or hepatic and intestinal) and the verification of kdeg values for the various enzymes.*

EMA Issue 1 – Pooling of Data Across Enzymes (2)

- *4 contexts of use (CoU) are defined; however, the analyses are not submitted per CoU. The CoUs are defined mechanistically while analyses were shown per enzyme for all 3 CoU together or for all enzymes combined per mechanism of inhibition.*

Enzyme	CI	MBI	ALL
CYP1A2	42	0	42
CYP2C8	7	10	17
CYP2C9	25	3	28
CYP2C19	15	13	28
CYP2D6	32	14	46
CYP3A4/5	66	28	94
Total	187	68	255

- Analyses are now presented as:
- Each enzyme per mechanism & COU (CYP1A2, CYP2D6, CYP2C8, CYPC29, CYPC19, CYP3A4)
- All enzymes combined per mechanism & COU

EMA Issue 1 – Pooling of Data Across Enzymes (3)

- *Discuss whether pooling of the DDI data for the various CYP enzymes is appropriate for each CoU and whether DDI data for the two mechanisms of inhibition can be combined per enzyme.*

- For prediction of DDIs, key components are:
  - Fraction of the victim dose that is cleared by the pathway that is being inhibited (fm)
  - Potency of the inhibitor (Ki or inactivation parameters)
  - Concentration of the inhibitor at the active site of the enzyme ([I])
  - k_{deg} for time-dependent inhibition (MBI)
    - same value for all enzymes in gut as it is reflective of enterocyte turnover
    - different values for each enzyme based on a meta-analysis of in vitro/in vivo data

EMA Issue 1 – Pooling of Data Across Enzymes (4)

- *Discuss whether pooling of the DDI data for the various CYP enzymes is appropriate for each CoU and whether DDI data for the two mechanisms of inhibition can be combined per enzyme.*

- COU1 - The Simcyp Simulator (V19 R1) can be used to predict the effects of weak and moderate CYP inhibitors on the exposure of a drug administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a strong CYP inhibitor has been conducted (**and used to verify the fmCYP**).

  - Defining the fmCYP for the drug as a substrate
  - Mechanism of action is not the focus here
  - Thus, appropriate to combine the two mechanisms
  - Appropriate to combine the enzymes

EMA Issue 1 – Pooling of Data Across Enzymes (5)

- *Discuss whether pooling of the DDI data for the various CYP enzymes is appropriate for each CoU and whether DDI data for the two mechanisms of inhibition can be combined per enzyme.*

- COU2 - The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated inhibitory effect of a drug on the exposure of other CYP substrates administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the competitive inhibition effect in vivo).
  - Defining the in vivo inhibitory potency for the drug as a competitive inhibitor
  - Mechanism of action is the focus here
  - Not appropriate to combine the two mechanisms
  - Appropriate to combine the enzymes

EMA Issue 1 – Pooling of Data Across Enzymes (6)

- *Discuss whether pooling of the DDI data for the various CYP enzymes is appropriate for each CoU and whether DDI data for the two mechanisms of inhibition can be combined per enzyme.*

- COU3 - The Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated MBI effect of a drug on the exposure of other CYP substrates administered orally under fasted conditions or intravenously in healthy subjects when a clinical study with a sensitive CYP substrate has been conducted (and used to verify the MBI effect in vivo).
  - Defining the in vivo inhibitory potency for the drug as a mechanism-based inhibitor
  - Mechanism of action is the focus here
  - Not appropriate to combine the two mechanisms
  - Although different kdeg values are used for enzymes in the liver, appropriate to combine the enzymes

EMA Issue 1 – Pooling of Data Across Enzymes (7)

- *Consider in this discussion that a rank order approach may be considered for hepatic reversible inhibition but not for MBI (ICH-M12), the location of inhibition (only hepatic or hepatic and intestinal) and the verification of kdeg values for the various enzymes.*

- For any single drug, the most potently inhibited enzyme *in vitro* should also be the one most affected *in vivo*.
- Thus, a rank order approach (ICH-M12 Guideline) should be reliable for using *in vitro* drug inhibition data in the planning of *in vivo* drug interaction studies.
- When a drug inhibits several CYP enzymes and *in vitro* Ki values are available from the same system, a reasonable strategy would be to conduct a clinical DDI study using a sensitive substrate for the enzyme that is most potently inhibited *in vitro*.
- Once a PBPK model has been developed for the drug and the clinical DDI with the sensitive substrate accurately predicted, simulations with other probe substrates could be run to determine the DDI potential of the drug *in vivo* for the other CYP enzymes using the *in vitro* Ki values.

EMA Issue 1 – Pooling of Data Across Enzymes (8)

- *Consider in this discussion that a rank order approach may be considered for hepatic reversible inhibition but not for MBI (ICH-M12), the location of inhibition (only hepatic or hepatic and intestinal) and the verification of kdeg values for the various enzymes.*

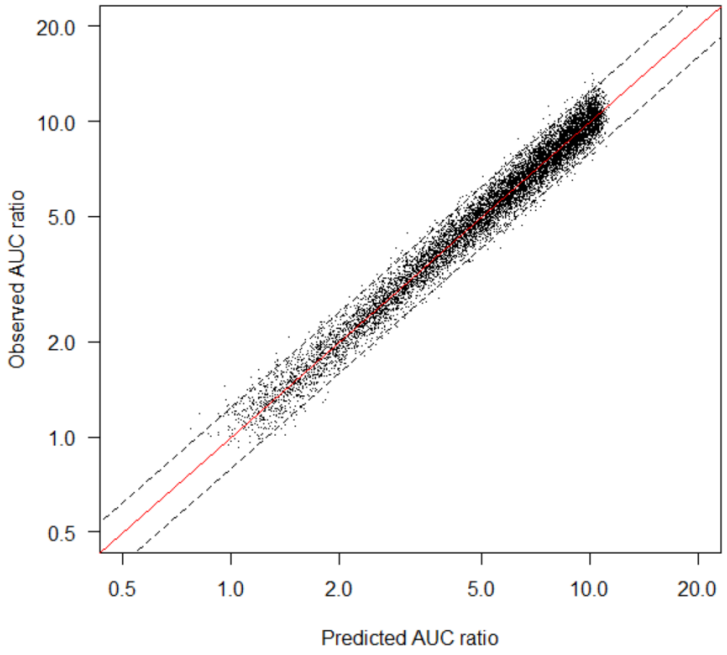
Table 2. Simulations of drug interactions with fluconazole – rank order approach

Substrate	Fluconazole Ki (uM)	Fluconazole dose	Predicted AUC ratio	Observed AUC ratio
Omeprazole (2C19)	2.0	100mg QD	6.76	6.29
Midazolam (3A4)	10.7	200mg QD	3.75	3.75
S-Warfarin (2C9)	23.0	300mg QD	2.27	2.27
Theophylline (CYP1A2)	>800 (DIDB); 800 used in simulation	100mg BD	1.02	1.19

NOTE: Supports combining different enzymes for COU 2

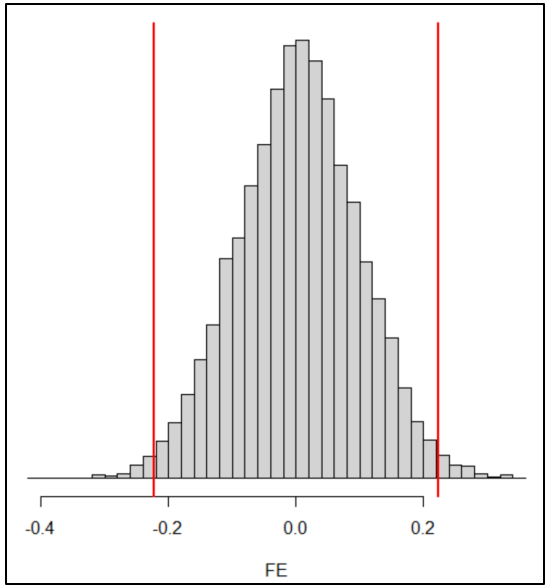
EMA Issue 2 – Model Predictive Performance (1)

- *Please discuss your views on the use of AFE and AAFE as performance metrics for assessing Simcyp's overall predictive performance and for detecting bias in specific subgroups within the DDI Qualification Matrix.*

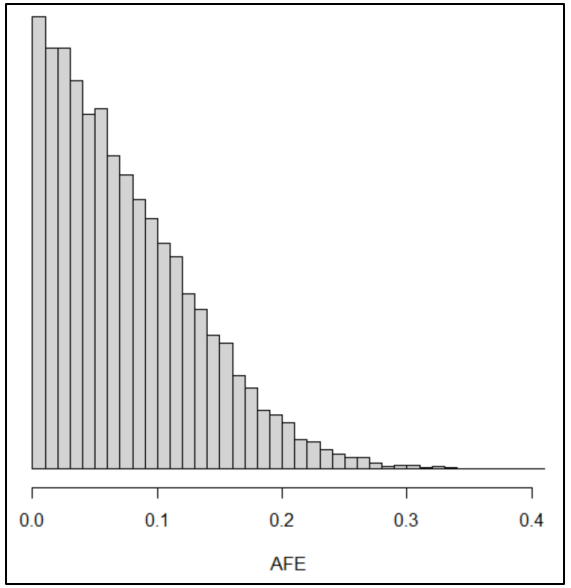


Predicted versus observed AUC ratios

BIAS

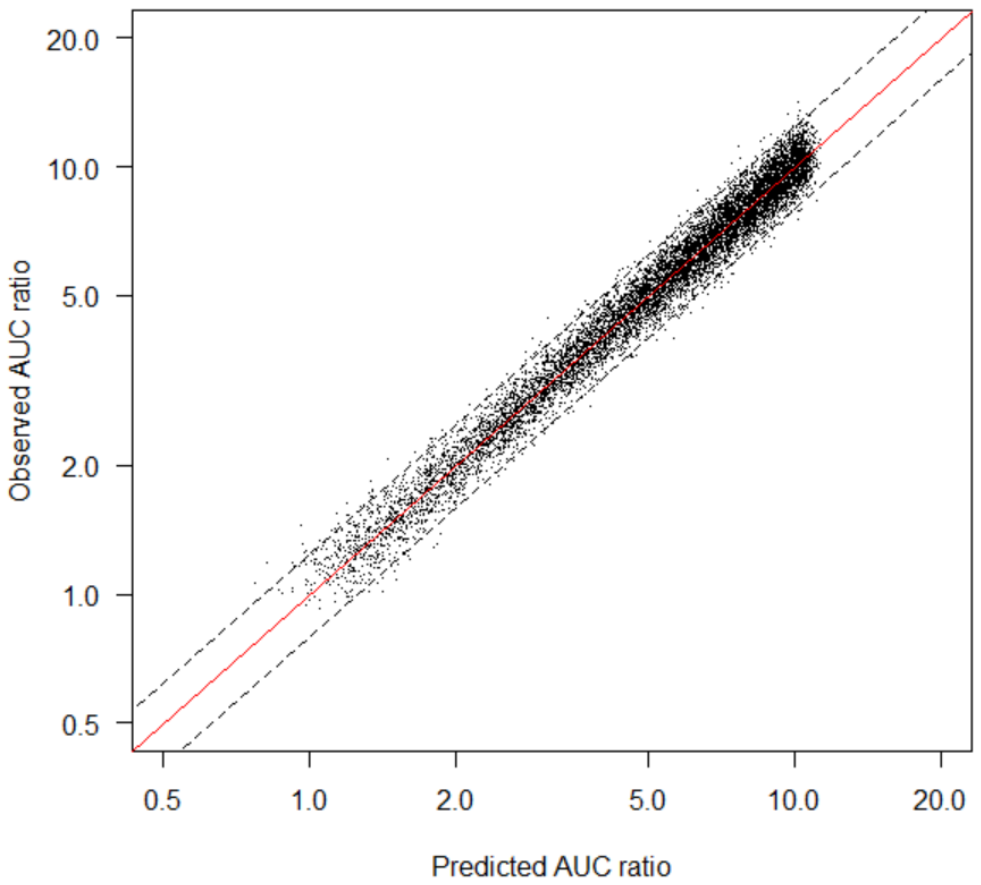


Histogram of fold errors (FE)
Average fold error is AFE



Histogram of absolute fold errors (AFE)
Average is AAFE

EMA Issue 2 – Model Predictive Performance (2)



Predicted *versus* observed AUC ratios

- AFE and AAFE are simple but have no other advantage over the visual plot on the left.
- Systematic bias would be more apparent on such a plot.
- Percentage of predictions within a certain fold error provides a measure of accuracy.
- AFE and AAFE are simple summaries. They should be put into context of the therapeutic window. They can be reported, but by themselves are not very helpful. That is: if they are both “small” (to be defined) then fine, otherwise we should go deeper.

EMA Issue 5 – Model Predictive Performance (1)

- *What is the interstudy variability for the in vivo DDI studies? Please provide the interstudy variability for all CoUs. Please discuss the option to incorporate variability of observed and predicted AUCRs in the assessment of performance.*
  - Inter-study variability is unavoidable and itself variable. It is usually confounded by inter-individual variability by lack of data.
  - Can be estimated from data when several similar studies are available for the same combination of drugs, and when individual data are available, at least for some studies.
  - Possible to do simulations of variability with our models but we do not have enough clinical data to perform an appropriate reality check.
  - So, given the current level of reporting, it seems challenging to go deeper.

EMA Issue 5 – Model Predictive Performance (2)

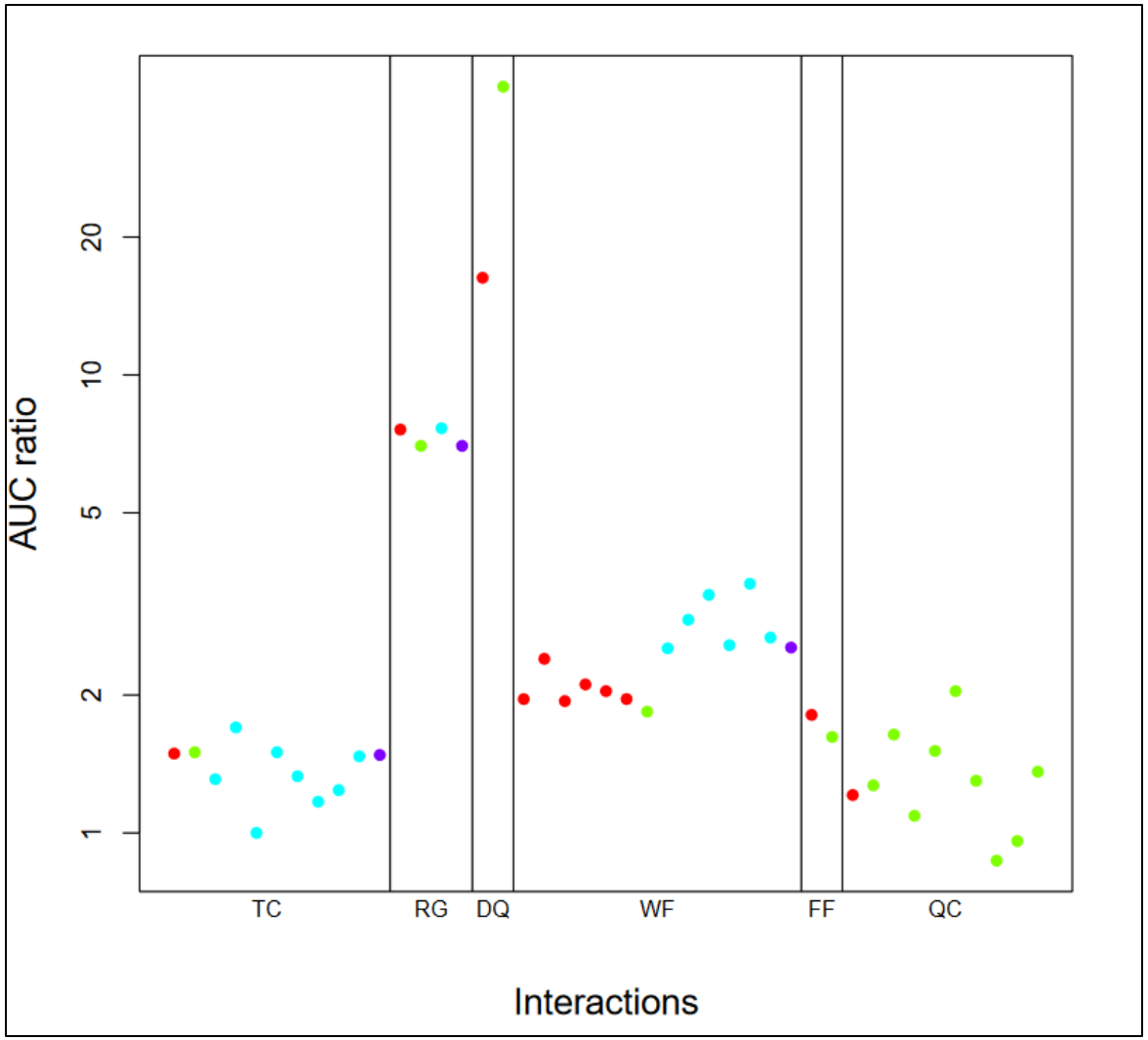


Figure 8: AUC ratios observed in different DDI studies for six pairs of drugs:

- TC: theophylline-ciprofloxacin;
- RG: repaglinide-gemfibrozil;
- DQ: dextromethorphan-quinidine;
- WF: warfarin-fluconazole;
- FF: flurbiprofen-fluconazole;
- QC: quinidine-cimetidine.

For each drug pair, the results of similar design studies have same color. Series of points of same color are individual values in the same study.

In that dataset both variances are not very large and are approximately of the same size. However, for a specific assessment at the level of individual chemical pairs, it is not possible to separate inter-subject from inter-study variability.

EMA Issue 6 – Model Predictive Performance (1)

- *Please discuss the option to perform an in-depth assessment of differences in study design such as different doses investigated and exposure time, time between administration of substrate and inhibitor separately. These could allow achieving a better understanding of Simcyp's predictive performance for different dose levels of the same perpetrator or its effect over time.*

  - A number of drug combinations have been used in simulations where multiple studies are available.

  - All study designs are indicated for the predicted *versus* observed datasets within each of the CYP data analyses.

EMA Issue 6 – Model Predictive Performance (2)

CYP1A2					INCLUDED
Substrate		**Inhibitor**		**n**	**n**
Caffeine	CYP1A2 index	Cimetidine	CYP1A2 weak	3	**3**
Caffeine	CYP1A2 index	Ciprofloxacin	CYP1A2 strong	12	**7**
Caffeine	CYP1A2 index	Fluvoxamine	CYP1A2 strong	5	**3**
Duloxetine	CYP1A2 sensitive	Fluvoxamine	CYP1A2 strong	3	**2**
Olanzapine	CYP1A2 moderate	Fluvoxamine	CYP1A2 strong	2	**1**
Theophylline (IV)	CYP1A2 moderate	Cimetidine	CYP1A2 weak	20	**7**
Theophylline (IV)	CYP1A2 moderate	Ciprofloxacin	CYP1A2 strong	7	**4**
Theophylline	CYP1A2 moderate	Cimetidine	CYP1A2 weak	11	**5**
Theophylline	CYP1A2 moderate	Ciprofloxacin	CYP1A2 strong	6	**2**
Theophylline	CYP1A2 moderate	Fluvoxamine	CYP1A2 strong	4	**4**
Theophylline	CYP1A2 moderate	Propranolol	CYP1A2 moderate	2	**2**
Tizanidine	CYP1A2 index	Ciprofloxacin	CYP1A2 strong	1	**1**
Tizanidine	CYP1A2 index	Fluvoxamine	CYP1A2 strong	1	**1**
				77	**42**

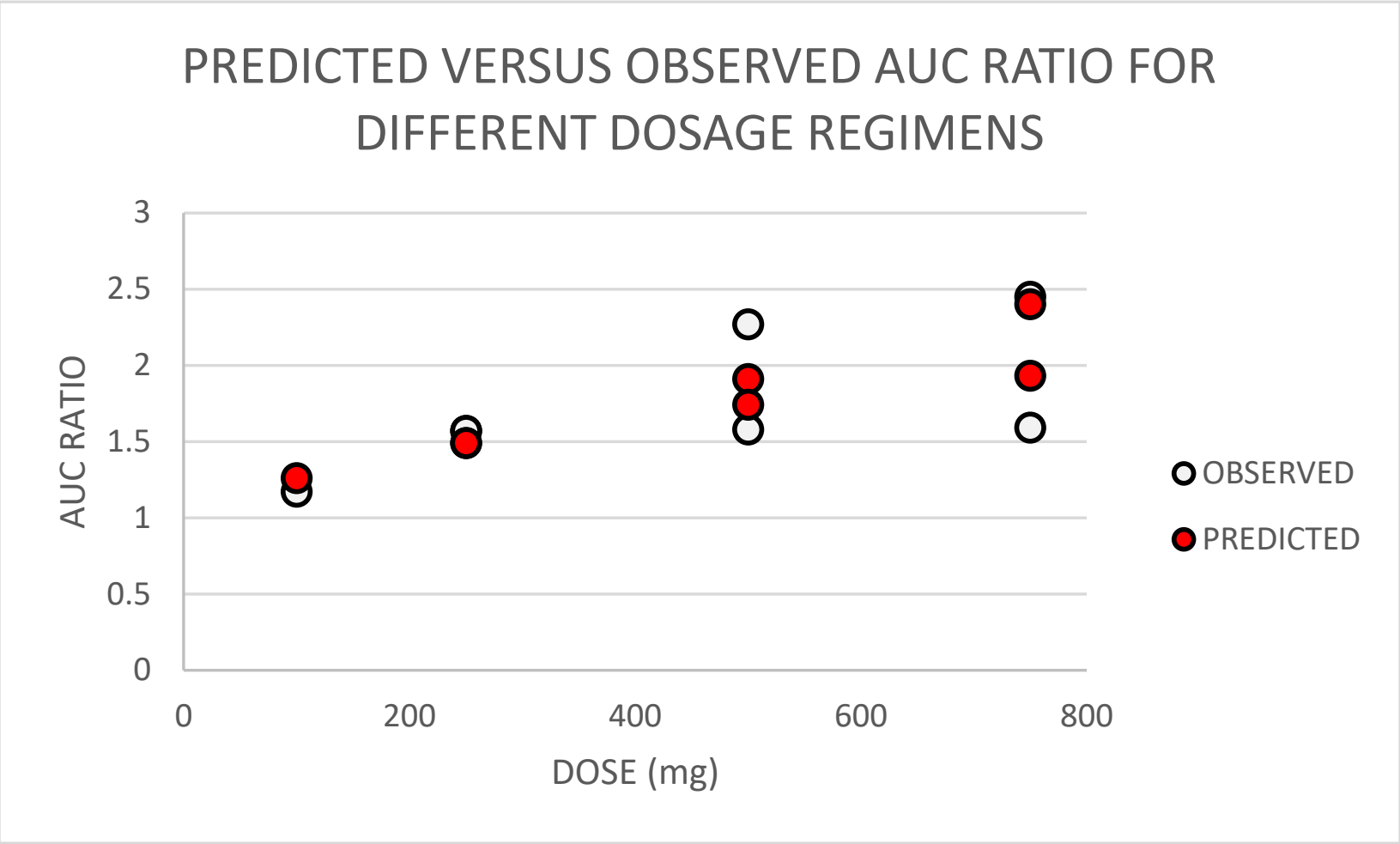
- Studies identified in DIDB
- Studies excluded on a case- by-case basis based on predefined criteria

EMA Issue 6 – Model Predictive Performance (3)

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
1	Harder et al., 1988	CYP1A2	Caffeine, 3 mg/kg SD (Day 4 @9:00 AM)	Ciprofloxacin, 100 mg BID for 4 days (7 doses)	1.07	1.17	1.12	1.26	1.04	1.08
23	Staib et al., 1987	CYP1A2	Caffeine 230 mg on Day 4	Ciprofloxacin 250 mg BID for 4 days	1.09	1.57	1.19	1.49	1.09	0.95
2	Harder et al., 1988	CYP1A2	Caffeine, 3 mg/kg SD (Day 4)	Ciprofloxacin, 250 mg BID for 4 days (7 doses)	1.09	1.57	1.18	1.49	1.09	0.95
24	Nicolau et al., 1995	CYP1A2	Caffeine 100 mg TID for 3 days	Ciprofloxacin 500 mg BID for 3 days	1.59	2.27	1.55	1.91	0.98	0.84
3	Harder et al., 1988	CYP1A2	Caffeine, 3 mg/kg SD (Day 4)	Ciprofloxacin, 500 mg BID for 3 days (6 doses) + 500 mg morning dose	1.17	1.58	1.23	1.74	1.05	1.10
18	Healy et al., 1989	CYP1A2	Caffeine, 100 mg SD (Day 2 @9 AM)	Ciprofloxacin, 750 mg BID for 2 days (3 doses)	1.10	1.59	1.26	1.93	1.14	1.21
6	Mahr et al., 1992	CYP1A2	Caffeine, 183 mg QD for 5 days	Ciprofloxacin, 750 mg BID for 7 days (14 doses)	1.14	2.45	1.46	2.4	1.28	0.98

- N=7 studies
- Ciprofloxacin dose range from 100 mg BID to 750 mg BID

EMA Issue 6 – Model Predictive Performance (4)



- N=7 studies
- Ciprofloxacin dose range from 100 mg BID to 750 mg BID

EMA Issue 6 – Model Predictive Performance (5)

Number	Study	CYP	Substrate Dose	Inhibitor Dose	Observed		Predicted		Predicted /Observed	
					Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
26	Lin et al., 1987	CYP1A2	Theophylline 5 mg/kg (IV) on Day 7 (Day 4 in simulation)	Cimetidine 300 mg every 6 hours for 6 days		1.46		1.62		1.10
27	Roberts et al., 1987	CYP1A2	Theophylline 5 mg/kg (IV) on Day 7 (Day 4 in simulation)	Cimetidine 300 mg every 6 hours for 6 days		1.41		1.62		1.15
31	Jennings et al., 1993	CYP1A2	Theophylline 5 mg/kg (IV) on Day 8	Cimetidine 300 mg every 6 hours for 10 days		1.36		1.44		1.06
28	Jackson et al., 1981	CYP1A2	Theophylline 6 mg/kg (IV) on Day 3	Cimetidine 300 mg every 6 hours for 2.75 days		1.64		1.52		0.92
29	Powell et al., 1984	CYP1A2	Theophylline 6 mg/kg (IV) on Day 4	Cimetidine 300 mg every 6 hours for 5 days		1.56		1.75		1.12
32	Loi et el., 1993	CYP1A2	Theophylline, 5 mg/kg SD IV infusion (30 minutes) (Day 5 @7 AM)	Cimetidine, 400 mg BID for 7 days (Day 1 @7 AM to Day 7 @7 PM) (14 doses)	-	1.34	-	1.29	-	0.96

- N=6 studies
- Cimetidine dose ranges from 800 mg/day to 1200 mg/day

EMA Issue 7 – Model Predictive Performance (1)

- *Please discuss whether intrinsic variability of compounds had an impact of the performance of the predictions. Please comment on separate consideration on orally administered drugs compared to IV administration (some compounds have a high inter- and intrasubject variability especially after oral administration. Intravenous administration filters some of the variability out).*
- There are 38 substrates and 28 inhibitors included in the analysis.
- Given the number of factors that could affect the intrinsic variability, we don't feel the sample size is large enough to assess this specific issue appropriately.
- A comparison of IV *versus* oral midazolam (predicted versus observed) was performed.

EMA Issue 7 – Model Predictive Performance (2)

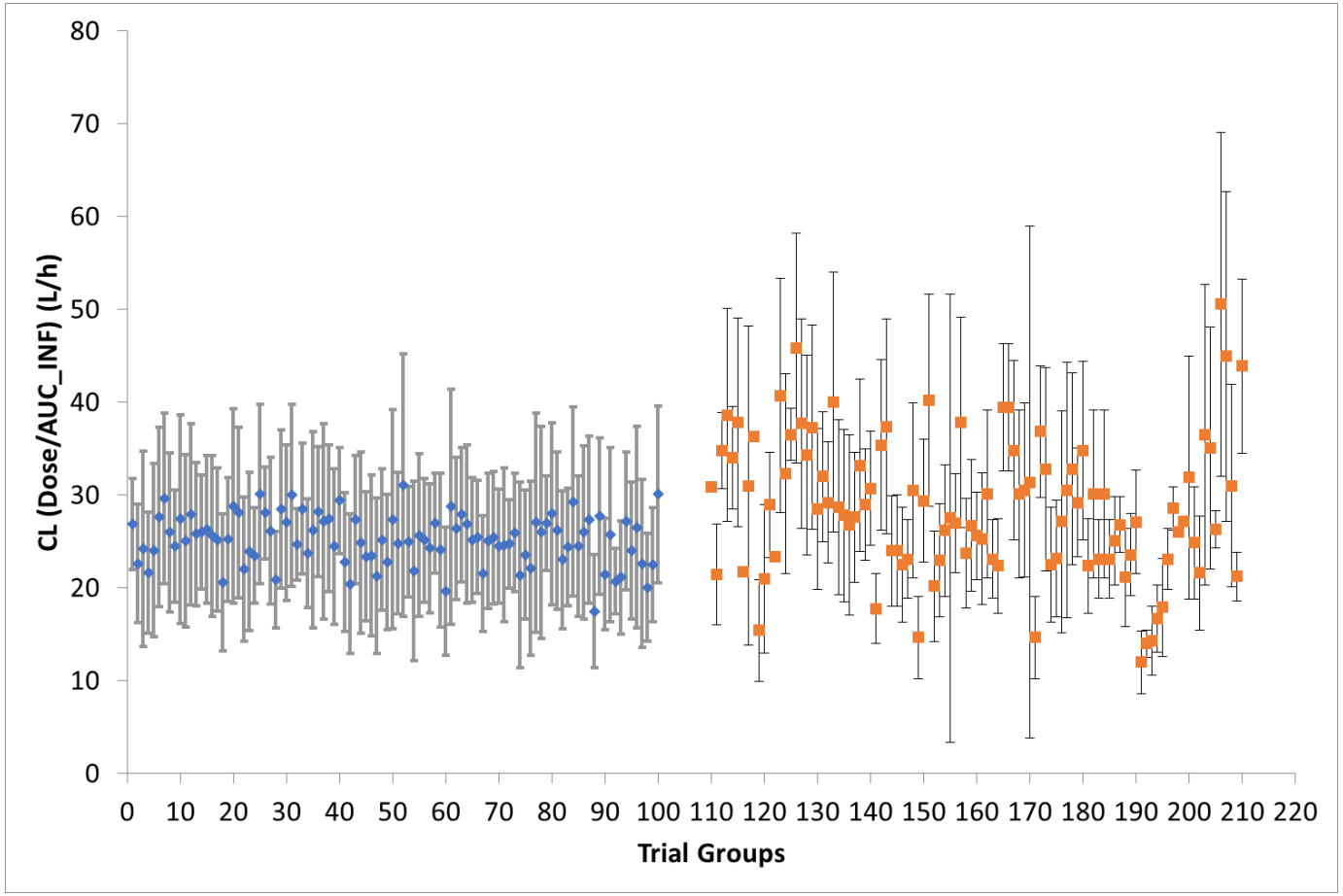
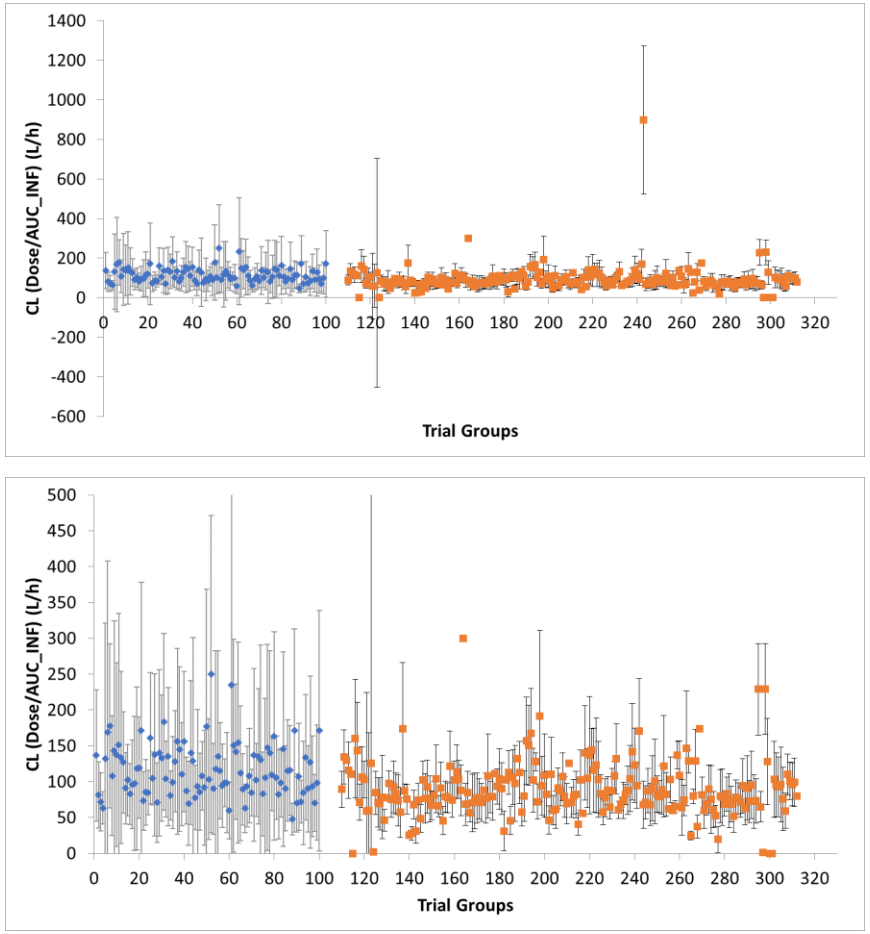


Figure 9. Simulated (blue) and observed (orange) CL (mean +/- SD) after **intravenous dosing** of midazolam. Each data point is an individual simulated or observed trial.

For IV administration, Simcyp simulations capture the observed mean of the means and the mean SD across studies, but not inter-study variance.

EMA Issue 7 – Model Predictive Performance (3)



For oral administration, Simcyp-simulated variability of study means appears to better match the observed inter-study variability.

Figure 10. Simulated (blue) and observed (orange) CL (mean +/- SD) after **oral dosing** of midazolam. Each data point is an individual simulated or observed trial. The lower panel is a zoomed view of the top panel.

EMA Issue 7 – Model Predictive Performance (4)

We performed simulations to examine the effects of various components of intrinsic variability on model performance assessment.

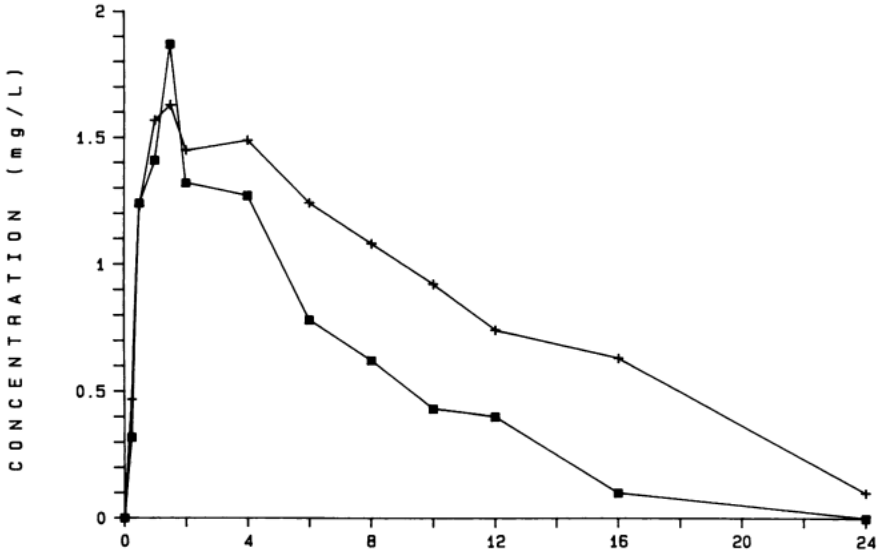
- The effect of between-subject variability is removed by study design (subject-level observations are paired).
- Inter-occasion variability affects the performance by spreading the predictions, but without bias.
- Bias affecting of between subject variability has no impact because its effect is still removed by the study design.
- Bias affecting inter-occasion variability does affects performance by shifting predictions. It could be important to correctly estimate inter-occasion variability.

EMA Issue 3 – Acceptance Criteria (1)

- *Please discuss the relevance of the proposed acceptance criteria (e.g. within 1.25-fold, within 1.5-fold, within 2-fold, within Guest criterion, misclassification rate) for the Context of Use considering exposure-response and therapeutic window.*
- A clinical study is a prerequisite for each COU.
- **Worst case scenarios will be assessed using a clinical study (strong inhibitor/sensitive substrate).**
- For a NCE, simulations will be run against weaker inhibitors (COU1) or less sensitive substrates (COU2/3).
- Percentages within 1.25-2.0-fold provide a level of confidence in the predicted DDI.
- Fold values can be applied to predicted exposure of NCE in the presence of inhibitor to determine whether it remains with the therapeutic window.

EMA Issue 3 – Acceptance Criteria (2)

Study conducted with strong inhibitor at a high dose – COU1



Caffeine (100 mg) given with ciprofloxacin (750 mg BID)

TABLE 2. Pharmacokinetic parameters for paraxanthine before and after three doses of ciprofloxacin (750 mg every 12 h)

Parameter[a]	Mean ± SD			P
	Before ciprofloxacin	After ciprofloxacin	% Change[b]	
C_{max} (μg/ml)	0.6 ± 0.2	0.6 ± 0.2	−10 ± 21	NS[c]
T_{max} (h)	6.2 ± 1.7	10.4 ± 2.7	81 ± 67	0.002
AUC_{0-10} (μg · h/ml)	4.6 ± 1.3	2.5 ± 0.8	−43 ± 17	<0.001

[a] C_{max}, Maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum.
[b] Calculated as the mean percent change from data for individual subjects (see text).
[c] NS, Not statistically significant ($P > 0.05$).

- The "therapeutic" range is widely reported to be 5–20 μg/mL

- Cmax (inhibited) = 2.3 μg/mL
- Predictions with weaker inhibitors will generate a lower Cmax (inhibited)
- Even a 2-fold scalar applied to this Cmax (inhibited) would not go above the safety threshold

EMA Issue 3 – Acceptance Criteria (3)

Study conducted with strong inhibitor at a high dose – COU1

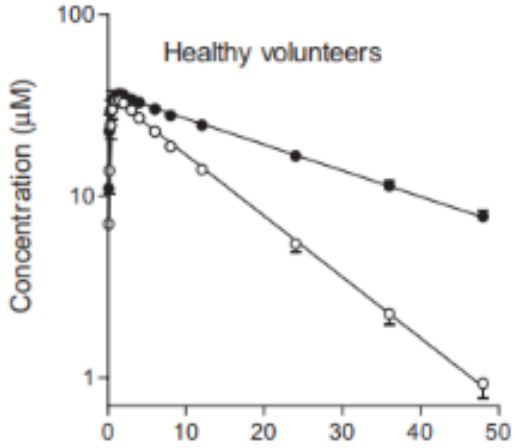


Table II. Effect of fluvoxamine on pharmacokinetic parameters of theophylline

			Patients with cirrhosis			
	Healthy subjects		*Child class A*		*Child class C*	
Parameter	*Placebo*	*Fluvoxamine*	*Placebo*	*Fluvoxamine*	*Placebo*	*Fluvoxamine*
CL/F (mL/min · kg)	0.844 ± 0.146	0.317 ± 0.037*	0.686 ± 0.181	0.329 ± 0.061*	0.294 ± 0.092†	0.263 ± 0.077‡
Ratio % and 95% CI	38 (33-43)		48 (40-55)		88 (76-100)	
V_z/F (L/kg)	0.665 ± 0.092	0.625 ± 0.055	0.630 ± 0.096	0.602 ± 0.050	0.738 ± 0.165	0.695 ± 0.124
Ratio % and 95% CI	95 (85-105)		93 (84-102)		95 (89-101)	
$t_{½}$ (h)	9.28 ± 1.73	22.90 ± 2.22*	10.60 ± 2.90	21.10 ± 2.50*	30.00 ± 21.40†	31.10 ± 18.20‡
Ratio % and 95% CI	252 (223-282)		207 (180-255)		109 (93-126)	
C_{max} (µmol/L)	38 ± 6	42 ± 8	42 ± 6	46 ± 9	36 ± 7	40 ± 8
Ratio % and 95% CI	114 (97-131)		110 (98-121)		110 (106-114)	
t_{max} (h) (median and range)	1.25 (0.33-2.00)	1.50 (0.33-2.00)	0.75 (0.33-1.50)	0.75 (0.33-2.00)	0.50 (0.33-1.50)	0.75 (0.33-2.00)
Ratio % and 95% CI	168 (25-311)		105 (27-163)		155 (59-252)	

CL, Systemic clearance; F, bioavailability; Ratio %, percent value of ratio between data in presence and absence of fluvoxamine with 95% confidence interval; CI, confidence interval; V_z, elimination-phase volume of distribution; $t_{½}$, elimination half-life; C_{max}, peak plasma concentration; t_{max}, time to peak plasma concentration.
*$P < .001$, versus placebo.
†$P < .001$, versus healthy subjects and patients with Child class A cirrhosis.
‡$P < .05$, versus healthy subjects and patients with Child class A cirrhosis.

Theophylline (4mg/kg) given on day 6 with fluvoxamine (50 mg BID)

NTID

- The “therapeutic” range is widely reported to be 55 to 110 µM
- Cmax (inhibited) = 42 µM
- Predictions with weaker inhibitors will generate a lower Cmax (inhibited)
- Even a 2-fold scalar applied to this Cmax (inhibited) would not go above the safety threshold

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EMA Issue 4 – Acceptance Criteria (1)

- *Please present an analysis of Observed vs. Predicted DDIs by strictly adhering to the context of use (CoU)1-3.*

- DIDB searches
  - excluded studies based on predefined criteria
  - consistent across enzymes
- For each enzyme
  - a range of substrates with differing fmCYP values were included
  - a range of inhibitors including weak, moderate and strong were included

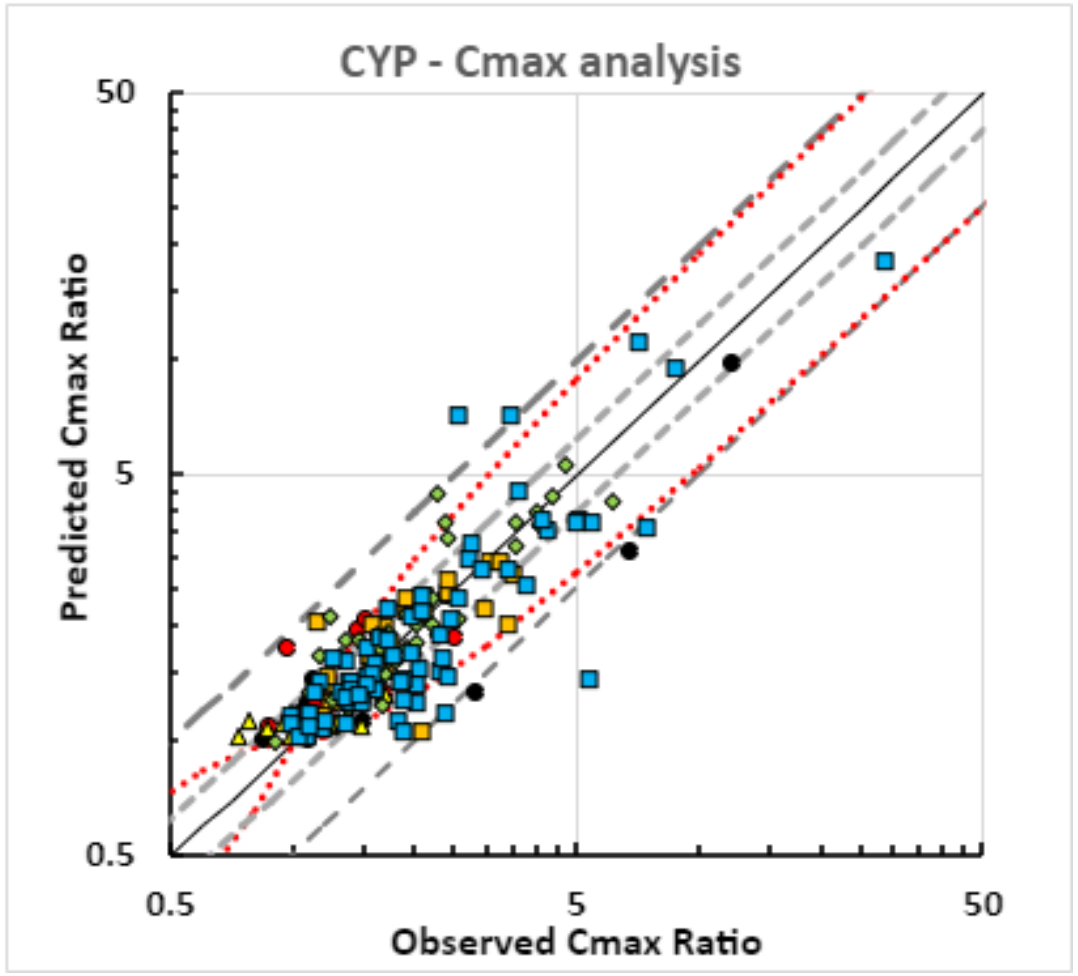
EMA Issue 4 – Acceptance Criteria (2)

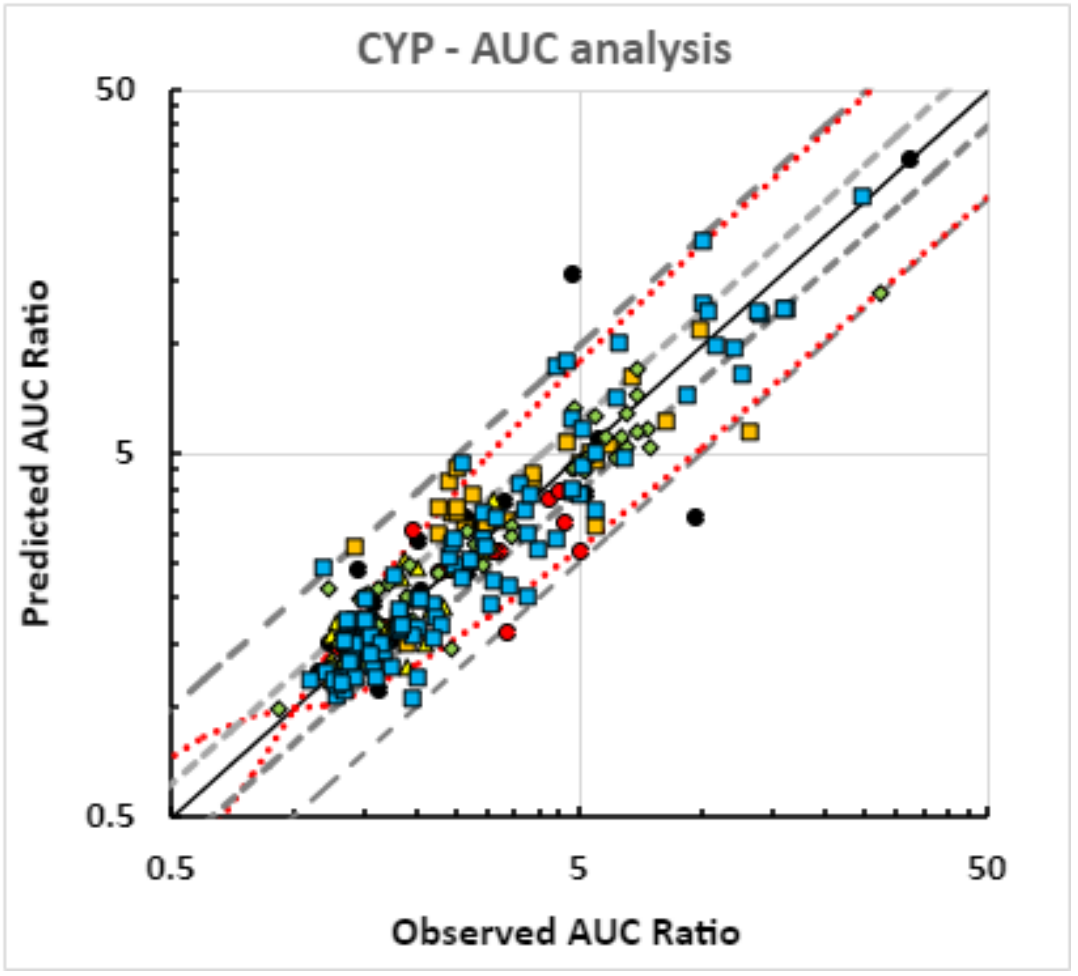
Breakdown of studies according to enzyme and mechanism of inhibition

Enzyme	CI	MBI	ALL
CYP1A2	42	0	42
CYP2C8	7	10	17
CYP2C9	25	3	28
CYP2C19	15	13	28
CYP2D6	32	14	46
CYP3A4/5	66	28	94
Total	187	68	255

EMA Issue 4 – Acceptance Criteria (3)

All enzymes and both mechanisms





EMA Issue 4 – Acceptance Criteria (4)

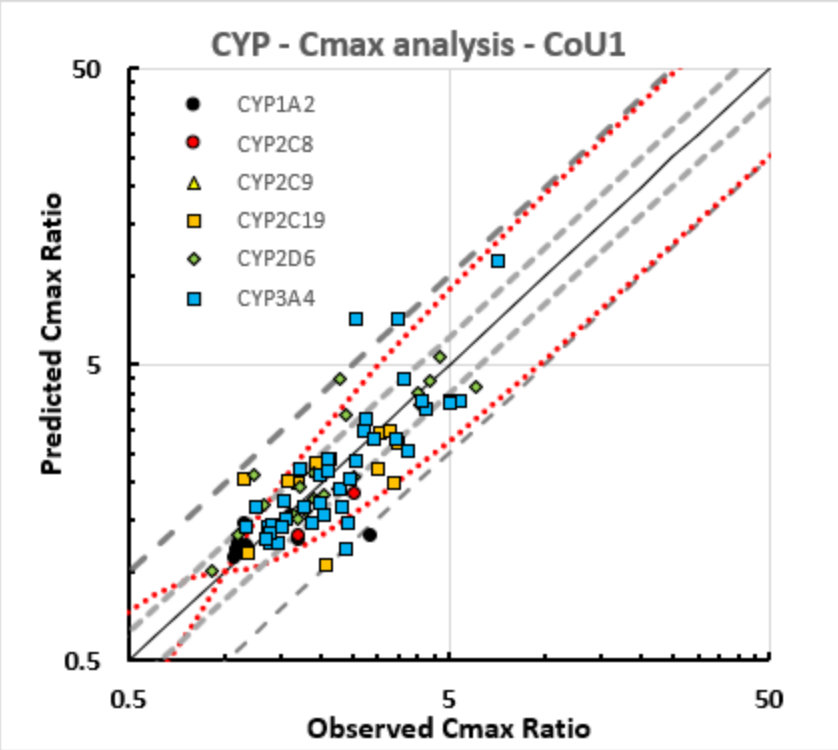
- We have presented the analyses in a number of different ways:
  - Each enzyme per mechanism and COU
    - CYP1A2, CYP2D6, CYP2C8, CYPC29, CYPC19, CYP3A4
  - All enzymes combined per mechanism and COU

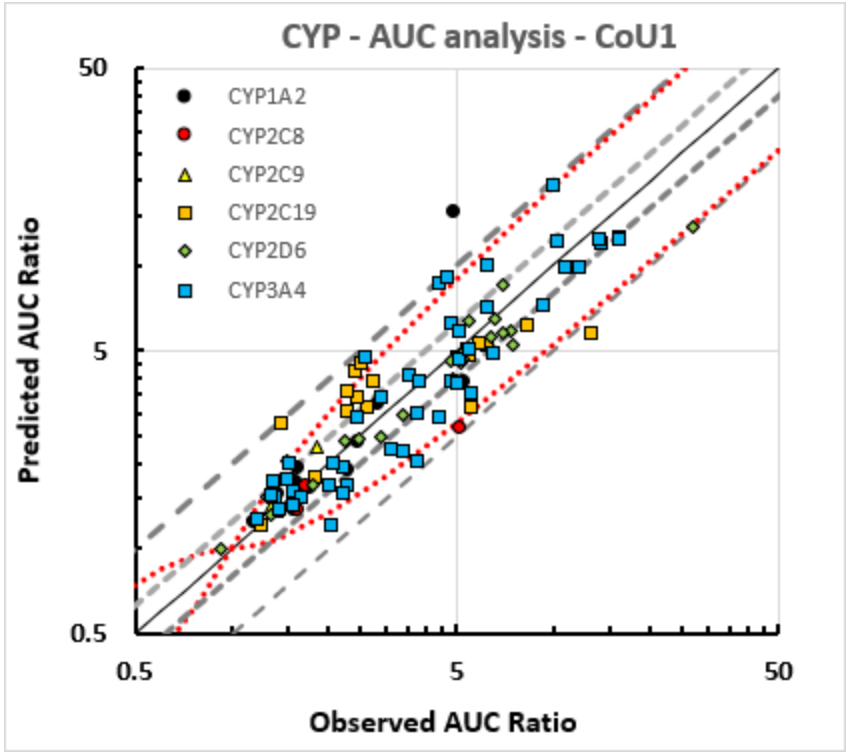
COU 1
Only include substrates with weak to strong inhibitors.

COU 2
Only include competitive inhibitors where a range of substrates including sensitive are available.

COU 3
Only include MBI where a range of substrates including sensitive are available.

EMA Issue 4 – Acceptance Criteria (5)





COU 1
Only included substrates with weak to strong inhibitors.

2-fold		1.5-fold		1.25-fold	
Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
3	2	11	19	30	37
83	108	83	108	83	108
96.39	**98.15**	**86.75**	**82.41**	**63.86**	**65.74**

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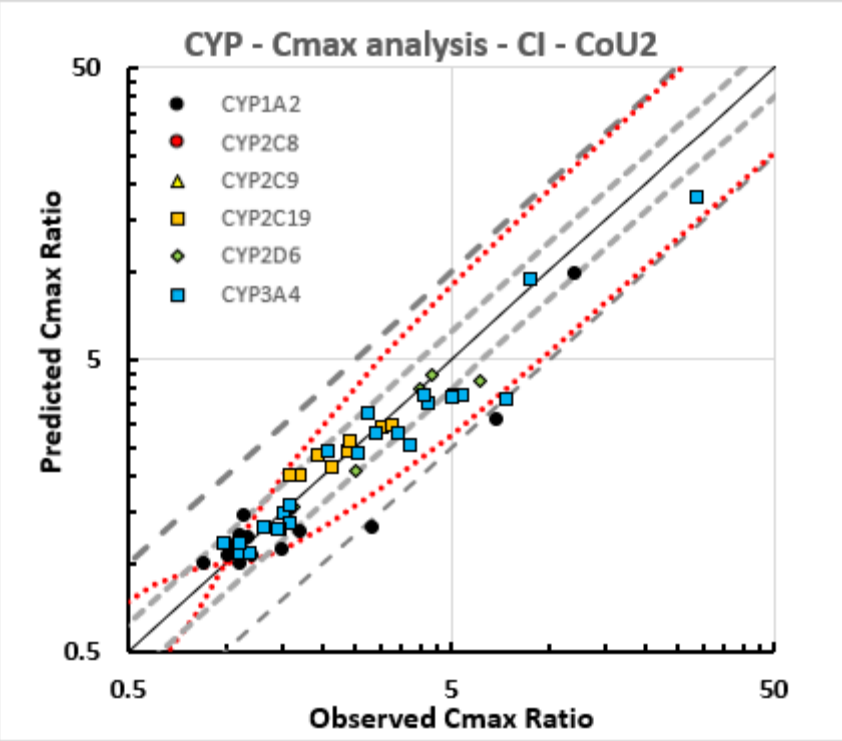
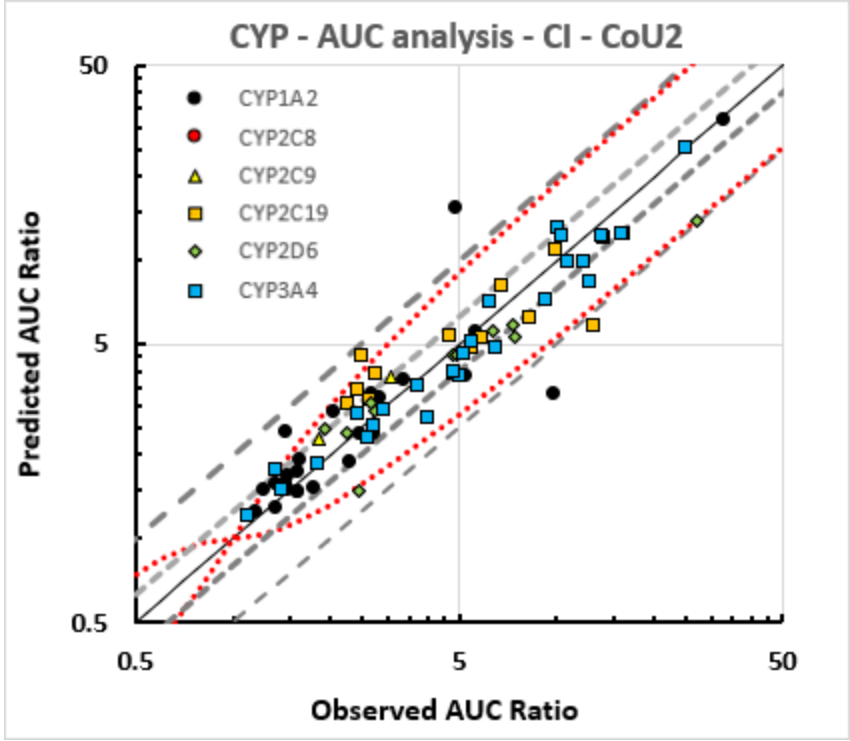
EMA Issue 4 – Acceptance Criteria (6)



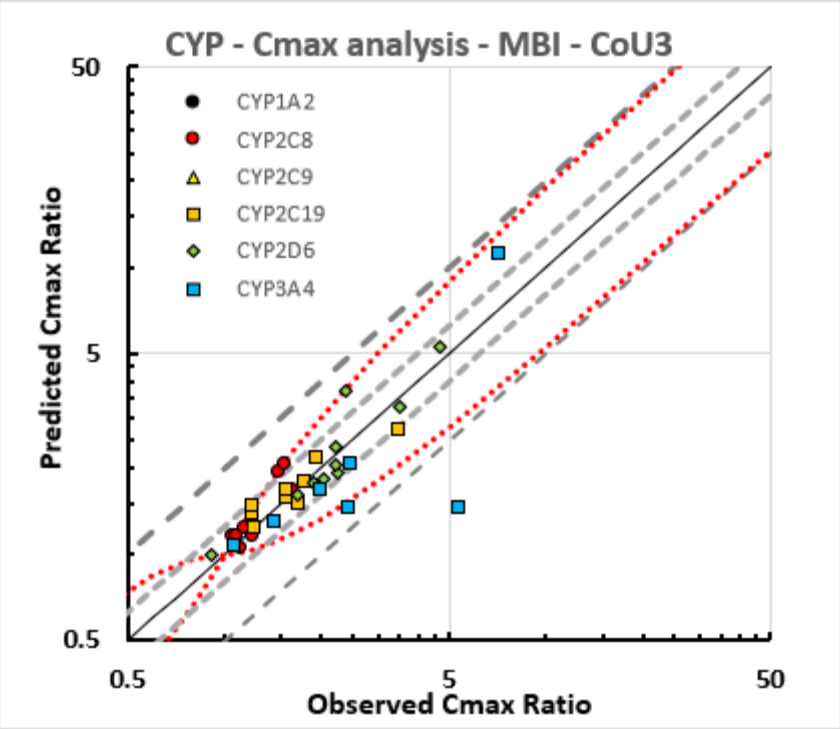


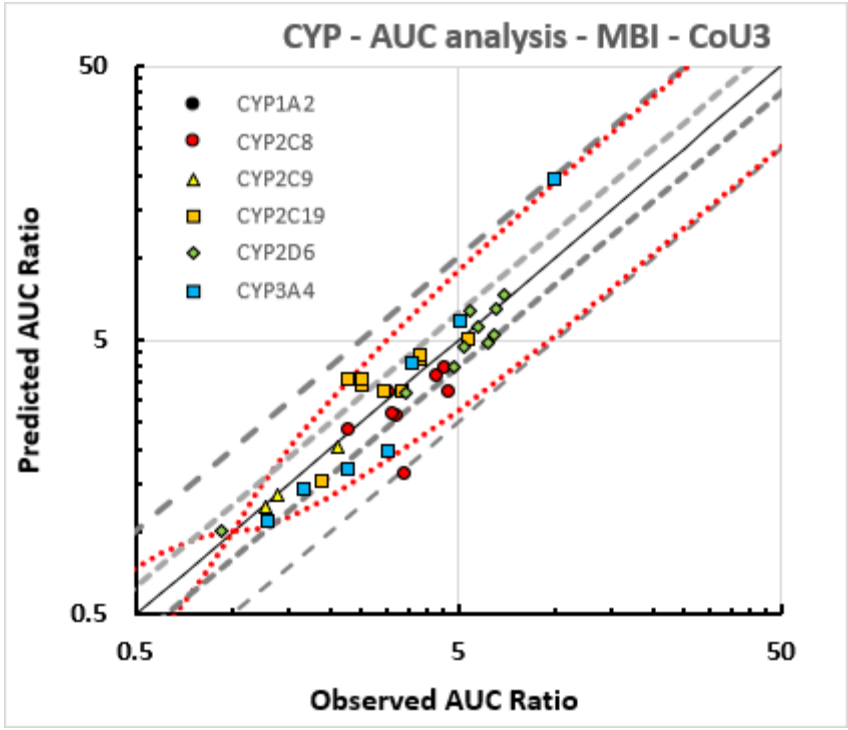
COU 2
Only included competitive inhibitors where a range of substrates including sensitive were available.

2-fold		1.5-fold		1.25-fold	
Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
3	**3**	**4**	**7**	**14**	**26**
58	81	58	81	58	81
94.83	**96.30**	**93.10**	**91.36**	**75.86**	**67.90**

CERTARA

EMA Issue 4 – Acceptance Criteria (7)





COU 3
Only included MBI where a range of substrates including sensitive were available.

2-fold		1.5-fold		1.25-fold	
Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio	Cmax Ratio	AUC Ratio
1	1	4	4	7	9
34	37	34	37	34	37
97.06	**97.30**	**88.24**	**89.19**	**79.41**	**75.68**

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EMA Issue 8 – Acceptance Criteria (1)

- *Please discuss the option to include separate acceptance criteria for Cmax, AUC and for different CoU.*

- A clinical study is a prerequisite for each COU.
- **Worst case scenarios will be assessed using a clinical study (strong inhibitor/sensitive substrate).**
- For a NCE, simulations will be run against weaker inhibitors (COU1) or less sensitive substrates (COU2/3).
- Percentages within 1.25-2.0-fold provide a level of confidence in the predicted DDI.
- Fold values can be applied to predicted exposure of NCE in the presence of inhibitor to determine whether it remains with the therapeutic window.

EMA Issue 8 – Acceptance Criteria (2)

- For all COU, the change in the exposure of the investigational drug is being evaluated

- Different acceptance criteria are probably more relevant to therapeutic window/dose response than for different COU

- For NTID, lower fold values may be needed for Cmax.

THANK YOU

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