esqlabs
we empower life sciences

Building an EMA-Qualifiable OSP Suite for Enzyme- and Transporter-Mediated DDI Prediction

Consolidation and Extension of the Qualification Framework



OSP Conference 2026 / Ingrid Michon & Zhixin Jiang / ESQlabs GmbH

Agenda

01 **Regulatory Context & OSP Suite Today**

Why EMA qualification, why now

02 **Five Workstreams**

Consolidating for assessor confidence

03 **Open Questions**

Risks and the path to EMA engagement

01

Why EMA Qualification, Why Now

Regulatory context, current OSP status, and the objective

Regulatory Drivers for PBPK DDI Qualification

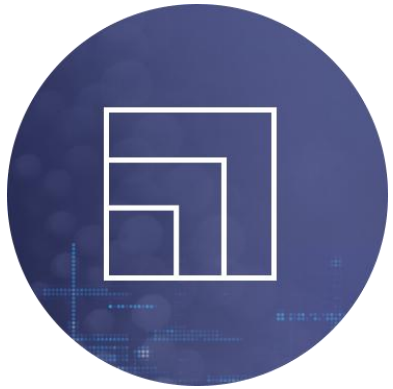
2018 → 2024 → 2026: increasing evidence needed



EMA PBPK Guideline

Reporting and qualification expectations for PBPK in the EU

Dec 2018



ICH M12

Harmonised DDI study design and PBPK modelling guidance

May 2024



ICH M15

Risk-based model credibility: evidence scaled to context of use

Jan 2026

Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation - Scientific guideline | European Medicines Agency (EMA)
ICH M12 on drug interaction studies - Scientific guideline | European Medicines Agency (EMA)
ICH M15 Guideline on general principles for model-informed drug development_Step 5

Qualification Opinion Simcyp EMA 01 August 2025



1 August 2025
Doc Ref: EMADOC-1700519818-2006369
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion for Simcyp Simulator

In scope:

- CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 interactions.
- Competitive inhibition and mechanism-based inhibition (MBI) via these enzymes.
- The qualification opinion is related to Simcyp Simulator (V19 R1)
- DDIs in a Caucasian, healthy subject population
- Prediction of average effect for AUC and Cmax

Out of scope:

- Non CYP enzymes (e.g. UGTs).
- DDIs involving transporters
- Induction mediated DDI predictions
- DDIs in non-Caucasian populations or patients
- Fed conditions / new dosing routes
- Predictions without a clinical DDI study to validate/optimise key parameters
- Prediction of between subject variability of the interaction

Qualification Opinion for Simcyp Simulator

Case Study: Use of Simcyp Platform Within Scope

Source: Qualification Opinion for Simcyp Simulator; see also Certara's CYP DDI perspective presentation, Yeo (Oct 2025)

Simcyp v19 predicts the average magnitude of CYP-mediated interactions (CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4/5) within a **deliberately narrow CoU**: fixed assumptions, settings, and population to manage model risk

1 Define the role of the drug

New drug X as a CYP substrate (CoU1), competitive inhibitor (CoU2), or mechanism-based inhibitor (CoU3)

2 Run the qualifying clinical DDI study

Pair X with a strong CYP inhibitor (CoU1) or a sensitive substrate of the same enzyme (CoU2/CoU3) — healthy Caucasian adults, oral fasted or IV

3 Simulate & verify parameters

PBPK model in Simcyp v19; observed vs. predicted AUCR/Cmax must match to verify fmCYP (CoU1), Ki (CoU2), or KI & kinact (CoU3)

4 Extrapolate to other drugs

Same PBPK model and settings predict DDIs with other inhibitors/substrates

Ki: Inhibition constant (competitive inhibition) ; *KI:* Inhibitor concentration at half-maximal inactivation rate; *Kinact:* Maximal inactivation rate constant

What “Qualification” Means, on Each Context

EMA Qualification Opinion

Voluntary, not required

It does not remove submission-level assessment.
No qualification does not mean non approval

Platform layer only

The Opinion frames platform qualification as an established layer;
Context of Use and Uncertainty Quantification of investigative drug still to be completed by Sponsor.

Issued to one version – Simcyp example

- Valid for Simcyp V19R1.
- Bridging to a newer version needs a documented justification each time, and often still needs updated results.

OSP Qualification Report

Validates against real clinical data

Models in qualifications have systematical evaluations.

Rerun with every new OSP version released

The automation, what triggers and regenerates this validation, also requalifies the platform on every new OSP Suite release, including new data or model changes.

Community experts-reviewed, not regulator-reviewed

- Reports are produced by the Qualification Runner and Reporting Engine, version-traceable, and signed off by the OSP community management team
- independent regulator assessment is missing

Where the OSP Qualification Stands Today

10 OSP packages in total — the DDI networks are the most complete, but not the whole story

5

DDI Networks

CYP3A4, CYP1A2, CYP2C19, P-gp, UGT1A. Inhibition and induction, across 50 DDI pairs.

The most complete

1

Special Populations

Chronic kidney disease

Outside the scope any qualified platform holds today.

4

Paediatric Ontogeny

Age-dependent CYP3A4, CYP2C8, P-gp and GFR scaling.

A different context of use (CoU) class

All of these packages already have released qualification reports

From Published Models to a Qualifiable Package

Open-source and openly developed under maintainer-controlled governance. No regulator review yet

	TODAY		GOAL
Evidence base	10 packages, 50+ DDI pairs, 5 DDI networks, but no uniform protocol.	→	One documented, systematic protocol per network.
Regulatory status	Community (management team) sign-off only. No regulatory assessment yet	→	An assessor-defensible package that can be referenced at submission.
Consolidation	Model files/version and expression profile differences	→	One consolidated, version-traceable reference set.
Scope	Covered: CYP3A4, CYP1A2, CYP2C19, P-gp, UGT1A1/1A9. Not covered: CYP2B6, CYP2C8, CYP2C9, CYP2D6, and other non-CYP related.	→	Coverage extended to the uncovered CYP networks.

The science already exists. The goal is a credible, submission-ready package.

02

Five Workstreams to an Assessor-Defensible Package

From consolidation to extension

Five Workstreams

Each one closes a specific gap between current packages and a submission-ready package

01

Evidence Sufficiency

One documented protocol for collecting and classifying every clinical DDI study.

02

Database Consensus

One expression database. One reference-concentration table.

03

Compound Files

Divergent file versions converged into a single reference set.

04

Reproducibility

Every report pinned to an exact software and data version.

05

Scope Extension

CYP2D6, 2B6, 2C8 formalised. Suggestion for CYP2C9 in the companion poster (Michon. et al)

Combine into a submission-ready package.

Workstream 1 · Evidence Sufficiency

One documented database, and a written record of changes

1. **Collect DDI pairs in public data**

   Data of every clinical DDI study pair maintained in the Database-for-observed-data.

2. **Cross-check each ratio**

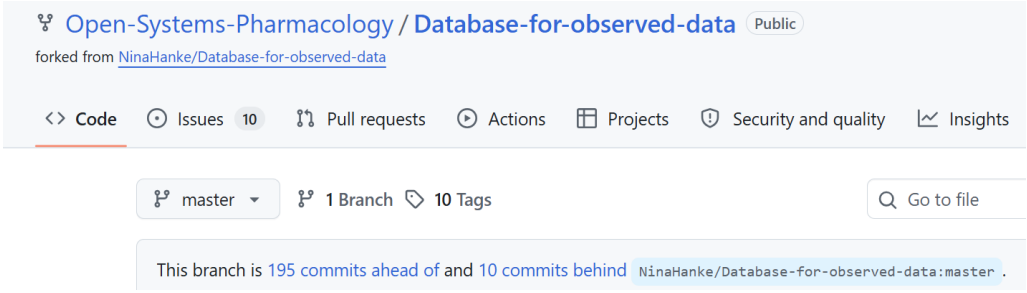
   Observed AUC ratios checked against published data.

3. **Select per network**

   Which candidates enter which network is a separate, documented decision.

4. **Refresh on a cycle**

   Literature re-checked quarterly, so new studies can be added



Workstream 2 · Database Consensus

One shared reference for expression and inhibition data for the entire network rather than per compound

	TODAY		TARGET
Expression naming	Differs across the CYP1A2, CYP2C19 and CYP3A4 plans. Eg. one transporter, two names: “P-gp” and “ABCB1”.	➡	One name per enzyme and transporter, used by every network.
Reference concentrations	Set per compound	➡	One consistent expression database, to be used in every report.
Traceability	Some values are not traceable to their cited source. Cheng-Prusoff conversion sometimes unclear	➡	Every parameter traced to its source; every Ki/IC_{50} ambiguity resolved.

Workstream 3 · Compound Files

Four recurring findings and the systemic fix for each

Different versions used

Eg. Fluconazole: qualification report pins v1.0 (CYP3A4 Ki = 10.7 µM), the latest release is v2.0 (CYP3A4 Ki = 13.1 µM)

→ **Version-traceability table**

Tier-label accuracy

Eg. Carbamazepine labelled as moderate inducer in report; but indexed by FDA as strong CYP3A4 inducer

→ **Cross-check every tier label against FDA For Healthcare Professionals (HCP) and ICH M12**

Duplicate models

Eg. 2 fluvoxamine versions, alt_v1.0 and v2.0, both in use

→ **One canonical file per compound, enforced by a repo check**

Compounds without version control

Compounds appear in qualification reports but have no validation report on its own (e.g. Caffeine)

→ **Publish every compound in qualification report as a versioned model + report**

For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems | FDA
ema.europa.eu/en/ich-m12-drug-interaction-studies-scientific-guideline

Workstream 4 · Current Reproducibility

3 levels

FULL SCOPE

Every OSP Suite release

All platform qualification reports and all model evaluation reports are regenerated centrally with the new Suite version across the complete scenario, not just a subset

FORMAT AND SCHEME

Every push and pull request is checked automatically: encoding, text, internal references and plan format.

No simulation is run at this level — the network itself is not re-executed.

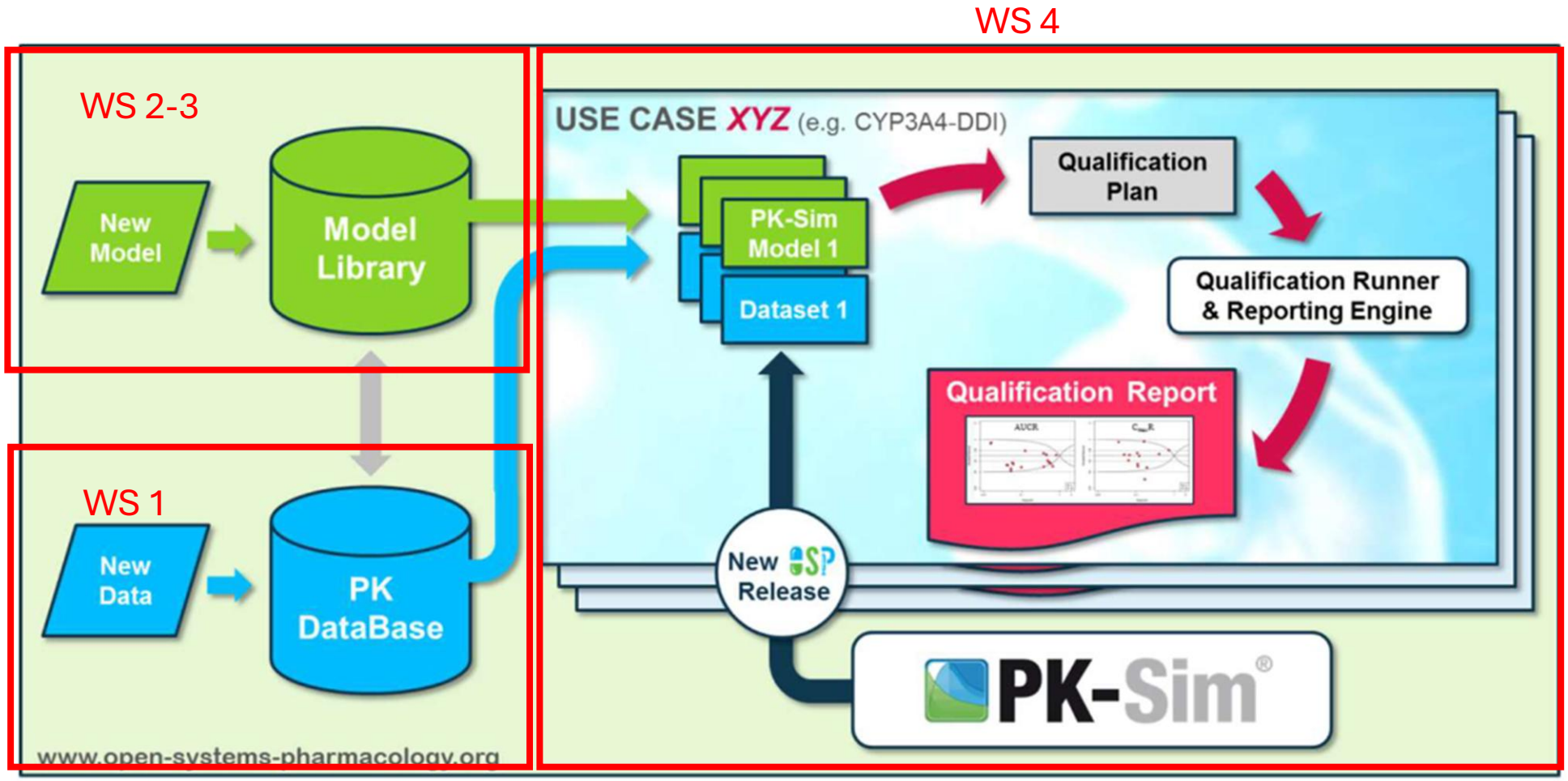
Qualification Report - SOP (Standard Operating Procedure)

Re-evaluate the model → **Update the version** → **Update the DDI file*** → **Qualification Runner** → **New report**

** Structure or process changes only. Runner overwrites the DDI project's compound building block from the pinned single-compound model implementing any changes automatically*

Workstream 4: Reproducibility

In line with OSP ecosystem: model library, PK database, plan, runner, report



Workstream 4 · Reproducibility

Models are reproduced across three stages with an overall report

ONE QUALIFICATION PLAN (JSON)
Projects · ObservedDataSets · Sections · Plots · Inputs

STAGE 1
Qualification Runner

- Reads the plan and **the specific version of model snapshots**.
- Exports simulations, extracts observed data, builds parameter tables from the models.

STAGE 2
Reporting Engine

- Runs every simulation.
- Generates every figure and statistic.
- Walks through the report outline section by section, filling in templated text, plots and tables.

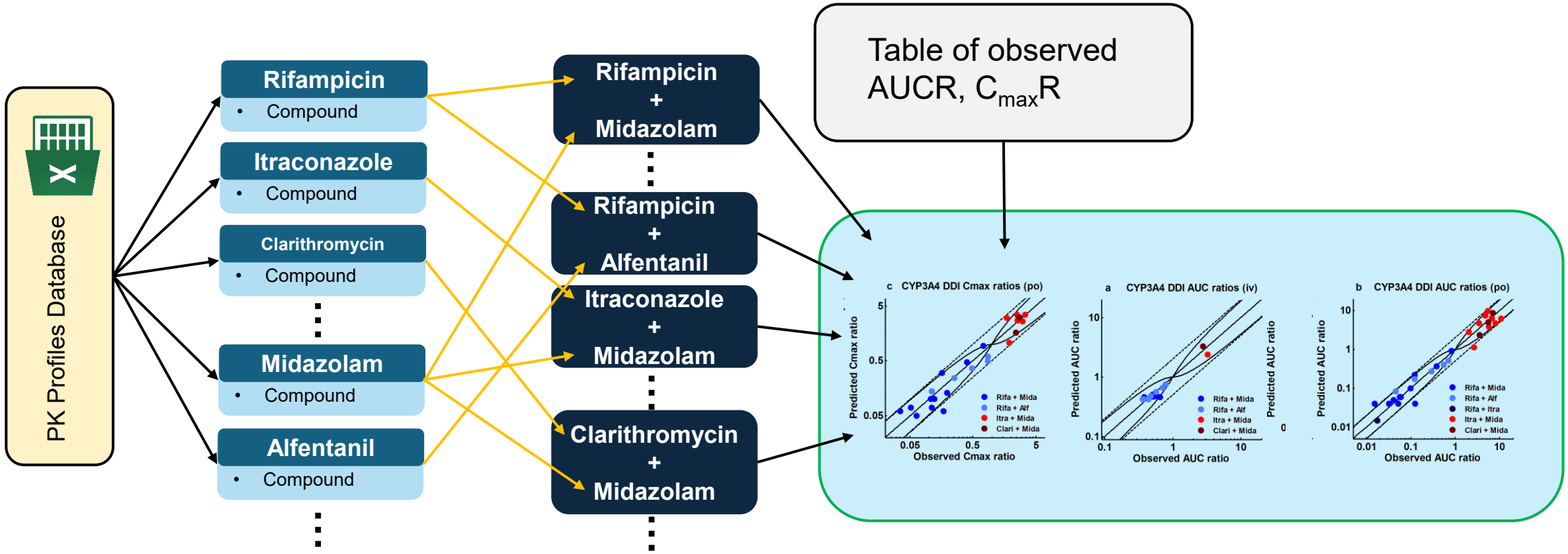
STAGE 3
Output

- The assembled report is written to a clean folder, as Markdown and as Word.

The same inputs always regenerate the same report.

From Compound Models to a Qualification Network

Every pair simulated and every prediction compared against its own observed study



Scope · Precipitant Tier Coverage

Every label checked against FDA's Health Care Professionals Examples Table

		WEAK	MODERATE	STRONG
CYP3A4	Competitive inhibition (CI)	cimetidine, fluvoxamine	fluconazole	itraconazole
	Mechanism-based inhibition (MBI)	–	erythromycin, verapamil	clarithromycin
	Induction	–	efavirenz, carbamazepine‡	rifampicin
CYP1A2	CI	Cimetidine	mexiletine	fluvoxamine
	MBI	–	oral contraceptives	–
CYP2C19	CI + MBI (dual)	omeprazole	moclobemide	–
	CI	–	–	fluvoxamine

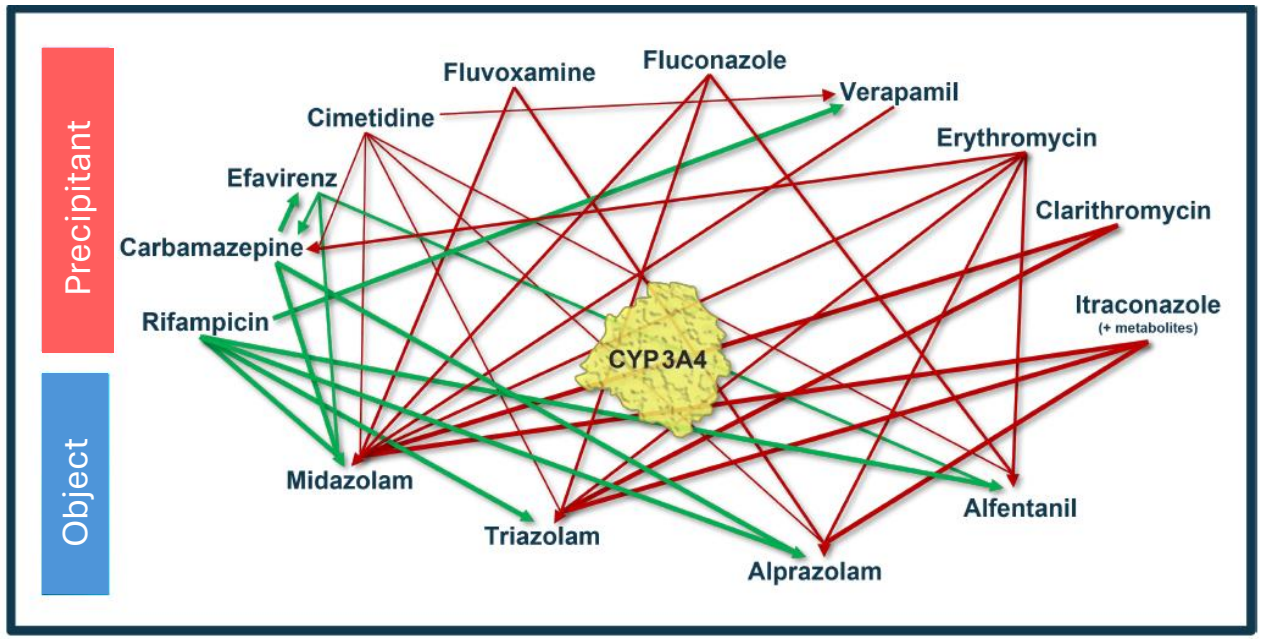
‡ *Carbamazepine is indexed as a CYP3A4 strong inducer by FDA/HCP*

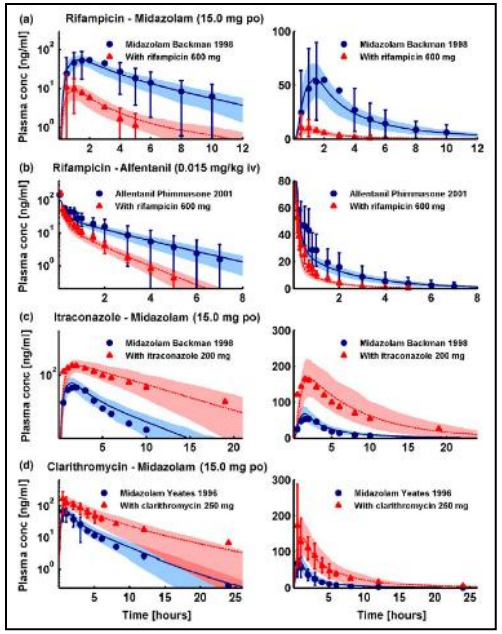
- **Eg. Cimetidine is also a weak inhibitor of CYP1A2, CYP2C9 and CYP2D6 -> increase coverage of weak precipitants**
- **EMA accepted cross-mechanism tier-coverage in the example of Simcyp qualification opinion**

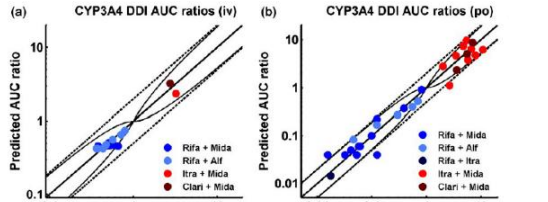
For Healthcare Professionals | FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems | FDA

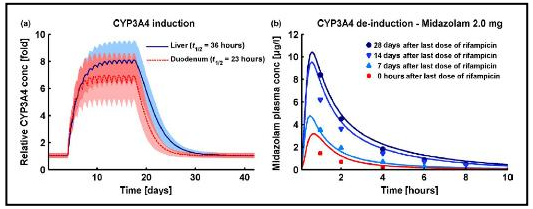
Example of Covered Scope · CYP3A4: The Network Realised

Verified precipitant and object, linked through shared clinical studies





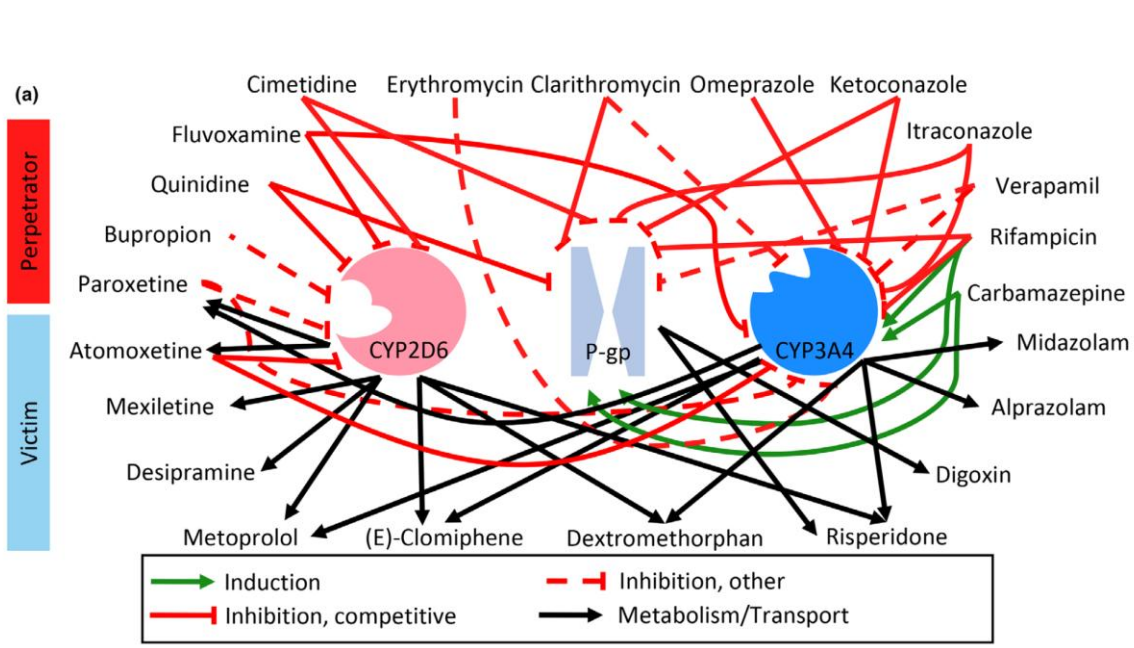


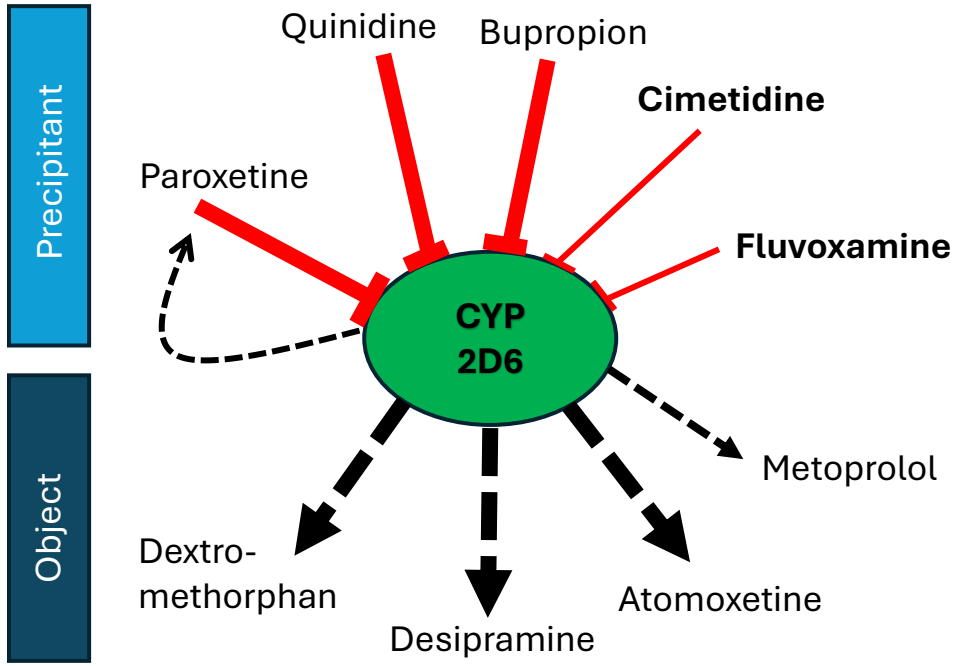


Published CYP3A4 DDI network (PMC6202474)

Workstream 5 · Scope Extension · Low hanging fruit: CYP2D6 network

Precipitant, object, and the models that already exist (Based on Rüdesheim et al. 2025)



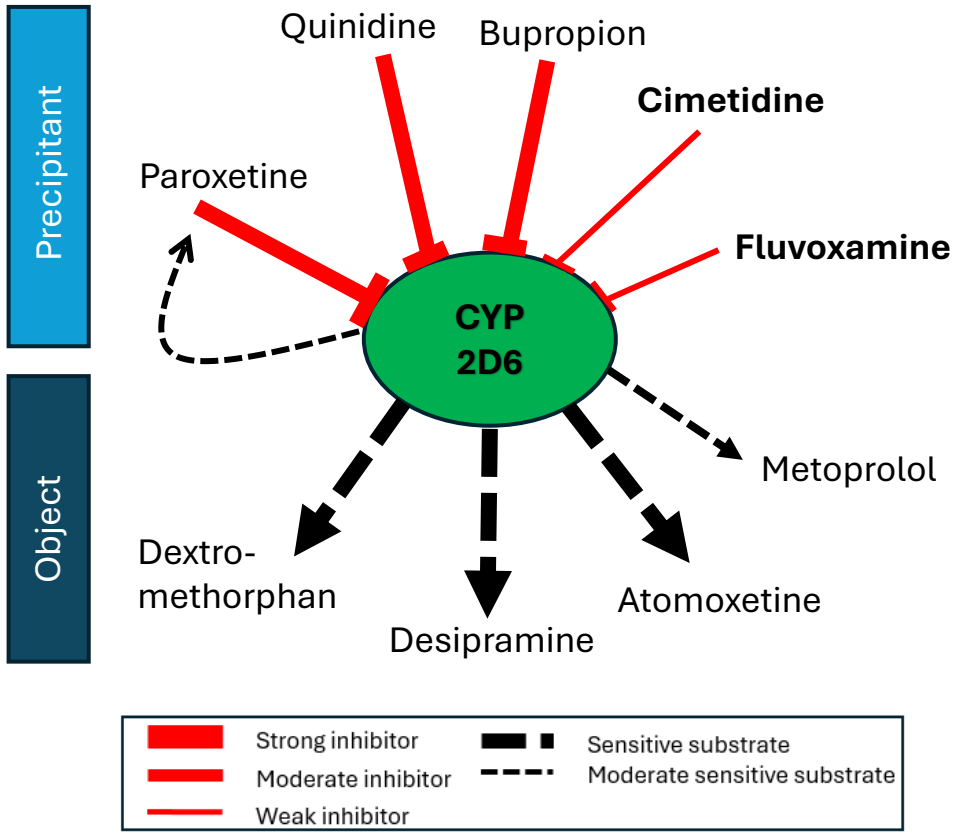




Reference network: Rüdesheim et al. 2025 · DOI 10.1002/cpt.3604 · PMID 39953671

Workstream 5 · Scope Extension Example· CYP2D6

Precipitant, object, and the models that already exist (Based on Rüdesheim et al. 2025)



Models already available:

- PK-Sim library: cimetidine and fluvoxamine -> CYP2D6 inhibtion to add
- GitHub repository: quinidine, paroxetine, bupropion, dextromethorphan, desipramine, atomoxetine, metoprolol

Published clinical studies available:

Precipitant \ Objects	dextromethorphan	Desipramine	atomoxetine	metoprolol
quinidine	7	1	0	2
paroxetine	2	2	2	5
bupropion	1	1	2	0
ritonavir	2	2	0	1
cimetidine	0	0	0	2
fluvoxamine	0	1	1	0

Same workflow applies to CYP2B6, CYP2C8, CYP2C9 DDI network

COMPANION POSTER, THIS CONFERENCE

A CYP2C9-Centered Perpetrator–Victim DDI Network as an Extension of the EMA Qualification Framework within the Open Systems Pharmacology Suite (Michon et al.)

Reference network: Rüdesheim et al. 2025 · DOI 10.1002/cpt.3604 · PMID 39953671

Prioritized Context of Use Roadmap

Ranked by the strength of the evidence that already exists

	CONTEXT OF USE	EVIDENCE IN PLACE TODAY
1	**CYP3A4 · Competitive Inhibition (CI)**	Complete three-tier coverage. Four sensitive objects. Peer-reviewed methodology paper.
2	**CYP3A4 · Mechanism-based Inhibition (MBI)**	Moderate-to-strong coverage. One weak-MBI compound would complete the coverage.
3	**CYP3A4 · induction**	Moderate-to-strong coverage. No qualified platform yet (not included in the Simcyp Qualification yet)
4	**CYP1A2 · CI**	Moderate and strong coverage. Needs fluvoxamine-file convergence. One weak-CI compound needed (e.g. cimetidine).
5	**CYP2C19 · CI + MBI**	Complete three-tier coverage. Needs fluvoxamine-file convergence
6	**P-gp · inhibition**	Ki values across five precipitants span a range of ~3000-fold. One object only (digoxin). Second object (dabigatran-etexilate) model would complete coverage
7	**UGT1A · inhibition**	Only 2 DDI pairs: atazanavir–raltegravir and mefenamic acid–dapagliflozin.

CYP2B6/2C8/2C9/2D6:

- **models and network identified**
- **no OSP qualification reports yet**

Scoped separately:

- **Chronic kidney disease**
- **Ontogeny**

- Different CoU classes

03

Discussion, Open Questions & Path Forward

Assessor confidence, risks, and next steps

The Precedent · Why a Point Estimate was not enough

What EMA flagged when a qualified platform reported only average fold error (AFE) / absolute average fold error (AAFE)

The limitation

Metric	CI AUC	CI Cmax	MBI AUC	MBI Cmax
AFE (bias)	0.99	0.95	1.02	1.01
AAFE (precision)	1.19	1.20	1.25	1.23
% within 2-fold	98.4%	96.4%	97.1%	94.8%
% within 1.5-fold	92.5%	86.7%	79.4%	93.1%
% within 1.25-fold	72.7%	63.9%	69.1%	75.9%
N studies	**187**	**130**	**68**	**60**

$$AFE = 10^{\frac{1}{n}\sum \log \frac{Predicted\ DDI}{Observed\ DDI}}$$

$$AAFE = 10^{\frac{1}{n}\sum \left|\log \frac{Predicted\ DDI}{Observed\ DDI}\right|}$$

AFE: Average Fold Error: Systemic bias (underestimate or overestimate)

AAFE: Absolute Fold Error: Absolute Bias

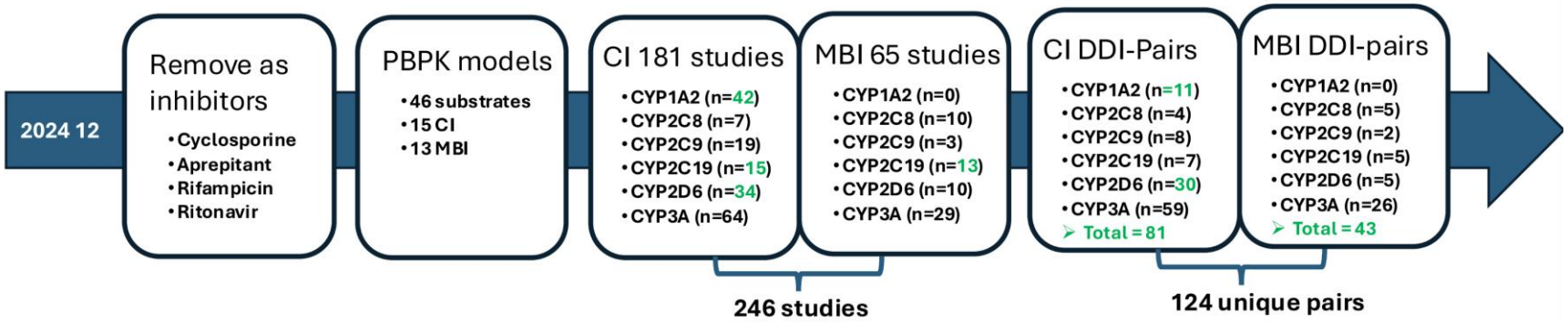
EMA concerns AFE:

- Cannot differentiate between CYP-specific bias
- Cannot differentiate between inhibitor strength–dependent bias
- Distribution shape of prediction errors: Are prediction errors normally distributed, skewed, or heavy-tailed? AFE reports only the central tendency, not the shape.
- Extreme outliers masked by averaging: How many individual studies fall outside a clinically meaningful boundary, regardless of the mean? AFE cannot identify these high-leverage failures.

AFE = 0.99 looks unbiased.
But: little difference between within 25% of the observed value, or half the studies over-predict 2-fold and half under-predict 2-fold.

Sources · *annex-6-sawp-discussion-meeting-6-march-2024_en.pdf*

The Solution · Simcyp vs OSP



Simcyp: Bayesian analysis

Prior × Likelihood = Posterior

- Producing the full probability distribution over the bias, not just a point estimate.
- Credible interval (90% CrI): there's a 90% probability the true GMR lies in this range.

Will OSP platform use this method as well?

- Final Simcyp Bayesian model does not include CYP-level hierarchical effects; CYP-agnostic pooling does not provide enzyme-specific precision
- Compound fm/Ki/kinact values still fit by classical fitting, not hierarchical/population methods
- ICH M15 asks for evidence matched to model risk, not a specific method

Source: Annexes 4–6 (DDI qualification matrix, briefing document, SAWP discussion records)

Discussion of OSP EMA Qualification · Uncertainty Analysis

What OSP reports today, and the limitation EMA is likely to flag

WHAT THE OSP QUALIFICATION REPORTS USE

Geometric mean fold error (GMFE) for AUCR and CmaxR, and a summary table against the Guest et al. (2011) criterion at δ = 1 as a point estimates of bias and pass/fail rate only.

ANTICIPATED GROUNDS FOR REJECTION

From previous qualification:

- no between-study variance
- no credible/confidence interval
- no probability statement for a CoU boundary

APPROACHES FOR UNCERTAINTY ANALYSIS ALREADY USED FOR OSP SUITE:

Krauss et al. 2015 PMID: 26431198
Bayesian - Markov Chain Monte Carlo (MCMC) parameter distribution

Teutonico et al. 2026 PMID: 41540733
Stochastic Approximation of the Standard Expectation Maximization (SAEM)

✓ **PROS**

✓ Population approach to correlation analysis

✕ **CONS**

✕ Untested at network scale

Thank you for your attention !

Acknowledgements

Zhixin Jiang (ESQlabs)

Raphaëlle Lesage (ESQlabs)

Stephan Schaller (ESQlabs)

Pavel Balazki (ESQlabs)

Robert McIntosh (ESQlabs)

Marco Siccardi (ESQlabs)

Cleo Demeester (ESQlabs)

Nina Nauwelaerts (ESQlabs)

Juri Solodenko (Bayer)

Interested in contributing? Please connect: ingrid.michon@ESQlabs.com

SCAN ME