

CYP2C19 DDI Qualification

Version	1.0-OSP9.1
OSP Version	9.1
Qualification Framework Version	2.2

This qualification report is filed at:

<https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports>

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1 Introduction

1.1 Objective

This qualification report evaluates the developed PBPK drug-drug interactions (DDI) models network for the ability to perform simulations with the intended purpose to predict cytochrome P450 2C19 (**CYP2C19**)-mediated DDI.

To demonstrate the level of confidence, the predictive performance of the platform for this Intended purpose is assessed via a network of PBPK models of selected index CYP2C19 DDI perpetrators, and respective sensitive CYP2C19 victim drugs and a comprehensive dataset from published clinical DDI studies. All PBPK models represent whole-body PBPK models, which allow dynamic DDI simulations in organs expressing CYP2C19.

The respective *qualification plan* to produce this *qualification report* is transparently documented and provided open-source (<https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports>). The same applies for all presented PBPK models including *evaluation reports* on model building and evaluation of each model (<https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library>).

Evaluation reports including descriptions on model building and detailed evaluations of the included models are documented separately (see [Section 1.2](#)).

Please refer to the [Appendix](#) to learn more details:

- An overview over the Open Systems Pharmacology Suite is given in chapter [Section 6.1](#)
- [Section 6.2](#) shows the implementation of the underlying mathematical equations for drug-drug interactions in the OSP suite.
- A detailed general description of the performed qualification workflow (*qualification plan*, *qualification report*, etc.) can be found in chapter [Section 6.3](#).

1.2 CYP2C19 DDI Network

CYP2C19 is an important enzyme for the metabolism of about 10% of therapeutical drugs, including proton pump inhibitors (PPIs, e.g., omeprazole), antidepressants (e.g., imipramine), anticonvulsants (phenytoin, S-mephenytoin), hypnotics and sedatives (e.g., phenobarbital), antimalarial (proguanil), antiretroviral (nelfinavir), antifungal (voriconazole), and antiplatelet drugs (clopidogrel) ([Goldstein 2001](#), [Desta 2002](#)). Genetic polymorphism exists for CYP2C19 expression, with approximately 3%–5% of European and 15%–20% of Asian populations being poor metabolizers with no CYP2C19 activity ([Goldstein 2001](#), [Bertilsson 1995](#)). Based on the metabolic capacity of CYP2C19, individuals can be divided into four categories: extensive metabolizers (EMs) carrying normal alleles, intermediate metabolizers (IMs) carrying one defective allele, poor metabolizers (PMs) carrying two defective alleles, and ultra-rapid metabolizers (UMs) homozygous for alleles which increase the CYP2C19 expression or activity higher than in EMs. Well-known substrates of CYP2C19 are mephenytoin, omeprazole, and moclobemide.

Like other CYPs, CYP2C19 is subject to induction and/or inhibition by a number of compounds, which can result in significant drug interactions in clinical practice.

The U.S. Food and Drug Administration (FDA) lists several perpetrator and victim drugs of interactions in the CYP2C19 network ([Goldstein 2001](#)). For instance, omeprazole is a sensitive index substrate for CYP2C19, and fluvoxamine is listed as a strong clinical index inhibitor for CYP2C19 pathway.

To qualify the developed models for the prediction of the CYP2C19 DDI potential of new drugs, a set of verified PBPK models of index perpetrators and respective CYP2C19 DDI victim drugs is specified to set up a CYP2C19-mediated DDI modeling network.

The following perpetrator compounds were selected:

- **Fluvoxamine** (strong CYP2C19 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Fluvoxamine-Model/releases/tag/v1.0>
- **Omeprazole** (moderate CYP2C19 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Omeprazole-Model/releases/tag/v1.0>
- **Moclobemide** (moderate CYP2C19 inhibitor)
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Moclobemide-Model/releases/tag/v1.0>

The following sensitive CYP2C19 substrates as victim drugs were selected:

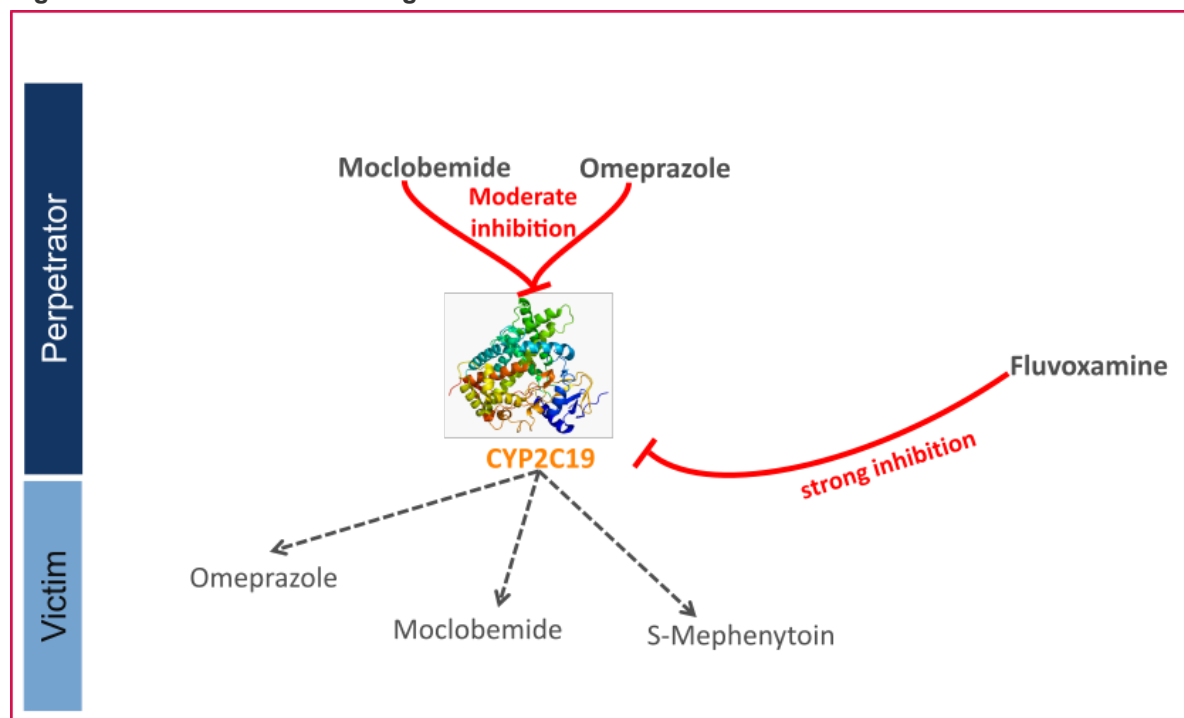
- **Omeprazole**
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Omeprazole-Model/releases/tag/v1.0>
- **S-mephenytoin**
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/S-mephenytoin-Model/releases/tag/v1.0>
- **Moclobemide**
Model snapshot and evaluation plan (*release v1.0*): <https://github.com/Open-Systems-Pharmacology/Moclobemide-Model/releases/tag/v1.0>

The following interaction studies were predicted and used to qualify/optimize the final network:

- Strong CYP2C19 inhibition
 - Fluvoxamine - omeprazole
 - Fluvoxamine - S-mephenytoin
- Moderate CYP2C19 inhibition
 - Omeprazole – moclobemide
 - Moclobemide - omeprazole

Figure 1 shows the specified and developed DDI modeling network of interacting perpetrator and victim drugs.

Figure 1: CYP2C19 DDI modeling network



The K_i values used to predict the interactions are listed in [Table 1](#).

Inhibitor category	Inhibitor	Substrate	K_i	Reference
Strong CYP2C19	Fluvoxamine	Omeprazole	3.6 nM	Jga 2016
		S-mephenytoine	2.6 nM	Jga 2016
Moderate CYP2C19	Moclobemide	Omeprazole	203.83 μM ¹ TDI 94.85 μM	Fit
	Omeprazole	Moclobemide	S-ome: 3.1 μM TDI 0.3 μM R-ome: 5.3 μM TDI 1.6 μM	Liu 2005 Wu 2014 Liu 2005 Wu 2014

Table 1: K_i values used in CYP2C19 DDI network. ¹Literature value = 204 μM

The published DDI studies between the respective perpetrators and victim drugs were simulated and compared to observed data. The following sections give an overview of the clinical studies being part of this qualification report.

Omeprazole - Moclobemide DDI

The omeprazole-moclobemide interaction was evaluated using clinical DDI studies listed in [Table 2](#).

Source	Route	Dose [mg] / Schedule *	Pop.	Sex	N	Form.	Comment
Cho 2002	p.o	20	HV asian	-	-	capsule	EM +/-moclobemide
Cho 2002	p.o	20	HV asian	-	-	capsule	PM +/-moclobemide

Table 2: Literature sources of clinical concentration data of omeprazole used for DDI prediction qualification with moclobemide. -: *respective information was not provided in the literature source*; *: *single dose unless otherwise specified*; EM: *extensive metabolizers*; PM: *poor metabolizers*

A dynamical DDI simulation with moclobemide and omeprazole was conducted and compared to literature data. Both compounds act as CYP2C19 inhibitors and victims. The predefined typical Japanese subject (age = 30 y, weight = 61.87 kg, height = 168.99 cm, BMI = 21.67 kg/m²) was used with CYP3A4, CYP2C19, CYP2D6 and CYP1A2 expressions from RT PCR database in PK-Sim and adapted CYP2C19 expression in gut (see evaluation report of omeprazole for more details). Additional enzyme "FMO (other)" was added and expressed in liver only.

In [Cho 2002](#), sixteen volunteers, of whom eight were extensive metabolizers (EM) and eight were poor metabolizers (PM) for CYP2C19, received oral doses of 40 mg omeprazole with or without 300 mg moclobemide co-administration.

The pharmacokinetic change of omeprazole, omeprazole sulphone and 5-hydroxyomeprazole concentrations were assessed to test for an interaction between omeprazole and moclobemide.

Omeprazole - Fluvoxamine DDI

The omeprazole-fluvoxamine interaction was evaluated using clinical DDI studies listed in [Table 3](#).

Source	Route	Dose [mg] / Schedule *	Pop.	Sex	N	Form.	Comment
Yasui-Furukori 2004	p.o.	40	HV japanese	M - F	6	omepral	hmEM +/- fluvoxamine
Yasui-Furukori 2004	p.o.	40	HV japanese	M - F	6	omepral	PM +/- fluvoxamine

Table 3: Literature sources of clinical concentration data of omeprazole used for DDI prediction qualification with fluvoxamine. *:single dose unless otherwise specified; hmEM: homozygous extensive metabolizers; PM: poor metabolizers

A dynamical DDI simulation with fluvoxamine as CYP2C19 inhibitor and omeprazole as victim was conducted and compared to literature data. The predefined typical Japanese subject (age = 30 y, weight = 61.87 kg, height = 168.99 cm, BMI = 21.67 kg/m²) was used with CYP3A4, CYP2C19, CYP2D6 and CYP1A2 expression from RT PCR database in PK-Sim and adapted CYP2C19 expression in gut (see evaluation report of omeprazole for more details). Additional enzyme "FMO (other)" was added and expressed in liver only. The Ki value of 3.6 nmol/l for the inhibition of CYP2C19 by fluvoxamine was selected in agreement with literature data ([Iga 2016](#)).

In [Yasui-Furukori 2004](#), eighteen volunteers, of whom six were homozygous extensive metabolizers (hmEMs), six were heterozygous EMs (htEMs) and six were poor metabolizers (PMs) for CYP2C19, received two six-day courses of either daily 50 mg fluvoxamine (split in 25 mg twice daily) or placebo in a randomized fashion with a single oral 40 mg dose of omeprazole on day six in both cases. Plasma concentrations of omeprazole and its metabolites, 5-hydroxyomeprazole, omeprazole sulphone, and fluvoxamine were monitored up to 8 h after the dosing.

S-Mephenytoin - Fluvoxamine DDI

The S-mephenytoin-fluvoxamine interaction was evaluated using clinical DDI studies listed in [Table 4](#).

Source	Route	Dose [mg]/ Schedule *	Pop.	Sex	N	Form.	Comment
Yao 2003	p.o.	100 mg s.d.	HV	m/f	12	-	S-mephenytoin, with and without Fluvoxamine MD of 37.5, 62.5 and 87.5 mg/day

Table 4: Literature sources of clinical concentration data of S-mephenytoin used for DDI prediction qualification with fluvoxamine. -: *respective information was not provided in the literature source*; *: *single dose unless otherwise specified*

A dynamical DDI simulation with fluvoxamine was used to predict the effect of a strong CYP2C19 inhibitor on S-mephenytoin exposure. The predefined "Standard European Male for DDI" individual (age = 30 y, weight = 73 kg, height = 176 cm, BMI = 23.57 kg/m²) with adapted CYP2C19 expression in gut (see evaluation report of omeprazole for more details) was used. Ki value of 2.6 nmol/l for the inhibition of CYP2C19 was selected.

Predictions were compared to clinical results from [Yao 2003](#), where the effect of different fluvoxamine doses in S-Mephenytoin was investigated. 100 mg S-mephenytoin were administered after 7 days of placebo or fluvoxamine treatment (27.5, 45.8, or 64.1 mg).

Moclobemide - Omeprazole DDI

The moclobemide-omeprazole interaction was evaluated using clinical DDI studies listed in [Table 5](#).

Source	Route	Dose [mg]/ Schedule *	Pop.	Sex	N	Form.	Comment
Yu 2001	p.o	300 s.d.	HV-Asian	m	8	tablet	EM +/- omeprazole

Table 5: Literature sources of clinical concentration data of moclobemide used for DDI prediction qualification omeprazole. *: *single dose unless otherwise specified*; EM: *extensive metabolizers*

A dynamical DDI simulation with moclobemide and omeprazole was conducted and compared to literature data. Both compounds act as CYP2C19 inhibitors and victims. 300 mg moclobemide with or without a single dose of 40 mg omeprazole (racemate, i.e. 20 mg S-omeprazole and 20 mg R-omeprazole) was simulated. The predefined typical Japanese subject (age = 30 y, weight = 61.87 kg, height = 168.99 cm, BMI = 21.67 kg/m²) was used with CYP3A4, CYP2C19, CYP2D6 and CYP1A2 expressions from RT PCR database in PK-Sim and adapted CYP2C19 expression in gut (see evaluation report of omeprazole for more details). Additional enzyme "FMO (other)" was added and expressed in liver only.

2 Qualification of Use Case CYP2C19-mediated DDI

The following section shows the correlations between observed and model-predicted AUC and C_{max} ratios, respectively.

Specifically, the PBPK model performance for the PK parameters **AUC ratio (AUCR)** and **C_{max} ratio (C_{MAXR})** is assessed via:

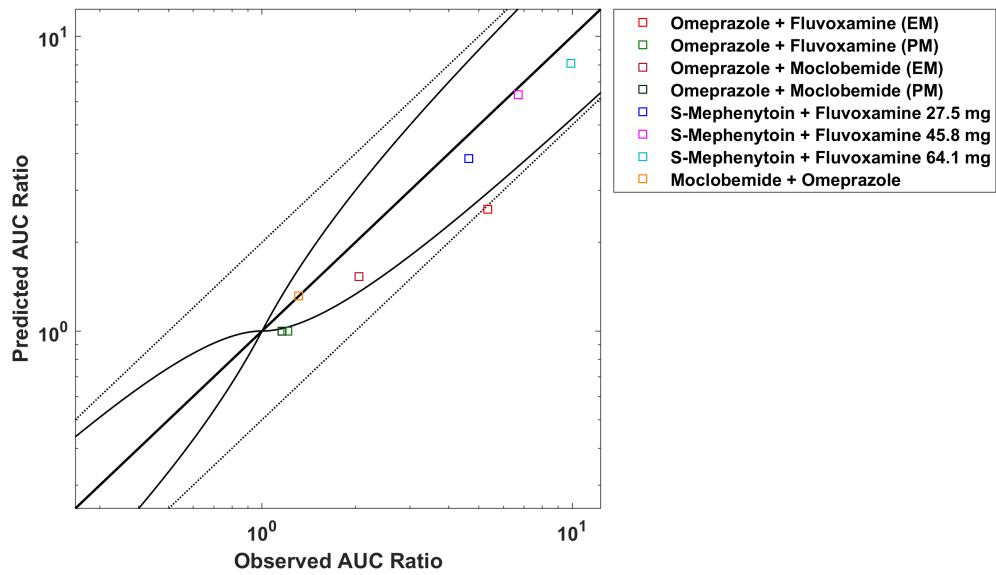
- predicted (*Pred*) vs. observed (*Obs*) plots
- *Pred/Obs* vs. *Obs* plots
- geometric mean fold error (GMFE):

$$10^{\frac{\sum |\log(\frac{Pred}{Obs})|}{n}}$$

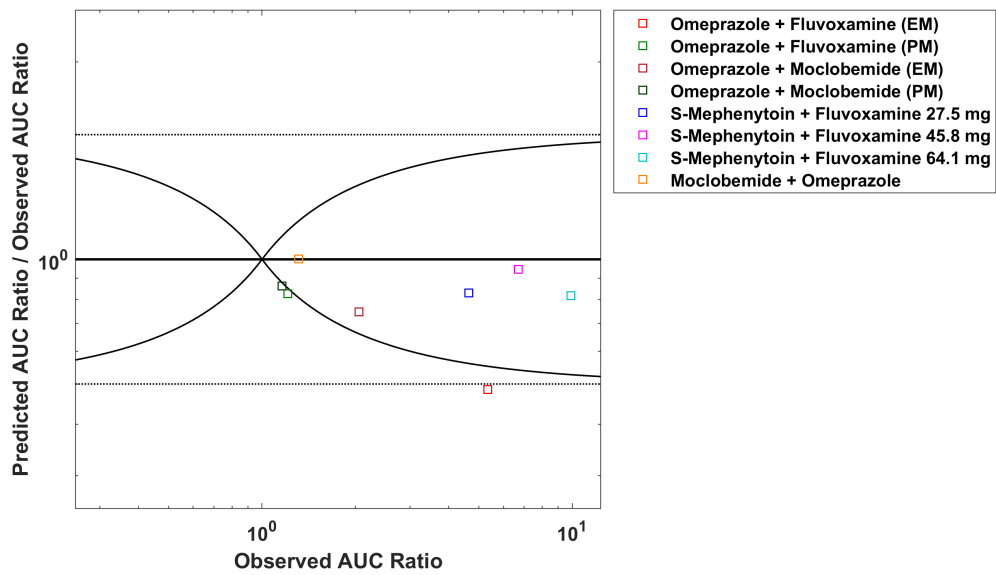
- number of AUCR and C_{MAXR} falling within 2-fold error range and within the limits as suggested by [Guest et al. 2011](#)
- detailed table of results for each study

In the plots,

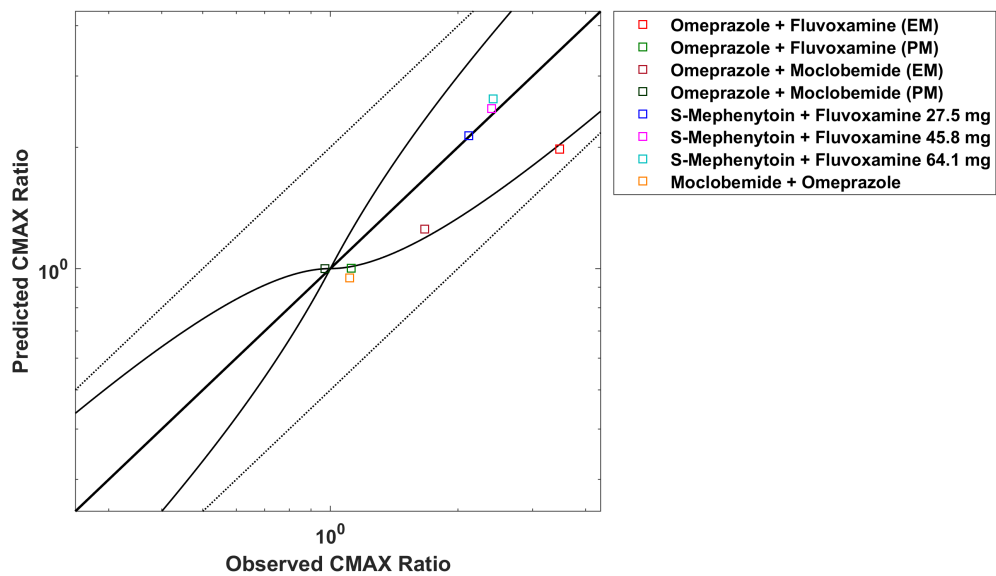
- the dotted lines denote 0.50–2.00 (2-fold) criterion,
- the solid lines denote the limits as suggested by [Guest et al. 2011](#),
- the bold solid line denotes the unity line,
- each color represents one combination of drugs



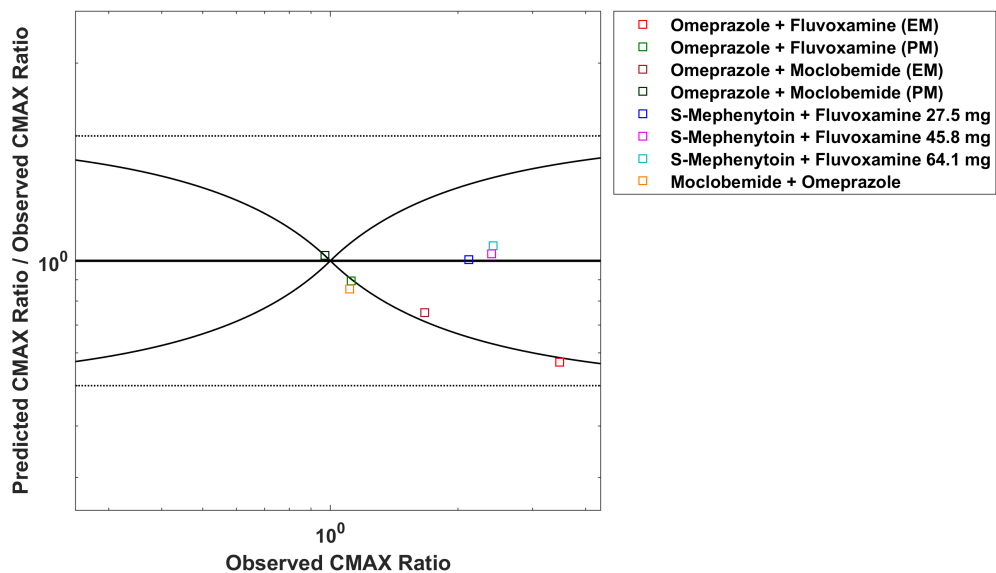
CYP2C19 DDI



CYP2C19 DDI



CYP2C19 DDI



CYP2C19 DDI

GMFE (AUC) = 1.252723

GMFE (CMAX) = 1.173696

	AUC	Number	Ratio [%]
Points total		8	-
Points within Guest et al.		5	62.5
Points within 2-fold		7	87.5

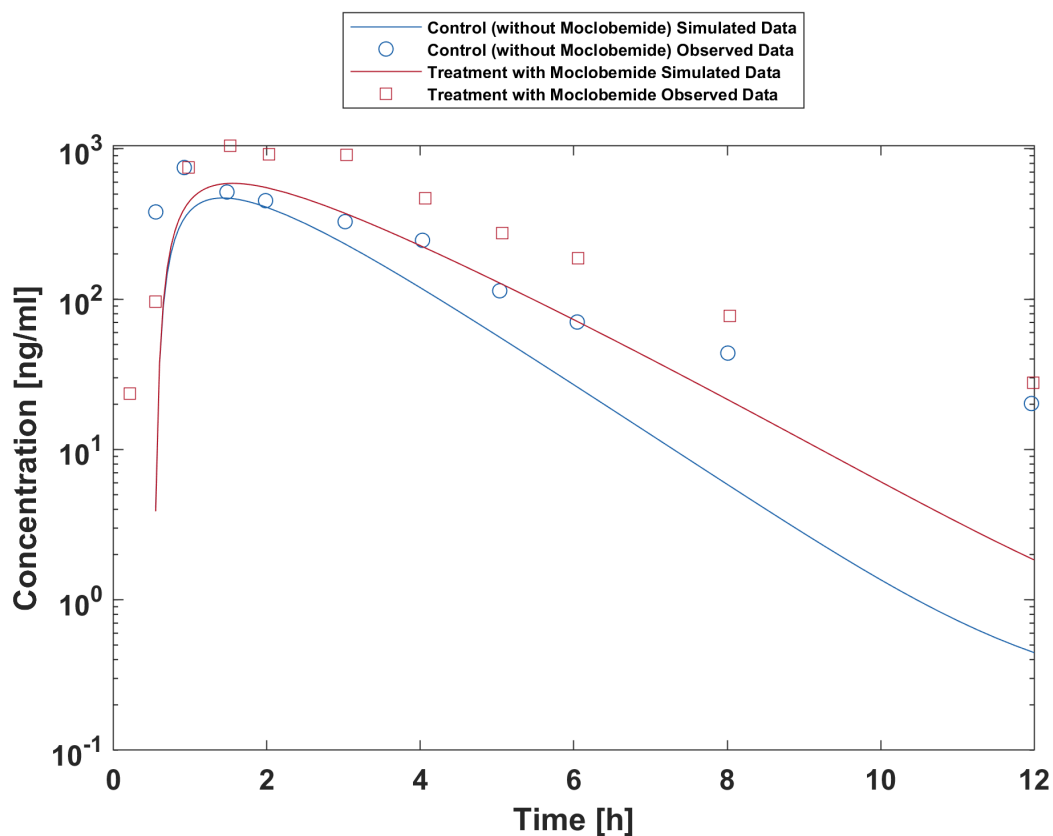
	CMAX	Number	Ratio [%]
Points total		8	-
Points within Guest et al.		4	50
Points within 2-fold		8	100

DatalD	Perpetrator	Victim	Predicted AUC Ratio	Observed AUC Ratio	Pred/Obs AUC Ratio	Predicted CMAX Ratio	Observed CMAX Ratio	Pred/Obs CMAX Ratio	Reference
10	Fluvoxamine, 50 mg, PO, NaN	Omeprazole, PO	2.5885	5.34	0.48474	1.9814	3.48	0.56937	Yasui-Furukori 2004
11	Fluvoxamine, 50 mg, PO, NaN	Omeprazole, PO	0.99972	1.21	0.82621	1.0009	1.12	0.89367	Yasui-Furukori 2004
20	Moclobemide, 300 mg, PO, NaN	Omeprazole, PO	1.5319	2.05	0.74725	1.252	1.67	0.74972	Cho 2002
21	Moclobemide, 300 mg, PO, NaN	Omeprazole, PO	1	1.16	0.86207	1.0003	0.97	1.0312	Cho 2002
30	Fluvoxamine, 27.5 mg, PO, NaN	S-Mephenytoine, PO	3.8495	4.64	0.82964	2.1351	2.12	1.0071	Yao 2003
31	Fluvoxamine, 45.8 mg, PO, NaN	S-Mephenytoine, PO	6.336	6.7	0.94567	2.492	2.4	1.0383	Yao 2003
32	Fluvoxamine, 64.1 mg, PO, NaN	S-Mephenytoine, PO	8.0763	9.89	0.81661	2.633	2.42	1.088	Yao 2003
40	Omeprazole, 40 mg, PO, NaN	Moclobemide, PO	1.3133	1.31	1.0025	0.94797	1.11	0.85403	Yu 2001

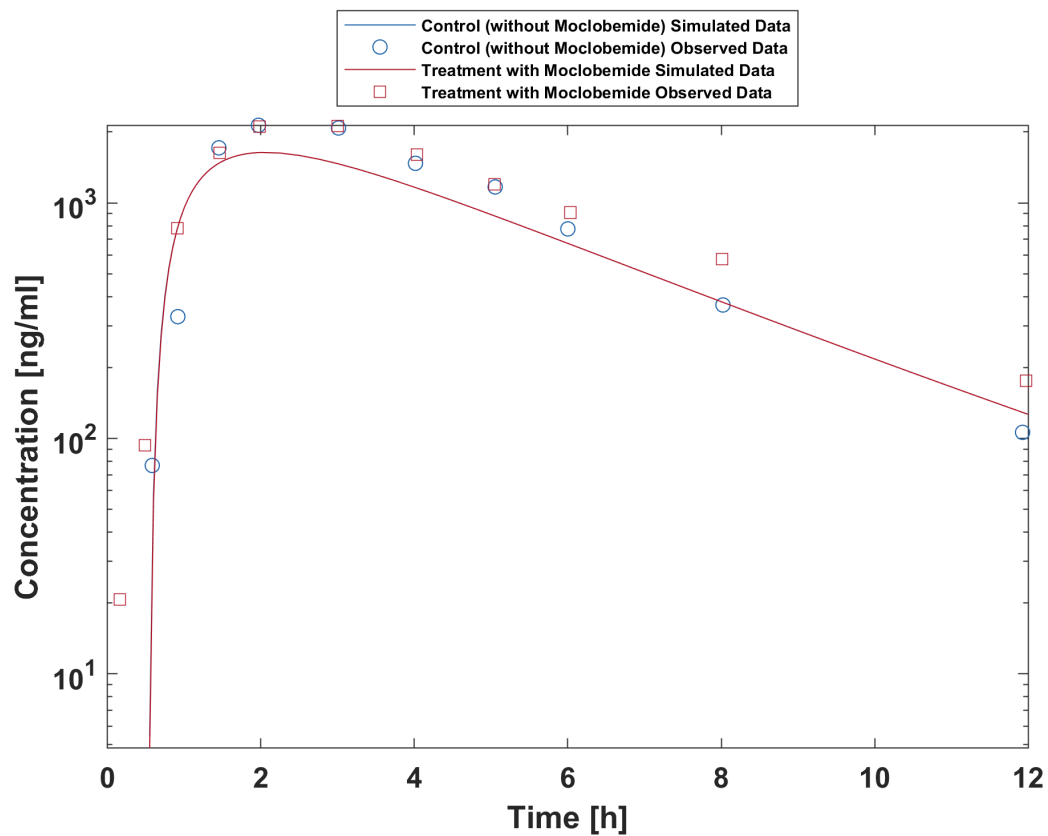
3 Concentration-Time Profiles

The following section shows concentration time profiles of the victim drugs of the simulated DDI studies in comparison to observed data.

3.1 Omeprazole - Moclobemide DDI

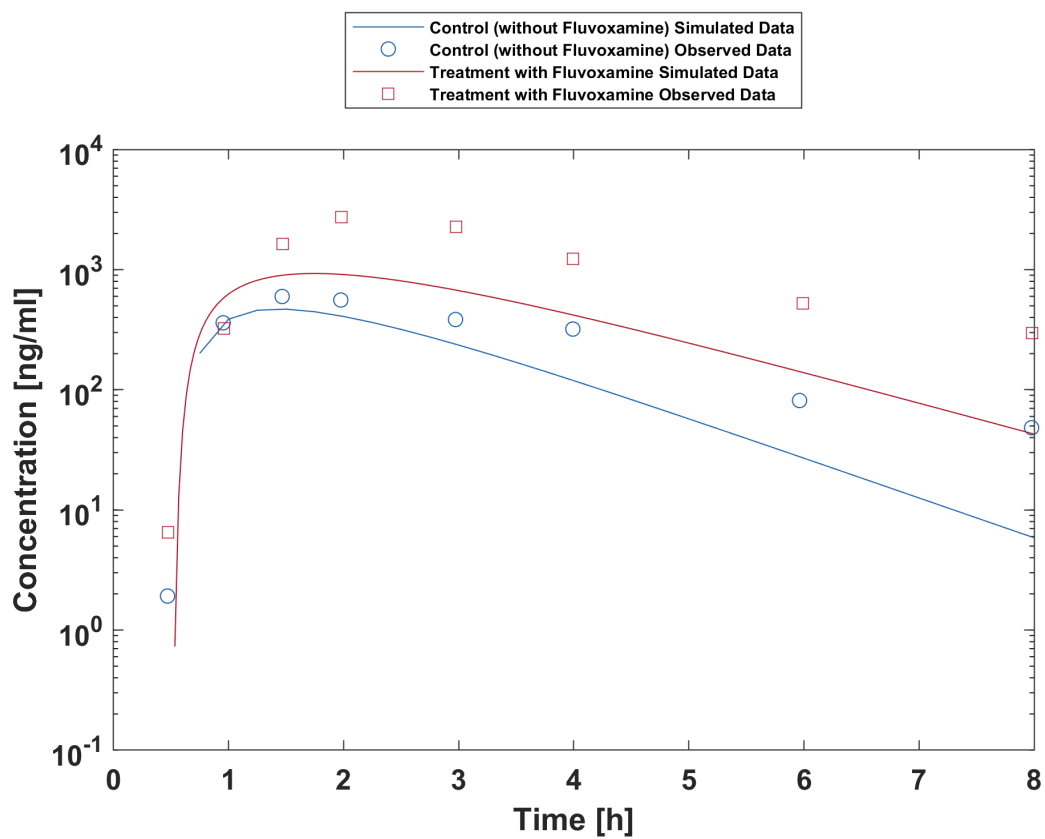


Cho 2002 (Omeprazole 40 mg po) Asian EM

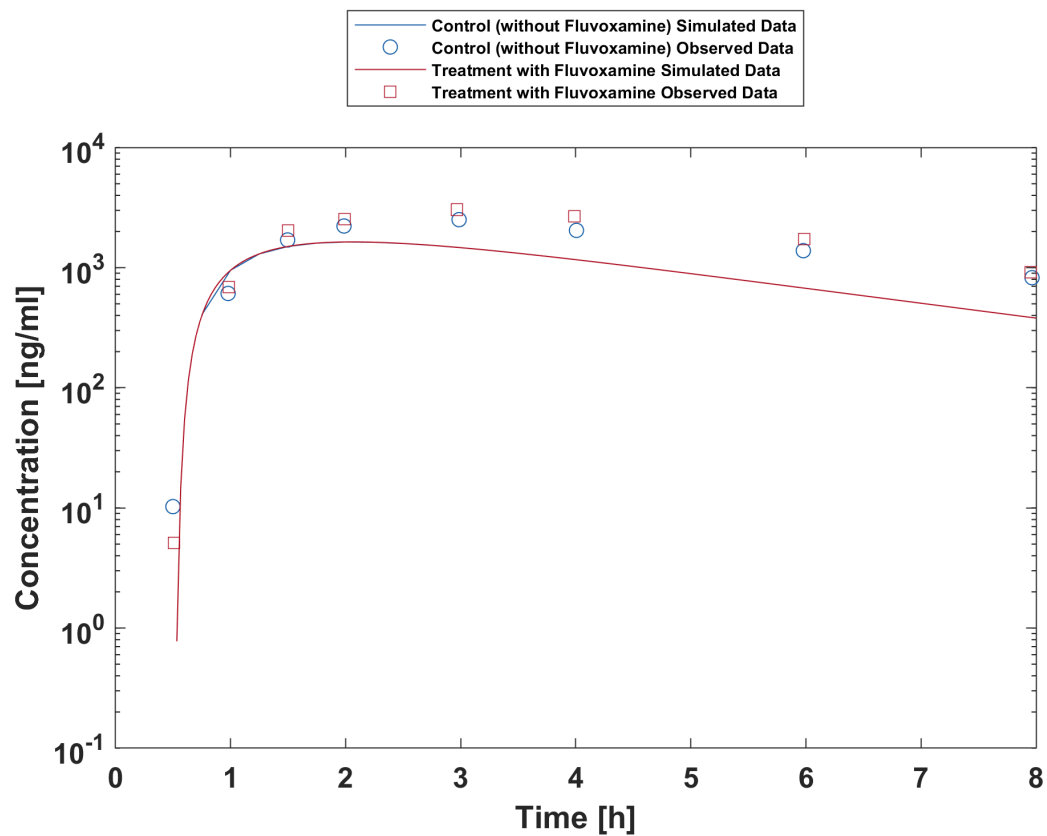


Cho 2002 (Omeprazole 40 mg po) Asian PM

3.2 Omeprazole - Fluvoxamine DDI



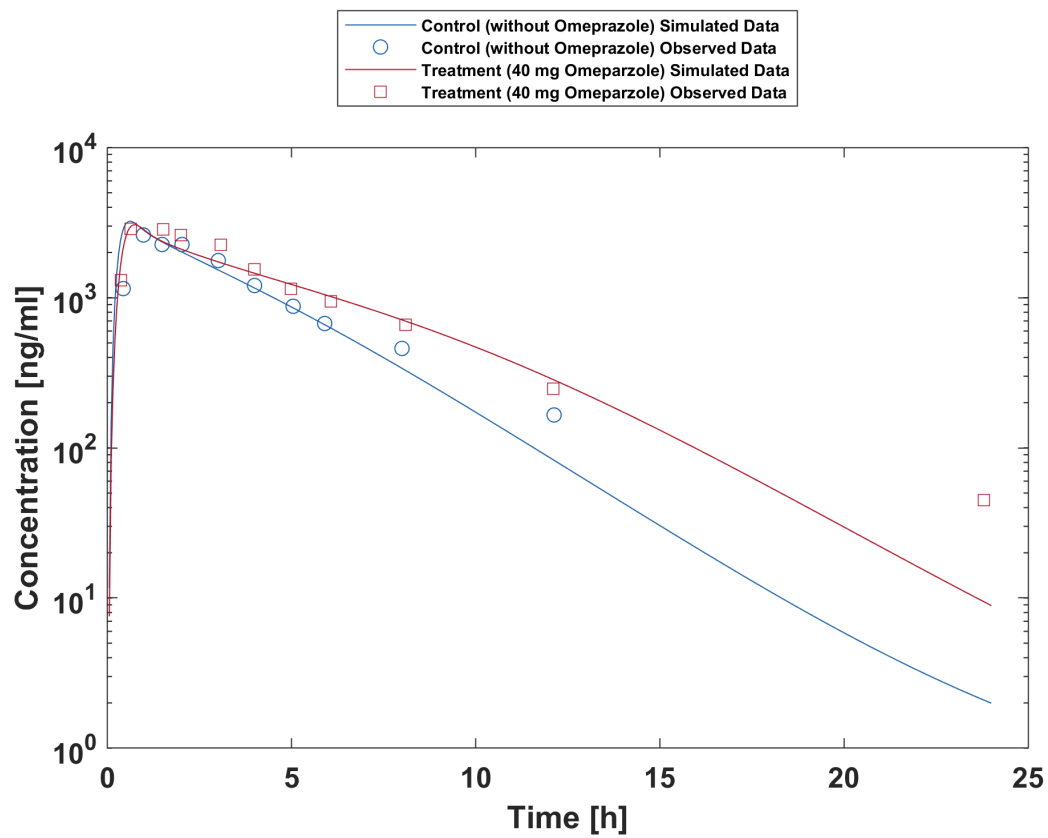
Yasui-Furukori 2004 (Omeprazole 40 mg po) Asian EM



Yasui-Furukori 2004 (Omeprazole 40 mg po) Asian PM

3.3 S-Mephenytoin - Fluvoxamine DDI

3.4 Moclobemide - Omeprazole DD



Yu 2001 (Moclobemide 300 mg po)

4 Conclusion

The predicted perpetrator/victim drug concentration-time profiles, DDI AUC and C_{max} ratios confirmed that the developed PBPK models are well suited to characterize the CYP2C19 DDI network over the full range of reported DDI studies. Identical K_i values could be used for the moderate CYP2C19 inhibitors and substrates moclobemide (204 μM) and omeprazole (R: 5.3 μM / S: 3.1 μM) in their dynamic DDI interactions. For the strong inhibition of CYP2C19 by fluvoxamine, substrate dependent K_i values were used: 3100 nM and 2.6 nM for Omeprazole and S-mephenytoin, respectively.

Fluvoxamine

- CYP2C19 inhibition:
 - DDI simulations with omeprazole as substrate demonstrate an excellent prediction (ratio pred/obs = around 1) of the inhibitory potential of fluvoxamine on CYP2C19 for both EM and PM for CYP2C19.
 - DDI simulations with s-mephenytoin as substrate demonstrate an excellent prediction (ratio pred/obs = around 1 and within 2-fold) of the inhibitory potential of fluvoxamine on CYP2C19. However, DDI predictions tend to get slightly overpredicted for higher fluvoxamine doses.

Omeprazole

- Perpetrator:
 - DDI simulations with omeprazole as inhibitor of CYP2C19 demonstrated a good prediction of moclobemide levels (within 2-fold).
- Substrate:
 - DDI simulations with fluvoxamine as inhibitor of omeprazole demonstrated an excellent prediction of omeprazole levels on CYP2C19 for both PM and EM (ratio pred/obs = around 1 and within 2-fold). Despite some model underprediction in both treatment and control groups, the predicted AUC and C_{max} ratios well match the observed ones.
 - DDI simulations with moclobemide as inhibitor of omeprazole demonstrated good prediction of omeprazole levels on CYP2C19. The levels for EM were slightly underpredicted (pred/obs C_{max}R = 0.77). Predictions for PM were excellent.

S-Mephenytoin

- Substrate: DDI simulations with S-mephenytoin as a substrate demonstrate an excellent prediction (ratio pred/obs = around 1 and within 2-fold) of the inhibitory potential of fluvoxamine on CYP2C19. However, DDI predictions tend to get slightly overpredicted for C_{max} with higher fluvoxamine doses.

Moclobemide

- Perpetrator: DDI simulations with moclobemide as inhibitor of omeprazole demonstrated good prediction of omeprazole levels for different CYP2C19 phenotypes. The levels for EM were slightly underpredicted. Predictions for PM were excellent.
- Substrate: DDI simulations with omeprazole as inhibitor of moclobemide demonstrated a good prediction of moclobemide levels.

5 References

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6 Appendix

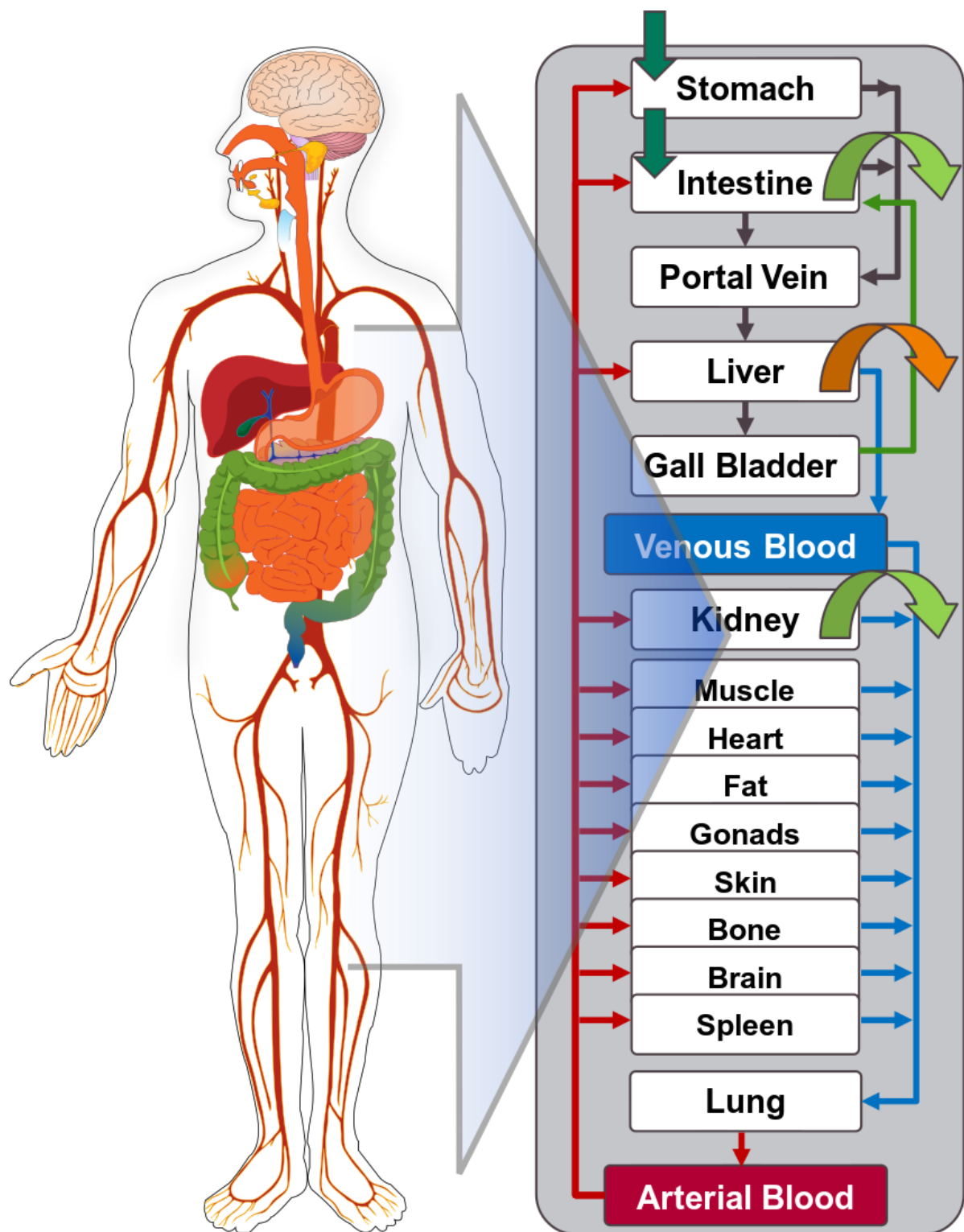
6.1 Open Systems Pharmacology Suite (OSPS) Introduction

Open Systems Pharmacology Suite (OSP suite) is a tool for PBPK modeling and simulation of drugs in laboratory animals and humans. PK-Sim® and MoBi® are part of the OSP suite [1]. PK-Sim® is based on a generic PBPK-model with 18 organs and tissues. One of the main assumptions is that all compartments are well-stirred. Represented organs/tissues include arterial and venous blood, adipose tissue (separable adipose, excluding yellow marrow), brain, lung, bone (including yellow marrow), gonads, heart, kidneys, large intestine, liver, muscle, portal vein, pancreas, skin, small intestine, spleen and stomach, as shown in **Figure 1**.

Each organ consists of four sub-compartments namely the plasma, blood cells (which together build the vascular space), interstitial space, and cellular space. Distribution between the plasma and blood cells as well as between the interstitial and cellular compartments can be permeability-limited. In the brain, the permeation barrier is located between the vascular and the interstitial space. PK-Sim® estimates model parameters (intestinal permeability [2] organ partition coefficients (tissue-to-plasma partition coefficients) [3,4], and permeabilities) from physico-chemical properties of compounds (molecular weight, pKa, acid/base properties) and the composition of each tissue compartment (lipids, water and proteins). Partition coefficients can be calculated using a variety of methods available in PK-Sim®, for example the internal PK-Sim® method [3,4] or that of Rodgers and Rowland [5-7].

Physiological databases included in the software incorporate the dependencies of organ composition, organ weights, organ blood flows and gastrointestinal parameters (gastrointestinal length, radius of each section, intestinal surface area, gastrointestinal transit times, and pH in different intestinal segments [2]), with the user-defined body weight and height and ethnicity of the individual [8]. Thereby, PK Sim® allows generating realistic virtual populations. For a detailed description of the PBPK model structure implemented in PK Sim®, see Willmann et al. [2,4,8,9] or the OSP Suite homepage (<https://docs.open-systems-pharmacology.org/mechanistic-modeling-of-pharmacokinetics-and-dynamics/modeling-concepts>).

Figure 1: Structure of the Whole Body PBPK Model integrated in PK-Sim®



References for OSPS introduction

[1] www.open-systems-pharmacology.org

[2] Willmann S, Schmitt W, Keldenich J, Lippert J, Dressman JB. A physiological model for the estimation of the fraction dose absorbed in humans. *J Med Chem*. 2004 Jul 29;47(16):4022-31.

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6.2 Mathematical Implementation of Drug-Drug Interactions

DDI modeling: Competitive inhibition

A detailed representation of the mathematical implementation of competitive enzyme inhibition can be found in the OSP manual [here](#).

DDI modeling: Mechanism-based inhibition

A detailed representation of the mathematical implementation of mechanism-based enzyme inhibition can be found in the OSP manual [here](#).

DDI modeling: Induction

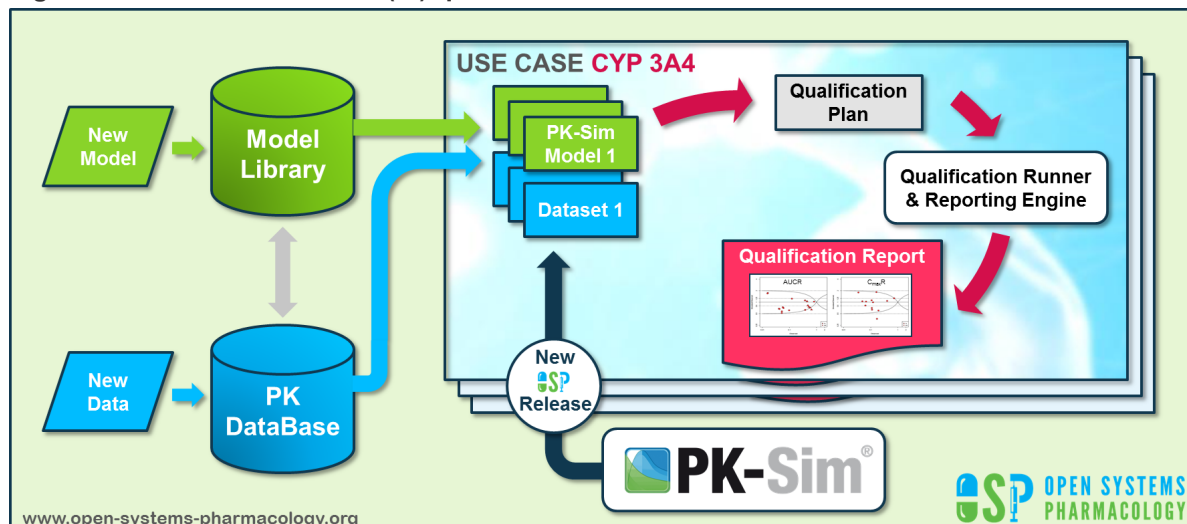
A detailed representation of the mathematical implementation of enzyme induction can be found in the OSP manual [here](#).

6.3 Automatic (re)-qualification workflow

[Open Systems Pharmacology](#) provides a dynamic landscape of model repositories and a database of observed clinical data. Additionally, a technical framework to assess confidence of a specific intended use has been developed (qualification runner and reporting engine). This framework allows for an automatic (re)-qualification workflow of the OSP suite, comprising the following steps (**Figure 1**):

- PBPK model development and verification with observed data,
- Qualification plan generation,
- Qualification plan execution,
- Qualification report generation.

Figure 1: OSP suite automatic (re)-qualification workflow

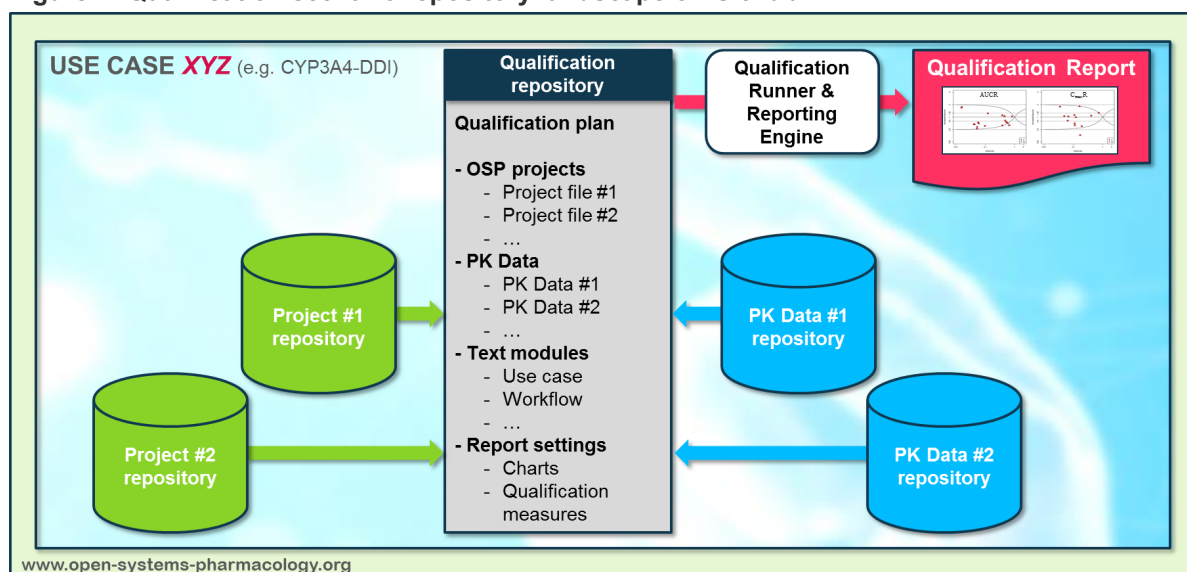


In a first step, the respective qualification scenario is saved in a special qualification repository on [GitHub](https://github.com). This qualification scenario repository contains a detailed qualification plan that links and combines respective models and data to address the use case that shall be qualified. Therefore, the qualification plan consists of:

- PK-Sim project files,
- Additional model building steps (if applicable),
- Description of potential cross-dependencies between PK-Sim project files (if applicable),
- Observed data (needed for model development and verification),
- Qualification scenario description text modules
- Detailed report settings to describe the generation of charts and qualification measures.

PK-Sim projects, observed data sets, and qualification scenario text modules are deposited in distinct repositories and are referenced by the qualification plan (**Figure 2**).

Figure 2: Qualification scenario repository landscape on GitHub



In a second step the [qualification runner](#) processes the qualification plan, i.e. all project parts are exported and prepared for the [reporting engine](#). The reporting engine provides a validated environment (currently implemented in MATLAB®, a transfer to R is in development) for model execution and finally generates the qualification report. This report contains the evaluation of the individual PBPK models with observed data (i.e. standard goodness of fit plots, visual predictive checks) and a comprehensive qualification of the specific use case assessing the predictive performance of the OSP suite by means of a predefined set of qualification measures and charts.

The automated execution of the described workflow can be triggered to assess re-qualification in case new data, changes in model structure or parameterization, or new OSP suite releases arise.

7 Glossary

ADME	Absorption, Distribution, Metabolism, Excretion
AUC	Area under the plasma concentration versus time curve
AUCinf	AUC until infinity
AUClast	AUC until last measurable sample
AUCR	Area under the plasma concentration versus time curve Ratio
b.i.d.	Twice daily (bis in diem)
CL	Clearance
Clint	Intrinsic liver clearance
Cmax	Maximum concentration
CmaxR	Maximum concentration Ratio
CYP	Cytochrome P450 oxidase
CYP1A2	Cytochrome P450 1A2 oxidase
CYP2C19	Cytochrome P450 2C19 oxidase
CYP3A4	Cytochrome P450 3A4 oxidase
DDI	Drug-drug interaction
e.c.	Enteric coated
EE	Ethinylestradiol
EM	Extensive metabolizers
fm	Fraction metabolized
FMO	Flavin-containing monooxygenase
fu	Fraction unbound
FDA	Food and Drug administration
GFR	Glomerular filtration rate
HLM	Human liver microsomes
hm	homozygous
ht	heterozygous
IM	Intermediate metabolizers
i.v.	Intravenous
IVIVE	In Vitro to In Vivo Extrapolation
Ka	Absorption rate constant
kcat	Catalyst rate constant
Ki	Inhibitor constant
Kinact	Rate of enzyme inactivation
Km	Michaelis Menten constant
m.d.	Multiple dose
OSP	Open Systems Pharmacology

ADME	Absorption, Distribution, Metabolism, Excretion
PBPK	Physiologically-based pharmacokinetics
PK	Pharmacokinetics
PI	Parameter identification
PM	Poor metabolizers
RT-PCR	Reverse transcription polymerase chain reaction
p.o.	Per os
q.d.	Once daily (quaque diem)
SD	Single Dose
SE	Standard error
s.d.SPC	Single doseSummary of Product Characteristics
SD	Standard deviation
TDI	Time dependent inhibition
t.i.d	Three times a day (ter in die)
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UM	Ultra-rapid metabolizers