Building and evaluation of a PBPK model for Sildenafil in healthy adults

Version	1.1-OSP11.3
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Sildenafil-Model/releases/tag/v1.1
OSP Version	11.3
Qualification Framework Version	2.3

This evaluation report and the corresponding PK-Sim project file are filed at:

https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/

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1 Introduction

Sildenafil is a cGMP-specific phosphodiesterase 5 inhibitor, indicated for erectile dysfunction and pulmonary arterial hypertension. It is mostly metabolized by CYP3A4 making it a sensitive probe and victim drug for the investigation of CYP3A4 activity *in vivo*. Other CYPs are involved in sildenafil metabolism: CYP2C9 and CYP2C19. It is a BCS class II compound. Sildenafil shows substantial first pass metabolism resulting in a bioavailability of 40%.

The model has been developed and evaluated by comparing observed data to simulations of a large number of clinical studies covering a dose range of 20 mg to 100 mg after intravenous and oral administrations. Furthermore, it has been evaluated within a CYP3A4 DDI modeling network as a victim drug.

Model features include:

- metabolism by CYP3A4

- metabolism by CYP2C9

- metabolism by CYP2C19

- a decrease in the permeability between the intracellular and interstitial space (model parameters `P (intracellular->interstitial)` and `P (interstitial->intracellular)`) in intestinal mucosa to optimize quantitatively the extent of gut wall metabolism

2 Methods

2.1 Modeling Strategy

The general concept of building a PBPK model has previously been described by Kuepfer et al. (Kuepfer 2016). Relevant information on anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in adults was gathered from the literature and has been previously published (Willmann 2007). The information was incorporated into PK-Sim® and was used as default values for the simulations in adults.

The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available PK-Sim® Ontogeny Database Version 7.3 (PK-Sim Ontogeny Database Version 7.3) or otherwise referenced for the specific process.

First, a mean model was built using clinical data from single dose studies with intravenous and oral administration of sildenafil by Muirhead et al. 2002 (Muirhead 2002a), Nichols et al. 2002 (Nichols 2002), the FDA 2009 (FDA 2009), and Walker et al. 1999 (Walker 1999). The mean PBPK model was developed using a typical male European individual. The relative tissue-specific expressions of enzymes predominantly being involved in the metabolism of sildenafil (CYP3A4) were considered (Meyer 2012).

A specific selected set of parameters (see below) was optimized using the Parameter Identification module provided in PK-Sim®. Structural model selection was mainly guided by visual inspection of the resulting description of data and biological plausibility.

Once the appropriate structural model was identified, a Weibull function was fitted using R 4.2.1 based on in vitro data (Sawatdee 2019), and the resulting dissolution kinetic parameters were implemented in the model.

The model was then evaluated by simulating further clinical studies reporting pharmacokinetic concentration-time profiles of sildenafil.

Details about input data (physicochemical, *in vitro* and clinical) can be found in Section 2.2.

Details about the structural model and its parameters can be found in Section 2.3.

2.2 Data

2.2.1 In vitro and physicochemical data

A literature search was performed to collect available information on physicochemical properties of sildenafil. The obtained information from literature is summarized in the table below, and is used for model building.

Parameter	Unit	Value	Source	Description
MW	g/mol	474.576	DrugBank DB00203	Molecular weight
pK$_{a1}$		5.97	Salerno 2021	Acid dissociation constant of conjugate acid; compound type: basic
pK$_{a1}$		6.78	Gobry 2000	Acid dissociation constant of conjugate acid; compound type: ampholyte
pK$_{a2}$		9.12	Gobry 2000	Acid dissociation constant of conjugate acid; compound type: ampholyte
Solubility (pH)	mg/mL	0.025 (7.1)	Takano 2016	Aqueous Solubility
		3.5	Salerno 2021	Aqueous Solubility
		3.5	DrugBank DB00203	Aqueous Solubility
		4.1	Jung 2011	Aqueous Solubility
		3.965 (3)	Wang 2008	Aqueous Solubility
		7.077 (4)	Wang 2008	Aqueous Solubility
		2.068 (5)	Wang 2008	Aqueous Solubility
		0.114 (6)	Wang 2008	Aqueous Solubility
		0.025 (7)	Wang 2008	Aqueous Solubility
		0.027 (8)	Wang 2008	Aqueous Solubility
		0.04 (9)	Wang 2008	Aqueous Solubility
		0.103 (10)	Wang 2008	Aqueous Solubility
		0.322 (11)	Wang 2008	Aqueous Solubility
logP		3.18	Gobry 2000	Partition coefficient between octanol and water
		2.70	Takano 2016	Partition coefficient between octanol and water
		2.70	Walker 1999	Partition coefficient between octanol and water
		2.24	Wang 2008	Partition coefficient between octanol and water
		1.59	Wang 2008	Partition coefficient between octanol and water
		1.8	DrugBank DB00203	Partition coefficient between octanol and water

Parameter	Unit	Value	Source	Description
		1.87	DrugBank DB00203	Partition coefficient between octanol and water
fu	%	4	Walker 1999	Fraction unbound in plasma (α1-acid glycoprotein)
	%	4.3	Muirhead 2002b	Fraction unbound in plasma (α1-acid glycoprotein)
	%	2.7	Muirhead 2002b	Fraction unbound in plasma (α1-acid glycoprotein)
	%	3.46	Muirhead 2002b	Fraction unbound in plasma (α1-acid glycoprotein)
V_{max}, K_m CYP3A4	pmol/min/pmol P450, µmol/L	78.6 4.34	Takano 2016	Recombinant CYP3A4 Michaelis-Menten kinetics
V_{max}, K_m CYP3A4	relative units, µmol/L	1.9 23.10	Warrington 2000	Recombinant CYP3A4 Michaelis-Menten kinetics
V_{max}, K_m CYP2C9	relative units, µmol/L	0.2 9.60	Warrington 2000	Recombinant CYP3A4 Michaelis-Menten kinetics
V_{max}, K_m CYP2C19	relative units, µmol/L	0.02 23.10	Warrington 2000	Recombinant CYP3A4 Michaelis-Menten kinetics

2.2.2 Clinical data

A literature search was performed to collect available clinical data on sildenafil in adults.

The following publications were found in adults for model building:

Publication	Arm / Treatment / Information used for model building
Muirhead 2002a	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 25 mg intravenous infusion
Nichols 2002	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil: - 50 mg intravenous infusion - 100mg oral tablet
FDA 2009	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil: - 20 mg intravenous infusion - 40 mg intravenous infusion - 80 mg intravenous infusion
Walker 1999	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 50 mg oral solution
Spence 2008	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 20 mg tablet
Lee 2021	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil: - 25 mg tablet (in the absence of itraconazole) - 25 mg tablet (in the absence of clarithromycin)
Abdelkawy 2016	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 50 mg tablet
Gillen 2017	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 50 mg tablet (Panel 1)
Jetter 2002	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 50 mg tablet
Murtadha 2021	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 50 mg tablet (non-smoker group)
Wilner 2002	Plasma PK profiles in healthy subjects with single dose administrations of a sildenafil 50 mg tablet (study I)

The following dosing scenarios were simulated and compared to respective data for model verification:

Scenario	Data reference
po SD 50mg	Al-Ghazawi 2010
	Hedaya 2006
	Wilner 2002
	Gillen 2017
po SD 100mg	Muirhead 2000
po MD 20/80 mg	Burgess 2008
po MD 20 mg	Gotzkowsky 2013

2.3 Model Parameters and Assumptions

2.3.1 Absorption

The model parameter `Specific intestinal permeability` was optimized to best match clinical data (see Section 2.3.4). A formulation without limitation to absorption was assumed for the oral solution, therefore its solubility was set to 100 mg/L. A default solubility of 3.5 mg/L was taken from the model of Salerno 2021 and used for tablets (see Section 2.2.1)

The dissolution of tablets was implemented via a Weibull dissolution tablet. The Weibull function was fitted using R 4.2.1 based on in vitro data (Sawatdee 2019), and the resulting dissolution kinetic parameters were fixed in the model.

2.3.2 Distribution

Sildenafil is highly bound to α1-acid glycoprotein in plasma (see Section 2.2.1). A value of 4% was used in this PBPK model for `Fraction unbound (plasma, reference value)`.

An important parameter influencing the resulting volume of distribution is lipophilicity. The reported experimental logP values are in the range of 3 (see Section 2.2.1) which served as a starting value. Finally, the model parameters `Lipophilicity` was optimized to match best clinical data (see also Section 2.3.4).

After testing the available organ-plasma partition coefficient and cell permeability calculation methods built in PK-Sim, observed clinical data was best described by choosing the partition coefficient calculation by `Rodgers and Rowland` and cellular permeability calculation by `PK-Sim Standard`.

2.3.3 Metabolism and Elimination

Three metabolic pathways were implement into the model via Michaelis-Menten kinetics

- CYP3A4
- CYP3A9
- CYP3A19

Relative kcat were calculated with the following inputs:

Input	Unit	CYP3A4	CYP2C9	CYP2C19	Reference
Contributions in vitro (scaled)*	µL/min/mg microsomal protein	0.79	0.20	0.01	Warrington 2000
CYP amount	pmol CYP/mg microsomal protein	108	96	19	Rodrigues 1999
Michaelis Menten constant (Km)	µmol/L	23.1	9.6	23.1	Warrington 2000
*The contribution in vitro has initially no unit. It was scaled multiplying it by 1 µL/min/mg microsomal protein. This is a joint scaling factor over the three CYPs to keep their relative hepatic contributions fixed. It was later optimized as part of kcat.					

The scaled contributions in vitro were converted to specific clearance per enzyme dividing by the respective CYP amount per milligram microsomal protein. Then these relative specific clearances per enzyme were multiplied by the Km value to obtain kcat values which were then in a next step optimized with a joint factor in the parameter identification to best match clinical data (see Section 2.3.4)

Calculated parameters	Unit	CYP3A4	CYP2C9	CYP2C19
CLspec/Enzyme	L/µmol/min	0.007324074	0.002083333	0.000436842
kcat	1/min	0.17	0.02	0.01

The CYP3A4 expression profiles is based on high-sensitive real-time RT-PCR (Nishimura 2003). Absolute tissue-specific expressions were obtained by considering the respective absolute concentration in the liver. The PK-Sim database provides a default value for CYP3A4 (compare Rodrigues 1999 and assume 40 mg protein per gram liver).

The first model simulations showed that gut wall metabolism was underrepresented in the PBPK model. In order to increase gut wall metabolism, the "mucosa permeability on basolateral side" (jointly the model parameters in the mucosa: `P (interstitial->intracellular)` and `P (intracellular->interstitial)`) was estimated. A decrease in this permeability may lead to higher gut wall concentrations and, in turn, to a higher gut wall elimination. This parameter was preferred over other parameters such as relative CYP3A4 expression or fraction unbound (fu) in the gut wall as it is technically not limited to a maximum value of 100%.

2.3.4 Automated Parameter Identification

This is the result of the final parameter identification for the base model:

Model Parameter	Optimized Value	Unit
`Lipophilicity`	2.84	Log Units
`Fraction unbound`	0.04 (FIXED)	
`Specific intestinal permeability`	1.21E-3	cm/min
Basolateral mucosa permeability (`P (interstitial->intracellular)`, `P (intracellular->interstitial)`)	6.07E-4	cm/min
`kcat` (CYP3A4)	27.21	1/min
`kcat` (CYP2C9)	3.22	1/min
`kcat` (CYP2C19)	1.62	1/min
`Dissolution time`	4.16 (FIXED)	min
`Dissolution shape`	1.37 (FIXED)	

3 Results and Discussion

The PBPK model for sildenafil was developed and verified with clinical pharmacokinetic data.

The model was built and evaluated covering data from studies including in particular

- intravenous (infusions) and oral administrations (solutions and tablets).

- a dose range of 20 to 100 mg.

The model quantifies metabolism via CYP3A4, CYP2C9 and CYP2C19.

The next sections show:

1. the final model input parameters for the building blocks: Section 3.1.

2. the overall goodness of fit: Section 3.2.

3. simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: Section 3.3.

3.1 Final input parameters

The compound parameter values of the final PBPK model are illustrated below.

Formulation: Sildenafil Tablet

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	4.164698 min	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29
Lag time	0 min	
Dissolution shape	1.37405	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29
Use as suspension	Yes	

Compound: Sildenafil

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	3.5 mg/l	Publication-Salerno 2021	Measurement	True
Reference pH	7	Publication-Salerno 2021	Measurement	True
Solubility at reference pH	100 mg/l	Other-Assumption	Oral solution	False
Reference pH	7	Other-Assumption	Oral solution	False

Name	Value	Value Origin	Alternative	Default
Lipophilicity	2.8413676507 Log Units	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29	Measurement	True
Fraction unbound (plasma, reference value)	0.04	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29	Measurement	True
Permeability	0.0758702742 cm/min	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit' on 2022-08-12 15:40	Optimized	False
Specific intestinal permeability (transcellular)	0.0012071993309 cm/min	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29	Optimized	True
Is small molecule	Yes			
Molecular weight	474.58 g/mol	Internet-DrugBank DB00203		
Plasma protein binding partner	α1-acid glycoprotein			

Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard

Processes

Metabolizing Enzyme: CYP2C19-Warrington

Molecule: CYP2C19

Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.01009105 pmol/min/pmol rec. enzyme	Publication-Warrington 2000
Km	23.1 µmol/l	Publication-Warrington 2000
kcat	1.6232116026 1/min	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29

Metabolizing Enzyme: CYP2C9-Warrington

Molecule: CYP2C9

Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.02 pmol/min/pmol rec. enzyme	Publication-Warrington 2000
Km	9.6 µmol/l	Publication-Warrington 2000
kcat	3.2171312254 1/min	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29

Metabolizing Enzyme: CYP3A4-Warrington

Molecule: CYP3A4

Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	0.16918611 pmol/min/pmol rec. enzyme	Publication-Warrington 2000
Km	23.1 µmol/l	Publication-Warrington 2000
kcat	27.2146958692 1/min	Parameter Identification-Parameter Identification-Value updated from 'PI_All_DissoKineticFit_P calculated' on 2023-03-24 17:29

3.2 Diagnostics Plots

Below you find the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data used presented in Section 2.2.2.

The first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.
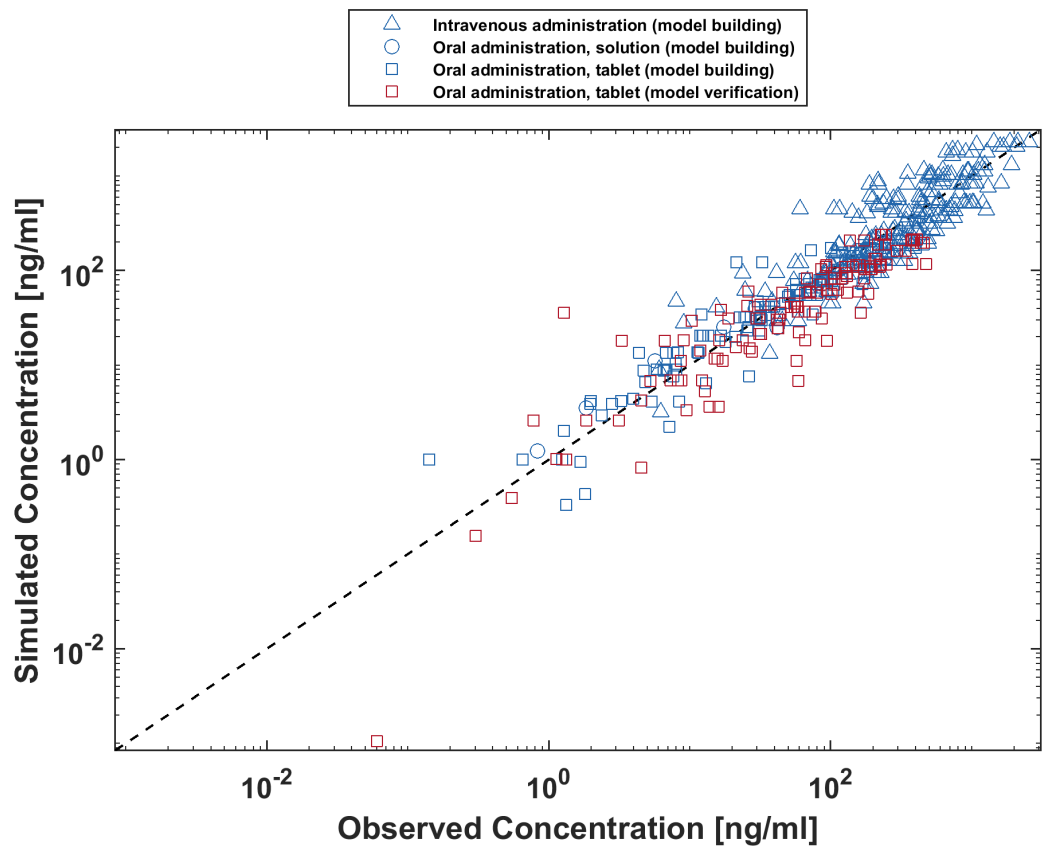
Sildenafil concentration in plasma
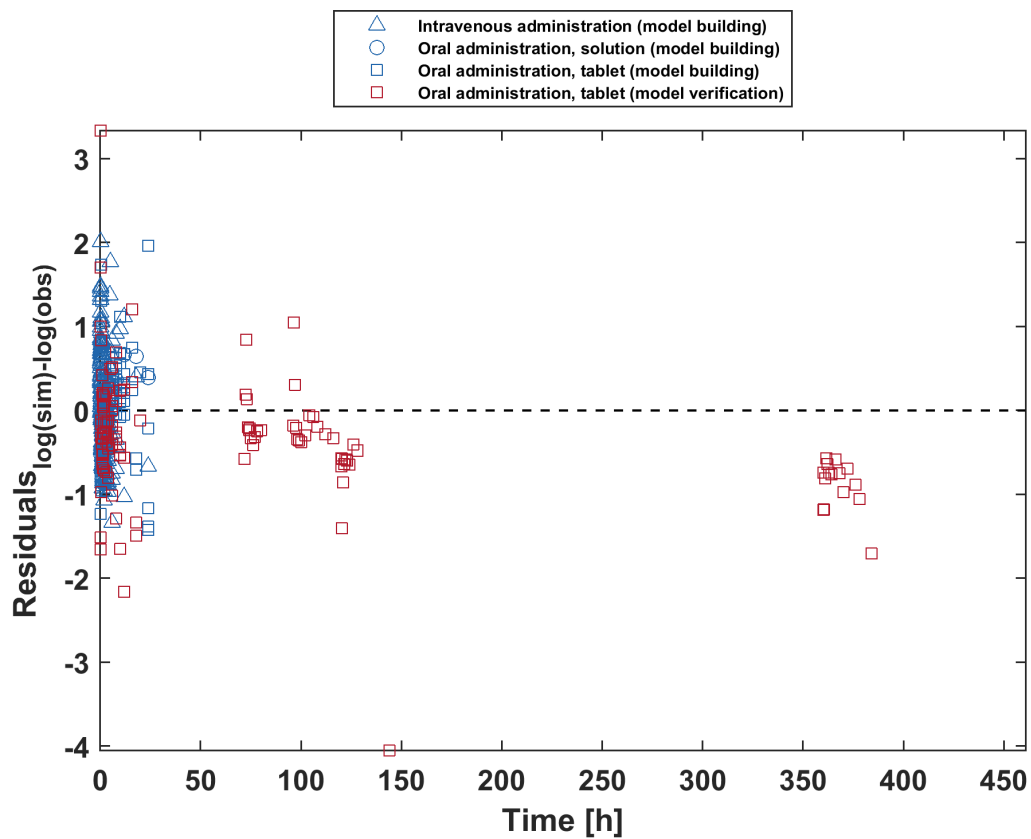
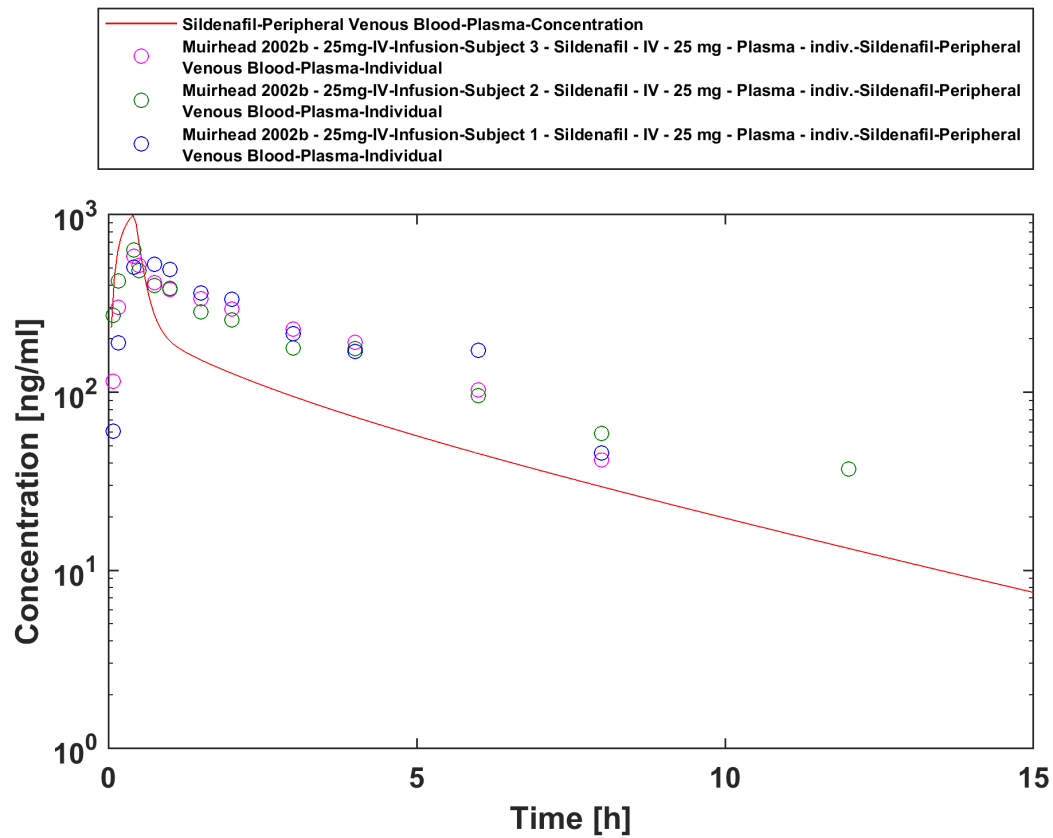Sildenafil concentration in plasma

GMFE = 1.621730

3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.
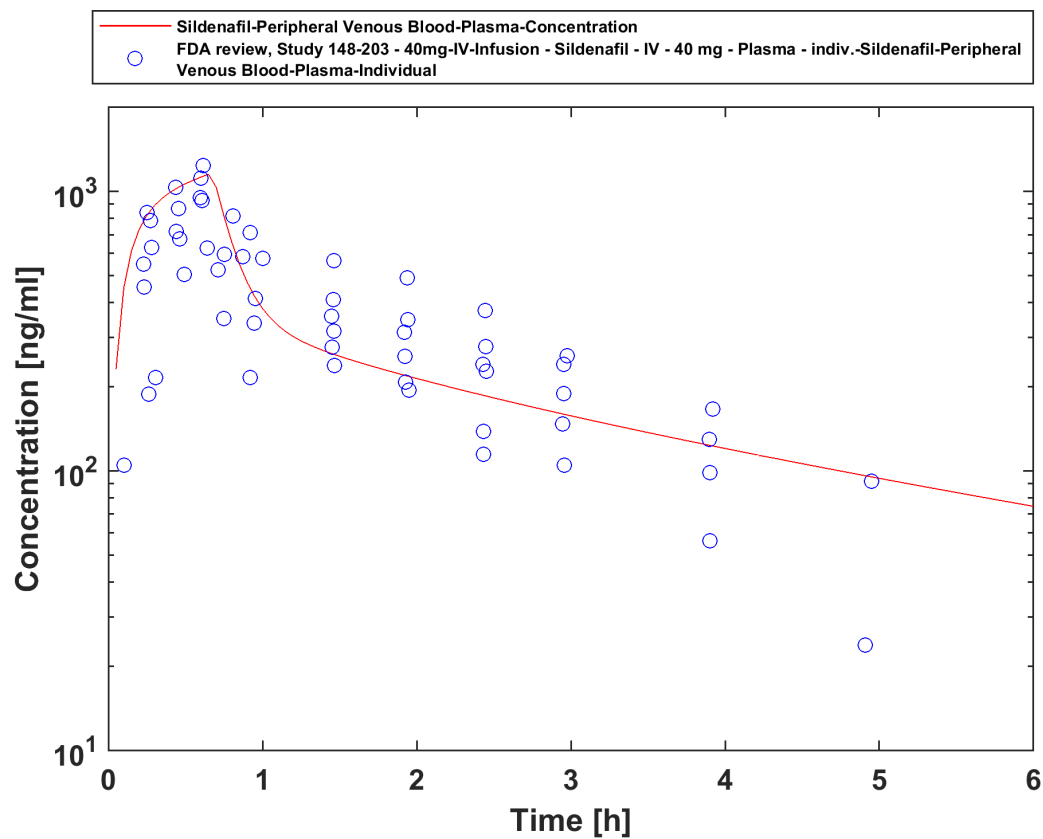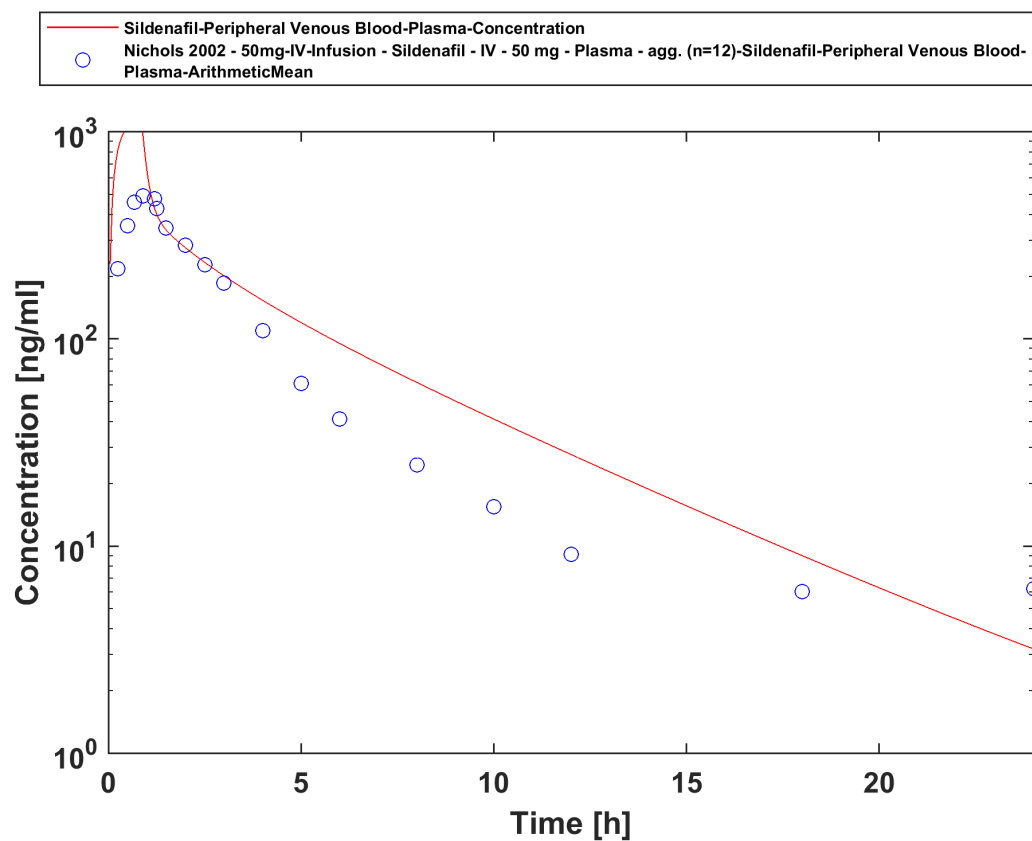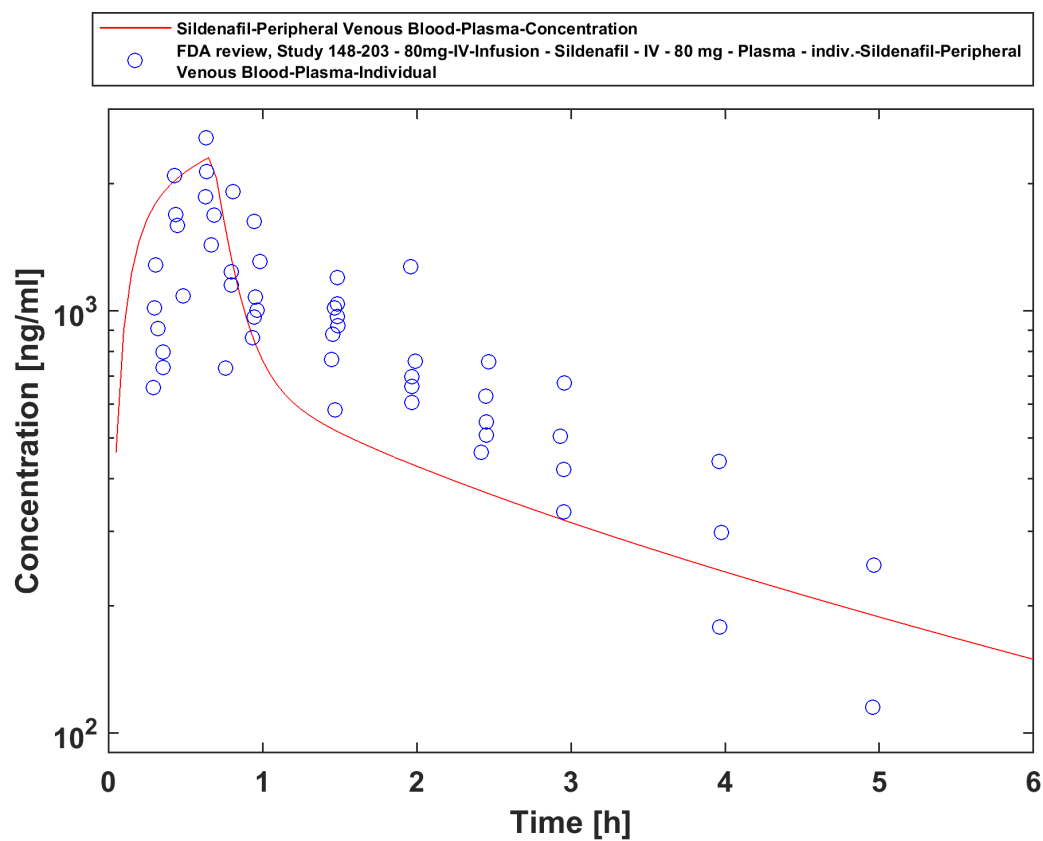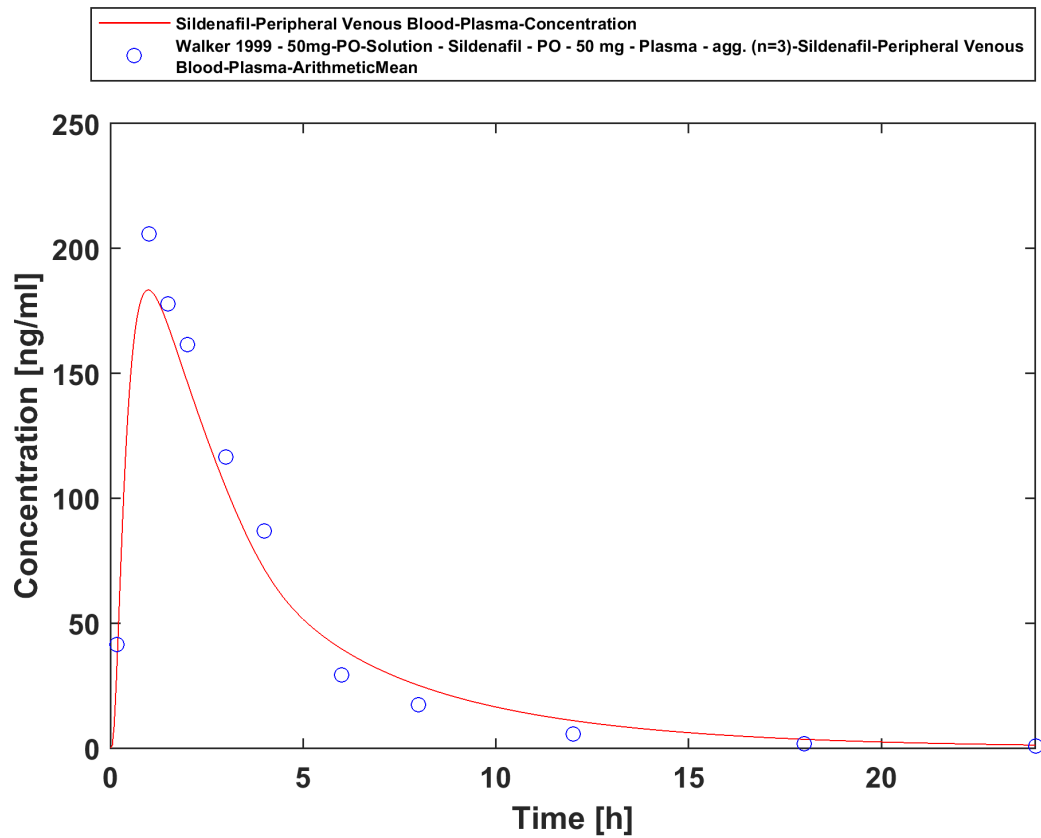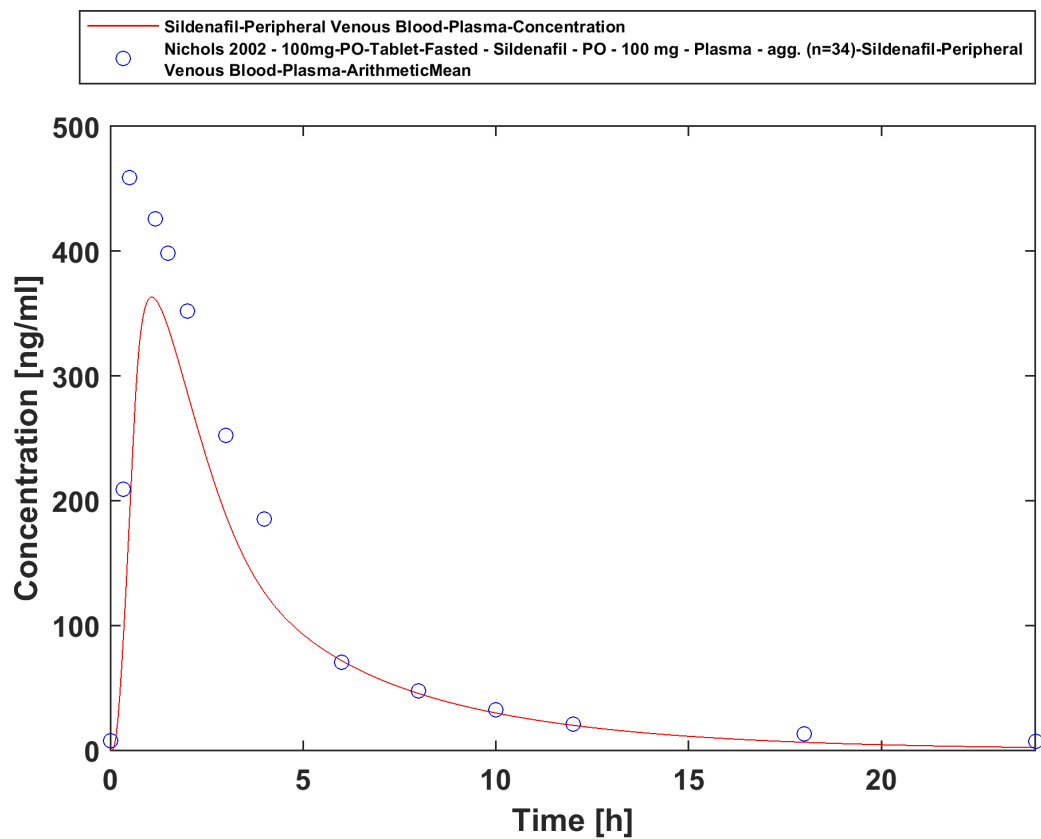
3.3.1 Model Building
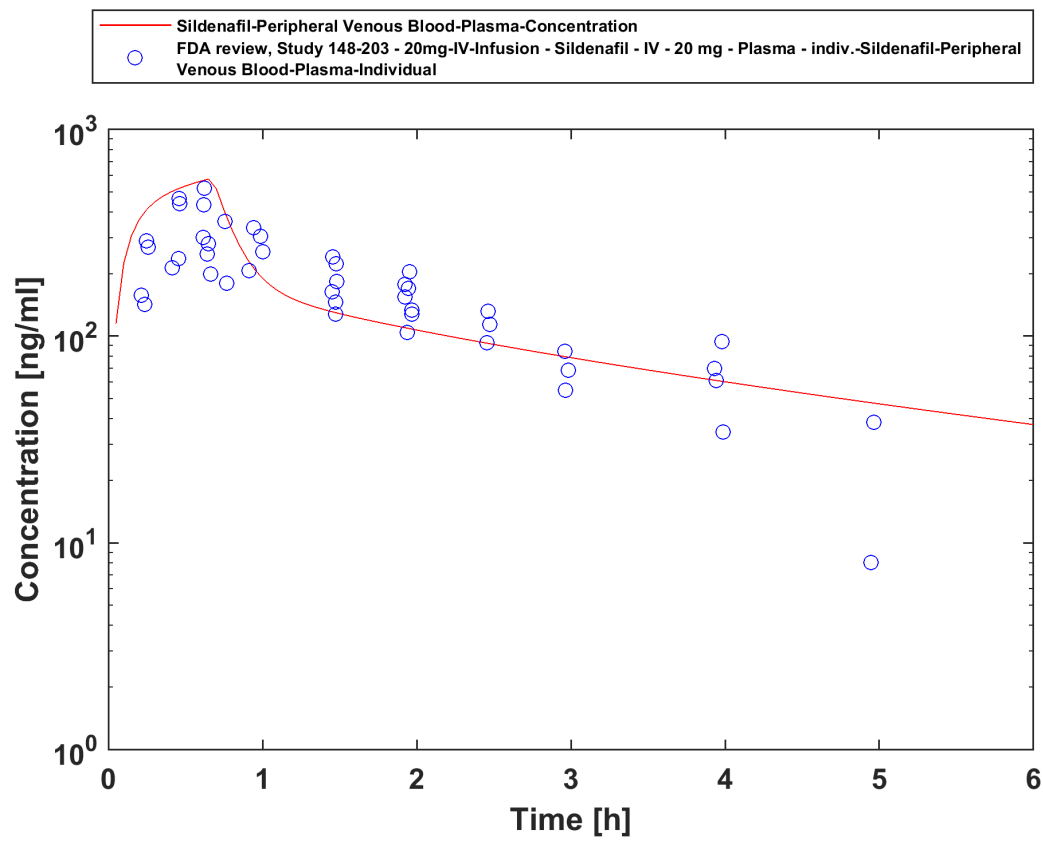
Time Profile Analysis

Time Profile Analysis
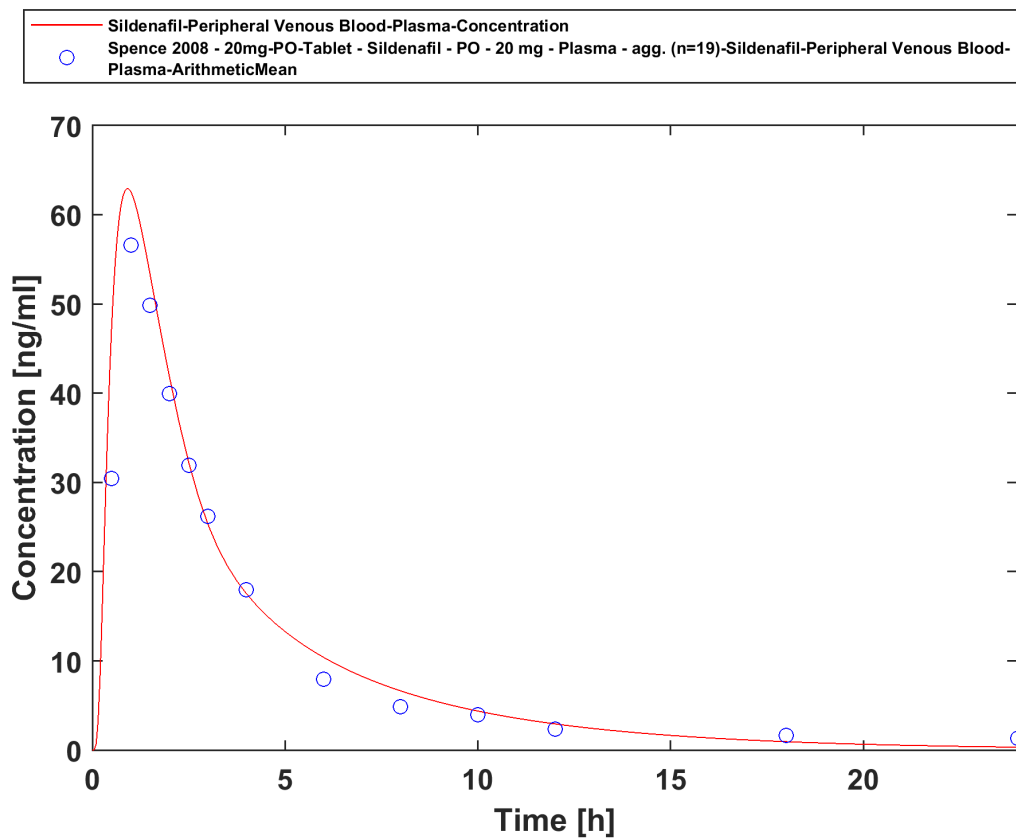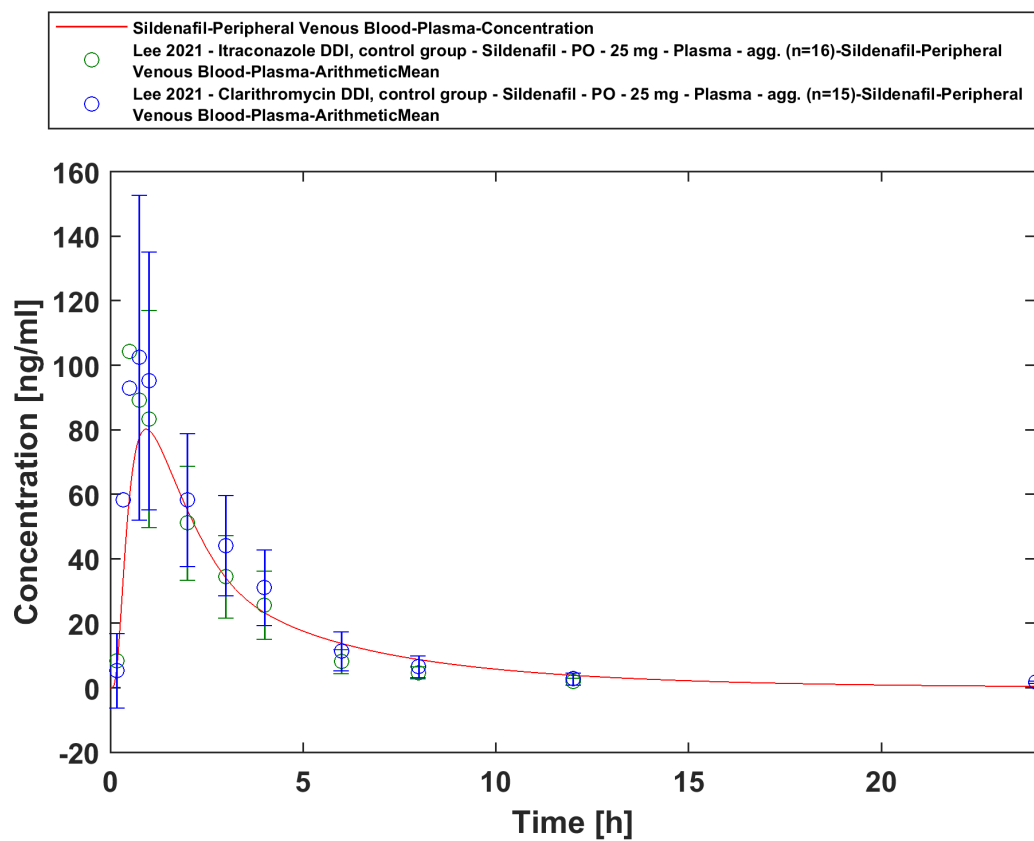

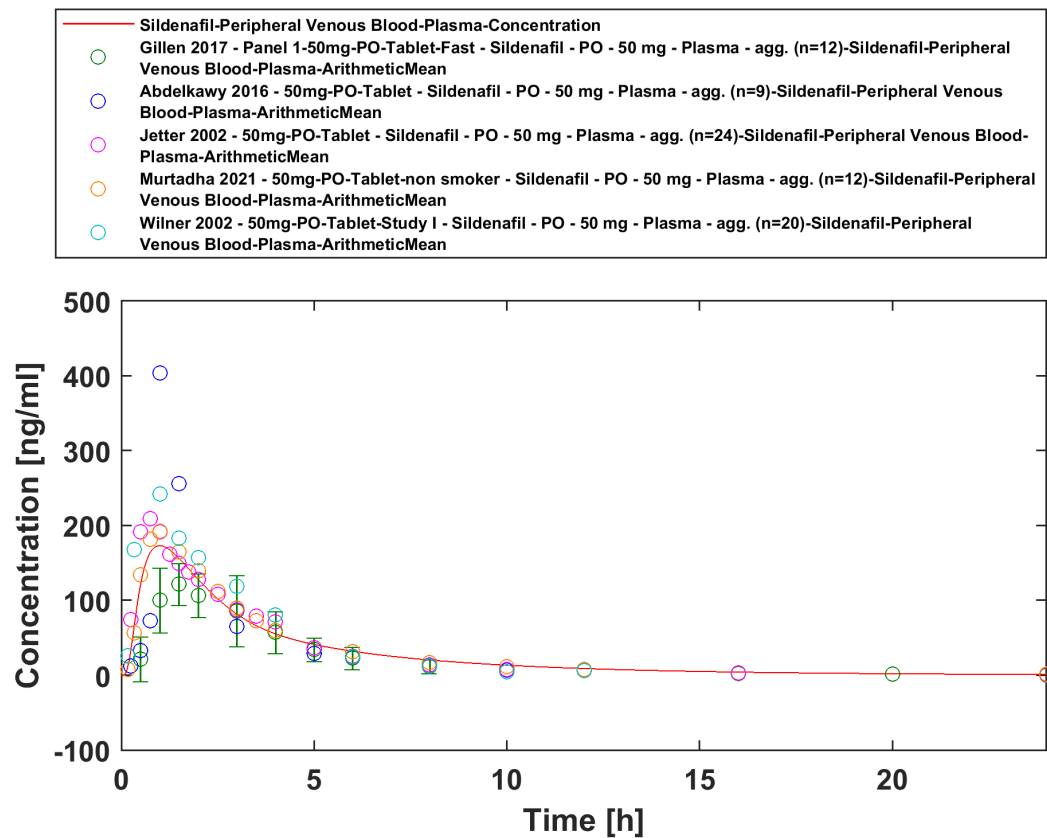Time Profile Analysis

Time Profile Analysis

Time Profile Analysis

Time Profile Analysis

Time Profile Analysis

Sildenafil-Peripheral Venous Blood-Plasma-Concentration

Spence 2008 - 20mg-PO-Tablet - Sildenafil - PO - 20 mg - Plasma - agg. (n=19)-Sildenafil-Peripheral Venous Blood-Plasma-ArithmeticMean

Time Profile Analysis

Sildenafil-Peripheral Venous Blood-Plasma-Concentration

Lee 2021 - Itraconazole DDI, control group - Sildenafil - PO - 25 mg - Plasma - agg. (n=16)-Sildenafil-Peripheral Venous Blood-Plasma-ArithmeticMean

Lee 2021 - Clarithromycin DDI, control group - Sildenafil - PO - 25 mg - Plasma - agg. (n=15)-Sildenafil-Peripheral Venous Blood-Plasma-ArithmeticMean

Time Profile Analysis

Time Profile Analysis

3.3.2 Model Verification

Time Profile Analysis

Time Profile Analysis

Time Profile Analysis

Time Profile Analysis
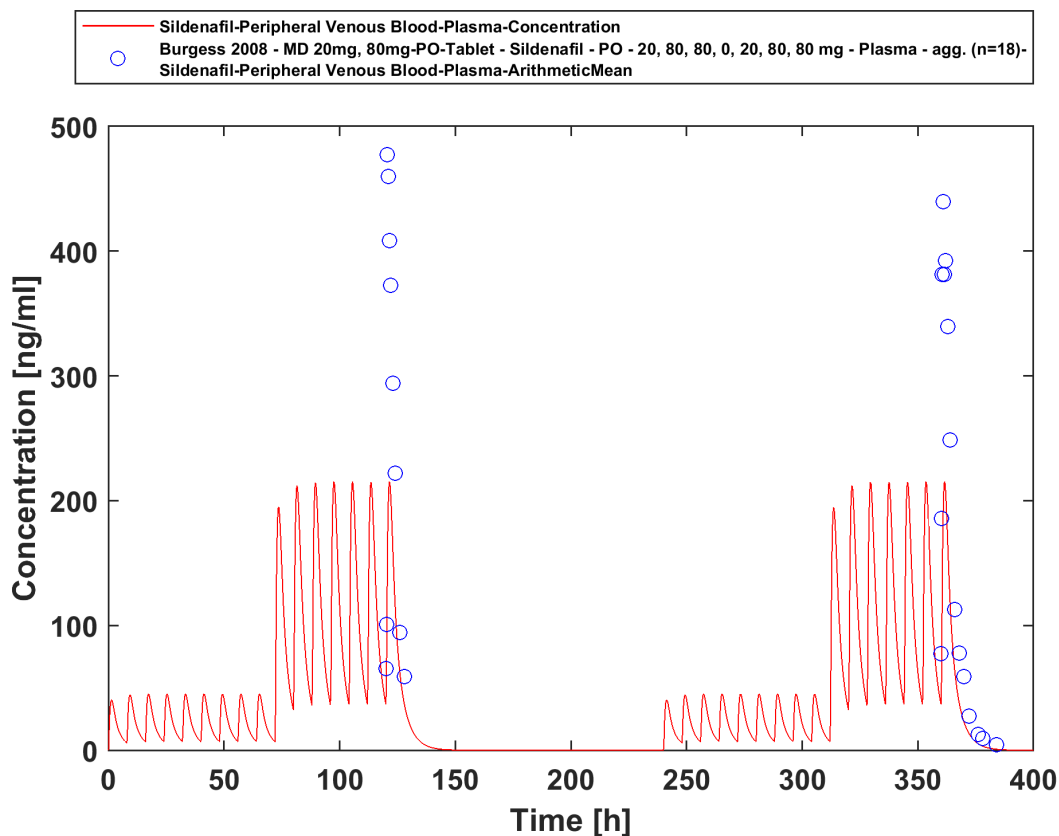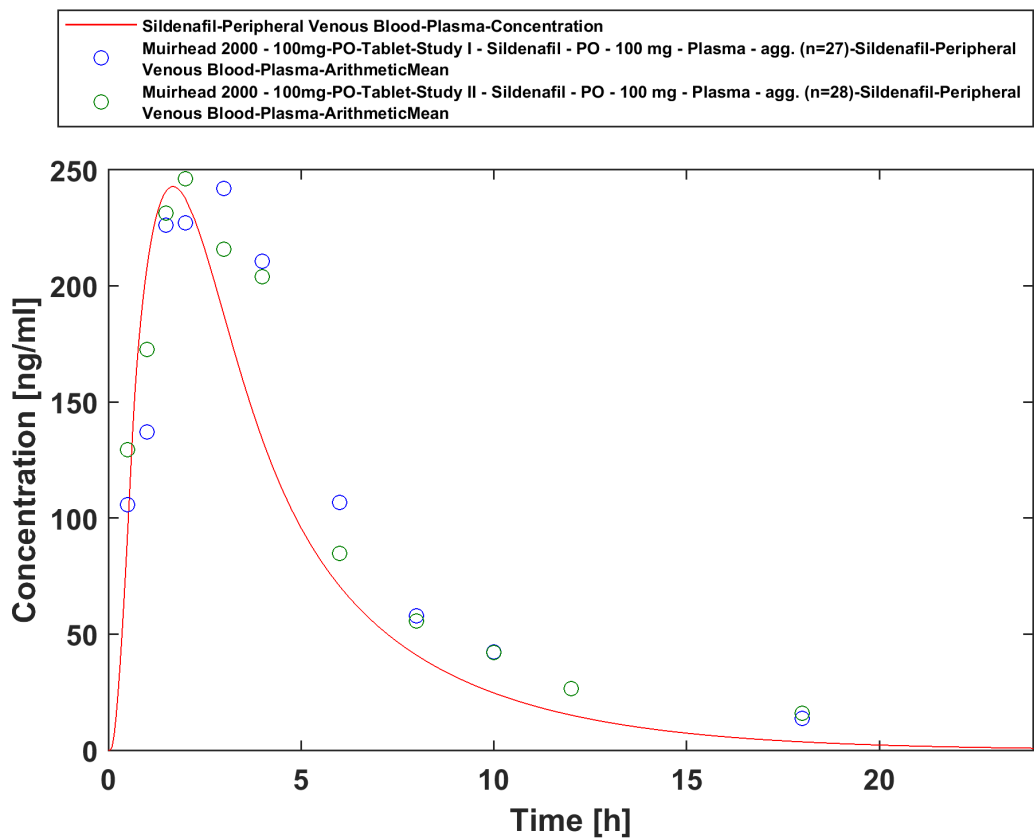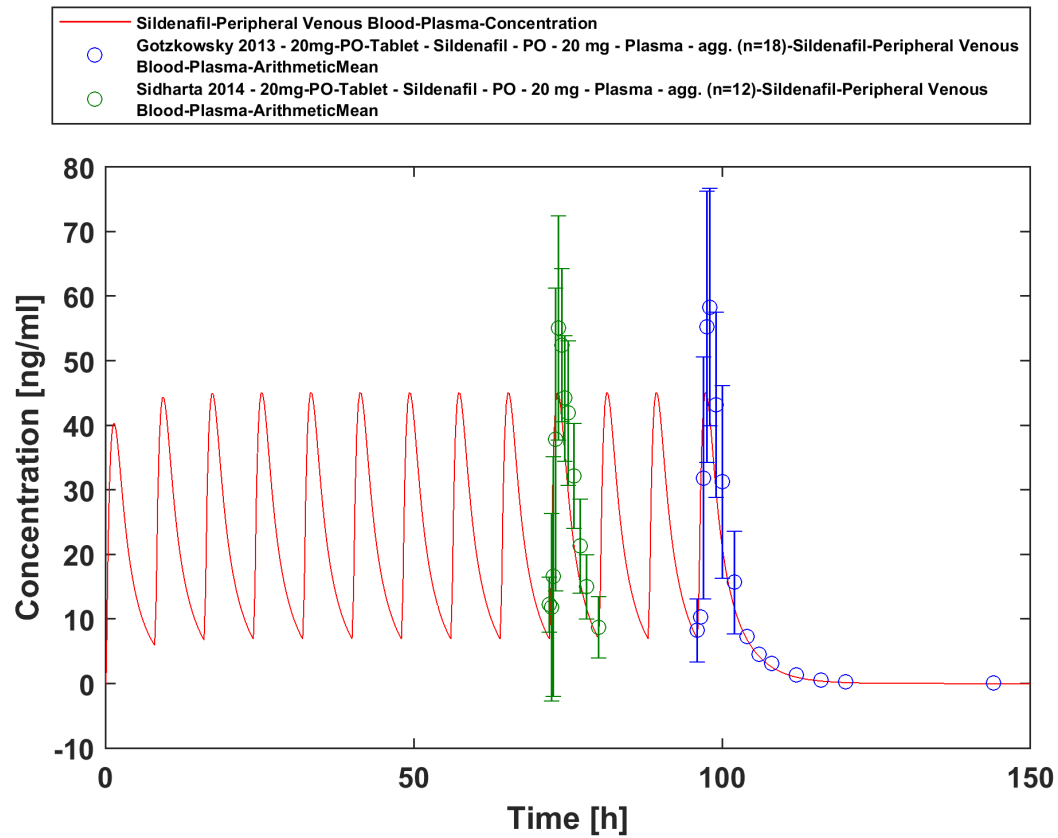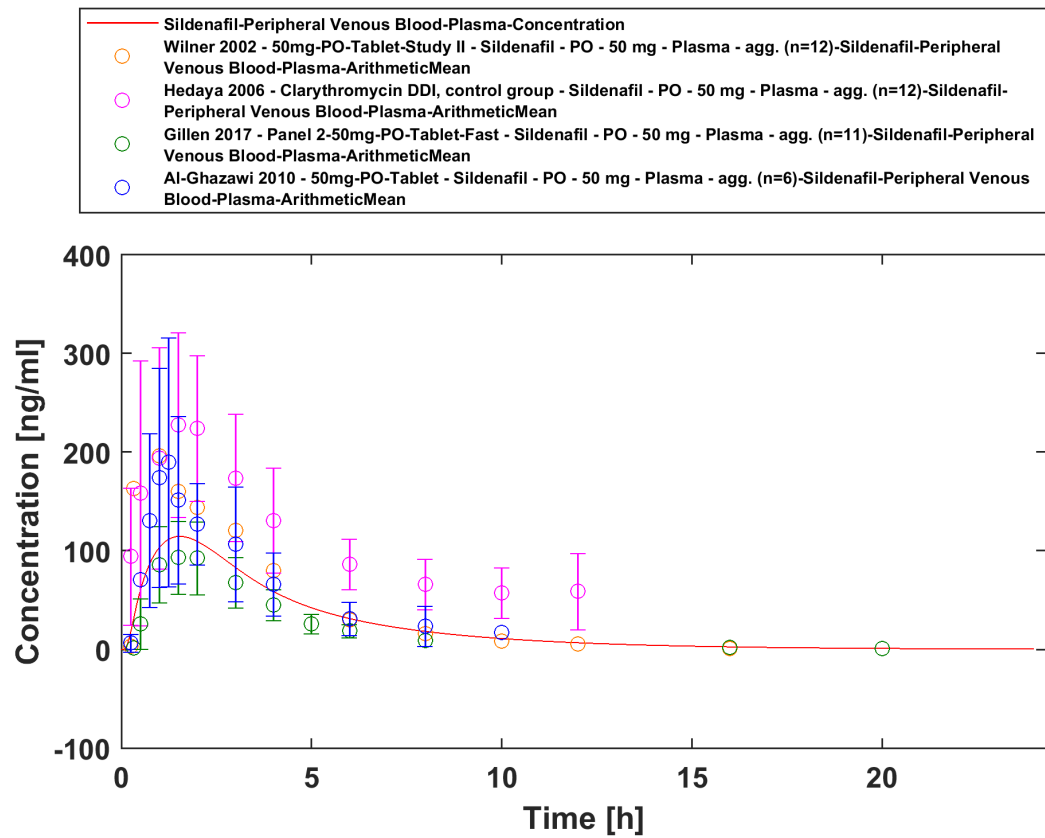
4 Conclusion

The herein presented PBPK model adequately describes the pharmacokinetics of sildenafil in adults.

In particular, it applies quantitative metabolism by CYP3A4, CYP2C9 and CYP2C19. Thus, the model is fit for purpose to be applied for the investigation of drug-drug interactions with regard to its CYP3A4 metabolism.

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