

Pediatric Qualification Package: GFR Ontogeny

Version	1.1-OSP9.1
Qualification Plan Release	https://github.com/Open-Systems-Pharmacology/Pediatric_Qualification_Package_GFR_Ontogeny/releases/tag/v1.1
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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Chapter 1: Introduction to Pediatric Translation

The presented qualification report evaluates the predictive performance of the OSP suite to predict glomerular filtration rate (GFR)-mediated drug clearance in children.

Therefore, PBPK models of specific *in vivo* probe substances covering children aged below 6 months up to adolescents were built and evaluated. All models are whole-body PBPK models, allowing for dynamic pediatric translation in all organs. The qualification report demonstrates the level of confidence of the OSP suite with regard to reliable PBPK predictions of age related GFR-mediated drug clearance during model-informed drug development. The presented PBPK models as well as the respective qualification plan and qualification report are provided open-source and transparently documented (<https://github.com/Open-Systems-Pharmacology/Pediatric-Qualification-Package-GFR-Ontogeny>).

Translation of Adult PBPK to Children

Using a developed and validated (adult) PBPK model for an *in vivo* probe substance, a pediatric PBPK model can be established for children by translating physiology, clearance processes (as parameterized in the adult model) and age-dependent protein binding including the variability therein.^[1]

The PBPK models are developed with clinical data of healthy adult subjects obtained from the literature. Plasma concentrations following multiple-dose application, mass balance information and other clinical measurements need to be included for model development, if available. During model translation from adults to children for a specific substance, uncertainties in data-quality caused by impact of disease or the target study population, inaccurate *in vitro* assay-techniques regarding mass balance, as well as study differences may cause not being able to adequately predict the PK in children for all reported studies.

Prediction performance of the PBPK model for these probe substances in children are then shown by means of e.g. predicted versus observed clearance-ratio plots, of which the results support an adequate prediction of the ontogeny function for the application of PBPK model translation of adult PBPK to children.

For qualification purpose, during the translation of adult PBPK to children the following assumptions and considerations were made:

- when translating an adult model to children, it was assumed that the metabolism and excretion pathways are qualitatively the same in children as in adults.
- no further changes to input parameters other than those for the physiology and protein binding. All other parameters (e.g. lipophilicity) were kept unchanged.

Anthropometric and Physiological Information

Regarding the age-dependencies of the relevant anthropometric (height, weight) and physiological parameters (e.g. blood flows, organ volumes, binding protein concentrations, hematocrit, cardiac output) in children was gathered from the literature and has been previously published [2]. The information was incorporated into PK-Sim® and was used as default values for the simulations in children.

The applied ontogeny and variability of plasma proteins that are integrated into PK-Sim® for translation to children are described in the publicly available 'PK-Sim® Ontogeny Database Version 7.3' [3] or otherwise referenced for the specific process.

Qualification of GFR ontogeny

For the qualification of the GFR elimination of compounds, the following probe substances was included:

- Amikacin [4]
- Vancomycin [5]

References

- [1] [Maharaj AR, Barrett JS, Edginton AN. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. The AAPS journal. 2013;15\(2\):455-464.](#)
- [2] [Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. Clin Pharmacokinet. 2006;45\(10\):1013-34.](#)
- [3] [OSPSuite.Documentation/PK-Sim Ontogeny Database Version 7.3.pdf](#)
- [4] [Amikacin-Model, Whole-body PBPK model of Amikacin. https://github.com/Open-Systems-Pharmacology/Amikacin-Model](#)
- [5] [Vancomycin-Model, Whole-body PBPK model of Vancomycin. https://github.com/Open-Systems-Pharmacology/Amikacin-Model](#)

Chapter 2: Pediatric translation qualification

Evaluation of Pediatric translation

All pediatric translations are pure retrospective predictions, no pediatric pharmacokinetic studies were used to inform model parameters. All parameters necessary to model the pediatric populations, such as demographics (age, weight, height), as well as dosing formulation information were taken from the respective pediatrics studies from literature in order to evaluate their predictive performance.

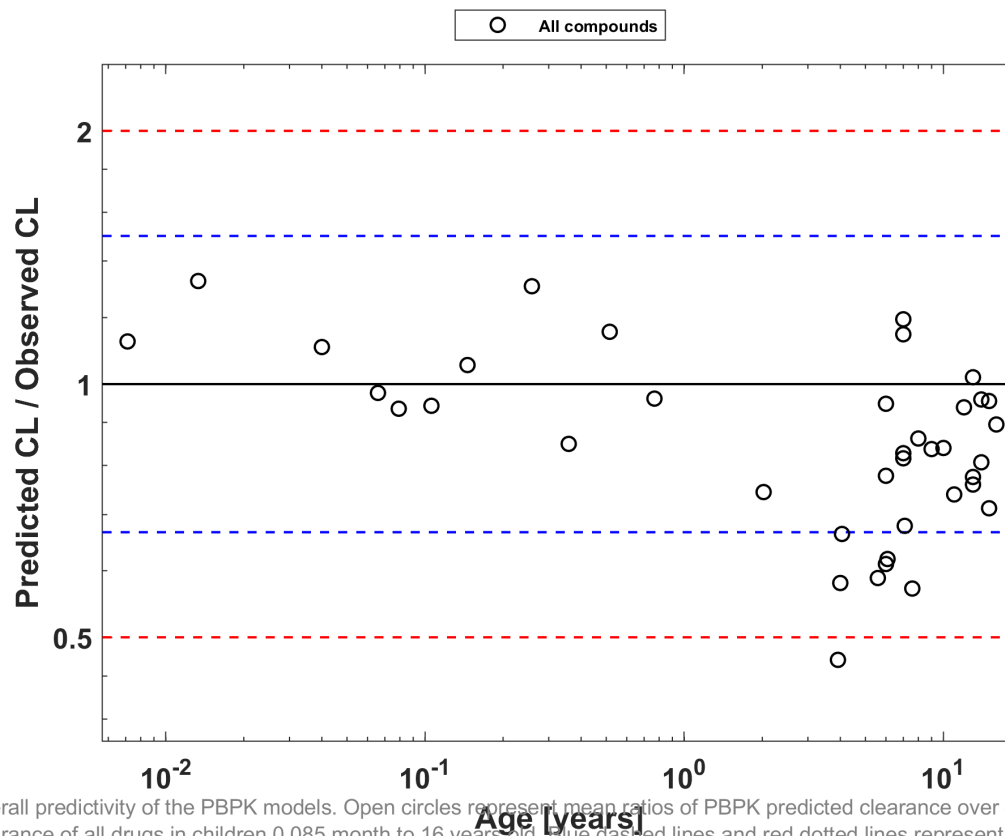
The models were evaluated by ratio plots of area under the plasma concentration-time curve (AUC), or clearance (CL) values resulting from our predictions to the values observed during clinical studies, and by comparison of concentration-time profiles if available. As a quantitative measure of the descriptive and predictive performance of each model, the geometric mean fold error was calculated according to Eq. 1:

Eq. 1: $GMFE = 10^{(\sum |\log_{10}(\text{pred PK parameter} / \text{obs PK parameter})|) / n}$

with GMFE = geometric mean fold error of all AUC or CL predictions of the respective model, pred PK parameter = predicted AUC or CL, obs PK parameter = observed AUC or CL, and n = number of observed values.

The ratios of predicted over observed mean AUC or CL values from all compound were also plotted across all age groups in the figure below. As illustrated, most of the prediction were within the 0.5 to 2.0 range (2-fold error).

In the next sections the demographics as well as the evaluation results of the predictive performance of the specific compound PBPK models in children can be found.



GMFE (CL) = 1.258017

CL	Number	Ratio [%]
Points total	39	-
Points within 1.5 fold	32	82.0513
Points within 2-fold	38	97.4359

Study ID	Age [y]	BodyWeight [kg]	Predicted CL [ml/min/kg]	Observed CL [ml/min/kg]	Pred/Obs CL Ratio
Vogelstein 1977	15	77	0.71181	1.74	0.71181
Vogelstein 1977	15	62.5	0.95476	1.44	0.95476
Vogelstein 1977	9	21.5	0.83703	2.56	0.83703
Vogelstein 1977	13	51	1.0188	1.35	1.0188
Vogelstein 1977	12	27.1902	0.93839	2.64	0.93839
Vogelstein 1977	7	27.4	0.81617	2.19	0.81617
Vogelstein 1977	4	14	0.58013	4.22	0.58013
Vogelstein 1977	6	17.3	0.94756	2.63	0.94756
Vogelstein 1977	6	15.5	0.61107	4.26	0.61107
Vogelstein 1977	7	15.9	1.1941	2.3	1.1941
Vogelstein 1977	14	39.5	0.95879	1.91	0.95879
Vogelstein 1977	10	32.8	0.83954	2.3	0.83954
Vogelstein 1977	14	45.5	0.80729	2.23	0.80729
Vogelstein 1977	11	35.2	0.73927	2.58	0.73927
Vogelstein 1977	13	27.7	0.77547	2.86	0.77547
Vogelstein 1977	8	20.8	0.86162	2.88	0.86162
Vogelstein 1977	6	15.5	0.77799	3.31	0.77799
Vogelstein 1977	13	49	0.75956	1.88	0.75956
Vogelstein 1977	7	20.6	1.1459	2.06	1.1459
Vogelstein 1977	16	35.0809	0.89535	2.47	0.89535
Treluyer 2002	0.013333	3.5867	1.3259	0.053	1.3259
Treluyer 2002	0.04	3.76	1.1067	0.073	1.1067
Treluyer 2002	0.065833	3.9279	0.97612	0.095	0.97612
Treluyer 2002	0.079167	4.0146	0.9348	0.106	0.9348

Study ID	Age [y]	BodyWeight [kg]	Predicted CL [ml/min/kg]	Observed CL [ml/min/kg]	Pred/Obs CL Ratio
Treluyer 2002	0.10583	4.1879	0.94232	0.118	0.94232
Treluyer 2002	0.14583	4.4479	1.0535	0.12	1.0535
Treluyer 2002	0.51583	6.8529	1.1539	0.127	1.1539
Treluyer 2002	0.7675	8.4888	0.96098	0.15	0.96098
Treluyer 2002	2.0242	12.3044	0.74412	0.181	0.74412
Treluyer 2002	4.0608	16.8869	0.66347	0.19	0.66347
Treluyer 2002	6.085	21.821	0.6195	0.196	0.6195
Treluyer 2002	7.09	24.434	0.67841	0.177	0.67841
Belfayol 1996	7	23.5	0.82769	56.3	0.82769
Schaad 1980	0.0071184	3.07	1.1238	3.6416	1.1238
Schaad 1980	0.25833	4.9	1.3072	8.0925	1.3072
Schaad 1980	0.35833	5.2	0.84901	14.0462	0.84901
Schaad 1980	3.917	15.5	0.47009	61.2428	0.47009
Schaad 1980	5.583	20	0.5881	59.0636	0.5881
Schaad 1980	7.583	26.7	0.57141	74.3584	0.57141

Chapter 2.1: Amikacin PK Ratio tables and Figures

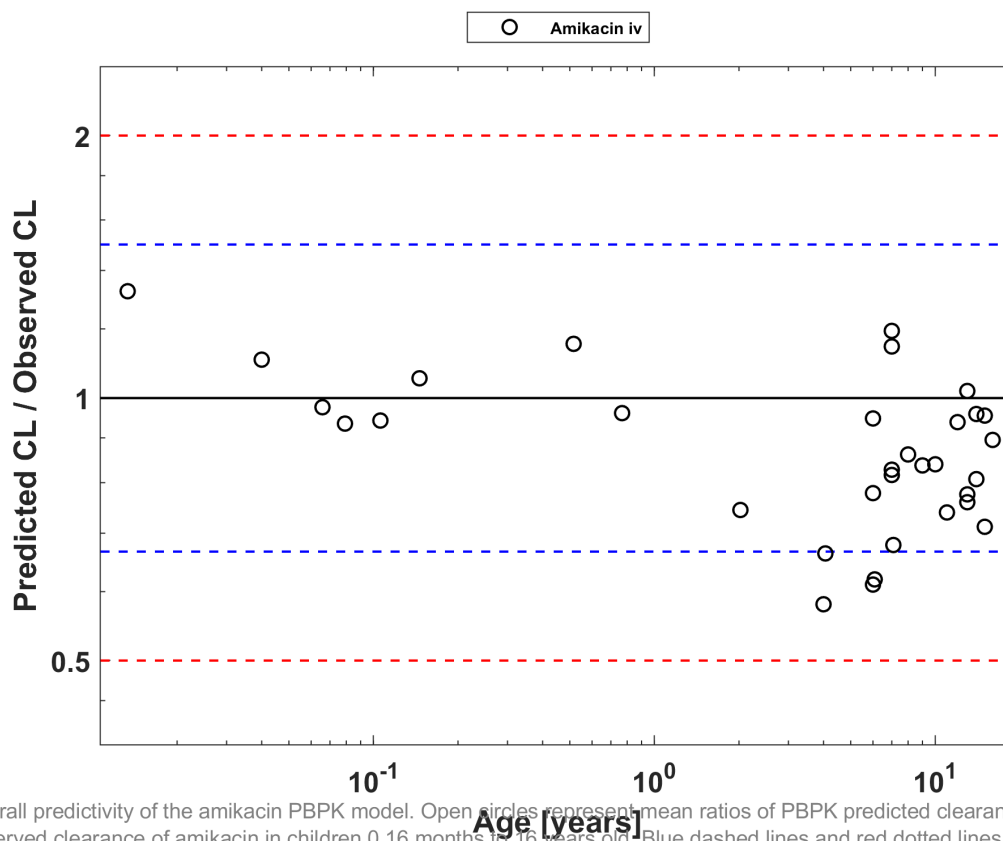
Amikacin model

Amikacin PBPK predictions in children were evaluated using pharmacokinetic (PK) data reported in the following studies:

- Tréluyer JM, Merlé Y, Tonnelier S, Rey E, Pons G. Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. *Antimicrob Agents Chemother.* 2002 May;46(5):1381-7.
- Vogelstein B, Kowarski A, Lietman PS. The pharmacokinetics of amikacin in children. *J Pediatr.* 1977 Aug;91(2):333-9.
- Belfayol L, Talon P, Eveillard M, Alet P, Fauvelle F. Pharmacokinetics of once-daily amikacin in pediatric patients. *Clin Microbiol Infect.* 1996 Feb;2(3):186-191.

The pediatric PBPK model reasonably well predicted the clearance values of amikacin pediatric studies across all available age groups, ranging from 0.16 months to 16 years old. The ratios of mean predicted over observed clearance values are illustrated in the table below as well as in the predicted versus observed clearance ratio plot, showing that all predictions in children were

within 2-fold error of observed values.



GMFE (CL) = 1.219861

CL	Number	Ratio [%]
Points total	33	-
Points within 1.5 fold	29	87.8788
Points within 2-fold	33	100

Study ID	Age [y]	BodyWeight [kg]	Predicted CL [ml/min/kg]	Observed CL [ml/min/kg]	Pred/Obs CL Ratio
Vogelstein 1977	15	77	0.71181	1.74	0.71181
Vogelstein 1977	15	62.5	0.95476	1.44	0.95476
Vogelstein 1977	9	21.5	0.83703	2.56	0.83703
Vogelstein 1977	13	51	1.0188	1.35	1.0188
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Vogelstein 1977	6	15.5	0.61107	4.26	0.61107
Vogelstein 1977	7	15.9	1.1941	2.3	1.1941
Vogelstein 1977	14	39.5	0.95879	1.91	0.95879
Vogelstein 1977	10	32.8	0.83954	2.3	0.83954
Vogelstein 1977	14	45.5	0.80729	2.23	0.80729
Vogelstein 1977	11	35.2	0.73927	2.58	0.73927
Vogelstein 1977	13	27.7	0.77547	2.86	0.77547
Vogelstein 1977	8	20.8	0.86162	2.88	0.86162
Vogelstein 1977	6	15.5	0.77799	3.31	0.77799
Vogelstein 1977	13	49	0.75956	1.88	0.75956
Vogelstein 1977	7	20.6	1.1459	2.06	1.1459
Vogelstein 1977	16	35.0809	0.89535	2.47	0.89535
Treluyer 2002	0.013333	3.5867	1.3259	0.053	1.3259
Treluyer 2002	0.04	3.76	1.1067	0.073	1.1067

Study ID	Age [y]	BodyWeight [kg]	Predicted CL [ml/min/kg]	Observed CL [ml/min/kg]	Pred/Obs CL Ratio
Treluyer 2002	0.065833	3.9279	0.97612	0.095	0.97612
Treluyer 2002	0.079167	4.0146	0.9348	0.106	0.9348
Treluyer 2002	0.10583	4.1879	0.94232	0.118	0.94232
Treluyer 2002	0.14583	4.4479	1.0535	0.12	1.0535
Treluyer 2002	0.51583	6.8529	1.1539	0.127	1.1539
Treluyer 2002	0.7675	8.4888	0.96098	0.15	0.96098
Treluyer 2002	2.0242	12.3044	0.74412	0.181	0.74412
Treluyer 2002	4.0608	16.8869	0.66347	0.19	0.66347
Treluyer 2002	6.085	21.821	0.6195	0.196	0.6195
Treluyer 2002	7.09	24.434	0.67841	0.177	0.67841
Belfayol 1996	7	23.5	0.82769	56.3	0.82769

Chapter 2.2: Amikacin Concentration-Time profiles in Children

Concentration-Time Profiles

Predicted versus observed plasma concentration-time profiles are listed below. Only simulations where observed data was available for comparison are shown. Depending if the observed data were individual data or aggregated data, individual predictions or population predictions including variability are shown, respectively.

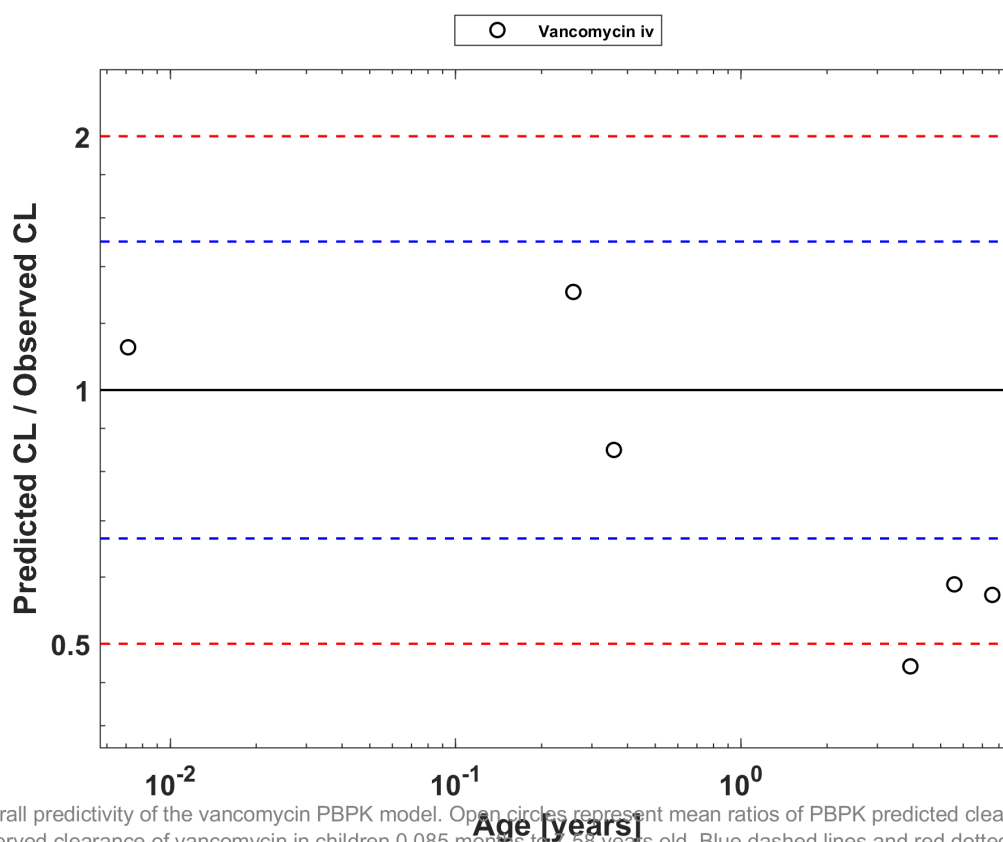
Chapter 2.3: Vancomycin PK Ratio tables and Figures

Vancomycin model

Vancomycin PBPK predictions in children were evaluated using pharmacokinetic (PK) data reported in the following studies:

- Schaad UB, McCracken GH Jr, Nelson JD. Clinical pharmacology and efficacy of vancomycin in pediatric patients. J Pediatr. 1980 Jan;96(1):119-26.

The pediatric PBPK model predicted the clearance values of vancomycin observed in pediatric studies reasonably across all available age groups, ranging from 0.085 months to 7.58 years old. The ratios of mean predicted over observed clearance values are illustrated in the table below as well as in the predicted versus observed clearance ratio plot, showing that all predictions in children were within 2-fold error of observed values.



GMFE (CL) = 1.490238

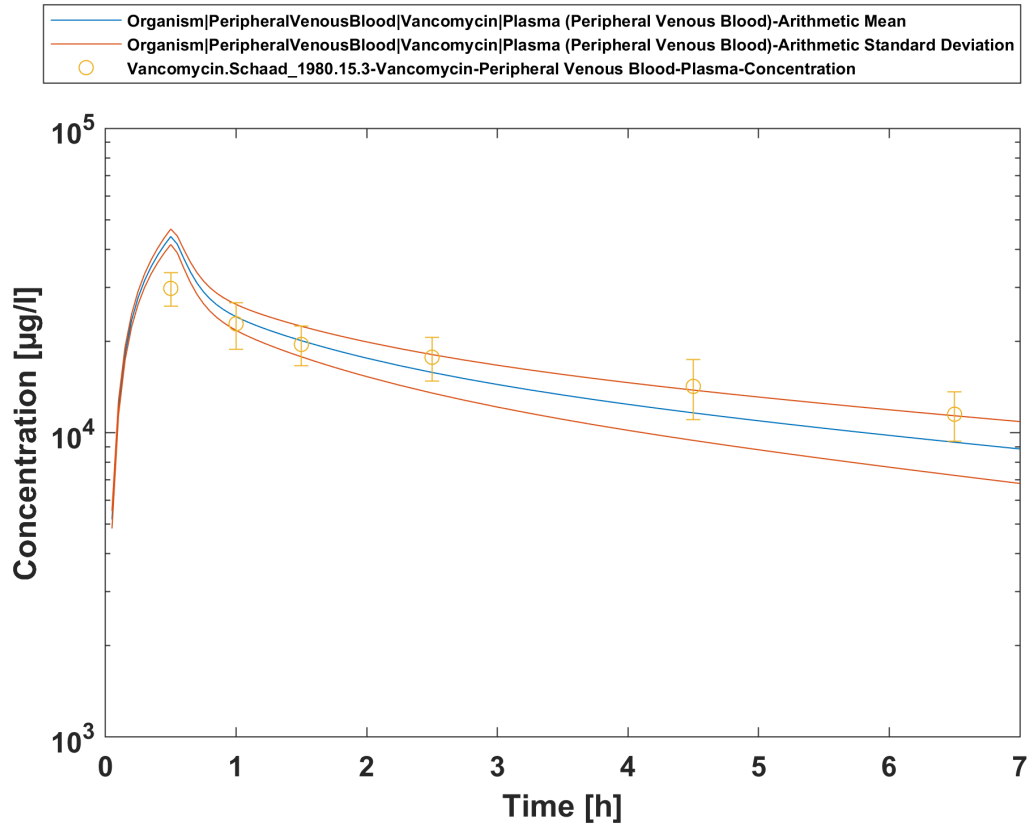
CL	Number	Ratio [%]
Points total	6	-
Points within 1.5 fold	3	50
Points within 2-fold	5	83.3333

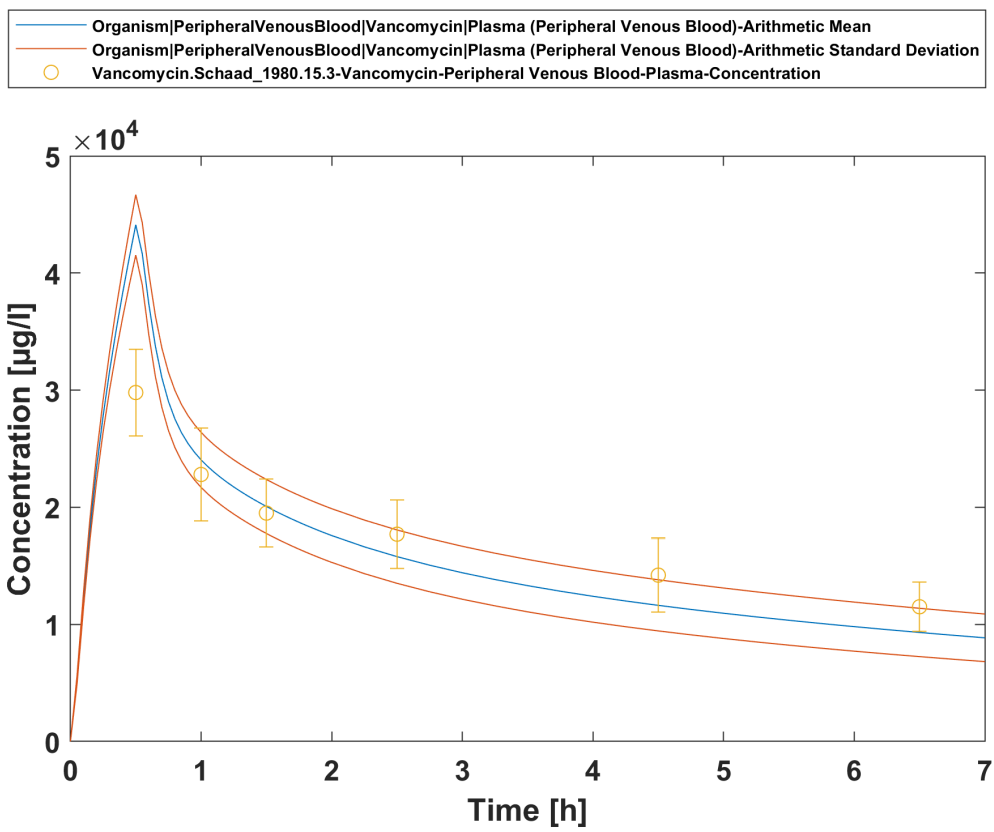
Study ID	Age [y]	BodyWeight [kg]	Predicted CL [ml/min]	Observed CL [ml/min]	Pred/Obs CL Ratio
Schaad 1980	0.0071184	3.07	1.1238	3.6416	1.1238
Schaad 1980	0.25833	4.9	1.3072	8.0925	1.3072
Schaad 1980	0.35833	5.2	0.84901	14.0462	0.84901
Schaad 1980	3.917	15.5	0.47009	61.2428	0.47009
Schaad 1980	5.583	20	0.5881	59.0636	0.5881
Schaad 1980	7.583	26.7	0.57141	74.3584	0.57141

Chapter 2.4: Vancomycin Concentration-Time profiles in Children

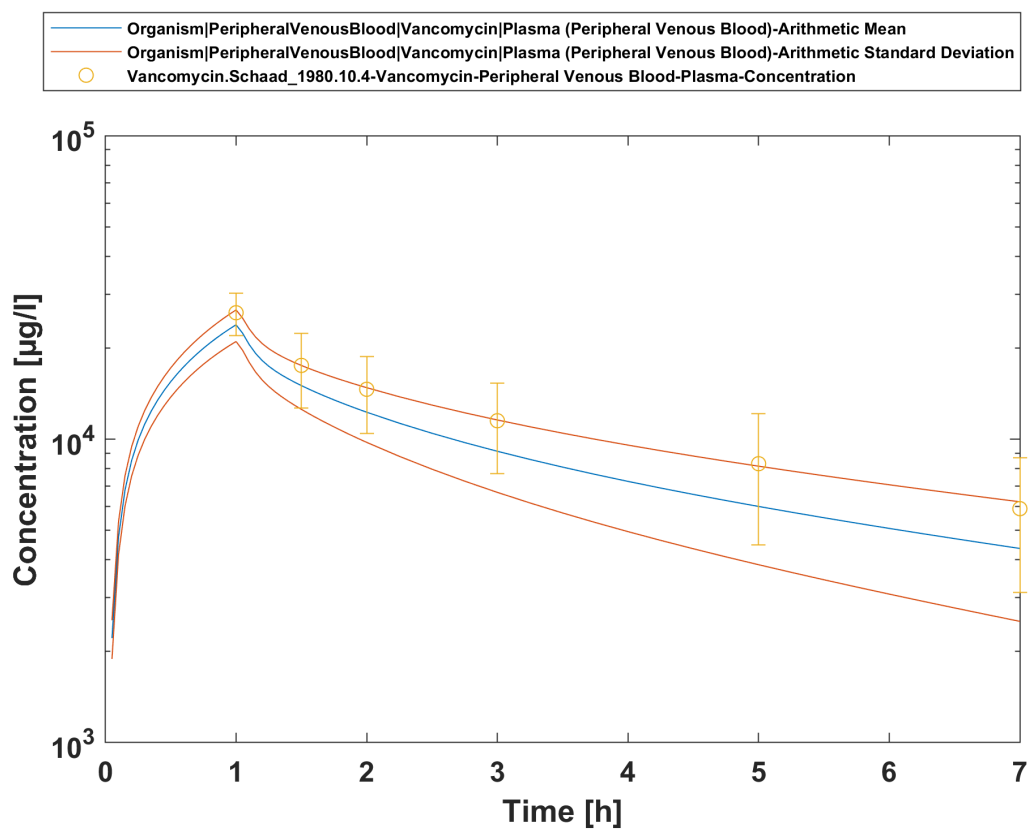
Concentration-Time Profiles

Predicted versus observed plasma concentration-time profiles are listed below. Only simulations where observed data was available for comparison are shown. Depending if the observed data were individual data or aggregated data, individual predictions or population predictions including variability are shown, respectively.

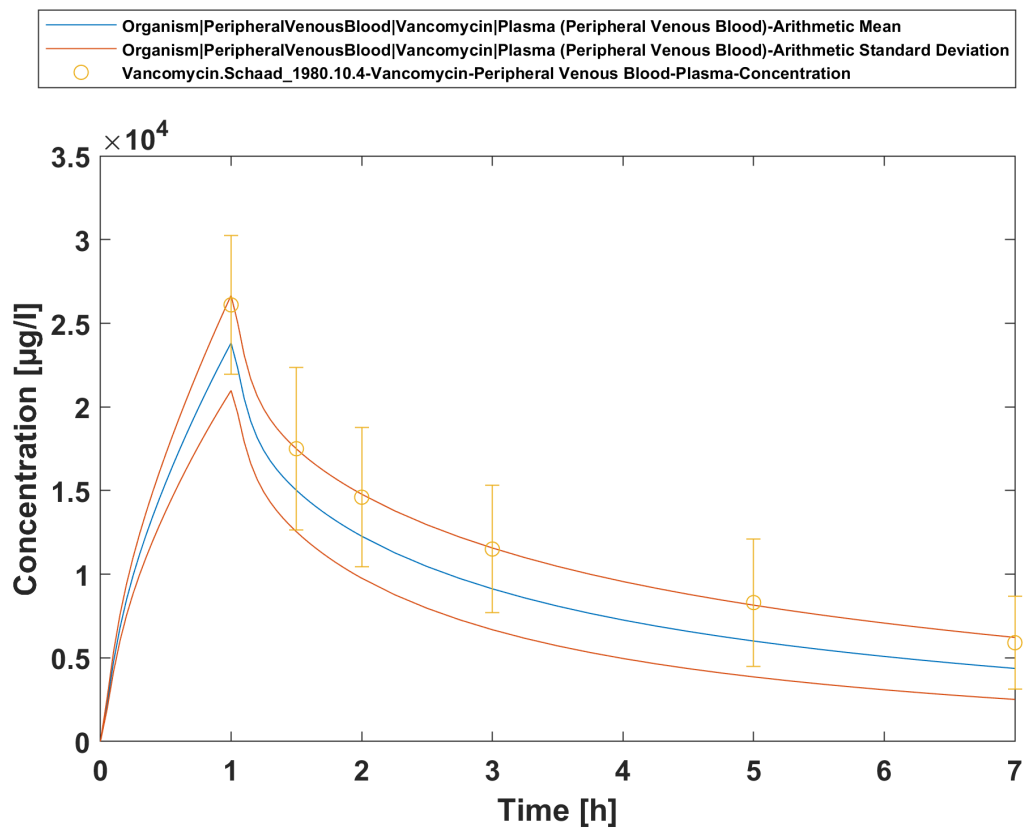




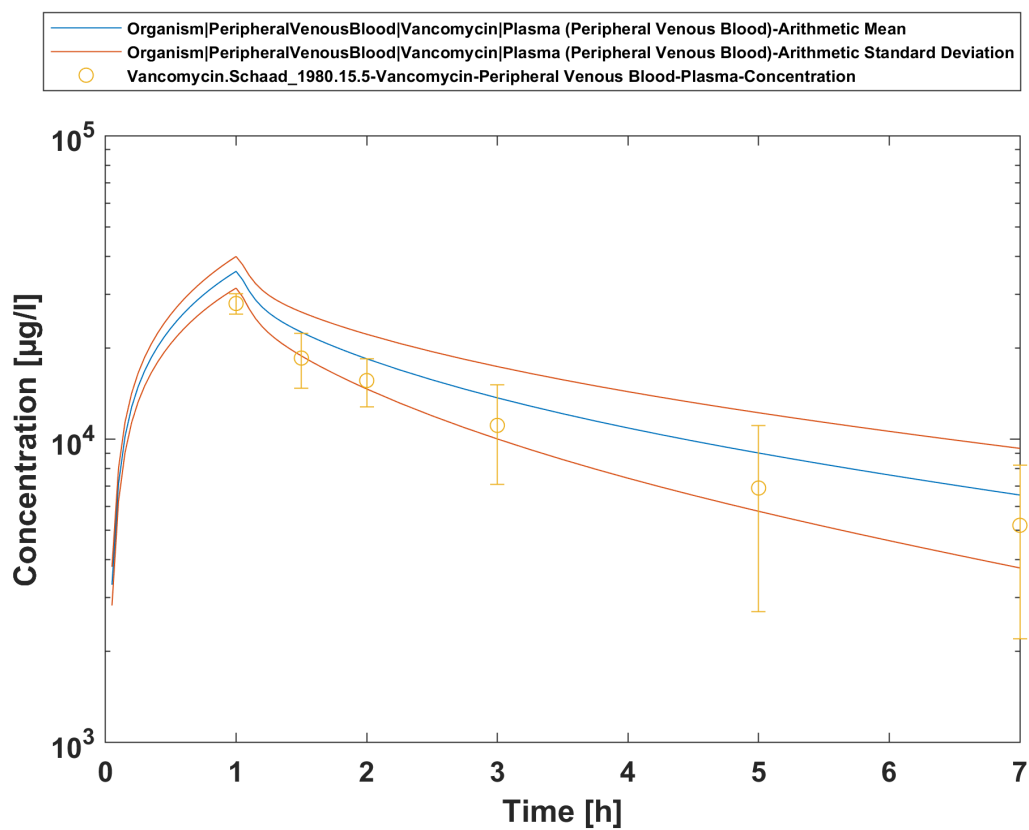
Time Profile Analysis 1



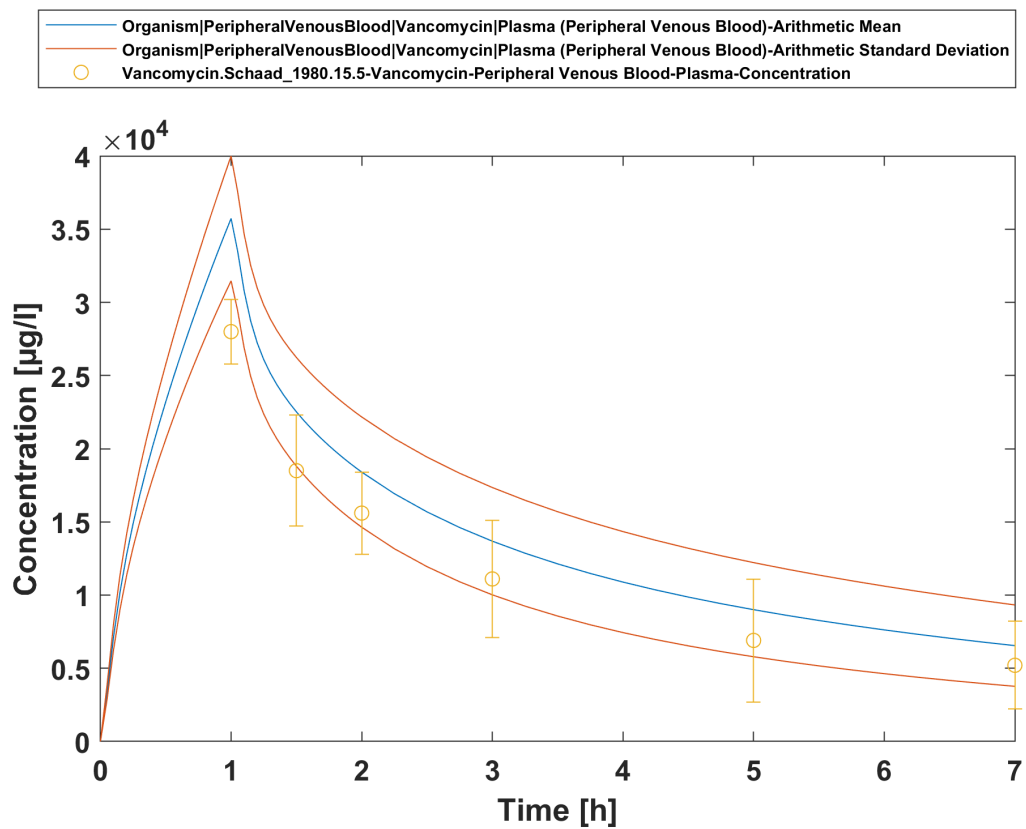
Time Profile Analysis



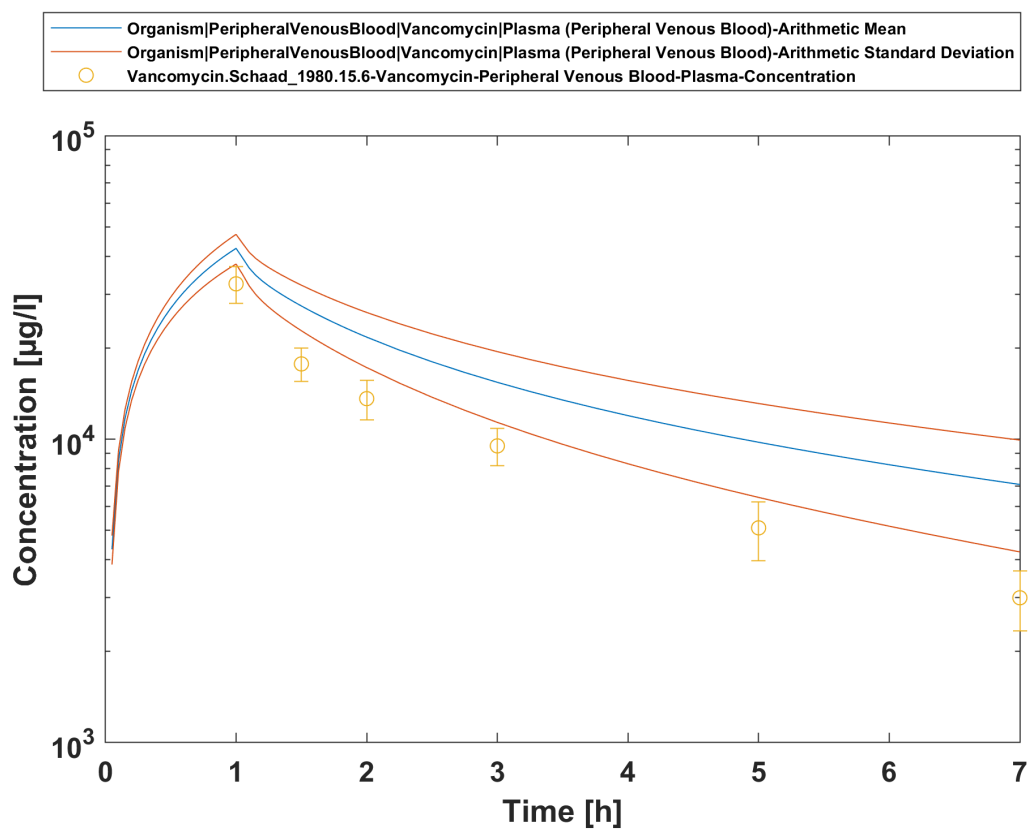
Time Profile Analysis 1



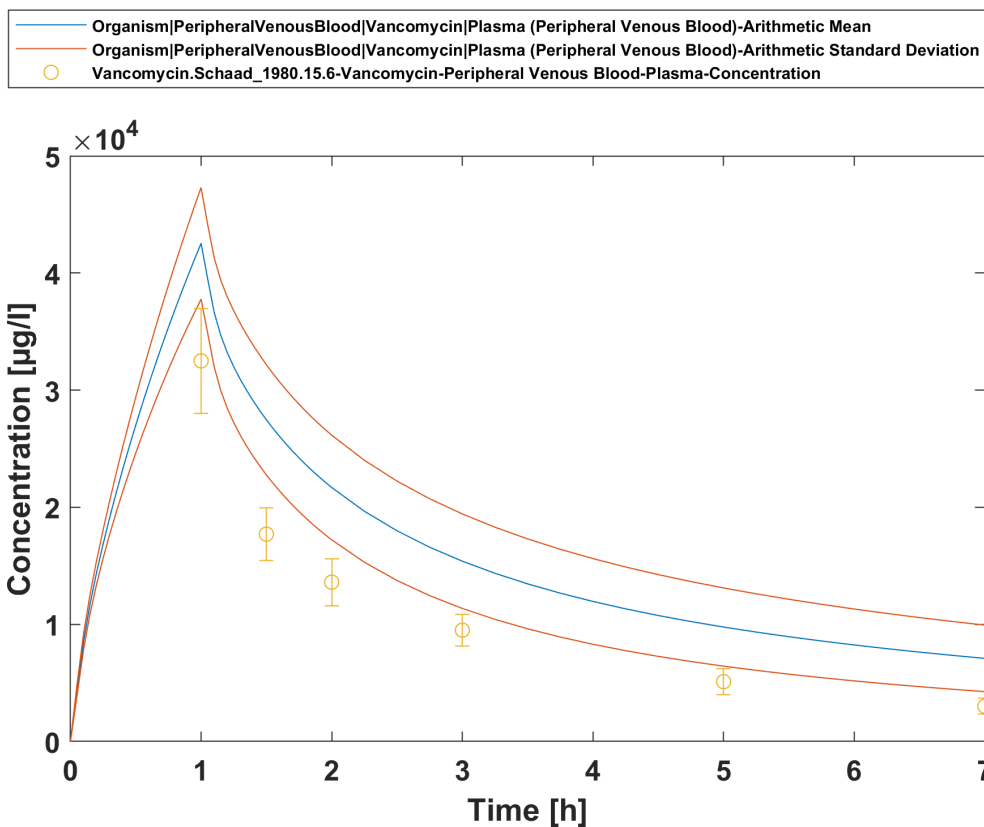
Time Profile Analysis



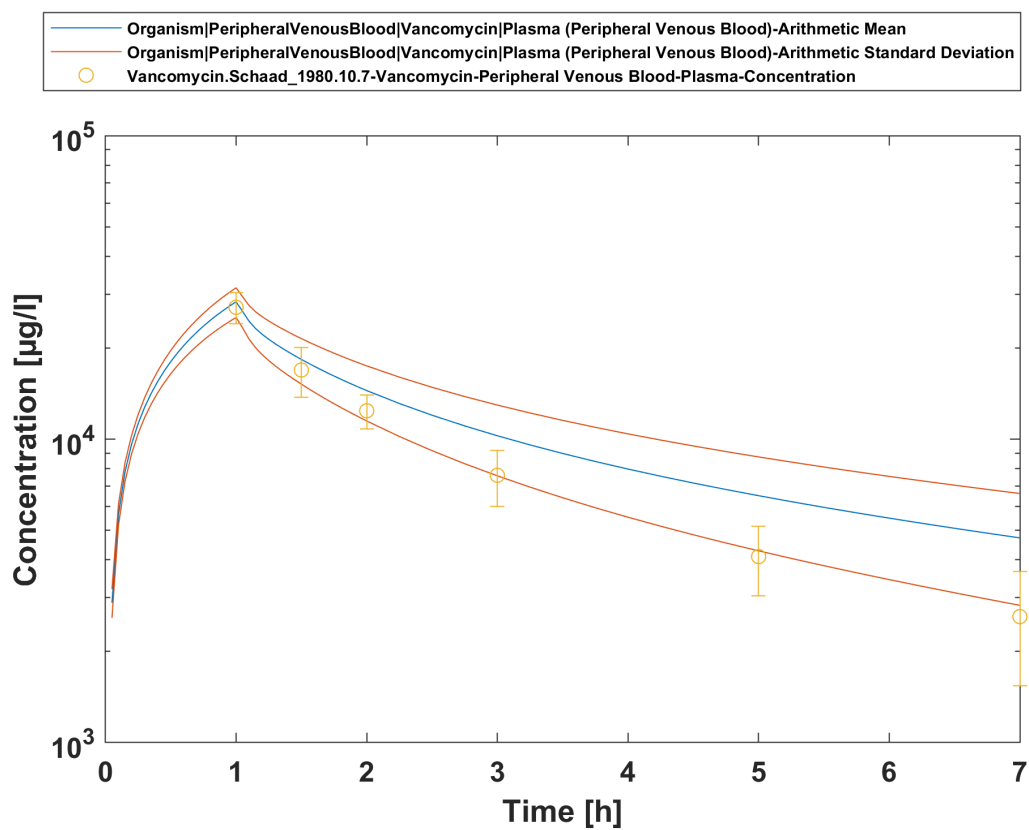
Time Profile Analysis 1



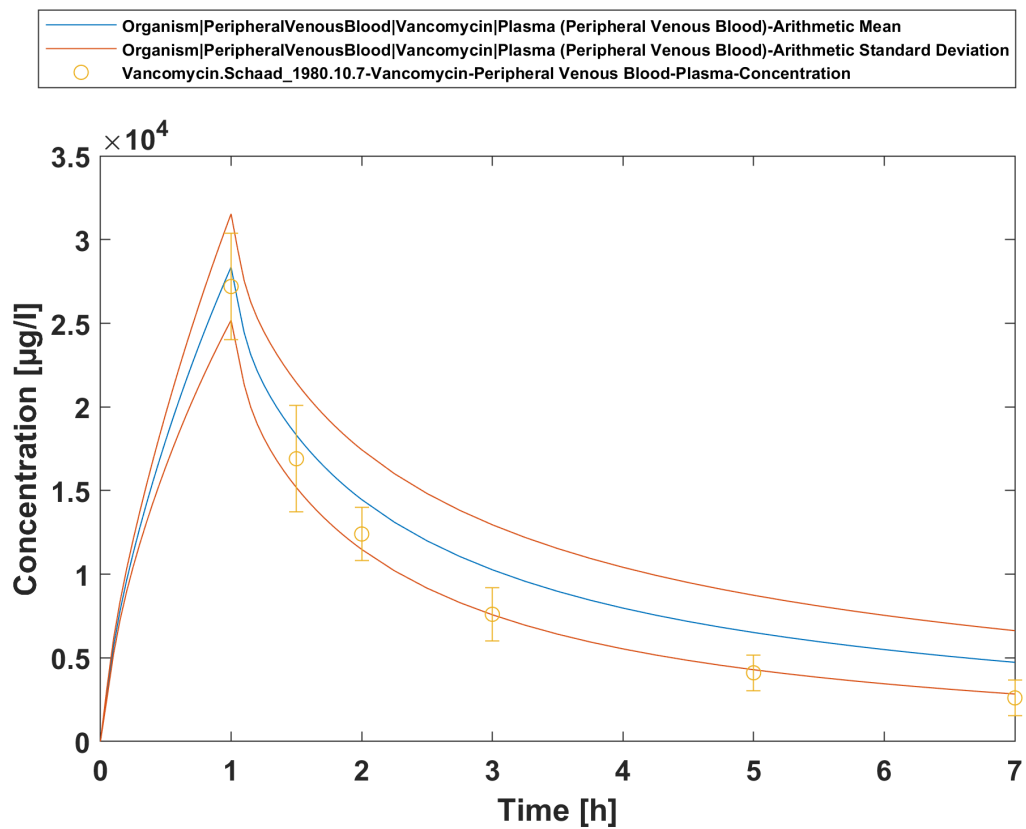
Time Profile Analysis



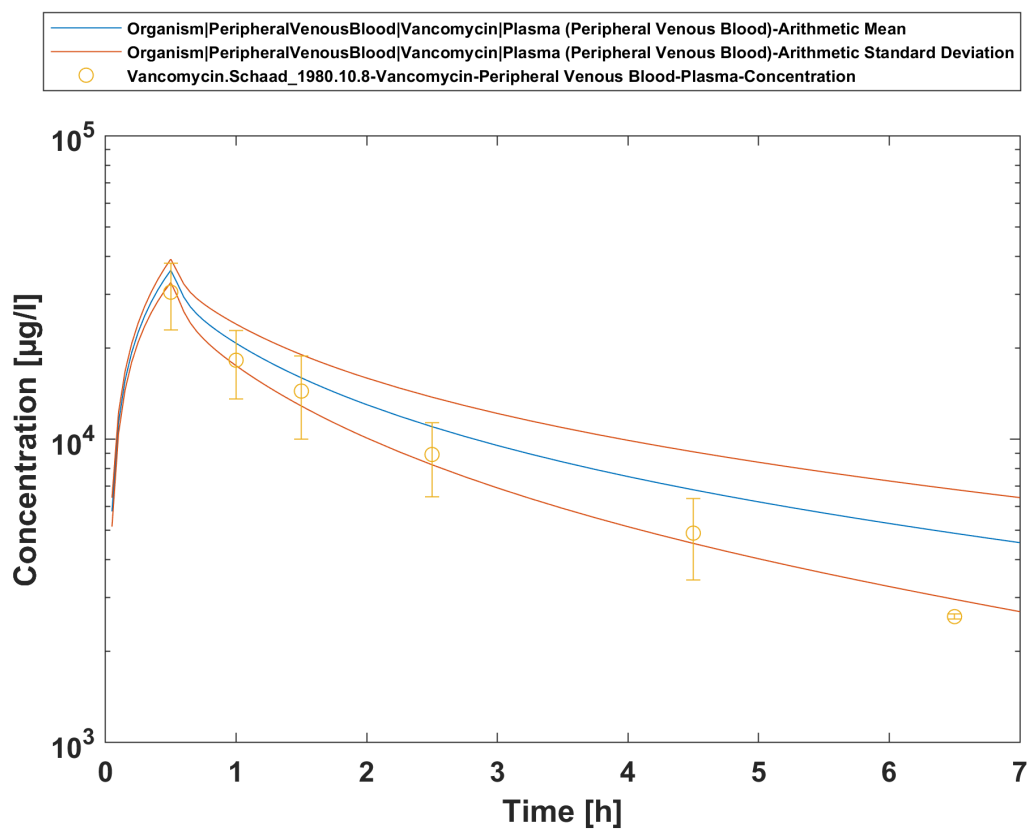
Time Profile Analysis 1



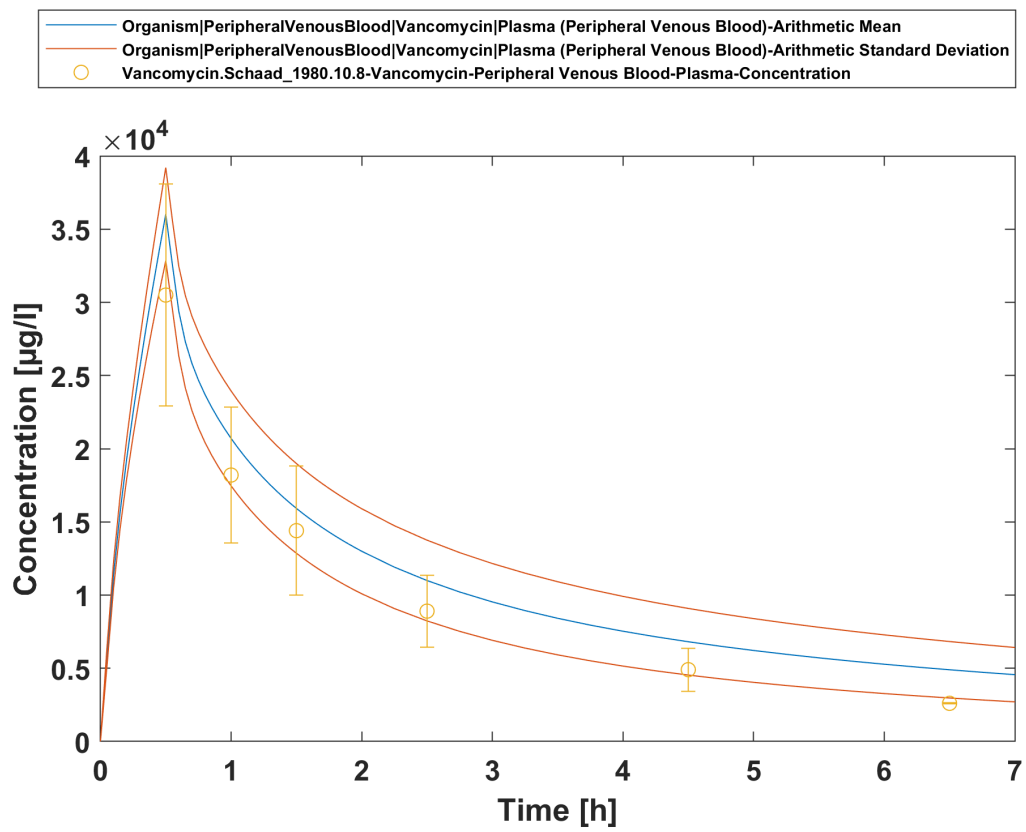
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1

Chapter 3: Adult PBPK model performance

Evaluation of Adult PBPK models

The PBPK models of **amikacin**, and **vancomycin** were developed with clinical pharmacokinetic data covering at least administrations given in children. Plasma concentrations following intravenous administration, oral administration, multiple dose application, fractions excreted to urine or bile and other clinical measurements were included for model development whenever available.

Chapter 3.1: Amikacin Input Tables

Amikacin adult PBPK model

Amikacin is a semi-synthetic aminoglycoside antibiotic used for a number of bacterial infections. Amikacin is administered in several forms, including intravenous or intramuscular injection. The PBPK of Amikacin has been previously developed in PK-Sim using clinical studies in preterm-neonates. [1] Here we have evaluated its predictive performance of glomerular filtration rate (GFR) mediated clearance in adults and term born children. In this chapter we show that amikacin adequately described the pharmacokinetics of amikacin in adults, based on the PBPK model build and reported in preterm-neonates.

The Amikacin model was evaluated in its performance in adults using data of the following publication:

- Walker JM, Wise R, Mitchard M. The pharmacokinetics of amikacin and gentamicin in volunteers: a comparison of individual differences. J Antimicrob Chemother. 1979 Jan;5(1):95-9.
(<https://academic.oup.com/jac/article/5/1/95/747852>)

References

[1] Claassen K, Thelen K, Coboeken K, Gaub T, Lippert J, Allegaert K, Willmann S1. Development of a Physiologically-Based Pharmacokinetic Model for Preterm Neonates: Evaluation with In Vivo Data. Curr Pharm Des. 2015;21(39):5688-98.

The compound properties used for input are illustrated below.

Compound: Amikacin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	185000 mg/l	Publication-In Vitro-Drugbank - YALKOWSKY,SH & DANNENFELSER,RM (1992)	Measurement	True
Reference pH	7	Publication-In Vitro-Drugbank - YALKOWSKY,SH & DANNENFELSER,RM (1992)	Measurement	True
Lipophilicity	-0.48 Log Units	Publication-Other-Claassen et al 2015	Measurement	True
Fraction unbound (plasma, reference value)	1	Publication-Other-Claassen et al 2015	Measurement	True
Is small molecule	Yes			
Molecular weight	588.6 g/mol	Publication-Claassen et al 2015		
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	PK-Sim Standard
Cellular permeabilities	PK-Sim Standard

Processes

Systemic Process: Glomerular Filtration-Claassen et al 2015

Species: Human

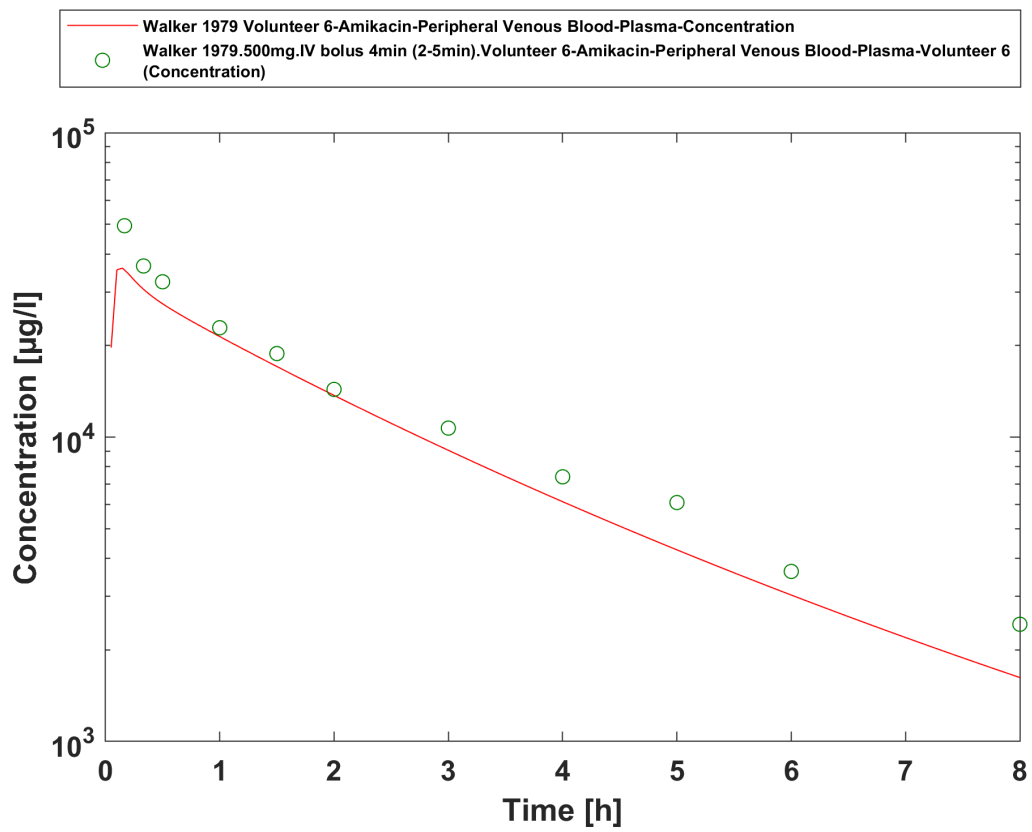
Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Claassen et al 2015

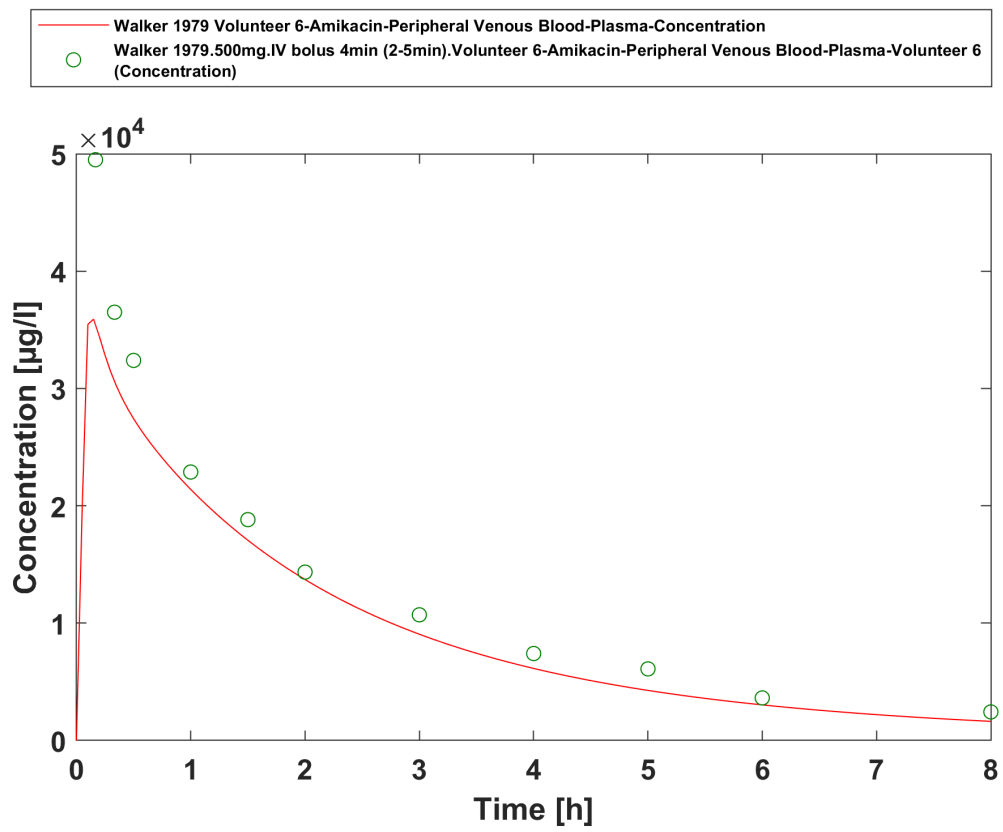
Chapter 3.2: Amikacin Concentration-Time profiles in Adults

Concentration-Time Profiles

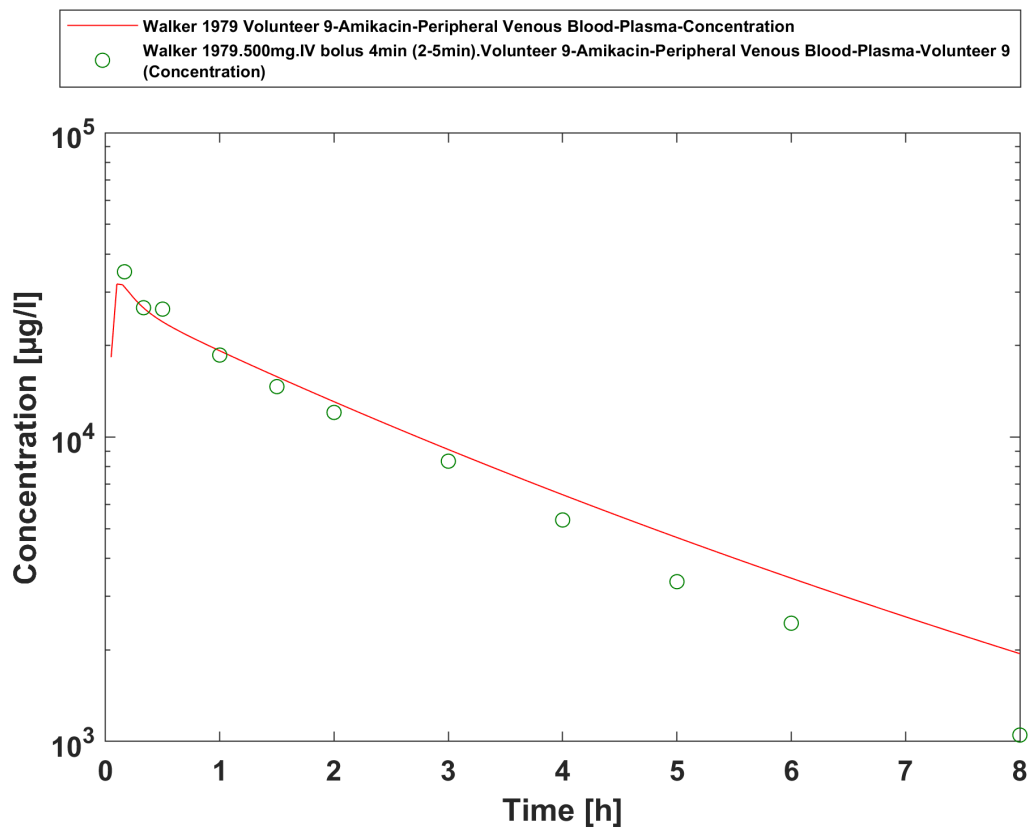
Simulated versus observed plasma concentration-time profiles of all data are listed below.



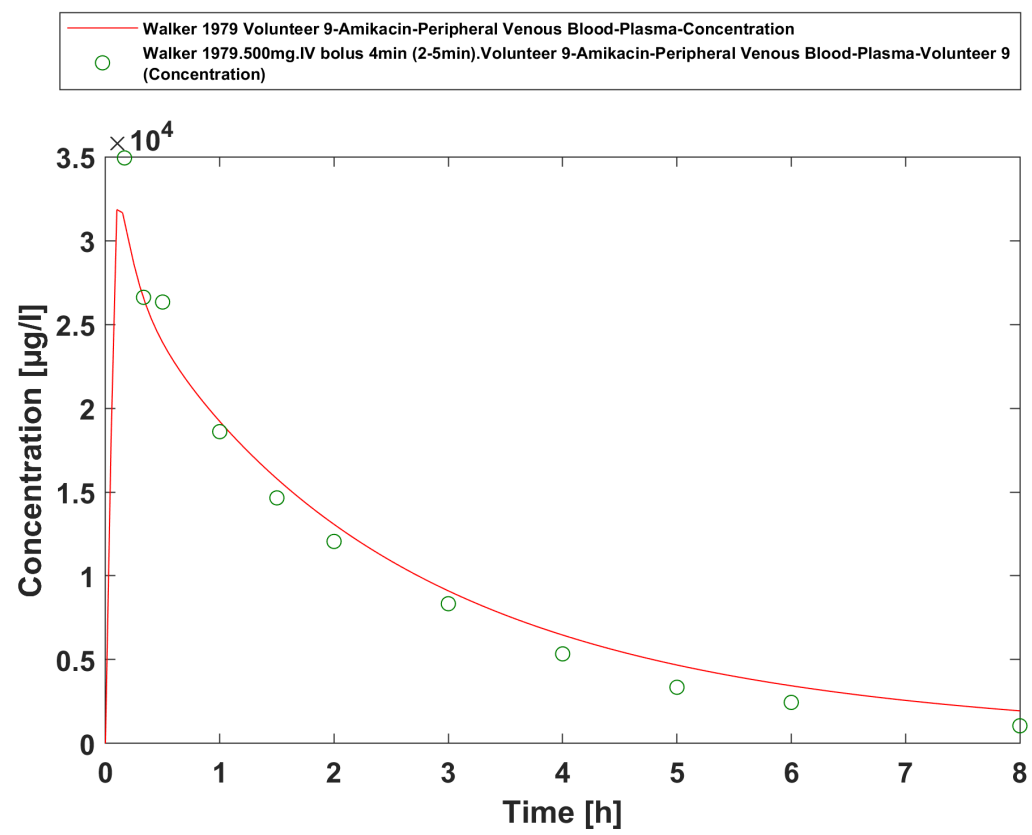
Time Profile Analysis



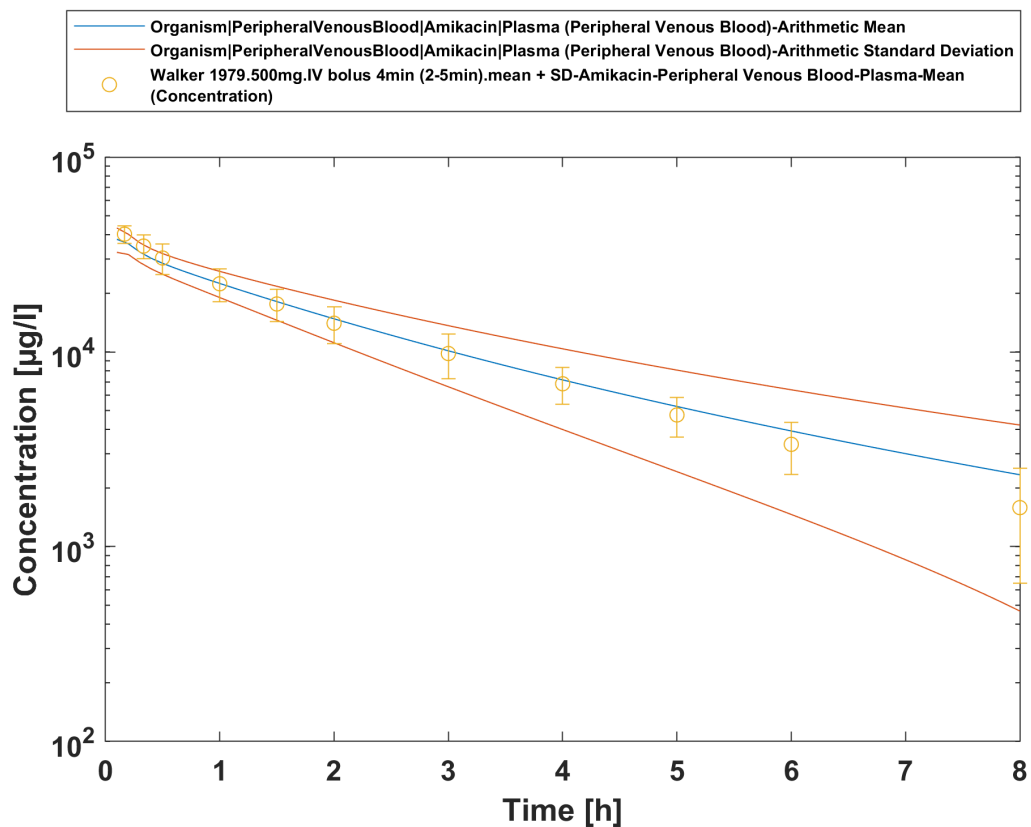
Time Profile Analysis 1



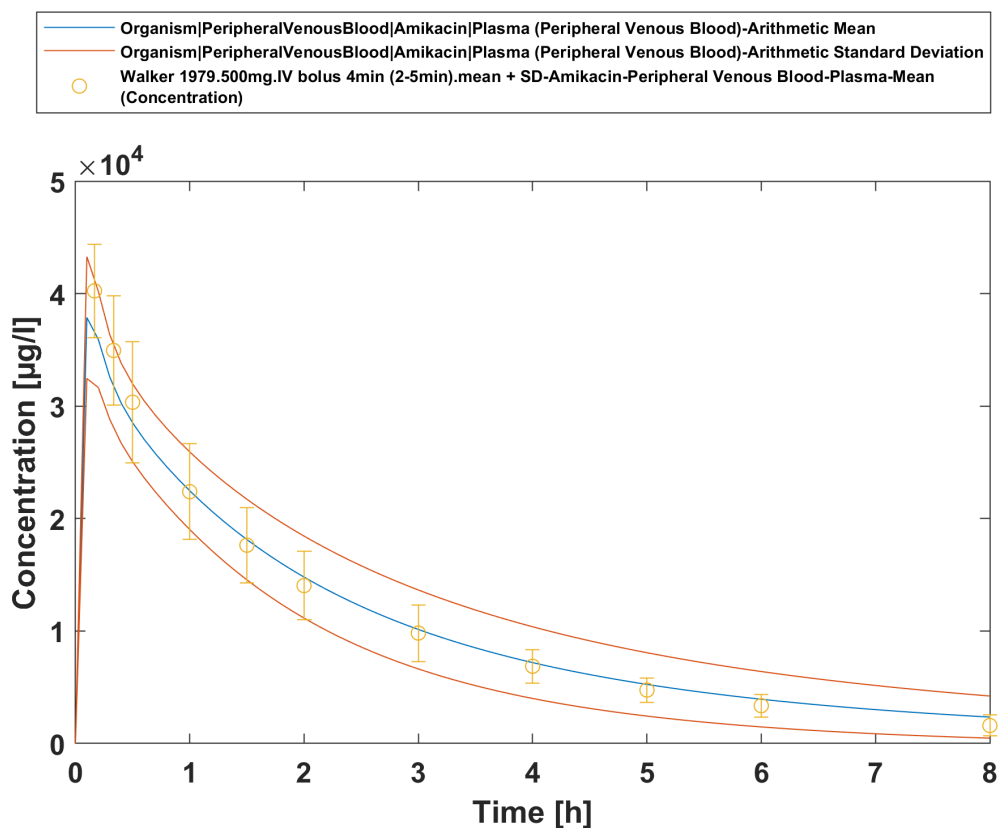
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1

Chapter 3.3: Vancomycin Input Tables

Vancomycin adult PBPK model

Vancomycin is a glycopeptide antibiotic related to ristocetin that inhibits bacterial cell wall assembly and is used to treat a number of bacterial infections. It can be administered intravenously, as well as orally in case of diarrhea therapy. Vancomycin is mainly eliminated via glomerular filtration (GFR). A previous PBPK model for vancomycin using PK-Sim was reported by Radke et al. [1], with the dose fraction excreted unchanged into urine in adults being 90% with 10% hepatic elimination. Our final vancomycin model was rebuilt that applies only GFR mediated clearance that adequately described the pharmacokinetics in adults. No further improvement of vancomycin pharmacokinetics could be determined after introducing hepatic clearance.

The vancomycin model was developed using data of the following publications:

- Boeckh M, Lode H, Borner K, Höffken G, Wagner J, Koeppe P. Pharmacokinetics and serum bactericidal activity of vancomycin alone and in combination with ceftazidime in healthy volunteers. *Antimicrob Agents Chemother.* 1988 Jan;32(1):92-5.
(<https://www.ncbi.nlm.nih.gov/pubmed/3279907>)
- Healy DP, Polk RE, Garson ML, Rock DT, Comstock TJ. Comparison of steady-state pharmacokinetics of two dosage regimens of vancomycin in normal volunteers. *Antimicrob Agents Chemother.* 1987 Mar;31(3):393-7.
(<https://www.ncbi.nlm.nih.gov/pubmed/3579256>)

References

[1] Radke C, Horn D, Lanckohr C, Ellger B, Meyer M, Eissing T, Hempel G. Development of a Physiologically Based Pharmacokinetic Modelling Approach to Predict the Pharmacokinetics of Vancomycin in Critically Ill Septic Patients. *Clin Pharmacokinet.* 2017 Jul;56(7):759-779. doi: 10.1007/s40262-016-0475-3.
(<https://www.ncbi.nlm.nih.gov/pubmed/28039606>)

The compound properties used for input are illustrated below.

Compound: Vancomycin

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	225 mg/l	Internet-Drugbank	Drugbank	True
Reference pH	7	Internet-Drugbank	Drugbank	True
Lipophilicity	2.2307891407 Log Units	Parameter Identification- Parameter Identification	LogP	True
Fraction unbound (plasma, reference value)	0.67	Parameter Identification- Parameter Identification	Measurement	True
Is small molecule	Yes			
Molecular weight	1449.3 g/mol	Publication-Other-Radke 2017		
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	Schmitt
Cellular permeabilities	Charge dependent Schmitt

Processes

Systemic Process: Glomerular Filtration-Zhou et al. 2016 GFR

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	Publication-Other-Zhou 2016

Systemic Process: Total Hepatic Clearance-Radtke 2017

Species: Human

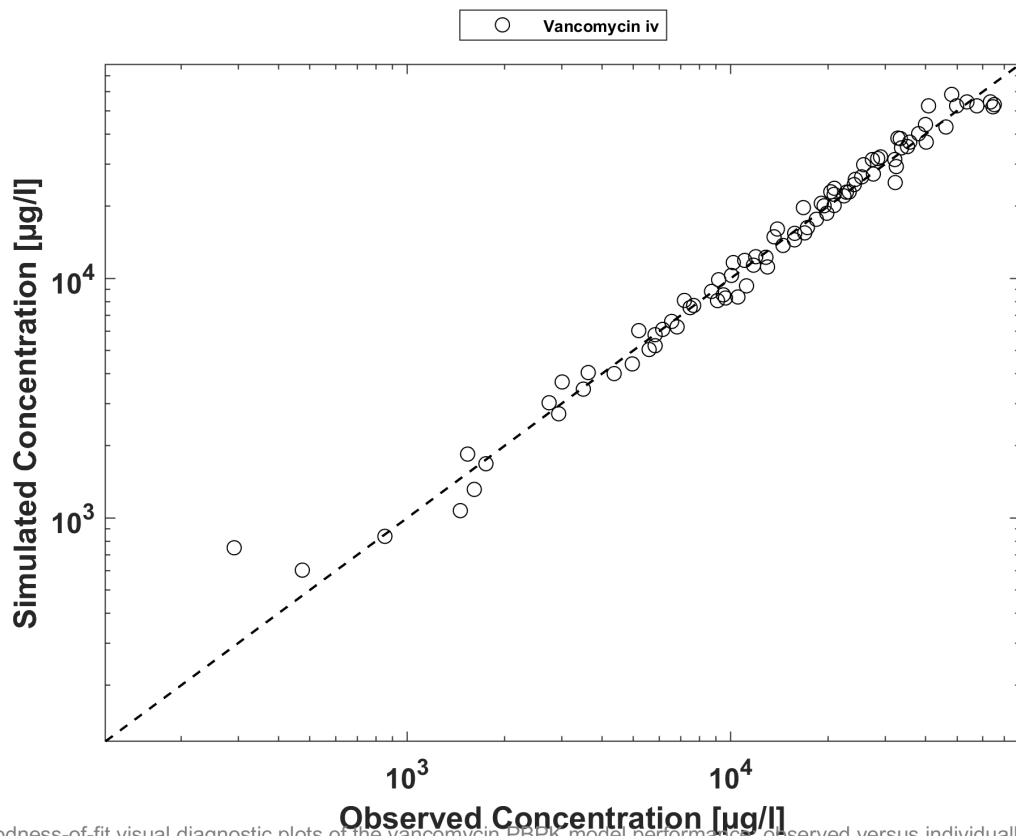
Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.67	
Lipophilicity (experiment)	2.45 Log Units	
Plasma clearance	0.11 ml/min/kg	
Specific clearance	0 1/min	Parameter Identification-Parameter Identification-Value updated from 'Parameter Identification 3' on 2018-07-13 11:16

Chapter 3.4: Vancomycin Diagnostics Plots

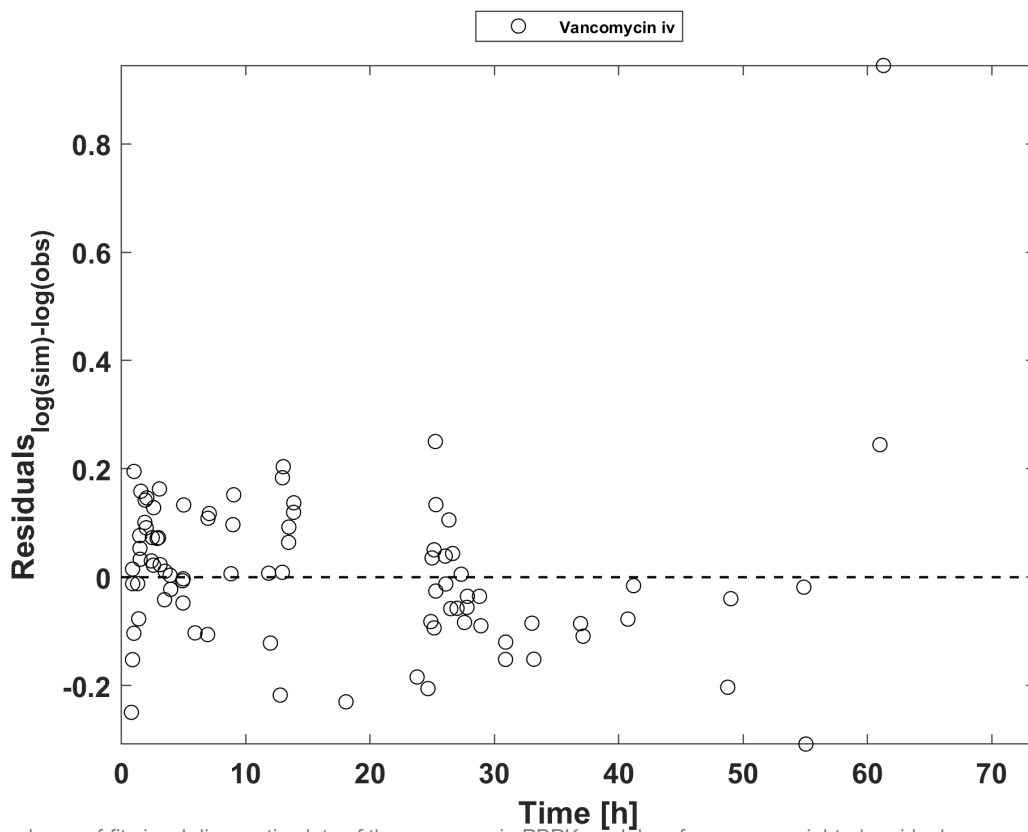
Vancomycin adult PBPK model performance

Below you find the input goodness-of-fit visual diagnostic plots for vancomycin PBPK model performance (observed versus individually simulated plasma concentration and weighted residuals versus time) of all adult data.



Goodness-of-fit visual diagnostic plots of the vancomycin PBPK model performance: observed versus individually predicted plasma concentration versus time of all adult data.

GMFE = 1.108921



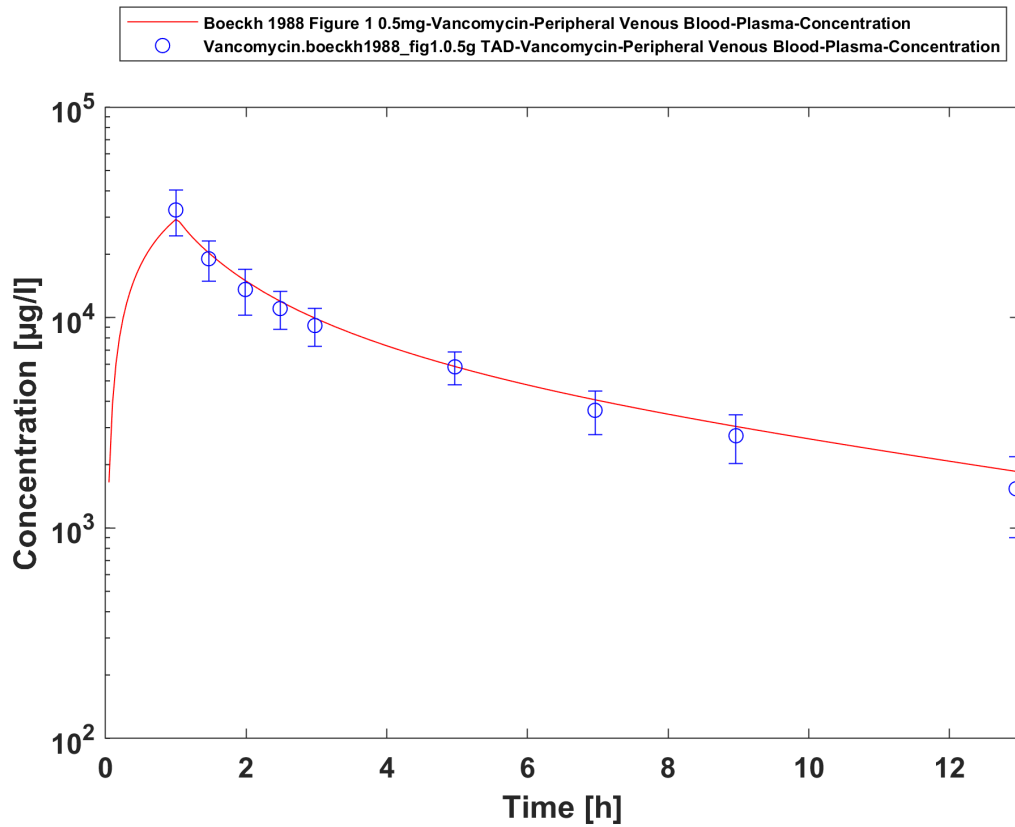
Goodness-of-fit visual diagnostic plots of the vancomycin PBPK model performance: weighted residuals versus time of all adult data.

GMFE = 1.108921

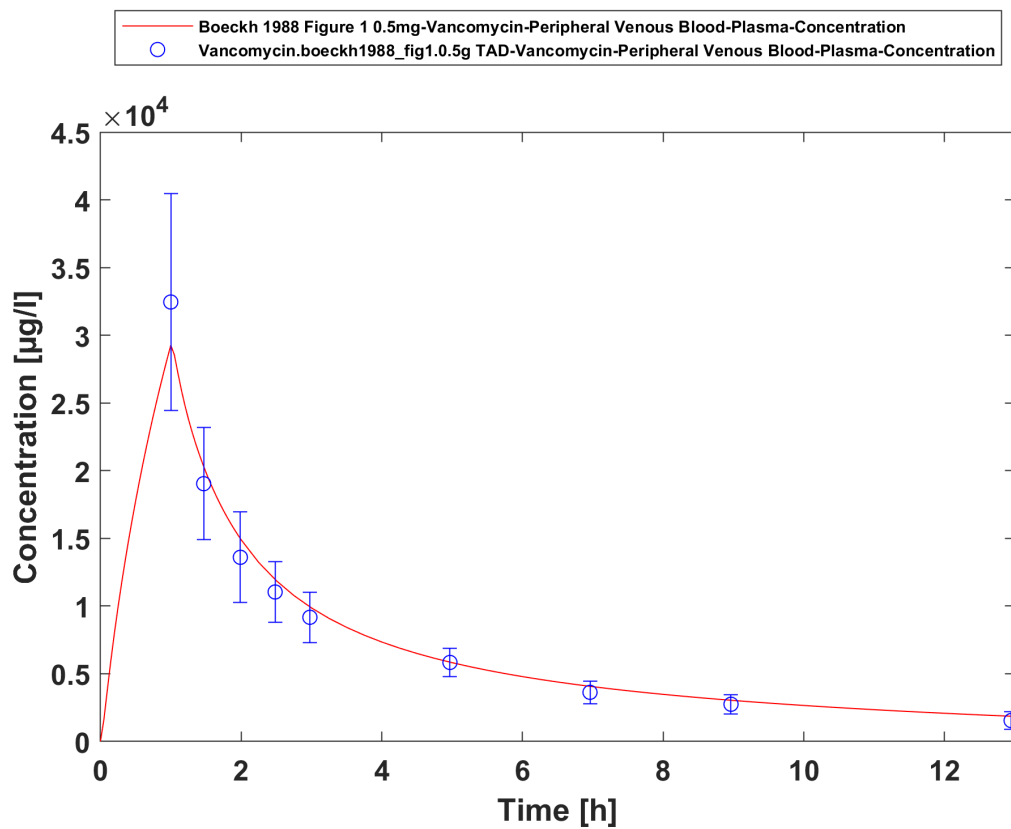
Chapter 3.5: Vancomycin Concentration-Time profiles in Adults

Concentration-Time Profiles

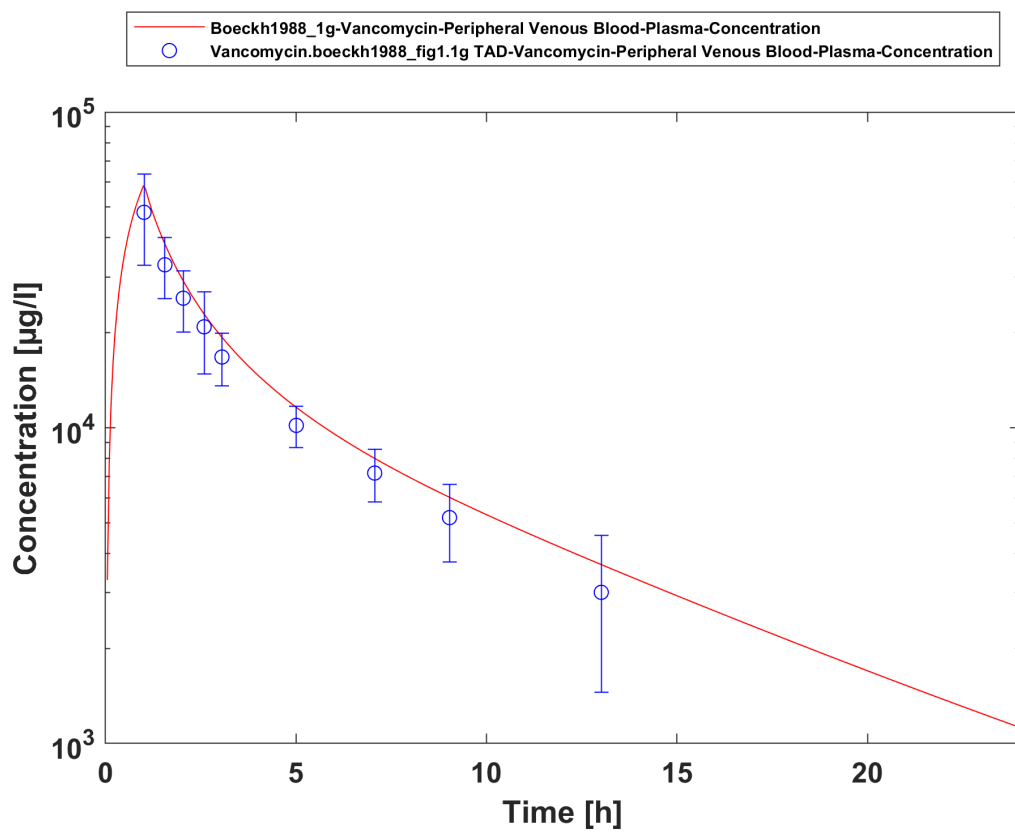
Simulated versus observed plasma concentration-time profiles of all data are listed below.



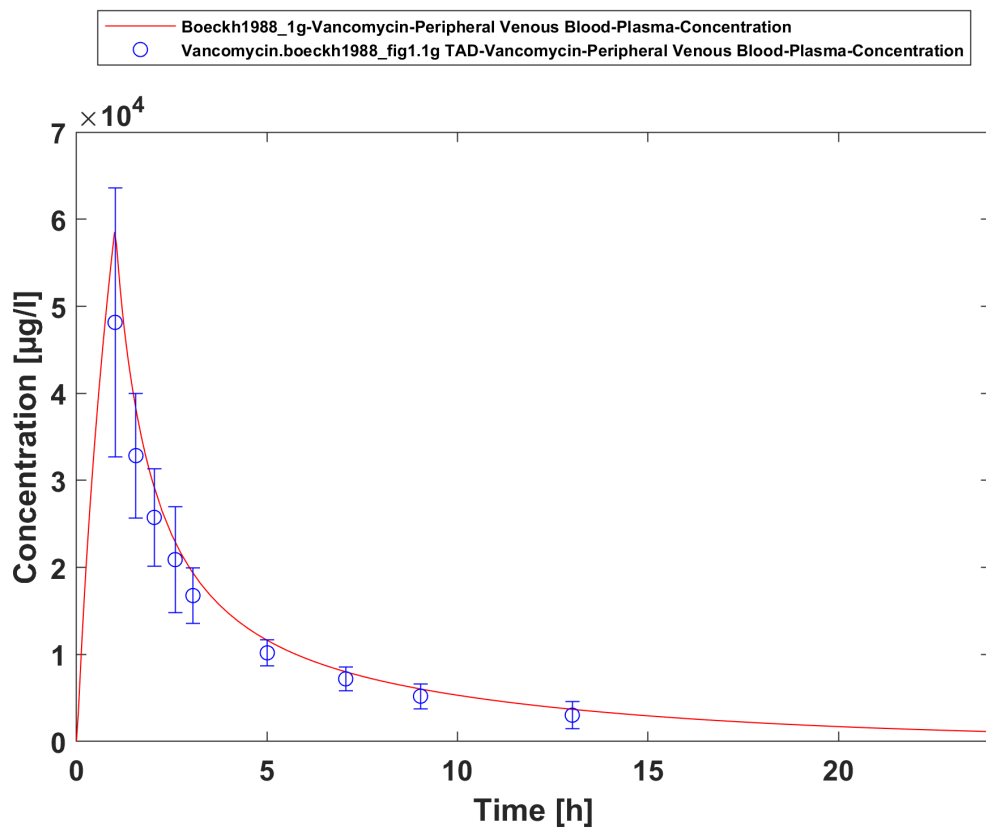
Time Profile Analysis



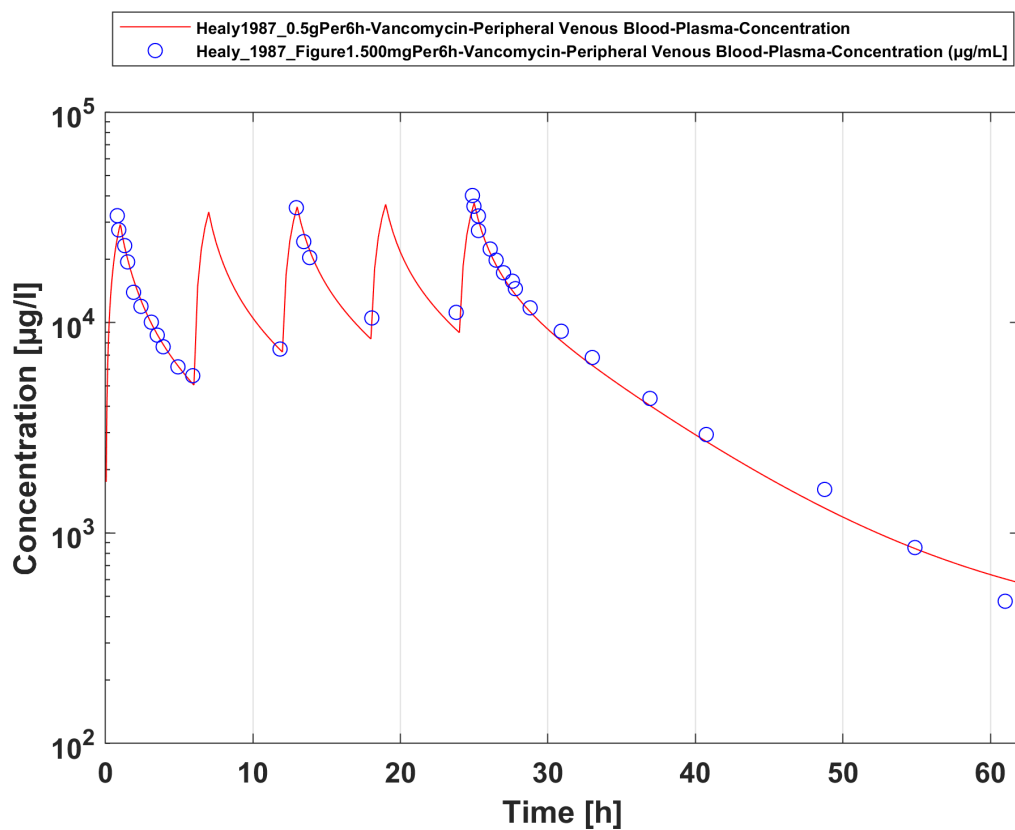
Time Profile Analysis 1



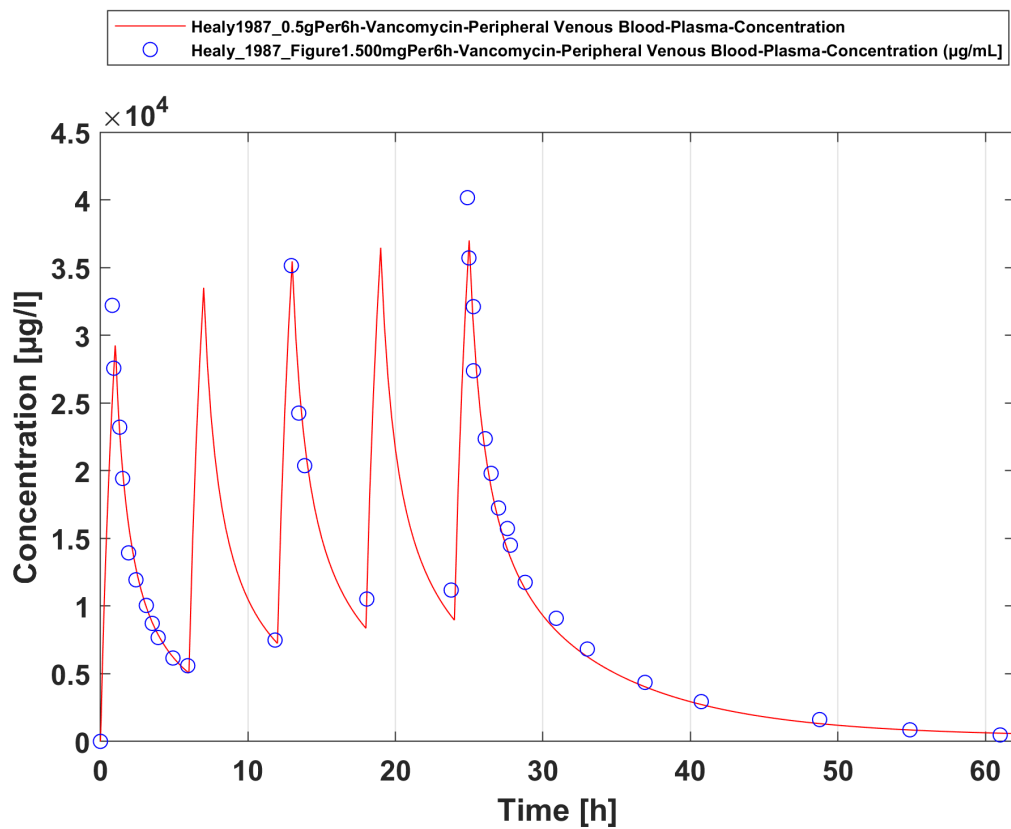
Time Profile Analysis



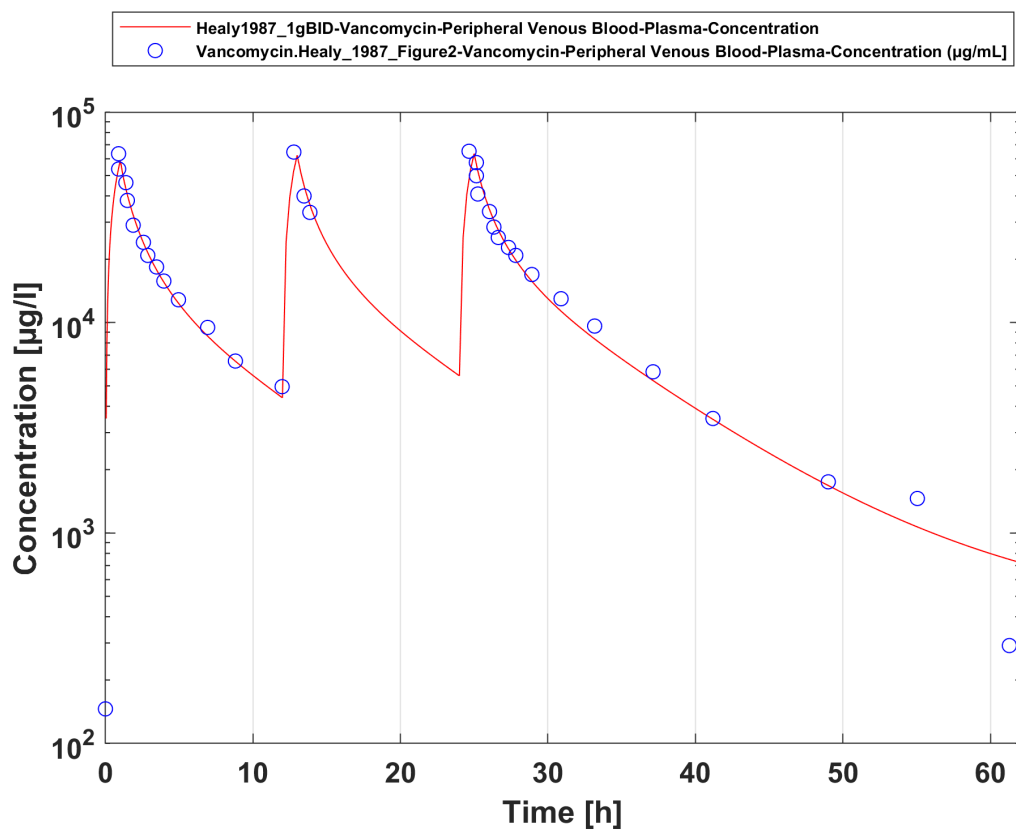
Time Profile Analysis 1



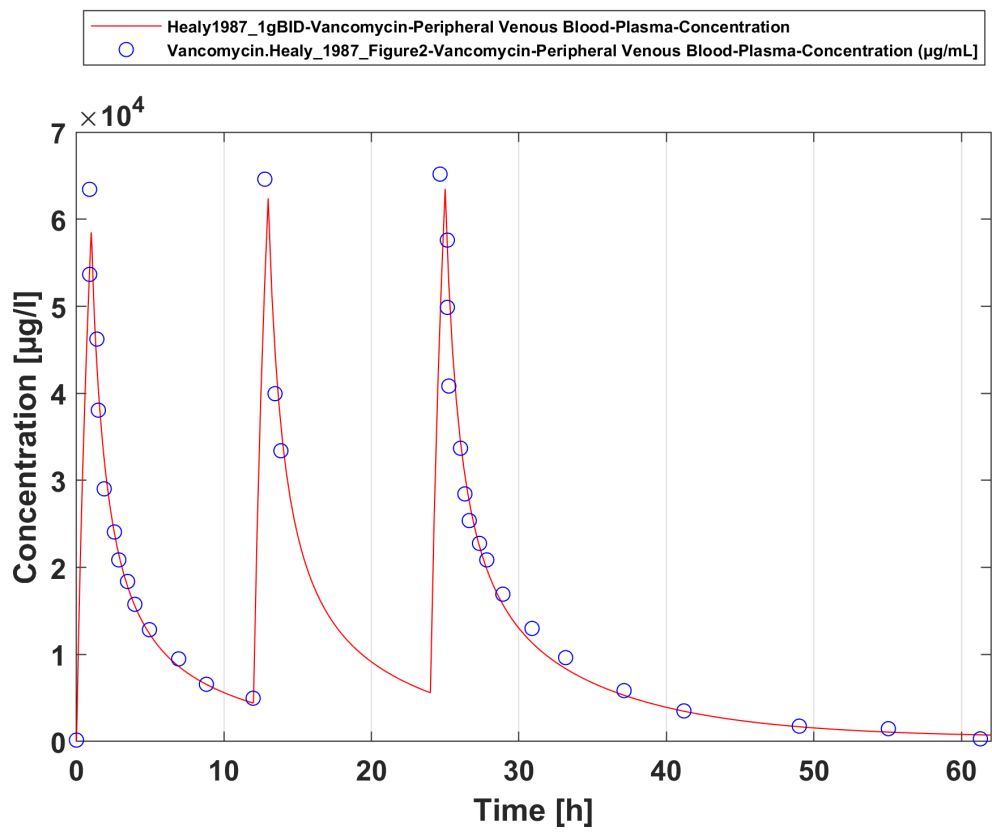
Time Profile Analysis



Time Profile Analysis 1



Time Profile Analysis



Time Profile Analysis 1