



Release 2.40



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1 INTRODUCTION

1.1 Purpose

This document lists the changes and fixes in release 2.40 of Edsim++ and MwPharm++. A complete list of fixed issues is given in chapter 7 (overview of issues). The most important changes are discussed in more detail in this document. Supplementary documents are identified in paragraph 2.6.

1.2 Scope

This document is intended for all users of Edsim++ and MwPharm++.

1.3 Summary of Edsim++ + changes

The most important changes in Edsim++ are listed below.

- ☑ Added BatchFit command-line utility for batch fitting multiple patients.
- ☑ Added BatchSim command line utility for performing Monte Carlo simulations.
- ☑ Improved patient merge (Excel import) functionality supporting date and time strings.
- ☑ Improved TCCRT object
- ☑ Extended TPeripheralEx object.

1.4 Summary of MwPharm++ changes

The most important changes in MwPharm++ are listed below.

- ☑ Added new population models.
- ☑ Added new renal function calculation methods for adults, children and neonates.
- ☑ Better support for application virtualization (multi-user mode).
- ☑ Improved application stability (avoiding red-cross issue).
- ☑ Added option to show classic simulation view.
- ☑ Population curves and 95%-confidence intervals can now also be tracked with the cursor.
- ☑ Time variant body volume and clearance can now be visualized.
- ☑ Added feedback with respect to the quality of the fit (bias and precision).
- ☑ Better handling of continuous renal replacement therapy (CRRT).
- ☑ Added documentation about AUC and half-life calculation.

2 POPULATION MODELS

2.1 New Models

New population models (6x) for several drugs (3x) were added as shown in the table below.

Drug	Model	Roa	Pop.	Author	PMID
Linezolid	linezolid_Tietjen_2021	IV, PO	A	Tietjen (10)	#34622478
Teicoplanin	Teicoplanin-Byrne-2017	IV	A	Byrne (2)	#28267636
Vancomycin	vancomycin_NEO_Aigrain_2019	IV	N	Aigrain (6)	#31049551
	vancomycin_NEO_Aigrain_2019_TDM				
	vancomycin_NEO_Dao_2020	IV	N	Dao (3)	#31108184
	vancomycin_NEO_Dao_2020_TDM				
	vanco_adult_KOREA_Bae_2019_S	IV	A	Bae (1)	#31075931
	vanco_adult_KOREA_Bae_2019_T				
	vanco_adult_JAPAN_Yasuhara_1998	IV	A	Yasuhara (11)	#9558127

2.2 TDM Model Variants

The residual error in some models is quite large. E.g., the vancomycin plasma concentration in the model from Dao (3) is 28%. With such a high error the effect of observed plasma concentrations is relatively limited. Therefore, we created special TDM variants of models with a residual error higher than 25%, in which the assay error was set to the maximum allowed by the EMA/FDA (15%). However, we recommend always to use the assay error of the drug as determined by your own laboratory.

2.3 Populations

All models are associated with an adult (A) and/or neonate population (N).

2.4 Laboratory and Covariates

Appendix C (chapter 8) gives a complete overview of laboratory and covariate values associated with all new models.

2.5 Database Update

All new population models can be found in the installation folder of Edsim++ and/or MwPharm++ at the following location.

Location: \Models\EDX\MwPharm\Additional

When you launch MwPharm++ for the first time after installing the new release, the new models will be automatically added to the existing user database. The update is identified as PATCH013.

2.6 Supplementary Documents

The new population models have been described in detail in the following documents.

- ☐ Linezolid.pdf
- ☐ Teicoplanin.pdf
- ☐ Vancomycin-NEO.pdf
- ☐ Vancomycin-KOREA.pdf
- ☐ Vancomycin-JAPAN.pdf

More detailed information about specific subjects can be found in the following documents:

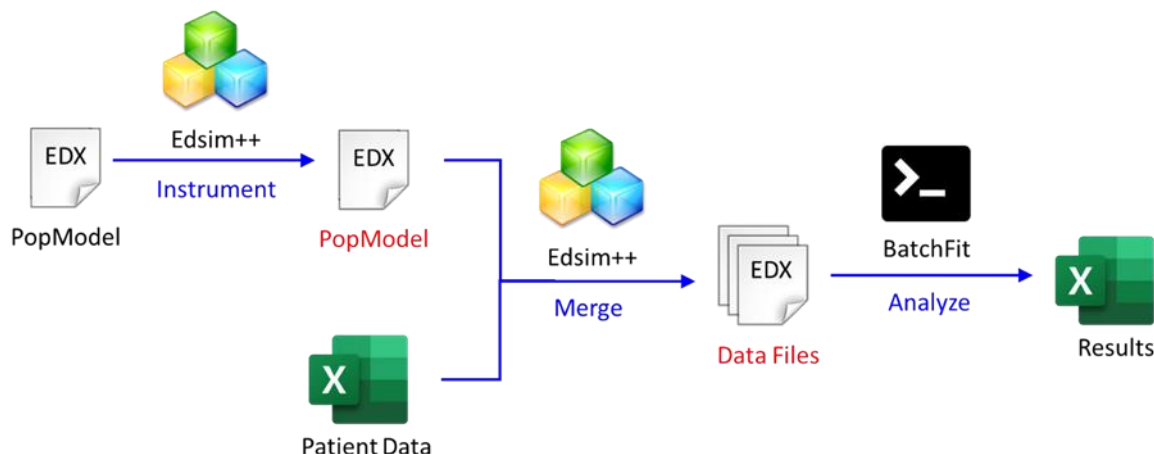
- ☐ Half-calculation (Edsim++Half-Life.pdf)
- ☐ Poly-exponential equations (Edsim++Half-Life-.xlsx)
- ☐ BatchFit manual (BatchFit.pdf)
- ☐ BatchSim manual (BatchSim.pdf)

3 EDSIM++ CHANGES

3.1 BatchFit Command Line Tool

The BatchFit command line tool allows for the analysis of a large number of patient cases in an uniform way. In the past the same could also be achieved by KinPop++. However, the reports generated by KinPop++ were very specific for population analysis, whereas the report generation by BatchFit can be fully customized by instrumenting the population model.

The basic workflow for the tool is shown in the figure below.



The BatchFit folder in the Edsim++ installation directory contains a sample data set.

```
C:\WINDOWS\system32\cmd. x + v
C:\Mediware\Edsim++\BatchFit>batchfit -p data
```

```
C:\WINDOWS\system32\cmd. x + v
Progress 100%, Sims: 7 / 12, Tasks: 11, M-Threads 17, P-Threads 28, H-Threads 32 00:00:00 / 00:00:01
```

```
C:\WINDOWS\system32\cmd. x + v
Launching Excel ...
Ready.
Reporting 100%, 00:00:00 / 00:00:03
C:\Mediware\Edsim++\BatchFit>
```

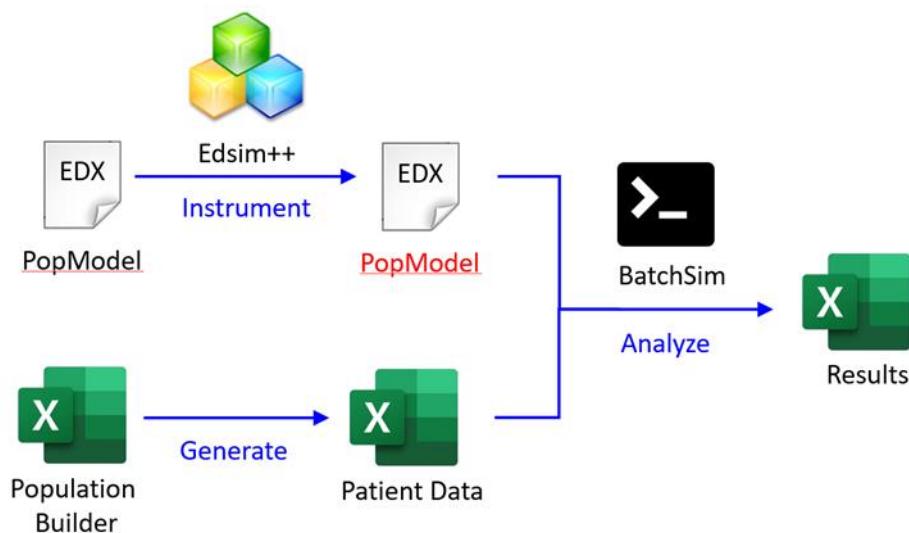
An Excel report is automatically generated after the procedure has been completed.

The BatchFit folder in the Edsim++ installation directory also contains the BatchFit manual (BatchFit.pdf) with detailed operating instructions.

3.2 BatchSim Command Line Tool

The BatchSim tool was designed for simulating a large number of virtual patients while generating detailed user configurable reports. This tool replaces the well known MicLab tool which had many limitations.

The basic workflow for the tool is shown in the figure below.



The population model defines the distribution of the PK population parameters. The Population Builder spreadsheet defines the demographics of the population. The BatchSim folder in the Edsim++ installation directory contains a sample data set.

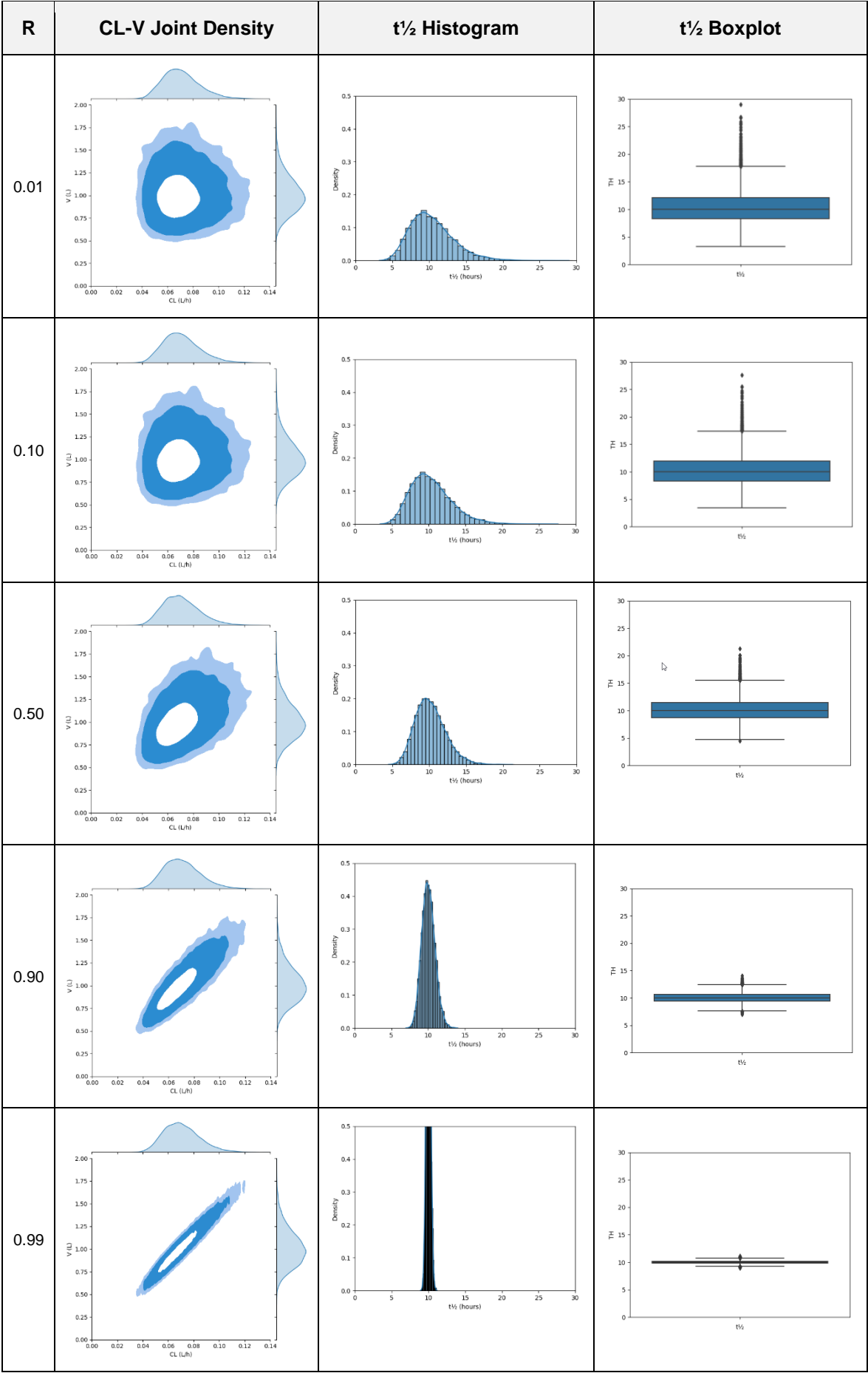
```
C:\WINDOWS\system32\cmd. x + v
C:\Mediware\Edsim++\BatchSim>batchsim -p data\meropenem.edx -x data\popgen.xlsm
```

```
C:\WINDOWS\system32\cmd. x + v
Initialization 47%, 00:00:04 / 00:00:08
```

```
C:\WINDOWS\system32\cmd. x + v
Ready.
Progress 100%, Sims: 1000 / 1000, Tasks: 0, M-Threads 32, P-Threads 43, H-Threads 32 00:00:06 / 00:00:09
C:\Mediware\Edsim++\BatchSim>
```

An Excel report is automatically generated after the procedure has been completed.

The BatchSim folder in the Edsim++ installation directory also contains the BatchSim manual (BatchSim.pdf) with detailed operating instructions. There are also subfolders containing data post processing scripts for Python (PY), Rstat (R) and Excel (XL). An example of the output of the python script is shown on the next page.



3.3 Improved Patient Merge (Excel import)

Dates and times in the MwPharm++ data spreadsheet had to be entered as Excel dates (date serial) and times (fraction of a day) as shown below.

Date Format

	A	B	C	D	E	F	G	H
1	ID	Date	Time	Roa	Value	Unit	No	Tint
2					mg			h
3	N001	30-06-1993	18:00	iv	240	mg		1
4	N001	30-06-1993	19:06					
5	N001	01-07-1993	08:16					
6	N001	01-07-1993	18:00	iv	240	mg		4

Format Cells

Number Alignment Font Border Fill Protection

Category: General Number Currency Accounting **Date** Time Percentage Fraction Scientific Text Special Custom

Type: Sample
30-06-1993
*14-03-2012
*woensdag 14 maart 2012
2012-03-14
14-3
14-03-12
14-03-12
14-mrt

Locale (location): Dutch (Netherlands)

OK Cancel

Date formats display date and time serial numbers as date values. Date formats that begin with an asterisk (*) respond to changes in regional date and time settings that are specified for the operating system. Formats without an asterisk are not affected by operating system settings.

Time Format

	A	B	C	D	E	F	G	H
1	ID	Date	Time	Roa	Value	Unit	No	Tint
2					mg			h
3	N001	30-06-1993	18:00	iv	240	mg		1
4	N001	30-06-1993	19:06					
5	N001	01-07-1993	08:16					
6	N001	01-07-1993	18:00	iv	240	mg		4

Format Cells

Number Alignment Font Border Fill Protection

Category: General Number Currency Accounting **Date** **Time** Percentage Fraction Scientific Text Special Custom

Type: Sample
18:00
uu:mm
dd-mm-jiji
dd-mm-jj
dd-mm
mm-mj
u:mm AM/PM
u:mmss AM/PM
uu:mm
uu:mm:ss
dd-mm-jiji uu:mm
mm:ss
mm:ss.0
@

Delete

Type the number format code, using one of the existing codes as a starting point.

OK Cancel

The latest version of Edsim++ is more forgiving and now also accepts date and times formatted as strings.

3.4 Improved TCCRT Object (Continuous Renal Replacement Therapy).

The TCRRT object for modelling continuous renal replacement therapy (9), which was introduced in release 2.30, has been improved. The most important change is the parametrization of the object.

CRRT on/off is controlled by the blood flow specified in an event entry. The other 4 variables influencing CRRT are:

- ☒ Hct : Haematocrit
- ☒ Quf : Ultrafiltrate flow
- ☒ Qrep : Replacement flow
- ☒ Qd : Dialysis flow

The plasma flow is calculated as follows.

$$Q_p = Q_b \cdot (1 - Hct)$$

The total effluent flow is given by the following equation.

$$Q_{ef} = Q_{uf} + Q_{rep} + Q_d$$

In addition to the TCRRT object, we also introduced the XCRRT object which shares the above mentioned variables with a TCRRT object in the model. This allows for easy selection of different CRRT filters in the model.

3.5 Denormalized Time-Variant Volume and Clearance

Population parameters in Edsim++ can be modulated by covariates according to the following equation.

$$P = P_{pop} \cdot F_{size} \cdot F_{org} \cdot F_{mat} \cdot F_{birth} \cdot F_{vent} \cdot F_{age} \cdot F_{sex} \cdot F_{pgx} \cdot F_{cyc}$$

Here P_{pop} is the normalized population parameter, which is time-invariant (constant), and P represents the denormalized parameter which takes into account the effect of one or more covariates. P is time-variant because the covariate values may change over time.

Unfortunately P can not be visualized because it is a parameter. In order to overcome this limitation two new variables were added some objects in the PKPD-library.

Variable	Description	Objects
Vt	Volume	TCompartment (Vt = V), TBody
CLt	Clearance	TElimination (CLt = CL), TBody

CLt and Vt in TBody represent the total body time-variant denormalized clearance and volume.

3.6 Extended TPeripheralEx object.

The Vancomycin model by Yasuhara et al. (11) uses a very uncommon model parametrization of the 2-compartment vancomycin model which is aimed at a Japanese population.

The default parametrizations of the standard peripheral compartment (TPeripheral) are using k_{12} , k_{21} (rate mode) or Q , V_2 (clearance mode) parameters. We already introduced an alternative parametrization with the TPeripheralEx object which uses Q , FV_1 , V_{ss} (clearance mode) parameters. Here FV_1 is the fraction of V_{ss} for obtaining V_1 ($V_1 = FV_1 \cdot V_{ss}$) while the mode was fixed to clearance (Cefepime Shoji-2016).

The Yasuhara model required yet another parameterization using k_{12} , k_{21} and V_{ss} as the primary parameters. We now allow the mode in the TPeripheralEx object to be set to rate or clearance (not half-life). In clearance mode the Shoji parametrization is used and in rate mode the Yasuhara parametrization. The default mode is set to clearance in order to preserve exiting models.

The following symbols are used.

Symbol	Unit	Description
V_1	L	Volume of central compartment
V_2	L	Volume of peripheral compartment
V_{ss}	L	Volume at steady state ($V_{ss} = V_1 + V_2$)
Q	L/h	Distribution clearance
k_{12}	1/h	Distribution rate constant central to peripheral
k_{21}	1/h	Distribution rate constant peripheral to central
FV_1	-	Fraction of V_{ss} for obtaining V_1 ($V_1 = FV_1 \cdot V_{ss}$)

The implemented equations are shown in the table below.

Object	Mode	Parameters	Equations
TPeripheral	Clearance	Q, V ₂	$V_{ss} = V_1 + V_2$
			$k_{12} = \frac{Q}{V_1}$
			$k_{21} = \frac{Q}{V_2}$
	Rate	k ₁₂ , k ₂₁	$Q = k_{12} \cdot V_1$
			$V_2 = \frac{k_{12}}{k_{21}} \cdot V_1$
			$V_{ss} = V_1 + V_2$
TPeripheralEx	Clearance	Q, V _{ss} , FV ₁	$V_1 = FV_1 \cdot V_{ss}$
	Shoji-2016		$V_2 = V_{ss} - V_1$
	Cefepime		$k_{12} = \frac{Q}{V_1}$
			$k_{21} = \frac{Q}{V_2}$
	Rate	V _{ss} , k ₁₂ , k ₂₁	$V_1 = \frac{V_{ss}}{\left(1 + \frac{k_{12}}{k_{21}}\right)}$
	Yasuhara-1998		$V_2 = V_{ss} - V_1$
	Vancomycin		$Q = k_{12} \cdot V_1$

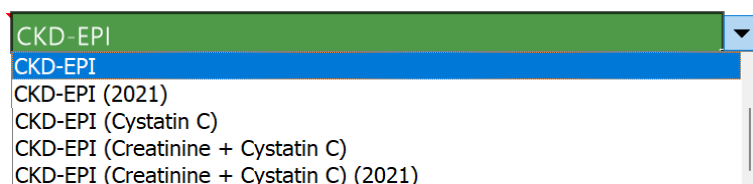
4 MWPHARM++ CHANGES

4.1 Status Screen

4.1.1 New eGFR Equations

4.1.1.1 Adults

In 2009 Levey et al. (7) published the first CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation for calculating eGFR from serum creatinine levels. In 2012 this equation was extended with cystatin-C by Inker et al. (4). Both equations were already implemented in MwPharm++. In 2021 a new version of the equation was published by Inker et al. (5) in which the race factor was removed. This latest version of MwPharm++ now also contains this race-free version of the CKD-EPI equations.



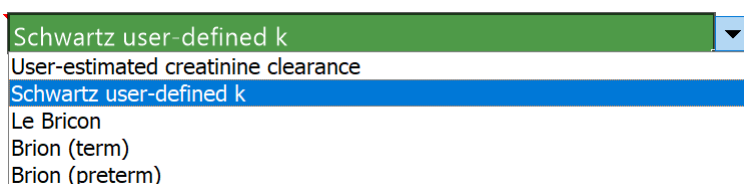
4.1.1.2 Children

This latest version of MwPharm++ adds a number of new eGFR equations for children (8).

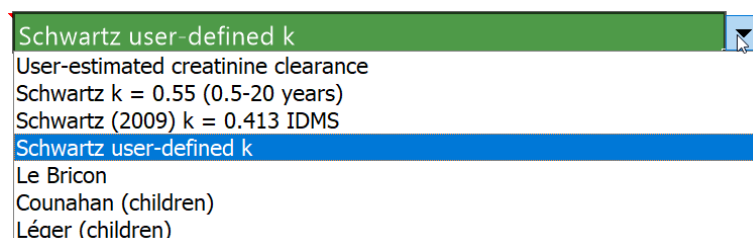
- ☒ Brion function for preterm
- ☒ Brion function for term infants
- ☒ Counahan-Barratt for pediatric and neonatal patients in age 0.167–14 years
- ☒ Léger Formula for ages 0.8–18 years

The list of selectable equations is determined by the age of the child.

For a new born:



For a 1-year old:



4.1.2 Age Validation of eGFR Equations

The available eGFR equations are now stricter validated for age as shown in the table on the next page.

The table below lists the age range (min-max, years) in which an eGFR equation can be used together with the number of required creatinine and cystatin-C inputs. The user estimated GFR can be used for all ages!

ID	Age (y)		Inputs		Description
	Min	Max	Ccr	Ccy	
ERFunc.COCKCROFT	18	999	1	0	Cockcroft & Gault
ERFunc.JELLIFFE1	18	999	1	0	Jelliffe I
ERFunc.JELLIFFE21	18	999	1	0	Jelliffe II - 1 serum creatinine level
ERFunc.JELLIFFE22	18	999	2	0	Jelliffe II - 2 serum creatinine levels
ERFunc.MDRD	18	999	1	0	MDRD
ERFunc.MDRD_IDMS	18	999	1	0	MDRD revised IDMS (175)
ERFunc.CKD_EPI	18	999	1	0	CKD-EPI
ERFunc.CKD_EPI_CR_2021	18	999	1	0	CKD-EPI (2021)
ERFunc.LM_R	18	999	1	0	Lund-Malmö Revised
ERFunc.LM_LBM_R	18	999	1	0	Lund-Malmö Revised (LBM variant)
ERFunc.USER	0	999	0	0	User-estimated creatinine clearance
ERFunc.SCHWARTZ	0.5	20	1	0	Schwartz k = 0.55 (0.5-20 years)
ERFunc.SCHWARTZ_IDMS	0.5	20	1	0	Schwartz (2009) (k = 0.413 IDMS)
ERFunc.SCHWARTZ_USER	0	20	1	0	Schwartz user-defined k
ERFunc.CAPA	18	999	0	1	CAPA (Cystatin C)
ERFunc.CKD_EPI_CYS	18	999	0	1	CKD-EPI (Cystatin C)
ERFunc.CKD_EPI_CR_CYS	18	999	1	1	CKD-EPI (Creatinine + Cystatin C)
ERFunc.CKD_EPI_CR_CYS_2021	18	999	1	1	CKD-EPI Creatinine + Cystatin C) (2021)
ERFunc.BRICON	0	20	0	1	Le Bricon
ERFunc.BRION	0	0.1	1	0	Brion (term)
ERFunc.BRION_PRETERM	0	0.1	1	0	Brion (preterm)
ERFunc.COUNAHAN	0.167	14	1	0	Counahan (children)
ERFunc.LEGER	0.8	18	1	0	Léger (children)

4.1.3 Preferred eGFR Equation

The applied eGFR equation is in principle determined by the population model. In MwPharm++ 2.30 we introduced the option to overrule the setting in the population model by checking the checkbox in front of the renal function method field.

Renal Function ☒ CKD-EPI

In this release two changes were made with respect to the preferred eGFR equation.

1. Only super users and admins can set the preferred renal function method.
2. The preferred eGFR can now be set for 5 different age categories (see table below).

Category	Age (y)	
	Min	Max
Adult	20	999
Adolescent	18	20
Child	0.5	18
Infant	1/12	0.5
Neonate	0	1/12

Use the following procedure for setting the preferred eGFR equation for a particular age category.

1. Login as super user or admin
2. Enter a birthdate yielding a patient with an age in a particular category
3. Uncheck the checkbox if it is checked
4. Select the preferred eGFR equation
5. Check the checkbox (again)
6. Repeat for each category

4.2 Simulation Screen

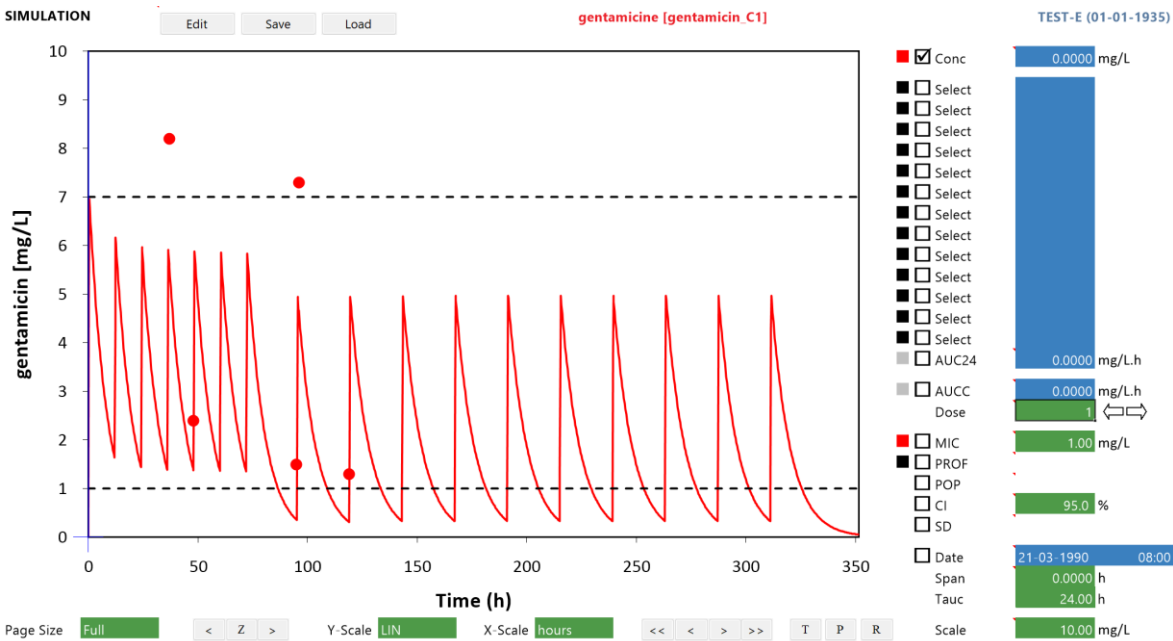
4.2.1 Classic Simulation View

In MwPharm++ 2.20 the simulation screen was redesigned in order to accommodate non-standard covariates and laboratory values introduced with the new models. In addition, with older models the simulation screen is less cluttered which makes it easier to keep an overview. However, some users would like to be able to restore the old screen layout (classic view). This can be accomplished by clicking the [Load] button while pressing the SHIFT-key as shown in the popup navigation help window.

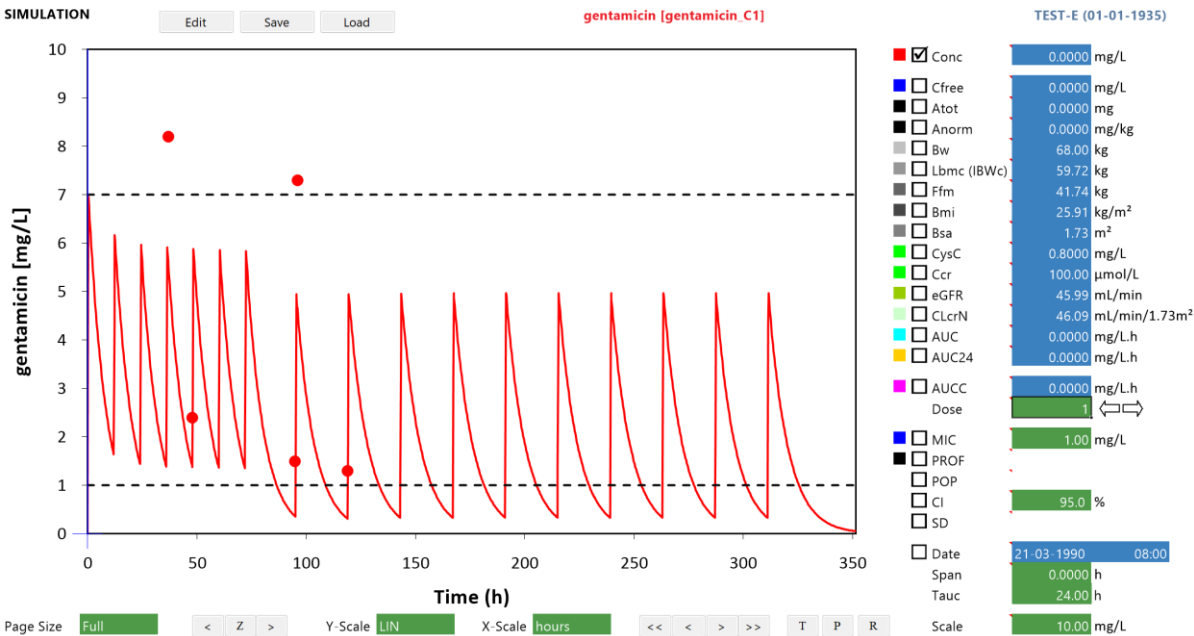
Shift + [Load] = Classic view

For older models the classic view is now applied by default (including colour scheme).

Default view of patient TEST-E:



Classic view of patient TEST-E:

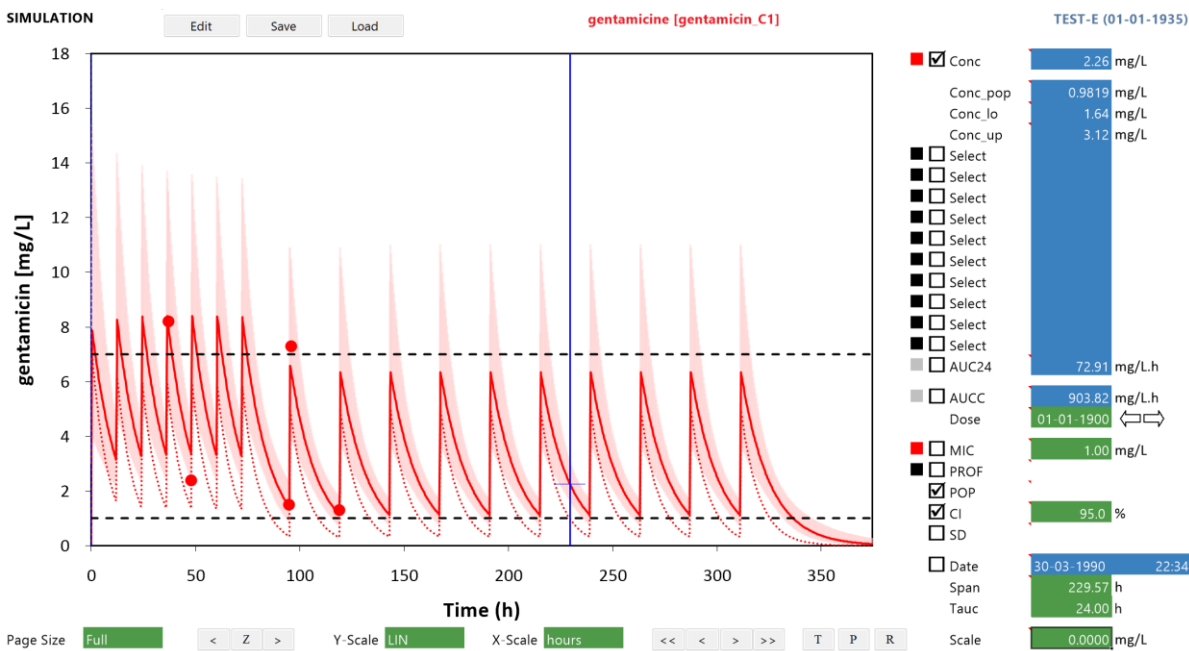


4.2.2 Cursor Read-Out of Population Curve and 95%-Confidence Intervals.

When the population curve and/or 95%-confidence intervals are selected for display, the associated cursor values can also be displayed.

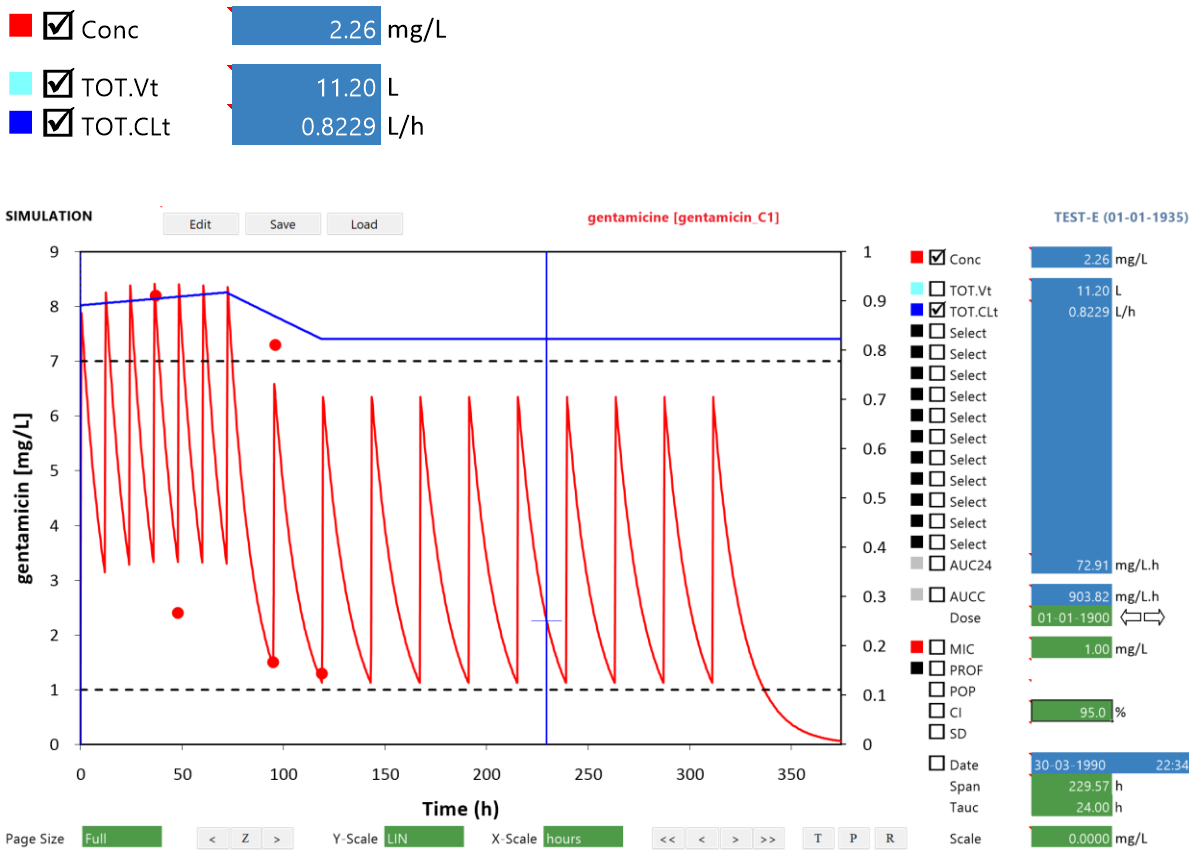


This is demonstrated in the following simulation.



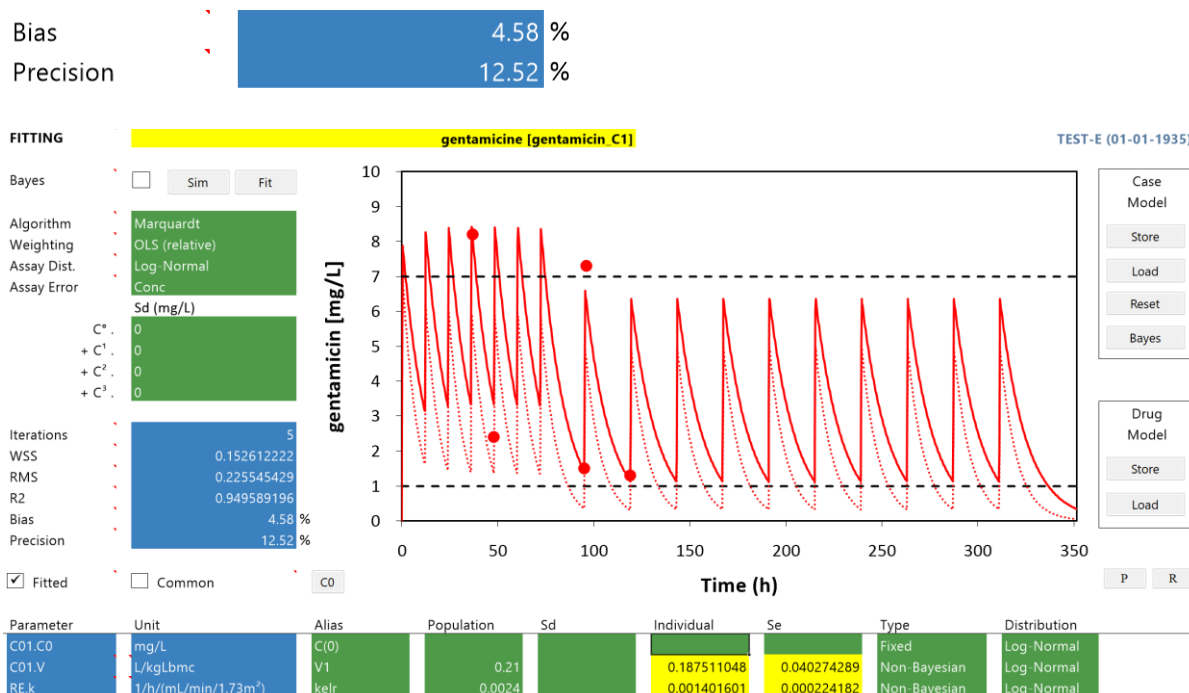
4.2.3 Display of Denormalized Time-Variant Volume and Clearance.

It is now also possible to visualize the time-dependent effect of covariates on total body clearance and volume.



4.3 Fitting Screen

The fitting screen now also quantifies the quality of the fit by reporting the bias and precision as shown in the fit below.



These quantities are defined as follows:

Bias : Median prediction error (MPE)
Precision : Median absolute prediction error (MAPE)

It may be advisable to discard part of the medication history if these values are above 20%.

4.4 History Screen

The TCRRT object for modelling continuous renal replacement therapy has been reparametrized. This is reflected in the columns of the medication history screen.

Date	Time	Roa	Value	Unit	Hct	Quf	Qrep	Qd
RST					÷	mL/h	mL/h	mL/h
31-10-2023	08:00	st150	200	mL/min	0.3	50	500	500

The plasma flow is calculated as follows.

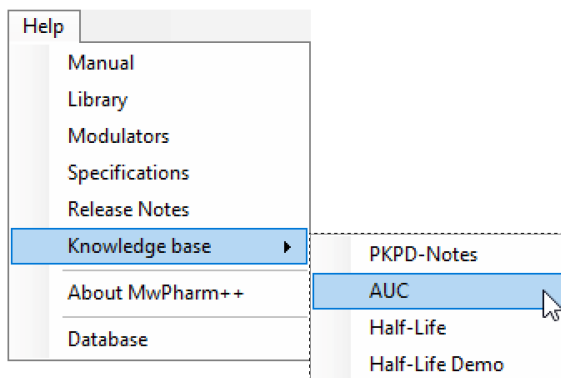
$$Q_p = Q_b \cdot (1 - Hct)$$

The total effluent flow is given by the following equation.

$$Q_{ef} = Q_{uf} + Q_{rep} + Q_d$$

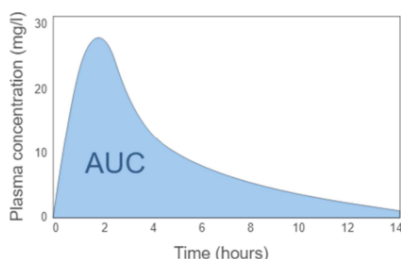
4.5 Documentation

Documentation regarding AUC and half-life calculation was added to the MwPharm++ menu.



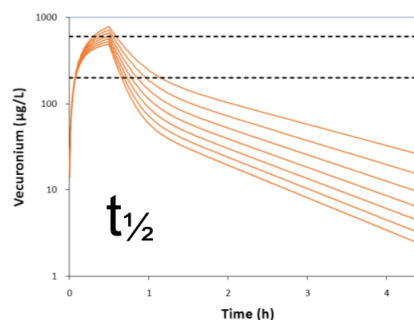
Edsim++ / MwPharm++ Area Under the Curve

AUC Calculations



Edsim++ / MwPharm++

Half-Life



4.6 Multi-User Mode

MwPharm++ requires write access to the application folder (C:\Mediware\MwPharm++) in order to function properly. However, this can be avoided by starting MwPharm++ in multi-user mode by adding the MULTI command-line parameter, after which the following storage locations will be used.

Database : %ProgramData%\Mediware\MwPharm++
Settings : %AppData%\Mediware\MwPharm++
Docs : %UserProfile%\Documents\Mediware\MwPharm++

This is especially helpful in case of application virtualization (Citrix). The LOCAL and ROAMING command-line parameters have been deprecated.

4.7 Improved Stability

Some users have reported stability problems, especially on surface laptops. Problems were exposed by a red cross in the simulation screen. We made some fundamental changes regarding how some user interface components are used. We could not reproduce the problem in the current release using extensive automated stress tests.

5 REFERENCES

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6 APPENDIX-A: QA-Metrics

6.1 Introduction

Before each release, the PKPD modeling engine of Edsim++ and MwPharm++ is subjected to a regression test in which all demo models accumulated so far are simulated, and if possible, fitted. The results are compared with a reference data set and any deviations are reported.

6.2 Metrics

Release 2.40 is associated with the following test metrics.

Models simulated	:	926	
Models fitted	:	149	
Errors	:	0	
Total duration	:	03:25	(i9-13900K)

7 APPENDIX B: OVERVIEW OF ISSUES

ID	APP	Description
EDSIMM-06	MwPharm++	Drug model for linezolid
EDSIMM-13	MwPharm++	Drug model for teicoplanin
EDSIMM-61	MwPharm++	Vancomycin-NEO model (neonates)
EDSIMM-70	MwPharm++	Vancomycin-KOREA model
EDSIMM-81	MwPharm++	Vancomycin-JAPAN model
EDSIMP-189	MwPharm++	Extension of Renal Function for Pediatric and Neonatal Use
EDSIMP-190	MwPharm++	Automatic selection of the function for neonate patients
EDSIMP-203	DatMan	DatMan Improvements
EDSIMP-210	Edsim++	In addition to XLevel also support XOnOff and XBinary in status screen
EDSIMP-211	LINQpad	Create LINQpad library for validating Edsim++ models
EDSIMP-213	MwPharm++	C0-Wizard improvements
EDSIMP-214	MwPharm++	Implementation of new RF CKD-EPI (2021)
EDSIMP-215	DatMan	New icon for DatMan
EDSIMP-216	Edsim++	Add option to only sample a specific dose event (TSample, TSampleFast)
EDSIMP-217	Edsim++	TSample gets confused in case of an input with a lagtime ($t_0 > 0$)

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EDSIMP-218	Edsim++	EDSIMP-209 is a problem for some models in existing databases
EDSIMP-220	Edsim++	Tmax\Tmin variables in TSample(Fast) does not take lag-time t0 into account
EDSIMP-221	DatMan	DatMan must enforce Invariant Culture at startup
EDSIMP-222	Edsim++	Tobs in TSampleFast should include lag time
EDSIMP-223	MwPharm++	Loading dose note in History & Dosing setting
EDSIMP-226	Edsim++	Target NET48 in order to allow development on Win11
EDSIMP-229	Edsim++	TSample.Vobs does not work in case Tint is not set (0)
EDSIMP-230	Edsim++	TSample access Min/Max output trigger variable
EDSIMP-231	MwPharm++	List of SQL commands
EDSIMP-232	Edsim++	Completely redesign TSample
EDSIMP-233	Edsim++	TSample and TSampleFast must ignore non-input events such as dialysis
EDSIMP-234	MwPharm++	Tooltip for all parameters in status screen
EDSIMP-235	Edsim++	Tag variables that are only updated after one interval
EDSIMP-236	Edsim++	Synthetic internal observations in TSample must set exclude flag
EDSIMP-237	Edsim++	Relative time above level in TLevel(A) not working correctly
EDSIMP-238	Edsim++	The Fitter object must call ExpandObservations on the model
EDSIMP-239	Edsim++	Information message about the obsolete version
EDSIMP-240	MwPharm++	Workbook with detailed calculation of $t_{1/2-1}$, $t_{1/2-2}$, $t_{1/2-3}$

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EDSIMP-241	MwPharm++	Tooltips for Half-life symbols ($t_{1/2-1}$, $t_{1/2-2}$, $t_{1/2-3}$)
EDSIMP-244	KinPop++	KinPop++ fails with models without a patient object
EDSIMP-251	MwPharm++	Make MwPharm++ Multi-User and Citrix-friendly
EDSIMP-252	MwPharm++	Add button to setup "old" view settings in Simulation screen.
EDSIMP-253	MwPharm++	AUC24 cannot be restored
EDSIMP-254	MwPharm++	Improper dosing
EDSIMP-255	MwPharm++	Enable non-default multi-user mode with command-line argument (MULTI)
EDSIMP-256	MwPharm++	Add PDF document on AUC and Half-Life to MwPharm++ help menu
EDSIMP-257	MwPharm++	Update SpreadsheetGear component to latest version (8.0.64.102 → 8.1.26.102)
EDSIMP-259	MwPharm++	PGX field not displayed in status screen if more objects are linked to XObserved
EDSIMP-261	MwPharm++	Status screen should not rely on PK.Status for showing parameters as "n.d."
EDSIMP-262	MwPharm++	Status screen changes
EDSIMP-263	MwPharm++	Medication Date & Date of Change Tooltips
EDSIMP-264	Edsim++	Excel import routine should respect existing variable Label values
EDSIMP-266	MwPharm++	LBMc visibility change & Tooltips
EDSIMP-267	MwPharm++	Availability of POP value, CI interval values in Simulation screen
EDSIMP-268	Edsim++	Excel import should recognize date\times formatted as strings
EDSIMP-269	Edsim++	TPatient(Ex) should respect existing Ccy and CLcr labels

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EDSIMP-270	Edsim++	XInputController should respect existing F values in connected inputs
EDSIMP-271	Edsim++	Migrate RxODE model export to RxODE version 2
EDSIMP-272	Edsim++	Move model compatibility checks into shared library
EDSIMP-274	MwPharm++	Printed chart size influenced by Windows scale setting
EDSIMP-275	MwPharm++	Historical changes of the fitted parameters in Simulation
EDSIMP-276	Edsim++	Synchronize thread access to model (de)serialization methods using LOCK
EDSIMP-277	MwPharm++	Message that the model was not fitted well
EDSIMP-278	MwPharm++	Different dosage calculation depending on the sequence of steps
EDSIMP-279	BatchFit / BatchSim	Added BatchFit and BatchSim apps to repo
EDSIMP-280	Edsim++	Add spline transformation object (XSpline) based on 2 knots
EDSIMP-281	BatchSim	BatchSim: Allow setting of dose in population spreadsheet
EDSIMP-282	BatchSim	BatchSim: Patient ID must have more leading zeros
EDSIMP-283	BatchSim / BatchFit	BatchSim/BatchFit: Create and initialize models sequentially
EDSIMP-284	BatchSim	BatchSim: Add option for a dose calculation of each randomized patient
EDSIMP-285	BatchSim / BatchFit	BatchFitSim: Issue with simulation time units other than hours
EDSIMP-286	BatchFit	BatchFit: Abort and display error message for patients with zero doses
EDSIMP-287	Edsim++	TCRRT must take into account the total or free concentration model
EDSIMP-288	BatchSim	BatchSim: Activate -a option (ANOVA)

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EDSIMP-291	MwPharm++	Do not store open passwords in DB
EDSIMP-293	MwPharm++	DrugNames.xlsx is not actual
EDSIMP-295	MwPharm++	Extended error message when importing incompatible model in MwPharm++
EDSIMP-296	MwPharm++	Support automation in MwPharm++ for testing and demo purposes
EDSIMP-297	MwPharm++	MwPharm test script application
EDSIMP-298	MwPharm++	Serum creatinine value in Status page & User estimated RF
EDSIMP-299	MwPharm++	Automatic RF change & Information message
EDSIMP-301	MwPharm++	Cursor not working in simulation screen
EDSIMP-302	MwPharm++	Version 2.3.1.227 - Renal function update not working well
EDSIMP-304	BatchFit	Minor BatchFit fixes
EDSIMP-305	BatchSim	BatchSim Improvements
EDSIMP-306	Edsim++	Incorrect event sorting
EDSIMP-307	MwPharm++	Redesign TCRRT (different parametrization)
EDSIMP-313	Edsim++	An incorrect clearance value is calculated in TCRRT
EDSIMP-314	MwPharm++	Repeated adjacent CRRT periods don't work
EDSIMP-315	MwPharm++	Hide graph column in Status where age is not relevant
EDSIMP-316	MwPharm++	Change of the unit in History will not change TReference values
EDSIMP-317	BatchSim / BatchFit	Additional label for BatchFit and BatchSim

EDSIMP-318	Edsim++	Create new TPeripheral compartment variant for Yasuhara vancomycin model
EDSIMP-319	Edsim++	In XOnOff the level operators should be \leq and $>$, not $<$ and $>$
EDSIMP-320	MwPharm++	Add latest models to distro and database
EDSIMP-321	DatMan	DatMan stopped working because of missing NLog assembly
EDSIMP-322	MwPharm++	Only admin and super users may fix the renal function method
EDSIMP-323	MwPharm++	A protol regimen can now be added at a specific date and time
EDSIMP-324	MwPharm++	Make simulation end time decay level a user setting in MwPharm.cfg
EDSIMP-328	-	Create release notes for version 2.40
EDSIMP-329	-	Set version number to 2.40
EDSIMP-332	MwPharm++	Colour restoration for charts after using of Shift+Load
EDSIMP-333	Edsim++	CLcrN must be updated during a simulation at observed Ccr, Ccy, Bh and Bw
EDSIMP-334	MwPharm++	CO-wizard dialogs should handle ENTER-key as OK-Click
EDSIMP-335	MwPharm++	eGFR column not shown when switching to user estimated CLcr
EDSIMP-336	MwPharm++	Default preset of the charts in the Simulation screen
EDSIMP-337	Edsim++	Remove references to actipro syntax editor from Edsim++ licenses.licx
EDSIMP-338	MwPharm++	Crash (red-cross) in simulation screen after chart edit
EDSIMP-339	MwPharm++	Dosing report may fail in reference and protocol modes
EDSIMP-340	MwPharm++	First record in table MwpUser can't be deleted

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EDSIMP-341	MwPharm++	Button click not handled when in Edit mode
EDSIMP-342	MwPharm++	Passwords with special chars are not working
EDSIMP-344	MwPharm++	Support database dump to SQLite format
EDSIMP-345	MwPharm++	Must show button for conversion to continuous infusion only for TInfusion inputs

8 APPENDIX C: COVARIATES AND LABORATORY VALUES

Drug	Model	Status Screen		History Screen	
		Symbol	Description	Symbol	Description
Linezolid	linezolid_Tietjen_2021	Bw	Body weight	Bw	Body weight
Teicoplanin	Teicoplanin-Byrne-2017	Bw	Body weight	Bw	Body weight
		CLcr	Creatinine clearance	CLcr	Creatinine clearance
Vancomycin	vancomycin_NEO_Aigrain_2019	Bw	Body weight	Bw	Body weight
		Ccr	Serum creatinine	Ccr	Serum creatinine
		PMA	Post menstrual age	-	-
		MAL	Malaysian	-	-
	vancomycin_NEO_Dao_2020	Bw	Body weight	-	-
		Ccr	Serum creatinine	-	-
		PMA	Post menstrual age	-	-
	vanco_adult_JAPAN_Yasuhara_1998	CLcr	Creatinine clearance	CLcr	Creatinine clearance
	vanco_adult_KOREA_Bae_2019_S	Bw	Body weight	Bw	Body weight
		CLcr	Creatinine clearance	CLcr	Creatinine clearance
		CRRT	Cont. Ren. Rep. Ther.	-	-
		HD	Haemodialysis	-	-
	vanco_adult_KOREA_Bae_2019_T	Bw	Body weight	Bw	Body weight
		CLcr	Creatinine clearance	CLcr	Creatinine clearance
		-	-	CRRT	Cont. Ren. Rep. Ther.
		-	-	HD	Haemodialysis