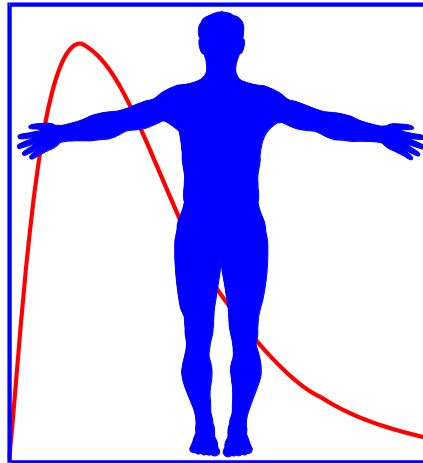


# An Overview of Therapeutic Drug Monitoring Software

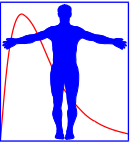


European Association of Hospital Pharmacists  
Academy Seminar on TDM, 20 October 2018, Warsaw

Nieko Punt, Medimatics, Maastricht, The Netherlands

# CONFLICT OF INTEREST

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Worked as a consultant for Mediware a.s.,  
the manufacturer of the TDM software  
package MwPharm++



# Nieko Punt

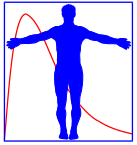
---



- Pharmacy and Pharmaceutical Technologies, University of Groningen (81-86). **Student**.
- **Research** on calcium antagonists in ischemic heart disease (87-90).
- **Software engineer** Mediware BV (90-95).  
TDM software development (MwPharm).
- **Software analyst** IBM (96-98).  
Embedded software for digital video systems.
- **Consultant** at Medimatics (99-18). Software and PKPD-model development.

# THERAPEUTIC DRUG MONITORING

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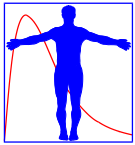
Why do we require TDM?



Variability in exposure (PK) and response (PD)!

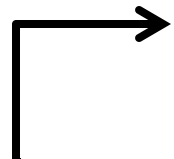


# PKPD VARIABILITY FACTORS



- Genetic

- Gender
- Race
- Polymorphism



- Dimension

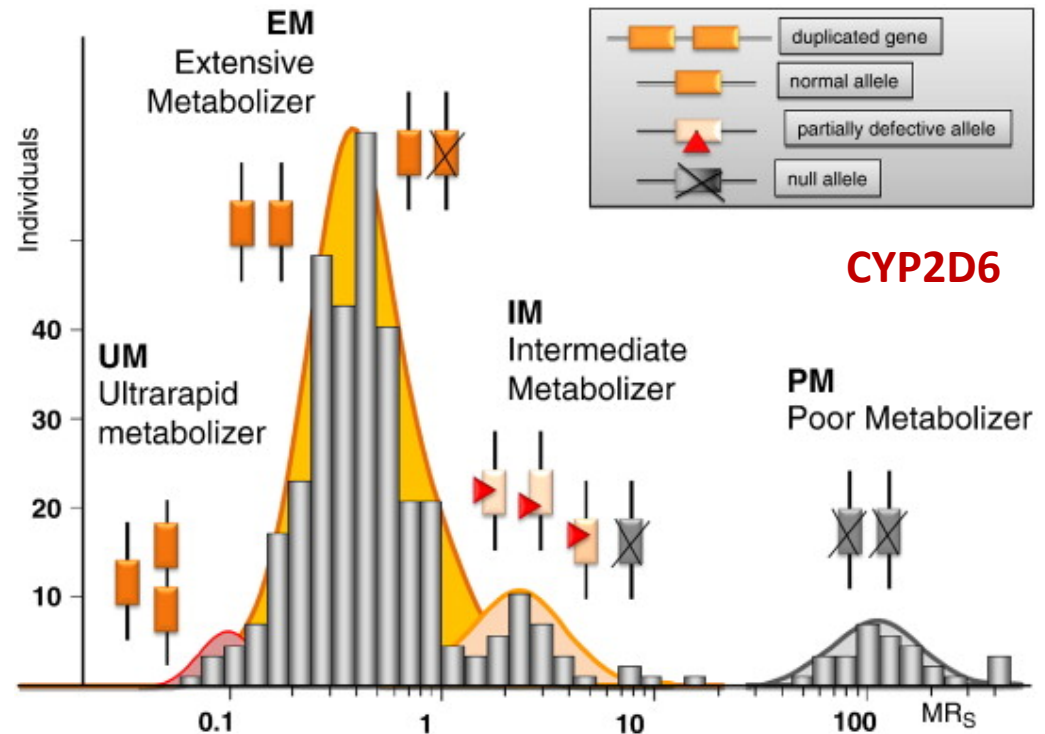
- Weight
- Height

- Function

- Renal function
- Liver function

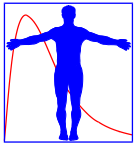


- Age (maturation, aging)
- Disease
- Interactions



Sparteine oxidation phenotype and genotype distribution in a German population (n=308). MRS: urinary metabolic ratio for sparteine (Raimundo et al., 2004; Zanger, 2008).

# ETHNIC PK-PROFILE ROSUVASTATIN



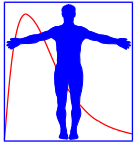
Substrate	Race	Gender	N	Dose (mg)	CL/F (L/h)	C <sub>max</sub> (ng/ml)
Rosuvastatin	Japanese	M	10	6 (i.v.), 40 (p.o.)	114 <sup>a</sup>	40.7 <sup>a</sup>
	Caucasian	M	10	8 (i.v.), 40 (p.o.)	242 <sup>a</sup>	18.8 <sup>a</sup>
	Chinese	M32F3	35	40 (p.o.)	80	59.1
	Asian Indian	M26F9	35	40 (p.o.)	113	42
	Malay	M17F18	35	40 (p.o.)	96.9	50
	White	M31F5	36	40 (p.o.)	185 <sup>a</sup>	25.0 <sup>a</sup>

Tomita Y et al. Clin Pharmacol Ther. 2013 Jul;94(1):37-51.

Given that the rate-determining process of hepatic clearance of rosuvastatin seems to be the hepatic uptake process, it is possible that OATP1B1 ([SLCO1B1](#)), the major uptake (influx) transporter for this drug, is a factor to be considered in understanding the role of ethnicity. In the United States, the recommended initial dose of rosuvastatin for Asians is 5 mg, which is half of the dose recommended for Caucasians.

# TDM SOFTWARE TOOLS

---



The amount of input data (covariates) and the complexity of the calculations (fitting, dosing) required for TDM analysis make the use of computer software tools inevitable.

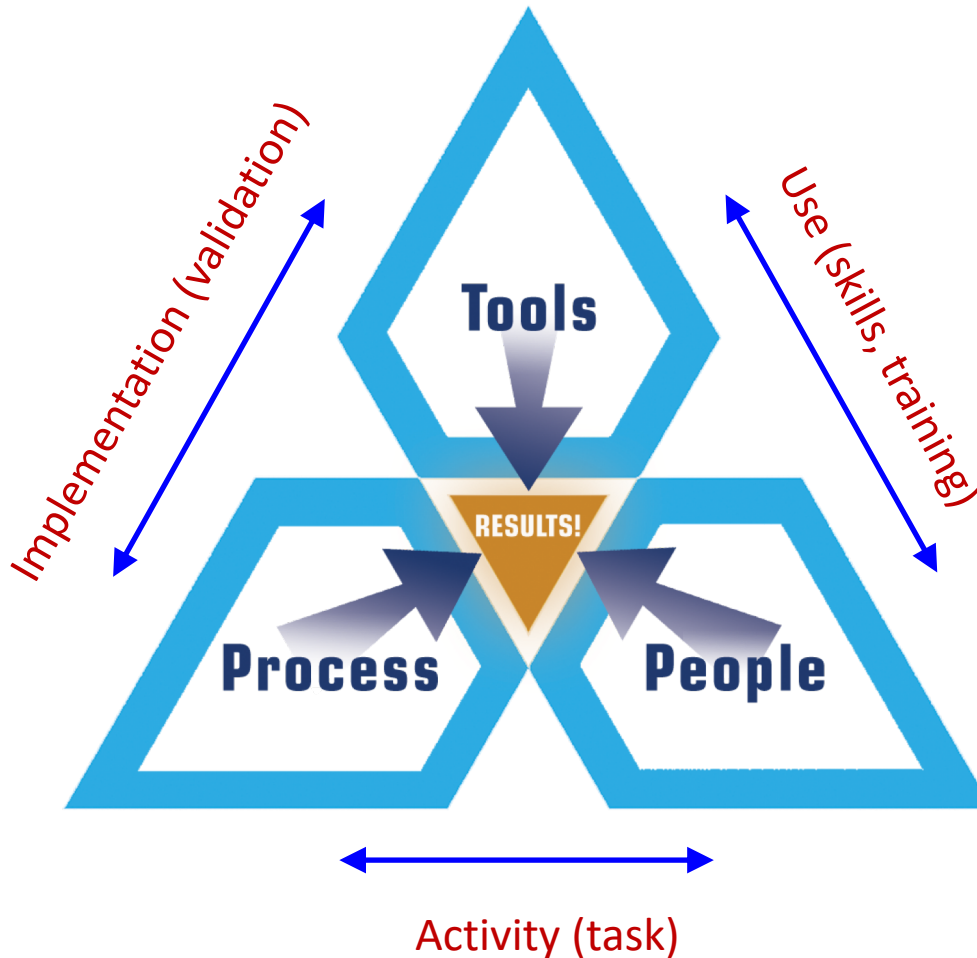
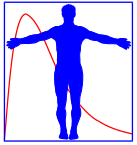


Many Data



Complex Algorithms

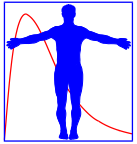
# PROCESS, PEOPLE AND TOOLS



A tool will enhance efficiency NOT effectiveness!

# PROCESS AND SOFTWARE TOOLS

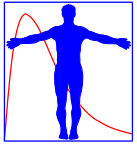
---



- ✓ Software **tools** are aimed at supporting a **business process** in order to increase the **efficiency** (implementing a process).
- ✓ In order to fully understand the requirements for a **TDM software tool** we must therefore describe and understand the **TDM process** in detail.

# TDM AS A (CLINICAL) PROCESS

---



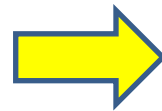
PERSONALIZED MEDICINE



THERAPEUTIC DRUG MANAGEMENT



THERAPEUTIC DRUG MONITORING

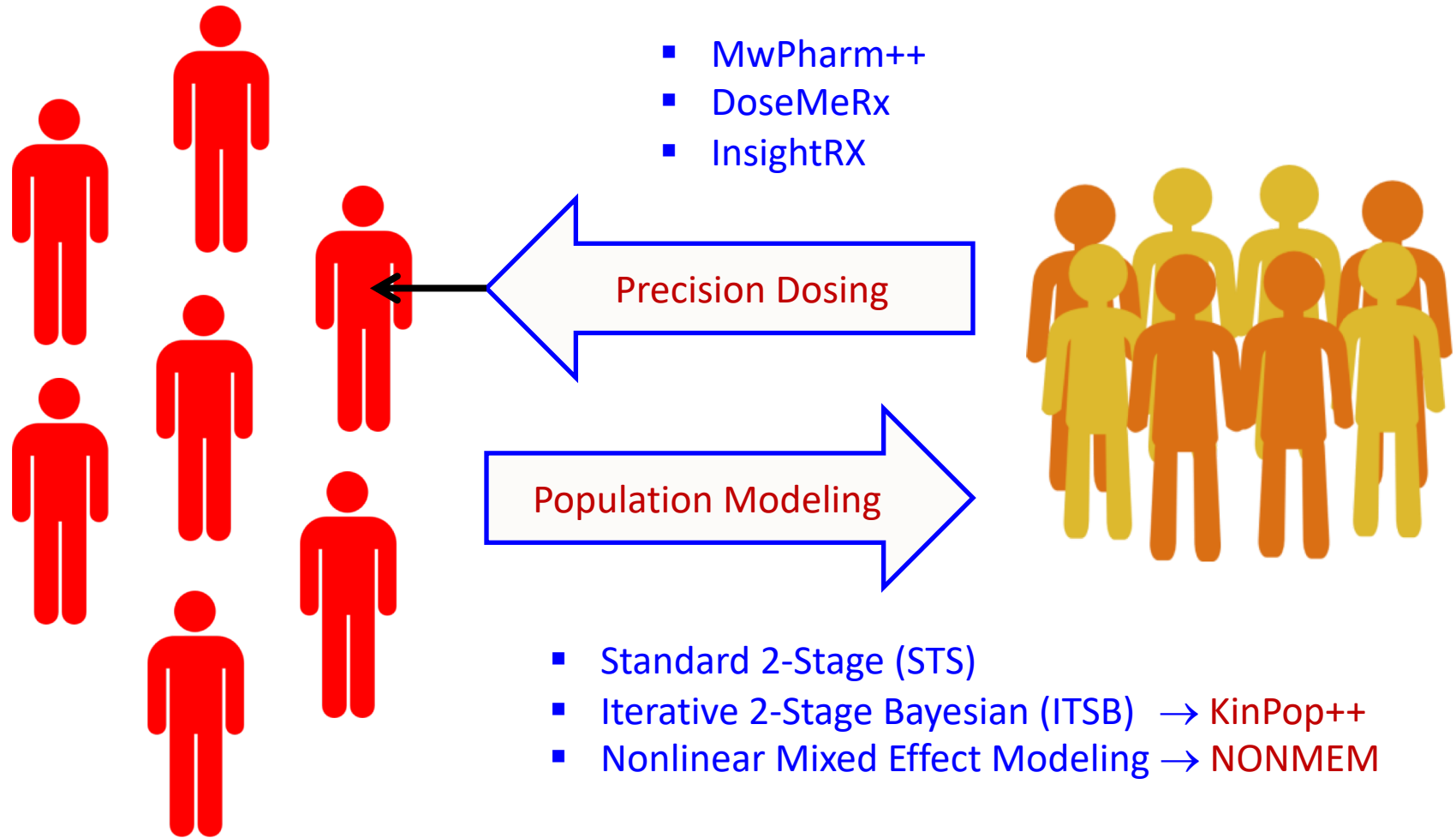
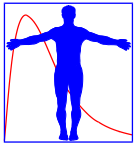


MODEL INFORMED PRECISION DOSING



POPULATION MODELING (R&D)

# PHARMACOMETRIC PROCESSES

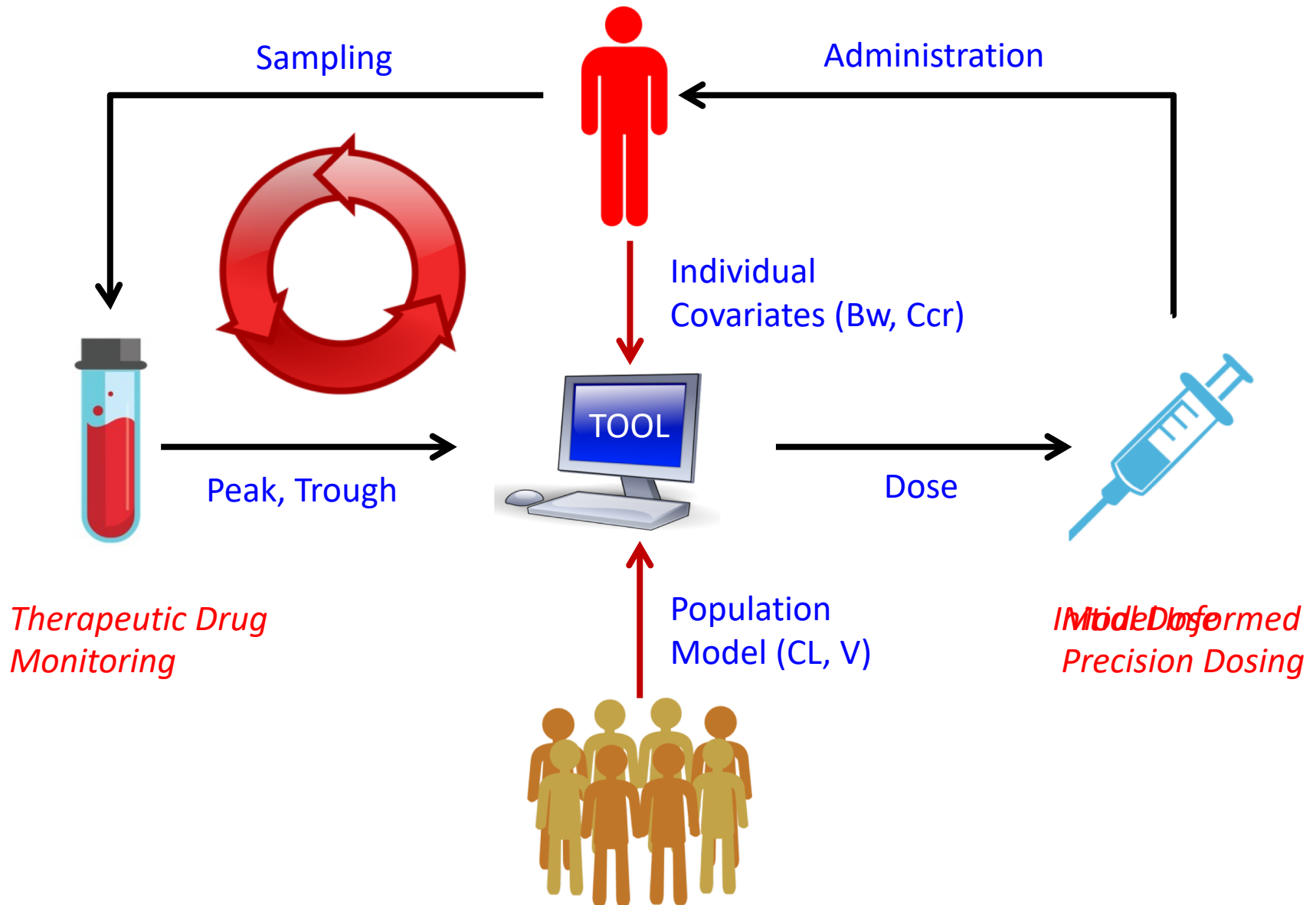
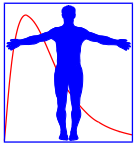


Individuals

Populations

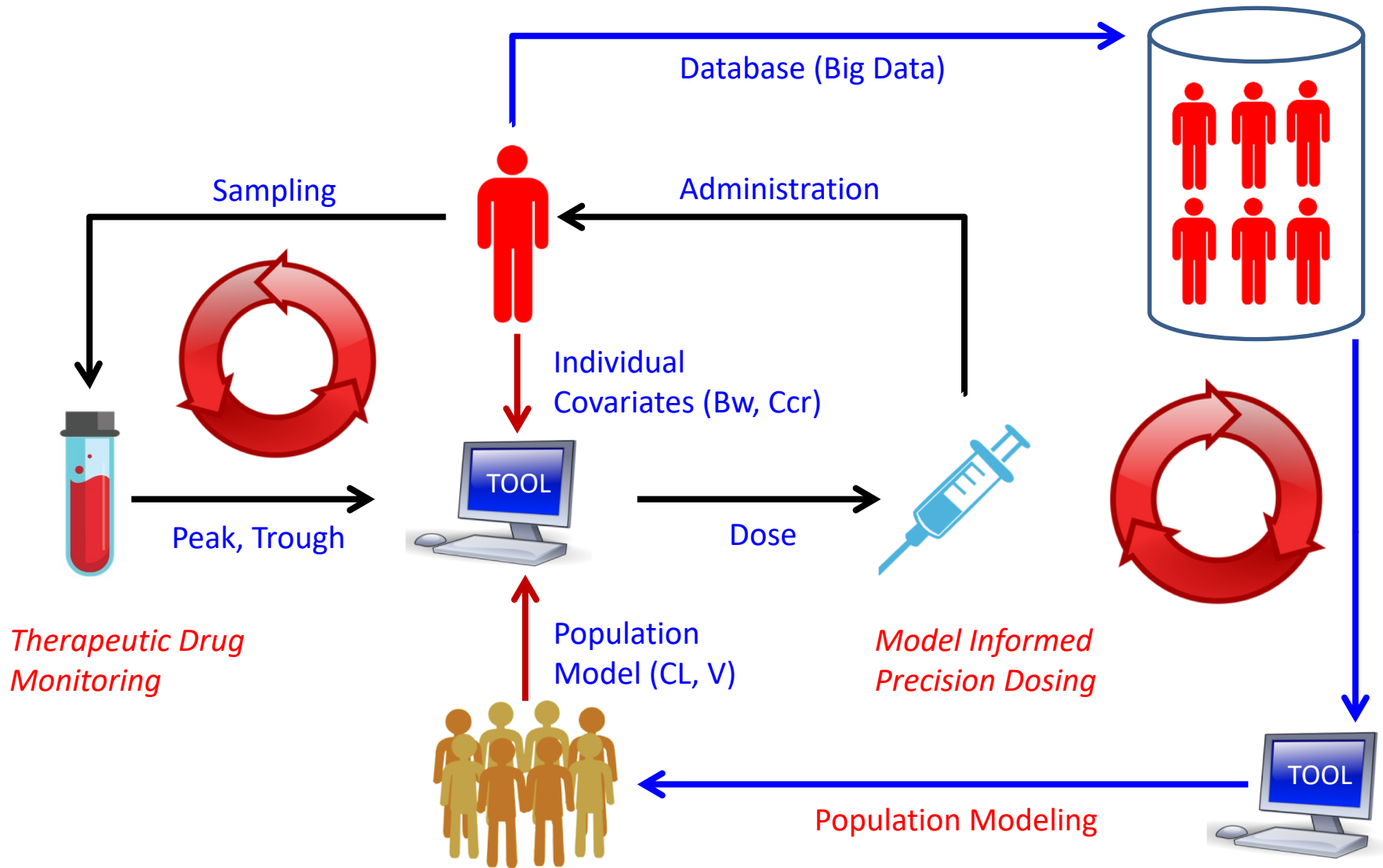
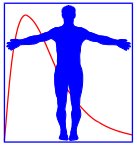
- Standard 2-Stage (STS)
- Iterative 2-Stage Bayesian (ITSB) → KinPop++
- Nonlinear Mixed Effect Modeling → NONMEM

# PRECISION DOSING



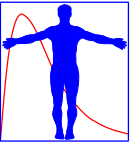


# POPULATION MODELING



# THOMAS BAYES

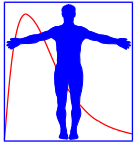
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- 1702-1761, England
- Presbyterian reverend in Tunbridge Wells
- Mathematician
- 1763: Essay towards solving a problem in the doctrine of chances

# BENEFITS OF BAYSIAN ANALYSIS

---



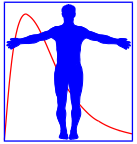
The Bayesian method uses **all** sources of relevant **information** including their uncertainty (distribution):

- **A priori** information (population model)
- **A posteriori** information (plasma samples)
- **Pertinent** information (patient data, dose schedule)

The **most likely results** (individual parameter values) can be obtained with a only **limited number of samples**. In theory only one sample could already be sufficient (if taken at an optimal sampling time).

# STANDARD FITTING

---

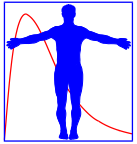


## Non-Linear Least Squares

$$OBJ = \sum_{i=1}^n \left( \frac{C_{obs,i} - C_{est,i}}{\sigma_{obs,i}} \right)^2$$

- $C_{obs}$  = measured plasma concentration  $i$  (1..n)
- $C_{est}$  = estimated plasma concentration  $i$  (1..n)

# MAP BAYESIAN FITTING

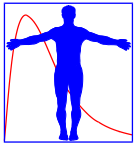


## Maximum a Posteriori Probability

$$OBJ = \sum_{i=1}^n \left( \frac{C_{obs,i} - C_{est,i}}{\sigma_{obs,i}} \right)^2 + \sum_{j=1}^m \left( \frac{P_{pop,j} - P_{ind,j}}{\sigma_{pop,j}} \right)^2$$

- $C_{obs}$  = measured plasma concentration  $i$  (1..n)
- $C_{est}$  = estimated plasma concentration  $i$  (1..n)
- $P_{pop}$  = population PK-parameter  $j$  (1..m)
- $P_{ind}$  = estimated (individual) PK-parameter (1..m)

# INFORMATION BATTLE



A Priori Team

A Posteriori Team



*Population Parameter(s)*

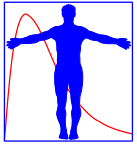
*Individual Observations*

Final Outcome: The most likely individual parameter values.

Note: The a posteriori team gets stronger over time.

# TDM SOFTWARE TOOL REQUIREMENTS

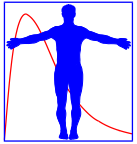
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1. Support the full TDM process cycle.
2. Support MAP Bayesian fitting of historic data.
3. Support linear and non-linear PK-models.
4. Support irregular administration and sampling patterns (also at non-steady state conditions).
5. Support dose calculation for several routes of administration.
6. Include a drug (model) and patient (case) database.
7. EHR integration (direct (HL7) or datawarehouse (SQL))
8. High quality helpdesk (24 hour) and training.
9. Large and active community of users.
10. Solid company behind the tool (continuity)

# TDM SOFTWARE (PART 1)

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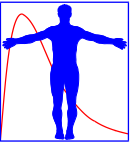


- USC\*PACK (**Jelliffe and Neely**, USA)
- TCIworks (University of Queensland, Australia)
- JPKD (JavaPK for Desktop, University Taiwan)
- Rx Kinetics (Creighton University, USA)
- Kinetidex (Micromedex USA)
- TDMS 2000 (Gupta Healthware Inc. USA)
- RADKinetics (RADSoft Co, USA)
- MwPharm++ (**Hans Proost**, Mediware a.s., Prague)
- AutoKinetics (**Paul Elbers**, VUmc, Amsterdam)
- DoseMeRx (**Robert McLeay**, DoseMe, Australia)
- InsightRX (**Ron Keizer**, InsightRX, San Francisco)



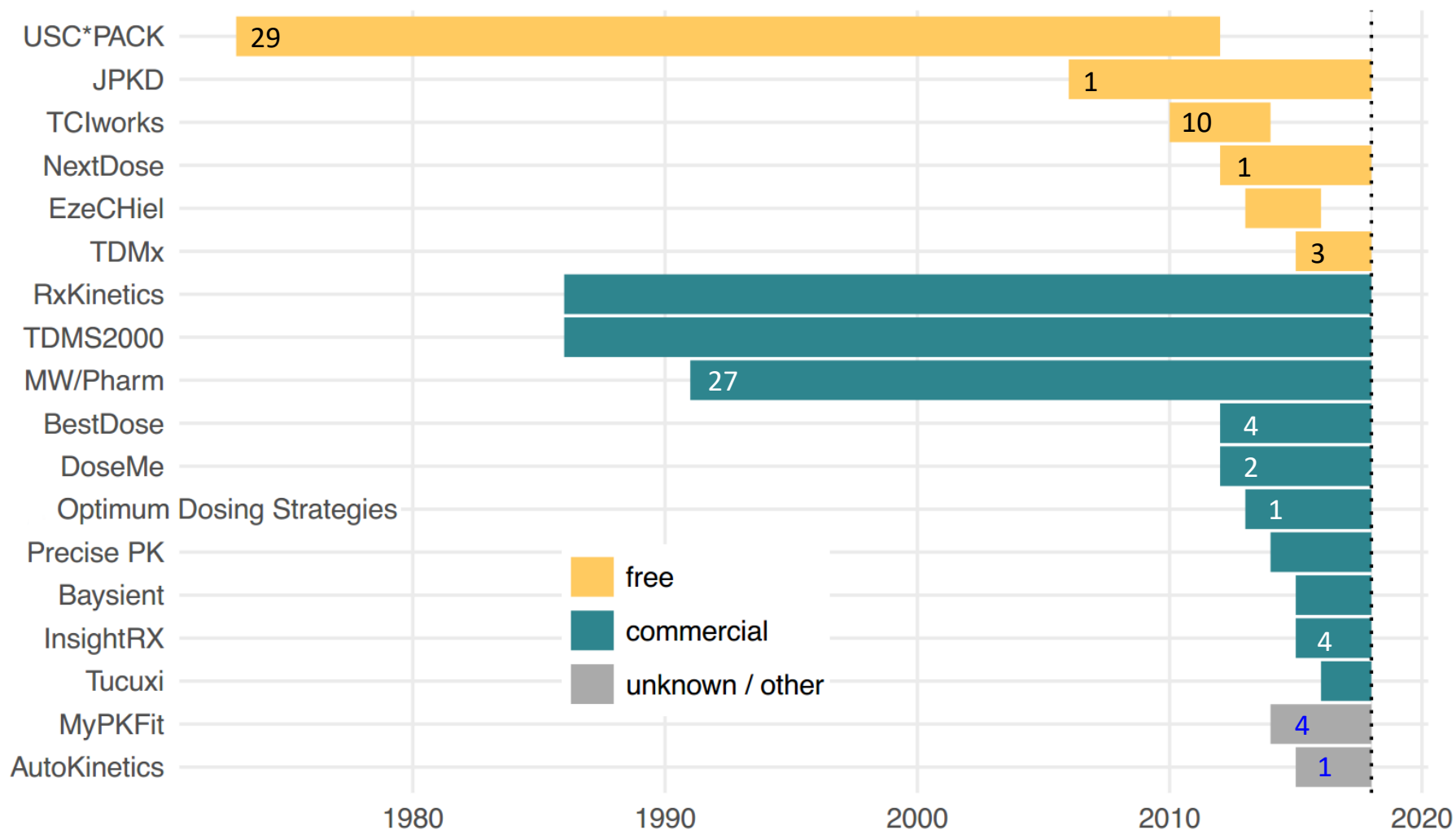
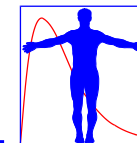
# TDM SOFTWARE (PART 2)

---



- TDM for R (University Taiwan)
- NextDose (**Sam Holford & Nick Holford**, New Zealand)
- EzeCHiel (REDS institute, Switzerland)
- TDMx (Sebastian Wicha, Hamburg, Germany)
- BestDose (**Michael Neely**, Lab. of Applied PK, USA)
- ID-ODS (Optimum Dosing Strategies, USA)
- Precise PK (formerly TDMS2000, Healthware Inc., USA)
- Baysient (a.k.a iDose, **Diane Mould**, Baysient LLC, USA)
- Tucuxi (University of Applied Sciences, Switzerland)
- MyPKFit for Advate<sup>®</sup> (Shire Pharmaceuticals Group)

# TOOL TIMELINE AND PUBMED HITS



Numbers in the bars indicate the number of PubMed hits.

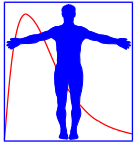
Data Sources:

Fuchs et al. Clin Pharmacokinet 2013

<http://campus.usal.es/~galenica/clinpk/in/software.htm>

# TDM SOFTWARE BENCHMARK

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Clin Pharmacokinet (2013) 52:9–22  
DOI 10.1007/s40262-012-0020-y

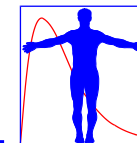
REVIEW ARTICLE

## **Benchmarking Therapeutic Drug Monitoring Software: A Review of Available Computer Tools**

**Aline Fuchs · Chantal Csajka · Yann Thoma ·  
Thierry Buclin · Nicolas Widmer**

Did not include InsightRX and DoseMeRx

# BENCHMARK RESULTS



**Table 4** Weighted scores for each category and overall category rounded to unit and ranking

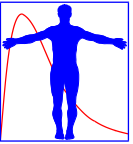
12x

Category	MM-USC* Pack©	MwPharm©	TCIworks	JPKD®	TDM for R	Antibiotic Kinetics©	APK	Kinetics©	Kinetidex®	T.D.M.S. 2000™	Data Kinetics™	RAD Kinetics
General characteristics												
User interface	79 (10)	95 (4)	89 (7)	90 (6)	73 (11)	105 (3)	111 (1)	106 (2)	92 (5)	80 (9)	83 (8)	61 (12)
Interfacing	13 (5)	26 (1)	13 (5)	13 (5)	13 (5)	18 (2)	18 (2)	18 (2)	13 (5)	13 (5)	13 (5)	13 (5)
Storage	34 (7)	46 (1)	30 (8)	16 (10)	16 (10)	16 (10)	46 (2)	46 (2)	36 (5)	34 (6)	37 (4)	29 (9)
Report	16 (10)	58 (1)	45 (7)	36 (8)	13 (12)	34 (9)	56 (2)	56 (2)	50 (6)	50 (6)	53 (4)	16 (10)
Cost	26 (4)	19 (8)	28 (3)	23 (6)	23 (6)	23 (5)	28 (1)	28 (1)	12 (12)	19 (8)	16 (10)	16 (11)
Computational aspects	60 (3)	59 (4)	78 (1)	66 (2)	53 (10)	58 (5)	58 (5)	58 (5)	51 (11)	55 (9)	58 (5)	41 (12)
Total	228 (10)	304 (3)	284 (4)	244 (9)	191 (11)	253 (7)	317 (1)	311 (2)	253 (6)	251 (8)	259 (5)	176 (12)
Pharmacokinetic aspects												
Population and drug	59 (7)	76 (1)	60 (6)	70 (2)	40 (11)	53 (9)	65 (3)	56 (8)	62 (5)	63 (4)	49 (10)	33 (12)
Models	191 (1)	179 (3)	184 (2)	120 (9)	117 (10)	139 (8)	148 (7)	153 (6)	174 (4)	174 (5)	117 (11)	98 (12)
Modularity	48 (7)	43 (8)	53 (1)	53 (1)	33 (11)	48 (4)	48 (4)	48 (4)	49 (3)	39 (9)	33 (11)	38 (10)
Plot	42 (1)	34 (3)	37 (2)	26 (10)	15 (11)	32 (6)	32 (6)	32 (6)	34 (3)	34 (3)	32 (6)	15 (11)
Various	22 (9)	34 (2)	25 (7)	19 (11)	19 (11)	25 (5)	25 (5)	23 (8)	31 (4)	33 (3)	35 (1)	20 (11)
Total	363 (2)	366 (1)	358 (3)	288 (9)	225 (11)	297 (8)	317 (6)	311 (7)	350 (4)	342 (5)	266 (10)	204 (12)
Authors												
Expertise of authors	51 (1)	51 (1)	49 (3)	32 (9)	32 (9)	37 (6)	37 (6)	37 (6)	23 (12)	42 (5)	42 (4)	32 (9)
Global score	641 (5)	720 (1)	692 (2)	564 (10)	448 (11)	587 (8)	671 (3)	659 (4)	627 (7)	636 (6)	567 (9)	412 (12)

All data given as weighted score (rank). Rankings were given from 1 for the best classified to 12 for the worst classified

# SHORT LIST

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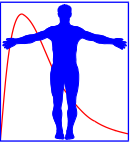


Most of the **free** tools are academic efforts, often focusing on one drug, that lack professional **support** and **continuity**. The following commercially available tools comply with all 10 requirements for TDM software tools.

- ✓ **MwPharm++** : Prague, Czech Republic
- ✓ **InsightRx** : San Francisco, USA
- ✓ **DoseMeRx** : Queensland, Australia

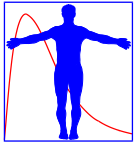
# MWPHARM++

---



MW  PHARM ++

# MWPHARM++ LOGIN SCREEN



## Therapeutic Drug Management

**MEDIWARE** **MWPHARM++**

### Therapeutic Drug Management

*MwPharm++ is an efficient TDM application for establishing a proper dosing regimen based on population PK parameters from an extensive drug database and individual physiological patient parameters.*

Username

admin

Password

Login

Author

Mediware Development Team

Name

MwPharm

Date

24-03-2018

Copyright

Mediware a.s.

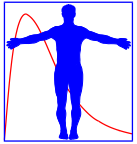
Version

1.6.0.83

Translation

Nieko Punt

# PATIENT REGISTRATION



## PATIENT

Patient Number	1
Name and Initials	MW
Date of Birth	09-04-1963
Sex	Male
Address	
Postcode / Zipcode	
City	
Family Doctor	
Requesting Physician	
Ward	
Room Number	
Description	
Medication Date	26-03-2018
Age	55 years
Last Medication	
Date of Change	

<input type="checkbox"/> Dob	<input type="checkbox"/> Number	<input type="checkbox"/> Name
11-11-1950	!C001	!CASUS 001
11-11-1945	!C002	!CASUS 002
21-08-1936	!C003	!CASUS 003
11-11-1946	!C004a	!CASUS 004a
11-05-1993	!C004b	!CASUS 004b
11-11-1922	!C005	!CASUS 005
11-11-1992	!C006	!CASUS 006
11-11-1915	!C007	!CASUS 007
13-09-1990	!C008	!CASUS 008
11-11-1924	!C009	!CASUS 009
11-11-1977	!C010	!CASUS 010
26-04-1926	!N001	!NPEM 001
27-12-1929	!N002	!NPEM 002
26-04-1923	!N003	!NPEM 003
22-11-1984	!N004	!NPEM 004
22-03-1921	!N005	!NPEM 005
31-10-1942	!N006	!NPEM 006
15-04-1910	!N007	!NPEM 007
30-08-1926	!N008	!NPEM 008
11-05-1930	!N009	!NPEM 009
27-12-1949	!N010	!NPEM 010
07-10-1936	!PAO-001	!CASUS PAO 1
22-11-2004	!PAO-002	!CASUS PAO 2
13-03-1965	!PAO-003	!CASUS PAO 3
12-05-1965	!PAO-004	!CASUS PAO 4
12-09-1955	!PAO-005	!CASUS PAO 5
25-09-1947	!PAO-006	!CASUS PAO 6
27-07-2014	!PAO-007	!CASUS PAO 7

Standard

Import

P R

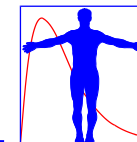
List Mode

Number-Name

Insert



# PATIENT STATUS



## STATUS

Weight 70.0 kg  
 Height 175 cm  
 Term 40 weeks

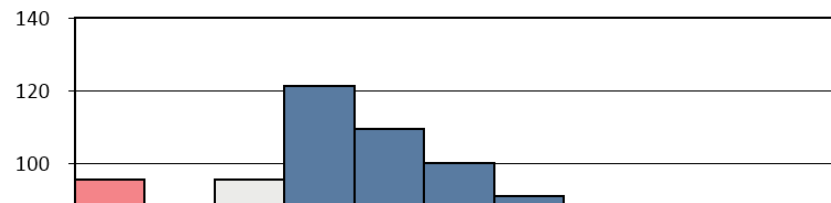
Bsa 1.85 m<sup>2</sup>  
 Bmi 22.9 kg/m<sup>2</sup>

Sex Male  
 Race Caucasian

Lbm 70.0 kg  
 Lbmc 70.0 kg

## Renal Function (mL/min)

MW (09-04-1963)



## Renal Function

CKD-EPI (Creatinine + Cystatin C)

## Serum Creatinine

70 μmol/L

## Liver Function

100 %

Seru

Normal

## Cystatin C

0.80 mg/L

Crea

## eGFR

101.3 mL/min/1.73m<sup>2</sup>

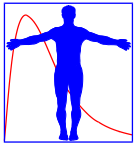
Path

108.2 mL/min

P

R

# CASE MANAGEMENT



## CASE

gentamicin [gentamicin\_C1]

TEST-E (01-01-1935)

Drug gentamicin  
 ATC J01GB03  
 Descript. Antibiotic

Model gentamicin\_C1  
 PMID  
 Descript. Goodman & Gilman's 10th ed. (2001)

Drug gentamicin  
 Model gentamicin\_C1  
 Descript.

- fluorouracil
- flurazepam
- furosemide
- gentamicin**
- haloperidol
- hexobarbital
- hydralazine
- hydrochlorothiazide
- ibuprofen
- imipramine
- indomethacin
- isoniazid
- isosorbide dinitrate
- isosorbide-2-mononitrate
- isosorbide-5-mononitrate
- kanamycin
- ketamine
- labetalol
- lidocaine
- lincomycin
- lithium
- lorazepam
- lorcainide

- !gentamicin\_icu\_C1
- #gentamicin\_adult\_C1
- #gentamicin\_adult\_ic\_C1
- #gentamicin\_adult\_ip\_C1
- #gentamicin\_adult\_k\_C1
- #gentamicin\_child\_10\_16y\_C1
- #gentamicin\_child\_1\_5y\_C1
- #gentamicin\_child\_1\_6m\_C1
- #gentamicin\_child\_5\_10y\_C1
- #gentamicin\_child\_6\_12m\_C1
- #gentamicin\_neonate\_0.5\_1m\_C1
- #gentamicin\_neonate\_0\_0.5m\_C1
- #gentamicin\_neonate\_ST\_1500g\_C1
- gentamicin\_C1**
- gentamicin\_C2

Insert >

Copy >

- 21-03-1990 08:00 gentamicin\_C1

Drug   
 All

Model

Date   
 Drug

Copy Import

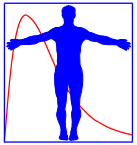
Active Export

Delete Update Insert

Delete Update Default

Delete Update Load

# MEDICATION HISTORY



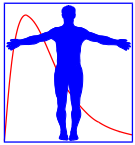
HISTORY

gentamicin [gentamicin\_C1]

TEST-E (01-01-1935)

Date	Time	Roa	Value	Unit	No	Interv [h]	T(inf) [h]	Conc. [mg/L]	Weight [kg]	Creat. [μmol/L]	Liver [%]	Note
21-03-1990	08:00		iv	90	mg			0.5		68	100	
21-03-1990	20:00		iv	60	mg		12	0.5				
22-03-1990	21:00								14			
23-03-1990	07:55								8			

# MAP BAYESIAN FITTING



## FITTING

gentamicin [gentamicin\_C1]

TEST-E (01-01-1935)

Bayes   Sim  Fit

Algorithm: Marquardt

Weighting: WLS (observed)

Assay Dist.: Log-Normal

Assay Error: Sd (mg/L)

C°: 0.1

+ C¹: 0.035

+ C²: 0

+ C³: 0

Iterations: 4

WSS: 18.73744118

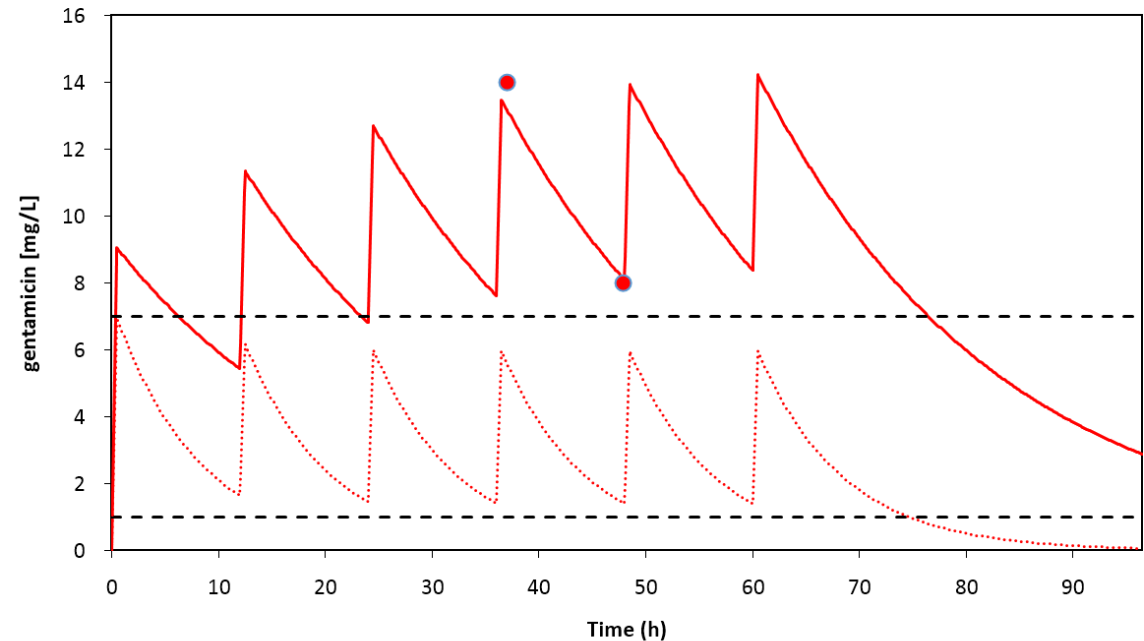
RMS: 2.164338304

R2: 0.972810335

Akaike: 11.20783018

LCN: 4

Fitted  Common

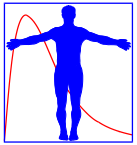


Case Model

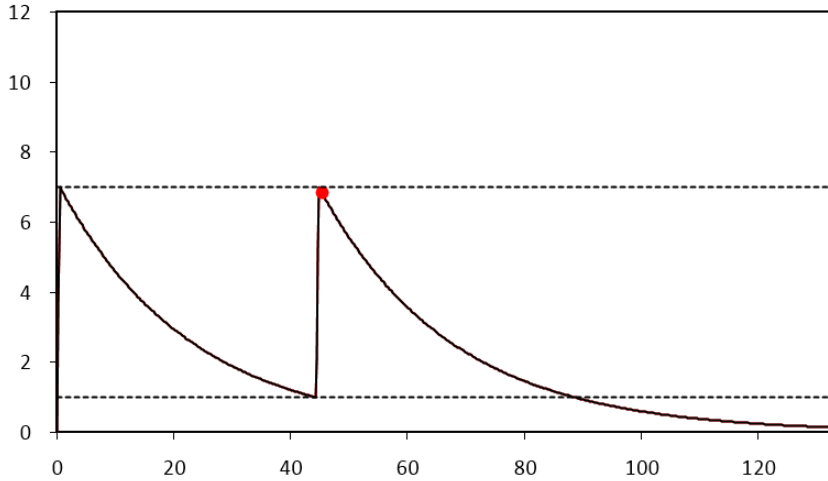
Drug Model

Parameter	Unit	Alias	Population	Sd	Individual	Se	Type	Distribution
C01.V	L/kgLbmc	V1	0.21	0.02	0.164718587	0.023919078	Bayesian	Log-Normal
RE.k	1/h/(mL/min/1.73m²)	kelr	0.0024	0.001	0.000637501	0.000183007	Bayesian	Log-Normal

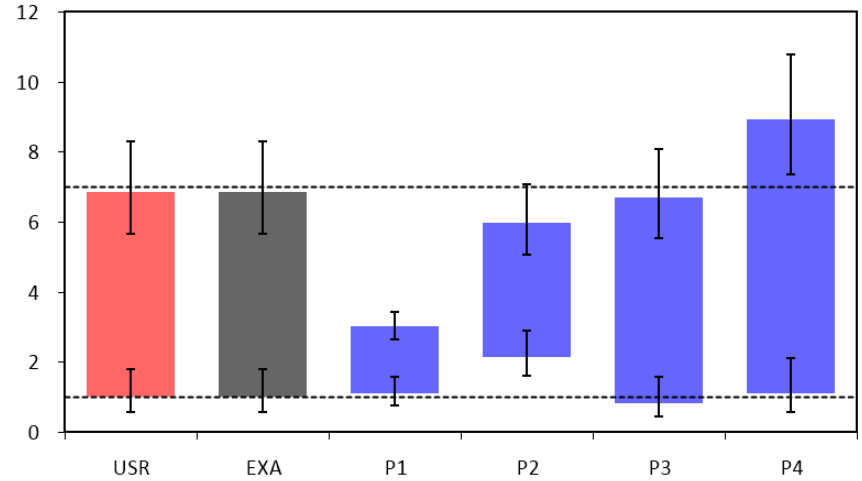
# DOSE CALCULATOR



DOSE CALCULATOR gentamicin [gentamicin\_C1] C01.C (mg/L)



C01.C (mg/L) TEST-E (01-01-1935)



**Profile**

	User	Exact	P1	P2	P3	P4	
Load	69.6	69.6	60	60	60	80	mg
Dose	59.9	59.9	20	40	60	80	mg
Tint	44.35	44.35	24	24	48	48	h
Ndos	2	2	6	2	3	3	-
Tdur	0.50	0.50	0.50	0.50	0.50	0.50	h
Peak	6.85	6.85	3.02	5.97	6.68	8.91	mg/L
Min	1.00	1.00	1.09	2.15	0.83	1.11	mg/L
Tpeak	1.00	1.00	1.00	1.00	1.00	1.00	h
Tmin	44.35	44.35	24.00	24.00	48.00	48.00	h
Ave	3.13	3.13	1.94	3.84	2.89	3.85	mg/L
pSS	100	100	100	99	100	100	%

**Targets**

- Max  7.00 mg/L
- Min  1.00 mg/L
- Ave  4.00 mg/L
- Tint  12.00 h

**Reference**

- Levels R01
- Variable C01.C

**Method**

- Load Optimal
- Dose Min-Max
- Algorithm EXP
- Force DIF

**Input** IV

**AUC24**  96.00 mg/L.h

**Error** CI

**Speed** 24 ms

Log Scale

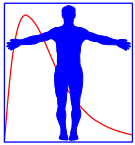
Reference Mode

Add to History

P R



# DOSE ADJUSTMENT



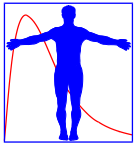
## HISTORY

gentamicin [gentamicin\_C1]

TEST-E (01-01-1935)

Date	Time	Roa	Value	Unit	No	Interv [h]	T(inf) [h]	Conc. [mg/L]	Weight [kg]	Creat. [μmol/L]	Liver [%]	Note
21-03-1990	08:00		iv	90	mg	1		0.5		68	100	
21-03-1990	20:00		iv	60	mg	5	12	0.5				
22-03-1990	21:00								14			
23-03-1990	07:55								8			
26-03-1990	08:19		iv	59.89	mg	1	44.35	0.5				Loading dose advice (optimized)
28-03-1990	04:39		iv	59.89	mg	1	44.35	0.5				Maintenance regimen advice (user)

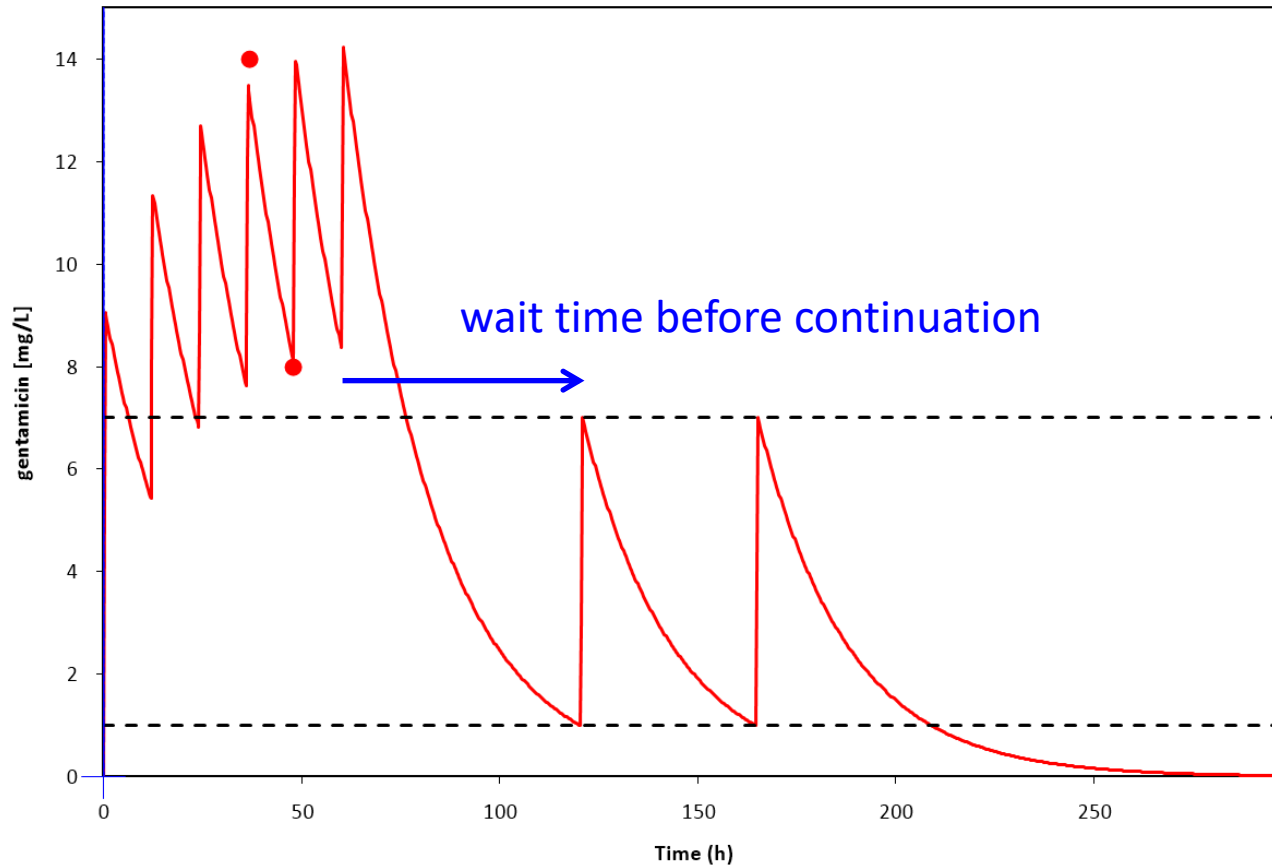
# WAIT AFTER OVERDOSE



SIMULATION

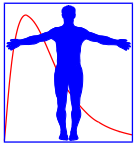
gentamicin [gentamicin\_C1]

TEST-E (01-01-1935)



<input checked="" type="checkbox"/> Conc	0.0000 mg/L
<input type="checkbox"/> Cave	0.0000 mg/L
Effect	n.a. -
<input type="checkbox"/> AUC	0.0000 mg/L.h
<input type="checkbox"/> AUCC	-290.45 mg/L.h
Dose	1
<input type="checkbox"/> Ccr	100.00 $\mu$ mol/L
<input type="checkbox"/> CLcr	45.98 mL/min
<input type="checkbox"/> CLcrN	46.08 mL/min/1.73m <sup>2</sup>
<input type="checkbox"/> Bsa	1.73 m <sup>2</sup>
<input type="checkbox"/> Lbmc	59.72 kg
<input type="checkbox"/> Bw	68.00 kg
<input type="checkbox"/> Total	0.0000 mg 0.0000 mg/kg BW
<input type="checkbox"/> POP	
<input type="checkbox"/> CI	95.0 %
<input type="checkbox"/> SD	
Date	21-03-1990 dd-mm-yy
Time	08.00 hh:mm
Span	0.00:00 d.hh:mm
	0.0000 h
Scale	15.00 mg/L

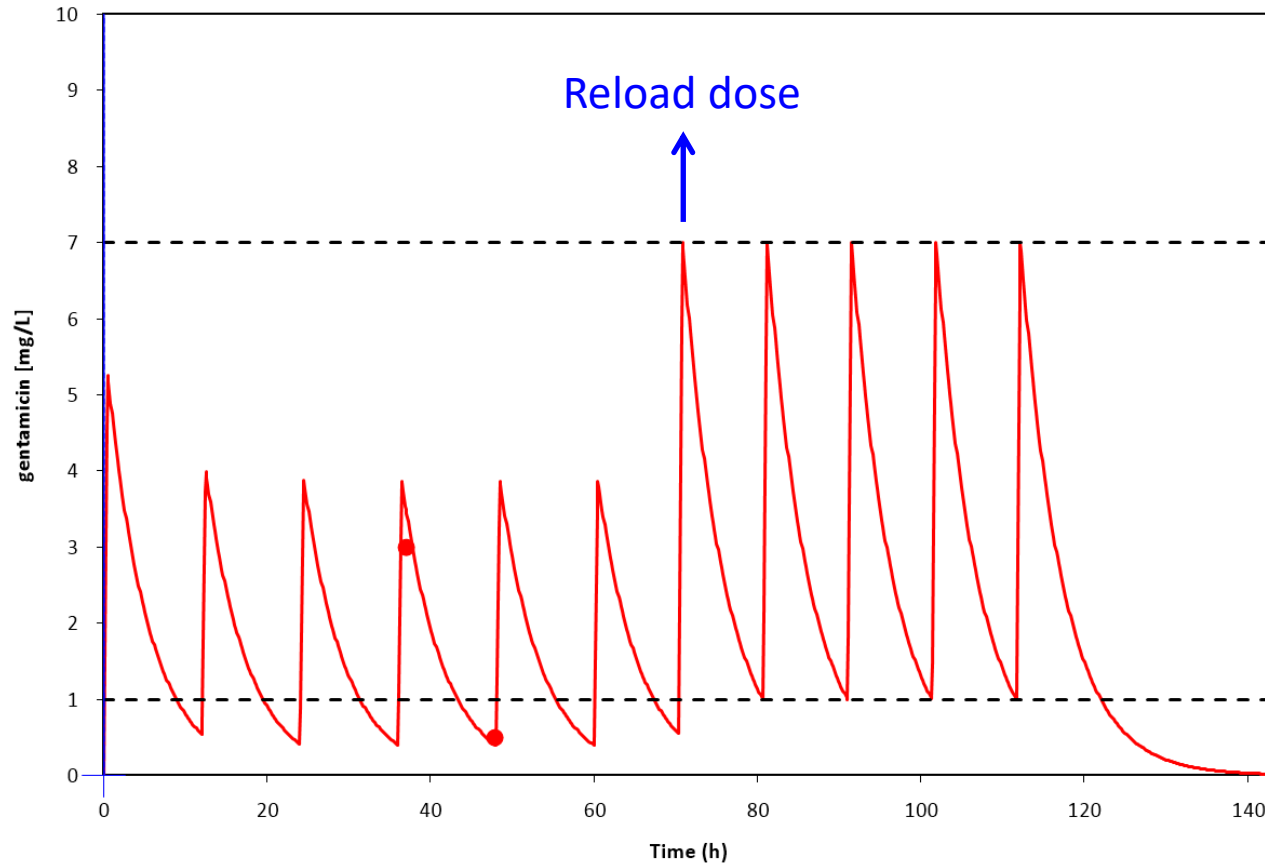
# RELOAD AFTER UNDERDOSE



SIMULATION

gentamicin [gentamicin\_C1]

TEST-E (01-01-1935)



<input checked="" type="checkbox"/> Conc	0.0000 mg/L
<input type="checkbox"/> Cave	0.0000 mg/L
Effect	n.a. -
<input type="checkbox"/> AUC	0.0000 mg/L.h
<input type="checkbox"/> AUCC	0.0000 mg/L.h
Dose	1
<input type="checkbox"/> Ccr	100.00 $\mu$ mol/L
<input type="checkbox"/> CLcr	45.98 mL/min
<input type="checkbox"/> CLcrN	46.09 mL/min/1.73m <sup>2</sup>
<input type="checkbox"/> Bsa	1.73 m <sup>2</sup>
<input type="checkbox"/> Lbmc	59.72 kg
<input type="checkbox"/> Bw	68.00 kg
<input type="checkbox"/> Total	0.0000 mg 0.0000 mg/kg BW
<input type="checkbox"/> POP	
<input type="checkbox"/> CI	95.0 %
<input type="checkbox"/> SD	
Date	21-03-1990 dd-mm-yy
Time	08:00 hh:mm
Span	0.00:00 d.hh:mm
Scale	0.0000 h 10.00 mg/L

Page Size

Full



Y-Scale

LIN

X-Scale

hours



Edit

Save

Load

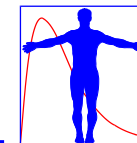
T

P

R



# CUSTOM REPORT GENERATION



MW PHARM ++

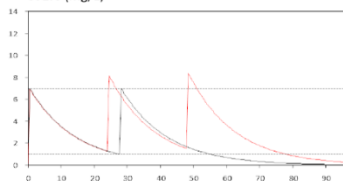
## DOSAGE ADVICE

### PATIENT DATA

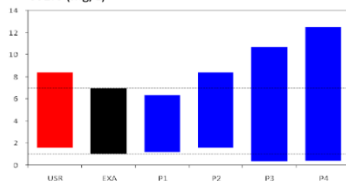
Number : 1234 Address :  
 Name : TEST-E City :  
 Date of Birth : 01-01-1935 Department :  
 Sex : Female Medication : gentamicin  
 Family Doctor : Requested by :

### Pathology

C01.C (mg/L)



C01.C (mg/L)



Regimen	Advice	Exact	Target	Unit	Route
Load	80.00	80.94		mg	IV
Dose	80.00	69.78		mg	Repeated Admin
Tint	24.00	27.63	12.00	h	Variable : C01.C
Tdur	0.5000	0.5000		h	Target : MIN_MAX
Ctrough	1.56	1.0000		mg/L	Ref. Mode : No
Cpeak	8.13	6.75		mg/L	Auc Mode : No
Cmin	1.56	1.0000	1.00	mg/L	Advisor : Administrator
Cmax	8.42	7.00	7.00	mg/L	Date : 30-09-2018
Cave	4.17	3.10	4.00	mg/L	
Auc	99.98	74.41	48.00	mg/L.h	

### Note

VIDEŇSKÁ 1958/9  
140 21  
PRAHA 4 - ZŠRČ



INSTITUT KLINICKÉ A EXPERIMENTÁLNÍ MEDICÍNY

PRACoviŠTĚ LABORATORNÍCH METOD

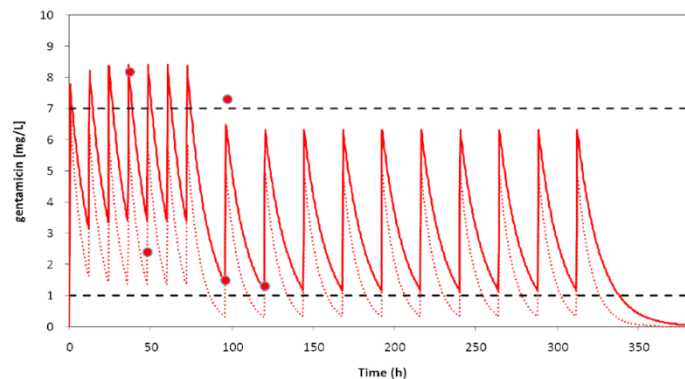
Přednosta: Prof. MUDr. Antonín Jabor CSc.

Kontakt: MUDr. Janka Franeková, Ph.D., 8225, 737 205 963, Mgr. Kornélie Chrapková, PG Dip, 8274, 8243

### Interpretace terapeutického monitorování léků

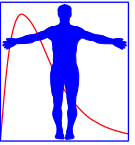
### PACIENTSKÁ DATA

Číslo : 1234 : gentamicin  
 Jméno : TEST-E :  
 Datum narození : 01-01-1935 :



Date	Time	Route	Dose	Unit	No	Tint	Tinf	Conc	Bw	Creat.
21-03-1990	08:00	iv	90 mg		1			0.5	68	100
21-03-1990	20:00	iv	60 mg		5	12		0.5		
22-03-1990	21:00								8.2	
23-03-1990	07:55								2.4	
24-03-1990	08:00	iv	60 mg		11	24		0.5	70	97
25-03-1990	07:55								1.5	
25-03-1990	09:00								7.3	
26-03-1990	07:55								1.3	110

### Závěr :



# Insight **RX**

**Presentation by Ron Keizer**



Precision dosing & clinical analytics at the point of care

# Quick overview



# USER LOGIN

## Secure, modern login page and functionality

Insight<sup>RX</sup>

Cloud-based dose individualization using quantitative pharmacology and state-of-the art Bayesian algorithms. Learn more....

username / email

password

Log In

Forgot password

**Standalone:** A new user login and password must be created

**EMR Integrated:** No login necessary (platform is launched directly from EMR) – your existing EMR user credentials are synced with InsightRX.

“Forgot password” self-service functionality

# PATIENT PAGE

Streamlined user interface is easy-to-learn and puts pertinent information all on one page.

The screenshot displays a comprehensive patient page for Vancomycin (children) with MRSA infection. The interface is divided into several key sections:

- Patient Panel:** Contains demographic information (Date of birth: 05/06/2012, Age: 5.5 years, Sex: Male), clinical data (Serum creatinine, Weight, Height, eGFR estimation, MIC), and physical characteristics (Absolute eGFR, Relative eGFR, BSA, BMI, Fat-free mass, Ideal weight, Adjusted weight, % height for age, % weight for age).
- Dose information:** Features a control panel to update doses, a 'last updated' timestamp, and a 'Reference table' for adjusting doses. The reference table includes columns for percentage change, dose, interval, infusion length, AUC<sub>24</sub>, C<sub>trough,ss</sub>, P<sub>auc</sub><sup>\*</sup>, and P<sub>conc</sub><sup>\*</sup>.
- Parameters & Predictions:** Shows pharmacokinetic parameters (CL, V<sub>c</sub>, t<sub>1/2</sub>) for both Population and Individual, along with a graph comparing 'Current' concentrations with 'TDM' (Therapeutic Drug Monitoring) data points over time.
- Drug monitoring:** A table listing individual doses with columns for Dose, Interval, Start time, Infusion length, TDM, Since dose, and Comments.

Patient Panel

Reference Table

PK Plots

Dosing History and TDM

# PATIENT PANEL

Useful patient information easily visible and accessible

InsightRX

- Person icon Patient list
- Group icon Teams
- Document icon Reference

**Charles Hendershot** ☰

MRN: 957102938

Notes (12/12/17 17:09 dcarvel) ▶

Date of birth 09/10/2011  
Age 6.3 years  
Sex Male

---

Drug Busulfan (children)  
Patient indications Malignant

---

Weight 18 kg 12/01/17  
Height 114 cm 12/01/17

Conditioning Clofarabine, fludarabine and busulfan regimen

---

BSA 0.76 m<sup>2</sup>  
BMI 13.9 kg/m<sup>2</sup>  
Fat-free mass 17.3 kg  
Ideal weight 21.4 kg  
Adjusted weight 20.1 kg  
% height for age 25%  
% weight for age 11%

Help

- Patient-specific “info button”
- Incorporate time-varying covariates (such as changes in CrCl)
- Print report

Review patient demographic information

- Obtain help via phone, email, or text
- Links to help and FAQ documentation

# REFERENCE TABLE

## Simulate and assess dosage and exposure

Ranvir Mangat

### Dose information

Update

last updated 2 days ago, starting with dose #25

Δ	Dose	Interval	Inf. length	AUC <sub>24</sub>	C <sub>trough,ss</sub>	P <sub>auc</sub> *	P <sub>conc</sub> *
<input checked="" type="checkbox"/>	55 mg	8 hours	1 hours	535 µg/mL·hr	15.2 µg/mL	100 %	12 %

### Reference table

	Dose	Interval	Inf. length	AUC <sub>24</sub>	C <sub>trough</sub>	P <sub>auc</sub> *	P <sub>conc</sub> *
<input type="checkbox"/>	-30 %	49 mg (10.21 mg/kg)	8 hours	1 hours	478 µg/mL·hr	13.6 µg/mL	97 % 8 %
<input type="checkbox"/>	-10 %	63 mg (13.12 mg/kg)	8 hours	1 hours	614 µg/mL·hr	17.5 µg/mL	100 % 25 %
<input type="checkbox"/>	previous	70 mg (14.58 mg/kg)	8 hours	1 hours	683 µg/mL·hr	19.4 µg/mL	100 % 44 %
<input type="checkbox"/>	+15 %	80.5 mg (16.77 mg/kg)	8 hours	1 hours	785 µg/mL·hr	22.4 µg/mL	100 % 70 %
<input type="checkbox"/>	+30 %	91 mg (18.96 mg/kg)	8 hours	1 hours	887 µg/mL·hr	25.3 µg/mL	100 % 84 %

\* P<sub>auc</sub>: probability that AUC is >400 (efficacy); P<sub>conc</sub>: probability that C<sub>trough</sub> is above 20 µg/mL (toxicity)

### Parameters & Predictions

Concentrations

	Population	Individual
CL	0.464	0.308 L/hr
V <sub>c</sub>	3.09	3.04 L
t <sub>1/2</sub>	4.62	6.84 hr

### Drug monitoring

Edit doses/TDM

	Dose	Interval	Start time	Infusion length	TDM	Since dose	Comments
1	60 mg		12/30/17 11:00	1 hours			
2	60 mg	7 h 29 m	12/30/17 18:29	1 hours			
3	60 mg	8 h 26 m	12/31/17 02:04	1 hours	10 mg/L	7 h 35 m	12/31/17 08:28 dc 416/9, no change (1)
4	60 mg	7 h 52 m	12/31/17 10:47	1 hours			
5	60 mg	7 h 43 m	12/31/17 18:30	1 hours			
6	60 mg	8 h 3 m	01/01/18 02:33	1 hours			
7	60 mg	8 h 44 m	01/01/18 11:17	1 hours	9 mg/L	7 h 27 m	01/01/18 12:27 dc 386/7.8, increase to 70 mg Q... (1)

- Custom dose field enables simulation of different dosing regimens and assessment of exposure metrics (AUC, C<sub>trough</sub>, C<sub>max</sub>)

- Dosing Reference Table
  - Customized to your institution's protocols
  - Review exposure metrics (AUC, C<sub>trough</sub>, C<sub>max</sub>)

# DOSING HISTORY AND DRUG LEVEL DATA (TDM)

Assess dosing history, incorporate TDM levels, and add notes

Ranvir Mangat
☰

### Dose information

⚙️

last updated 2 days ago, starting with dose #25

Δ	Dose	Interval	Inf. length	AUC <sub>24</sub>	C <sub>trough,ss</sub>	P <sub>auc</sub> *	P <sub>conc</sub> *
<input type="checkbox"/>	<input type="text" value=""/> mg	<input type="text" value="8"/> hours	<input type="text" value="1"/> hours				

**Reference table** ⓘ More info

<input type="checkbox"/>	-30 %	49 mg (10.21 mg/kg)	8 hours	1 hours	478 µg/mL·hr	13.6 µg/mL	97 % 8 %
<input type="checkbox"/>	-10 %	63 mg (13.12 mg/kg)	8 hours	1 hours	614 µg/mL·hr	17.5 µg/mL	100 % 25 %
<input type="checkbox"/>	<b>previous</b>	70 mg (14.58 mg/kg)	8 hours	1 hours	683 µg/mL·hr	19.4 µg/mL	100 % 44 %
<input type="checkbox"/>	+15 %	80.5 mg (16.77 mg/kg)	8 hours	1 hours	785 µg/mL·hr	22.4 µg/mL	100 % 70 %
<input type="checkbox"/>	+30 %	91 mg (18.96 mg/kg)	8 hours	1 hours	887 µg/mL·hr	25.3 µg/mL	100 % 84 %

\* P<sub>auc</sub>: probability that AUC is >400 (efficacy); P<sub>conc</sub>: probability that C<sub>trough</sub> is above 20 µg/mL (toxicity)

### Parameters & Predictions

⚙️ Concentrations ⌵

	Population	Individual	
CL	0.464	0.308 L/hr	
V <sub>c</sub>	3.09	3.04 L	
t <sub>1/2</sub>	4.62	6.84 hr	

### Drug monitoring

	Dose	Interval	Start time	Infusion length	TDM	Since dose	Comments
1	60 mg		12/30/17 11:00	1 hours			
2	60 mg	7h 29m	12/30/17 18:29	1 hours			
			12/31/17 02:04		10 mg/L	7h 35m	12/31/17 08:28 DC 416/9, no change (1)
3	60 mg	8h 26m	12/31/17 02:55	1 hours			
4	60 mg	7h 52m	12/31/17 10:47	1 hours			
5	60 mg	7h 43m	12/31/17 18:30	1 hours			
6	60 mg	8h 3m	01/01/18 02:33	1 hours			
			01/01/18 10:00		9 mg/L	7h 27m	01/01/18 12:27 DC 386/7.8, increase to 70 mg Q... (1)
7	60 mg	8h 44m	01/01/18 11:17	1 hours			

- Dosage history
- Administration time and date
- TDM

- Add notes



# PK PLOTS

## Visualize individual patient PK and dosing regimen

Ranvir Mangat

### Dose information

Update ⚙️

last updated 2 days ago, starting with dose #25

Δ	Dose	Interval	Inf. length	AUC <sub>24</sub>	C <sub>through,ss</sub>	P <sub>auc*</sub>	P <sub>conc*</sub>
<input type="checkbox"/>	<input type="text" value=""/>	mg	<input type="text" value="8"/>	hours	<input type="text" value="1"/>	hours	

**Reference table** More info

<input type="checkbox"/>	-30 %	49 mg (10.21 mg/kg)	8 hours	1 hours	478 µg/mL·hr	13.6 µg/mL	97 %	8 %
<input type="checkbox"/>	-10 %	63 mg (13.12 mg/kg)	8 hours	1 hours	614 µg/mL·hr	17.5 µg/mL	100 %	25 %
<input checked="" type="checkbox"/>	previous	70 mg (14.58 mg/kg)	8 hours	1 hours	683 µg/mL·hr	19.4 µg/mL	100 %	44 %
<input type="checkbox"/>	+15 %	80.5 mg (16.77 mg/kg)	8 hours	1 hours	785 µg/mL·hr	22.4 µg/mL	100 %	70 %
<input type="checkbox"/>	+30 %	91 mg (18.96 mg/kg)	8 hours	1 hours	887 µg/mL·hr	25.3 µg/mL	100 %	84 %

\* P<sub>auc</sub>: probability that AUC is >400 (efficacy); P<sub>conc</sub>: probability that C<sub>through</sub> is above 20 µg/mL (toxicity)

### Parameters & Predictions

Concentrations

	Population	Individual
CL	0.464	0.308 L/hr
V <sub>c</sub>	3.09	3.04 L
t <sub>1/2</sub>	4.62	6.84 hr

### Drug monitoring

Edit doses/TDM

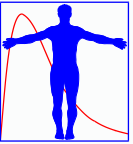
	Dose	Interval	Start time	Infusion length	TDM	Since dose	Comments
1	60 mg		12/30/17 11:00	1 hours			
2	60 mg	7 h 29 m	12/30/17 18:29	1 hours			
3	60 mg	8 h 26 m	12/31/17 02:55	1 hours			
4	60 mg	7 h 52 m	12/31/17 10:47	1 hours			
5	60 mg	7 h 43 m	12/31/17 18:30	1 hours			
6	60 mg	8 h 3 m	01/01/18 02:33	1 hours			
7	60 mg	8 h 44 m	01/01/18 11:17	1 hours	9 mg/L	7 h 27 m	01/01/18 12:27 dc 386/7.8, increase to 70 mg Q... (1)

- Assess individual PK versus population

- Simulate and visualize course of therapy

# DOSEMERX

---



# DoseMeRx

Presentation by Dallan London

# DoseMeRx Overview & Case Example

—  
Prepared for MediMatics

August 2018



## Patients at Demonstration Hospital

**+ Add Patient** Delete PatientSearch:  Show Archived Patients

Patient ID



Name



Date of Birth



Sex



Adding a patient is  
easy!

1. Go To Patients  
Tab

2. Click Add Patient

## Add Patient ✕



Patient ID

001



Family Name

Medmatics

Given Name(s)

Example

Date of Birth

06/06/1972

Sex

Female



Weight (kg)

57

Height (cm)  
OPTIONAL

160



Ward

Emergency



Save Patient

## Add Course to Patient



Drug

---



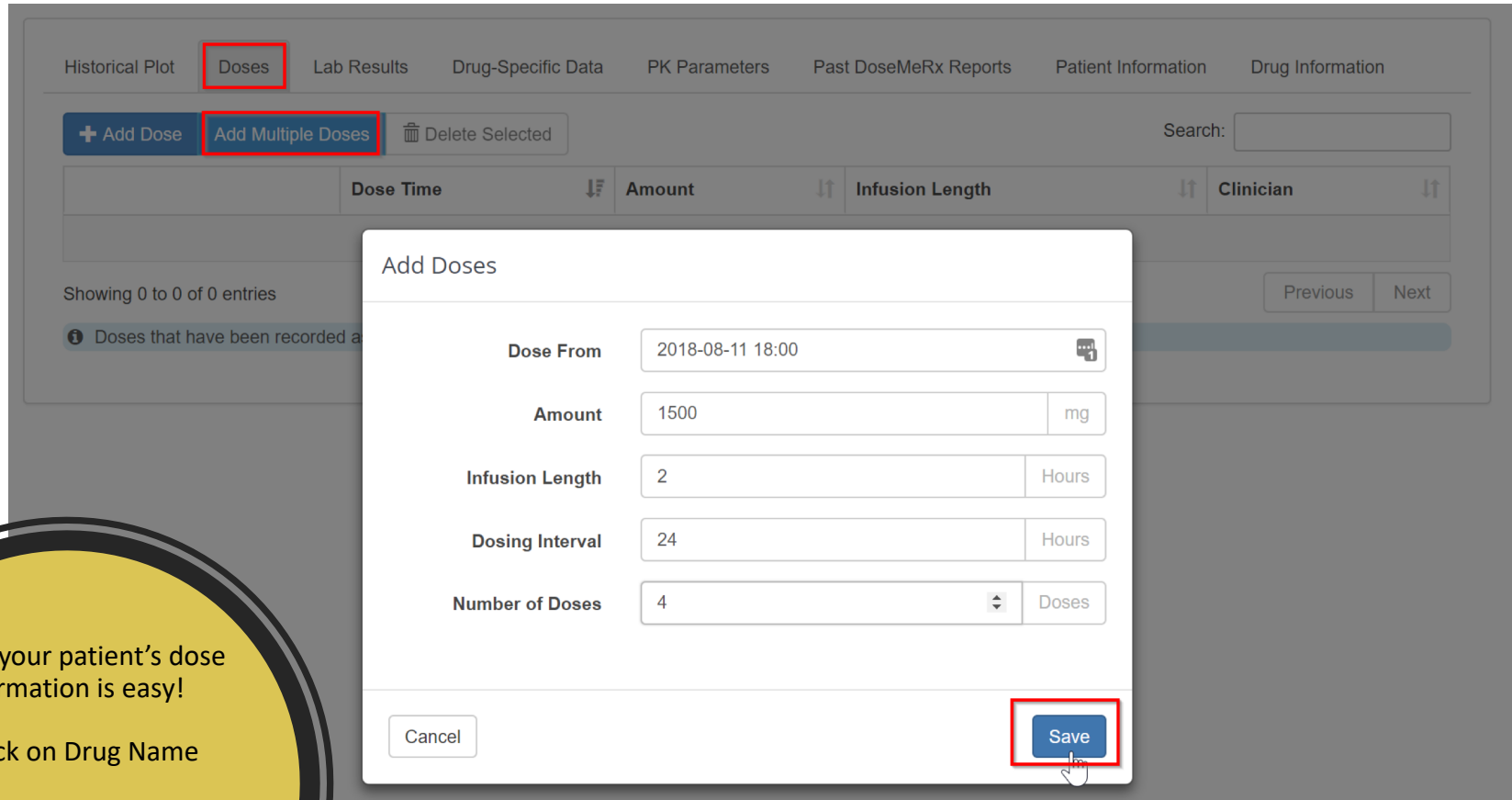
**i** Note: Drugs may be unavailable for selection due to limitations including height, weight, and age. E.g. DoseMe's pediatric-only drug models cannot be added to an adult patient.

Close

Add

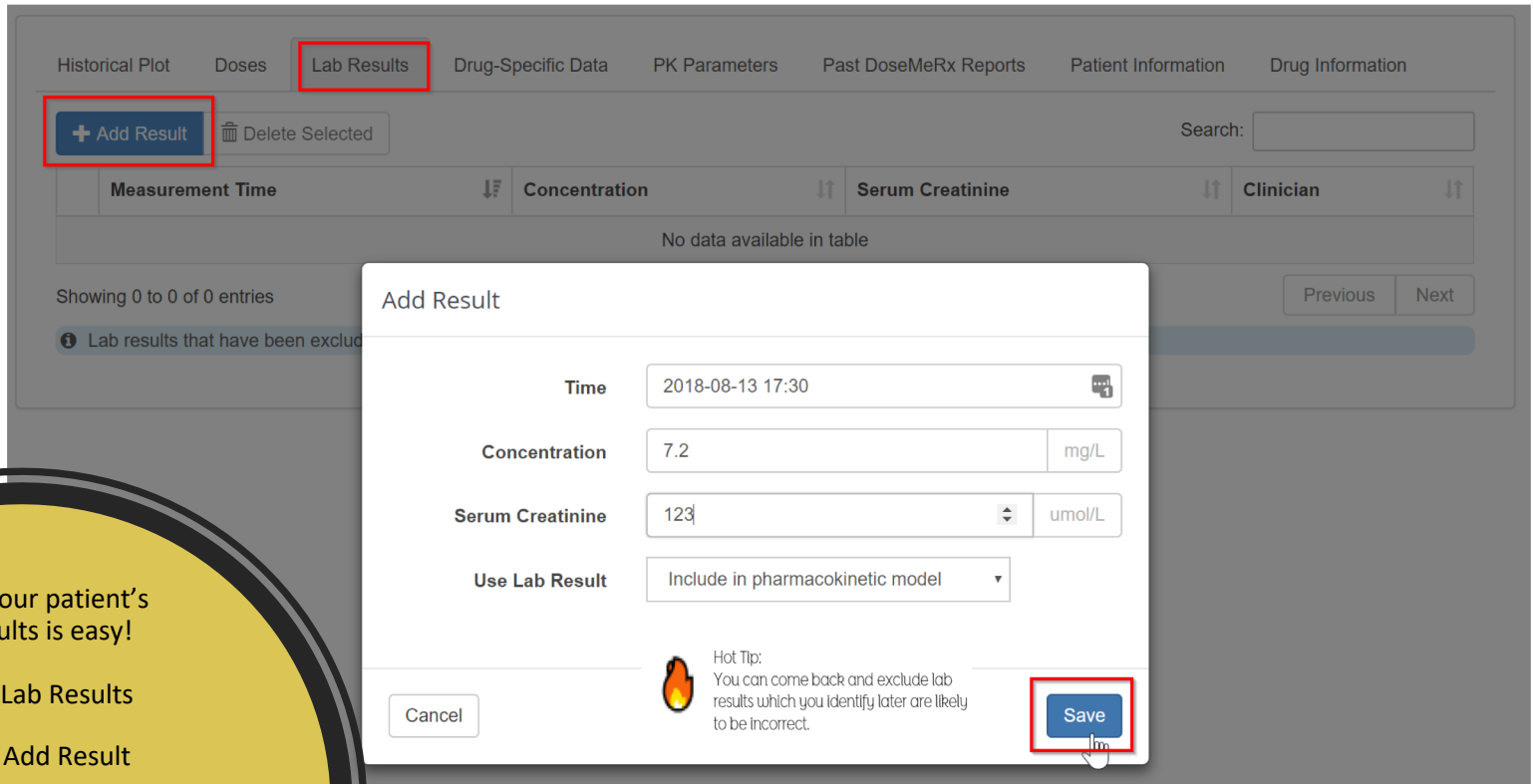
You can add a course from a wide range of drugs

1. Click on Patient ID
2. Click Add Course
3. Select Drug from Available List
4. Click Add

A screenshot of the DoseMe web application interface. The background is a dimmed view of the main dashboard with tabs for "Historical Plot", "Doses", "Lab Results", "Drug-Specific Data", "PK Parameters", "Past DoseMeRx Reports", "Patient Information", and "Drug Information". The "Doses" tab is selected and highlighted with a red box. Below the tabs are buttons for "+ Add Dose", "Add Multiple Doses" (highlighted with a red box), and "Delete Selected". A search bar is visible on the right. In the foreground, a white modal window titled "Add Doses" is open. It contains the following fields: "Dose From" (2018-08-11 18:00), "Amount" (1500 mg), "Infusion Length" (2 Hours), "Dosing Interval" (24 Hours), and "Number of Doses" (4). At the bottom of the modal are "Cancel" and "Save" buttons, with the "Save" button highlighted by a red box and a mouse cursor pointing to it.

Adding your patient's dose information is easy!

1. Click on Drug Name
2. Click on Doses tab
3. Add a Single Dose and/or Multiple Doses



The screenshot shows the DoseMe interface with the 'Lab Results' tab selected. A red box highlights the '+ Add Result' button. Below it, a table header is visible with columns for 'Measurement Time', 'Concentration', 'Serum Creatinine', and 'Clinician'. The table is currently empty, displaying 'No data available in table'. A modal form titled 'Add Result' is open, containing the following fields:

- Time:** 2018-08-13 17:30
- Concentration:** 7.2 mg/L
- Serum Creatinine:** 123 umol/L
- Use Lab Result:** Include in pharmacokinetic model

At the bottom of the modal, there is a 'Cancel' button, a 'Hot Tip' icon, and a 'Save' button. The 'Save' button is highlighted with a red box.

**Hot Tip:** You can come back and exclude lab results which you identify later are likely to be incorrect.

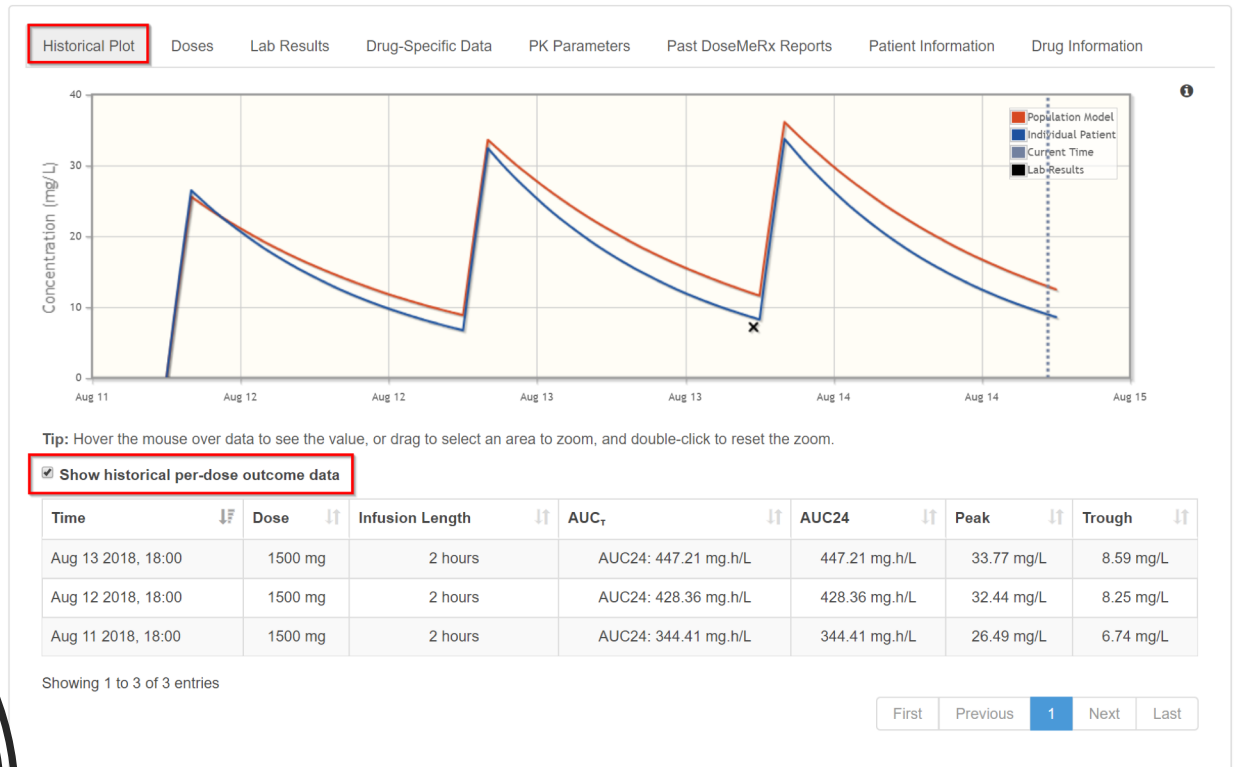
Adding your patient's lab results is easy!

1. Click Lab Results
2. Click Add Result
3. Click in Time field and Select/Type Date and Time of Result
4. Enter available result e.g. Drug Level, SeCr
5. Click Save



The red line shows the dose response of the population with the same characteristics as your patient.

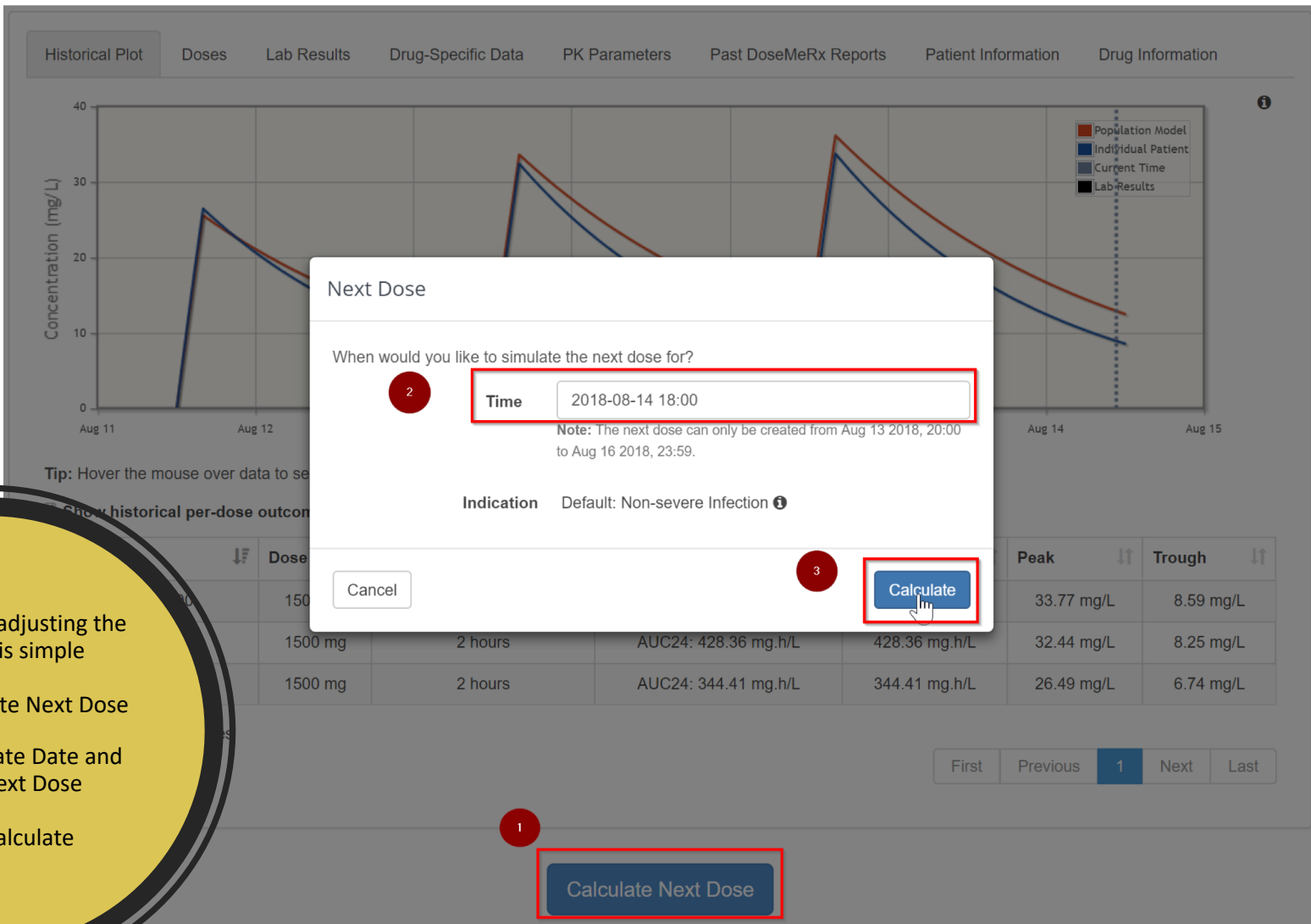
The blue line represents how your patient has responded to previous doses.



Calculate Next Dose

Let's see how your patient is going!

1. View Historical Plot based on Previous Doses & Lab Results
2. If needed, historical per-dose outcome data available with one click



Historical Plot   Doses   Lab Results   Drug-Specific Data   PK Parameters   Past DoseMeRx Reports   Patient Information   Drug Information

Concentration (mg/L)

Population Model  
Individual Patient  
Current Time  
Lab Results

Aug 11   Aug 12   Aug 14   Aug 15

Tip: Hover the mouse over data to see...  
Show historical per-dose outcomes

When would you like to simulate the next dose for?

2   Time   2018-08-14 18:00

Note: The next dose can only be created from Aug 13 2018, 20:00 to Aug 16 2018, 23:59.

Indication   Default: Non-severe Infection ⓘ

3   Calculate

	Dose			Peak	Trough
	1500 mg	2 hours	AUC24: 428.36 mg.h/L	33.77 mg/L	8.59 mg/L
	1500 mg	2 hours	AUC24: 428.36 mg.h/L	32.44 mg/L	8.25 mg/L
	1500 mg	2 hours	AUC24: 344.41 mg.h/L	26.49 mg/L	6.74 mg/L

First   Previous   1   Next   Last

1   Calculate Next Dose

Calculating or adjusting the next dose is simple

1. Click Calculate Next Dose
2. Select/Update Date and Time of Next Dose
3. Click Calculate

Review Individualized Dose Recommendation to achieve your hospital's default dosing target

Compare with Guideline or Label dose recommendation if required

Patients > Medmatics, Example (001) > Vancomycin > Dosing Report

<b>Name</b>	Medmatics, Example	<b>eCrCl</b>	41.7 mL/min (Cockcroft-Gault)
<b>DOB</b>	Jun 6, 1972 (46 years)	<b>Most Recent Dose</b>	1500 mg (Aug 13th 2018, 18:00)
<b>Weight</b>	57 kg (TBW: 57 kg)	<b>Most Recent Lab Result</b>	7.2 mg/L (Aug 13th 2018, 17:30)
<b>Height</b>	160 cm	<b>Indication</b>	Default: Non-severe Infection
<b>Clinician</b>	Ms Holly McCallum	<b>Drug</b>	Vancomycin (Adult)

**Default Individualized Target** ⓘ

750 mg over 1.5 hours twice daily for 3 days

**Target:** Trough: 15 mg/L


**Predicted:** Trough: 13.2 mg/L

Peak	25.5 mg/L
Trough	13.2 mg/L
AUC24	450.8 mg.h/L

Plot

**Guideline Dose** ⓘ

750 mg once daily for 3 days

 **Hot Tip:**  
You can choose your preferred guideline to include

Peak	17.5 mg/L
Trough	4.3 mg/L
AUC24	229 mg.h/L

Plot

**Label Dose** ⓘ

250 mg twice daily for one day

**Warning: Dose is less than 500 mg**  
**Warning: Dose is less than 10 mg/kg**

Peak	10.5 mg/L
Trough	5.3 mg/L
AUC24	184.8 mg.h/L

Plot



**Hot Tip:**  
You can set your default targets based on your preferred target – trough, peak, AUC or other methods

1. Click Target tab in  
Customize Box

2. Adjust target type/target  
value

3. Click Calculate to obtain a  
revised recommendation

### Customize ⓘ

**Target** Dose

DoseMeRx can calculate a dose based upon previously-processed pathology results. Please review against the guideline dose and consider the clinical implications carefully.

**Target** Trough Only ▾

**Target Trough** Trough only  
AUC24

**Infusion Length**  hours

**Dosing Interval**  hours

**Number of Doses**  doses

**Next Dose At**  ⓘ

**Note:** The next dose can only be created from Aug 13 2018, 20:00 to Aug 16 2018, 23:59.

**Calculate**

1. Click Dose tab in Customize Box
2. Enter your desired dose details
3. Click Calculate to see the expected outcomes of that dose

### Customize ⓘ

Target **Dose**

Dose

Infusion Length

Dosing Interval

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Number of Doses

Next Dose At  📅

Note: The next dose can only be created from Aug 13 2018, 20:00 to Aug 16 2018, 23:59.



**Hot Tip:**  
You can trial and error  
in our software and  
not on your patient!

Want more?  
Historical doses, results and predicted outcomes are all available

Historical Doses and Results

Record	Time	Infusion Length	Dose	Concentration	SeCr
Dose	Aug 11 2018, 18:00	2 hours	1500 mg	--	--
Dose	Aug 12 2018, 18:00	2 hours	1500 mg	--	--
Lab Result	Aug 13 2018, 17:30	--	--	7.2 mg/L	123 umol/L
Dose	Aug 13 2018, 18:00	2 hours	1500 mg	--	--

ⓘ Doses that have been recorded as given at a future time (i.e. not yet given) are italicized.  
 Lab results that have been excluded from use in the pharmacokinetic model are struck-out and gray.

Predicted Default Individualized Dose Outcomes

Dose #	Time	Infusion Length	Dose	AUC12	Peak	Trough
1	Aug 14 2018, 18:00	1.5 hours	750 mg	186.53 mg.h/L	21.27 mg/L	11.07 mg/L
2	Aug 15 2018, 06:00	1.5 hours	750 mg	207.47 mg.h/L	23.53 mg/L	12.24 mg/L
3	Aug 15 2018, 18:00	1.5 hours	750 mg	217.39 mg.h/L	24.6 mg/L	12.8 mg/L
4	Aug 16 2018, 06:00	1.5 hours	750 mg	222.1 mg.h/L	25.1 mg/L	13.06 mg/L

Customized Dose Profile [750 mg over 1.5 hours twice daily for 3 days]

25.34 mg/L	13.19 mg/L
25.46 mg/L	13.25 mg/L

pharmacokinetic literature model. Please



View Dose Report

**Default Individualized Target:** 750 mg over 1.5 hours twice daily for 3 days. Valid for 3 days only.

**Target:** Trough: 15 mg/L **Predicted:** Trough: 13.2 mg/L

Your clinical notes can go here!

Create Dose Report

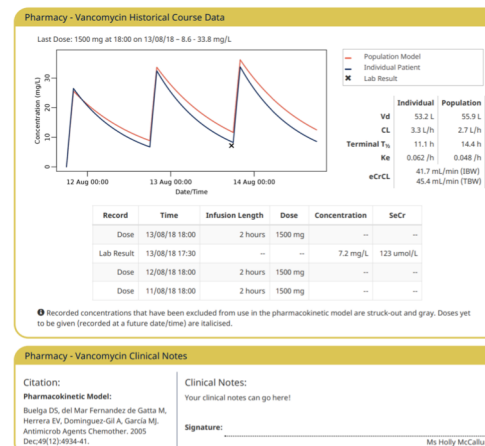
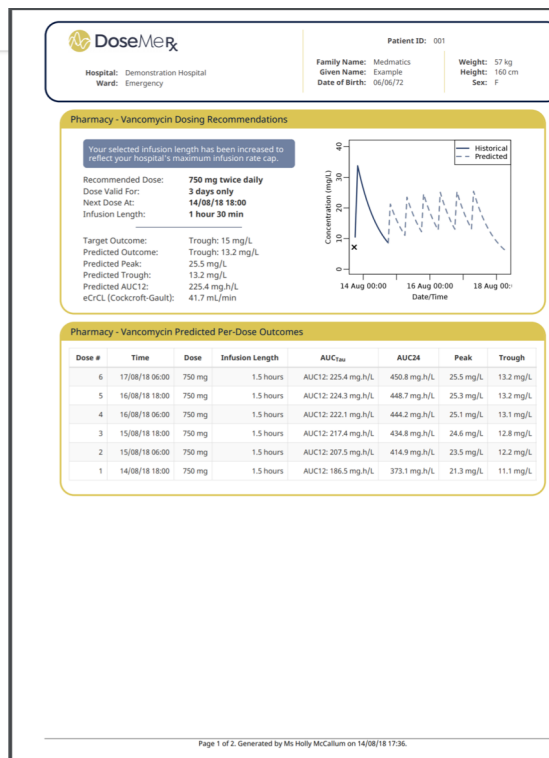
Predicted outcomes are based upon processed pathology results fitted to the mean estimate from the selected digitized published pharmacokinetic literature model and assume correct entry of data.

Please verify with continued monitoring.

1. Make your dose selection

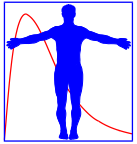
2. Enter any clinical notes (optional)

3. Click Create Dose Report



# CONCLUSIONS: STRENGTHS

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- **MwPharm++**
  - Open & transparent system (models & database)
  - Rich and responsive user interface (EN, NL, KO, CZ, PT, JA, ZH)
  - Clinical data export and import via Excel
  - Stand-alone (EHR integration via data warehouse)
  - Population modeling module available (KinPop++)
- **InsightRX**
  - Cloud based web application (single screen multi panel dashboard)
  - Direct EHR integration (Epic)
  - Handles inter occasion variability (IOV)
  - High-performance R-based back end (PKPDsim R package)
- **DoseMeRx**
  - Cloud based web application
  - Direct EHR integration (Epic, Cerner)
  - iOS apps for iPhone and iPad (point of care service)



# QUESTIONS

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