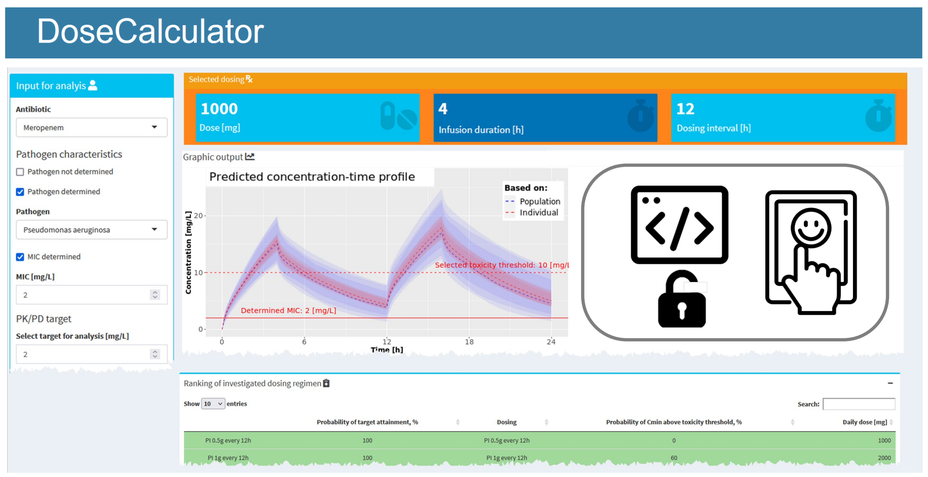
Successful validation of a model-informed precision dosing instrument for meropenem in critically ill patients, the DoseCalculator, against NONMEM®

F.E. Weber (1,2), F.A. Weinelt (1,2), C. Nyhoegen (1), F. Pfäfflin (3), A. Theloe (4), U. Trost (3), P. Kießling (5), W. Huisinga (2,6), S.G. Wicha (7), R. Michelet (1), S. Hennig (1,8,9), M.S. Stegemann (3), C. Kloft (1,2)

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universität Berlin, Germany, **(2)** Graduate Research Training program PharMetrX, Germany, **(3)** Dept. of Infectious Diseases, Respiratory Medicine and Critical Care, Charité - Universitaetsmedizin Berlin, Germany, **(4)** Pharmacy, Charité - Universitaetsmedizin Berlin, Germany, **(5)** Labor Berlin-Charité Vivantes GmbH, 13353 Berlin, Germany, **(6)** University of Potsdam, Institute of Mathematics/Institute of Biochemistry and Biology, Potsdam, Germany, **(7)** Institute of Pharmacy, University Hamburg, Germany, **(8)** School of Clinical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia, **(9)** Certara, Inc., Princeton, New Jersey, USA

Background and Objectives



MIPD instrument

- **Meropenem** therapy
- **Critically ill** patients

TDMxR

Figure 1: Graphical user interface of the model-informed precision dosing (MIPD) instrument 'DoseCalculator' for dosing optimisation of meropenem in critically ill patients[1,2,3,4].

Academic/industry standard NONMEM®

Objective:
Validation of DoseCalculator incorporated TDMxR algorithm against NONMEM for
(i) Estimation of **maximum *a posteriori* (MAP)** parameters,
(ii) **Simulations with MAP** parameters & **posterior distribution#**

Methods

Clinical data set[5]
- $n_{patients}$=53
- $n_{samples}$=181

NONMEM®

DoseCalculator

MAP parameter estimation

TDMxR::
estimate.map()

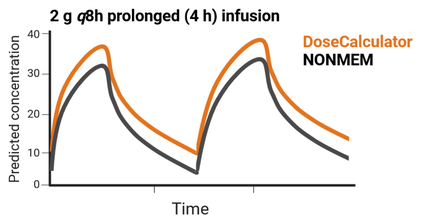
Correlation analysis: Parameter DoseCalculator vs Parameter NONMEM
Bland-Altman analysis: Parameter difference vs Parameter average (both software)

rBIAS<±10% 6,7
MARE <10%
rRMSE ↓
for MAP parameter CL, V1, V2

$ESTIMATION
MAXEVAL=0

C(t) simulation with MAP parameter & **posterior distribution#**

TDMxR::
simulate.scenario (type= "ind_var_vcov")



rBIAS <±20% 7,8,9
MARE <20%
rRMSE ↓
for $P_{0.05}$ $P_{0.50}$,$P_{0.95}$ of predicted concentration

Variance-Covariance (ETC) matrix from **.phi file**

Results

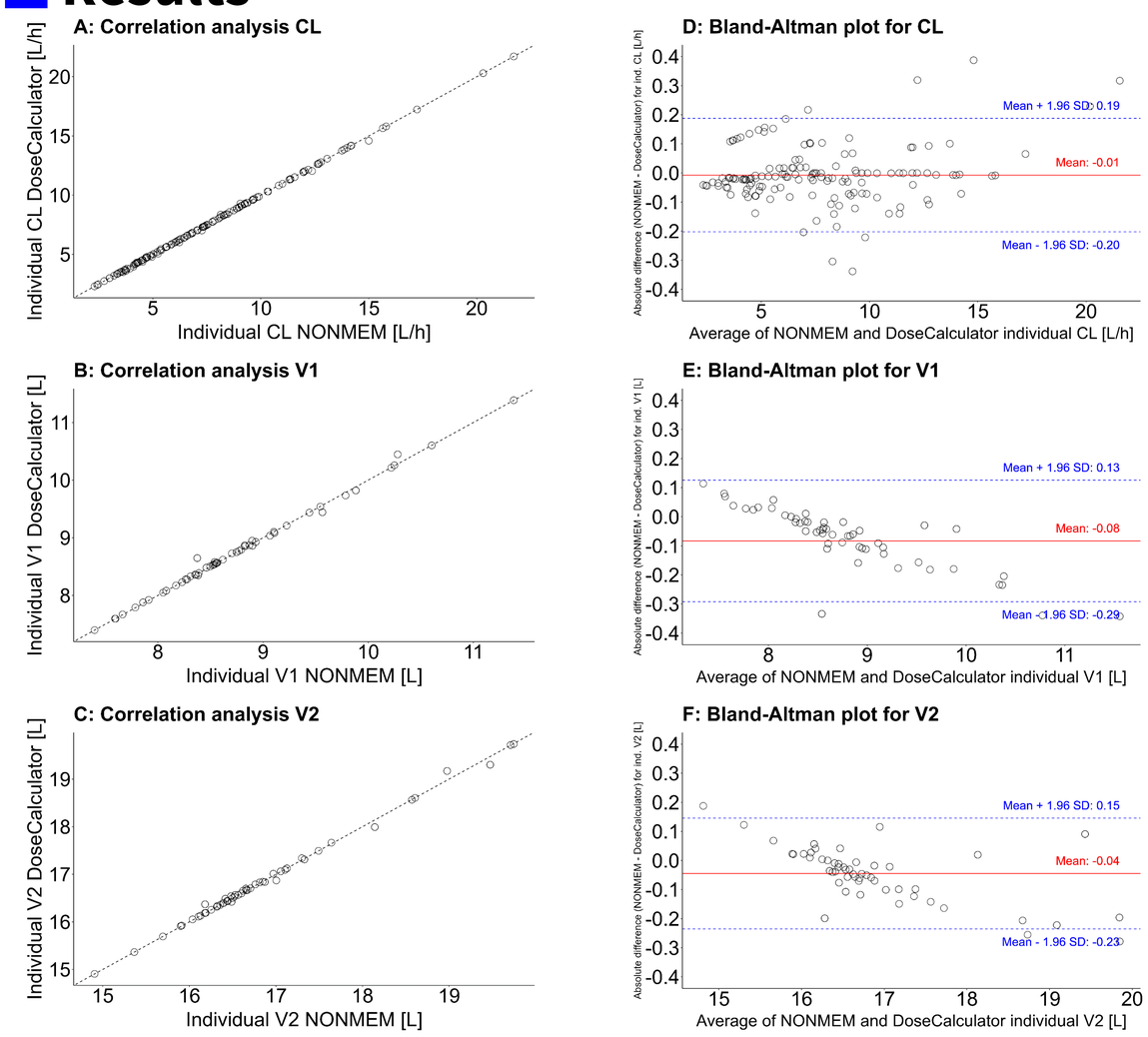


Figure 2: Comparative diagrams of maximum *a posteriori* Bayesian estimation results from 53 critically ill patients derived from DoseCalculator incorporated TDMxR algorithm versus NONMEM. Left panel: Correlation analysis plots of individually predicted PK parameters CL (A), V1 (B) and V2 (C). Dashed line: line of identity. Right panel: Bland-Altman plots for CL (D), V1 (E) and V2 (F) demonstrating absolute differences in each parameter (NONMEM - DoseCalculator) against average values derived from both methods, respectively. Solid red line: mean discrepancy; blue dashed lines: limits of agreement (mean ± 1.96 standard deviations).

Table 1: rBIAS, MARE and rRMSE for the individual maximum *a posteriori* (MAP) parameters CL, V1, V2 obtained from the DoseCalculator and the NONMEM (reference) after MAP estimation in the DoseCalculator and NONMEM (reference)

MAP parameter	rBIAS (%)	MARE (%)	rRMSE (%)
CL	-0.294	0.0674	1.07
V1	0.191	0.272	0.990
V2	0.0168	0.201	0.517

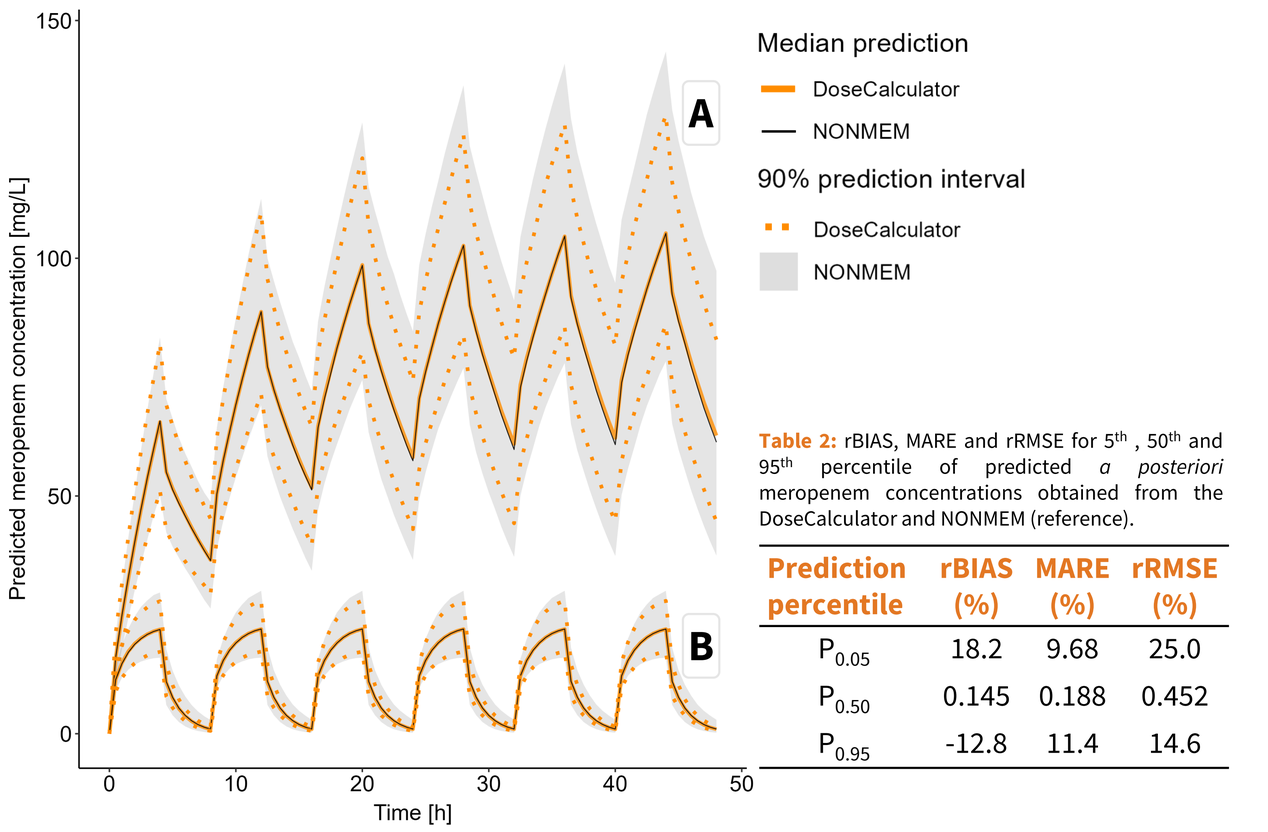


Figure 3: Comparative visualisation of *a posteriori* predicted meropenem concentrations over time in NONMEM and the DoseCalculator for 2 exemplary patients with $CLCR_{CG}$ of (A) 21 mL/min and (B) 408 mL/min and a total number of (A) two and (B) four meropenem samples considered in the Bayesian estimation.

Table 2: rBIAS, MARE and rRMSE for 5th , 50th and 95th percentile of predicted *a posteriori* meropenem concentrations obtained from the DoseCalculator and NONMEM (reference).

Prediction percentile	rBIAS (%)	MARE (%)	rRMSE (%)
$P_{0.05}$	18.2	9.68	25.0
$P_{0.50}$	0.145	0.188	0.452
$P_{0.95}$	-12.8	11.4	14.6

Discussion and Conclusions

- **Acceptance criteria met** with **high agreement in graphical analyses** (correlation analysis, Bland-Altman analysis, C(t) simulation plots) between **DoseCalculator incorporated TDMxR algorithm** compared to **NONMEM** for:
  - **MAP parameter estimation**
  - **Individual C(t) simulations (MAP parameter & posterior distribution#)**
- Higher deviations for $P_{0.05}$ and $P_{0.95}$ due to DoseCalculator using full variance-covariance matrix, whereas diagonal elements of ETC matrix used within NONMEM
- **MAP estimation and Bayesian simulation results of DoseCalculator incorporated TDMxR algorithm successfully validated against NONMEM**

Steps towards clinical implementation

DoseCalculator

- ✔ Internal evaluation of integrated PK model[3,4]
- ✔ Clinical benefit simulation study (PK/PD target attainment improvement, daily dose reduction)[2]
- ✔ Real-world evaluations (sampling time uncertainties, impact of integration of different eGFR formula values)
- ✔ Development of implementation concept[2]
- Clinical validation of Bayesian framework
- Evaluation for patients undergoing extracorporeal methods

References
[1] Wicha et al., Int. J. Antimicrob. Agents (2015)
[2] Weber et al., ECCMID (2023)
[3] Weinelt et al., Pharmaceutics (2021)
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[#] approximated by variance-covariance (ETC) matrix of individual ETAs

Abbreviations

CL	Clearance
$CLCR_{CG}$	Creatinine clearance based on Cockcroft-Gault
C(t)	Concentration-time
eGFR	Estimated glomerular filtration rate
ETC:	Variance-Covariance matrix of the individual ETA values
IIV	Interindividual variability
MAP	Maximum *a posteriori*
MARE	Median absolute relative error
MIPD:	Model-informed precision dosing
P	Percentile
PD	Pharmacodynamic
PK	Pharmacokinetic
q8h	Every 8 h
rBIAS	Relative bias
rRMSE	Relative root mean squared error
TDM	Therapeutic Drug Monitoring
V	Volume of distribution

Equations

$$\text{rBias}, \% = 1/N \sum_{1}^{i} \left(\frac{\theta_{i,DoseCalculator} - \theta_{i,NONMEM}}{\theta_{i,NONMEM}} \right) \times 100\%$$

$$MARE, \% = median \left(\left| \frac{\theta_{i,DoseCalculator} - \theta_{i,NONMEM}}{\theta_{i,NONMEM}} \right| \right) \times 100\%$$

$$\text{rRMSE}, \% = \sqrt{\frac{1}{N} \sum_{1}^{i} \frac{\left(\theta_{i,DoseCalculator} - \theta_{i,NONMEM}\right)^2}{(\theta_{i,NONMEM})^2}} \times 100\%$$

For more information:
Franz Weber,
franz.weber@fu-berlin.de
www.clinical-pharmacy.eu

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Poster PDF

AK Kloft