Application of PBPK Modeling for Inhalatives: Potential and Challenges

ASCPT 2019 Annual Meeting

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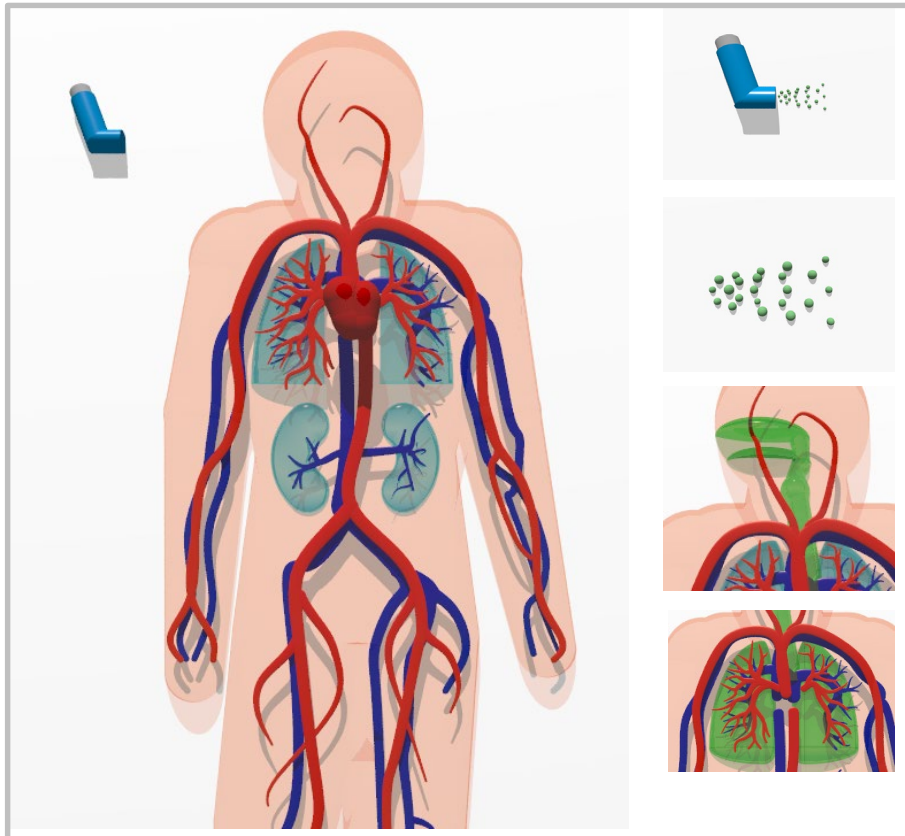
Mechanistic modeling for inhalation products

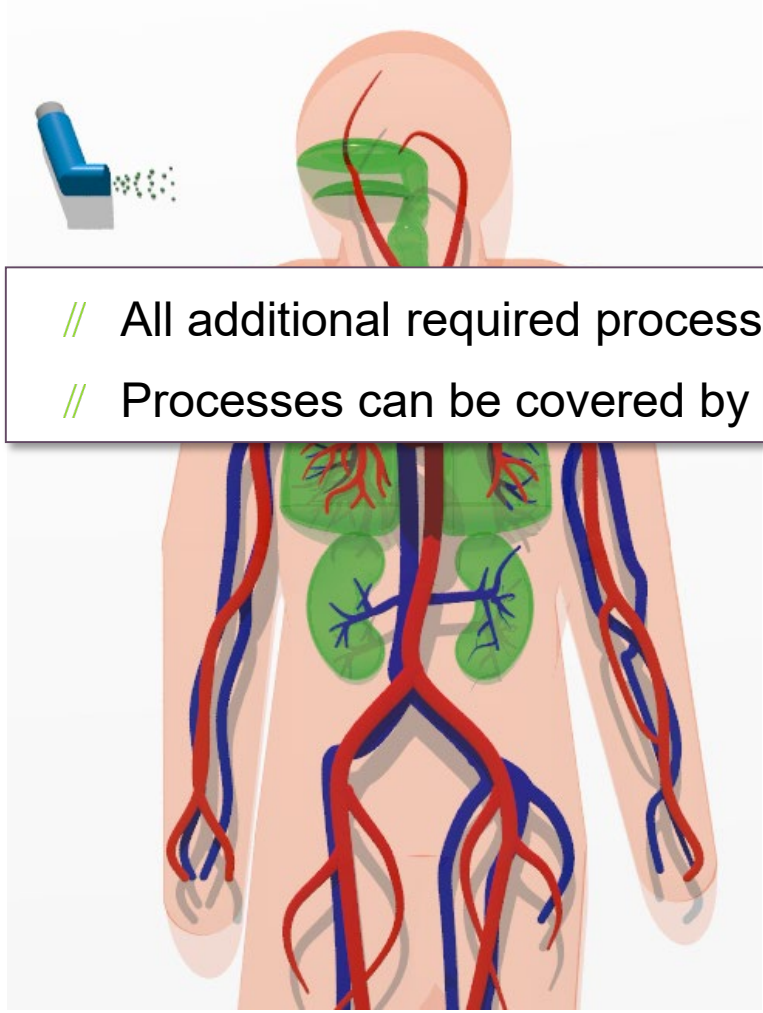
Sources of variability/uncertainty – topics potentially covered by mechanistic approaches

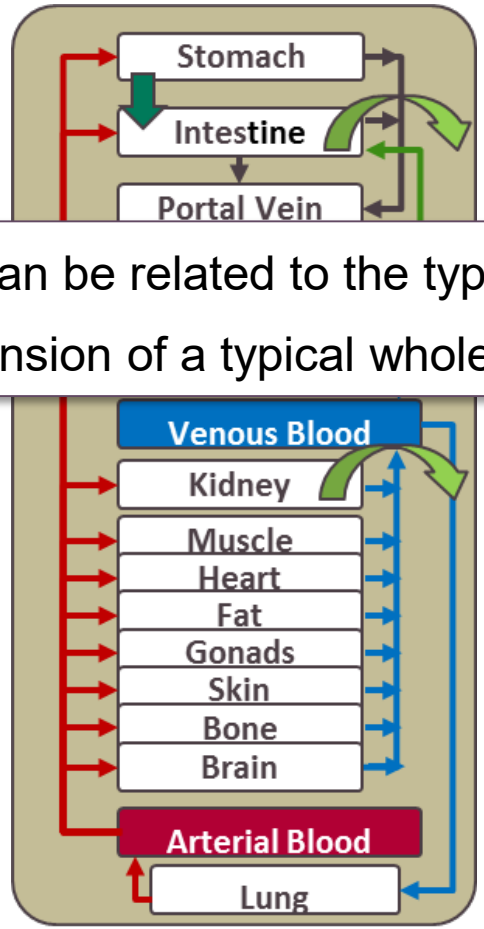


Relevant processes/properties	Modeling approaches	References
Particle delivery from device - Velocity - Spatial distribution	CFD Kinetic Monte Carlo Partial differential equations	Vulović 2018 Boger 2018 Yang 2014
- Particle size distribution - Inhalation	CFD Partial differential equations	Bäckman 2018 Boger 2018
- Amount of respiratory uptake - Swallowed dose - Particle distribution	CFD PBPK	Walenga 2016 Boger 2018 Katan 2016
- Mucoscillary transport - oral absorption after recirculation - Uptake to systemic exposure - Structure of the lung (airways) - Exhaled dose	CFD PBPK popPK NCA	Boger 2018 Salar-Behzadi 2017 Soulele 2018 Rohatagi 2003 Xu 2010 Katan 2016 Oakes 2018

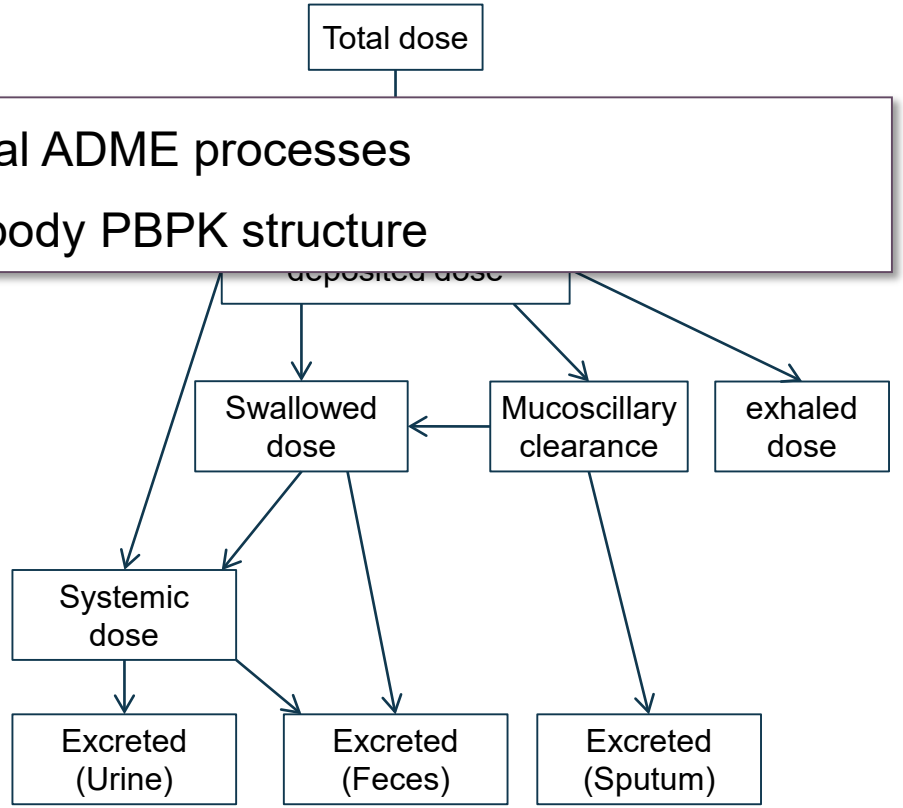
Mechanistic Modeling of Respiratory Drug Uptake

Why a PBPK model?





Extension of uptake/lung to cover all relevant processes



// All additional required processes can be related to the typical ADME processes

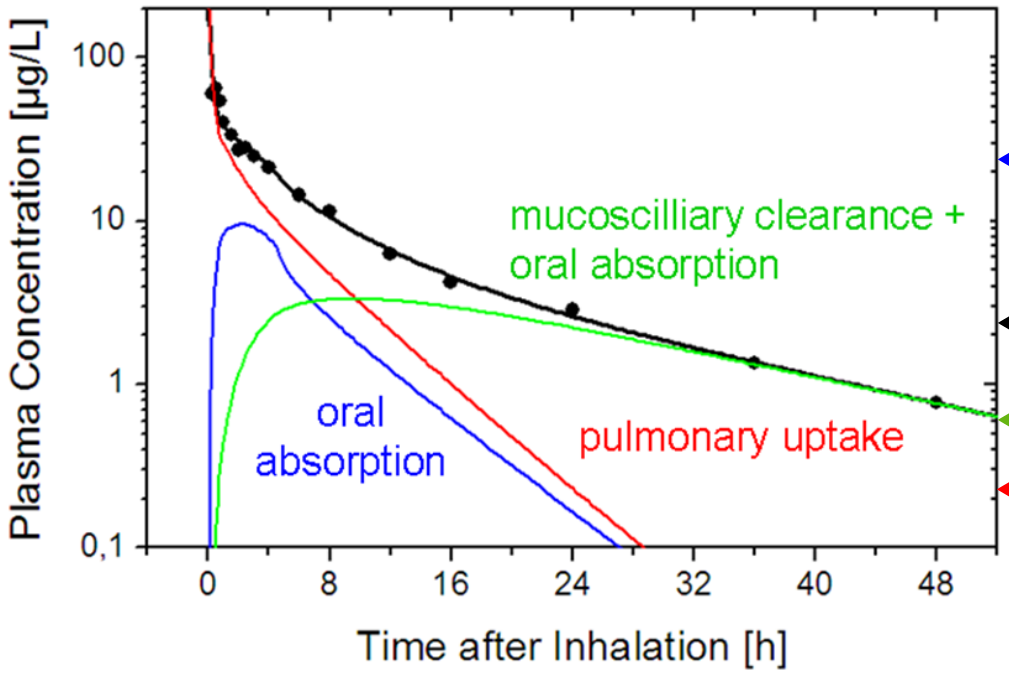
// Processes can be covered by extension of a typical whole-body PBPK structure

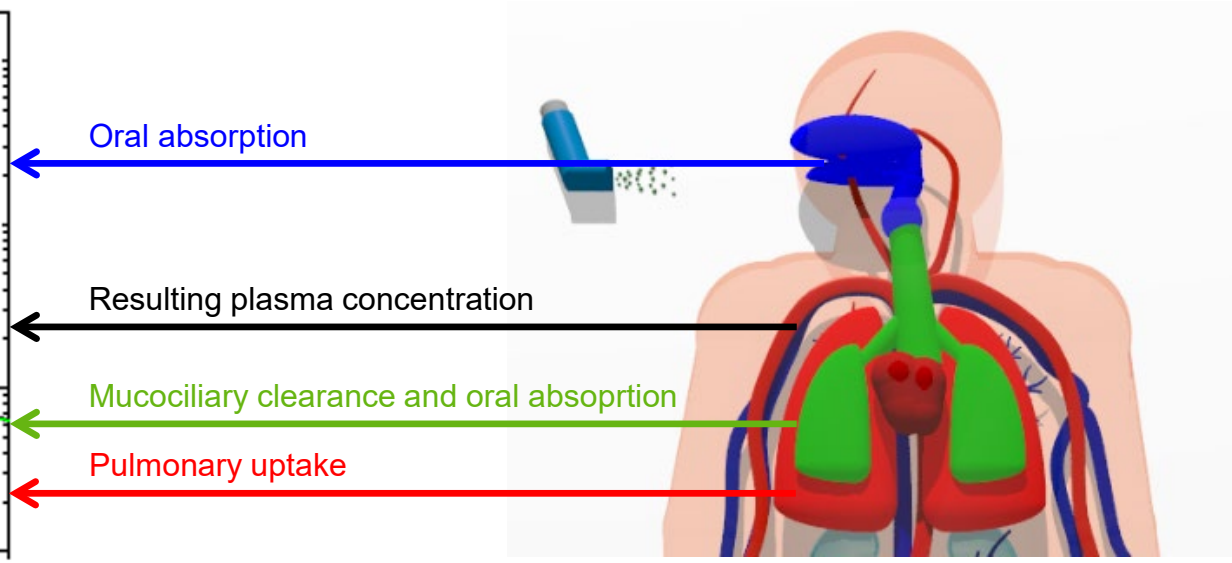
Example – Ciprofloxacin inhalation

- **Support of Clinical Development**
- **Dose finding → relevant to guide design of development program**
  - Is it possible to estimate the pulmonary deposition based on plasma level`s?
  - What is the expected systemic exposure for the clinical relevant doses?
- **Safety evaluation → labeling relevant Information**
  - What is expected in comparison to systemic exposure for p.o administration?
  - What exposure would be expected for renally impaired patients?
- **Validation of PK-methodology → important for the interpretation of PK measurements**
  - Influence of physiological processes (expectoration) on lung PK
  - Influence of PK sampling (ELF, sputum) on lung PK

Deconvolution of Ciprofloxacin Plasma PK

By use of PBPK different fractions deposited can be estimated



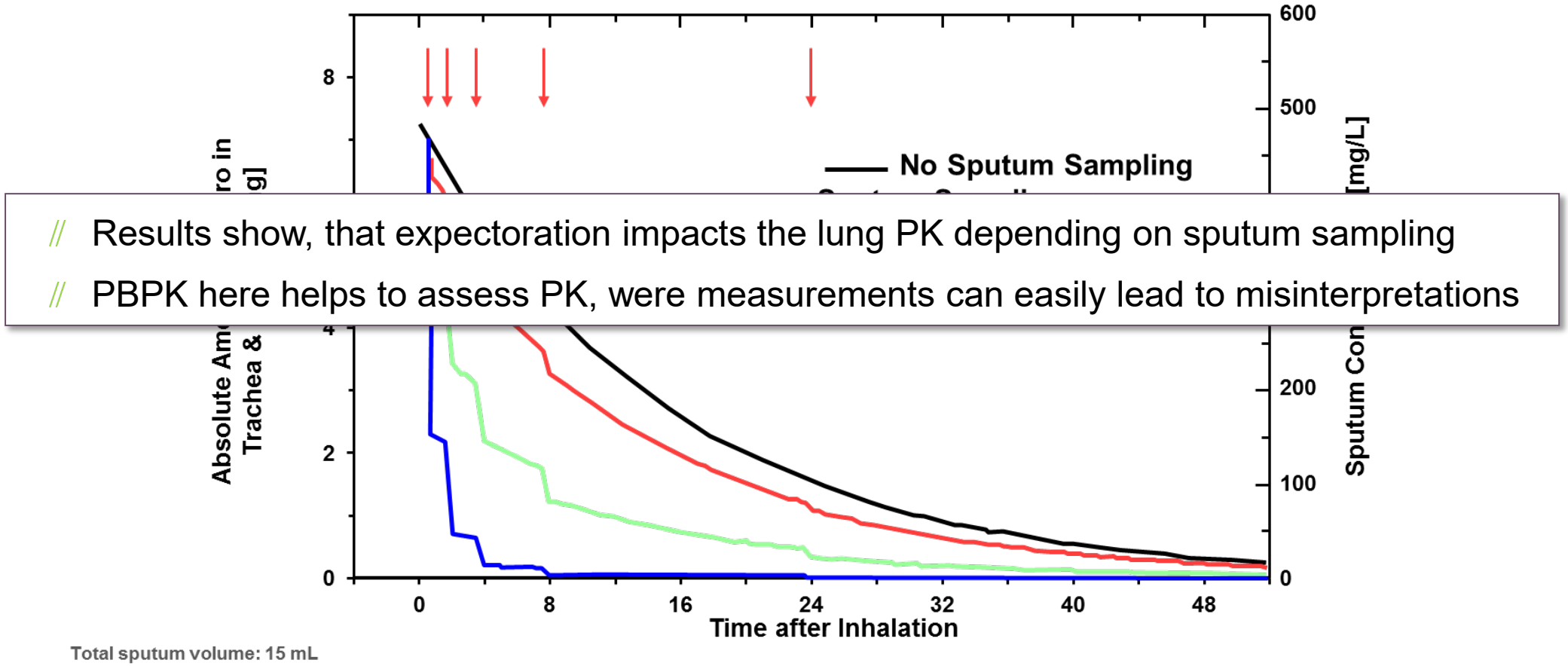


Observed plasma profile is explained as superposition of three different uptake mechanisms:

- Rapid uptake of fraction deposited in the alveolar space,
- oral absorption of the fraction deposited in the oral cavity
- a slow absorption process representing mucociliary transport from the bronchi to the oral cavity and subsequent oral absorption

Drug Clearance – Role of Expectoration

Use of PBPK-modeling to evaluate impact of Expectoration on lung PK - Example Ciprofloxacin DPI



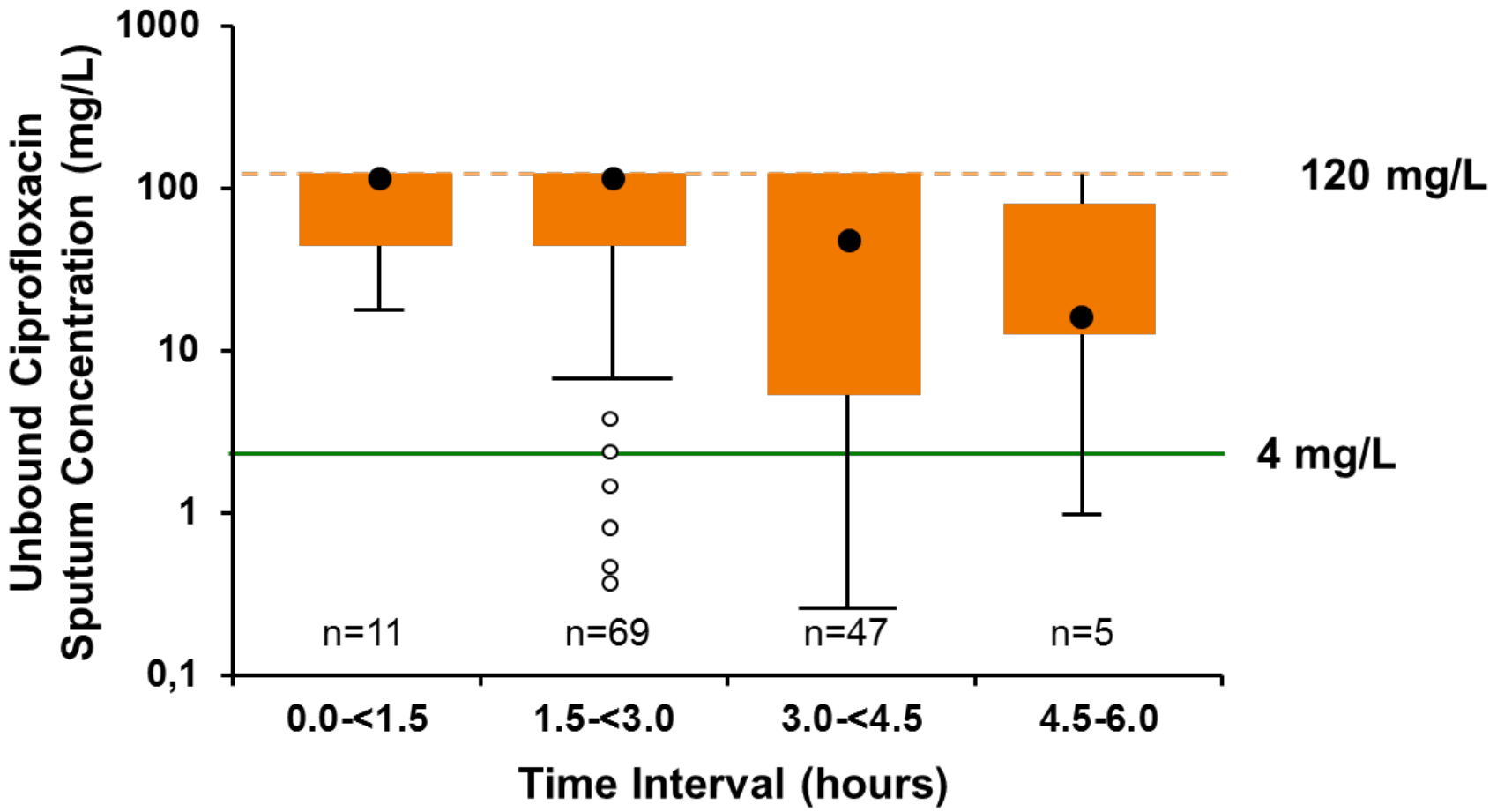
// Results show, that expectoration impacts the lung PK depending on sputum sampling

// PBPK here helps to assess PK, were measurements can easily lead to misinterpretations

Simulated amount of ciprofloxacin in trachea/bronchi over time with drug loss by expectoration or sputum sampling occuring at specific timepoint (red arrows)

Observed variability in lung PK

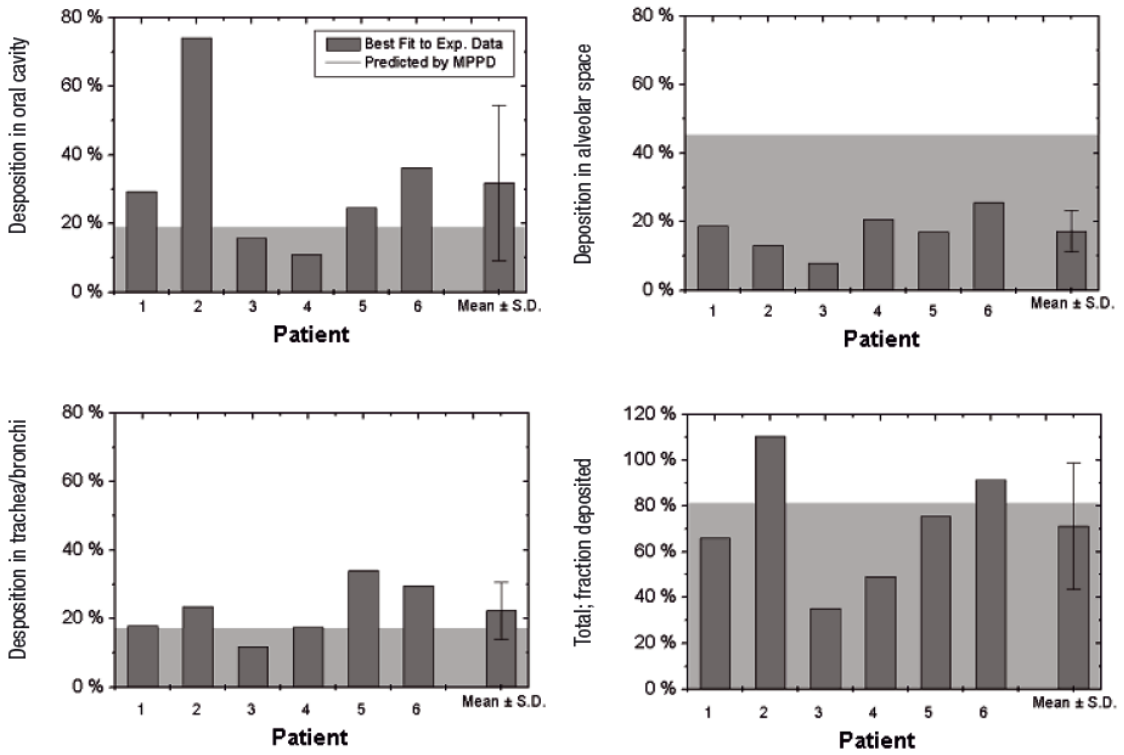
Example Ciprofloxacin DPI in NFCB patients



Deconvolution of Ciprofloxacin Plasma PK

Individual patient assessment by PBPK and comparison to standard MPPD tool

- The PBPK model is able to cover the relevant uptake route and allows an assessment of deposited dose fractions on an individual level after pulmonary delivery
- Results are consistent with results of typically used MPPD tool



S.D. = standard deviation; MPPD = multiple path particle dosimetry

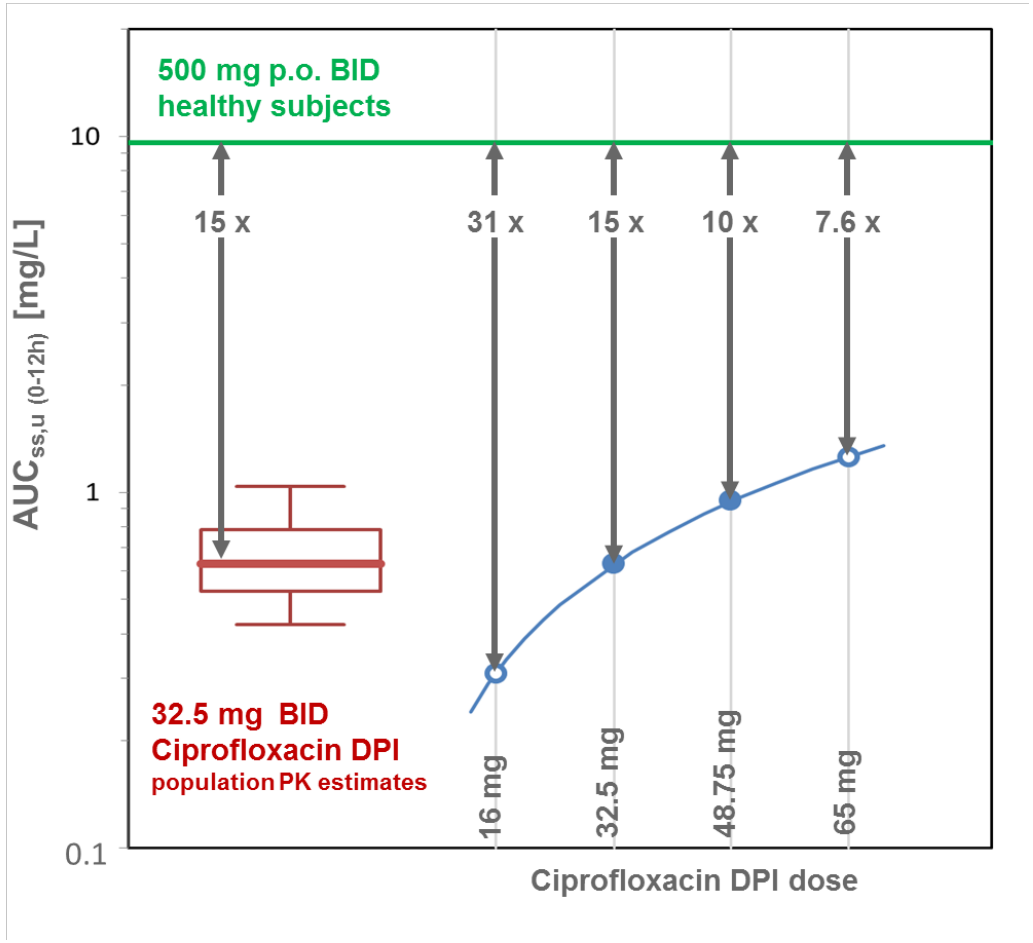
Percentage deposition of ciprofloxacin in the lung compartments following a single inhalation dose of 32.5 mg ciprofloxacin betaine as Ciprofloxacin Pulmosphere® Inhalation Powder

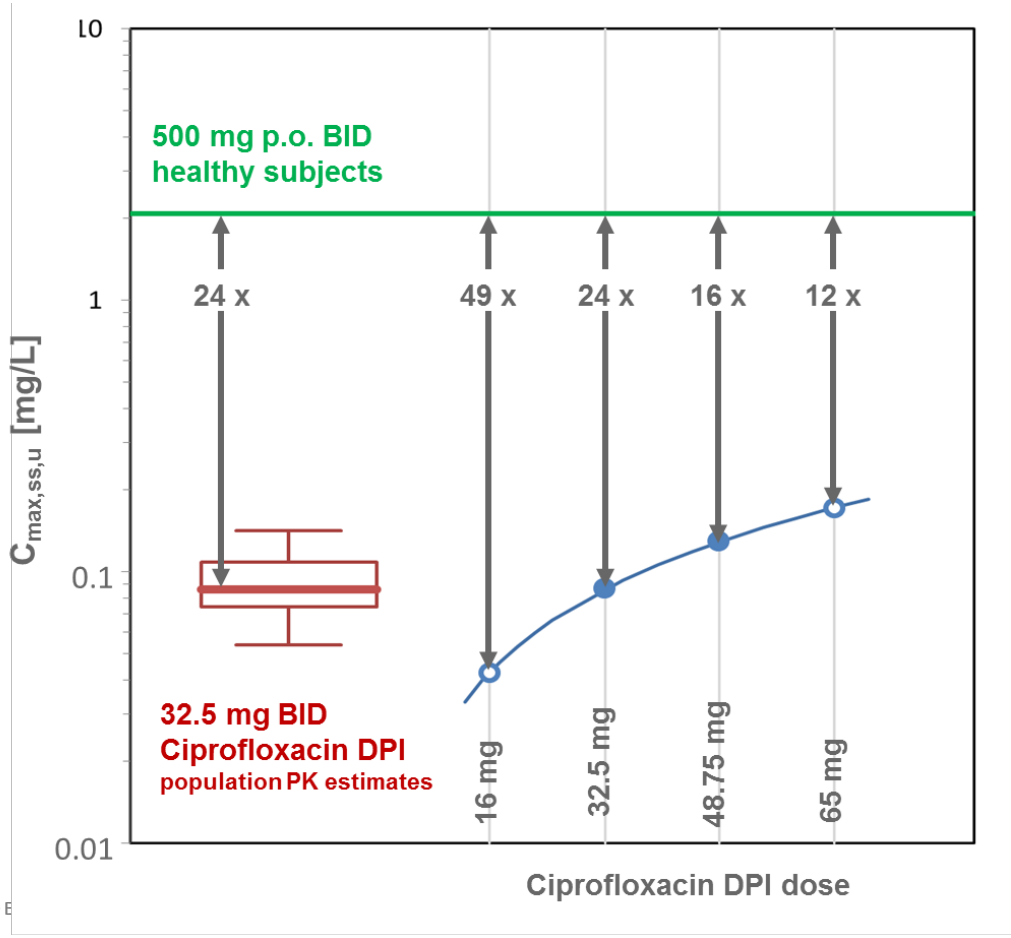
MPPD tool:
Multiple-Path-Particle Dosimetry

Prediction of systemic exposure following inhalative uptake

Comparison to the typical dose of 500 mg p.o. – assessment of systemic exposure

Predicted dose-exposure relationship

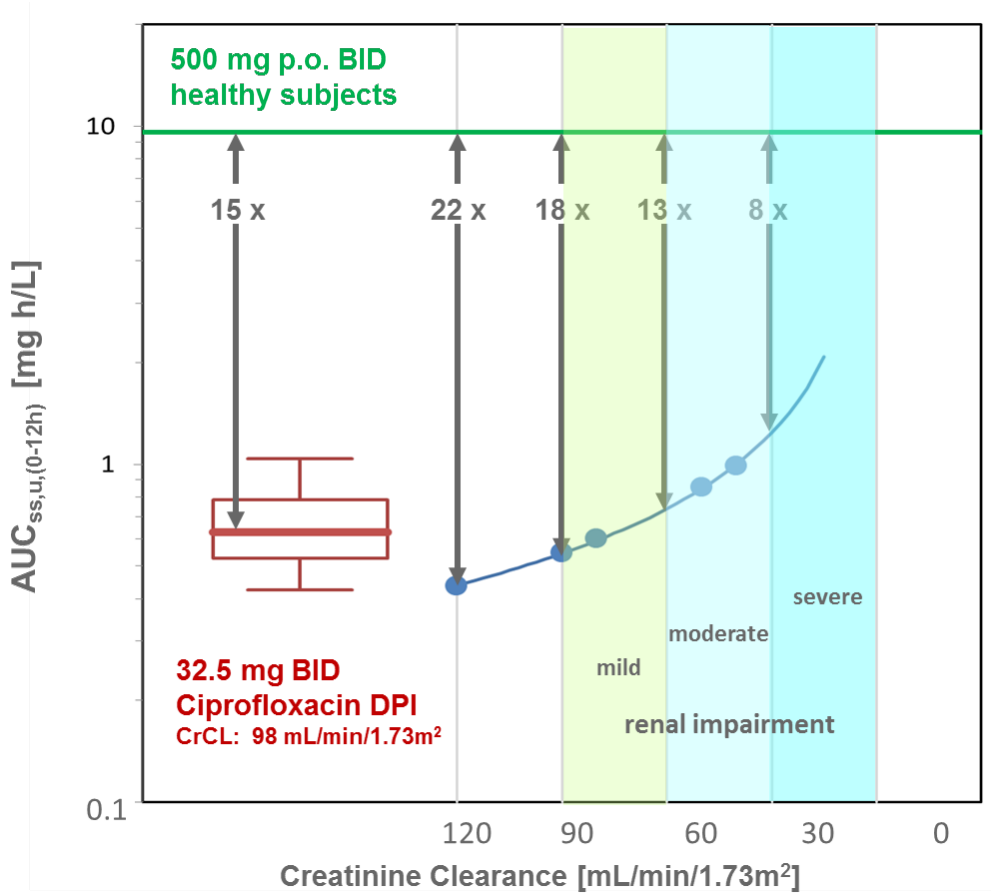


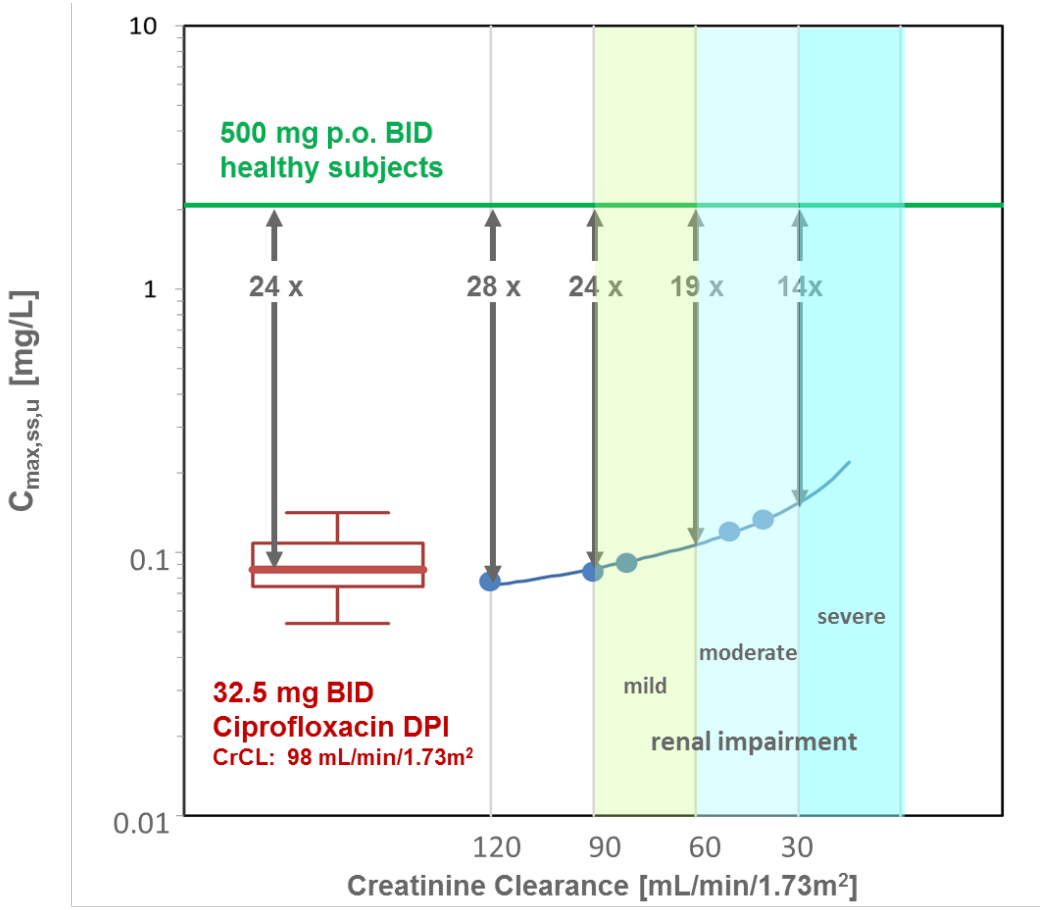


Prediction of systemic exposure following inhalative uptake

Comparison to the typical dose of 500 mg p.o. – assessment of systemic exposure under renal impairment

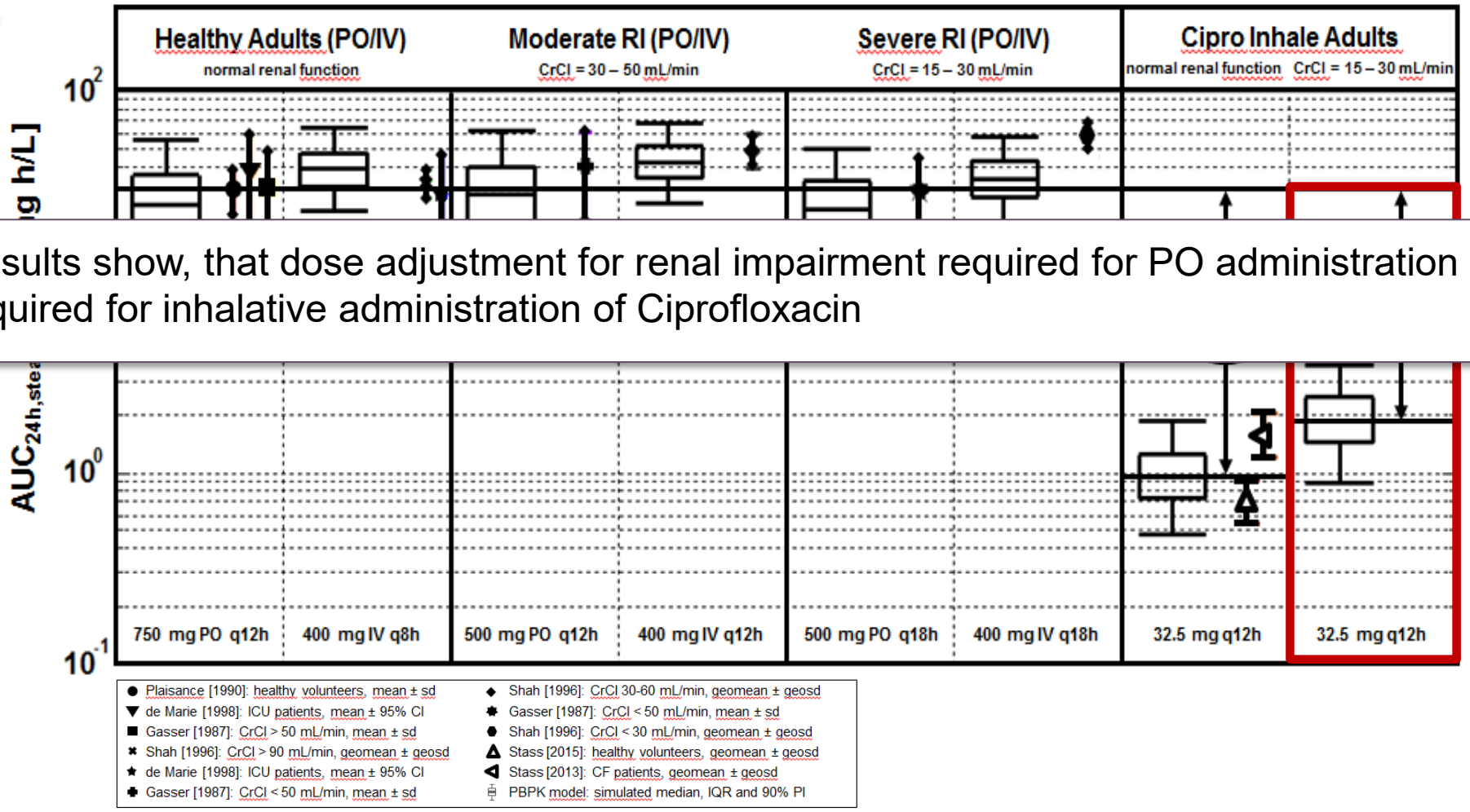
Dependency of exposure on renal function





Prediction of systemic exposure following inhalative uptake

Sufficient exposure margin predicted in renally impaired patients



// Results show, that dose adjustment for renal impairment required for PO administration is not required for inhalative administration of Ciprofloxacin

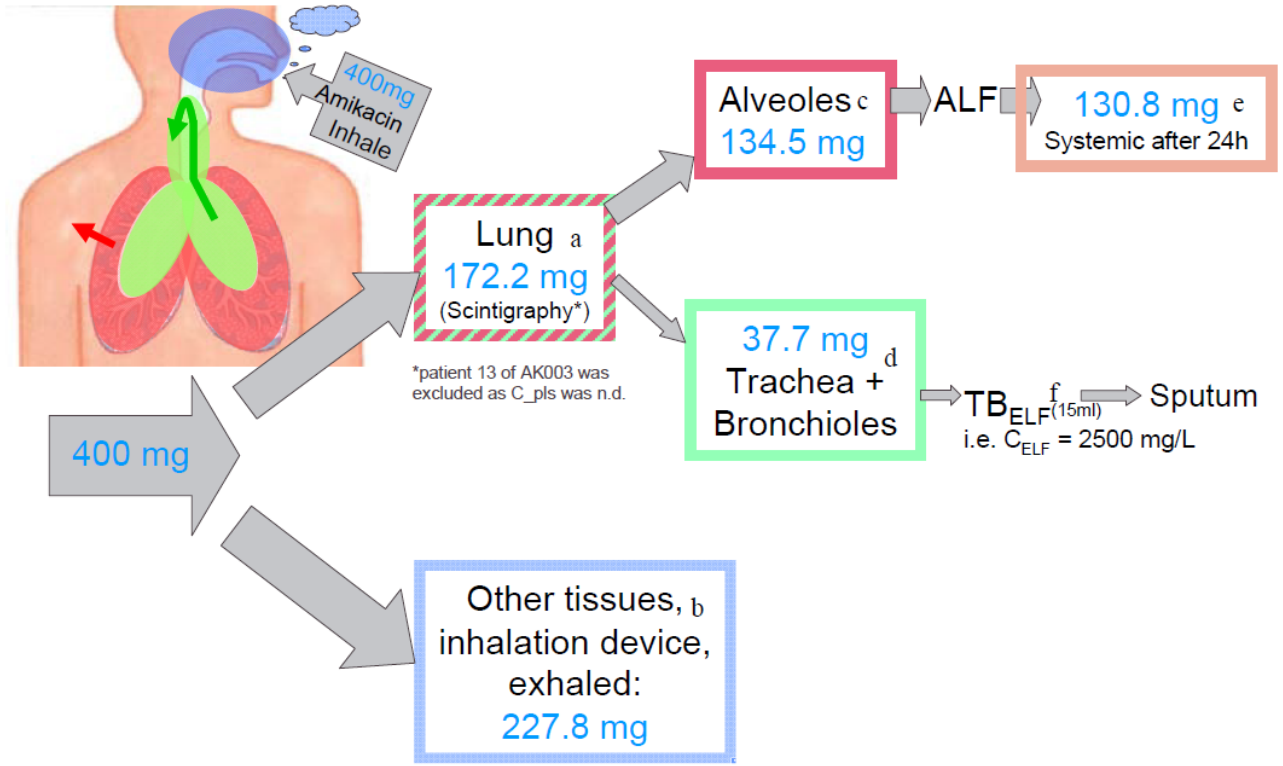
Example – Amikacin inhalation

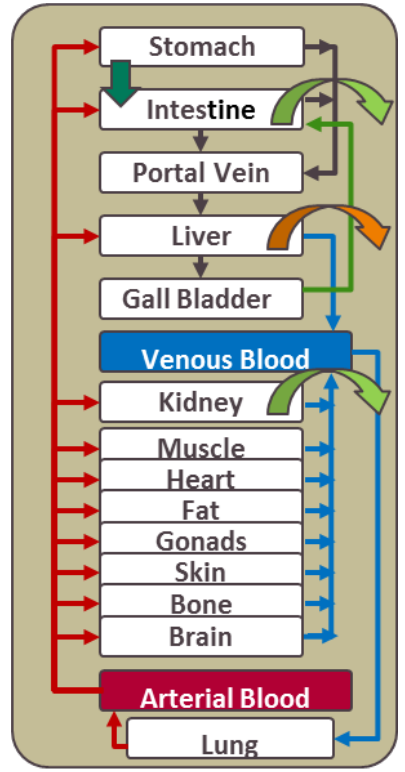
- Clinical question:
  - What PK in ALF is expected for an omitted dose?

Example – Amikacin inhalation

// Estimation of distribution of the different fractions of dose in the human body including the lung

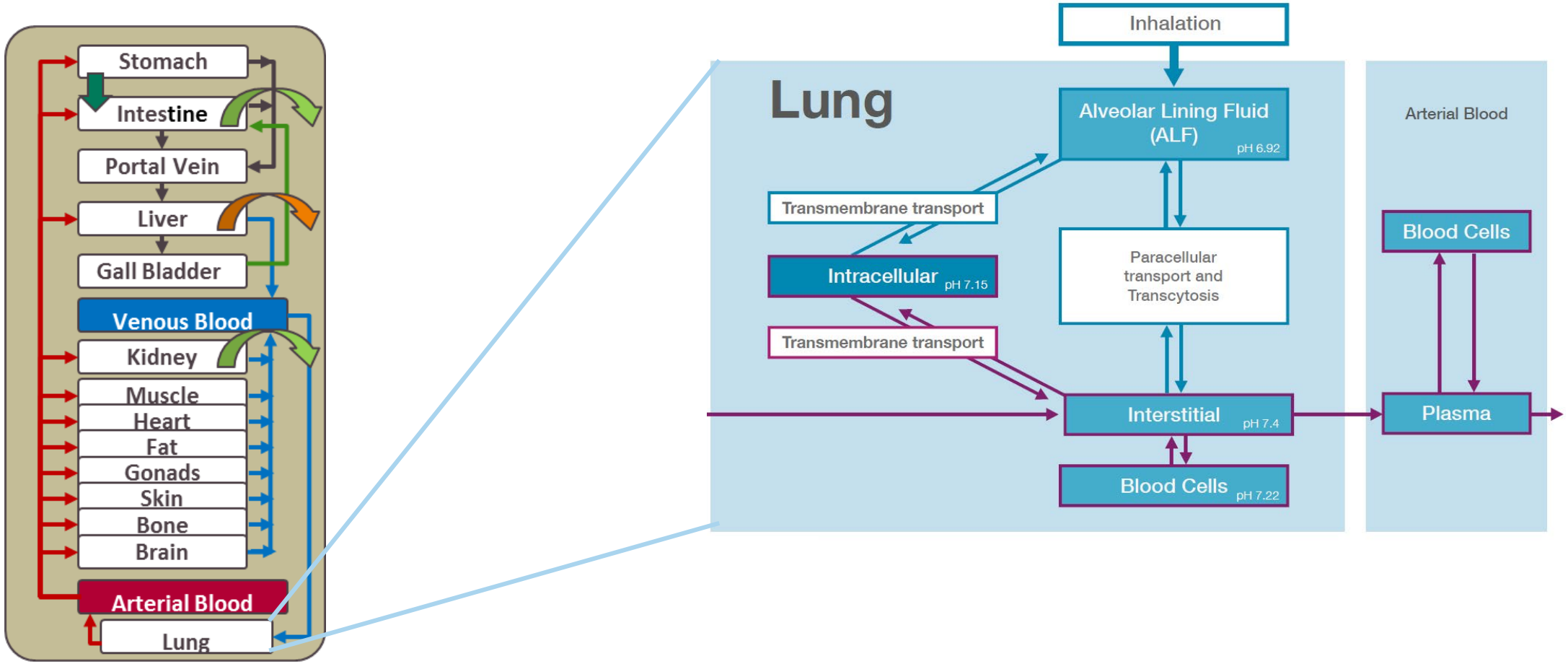
// Using the experimentally derived information to inform a PBPK model





Example – Amikacin inhalation

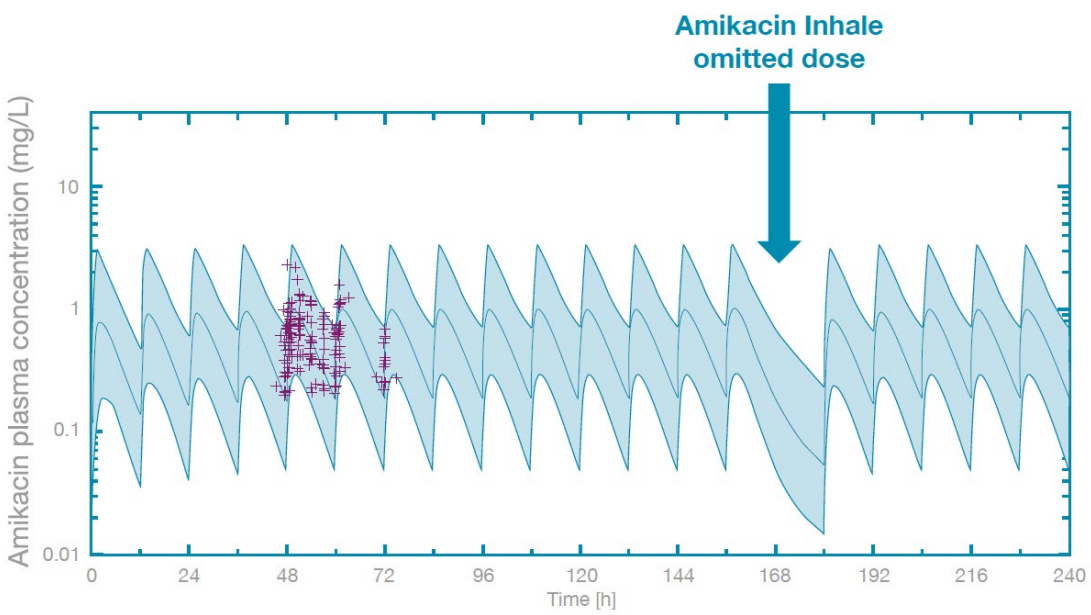
PBPK model covers the important transport processes in the lung

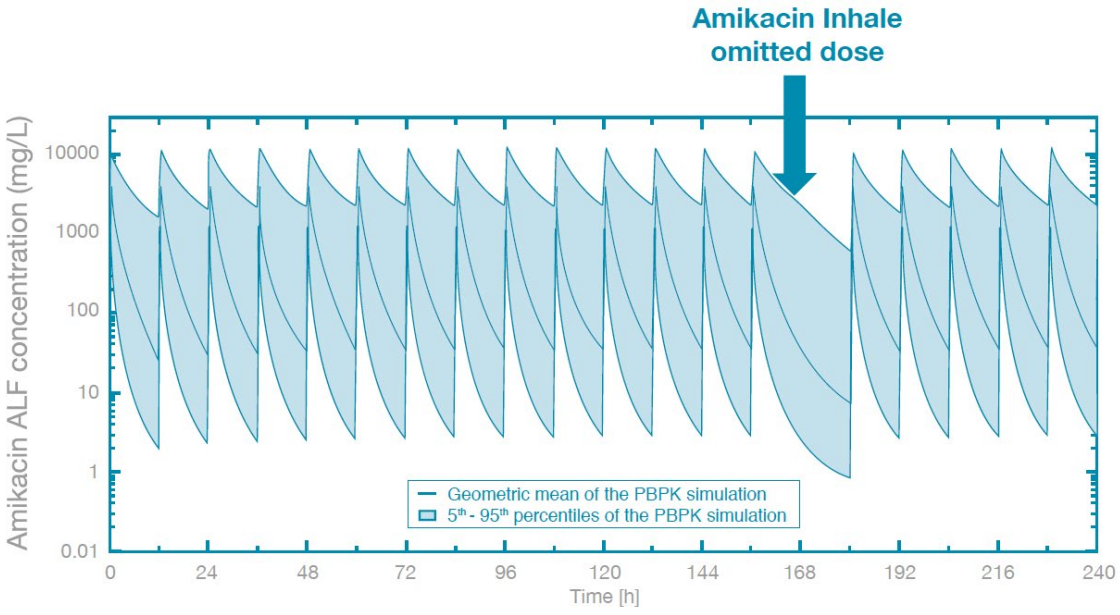


Prediction of Amikacin PK by PBPK

Observed Plasma PK in excellent agreement with the model simulations

// The ALF concentrations including an omitted dose can be predicted by use of the developed PBPK model





Summary

- PBPK modeling can be used for different relevant clinical questions
- Combining PBPK with results of different other methods (CFD, MPPD tool, …) is useful depending on the clinical question
- Results of other methods, describing in detail sources of variability in a mechanistic manner can be used as input for the model
- PBPK models are able to estimate/assess lung concentrations wich can not be easily assessed by measurements
- The expected differences/advantage of inhalative administration to other types of administration can be explored by PBPK modeling

PBPK modeling can support clinical development answering key questions during the development

Acknowledgements

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References (Ciprofloxacin, Amikacin):

Stass, H., Nagelschmitz, J., Willmann, S., Delesen, H., Gupta, A., and Baumann, S. (2013). Inhalation of a dry powder ciprofloxacin formulation in healthy subjects: a phase I study. *Clin Drug Investig* 33**,** 419-427.

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Stass H, Willmann S, Wendl T. Risk assessment for amikacin inhale in ICU patients using whole-body physiologically based PK-models. Poster 926. Society of critical care medicine (SCCM) 43rd critical care congress. San Francisco; 2014.

Thank you!