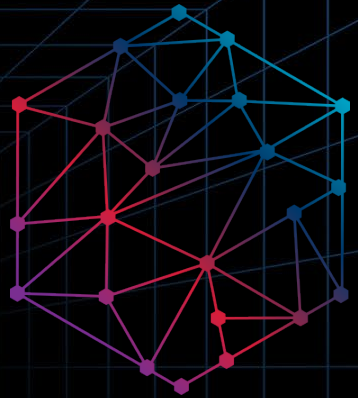
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Pharmacometrics in Phase 1: First in Human and Dose Selection for Phase 2

Yogesh Patel, PhD
Associate Director, Cognigen Corporation

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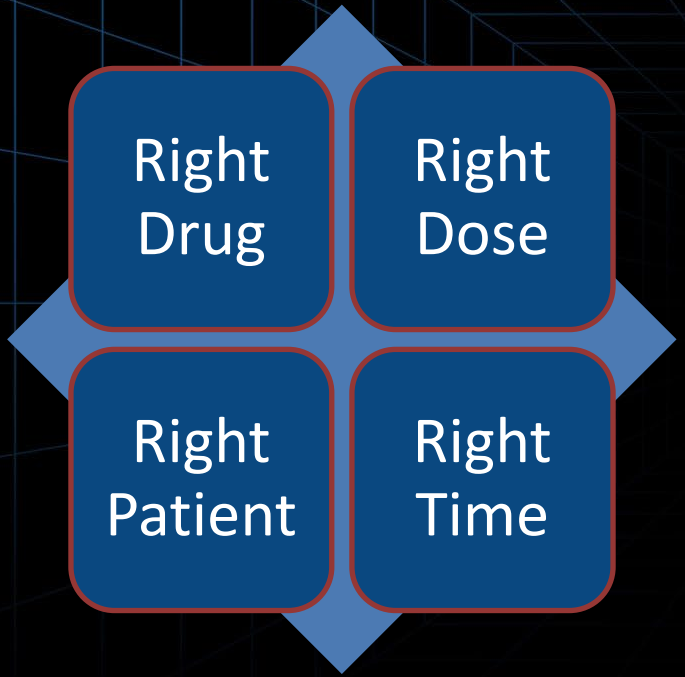
Outline

- Drug development and Phase 1 studies
- Application of MIDD during Phase 1 studies
  - FIH dose selection
  - Special populations
  - Dose prediction for a different indication
  - Proof of target engagement

Goals for Drug Development



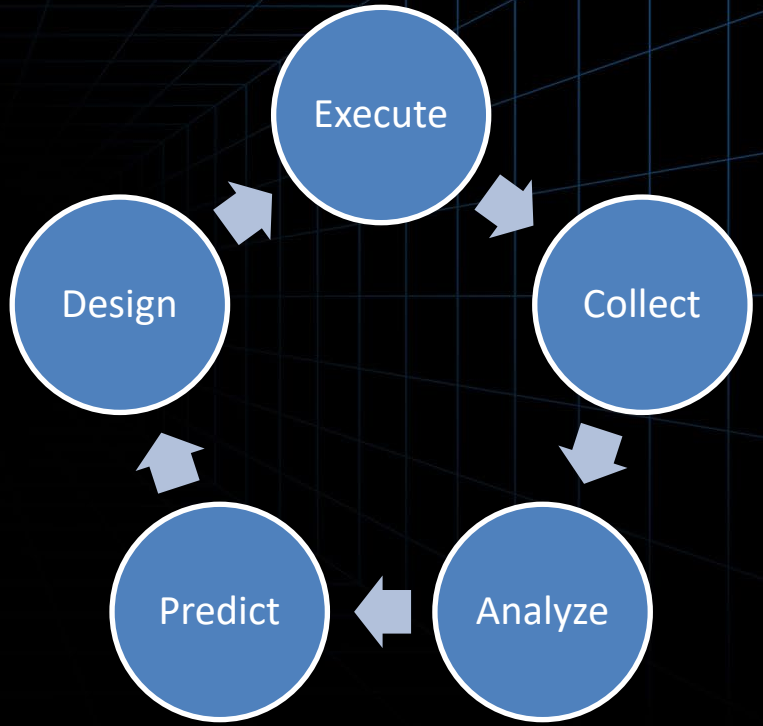
FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

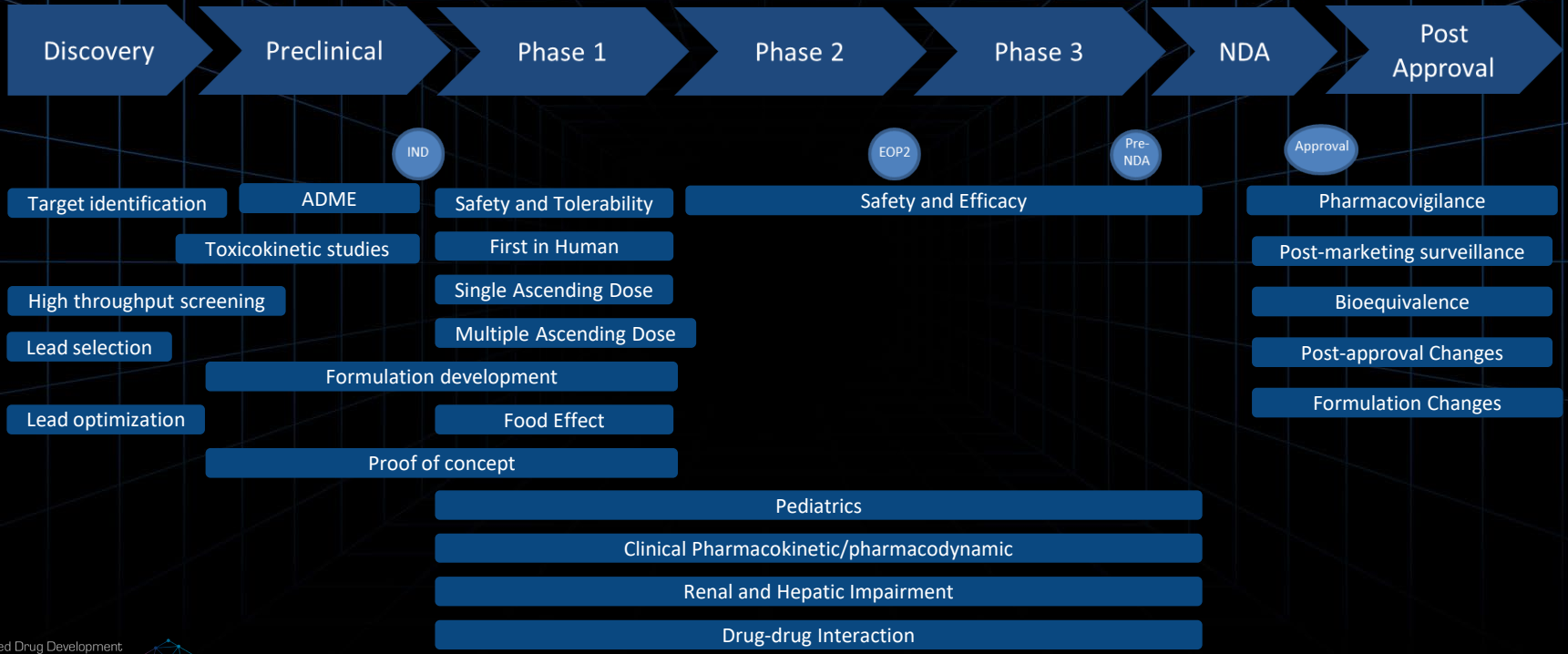
FDA Guidance for Industry

Drug Development Philosophy

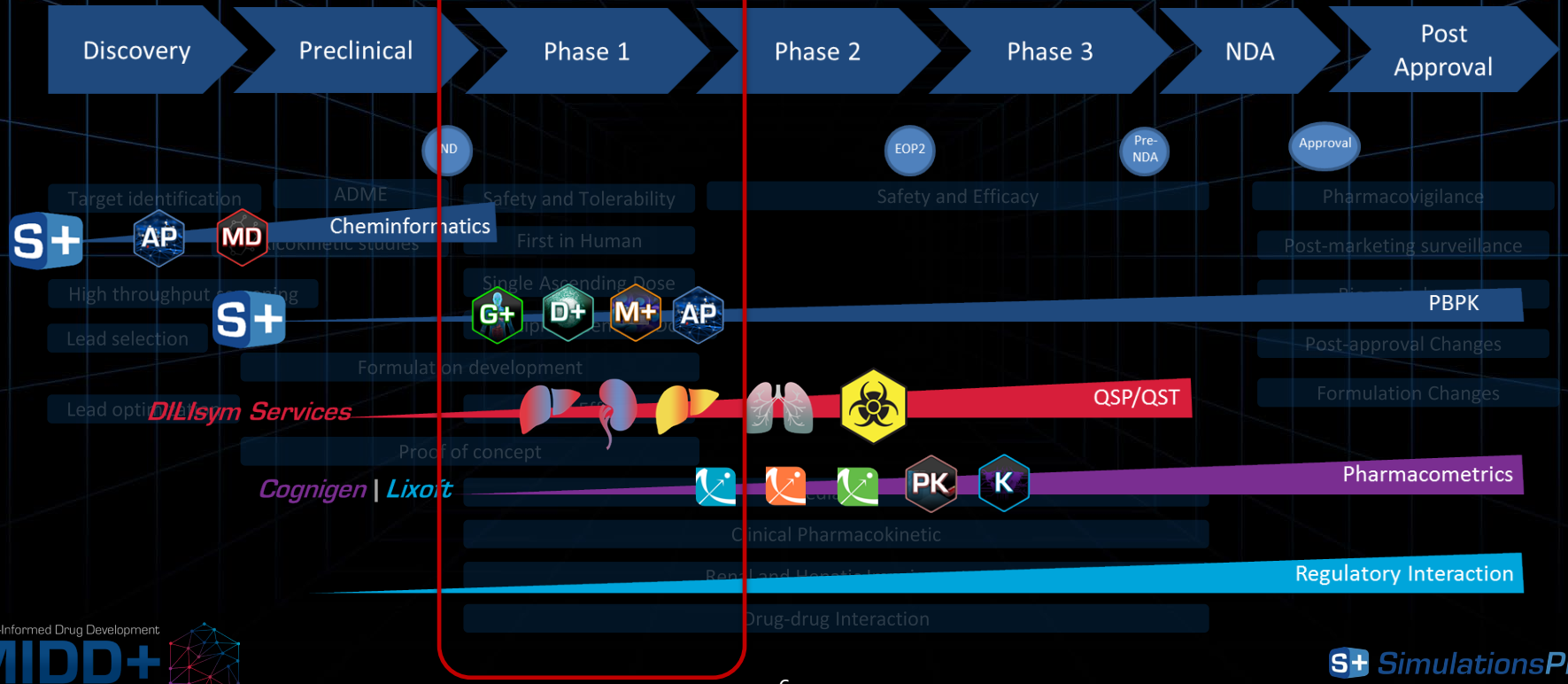
- Continuous process to gather information on safety and efficacy
- Information gathered from one study contributes towards design of the next study



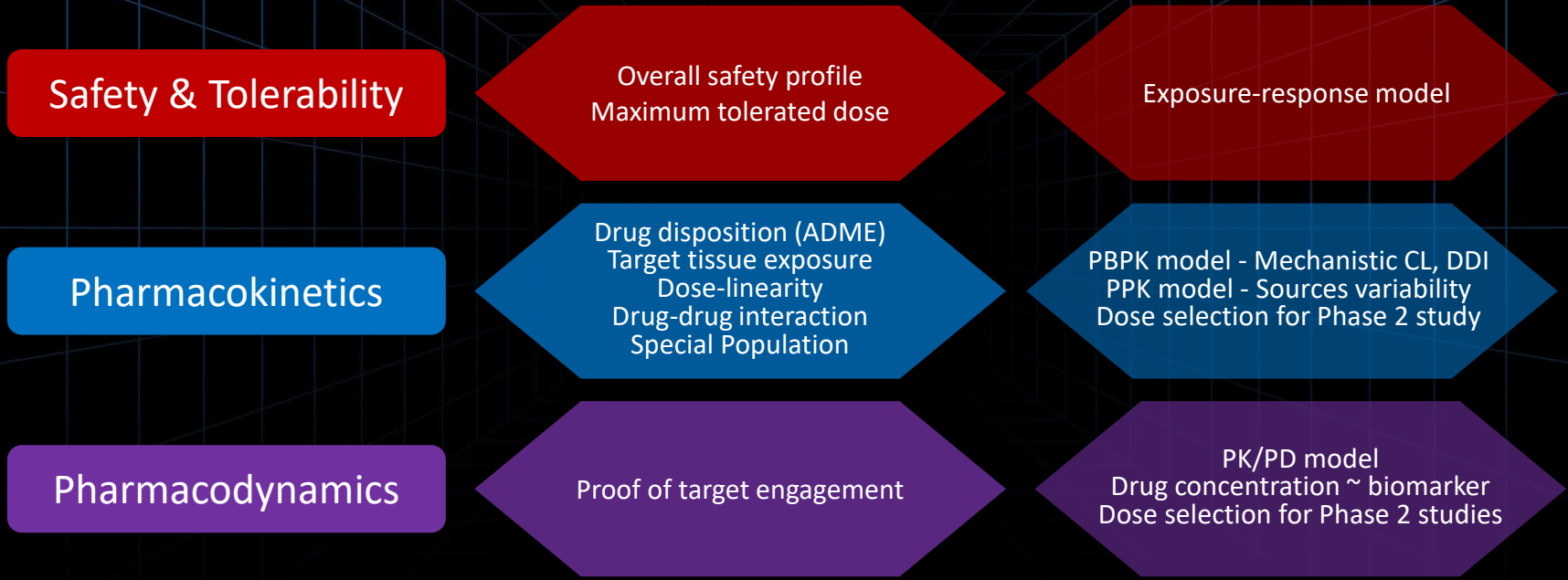
Drug Development Phases



Tools for Model Based Drug Development



Objectives of Phase 1 Studies



Phase 1 Study - Bridge Between Preclinical to Clinical Development

Information in planning Phase 1 Study

- Preclinical toxicokinetic studies to derive NOAEL level
- Preclinical ADME studies to predict drug clearance in human
  - Inter-species allometric scaling
  - Mechanistic PBPK model
- Preclinical biomarker/PD studies
  - Establish relationship between drug concentration and biomarker

Phase 1 study in future development

- Establish tolerated dose range
- Rich PK and PD samples contributes to develop structural PK/PD model
- Proof of target attainment
- Support dose selection for Phase 2 studies
- Dose selection for Special population (e.g. pediatrics, renal failure, hemodialysis)
- Drug-drug interaction
- Assessment of target tissue concentration

Case Study 1

Inter-species PBPK model to predict safe human dose

Drug X in Preclinical Development

- Being developed for the treatment of a rare disease
- Primarily eliminates via kidney (glomerular filtration and active reabsorption)
- Accumulates in kidney over time and causes renal toxicities at higher kidney exposures

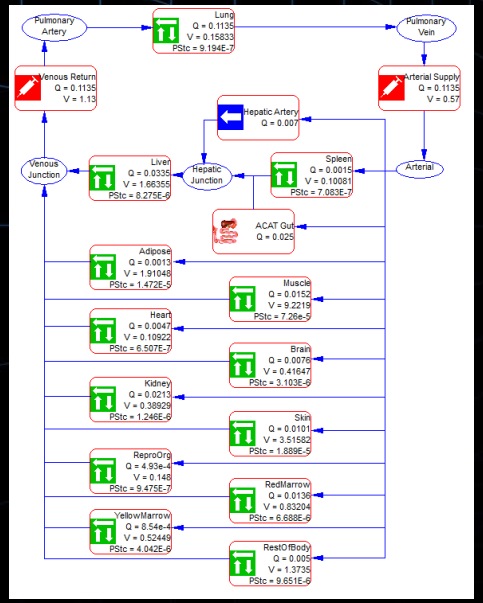
Can M&S using preclinical information help predict the safe human dose?

Data Available for Development and Validation of PBPK Model

	Species	Dosing Regimen	PK Collection
Model Development	Mouse	2 dose levels x 4 dosing schedules	Rich sampling scheme After single and multiple dose Plasma and tissue (including kidney) samples
	Rat	2 dose levels x 3 dosing schedules	Rich sampling scheme After single and multiple dose Plasma and kidney samples Pathological evaluation of kidney toxicities
	Dog	Multiple dose levels and schedules	Rich sampling scheme After single and multiple dose Plasma samples
Model Validation	Human	SAD	Rich sampling scheme After single dose Plasma and urine samples

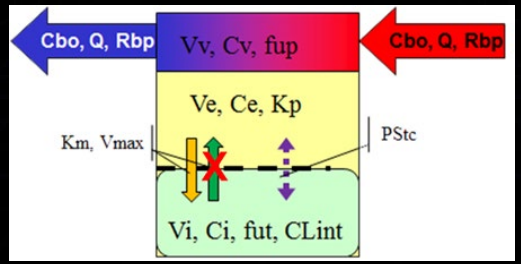
PBPK Model with Permeability-limited Tissue Model Described Drug Disposition

Full-body PBPK model

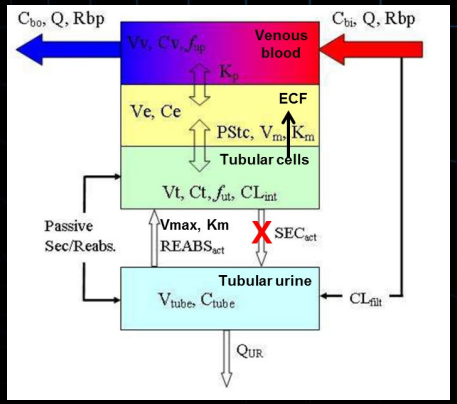


Optimized model parameters were consistent between species

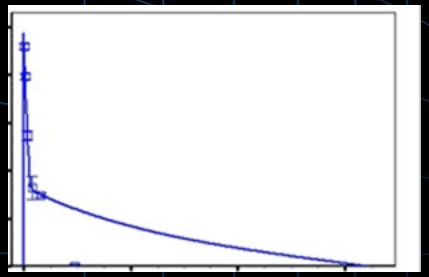
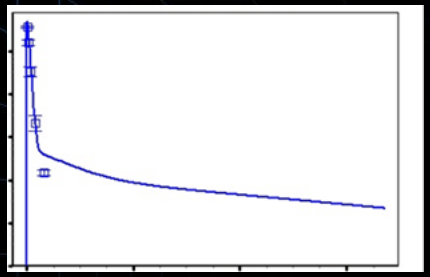
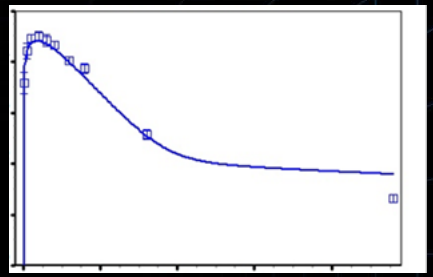
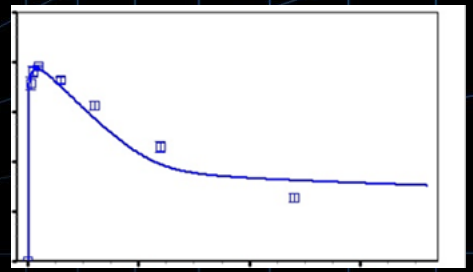
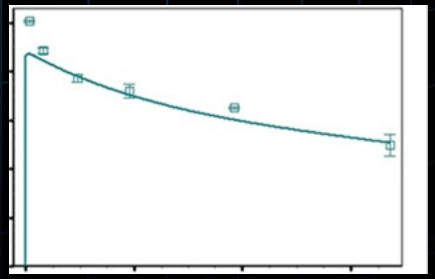
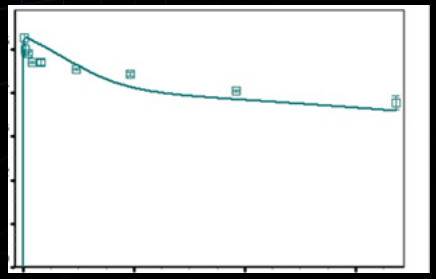
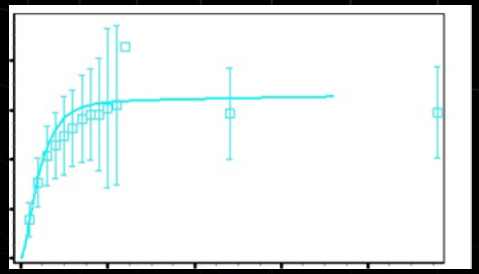
Permeability-limited Tissue Model



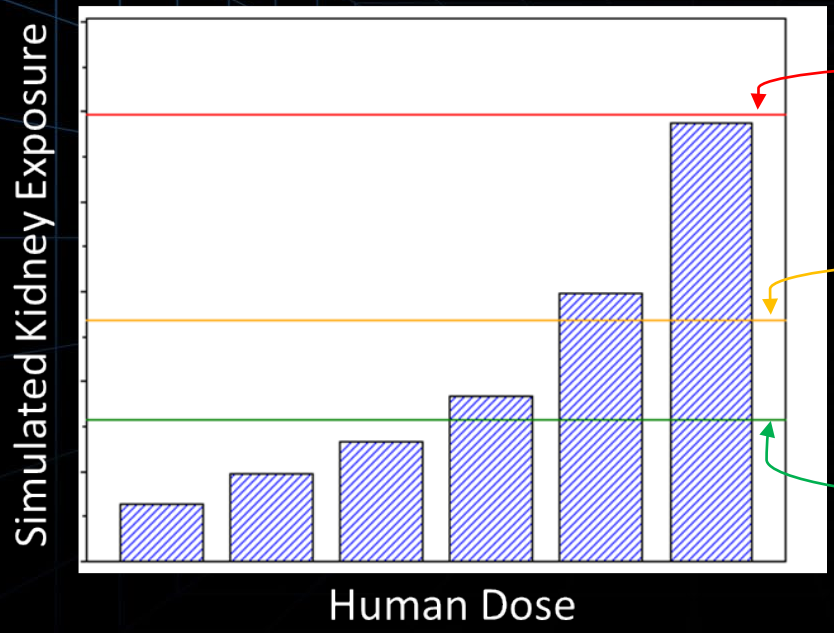
Permeability-limited Kidney Tissue Model



PBPK Model Described Plasma and Tissue Concentration Profiles Across Different Species

	Mouse	Rat	Dog	Human
Plasma				
Kidney/Urine				

PBPK Model Helped to Predict Human Dose Associated with Safe Kidney Exposure



Minimum kidney exposure in rat with renal toxicities

Minimum kidney exposure in rat with limited renal finding

Maximum kidney exposure in rat with no renal finding

Case Study 2

PPK Model Based on Adult and Phase 1 Pediatric Study Used for Dose Selection for Phase 2 Pediatric Study

Ceftolozane/Tazobactam

- Ceftolozane/tazobactam is a fixed-dose combination antibacterial agent comprising the antipseudomonal cephalosporin ceftolozane and the established beta-lactamase inhibitor tazobactam
- Approved for the treatment of cUTIs, cIAIs, HAP, and VAP in adults
- Primarily eliminated via kidney through glomerular filtration
- cIAI and cUTI dose: 1.5g (1g ceftolozane + 0.5g tazobactam), Q8H as 1-hr infusion
- HAP and VAP dose: 3g (2g ceftolozane + 1g tazobactam), Q8H as 1-hr infusion
- Dose adjustment in subjects with moderate and severe renal impairment, and with renal failure

Zhang et al, J Clin Pharmacol, 2021; Larson et al, Antimicrob Agents Chemother, 2019

Ceftolozane/Tazobactam

- PK/PD target for ceftolozane is %fT>MIC, which is the percentage of interdose interval when free drug concentration remains above MIC
- Neutropenic mouse thigh infection model: %fT>MIC ~ 30% for 1-log kill
- PK/PD target for ceftolozane is 30% fT>MIC for an MIC of 4 ug/mL (breakpoint for P. aeruginosa)

Larson et al, Antimicrob Agents Chemother, 2019

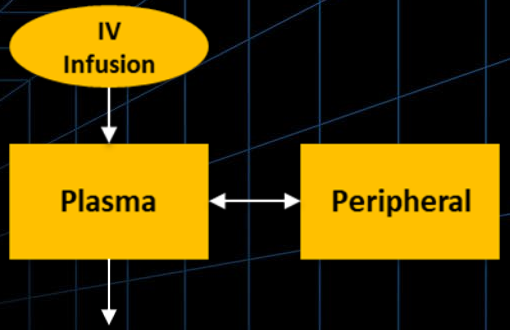
Ceftolozane/Tazobactam Phase 1 Study in Pediatrics

- Primary objectives were to evaluate safety, tolerability, and PK
- Single-dose study in pediatric patients with suspected or proven Gram-negative bacterial infections
- Enrollment based on 6 age groups including term and preterm neonates

Larson et al, Antimicrob Agents Chemother, 2019

Development of PPK Model for Ceftolozane and Tazobactam

- Data from Phase 1 pediatric study were pooled with 12 adult clinical studies for the development of PPK model
- 2-compartment model with first-order elimination described concentration-time profile



Ceftolozane

$$CL = 5.88 \times \left(\frac{wt}{70}\right)^{0.764} \times \left(\frac{eGFR}{100}\right)^{0.704}$$

$$VC = 10.6 \times \left(\frac{wt}{70}\right)^{1.12}$$

$$VP = 4.23 \times \left(\frac{wt}{70}\right)^{0.484}$$

$$Q = 2.55$$

Tazobactam

$$CL = 20.8 \times \left(\frac{wt}{70}\right)^{0.652} \times \left(\frac{eGFR}{100}\right)^{0.733} \times 0.677^{Infection}$$

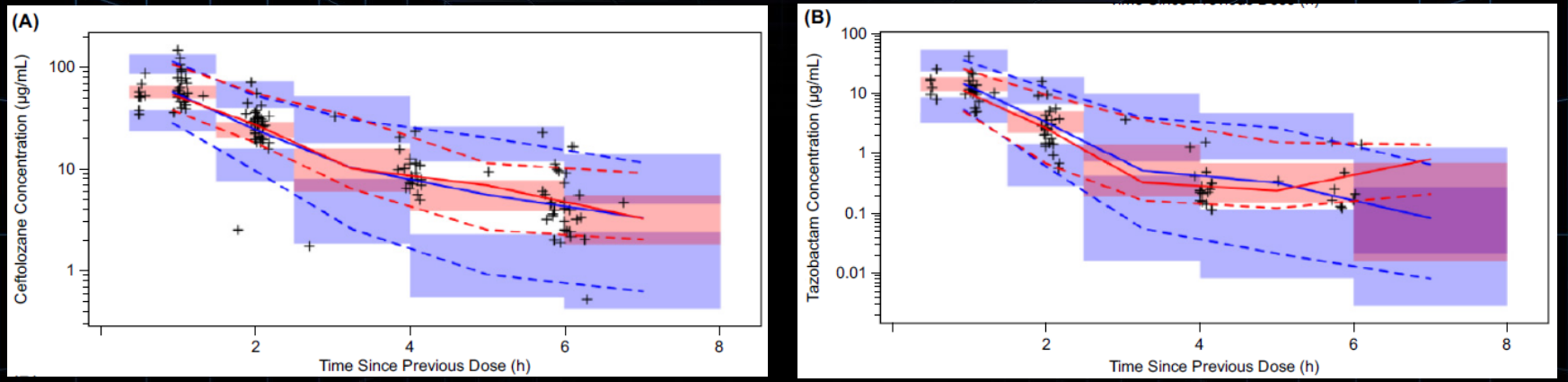
$$VC = 12.9 \times \left(\frac{wt}{70}\right)^{0.737}$$

$$VP = 5.06 \times \left(\frac{wt}{70}\right)^{0.830}$$

$$Q = 4.06 \times \left(\frac{wt}{70}\right)^{0.75}$$

Larson et al, Antimicrob Agents Chemother, 2019

PPK Models Describe Ceftolozane and Tazobactam Concentration-Time Profile Well in Pediatric Patients



Larson et al, Antimicrob Agents Chemother, 2019

Stochastic Simulation using PPK Model Predicted Exposure Comparable to Adults

Ceftolozane

Parameter and statistic	Value for the following patients:					
		Patients in pediatric age groups				
	Adult patients (n = 1,000)	12 to <18 yr (1,000 mg, n = 1,200)	≥7 to <12 yr (20 mg/kg, n = 1,000)	≥2 to <7 yr (20 mg/kg, n = 1,000)	≥3 mo to <2 yr (20 mg/kg n = 1,000)	Birth[a] to <3 mo (20 mg/kg, n = 1,200)
Steady-state AUC_{0-8} (μg/ml · h)						
Mean (SD)	213.36 (171.91)	172.11 (78.76)	176.08 (69.92)	153.13 (60.32)	162.04 (63.15)	157.36 (65.19)
Median	176.00	160.00	161.00	141.00	149.00	147.00
5th, 95th percentile	95.3, 388.0	73.2, 319.0	90.3, 315.0	77.0, 268.0	81.2, 276.5	71.3, 282.5
Steady-state C_{max} (μg/ml)						
Mean (SD)	69.66 (45.09)	86.04 (36.25)	92.68 (29.84)	82.37 (23.96)	74.37 (19.33)	62.06 (15.18)
Median	56.10	80.35	86.90	79.35	72.40	60.15
5th, 95th percentile	32.9, 154.0	37.8, 154.0	53.1, 150.0	47.8, 125.0	45.9, 109.0	39.9, 89.4

Tazobactam

Parameter and statistic	Value for the following patients:					
		Patients in pediatric age groups				
	Adult patients (n = 1,000)	12 to <18 yr (500 mg, n = 1,200)	≥7 to <12 yr (10 mg/kg, n = 1,000)	≥2 to <7 yr (10 mg/kg, n = 1,000)	≥3 mo to <2 yr (10 mg/kg, n = 1,000)	Birth[a] to <3 mo (10 mg/kg, n = 1,200)
Steady-state AUC_{0-8} (μg/ml · h)						
Mean (SD)	80.71 (148.87)	37.12 (23.29)	38.02 (24.49)	30.22 (19.18)	29.87 (19.05)	26.77 (16.50)
Median	29.80	31.20	32.30	26.10	25.00	22.30
5th, 95th percentile	15.4, 379.0	12.4, 83.1	12.3, 84.5	10.2, 62.9	10.0, 63.5	8.4, 57.3
Steady-state C_{max} (μg/ml)						
Mean (SD)	30.30 (34.73)	27.92 (14.51)	29.19 (14.69)	24.04 (11.78)	21.69 (10.54)	18.37 (8.81)
Median	17.70	24.75	26.45	21.80	19.50	16.80
5th, 95th percentile	10.3, 108.0	10.7, 54.6	11.7, 57.7	9.6, 46.1	8.5, 42.2	7.6, 35.2

A dose of 1/0.5g (ceftolozane/tazobactam) for patients aged 12 to <18 years and 20/10 mg/kg of body weight for patients aged birth to <12 years was selected for further evaluation

Larson et al, Antimicrob Agents Chemother, 2019

Stochastic Simulation using PPK Model Predicted PTA > 90% for All Age Groups

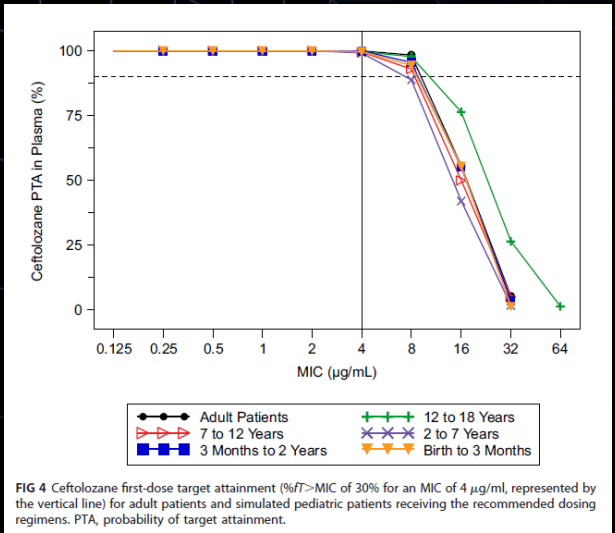


FIG 4 Ceftolozane first-dose target attainment (%fT>MIC of 30% for an MIC of 4 μg/ml, represented by the vertical line) for adult patients and simulated pediatric patients receiving the recommended dosing regimens. PTA, probability of target attainment.

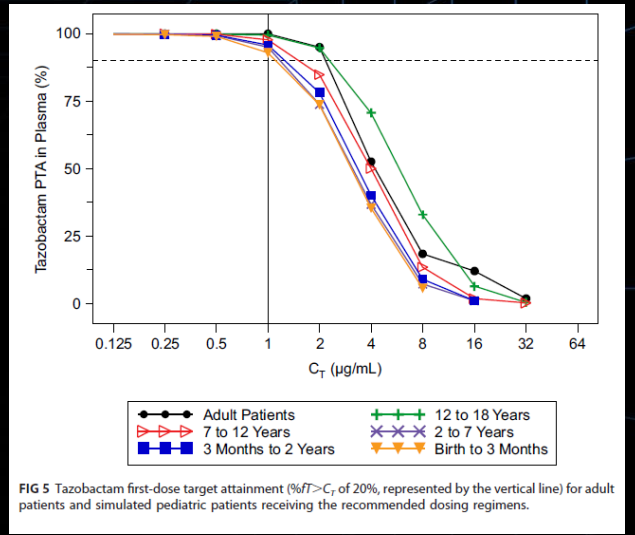


FIG 5 Tazobactam first-dose target attainment (%fT>C_T of 20%, represented by the vertical line) for adult patients and simulated pediatric patients receiving the recommended dosing regimens.

A dose of 1/0.5g (ceftolozane/tazobactam) for patients aged 12 to <18 years and 20/10 mg/kg of body weight for patients aged birth to <12 years was selected for further evaluation

Larson et al, Antimicrob Agents Chemother, 2019

Case Study 3

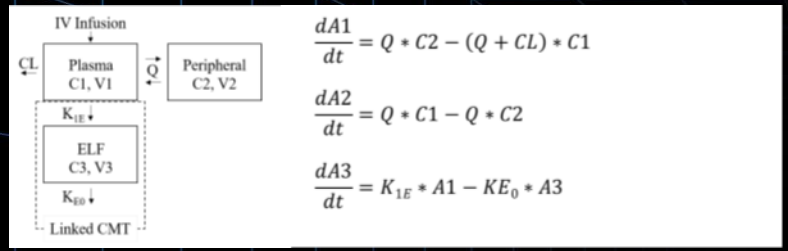
PPK Model Used to Guide Dose Selection for a Different Indication

Phase 1 Studies to Determine Intrapulmonary Penetration of Ceftolozane/Tazobactam

- Two Phase 1 Studies in healthy subjects and mechanically ventilated patients with proven/suspected pneumonia were performed to characterize the ceftolozane and tazobactam penetration in ELF in lung
- Study in healthy subjects evaluated a dose of 1.5g administered Q8H as 1-h infusion.
- Study in pneumonia patients evaluated a dose of 3g administered Q8H as 1-h infusion (dose adjustment for patients with renal impairment)
- Plasma samples (Pre-dose and 1, 2, 4, 6, and 8 hours post-dose) were collected after first (only for patient study) and last dose
- Subjects were randomly assigned to one sample time (1, 2, 4, 6, or 8 hours post-dose) to collected BAL sample (n = 5 per time point)
- Data from two Phase 1 studies were pooled with other adult studies including a Phase 3 study in pneumonia patients (plasma model only) in for the population analysis

Chandorkar et al, J Antimicrob Chemother, 2012; Caro et al, J Antimicrob Chemother, 2020

2-CMT Model with Linear Elimination and a Hypothetical Linked Compartment Described Plasma and ELF profile Well



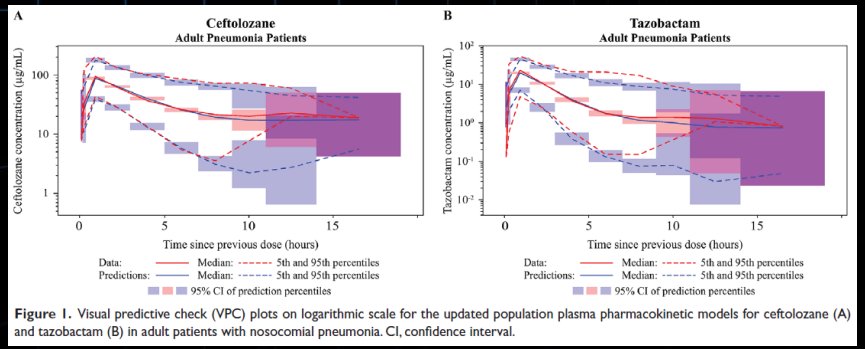
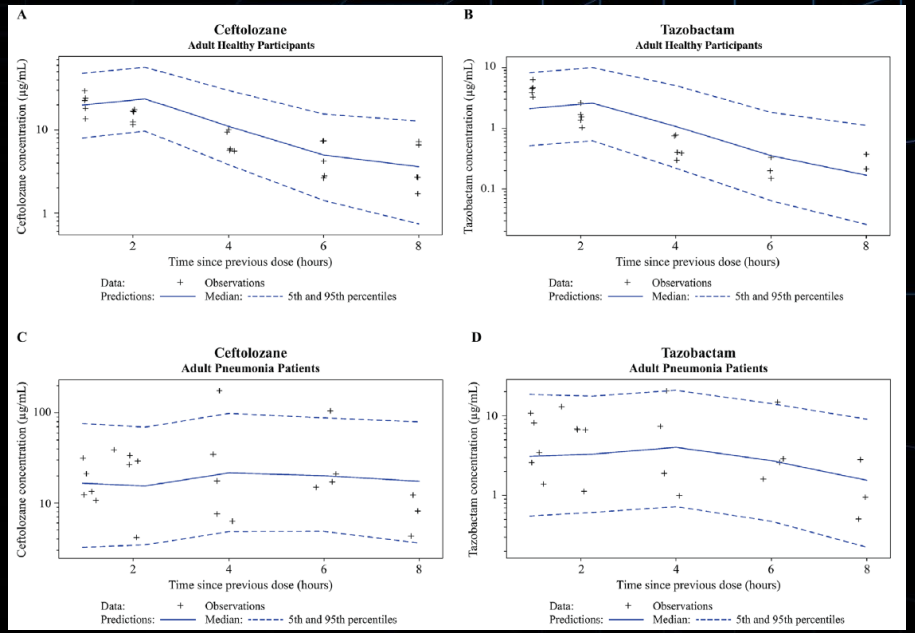


Figure 1. Visual predictive check (VPC) plots on logarithmic scale for the updated population plasma pharmacokinetic models for ceftolozane (A) and tazobactam (B) in adult patients with nosocomial pneumonia. CI, confidence interval.



Zhang et al, J Clin Pharmacol, 2021

Parameters for 2-Compartment Plasma PPK Models

Parameter-covariate relationships for ceftolozane were described as:

$$CL = 4.84 \times \left(\frac{CrCL}{100}\right)^{0.701} \times 1.18^{cUTI} \times 1.43^{cIAI} \times 0.32^{ESRD}$$

$$Vc = 9.23 \times \left(\frac{WTKG}{70}\right)^{0.684} \times 1.25^{cUTI} \times 1.59^{cIAI} \times 2.00^{Pneumonia} \times 2.14^{OINF} \times 1.30^{ESRD}$$

$$Vp = 4.78 \times \left(\frac{WTKG}{70}\right)^{0.484}$$

Parameter-covariate relationships for tazobactam were described as:

$$CL = 16.6 \times \left(\frac{CrCL}{100}\right)^{0.623} \times 0.626^{ESRD}$$

$$Vc = 13.1 \times \left(\frac{WTKG}{70}\right)^{0.629} \times 1.49^{cIAI} \times 2.17^{Pneumonia} \times 2.49^{OINF} \times 0.749^{ESRD}$$

$$Vp = 4.89 \times \left(\frac{WTKG}{70}\right)^{0.530} \times 1.25^{cUTI} \times 1.34^{cIAI} 2.06^{Pneumonia}$$

Volume of Distribution for Ceftolozane and Tazobactam Were Approximately Double in Pneumonia Patients Compared to Healthy Subjects

Zhang et al, J Clin Pharmacol, 2021

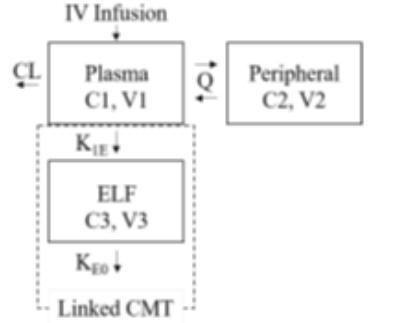
Parameters for ELF PPK Model (A Hypothetical Link Compartment Model)

Table 3. Parameter Estimates and Standard Errors of the Ceftolozane and Tazobactam Population Pharmacokinetic Model for ELF Data

	Ceftolozane				Tazobactam			
	Final Parameter Estimate		IIV/RV		Final Parameter Estimate		IIV/RV	
Parameter	Typical Value	%RSE	Magnitude	%RSE	Typical Value	%RSE	Magnitude	%RSE
K_{IE}, rate constant for disposition from plasma to ELF (/h)	0.808	11.6	39.6% CV[a] 81.2% CV[b]	28.1[a] 46.0[b]	0.262[c]	30.6	65.5% CV[a] 84.4% CV[b]	23.9[a] 34.5[b]
K_{EO}, rate constant for elimination from ELF (/h)	1.56	8.97	NE	NA	0.691[c]	25.1	NE	NA
Pneumonia on K_{IE} and K_{EO} (proportional)	0.034	44.0	NA	NA	0.479	44.0	NA	NA
RV proportional	0.025	12.7	92.7%-15.8% CV[d]	NA	0.055	12.3	23.4% CV	NA
RV additive	0.008	21.4	F (0.1-100 μg/mL)		—	—		
Minimum value of the objective function			20934.2			5258.2		

Zhang et al, J Clin Pharmacol, 2021

PPK Model for Plasma and ELF Concentration-Time Profile



$$\frac{dA1}{dt} = Q * C2 - (Q + CL) * C1$$

$$\frac{dA2}{dt} = Q * C1 - Q * C2$$

$$\frac{dA3}{dt} = K_{1E} * A1 - KE_0 * A3$$

Appropriate for Stochastic Simulation to Assess PK/PD Target Attainment in ELF and Plasma in pneumonia patients

Zhang et al, J Clin Pharmacol, 2021

Key Points

- M&S has many applications throughout drug development depending on study phase
- Mechanistic PBPK model can help predict the safe dose for first-in-human study
- M&S based on Phase 1 study help guide dose selection for Phase 2 study, special population, or a different indication
- Model informed drug development can help minimize overall study burden and maximize understanding of information gathered from a study

Q&A

Questions & Answers

Model-Informed Drug Development

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