Evaluation of Drug-Drug Interactions and Their Influence on Drug Dosing in the Pediatric Population

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- I receive funding for neonatal and pediatric clinical pharmacology research from the Eunice Kennedy Shriver National Institute for Child Health and Human Development (R01HD096435 and HHSN275201000003I)

- I will present examples that evaluate off label dosing of approved medications

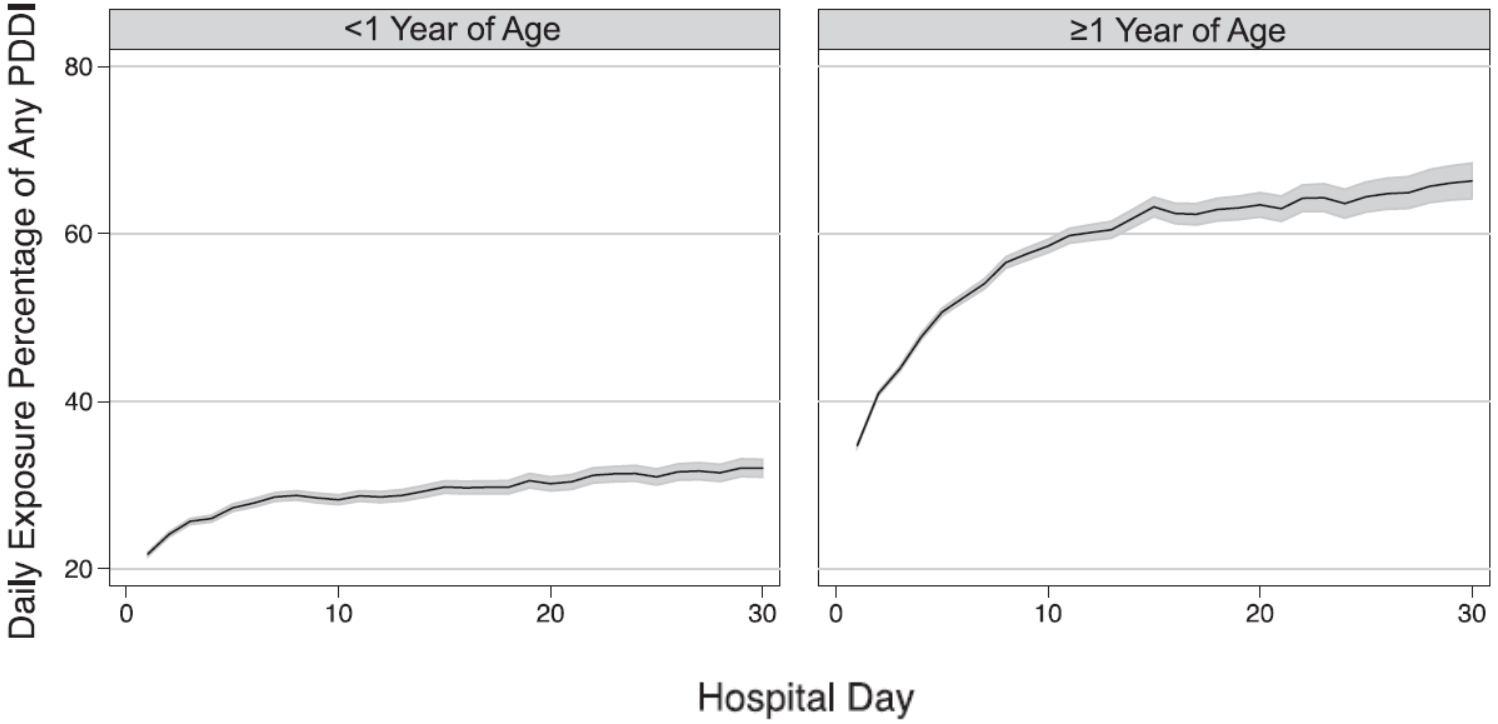
Objectives

- To describe the prevalence of potential drug-drug interactions (DDIs) in the pediatric population
- To summarize barriers to evaluating pediatric DDI potential and discuss potential differences in DDI potential between adults and pediatric patients
- To present examples that use pharmacometric approaches or real-word data to evaluate DDI potential in pediatric patients

Potential DDIs are Common in Hospitalized Pediatric Patients

- Retrospective cohort study using the Pediatric Health Information System database
- For infants <1 year of age, 21.8% exposed to a potential DDI on Day 1, increasing to 32% by Day 30
- For those ≥1 year of age, 34.7% and 66.3% were exposed to a potential DDI on Day 1 and Day 30, respectively

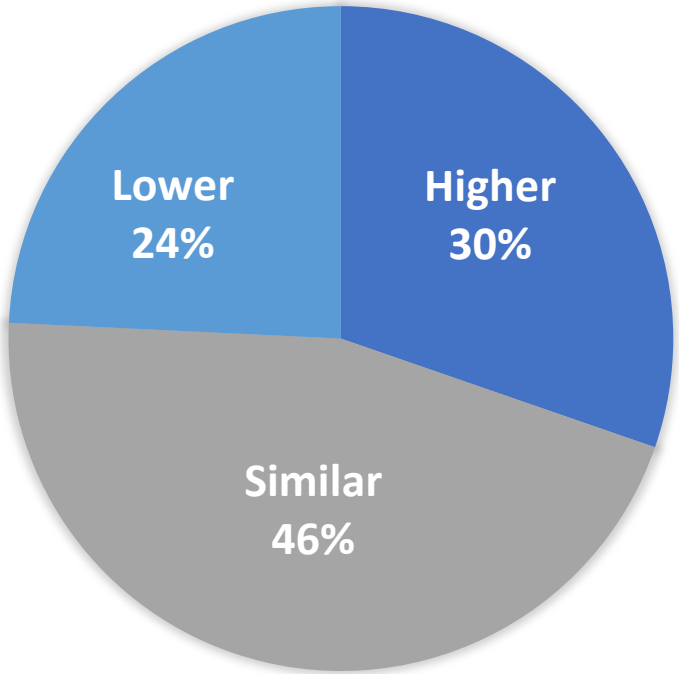
Proportion of Pediatric Patients Exposed to a Potential Drug-Drug Interaction (PDDI)



Feinstein J, et al. *Pediatrics.* 2015; 135(1):e99-108.

DDI Potential in Adults and Pediatric Patients Can Differ

- A systematic literature review was performed to compare the magnitude of reported DDIs in children and adults
- The magnitude of DDIs for 24 drug pairs from 31 studies could be assessed and compared with adults
- The fold interaction was compared using area under the concentration vs. time curve, clearance, or steady-state concentrations



Salem F, Rostami-Hodjegan A, Johnson TN. *J Clin Pharmacol.* 2013;53(5):559-566.

Challenges to Evaluating DDIs in the Pediatric Population

- No “healthy child volunteer”
- Ethical concerns
- Limited blood volume and timed sampling
- DDI potential may need to be assessed across pediatric age groups
- Low rates of parental informed consent
- Drug may be used in a critically ill population → increases variability

Proposed Workflow to Apply PBPK Modeling for Pediatric DDI Evaluation

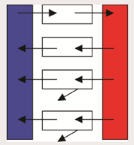
Develop Adult Model


drug properties

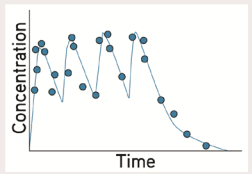

system properties


study protocol and formulation properties

Predict, learn, confirm

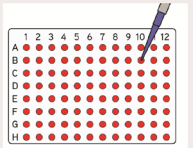


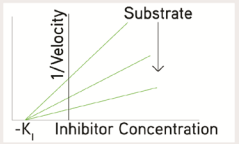
Evaluate using clinical data



Adult DDI Evaluation

Incorporate relevant experimental interaction data

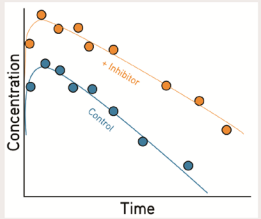

induction data



inhibition data

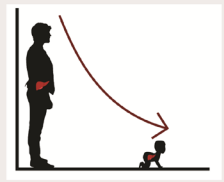
Predict, learn, confirm

Evaluate model using adult clinical DDI data



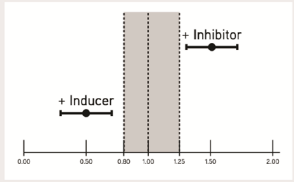
Pediatric Modeling and DDI Prediction

Scale PBPK model to children, including ontogeny functions



Evaluate pediatric PBPK model and scaling using pediatric clinical data

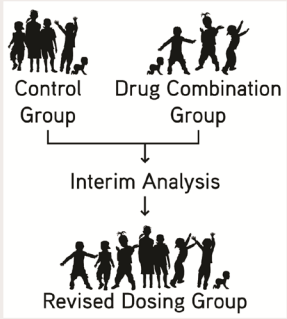
Predict DDIs and provide therapeutic modifications across pediatric ages



Evaluate PBPK Model Predictions

Approach 1: Collect opportunistic data in children receiving the drug combination per standard of care

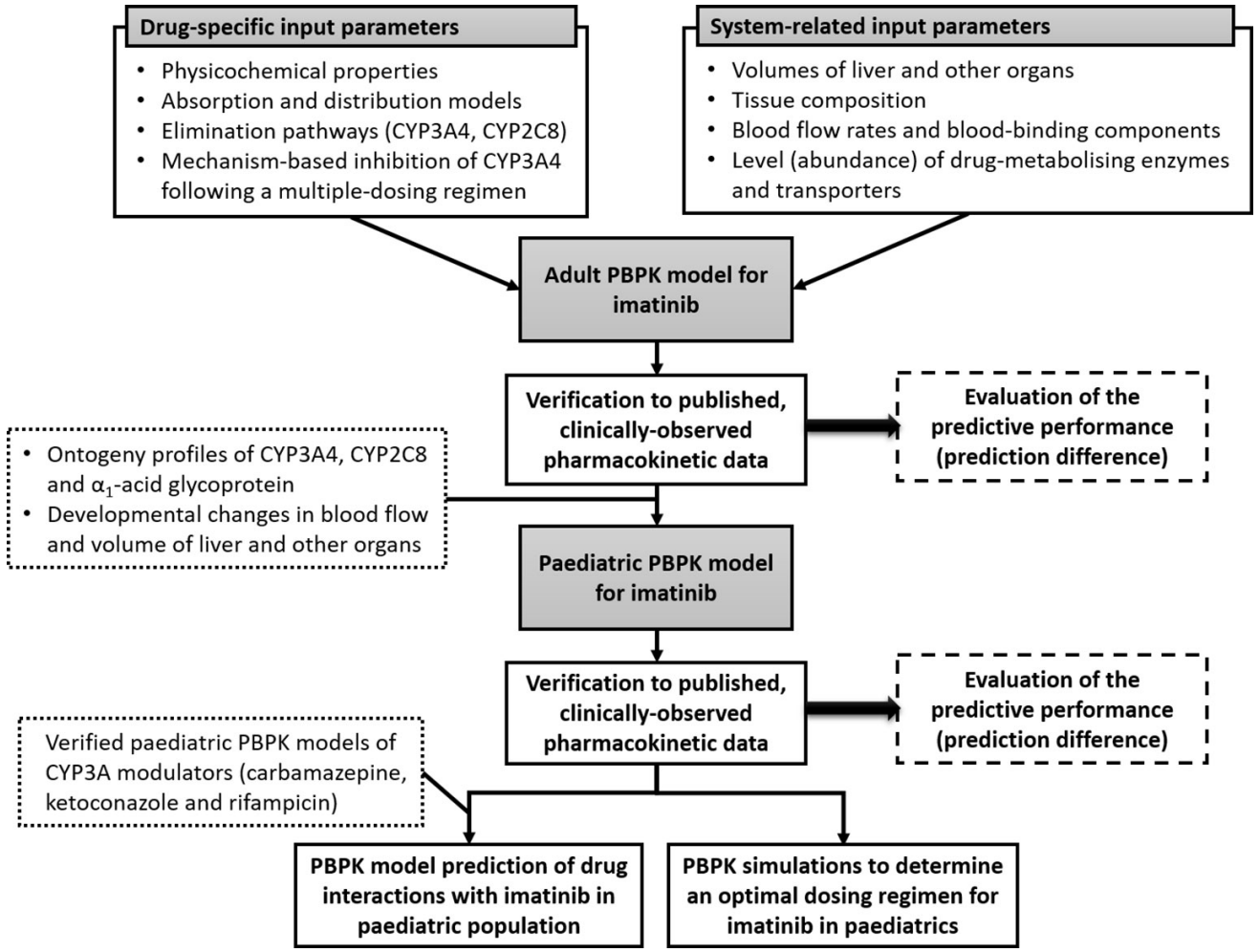
Approach 2: Prospectively evaluate revised dosing recommendations using an adaptive trial design



Salerno SN, et al. *Clin Pharmacol Ther.* 2019; 105(5):1067-1070.

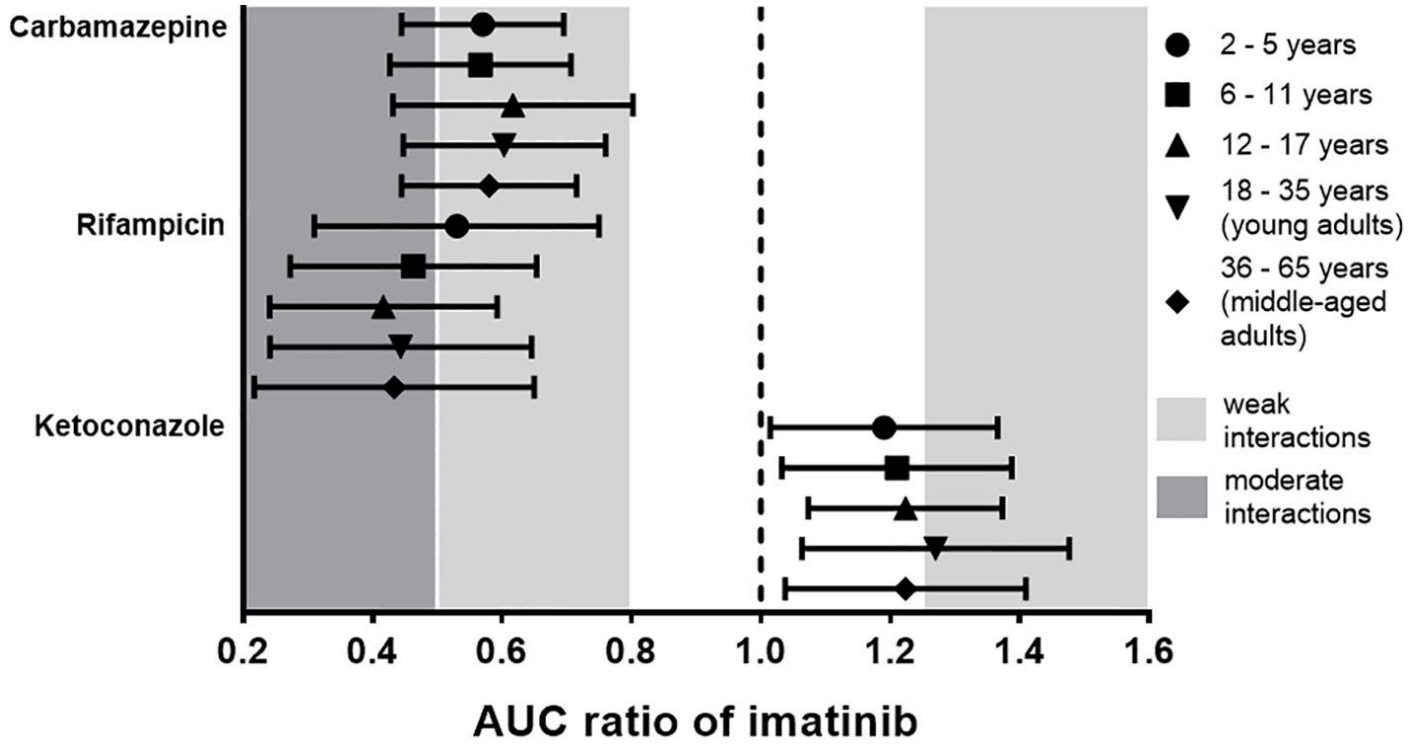
PBPK Model Developed to Characterize Imatinib's PK in Children and Adolescents

- The objective was to apply a PBPK modeling approach to investigate optimal dosing and potential DDIs for imatinib in the pediatric population
- An adult imatinib PBPK model was developed and evaluated, and then scaled to children and adolescents (2-18 years of age)
- PBPK models of CYP3A modulators were verified using published pediatric data



Adiwidjaja J, Boddy AV, McLachlan AJ. *Front Pharmacol.* 2020;10:1672.

PBPK Model Predicts Potential Imatinib DDIs in Children and Adolescents

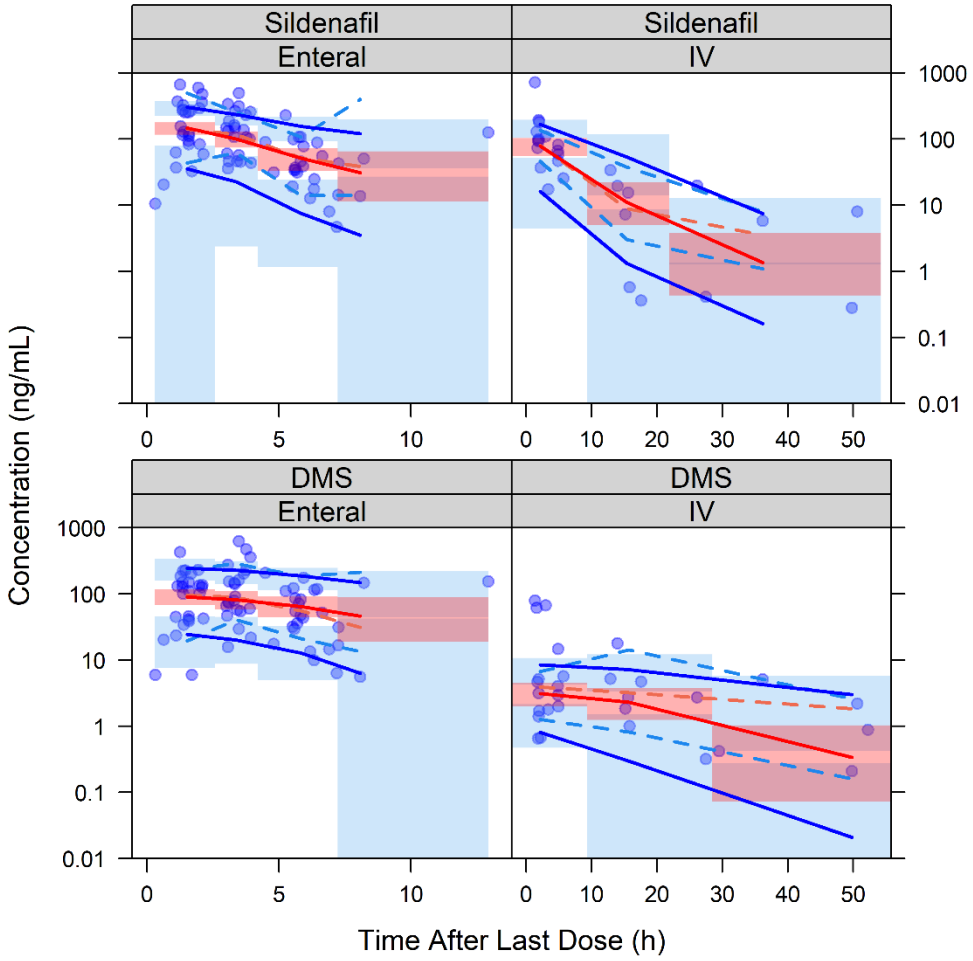


	Age band (years)	Dosing regimen of modulator	$C_{ss,max}$ of modulator (mg/L)
Carbamazepine	2 - 5	10 mg/kg bid	19.0
	6 - 11	300 mg bid	18.2
	12 - 17	400 mg bid	14.3
	18 - 35	600 mg bid	13.4
	36 - 65		16.3
Rifampicin	2 - 5	10 mg/kg/d	13.8
	6 - 11		13.5
	12 - 17		13.1
	18 - 35	600 mg/d	10.3
	36 - 65		9.5
Ketoconazole	2 - 5	6.6 mg/kg/d	8.0
	6 - 11		8.9
	12 - 17		9.6
	18 - 35	400 mg/d	7.4
	36 - 65		7.9

Adiwidjaja J, Boddy AV, McLachlan AJ. *Front Pharmacol.* 2020;10:1672.

PopPK Modeling Characterizes Fluconazole's Effect on Sildenafil Clearance

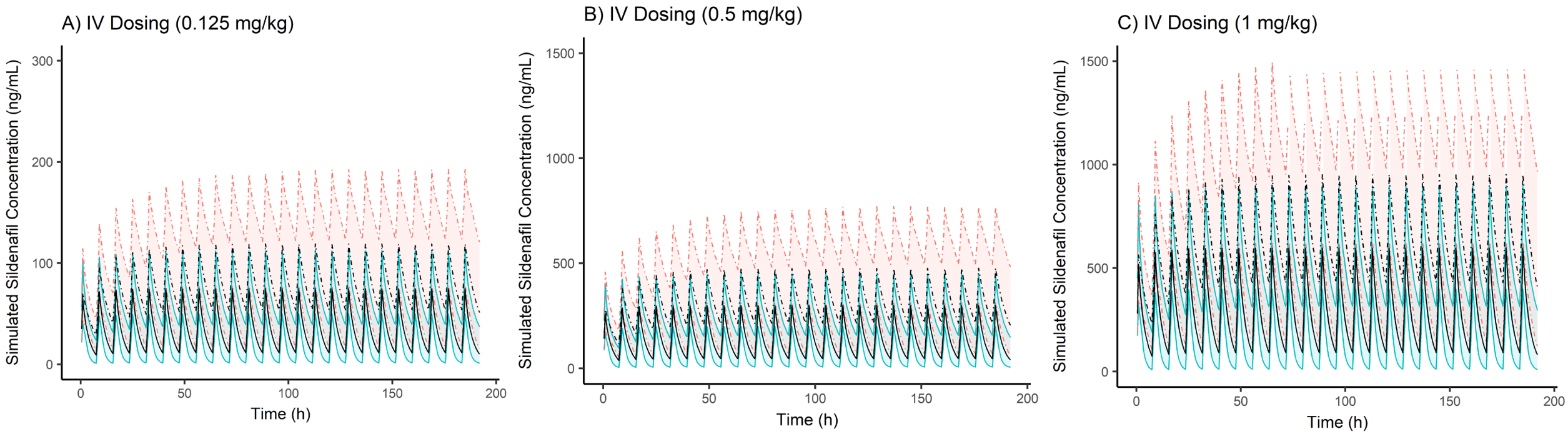
- 34 preterm infants; 109 plasma PK samples
- A two-compartment model for sildenafil and a one-compartment model for N-desmethyl sildenafil (DMS) characterized the data well
- Pre-systemic conversion of sildenafil to DMS was incorporated into the model
- After accounting for body weight, fluconazole co-administration was found to decrease sildenafil clearance by 59%



The dashed lines represent the 5th, 50th, and 95th percentiles of the observed data. The solid lines represent the 5th, 50th, and 95th percentiles of the predicted data. The shaded region represents the 90% confidence interval of the 5th, 50th, and 95th percentiles of the predicted data.

Gonzalez D, et al. *Br J Clin Pharmacol.* 2019;85(12):2824-2837.

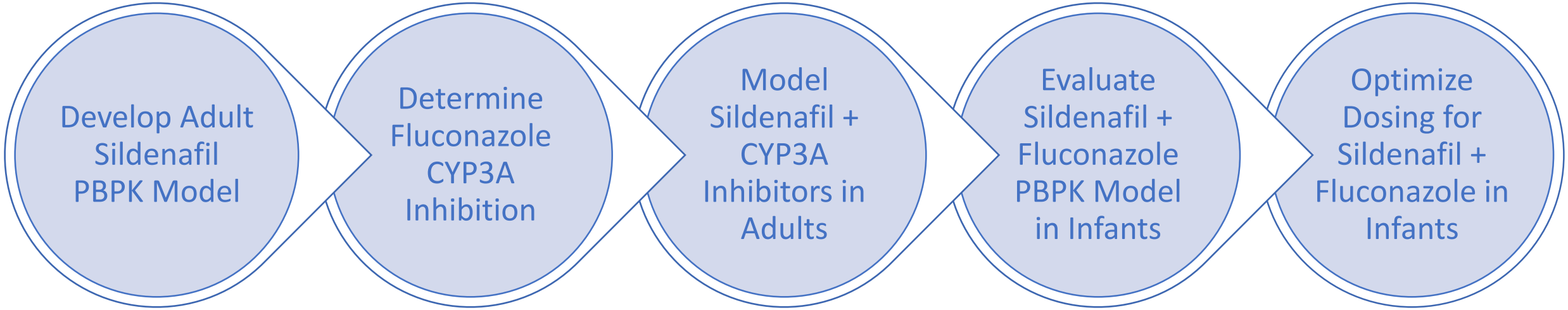
PopPK Model Simulations of the Sildenafil-Fluconazole DDI in Infants



*Pink and teal shaded regions represent the 95% prediction intervals for virtual infants with and without fluconazole, respectively.

Gonzalez D, et al. *Br J Clin Pharmacol.* 2019;85(12):2824-2837.

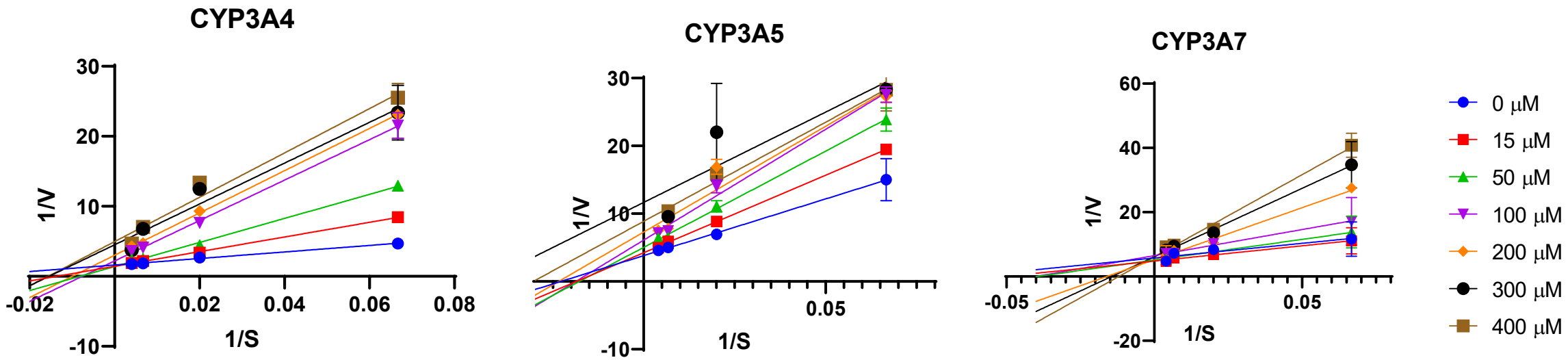
PBPK Modeling Workflow to Characterize the Sildenafil-Fluconazole DDI in Infants



Salerno SN, et al. *Clin Pharmacol Ther.* 2020; Jul 21. Online ahead of print.

Fluconazole CYP3A4/CYP3A5/CYP3A7 Inhibition

Lineweaver Burk plots for CYP3A4, CYP3A5, and CYP3A7 fluconazole inhibition



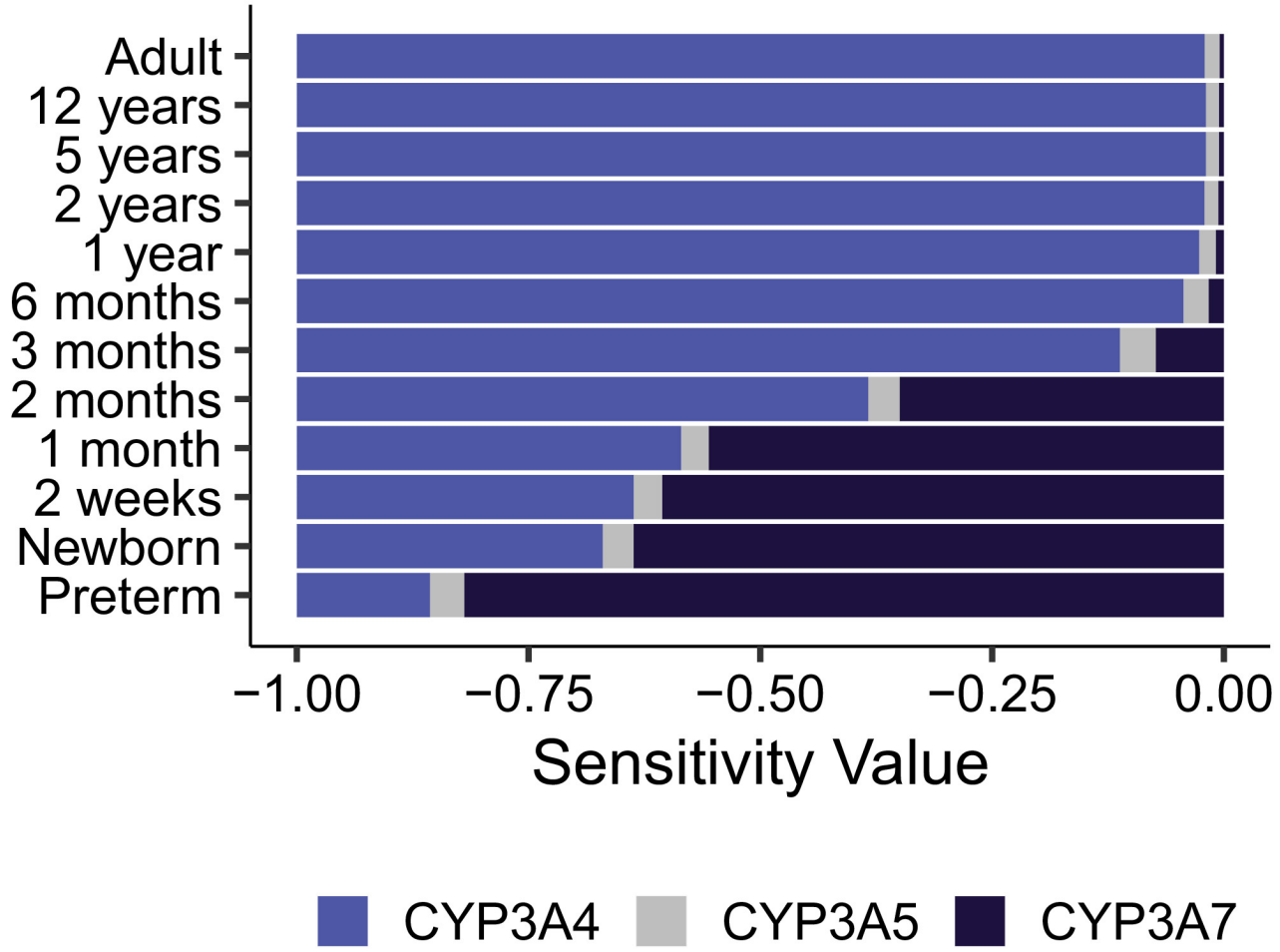
Fluconazole mixed inhibition parameters

Enzyme	Inhibition type	K_I (µM) global	Alpha	K_I (µM) competitive	K_I (µM) uncompetitive
CYP3A4	Mixed	29.4 (20.3-43.8)	16.6 (6.1-178)	20.9 (16.8-25.9)	83.1 (67.4-102.9)
CYP3A5	Mixed	182.5 (86.7-556.4)	2.6 (0.5-13.9)	70.8 (48.5-104.3)	238.7 (183.2-318.9)
CYP3A7	Mixed	84.8 (30.5-296.8)	13.5 (1.8-∞)	45.9 (21.7-88.9)	389.0 (266.7-610.3)

*Value and the 90% confidence interval based on triplicate samples using recombinant enzyme expressing either CYP3A4, CYP3A5, or CYP3A7.

Salerno SN, et al. *Clin Pharmacol Ther.* 2020; Jul 21. Online ahead of print.

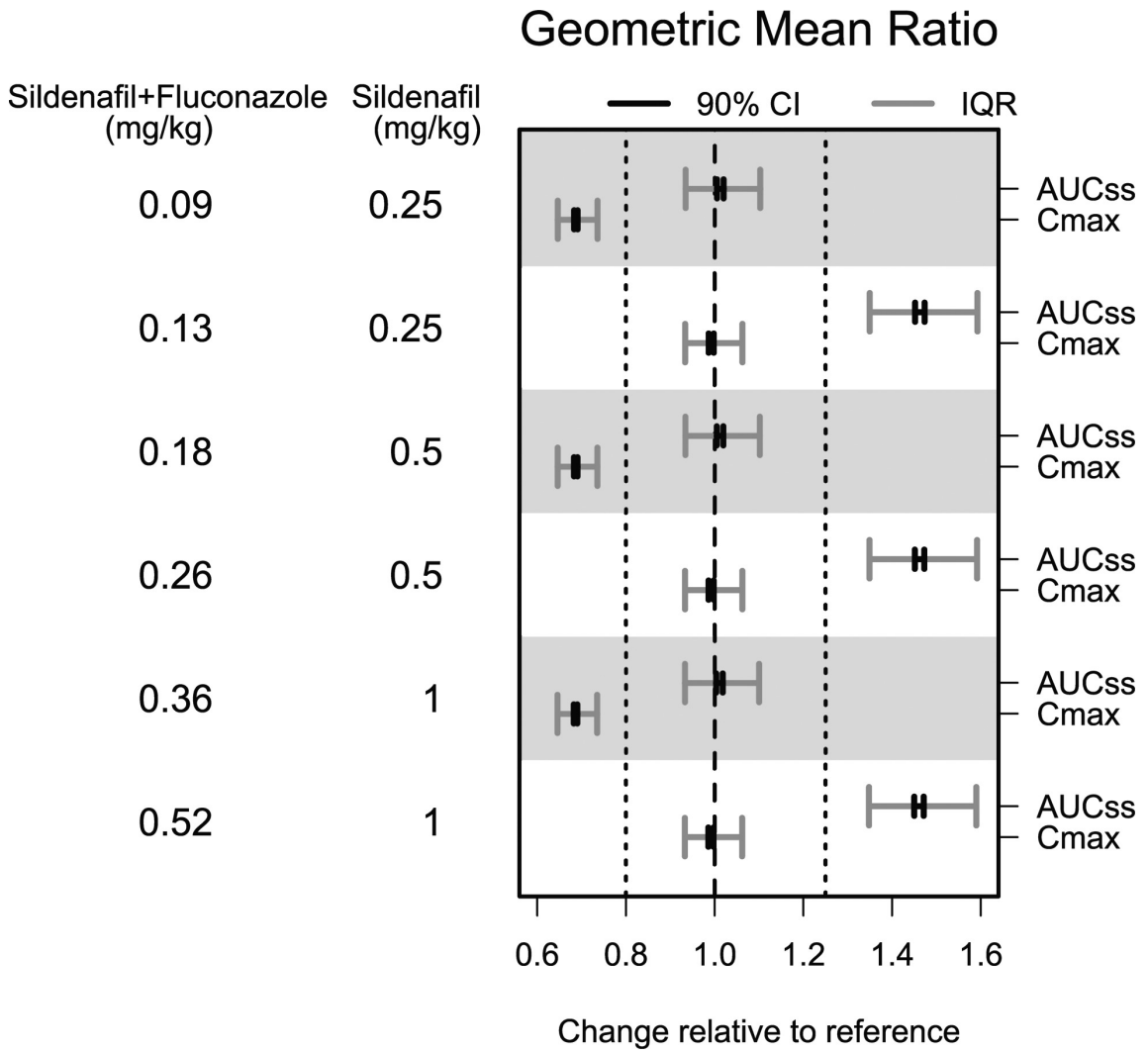
Sensitivity Analysis Comparing CYP3A Influence on Sildenafil AUC



Salerno SN, et al. *Clin Pharmacol Ther.* 2020; Jul 21. Online ahead of print.

PBPK Model Dosing Simulations

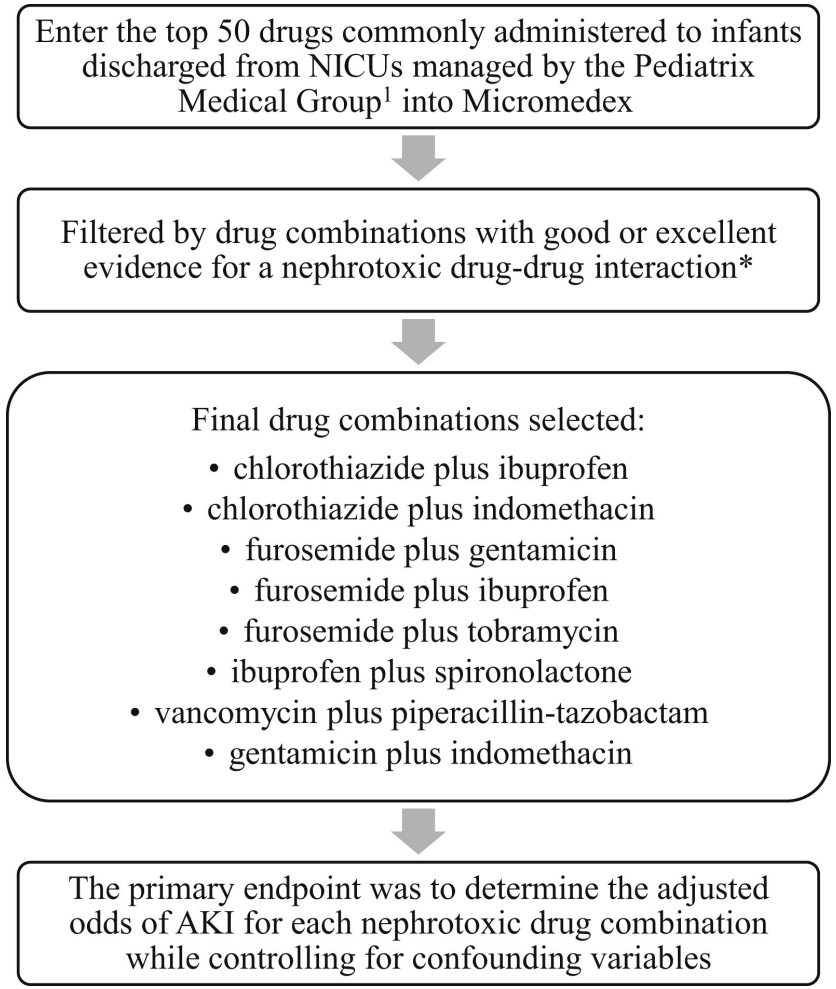
- **Sildenafil co-administration with treatment doses of fluconazole (12 mg/kg i.v. daily)**
  - Reducing the sildenafil dose by **64%** resulted in a geometric mean ratio of 1.01 for simulated AUC at steady-state, but simulated Cmax values were slightly lower
  - Reducing the sildenafil dose by **48%** resulted in a geometric mean ratio for simulated Cmax of 0.99, but overestimated simulated AUC at steady-state



Salerno SN, et al. *Clin Pharmacol Ther.* 2020; Jul 21. Online ahead of print.

Use of Real-World Data to Evaluate AKI Risk in Infants

- The objective was to determine the incidence of acute kidney injury (AKI) in infants exposed to nephrotoxic drug combinations
- Data from 268 neonatal intensive care units managed by the Pediatrix Medical Group
- We included infants born at 22-36 weeks gestational age, ≤120 days postnatal age, exposed to nephrotoxic drug combinations, with serum creatinine measurements available, and discharged between 2007 and 2016
  - Among 8286 included infants, 1384 (17%) experienced AKI
- We used the serum creatinine definition of AKI based on the Kidney Disease: Improving Global Outcomes criteria



Salerno SN, et al. *J Pediatr.* 2020; Aug 17. Online ahead of print.

Use of Real-World Data to Evaluate AKI Risk in Infants

Category	AKI Odds Ratio (95% Confidence Interval)	P-value
Nephrotoxic drug combination		
Chlorothiazide + Indomethacin	2.95 (0.50-17.5)	0.23
Furosemide + Gentamicin	0.94 (0.79-1.13)	0.51
Furosemide + Ibuprofen	0.76 (0.22-2.64)	0.67
Furosemide + Tobramycin	0.70 (0.52-0.95)	0.02
Vancomycin + Piperacillin-Tazobactam	0.77 (0.61-0.98)	0.03
Gentamicin + Indomethacin	Reference	
Duration of therapy (days)	1.04 (1.02-1.06)	<0.01
Baseline Creatinine	0.62 (0.50-0.78)	<0.01
Birth weight (g)		
≤750	1.35 (0.86-2.13)	0.19
751 to 1000	1.20 (0.78-1.86)	0.40
1001 to 1500	1.02 (0.69-1.52)	0.92
1501 to 2500	1.01 (0.75-1.37)	0.93
>2500	Reference	
Gestational age (weeks)		
<24	0.92 (0.58-1.46)	0.72
24 to 26	0.85 (0.58-1.26)	0.42
27 to 29	0.86 (0.60-1.21)	0.38
30 to 32	0.86 (0.65-1.15)	0.31
33 to 36	Reference	
Post-natal age (weeks)		
<2	1.33 (0.98-1.80)	0.07
2 to 3	0.98 (0.73-1.33)	0.91
4 to 5	0.81 (0.58-1.12)	0.20
6 to 7	1.05 (0.72-1.51)	0.81
8 to 16	Reference	
Male	1.03 (0.91-1.17)	0.62
Race/ethnicity		
Black	0.92 (0.78-1.10)	0.37
Hispanic	1.11 (0.94-1.31)	0.23
Other	0.82 (0.60-1.12)	0.22
White	Reference	
Sepsis	1.25 (1.09-1.44)	<0.01
Respiratory distress syndrome	0.96 (0.82-1.12)	0.59

*Results of a random effects logistic model of AKI among infants born at 22-36 weeks gestation between 2007 and 2016.

Salerno SN, et al. *J Pediatr.* 2020; Aug 17. Online ahead of print.

Conclusions

- Potential DDIs are common in hospitalized pediatric patients, but DDI studies are rarely performed in the pediatric population for ethical and practical reasons
- PBPK and population PK modeling can be used to characterize PK-mediated DDIs and evaluate dosing in infants, children, and adolescents
- Using PBPK modeling, adult DDI data can be leveraged, and opportunistic clinical data collected from pediatric patients receiving the drug combinations per standard of care can be used for model evaluation
- Real-world data available through electronic health record databases can be used to evaluate drug safety in infants receiving drugs that may interact with each other

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  - K23 (HD083465; PI: Gonzalez)
  - R01 (HD096435; PI: Gonzalez)

Renal Impairment in Pediatric Patients: Current Approaches to Drug Dosing

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Disclosure Statement

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

Goals of Drug* Dosing in Renal Impairment

Reduce risk of exposure-related toxicity

Maintain exposures in an effective range

Provide Data-Driven Information

about Need for Pediatric Dosing Adjustments in Labeling

* Refers to both small molecules and therapeutic biologics regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research

Overview

- Drug Characteristics and Intended Use
- Definition of Renal Impairment
- At Risk Pediatric Population
- Serum Creatinine-Based Prediction Equations
- Approaches to Assess Impact of Renal Impairment on Pharmacokinetics (PK)
- Ongoing Challenges

Drug Characteristics: Impact of Renal Impairment

Not Likely to Alter PK

- Single-dose use
- Locally-acting drugs
- Predominantly eliminated by lungs

Likely to Alter PK

- Multiple-dose
- Systemically-acting drugs
- Substantially eliminated by kidneys

Sept 2020 Guidance for Industry PK in Patients with Impaired Renal Function:
https://www.fda.gov/media/78573/download

Drug Characteristics

- "Substantially eliminated" by kidneys
  - Fraction of systemically available drug or active metabolite excreted unchanged in urine is > 30%
  - Contributed by glomerular filtration, tubular secretion, and/or tubular reabsorption

Sept 2020 Guidance for Industry PK in Patients with Impaired Renal Function:
https://www.fda.gov/media/78573/download

Impact of Renal Impairment on PK

- Decrease in renal excretion of drug or active metabolites
- Changes in absorption, plasma protein binding, and/or tissue distribution
- Alter some drug metabolism and transport pathways in liver and gastrointestinal tract

Normal Renal Maturation

Nephrogenesis completed by 36 weeks gestational age

Glomerular function reaches adult values by 2 years of age

Tubular function matures between 7-12 months of age

Age	Mean GFR (mL/minute/1.73m^2)	Standard Deviation (mL/minute/1.73m^2)
1 week	41	15
2-8 weeks	66	25
> 8 weeks	96	22
2-12 years	133	27
13-21 years (males)	140	30
13-21 years (females)	126	22

Hogg RJ, Furth S, Lemley KV, et al. Pediatrics 2003.

Definition of Renal Impairment

- Reversible reduction in glomerular filtration rate (GFR) as seen with acute kidney injury (AKI)
- Irreversible reduction in GFR as seen with chronic kidney disease (CKD)

Pediatric Populations with Renal Impairment

AKI

- Reduced kidney perfusion
- Intrinsic glomerular disease and/or tubular toxicity
- Urinary tract obstruction

CKD

Age	Cause
Birth to 4 years	Congenital anomalies of kidneys and urinary tract Hereditary diseases
5 to 14 years	Hereditary diseases Nephrotic syndrome Systemic diseases
15 to 19 years	Glomerular diseases Hereditary diseases

National Institute of Diabetes and Digestive and Kidney Diseases:
https://www.niddk.nih.gov/health-information/kidney-disease/children

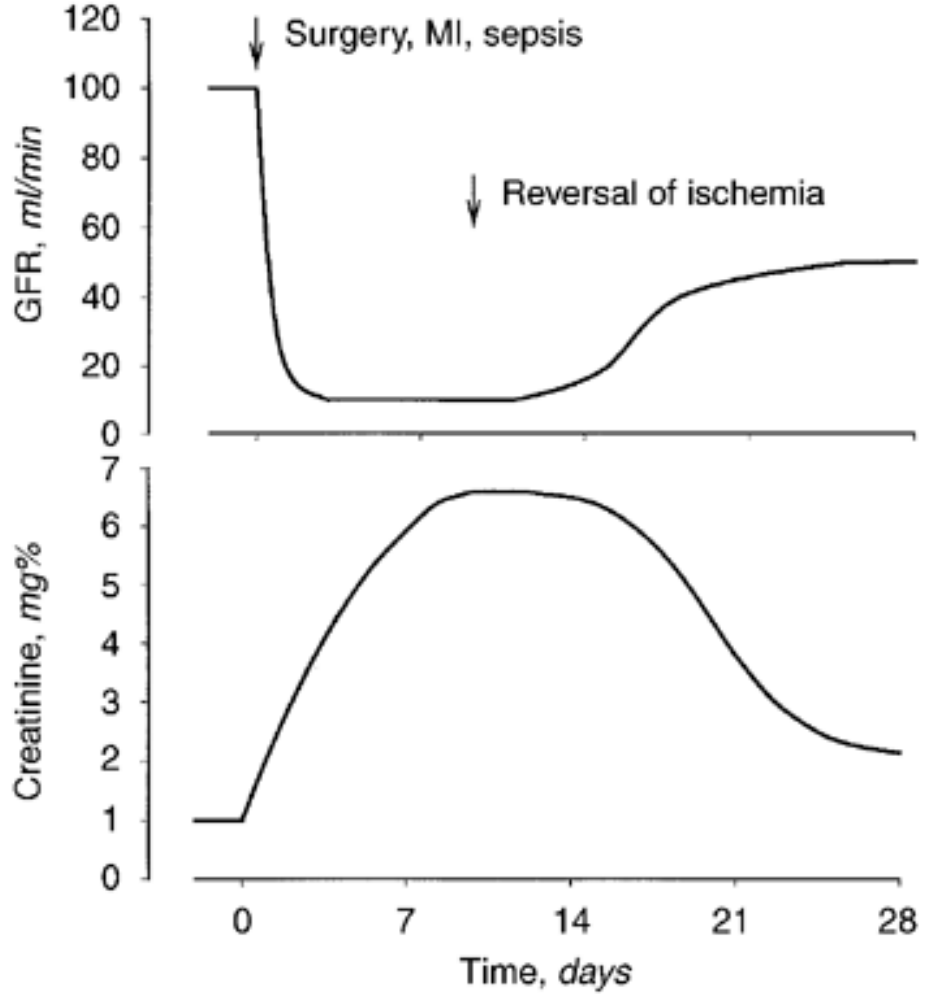
Acute Kidney Injury (AKI)

Stage	Serum Creatinine (SCr)	Urine Output
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dL increase	< 0.5 mL/kg/hr for 6-12 hrs
2	2.0-2.9 times baseline	< 0.5 mL/kg/hr for ≥ 12 hrs
3	3.0 time baseline; OR increase in SCr to > 4.0 mg/dL; OR start dialysis; OR estimated GFR < 35 mL/minute/1.73m^2 in age < 18 years	< 0.3 mg/kg/hr for ≥ 24 hrs; OR anuria for ≥ 12 hrs

KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury

Definition of Renal Impairment

- Reliance on absolute changes in SCr for drug dosing is problematic
- Reliance on serum creatinine (SCr) based prediction equation to estimate GFR most common
- Reliance on measured creatinine clearance (CrCl) less common
- CrCl ≒ eGFR



Star RA. Perspectives in Renal Medicine 1998.

eGFR Prediction Equations in Pediatrics

- Schwartz equations
  - Original Schwartz formula: eGFR = *k* x height in cm/SCr
    - Jaffe method to assay SCr
    - *k* constant directly proportional to muscle mass which varies with age and sex
  - Bedside Schwartz formula: eGFR = 0.413 x height in cm/SCr
    - Enzymatic reaction by isotope dilution mass spectrometry to assay SCr
  - Validated across GFR range of 15-75 mL/min/1.73m^2
- 2012 Multivariable Chronic Kidney Disease in Children (CKiD) equation: incorporates SCr and cystatin C

eGFR Prediction Equations in Pediatrics

- Inaccurate when SCr is rapidly changing
- Useful indicator of GFR over time when measured sequentially and when SCr has stabilized
- Can underestimate true GFR when Cr production is increased (e.g. creatine supplements)
- Can overestimate true GFR when Cr production is decreased (e.g. reduced muscle mass, malnutrition)
- Widely used to guide drug dosing decisions at bedside

Approaches:
Assess Impact of Renal Impairment on PK in Adults

- Dedicated renal impairment study
  - More common approach
- Population PK analysis
  - Leverage PK data across studies available for a specific program
  - Less common approach
  - Phase 3 trials often exclude enrollment of patients with comorbidities such as severe renal impairment

Dedicated Renal Impairment Study

- Single-dose: Dose-proportional and time-independent PK at anticipated concentrations
- Compares adults with a range of renal impairment to control group of adults with normal renal function
- Can include pharmacodynamic measure(s)
- Dose recommendations in renal impairment group based on exposure matching to control group

Sept 2020 Guidance for Industry PK in Patients with Impaired Renal Function:
https://www.fda.gov/media/78573/download

Dedicated Renal Impairment Study

Classification of Kidney Impairment

Description	Range of Values for Renal Function (mL/ minute)
Control (normal renal function)	≥ 90
Mild Impairment	60-89
Moderate Impairment	30-59
Severe Impairment	15-29
Kidney Failure	< 15 mL/minute OR on dialysis

Values derived from SCr-based prediction equations validated for use in adults or CrCl using Cockcroft-Gault equation

Dedicated Renal Impairment Study

Assumptions

- Dose adjustment to match exposures will result in similar risk-benefit profile as that observed in adult phase 3 population
  - Underlying renal disease and associated co-morbidities may alter exposure-response relationship and overall risk-benefit profile

Approaches:
Assess Impact of Renal Impairment on PK in Pediatrics

- Dedicated renal impairment study NOT common
  - Feasibility concerns due to relatively smaller CKD population
  - Ethical considerations with single-dose design offering benefit to pediatric population being studied
- Application of same adult renal dosing recommendations to pediatric patients based on adult renal impairment PK data more common
  - Assumes similar proportional effects of renal impairment on PK between adults and pediatric patients
  - Often without observed pediatric data to validate this assumption

Approaches:
Assess Impact of Renal Impairment on PK in Pediatrics

- Deriving pediatric renal dose adjustments from adult renal impairment data may be reasonable in patients > 2 years of age on case by case basis
- Open phase 3 trial enrollment to pediatric patients with CKD, AKI, or both for PK assessment

Ongoing Challenges

- Greater uncertainty with deriving dosing recommendations in pediatric patients with immature renal function
- Greatest need for reliable estimate of GFR to allow accurate and precise dose adjustments
  - AKI when eGFR values are likely to be least reflective of true GFR
  - Drugs with narrow safety margin

Thank You!

Predictive Performance of PBPK Dose Estimates for Pediatric Trials

Dr. Ibrahim Ince
Dr. André Dallmann

Bayer AG

2020-10-22

Online FDA/MCERSI
Pediatric Dose Selection Workshop

Conflicts of interest / disclaimer

All authors are full time employees of Bayer AG

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Disclaimer: *The views expressed in this presentation do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.*

PBPK modelling has been the scientific foundation for predictive exposure matching based on clinical studies for almost 2 decades

- Physiology based pharmacokinetic (PBPK) models have often supported the development and guidance of dosing strategies in children.
- These models incorporate age dependent changes of the relevant anthropometric and physiological parameters and apply ontogeny and variability of active processes involved in the elimination of pharmaceutical compounds.
- As most changes occur in the first 2 years of life, a good understanding of age-related changes in these processes is of upmost importance.
- Several studies have been performed for Bayer compounds, applying dosing schemes in children based on PBPK predictions.

PBPK modeling in adults and translation to children in Open Systems Pharmacology (PK-Sim / MoBi)

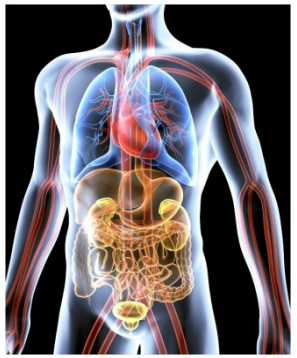
Building blocks of a PBPK model for adults

Drug properties

Physicochemical properties
- Lipophilicity
- Molecular weight
- pKa/pKb

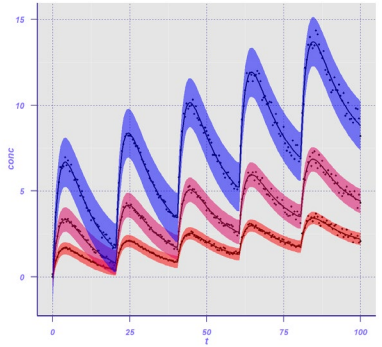
Drug-biology interaction
- Fraction unbound
- Partition coefficients
- Mass Balance
- Fractional CL contributions
- Permeability
- Active processes (K_m, V_{max})

Organism properties



Anatomy & physiology
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

Study protocol and formulation properties



Formulation
(empirical or mechanistic dissolution function)

Administration protocol
(dose and dosing regimen)

Special events
(food intake, exercise, EHC)

Building blocks of a PBPK model for children

Drug properties

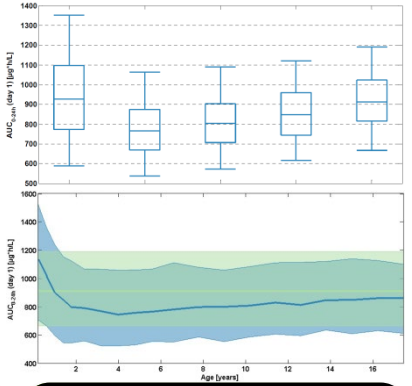
Physicochemical properties
- Lipophilicity
- Molecular weight
- pKa/pKb

Organism properties

Age-dependent changes in anatomy & physiology

Resulting age-dependent changes in drug-biology interaction

Study protocol and formulation properties



Modified formulations
(e.g. minitablets, syrup)

Adjusted administration protocol
(e.g. mg/kg dosing)

Different special events

Bridging from adults to children - Workflow

Step 1:

Development and verification
of a PBPK model for adults

Step 2:

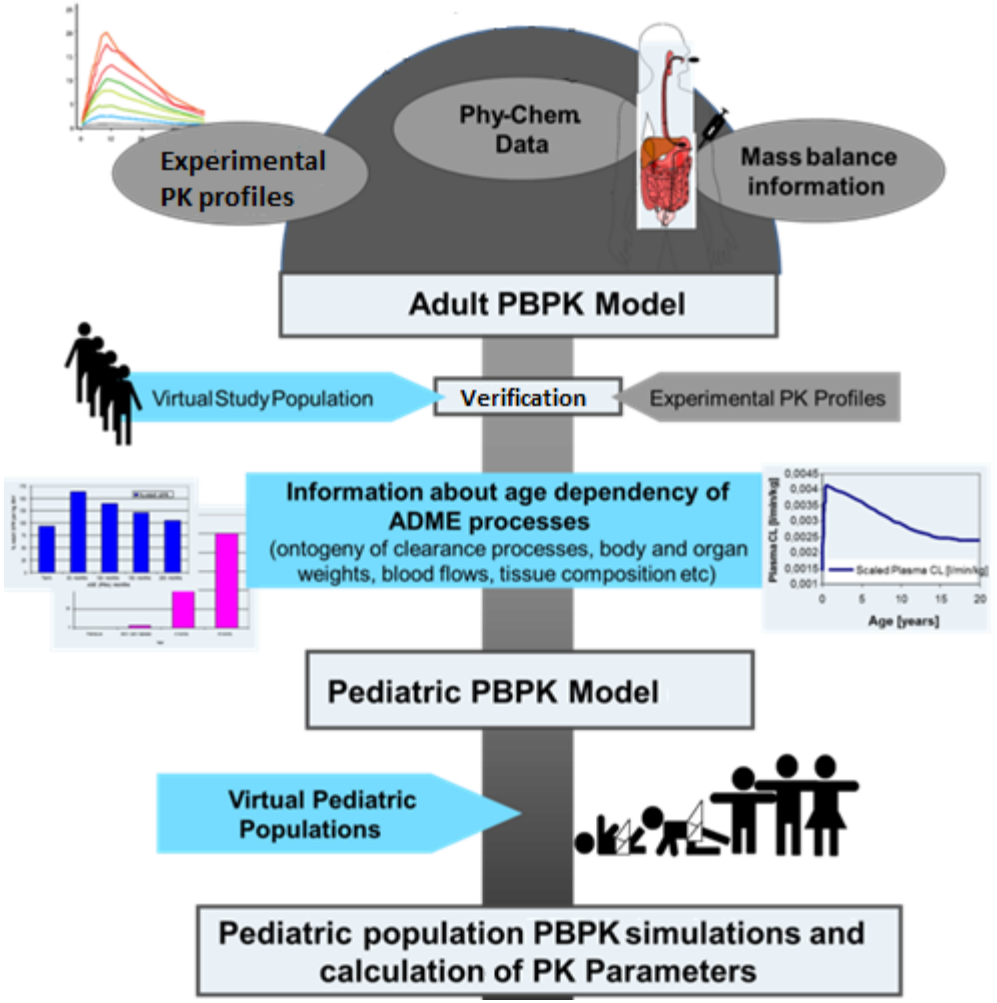
Translation of the adult PBPK model
to children using prior physiological information
about growth and maturation of relevant
processes

Step 3:

Prediction of pharmacokinetics
in children by means of simulations of virtual
pediatric trials

Step 4:

Support of clinical decision process by evaluating
adequate dosing, sampling or cohort size



Ince I. et al. J. Clin. Pharmacol. 59(S1), 2019

Pediatric dosing schemes in children supported by PBPK predictions

Overview of Bayer small molecule compounds applied in children since 2005

Market Name	Age range (years)	Involved processes in PBPK model
Amikacin	0.01 – 16	GFR
Ciprofloxacin	0.2 – 6.6	CYP1A2, TS, GFR, Bil.CL
Copanlisib	13 – 17	CYP3A4, PgP, PIK3a
Gadovist	0.2 – 18	GFR
Levonorgestrel	12 – 18	Hepatic CL
Magnevist	0.2 – 2	GFR
Moxifloxacin	0 – 18	UGT1A1, SULT2A1, Bil.CL, TS/GFR
Regorafenib	2 – 17	CYP3A4, UGT1A9, Bil.CL
Riociguat	6 – 18	CYP1A1, CYP3A4, CYP3A5, CYP2C8, CYP2J2,UGT1A2, UGT1A9, Bil.CL (Pgp, BCRP), TS/GFR
Rivaroxaban	0 – 18	CYP3A4, Plasma Hydrolysis, GFR, TS, CYP2J2
Sorafenib	1 – 19	CYP3A4, UGT1A9, Reduction, Unspecific CL

** TS : tubular secretion, Bil.CL: biliary clearance, PIK3a: phosphatidylinositol 3-kinase alpha*

Prospective evaluation of PBPK predictions with data observed during clinical studies in children are continuously performed

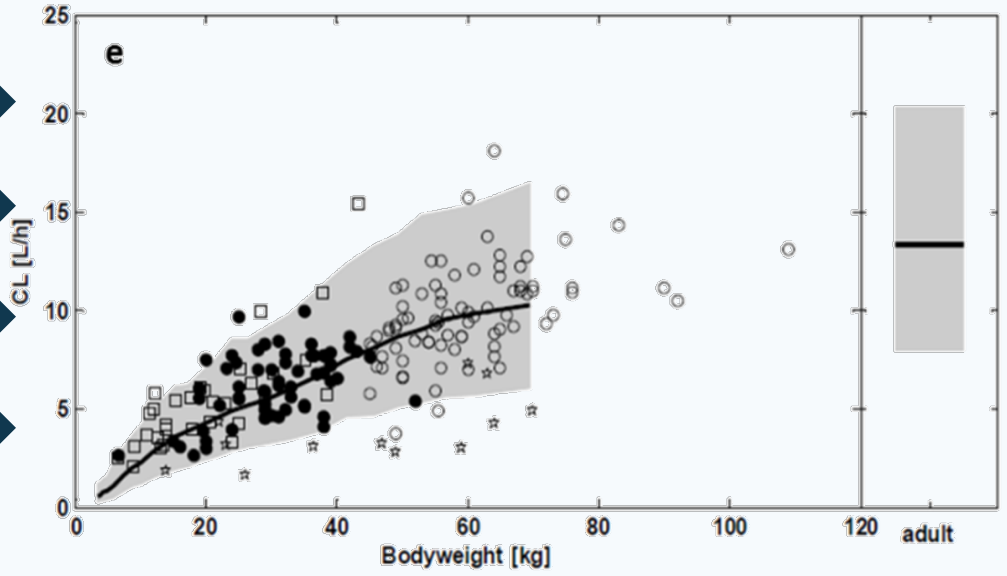
SULT2A1

UGT1A1

biliary

renal

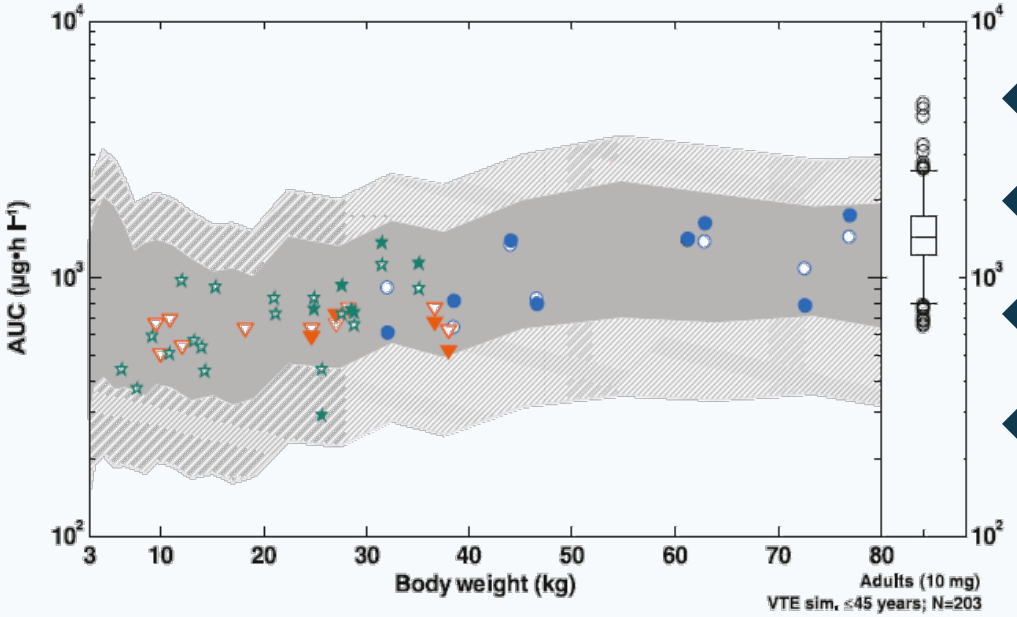
Example: Moxifloxacin



// black line: PBPK prediction for children (median)
// gray shaded area: PBPK prediction for children (90% interval)
// symbols: individual data derived from clinical observations using population PK modelling in pediatric phase 1 and 3 trials following single or multiple oral or intravenous doses

Willmann et al., *J Clin Pharmacol.* (2019)

Example: Rivaroxaban



// dark gray area: PBPK prediction for children (90% interval)
// light gray area: extended PBPK prediction range (0.5 x 5th to 1.5 x 95th percentile)
// symbols: individual data derived from clinical observations following single administration of 10 mg-equivalent dose

Willmann et al., *Thrombosis Journal* (2018)

CYP3A4

CYP2J2

hydrolysis

renal

Evaluation of 10 Bayer Compounds applied in Children

// Evaluated pediatric PBPK models for 10 Bayer compounds

// Via Ratio-calculation PBPK vs reported PK (popPK and NCA of clinical data)

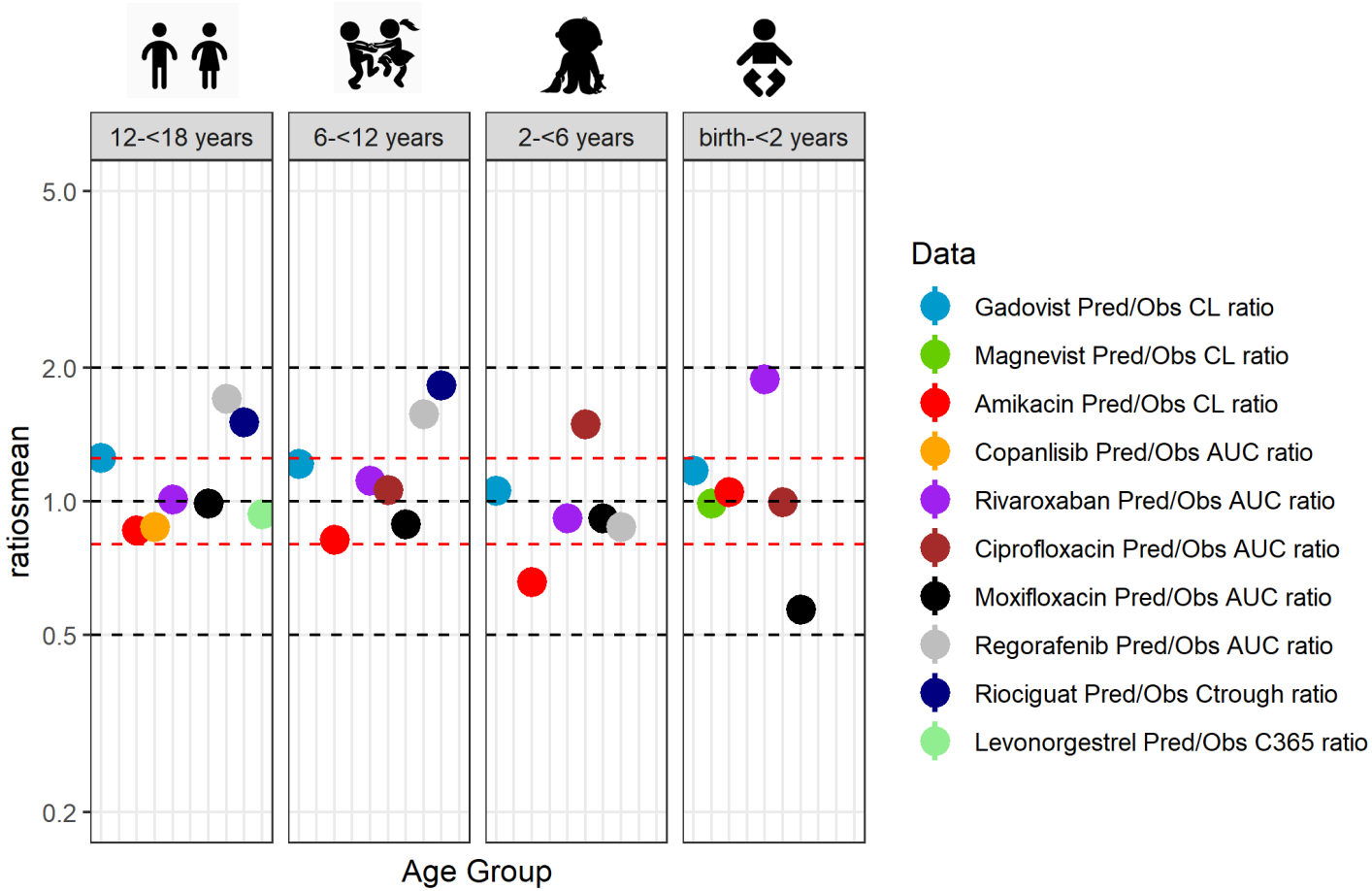
Evaluation of predictive performance	**Ratio of Predicted PBPK vs PopPK and NCA of clinical data-based PK-Parameters** **$AUC_{24,ss}$** **C_{trough}** **$C_{365days}$** **Clearance**
Predefined age groups	**0-<2** years **2-<6** years **6-<12** years **12-<18** years
PBPK simulation software	Open Systems Pharmacology **(OSP)** Suite (PK-Sim / MoBi) * (or formerly BTS Computational Systems Biology Suite)
Calculation & Illustration software	**Rstudio** Version 1.2.5033

** http://www.open-systems-pharmacology.org/*

Confirmation of predictive power of PBPK

Predicted versus observed

- **For all pediatric age groups**
  - **100% of observed data within 2-fold range of prediction**
  - **67% within BE interval**



Discussion

- Successful and adequate prediction of PBPK models for 10 compounds
  - Clear illustration of the predictive power of PBPK for guiding dosing schemes for compounds in the pediatric population.

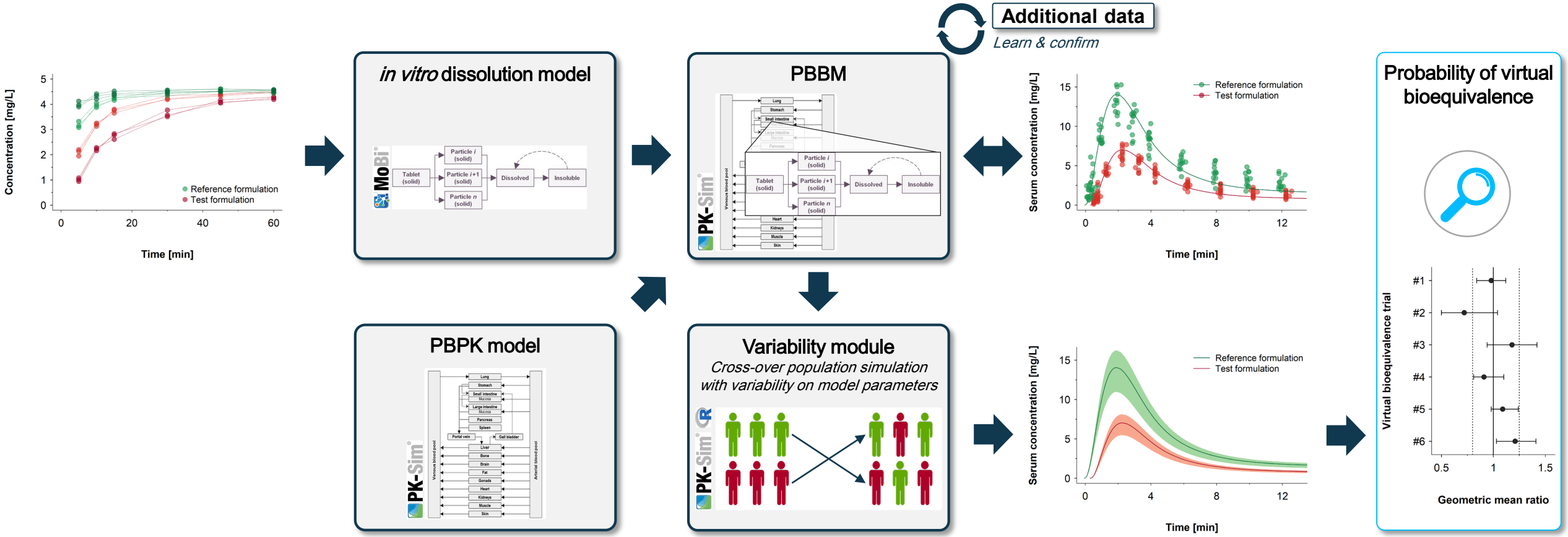
- Distribution and clearance in children are now relatively well understood, whereas dissolution and absorption often lack a more systematic and mechanistic understanding [1]

- The use of PBPK modeling for biopharmaceutics applications in adults and children is an area of ongoing research

[1] Ince I. et al. *J. Clin. Pharmacol.* 59(S1), 2019. https://doi.org/10.1002/jcph.1497

Filling the gap: PBPK modeling for biopharmaceutics applications

Workflow for virtual bioequivalence testing

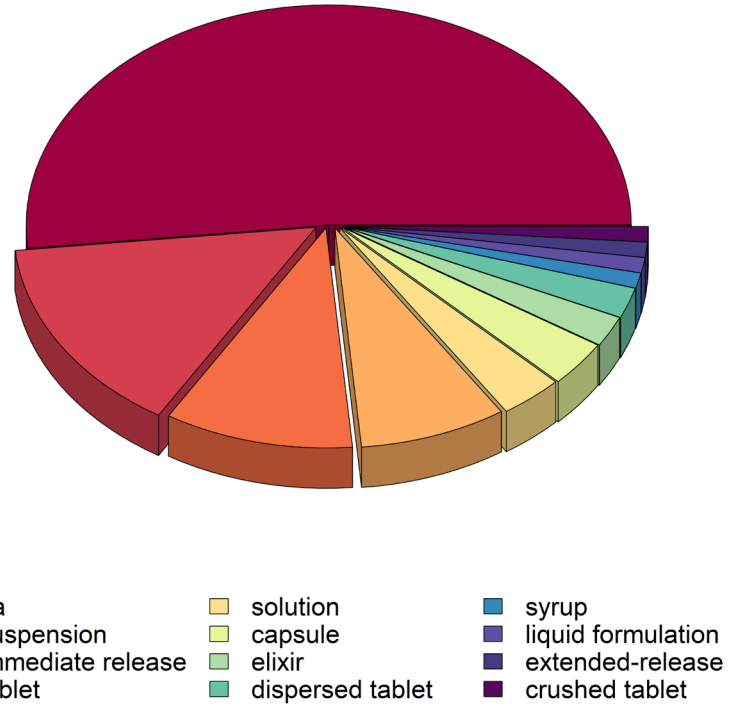


Note: Developed in collaboration with Andrea Edginton (University of Waterloo), Michael Neely (Children's Hospital Los Angeles), and Eleftheria Tsakalozou (FDA); overall support for this work provided by a grant from the FDA (award number: U01FD006549).

Filling the gap: PBPK modeling for biopharmaceutics applications

- FDA encourages the use of PBPK modeling for bio-pharmaceutics applications under certain conditions [1]
- Pediatric PBPK models for oral drug formulations haven been successfully used to predict drug pharmacokinetics
- Recently, first efforts were made to use pediatric PBPK models for virtual bioequivalence assessment [2,3]
- Biorelevant media are unlikely to be biopredictive for children; adaptations may be required
- Technical frameworks for virtual bioequivalence testing with OSP are being developed

Oral dosage forms in published pediatric PBPK models (*n* = 89)



[1] FDA Draft Guidance for Industry: The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls. September 2020.

[2] Vaidhyanathan S. et al. *J. Pharm. Sci.* 108(1), 2019. https://doi.org/10.1016/j.xphs.2018.11.005

[3] Miao L et al. *AAPS J.* 22(107), 2020. https://doi.org/10.1208/s12248-020-00493-6

Thank you!

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Katrin Coboeken
Stefan Willmann
Michael Block
Michaela Meyer
Thomas Eissing
Rolf Burghaus
Joerg Lippert

Pharmacogenetics and Drug Dose Selection
A Case Study of Thiopurines

Jun J. Yang PhD

Professor

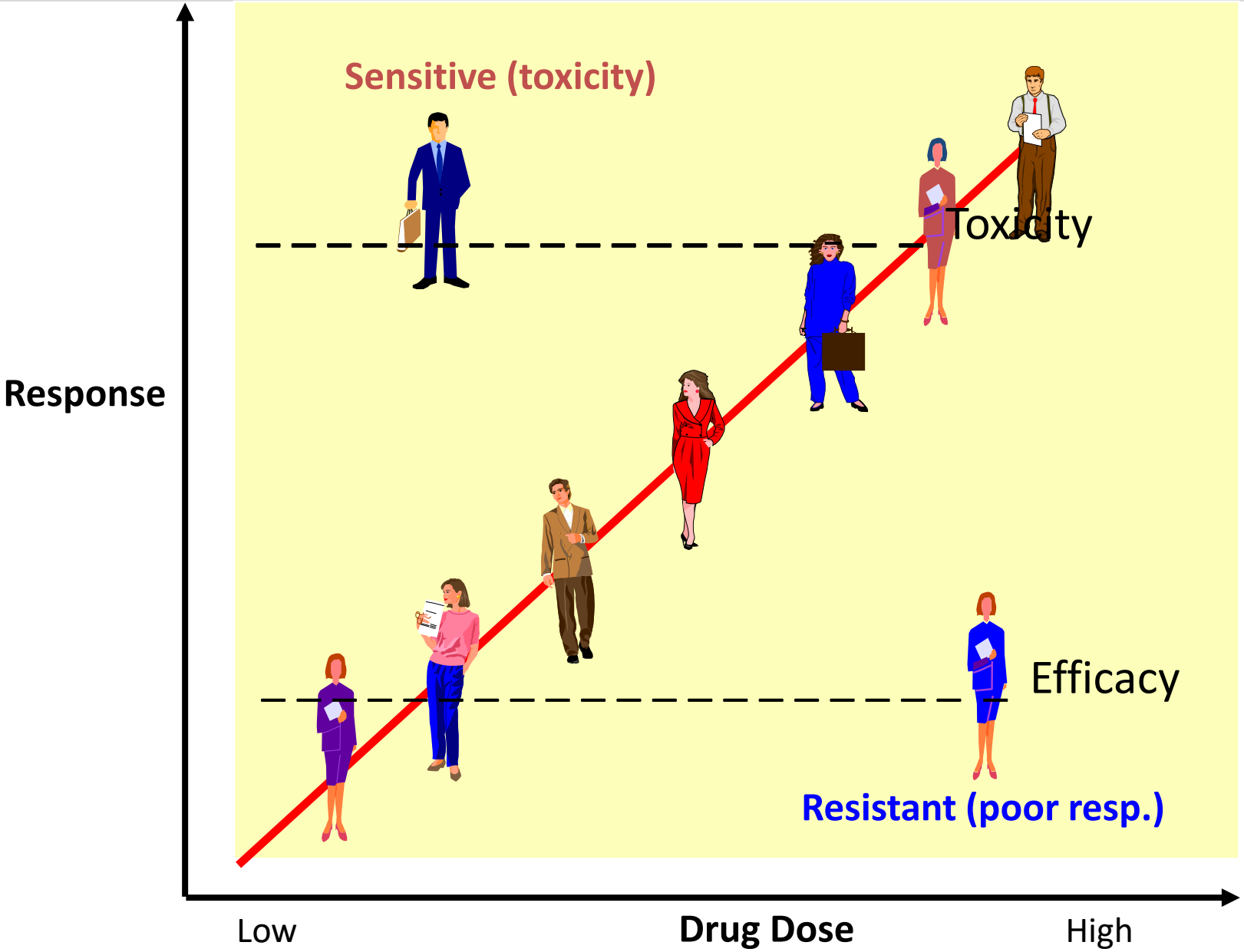
Dept Pharm Sci.

St. Jude Children's Research Hospital

Oct 2020

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Common Relationship between Drug Dose and Response



Pharmacogenetics: Genetic Variation Linked to Drug Response

Does the variation in our genetic make-up explain the variability in drug response?