

Pediatric Applications of PBPK Modeling and Simulation in Drug Regulatory Science: Where are we now?

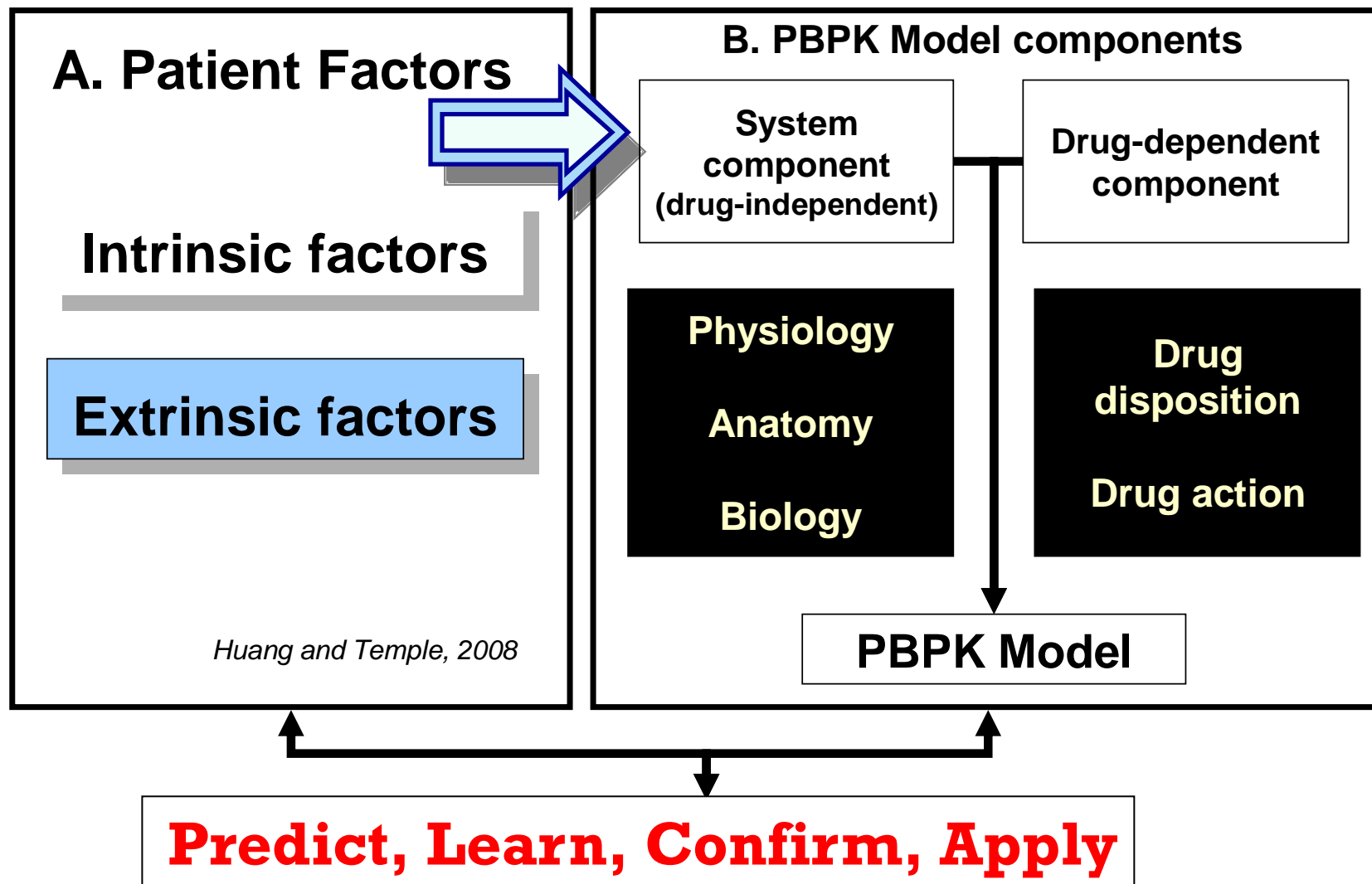
Joseph A. Grillo, Pharm.D.

Associate Director for Labeling and Health Communication (Acting)
Office of Clinical Pharmacology, Immediate Office
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

***The views expressed in this presentation are personal opinion and do not
reflect the official policy of the FDA***

Outline

- Overview of PBPK related submission characteristics in the Office of Clinical Pharmacology (OCP)
- Overview of pediatric submissions to OCP
- Challenges to the application of PBPK to pediatrics
- Pediatric workflow considerations
- Tips for submitting PBPK related information to FDA
- Summary and the path forward

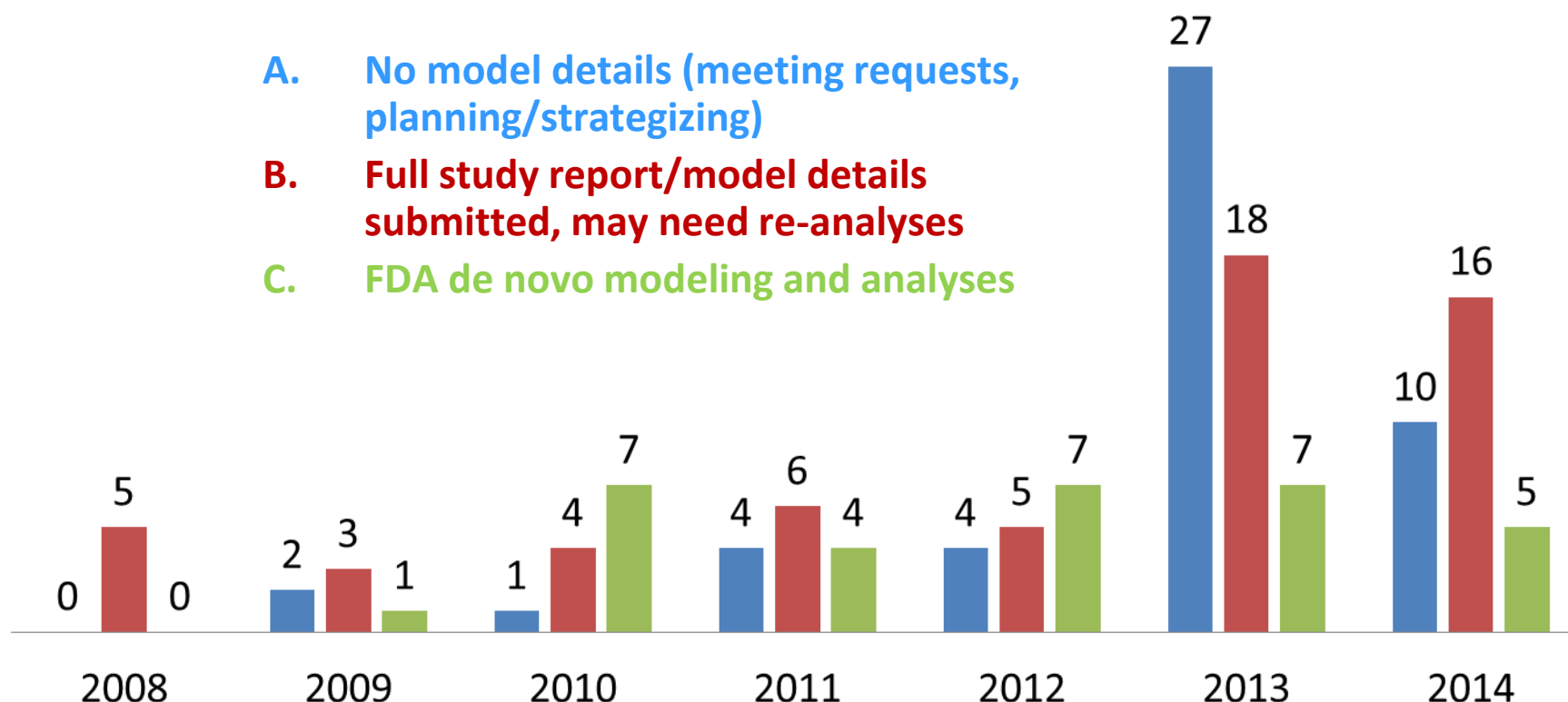


PBPK Team at the FDA

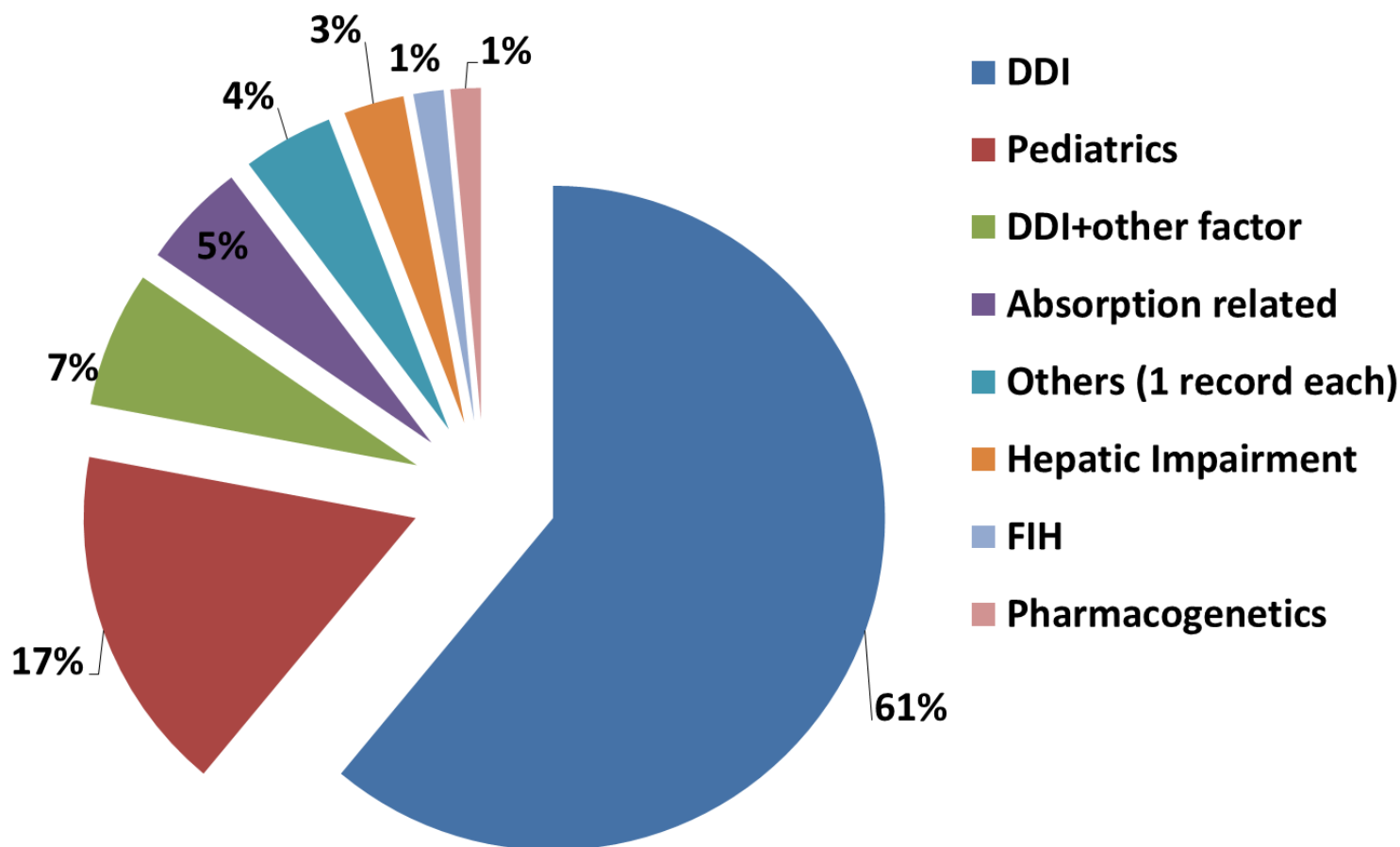
- Policy
 - Develop best practices and guidance documents for industry on the use of PBPK
- Review
 - Centralized unit for coordination of PBPK reviews
 - Conducts in-house PBPK analyses when required
 - Maintains a regulatory knowledgebase for consistency
- Research and training
- Outreach
 - To harmonize with non US regulators
 - Foster communications with thought leaders

OCP PBPK Reviews Increasing

*Updated October 22, 2014
(136 submissions)*



....And Becoming More Diverse

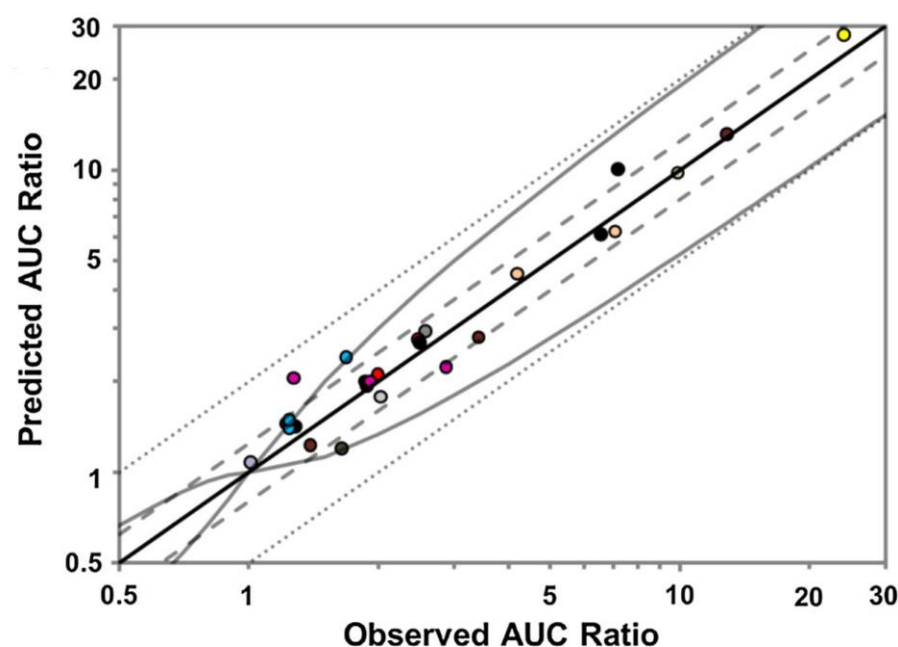
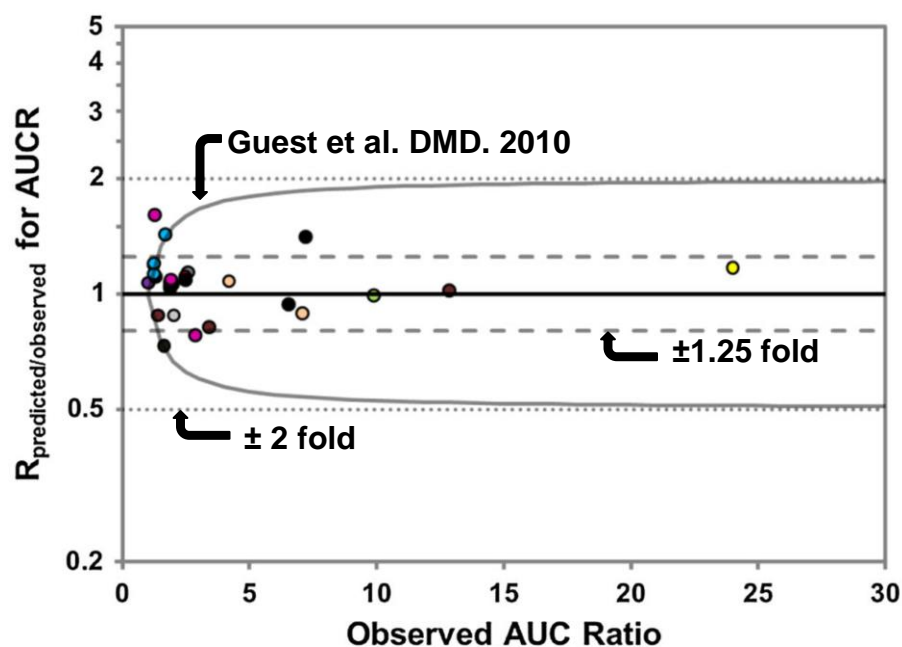


**Updated October 22, 2014
(136 submissions)**

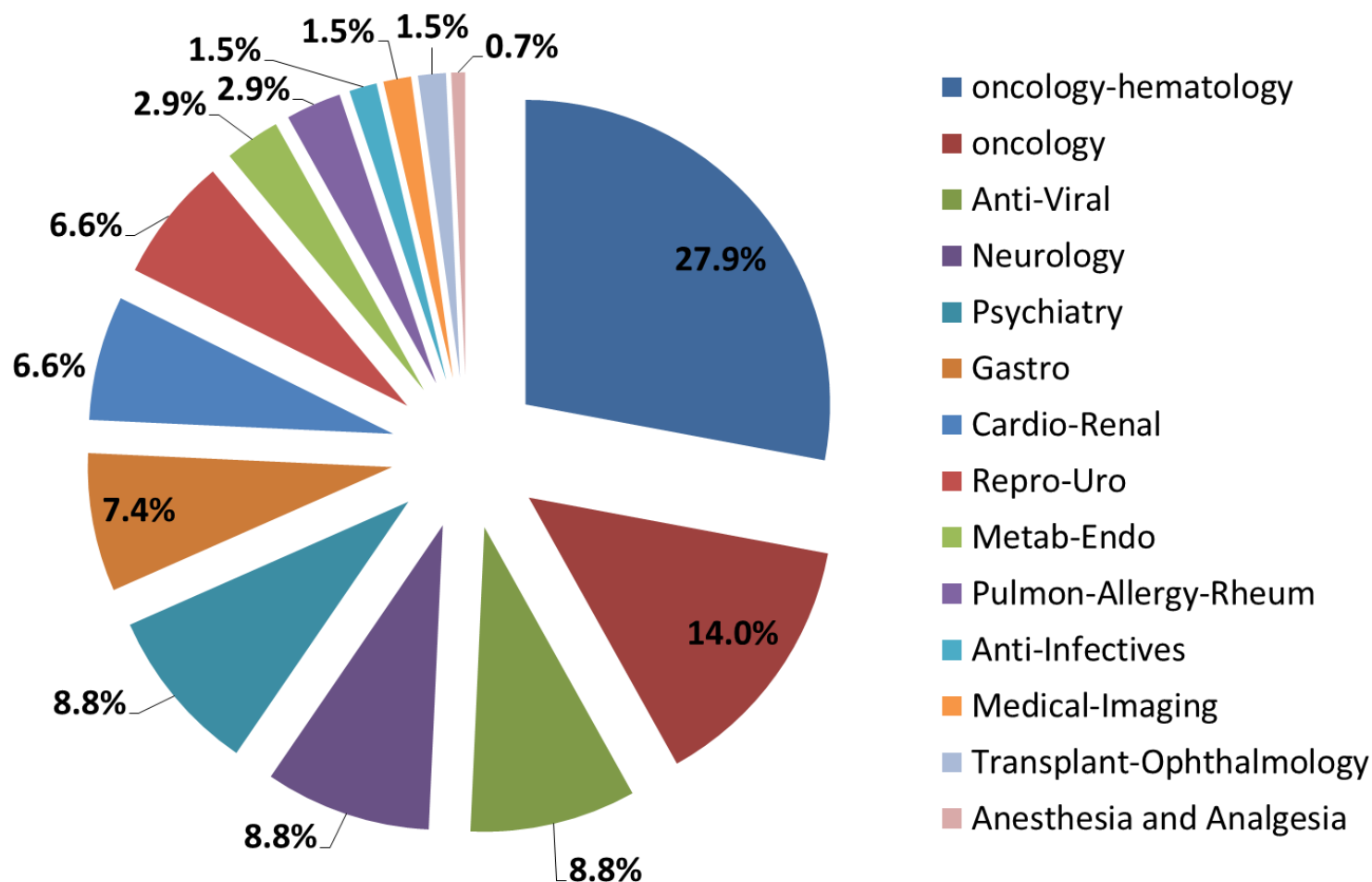
DDI Prediction in Adults

Cross Drug Analysis of Drug as Enzyme Substrate using FDA PBPK knowledgebase

- *Criteria*
 - (a) *model simulated PK and observed PK comparable;*
 - (b) *clinical interaction data were not used for model building*



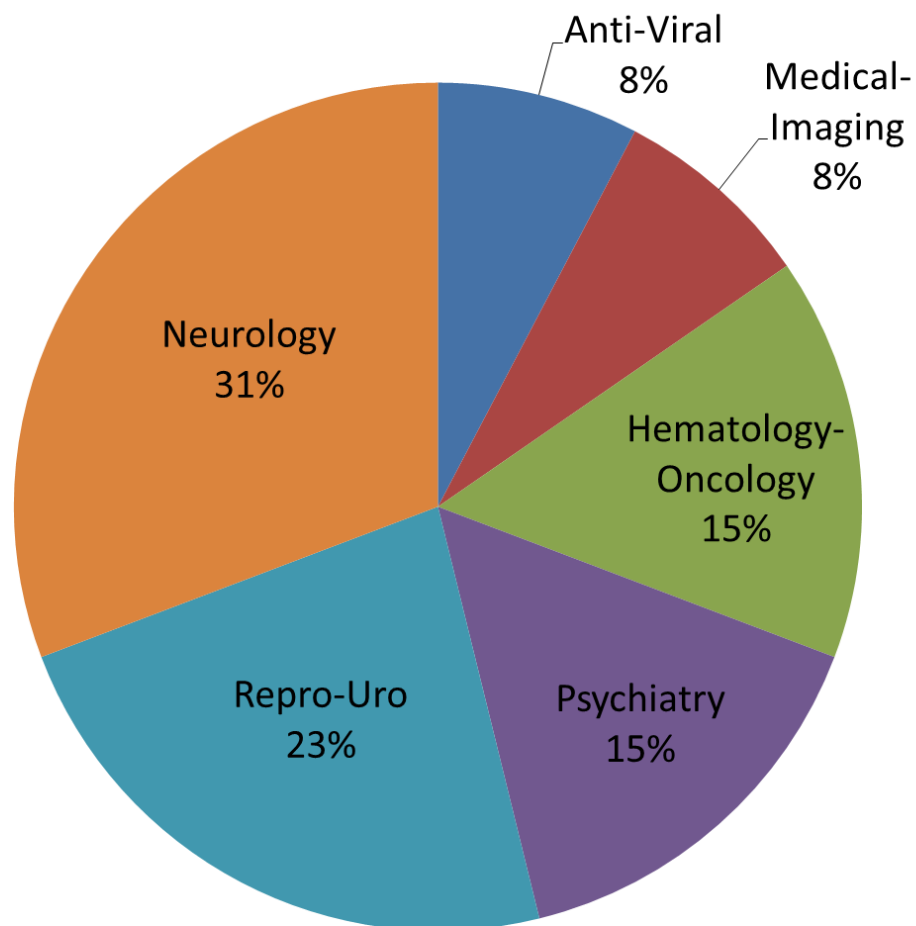
15 substrates, 9 sponsors; with 26 interaction studies



Updated October 22, 2014
(136 submissions)

Pediatric Submissions 2010-2013

N=13



Application of PBPK in Recent Pediatric Submissions

- Scale adult data into pediatric population
- Dose
 - Estimate pediatric doses for a safety and efficacy trial
 - Predict exposure in pediatric subjects in a specific age group not studied in vivo
 - Predict low systemic exposure after dermal application of the drug
 - Age-appropriate dosing in postmenarche adolescents
- Demonstrate age dependent renal clearance of the drug in pediatrics

Predicting PK in Children is Challenging

Changes in drug absorption⁵ due to

Changes in gastric emptying and intestinal transit time

pH changes in different intestinal segments

Changes in intestinal transporters and in enzymes causing first-pass metabolism

Changes in drug distribution⁵ due to

Changes in body fluid compartments (e.g., total body water is 78% in neonates vs. 55% in adults, extracellular fluid space also is relatively greater, intracellular fluid space is relatively smaller)

Relative percentage of body fat is lower in children than in adults

Protein binding of drugs is less in infants and children than in adults

Blood–brain barrier is more permeable in infants and children than in adults

Changes in hepatic metabolism^{24,25}


Liver size is relatively greater in infants and children than in adults²⁶

Drug metabolizing enzymes undergo age-specific changes (e.g., glucuronidation and sulfation are immature in neonates)¹⁷

Changes in renal excretion of drugs and drug metabolites^{24,25}

Glomerular filtration rate is less in infants and children than in adults

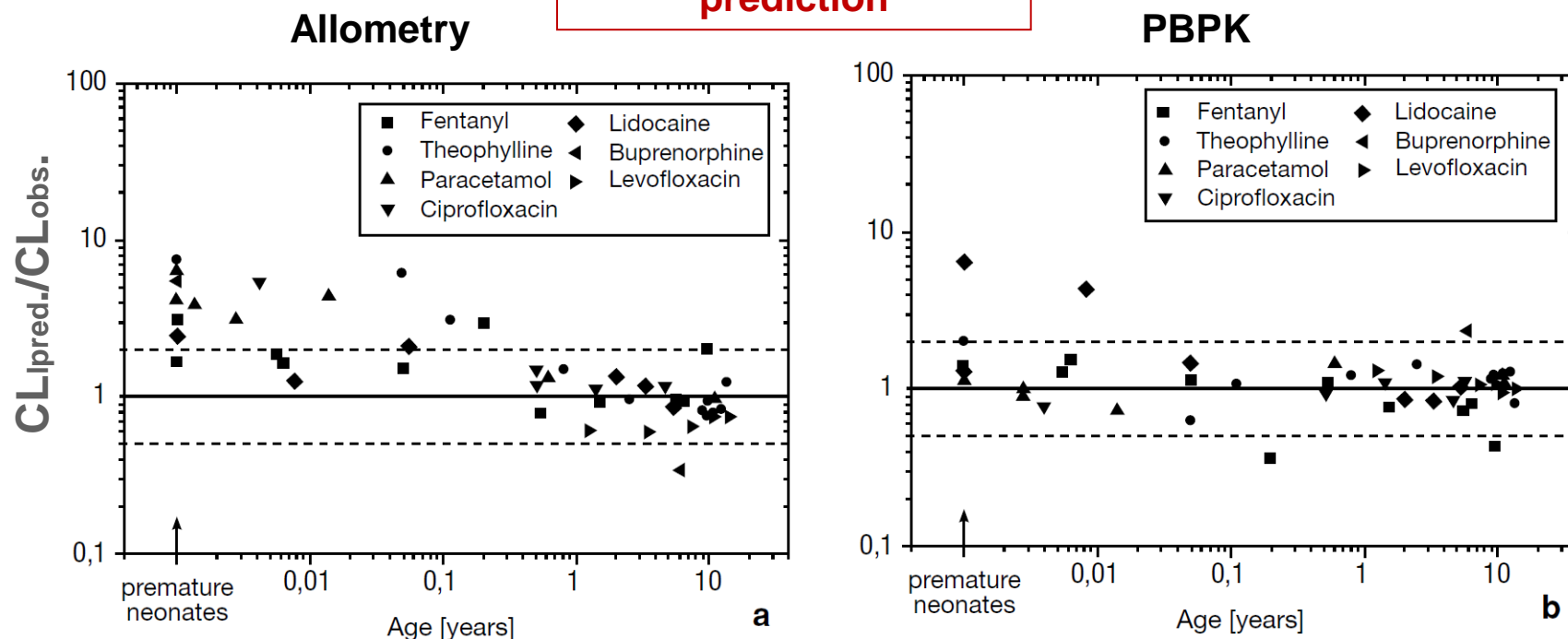
Renal tubular absorption and secretion are less in infants and children than in adults



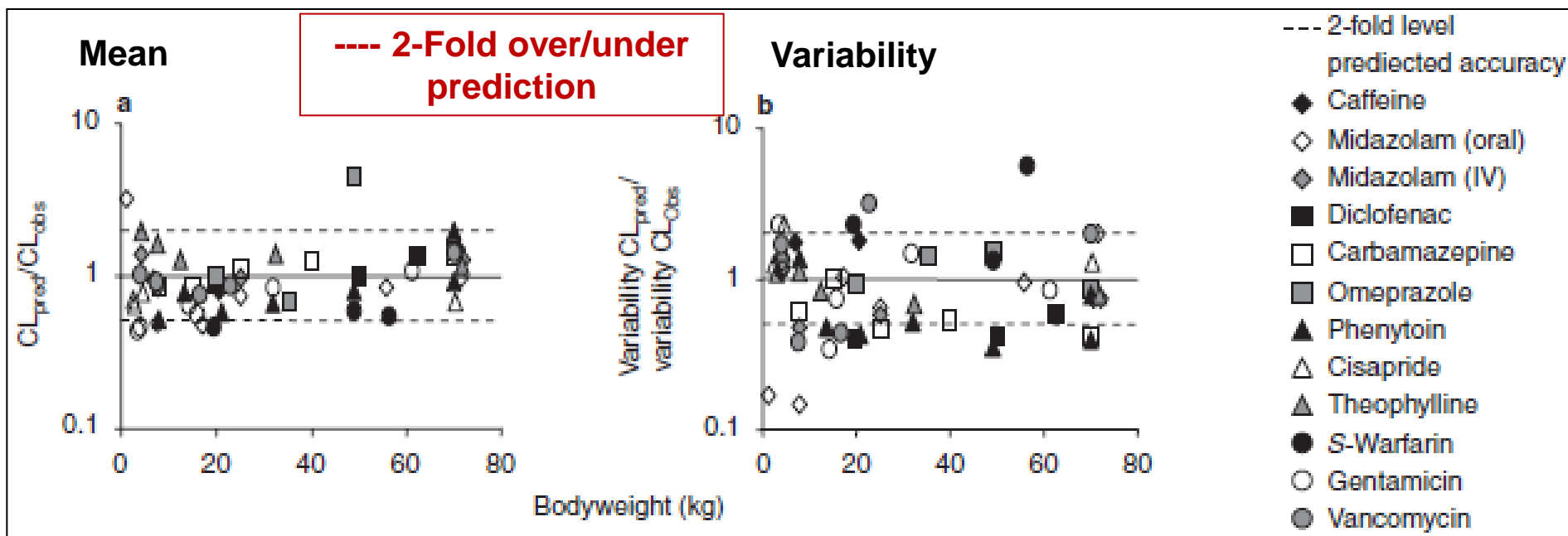
Human growth and maturation make PK prediction in pediatrics especially challenging

Especially in the Very Young

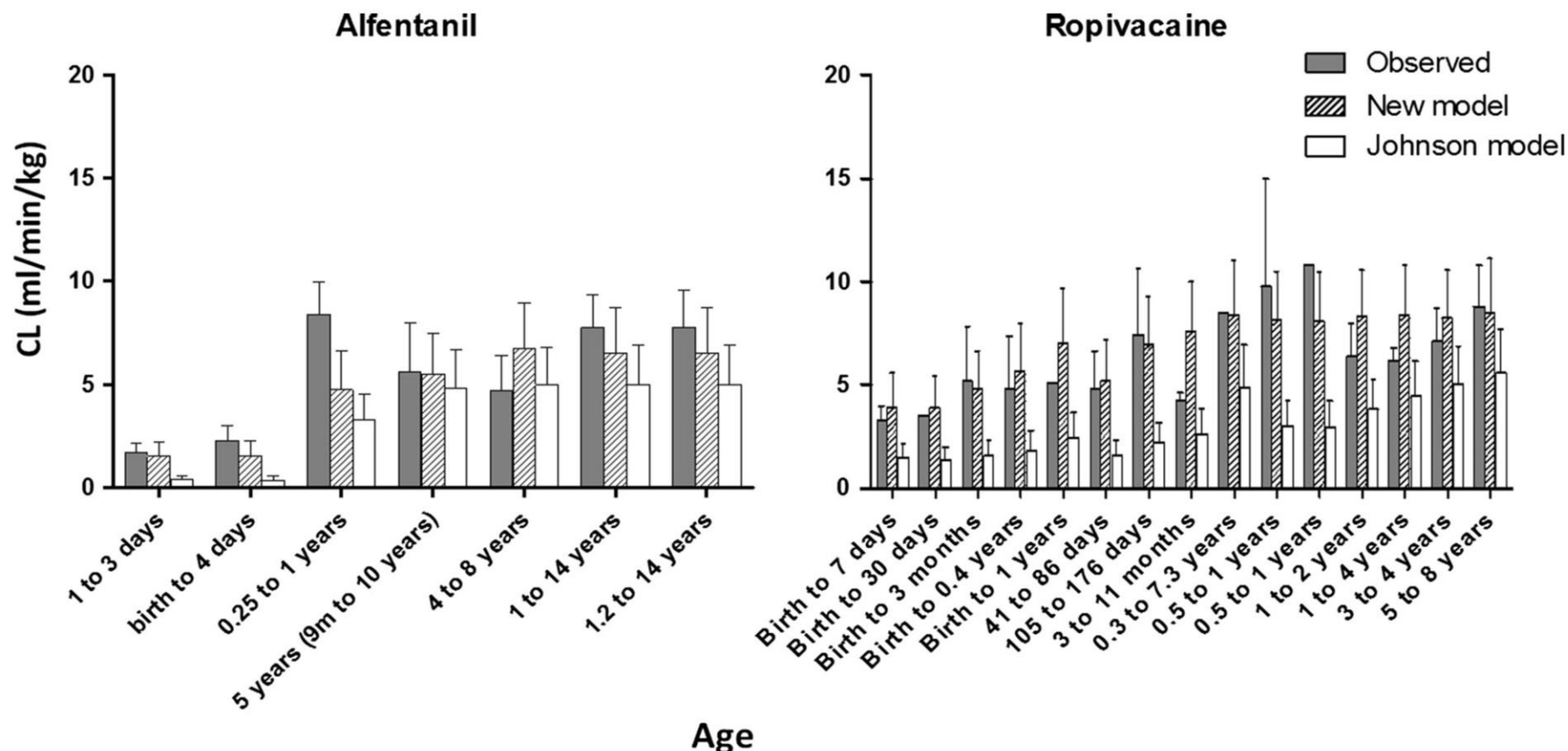
---- 2-Fold over/under prediction



PBPK may offer a predictive PK advantage in Children less than a year old



Variability is still greatest in the youngest age group with the PBPK approach



Accounting for the impact of known clinical conditions may improve predictability

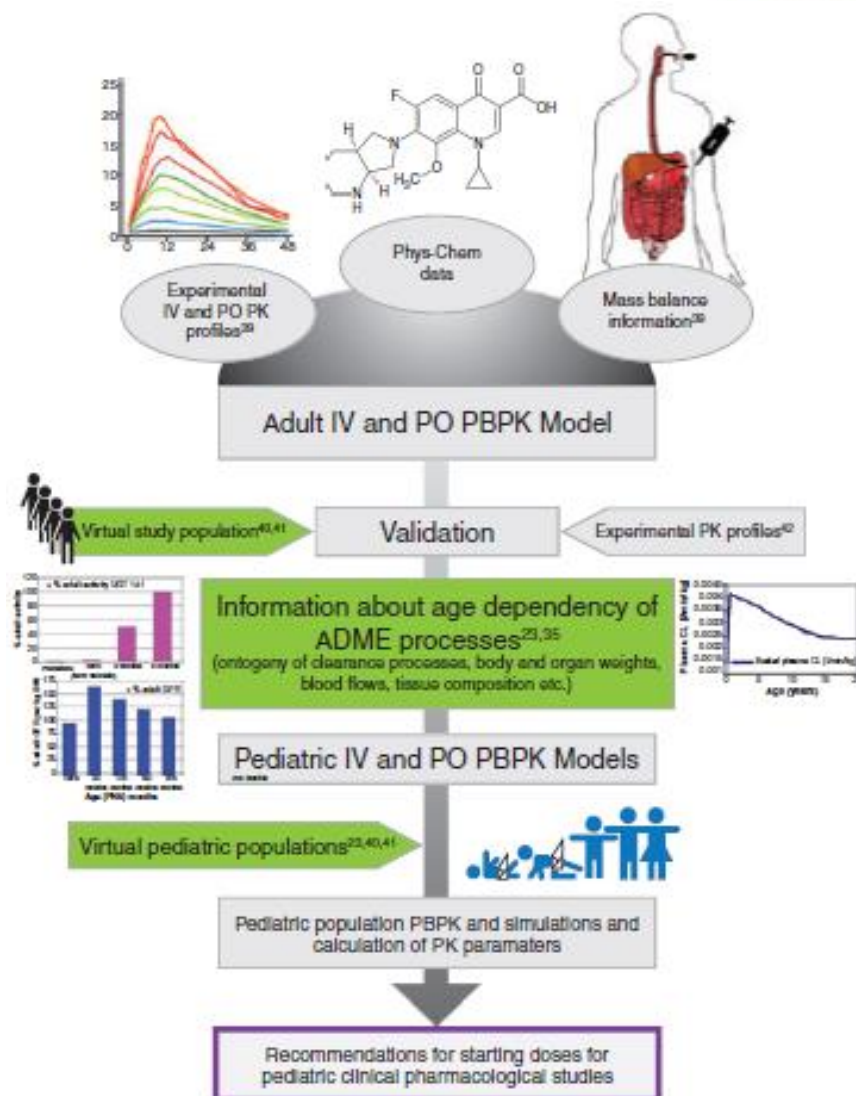
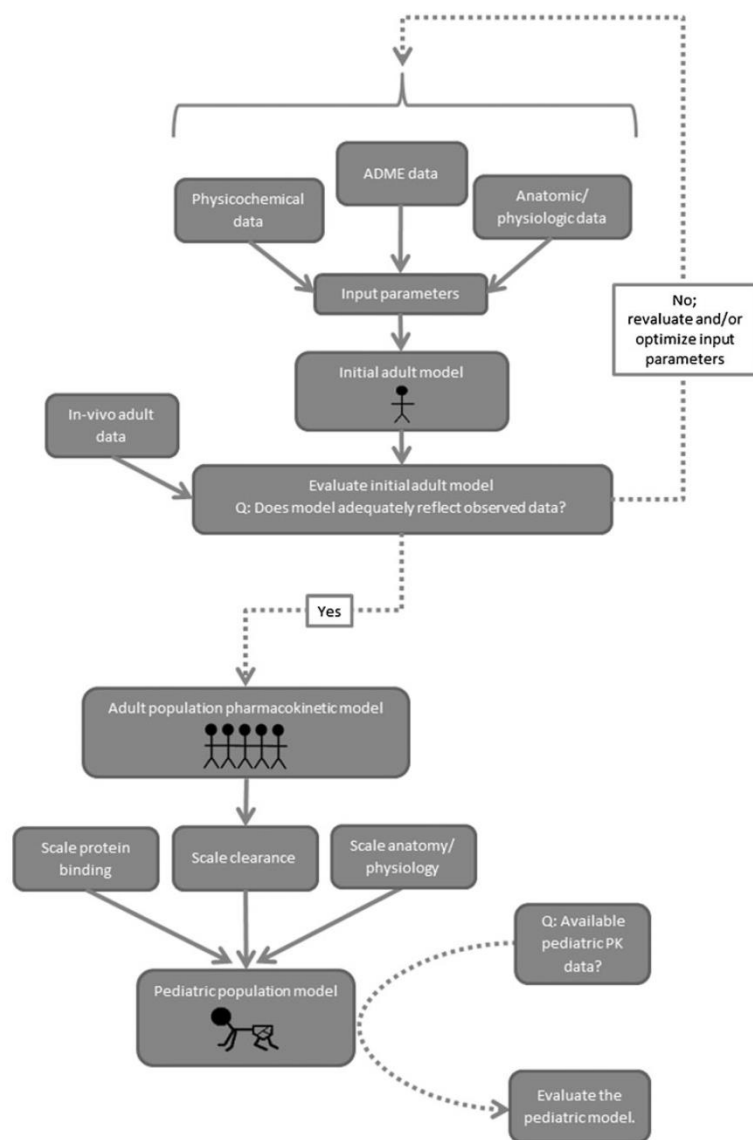
Potential Barriers to Pediatric Model Development

- Lack of PK data in children less than 5 years to assess model suitability
- Available pediatric PK trials often recruit a small number of patients
- Key details regarding demographics and clinical course are often lacking
 - E.g., enzyme phenotypes
- Impact of known clinical conditions on system and drug dependent model components often lacking

Regulatory Experience

Applications		Status
Drug-drug Interactions	<i>Drug as enzyme substrate</i>	<ul style="list-style-type: none"> Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling
	<i>Drug as enzyme perpetrator</i>	<ul style="list-style-type: none"> Use to confirm the lack of enzyme inhibition Additional evidence needed to confirm predictive performance for positive interactions
	<i>Transporter-based</i>	<ul style="list-style-type: none"> In vitro-in vivo extrapolation not mature due to lack of information, Complicated by transporter-enzyme interplay Predictive performance yet to be demonstrated
Specific populations	<i>Organ impairment (hepatic and renal)</i>	<ul style="list-style-type: none"> Predictive performance yet to be improved System component needs update
	<i>Pediatrics</i>	<ul style="list-style-type: none"> Allometry is reasonable for PK down to 2 years old Less than 2 years old ontogeny and maturation need to be considered
Additional specific populations and situations	Pregnancy, ethnicity, geriatrics, obesity, disease states Food effect, formulation change, PH effect (including DDIs on gastric PH) Tissue concentration	

A Clear Workflow is Key...



PBPK model in adults

Drug-dependent
parameters

+

Systems-dependent
parameters (adults)

Develop, verify, and refine adult PBPK model



PBPK model in children

Drug-dependent
parameters

+

Systems-dependent
parameters (pediatrics)

Develop, use, and refine PBPK model in pediatrics

- Simulate pediatric PK in all age groups
- Optimize design of "first-in-pediatric" PK study (dosage, formulation, sampling time)

Verify PBPK model with available pediatric data

- Data from conventional studies
- Data from small trial with intense PK sampling



Acetaminophen (APAP) PBPK Model

Development and Validation Work Flow

Development of adult PBPK Model

- *In vitro* enzyme kinetic studies
- Human pharmacogenetics studies (UGT1A1, 1A6 and 2B15)
- Intravenous (I.V.) PK data in healthy adults
- Oral PK data in healthy adults (solutions, tablets and syrups/elixirs)

Validation of PBPK model with independent adult PK data

- I.V. PK data in healthy adults (bolus and infusion)
- Oral PK data in healthy adults (solutions, tablets and syrups/elixirs)
- Oral PK data in cirrhosis patients (tablets)

Pediatric simulation with developed PBPK Model

- I.V. PK data (infusion)
- Oral PK data (solutions and syrups/elixirs)

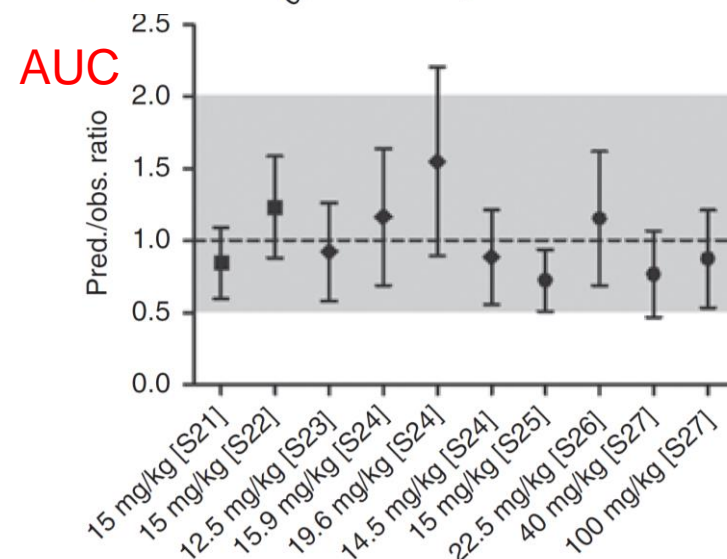
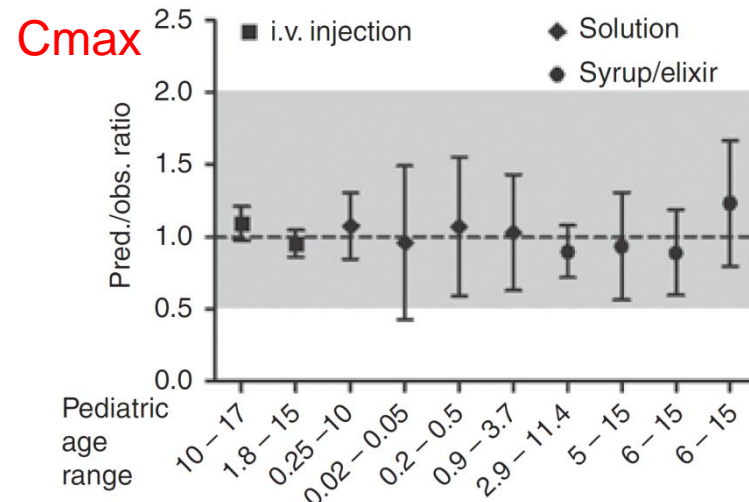
Prediction of PK and Metabolism

15 mg/kg, 0.25-h i.v. infusion

Ratio	APAP-G/APAP-S	
	Observation	Prediction
Neonates	0.60	0.54 (0.22, 0.94)
Infants	0.97	1.11 (0.56, 1.84)
Children	1.38	1.34 (0.76, 2.22)
Adolescents	1.24	1.43 (0.78, 2.33)

Ratio	APAP-GSH/APAP-S	
	Observation	Prediction
Neonates	0.12	0.06 (0.02, 0.15)
Infants	0.17	0.16 (0.06, 0.36)
Children	0.17	0.24 (0.09, 0.50)
Adolescents	0.24	0.24 (0.10, 0.47)

APAP, acetaminophen; APAP-G, APAP-glucuronide; APAP-GSH, APAP-glutathione; APAP-S, APAP-sulphate.



Workflow Assessment for PBPK Related Pediatric submissions

	<u>Drug A</u>	<u>Drug B</u>	<u>Drug C</u>	<u>Drug D</u>	<u>Drug E</u>
<u>Drug-specific data in adult PBPK model</u>					
<i>Integrate Physico-chemical data</i>	✓	✓	✓	✓	✓
<i>Integrate ADME data</i>	✓	✓	✓	✓	✓
<u>Pediatric PBPK model development</u>					
<i>Verify adult model using i.v. and p.o. data</i>	✓	✓	✓	✓	✓
<i>Demonstrate adequacy of adult model</i>	✓	✓	✓	✓	✓
<i>Justify age-dependent ADME processes</i>	✓	✓	✓	✓	✓
<u>Application of the pediatric PBPK model</u>					
<i>Plan dedicated “first in pediatric” PK study</i>	✓	✓		✓	
<i>Optimize study design</i>	✓	✓		✓	
<i>Verify model of certain age groups</i>	✓		✓		
<i>Recommend starting dose by targeting appropriate steady-state exposure</i>	✓	✓		✓	
<i>Inform enzyme ontogeny using bench-mark drug</i>				✓	
<i>Facilitate covariate analysis</i>			✓		✓

PBPK Submissions to FDA Should Ideally Include:

- **Summary of model input parameters & software version**
 - Ideally compiled in table format
 - Parameter name, parameter values (mean and/or variability), source of the parameter values and assumptions
 - Any modification of the default parameter values should be declared and justified
- **Logical description of model building and verification processes**
 - A simple comparison with observed (PK) data may not be sufficient for establishing model confidence
 - Parameters with uncertainty that are expected to influence the model prediction should be tested via sensitivity analysis
 - Pre-specify calibration method
 - Post hoc model optimization must be justified

PBPK Submissions to FDA

Should Ideally Include:

- **The details of all simulation conditions**
 - Demographics of virtual population(s), number of trials, number of subjects in each trial, dosing scheme, sampling scheme, etc.
- **Model files in a executable format**
 - Please do not convert software specific files to pdf
 - Pursue electronic gateway capability
 - Submission of CD or other acceptable media
 - Ideally 5 copies
- **Early communication with the Agency regarding the inclusion of PBPK into your development plan is strongly encouraged**

Thoughts on PBPK Model Verification

- **The predictive performance should be reflected by the ability of a model in describing all available data sets**
- **Biological plausibility of the model components should be demonstrated**
- **The ability to describe an EXTERNAL (plasma PK) dataset is only part of the model verification and likely may only verify certain aspect of the model**

E.g. Interaction/Genetic data to confirm fractional clearance

- **Because the system component accounts for the majority of the model structure, predictive performance should be demonstrated through modeling of multiple drugs**
- **Predictability of PBPK is in context of its intended use**

Summary

- The use of PBPK is increasing
- PBPK modeling is being applied to a variety complex drug development issues including pediatrics
- Developing models in pediatrics is particularly challenging in the youngest age group (i.e., < 2 yrs. old)
 - Focus should be primarily the system component (i.e., transporter ontogeny, age effect on absorption, etc)
- A clear and consistent workflow is key
- Early interaction with FDA is important
- More academic interest and skilled users are needed
- PBPK Guidance for Industry is planned

- YOU can help OCP achieve its goal of translating its regulatory reviews into understandable and actionable labeling language
- Provide feedback on the quality, clarity and utility of the professional and consumer drug labeling you are using



EMAIL: OCP@FDA.HHS.GOV

Acknowledgements

- OCP/OTS/CDER/FDA
 - Ping Zhao, Yuzhuo Pan, Christian Wagner, Ruby Leong, Shiew Mei Huang, Vikram Sinha, Issam Zineh
- MPA/EMA colleagues
- External industry and academic thought leaders

Questions?

