Application of PBPK Modeling and Simulations in Pediatric Drug Development

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Disclosures and Acknowledgements

- Disclosures
  - The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

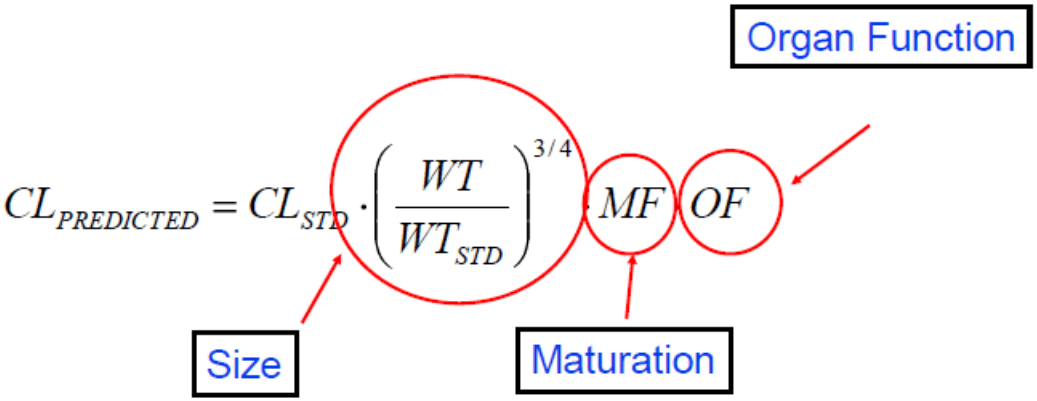
- Contributors to the ideas presented today
  - Division of Pharmacometrics/Office of Clinical Pharmacology

Outline

- Pediatric PK/PD – Dosing in Children
- Update of FDA Public Workshop (March 10, 2014)
- Predicting drug concentrations in children: Current experience and thinking

Drug Development (1 of 2)

- Drug developers are encouraged by regulatory agencies to carry out studies in children and use models for PK and PD relevant to children
- From a PK perspective – in children, infants—especially *neonates*—size, maturation processes and organ function are important



- The missing piece is the link between drug concentrations and clinical outcomes

Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet. 2008;47(4):231-43.

Drug Development (2 of 2)

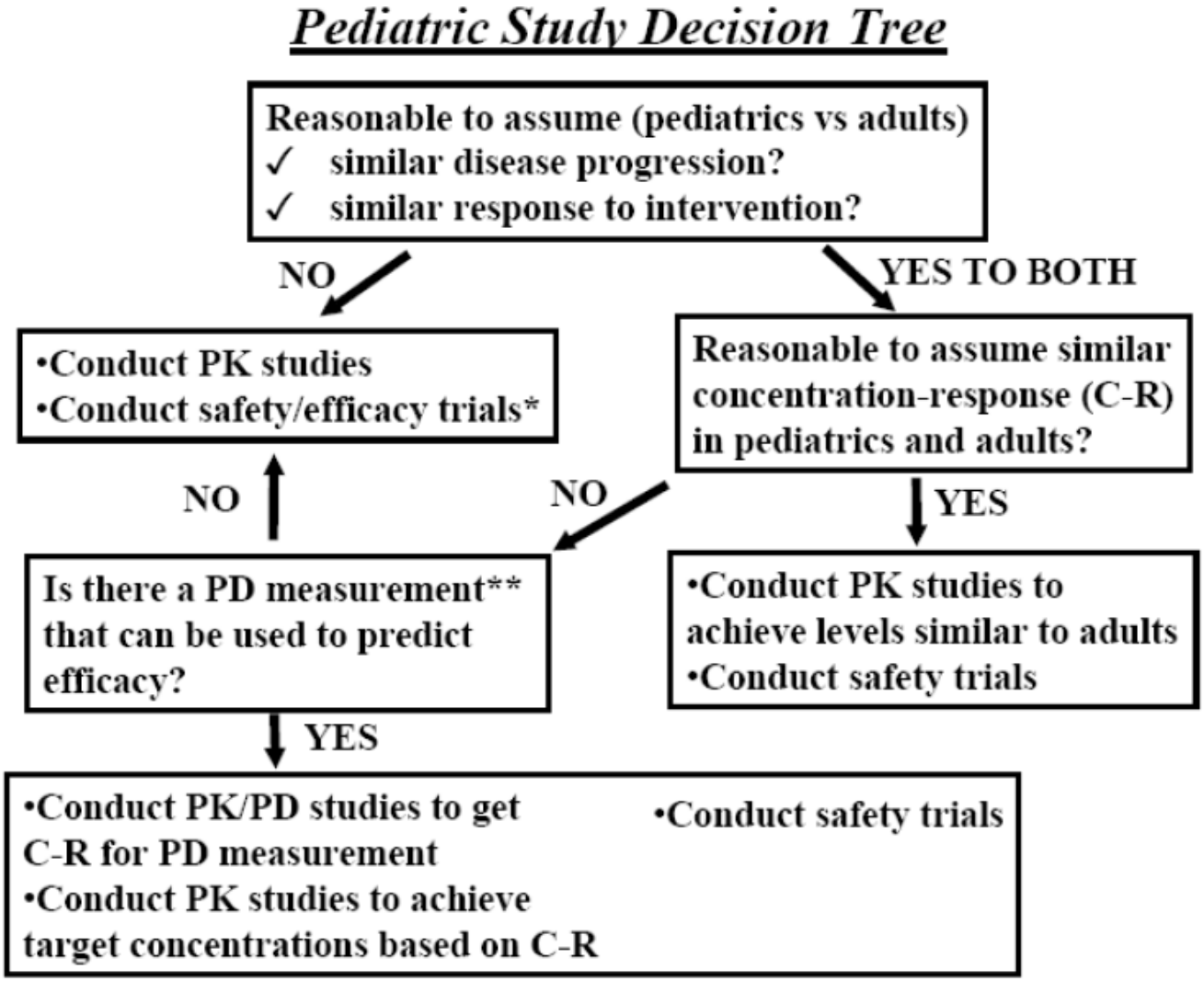
- The ability to study each age group (e.g., neonates, infants, young children, and older children) is small and we are interested in the most scientific and practical drug development programs for each group.
- We can combine data across all pediatric populations to develop an integrated view of human pharmacology.
- If PK is "known", doses can be calculated rationally by understanding the concentration-response relationship:

$$\text{Dose Regimen} = \text{Target Concentration} \times \text{CL (age group)}^{1}$$

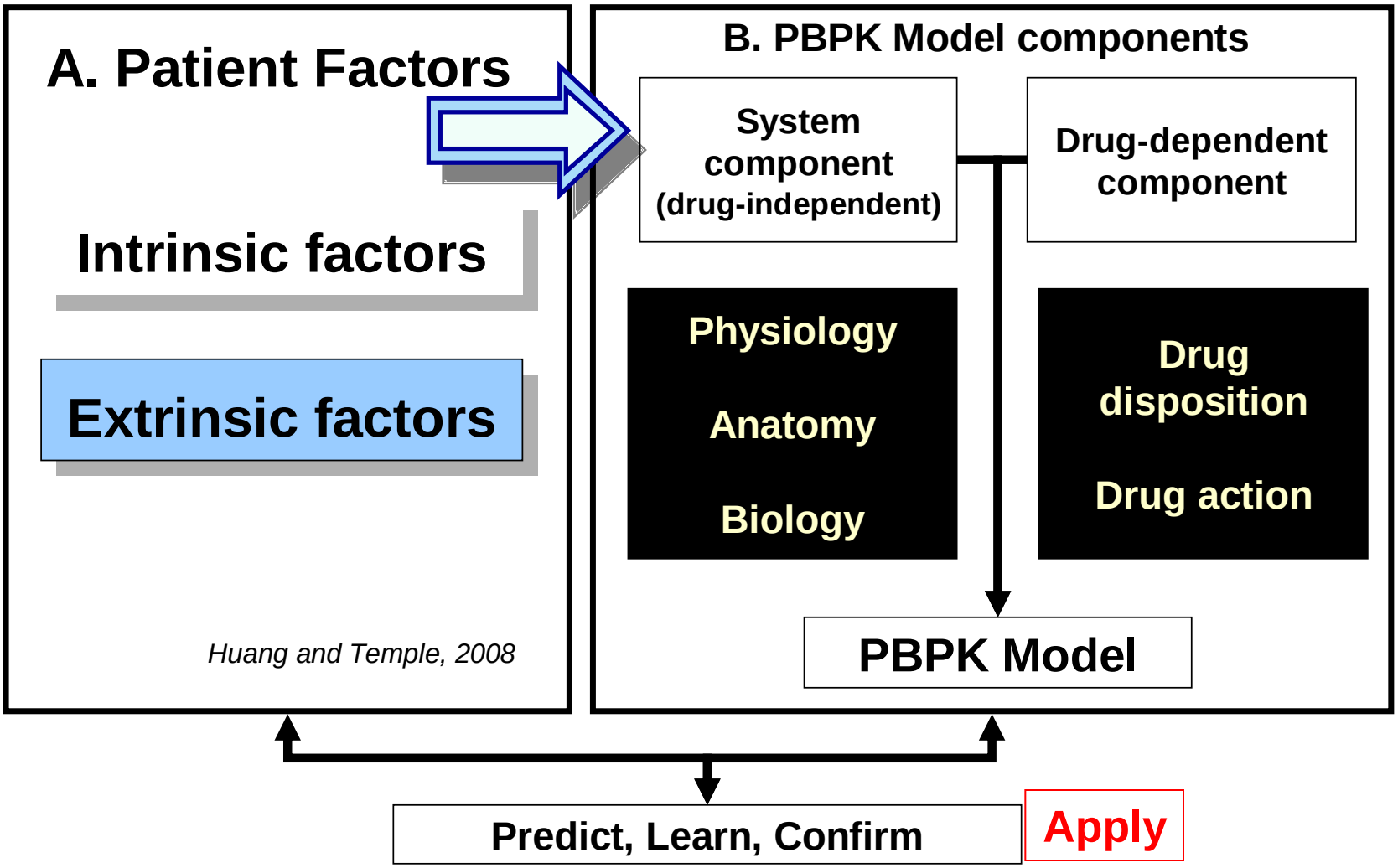
➢ Therefore, any "system/approach" should be geared to understanding dosing in children and whether pharmacodynamics behavior in pediatrics differs from that in adults.

[1]Target concentration approach includes multiple elements including identifying a desired target effect.
One example: Morphine dose in Humans. Paediatr Anaesth. 2012;22(3):209-22.; Br J Clin Pharmac 2011; 71: 88-94. illustrates how an allometric model with a maturation model can be used versus an empirical model.

Decision Tree



Application of PBPK in Regulatory Decision Making



Adapted from Zhao P, et al Clin Pharmacol Ther 2011

FDA Public Workshop

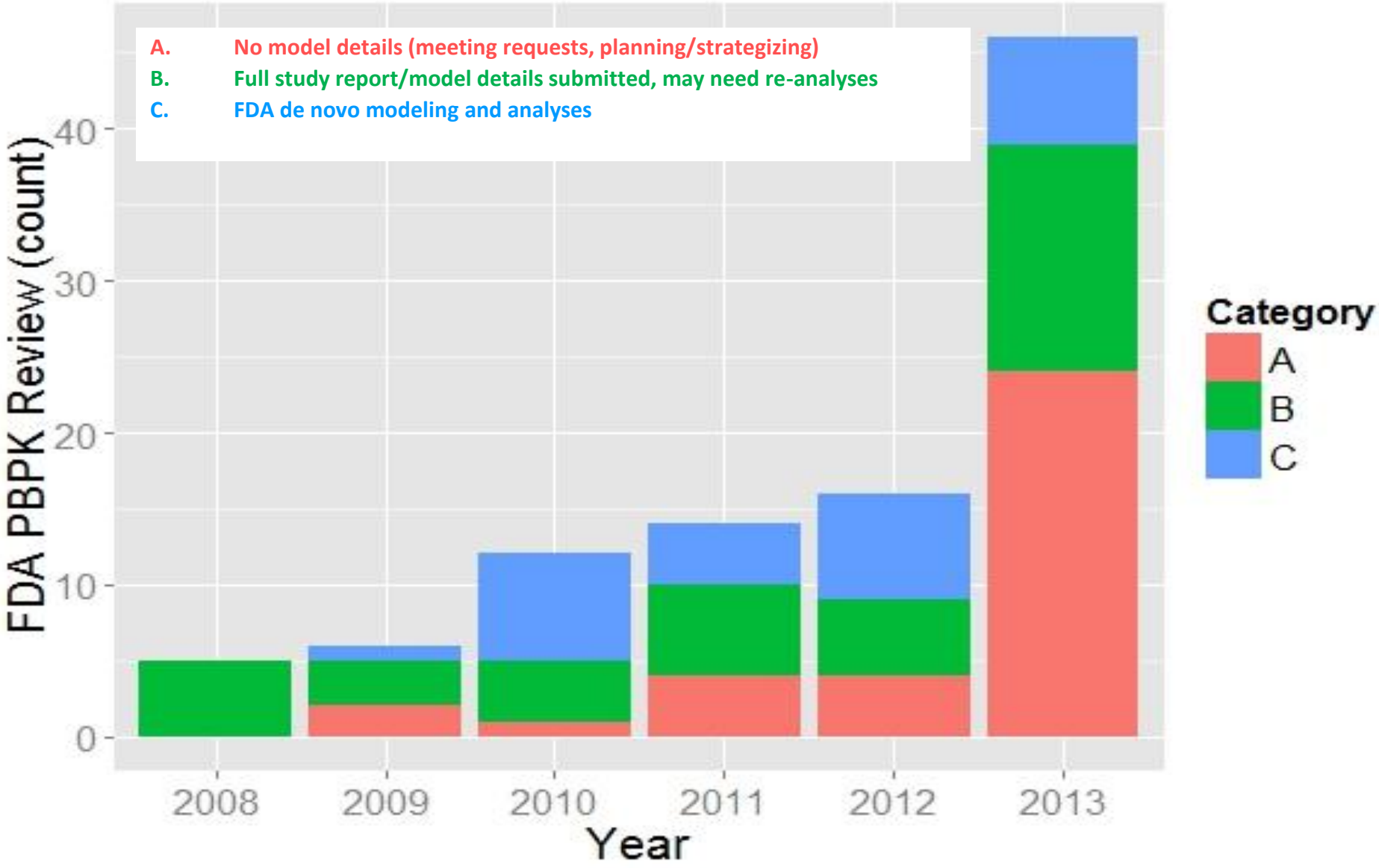
Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection

March 10, 2014
White Oak, Maryland

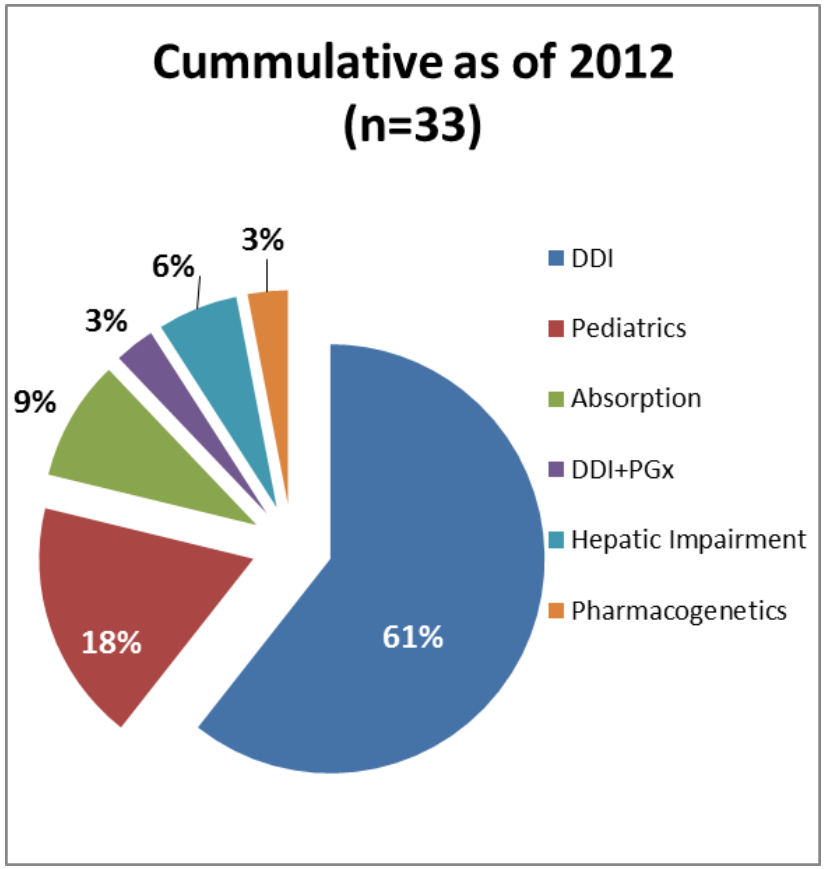
1. Applications of PBPK: Discussed potential applications of PBPK in drug evaluation, and to determine which areas relevant to drug development and review are currently amenable to the use of PBPK

2. PBPK Model Verification and Reporting in Regulatory Submissions: Discussed assessment of model fidelity and best practices in reporting.

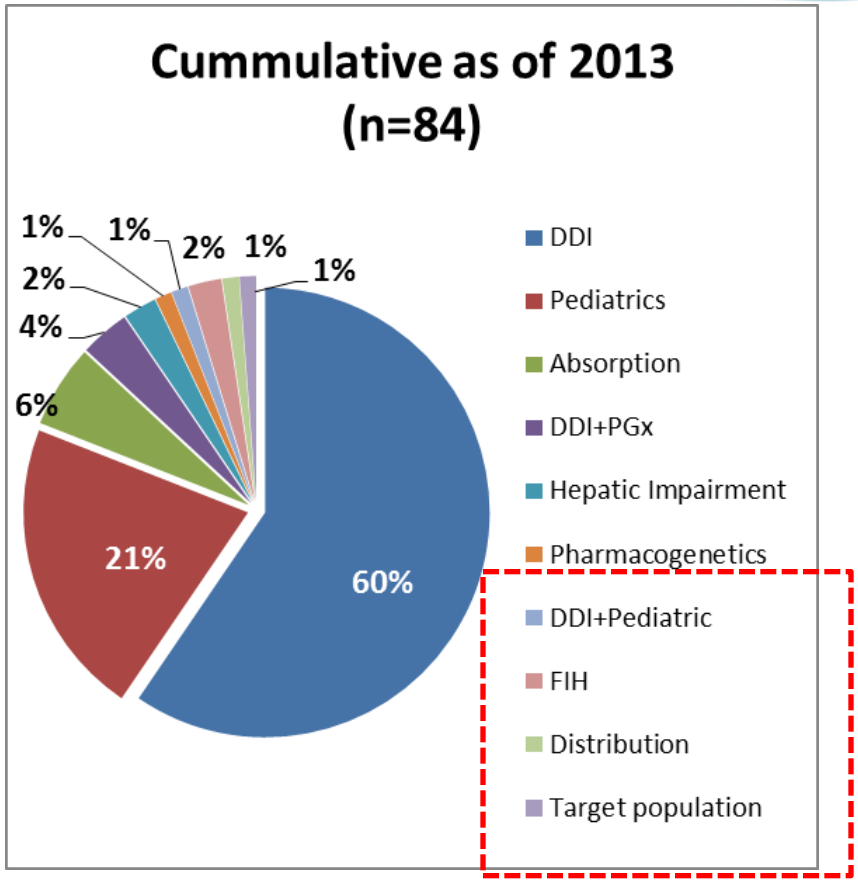
PBPK regulatory review experience



By Sponsors, How is PBPK Being Utilized?



Huang et al, J Pharm Sci, 2013



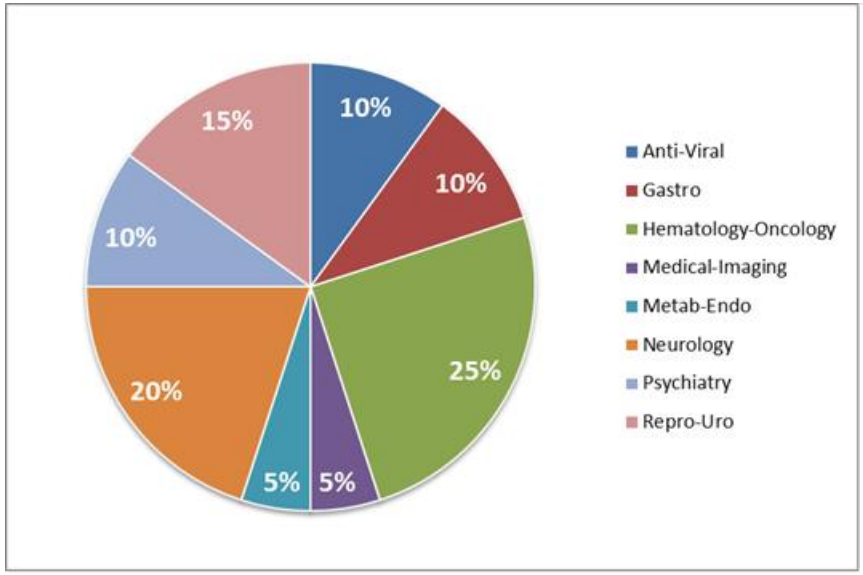
Pan, ASCPT Annual Meeting, 2014, Atlanta, GA

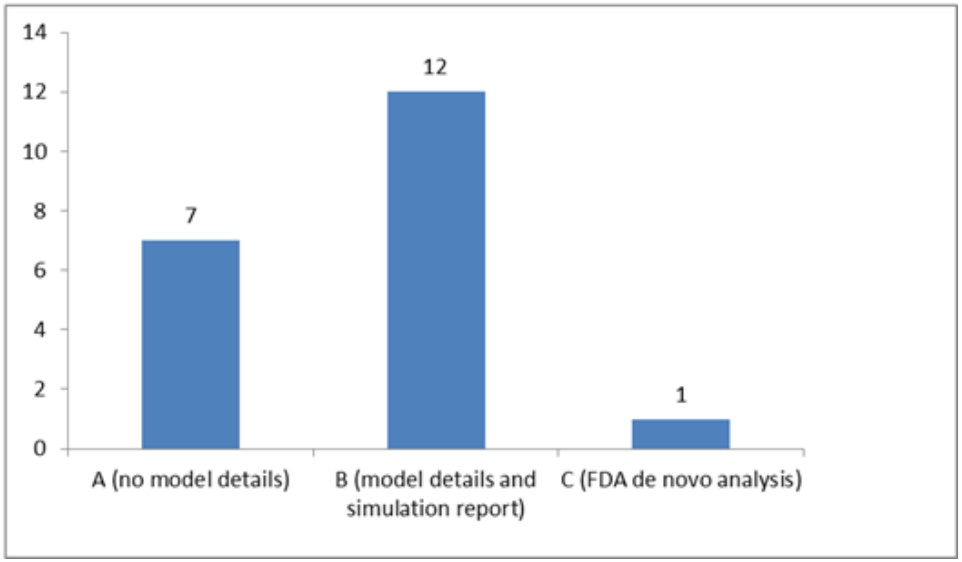
- **Increased use of PBPK by drug developers**
- **Majority of the cases were related to drug-drug interactions (~ 60%); pediatrics ranks the second**

PBPK applications: Current status

	Applications	Status
Drug-drug Intearctions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *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	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs more information*
	Pediatrics	• *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**	• *Yet to be determined*

PBPK and Pediatrics





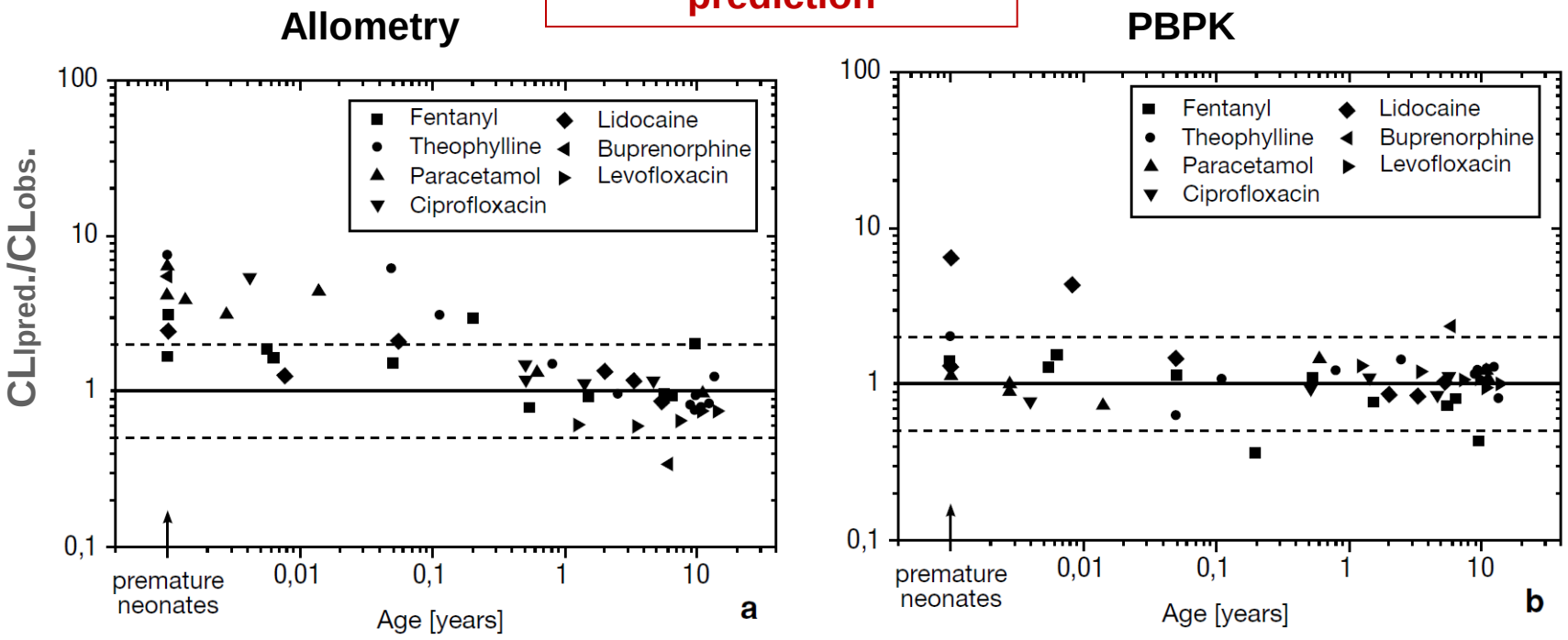
Pediatric submissions containing PBPK

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

Updated from Leong et al, Clin Pharmacol Ther, 2012

Predicting PK in Children

---- 2-Fold over/under prediction



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)

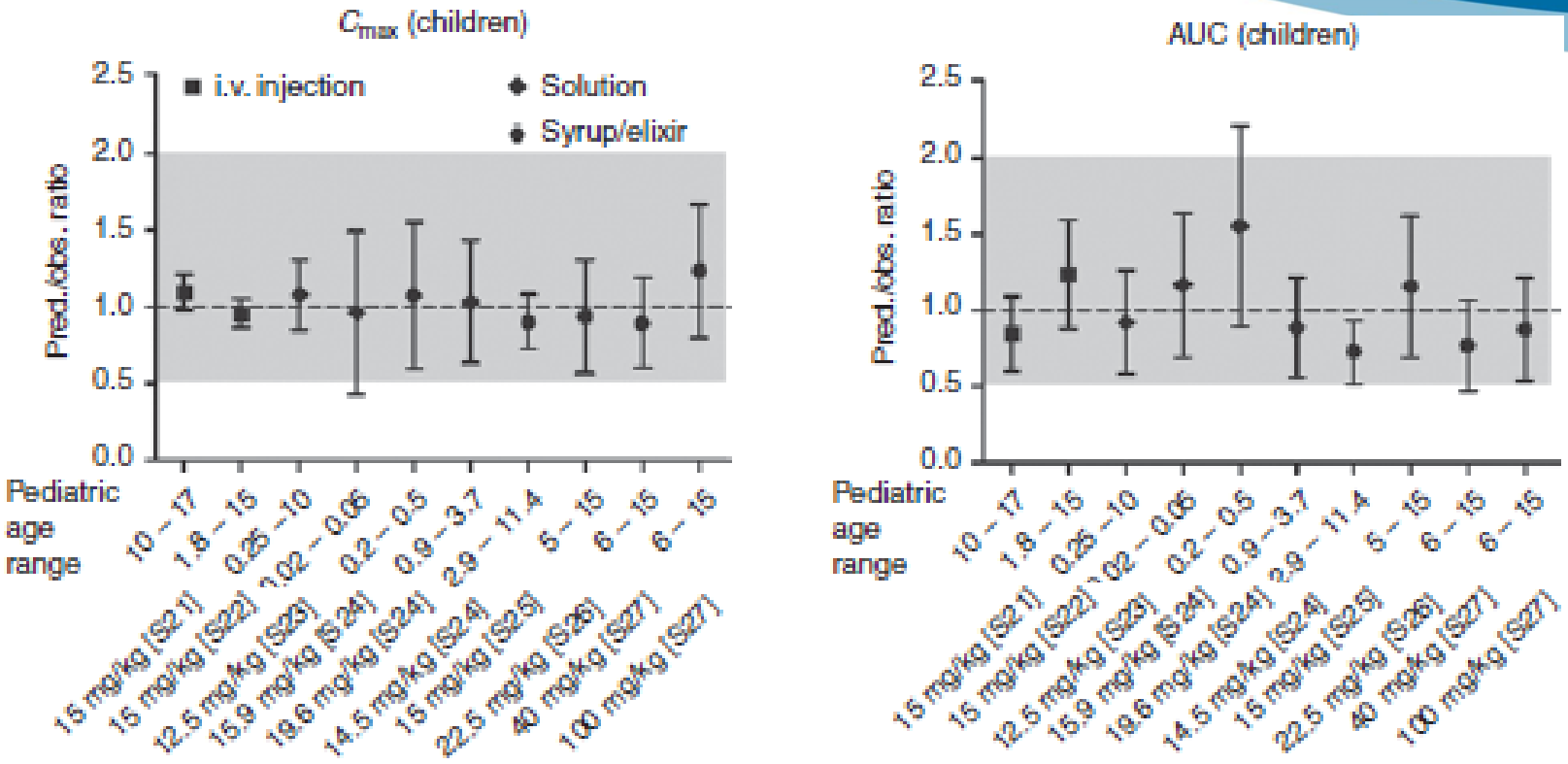
Validation of PBPK model with independent adult PK data

- 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

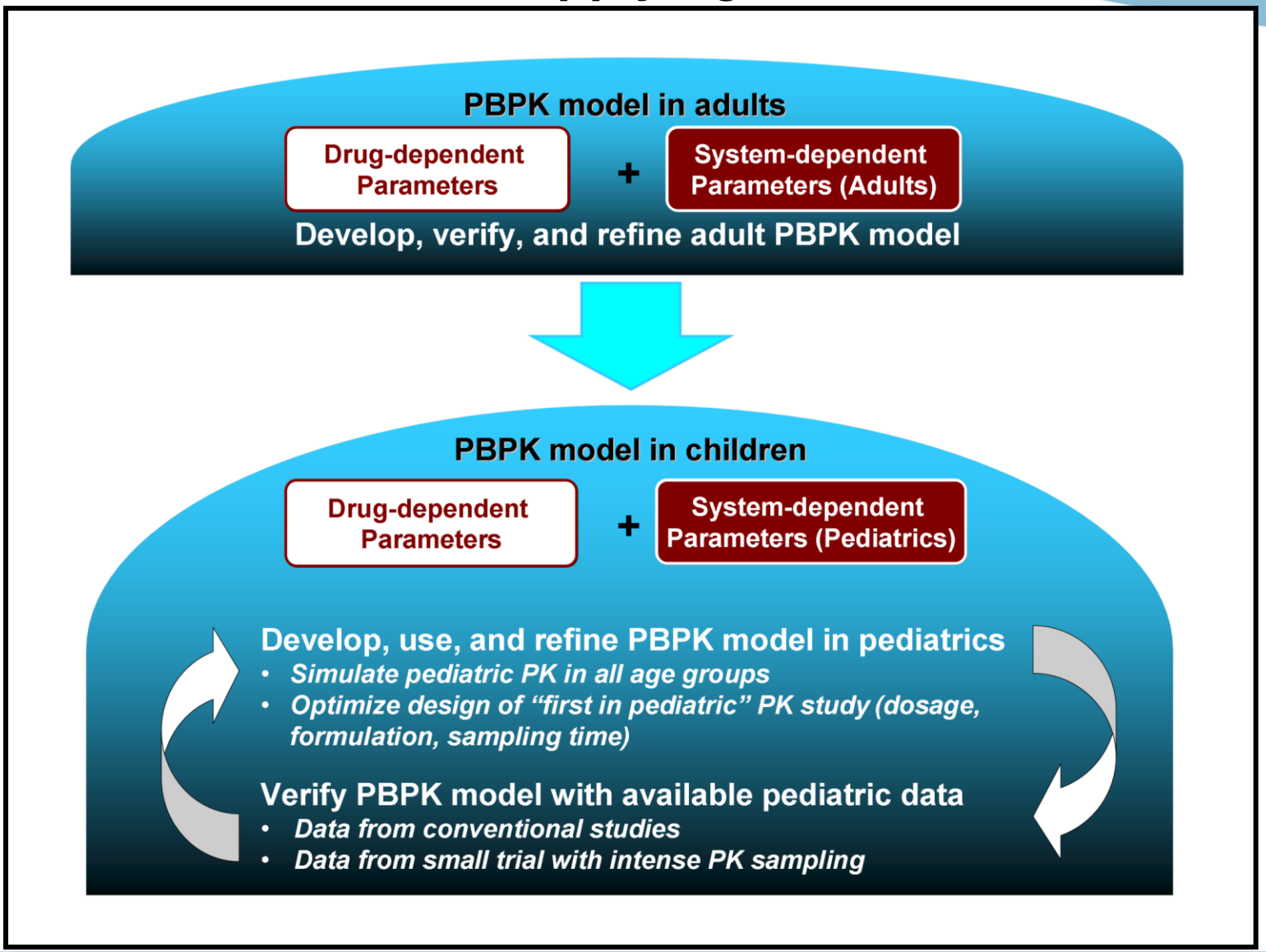
- I.V. PK data (infusion)
- Oral PK data (solutions and syrups/elixirs)

APAP: Prediction of PK AND Metabolism



Age Groups		Urinary APAP-Glucuronide/APAP-Sulfate Ratio (Steady State)		
		(12.5 and 15 mg/kg)	Model Prediction (12.5 mg/kg)	Model Prediction (15 mg/kg)
Neonates	(0 – 0.08 year)	0.603 (N = 2)	0.566 (N = 100)	0.570 (N = 100)
Infants	(0.08 – 2 years)	0.970 (N = 13)	1.12 (N = 100)	1.11 (N = 100)
Children	(2 – 12 years)	1.38 (N = 15)	1.44 (N = 100)	1.44 (N = 100)
Adolescents	(12 – 16 years)	1.24 (N = 13)	1.45 (N = 100)	1.45 (N = 100)

Verify Adult PBPK Before Applying in Children



Leong et al, Clin Pharmacol Ther, 2012

Submitting PBPK Information to FDA

- Summary of model input parameters and software version
- Logical description of model building and verification processes
- The details of all simulation conditions
- Model files in a executable format

Early communication with the Agency regarding including PBPK into your development plan is strongly encouraged

Summary

- ❑ **Increased PBPK submissions to the FDA. Experience and confidence differ among different applications**
- ❑ **For pediatrics PK prediction, use PBPK where the question justifies its use and consider integration of predicted concentrations with exposure-response analysis**
- ✓ **PBPK may complement allometry for predicting PK in younger age groups (e.g. < 2 years old)**
- ✓ **Model should be verified in healthy adult subjects before it can be used to predict pediatric PK**
- ❑ **Predictive performance needs to be improved and focus should be on updating the system component**

Acknowledgement

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