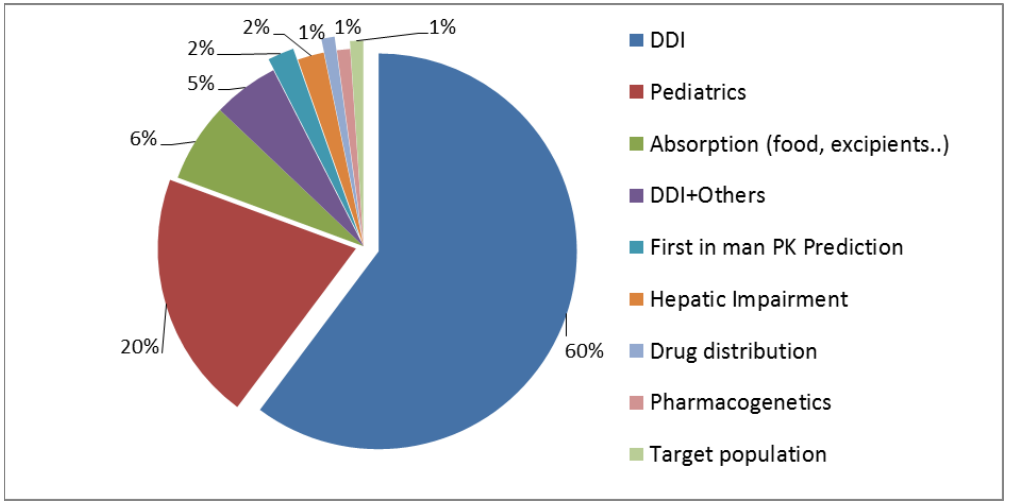
Application of Physiologically-based Pharmacokinetic Modeling to Support Dosing Recommendations – The US Food and Drug Administration Experience

Ping Zhao, PhD

Division of Pharmacometrics/Office of Clinical Pharmacology/OTS/CDER/FDA

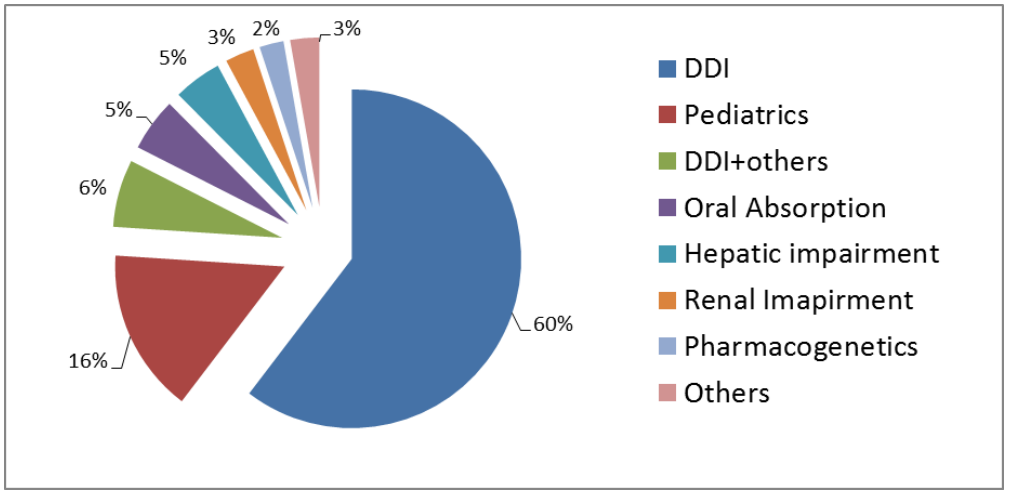
2016 EMA Workshop on PBPK Guideline

By sponsors, how is PBPK being utilized?



Cumulative as of June 18, 2014 (n=96)

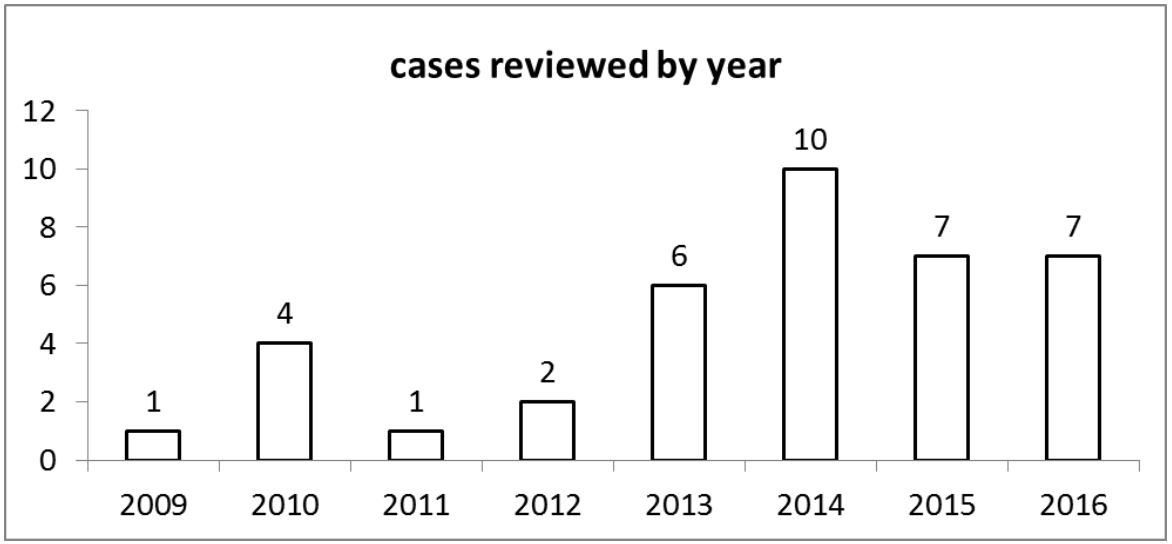
Sinha, MHRA PBPK Workshop 2014, London, UK



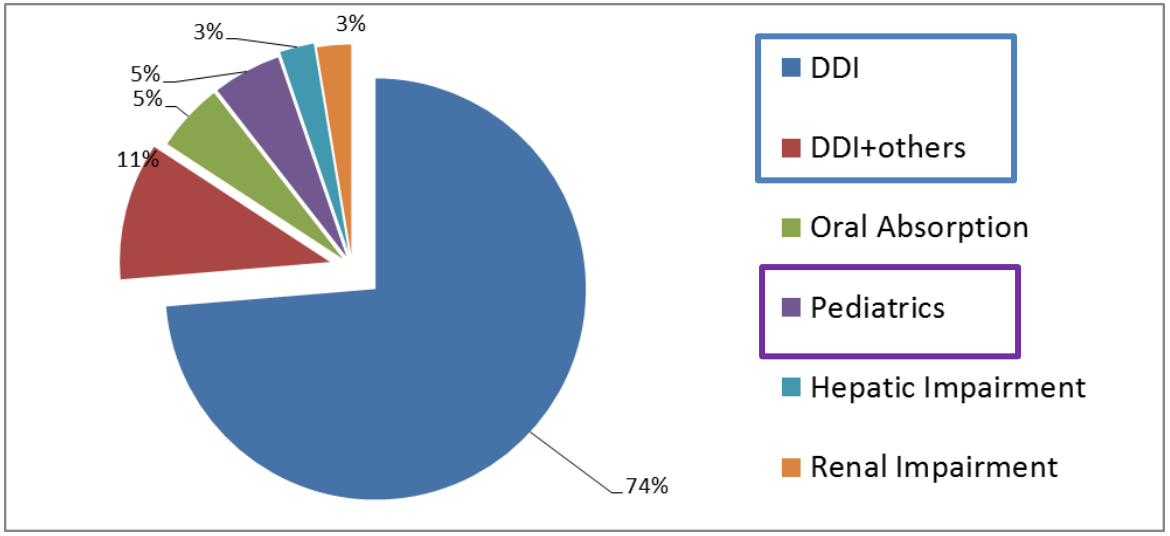
Cumulative as of Aug 1, 2016 (n=217)

Majority related to drug-drug interactions (DDIs, ~ 60%); pediatrics ranks the second

PBPK supporting dosing recommendations in US prescribing information (38 cases 2009-2016)



2016: as of Aug 1



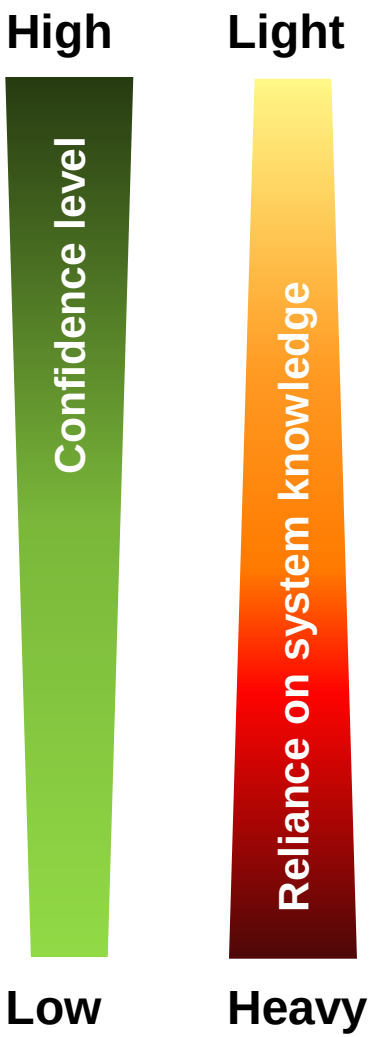
DDI/DDI+others: 32

Pediatrics: 2

PBPK applications: current status

	Applications	Status
Drug-drug Interactions	*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* • *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 an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experiences	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration*	

Wagner, CPT-PSP, 2015



Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

PBPK Model Describes the Effects of Comedication and Genetic Polymorphism on Systemic Exposure of Drugs That Undergo Multiple Clearance Pathways

MdLT Vieira[1], M-J Kim[1], S Apparaju[1], V Sinha[1], I Zineh[1], S-M Huang[1] and P Zhao[1]

Clin Pharmacol Ther, 2014

Predicting the Effect of Cytochrome P450 Inhibitors on Substrate Drugs: Analysis of Physiologically Based Pharmacokinetic Modeling Submissions to the US Food and Drug Administration

Christian Wagner · Yuzhuo Pan · Vicky Hsu · Joseph A. Grillo · Lei Zhang · Kellie S. Reynolds · Vikram Sinha · Ping Zhao

Clin Pharmacokinet 2015

Predicting the Effect of CYP3A Inducers on the Pharmacokinetics of Substrate Drugs Using Physiologically Based Pharmacokinetic (PBPK) Modeling: An Analysis of PBPK Submissions to the US FDA

Christian Wagner[1] · Yuzhuo Pan[2] · Vicky Hsu[1] · Vikram Sinha[1] · Ping Zhao[1]

Clin Pharmacokinet 2016

Can PBPK PROSPECTIVELY predict the effect of CYP modulation?

$$R_{pred/obs} = \frac{Pred.\,Exposure\ Ratio}{Obs.\,Exposure\ Ratio}$$

	CYP Inhibition (Vieira, 2014)	**CYP Inhibition** (Wagner/Pan, 2015)	**CYP Induction** (Wagner, 2015)
Substrates evaluated	4	15	11
DDI cases to predict	20	26	13
Organization	FDA	9 sponsors	6 sponsors
Substrate model predicts base PK ≤2-fold of obs. CL	100%	87%	91%
$0.80 \leq R_{pred/obs} \leq 1.25$	72% AUC; 70% Cmax	81% AUC; 77% Cmax	77 % AUC; 83% Cmax
$0.50 \leq R_{pred/obs} \leq 2.00$	100%	100%	77% AUC; 92% Cmax
$R_{pred/obs} > 2.00$	0	0	23% AUC; 8% Cmax

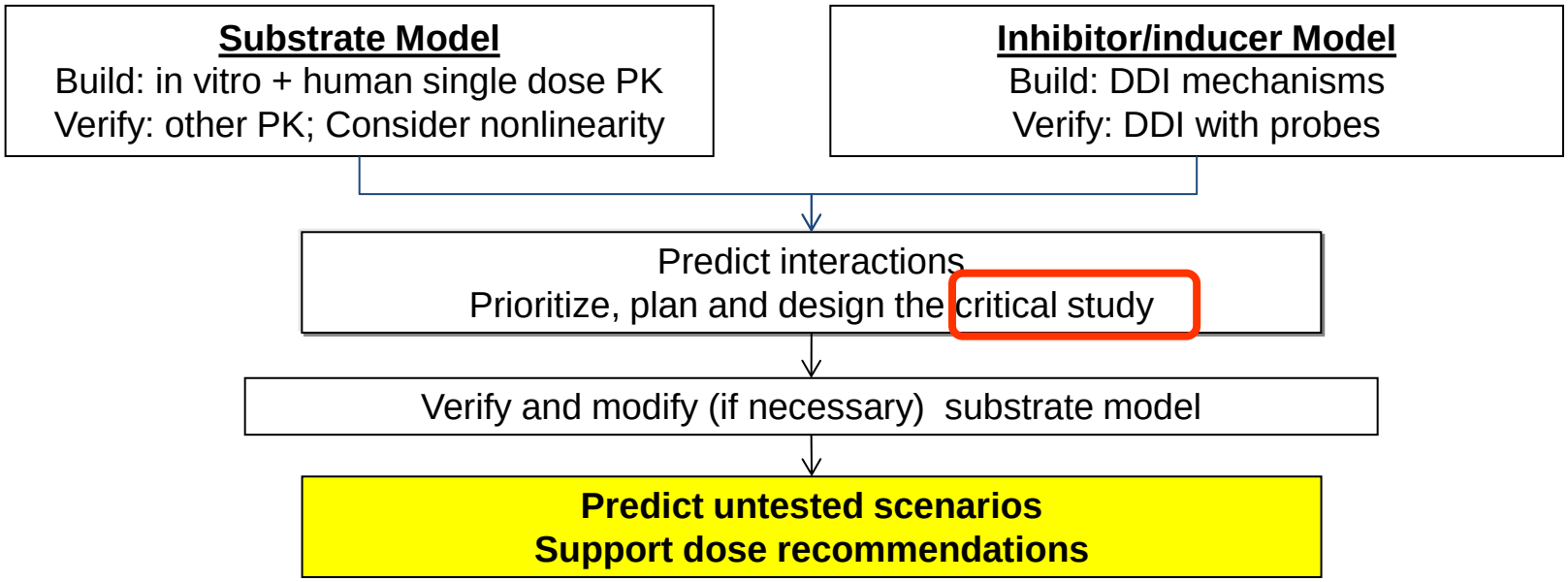
Cut-off values are arbitrary

PBPK prediction of CYP modulation

- Predictive performance demonstrated

Vieira, Clin Pharmacol Ther, 2014; Wagner, Clin Pharmacokinet 2015, 2016

- Workflow proposed



Wagner, CPT-PSP, 2015

Eliglustat (CERDELGA, approved 2014)

- ❑ Rare disease, priority review
- ❑ Metabolized by CYP2D6 (~80%) and CYP3A (~20%)
- ❑ High clearance, nonlinear PK: time-dependent CYP2D6 inhibitor
- ❑ Clinical drug interaction studies
  - *With strong CYP2D6 inhibitor paroxetine: AUC increased by ~8-fold*
  - *With strong CYP3A inhibitor ketoconazole: AUC increased by ~4-fold*
- Pharmacogenetic effects: AUC ratio poor metabolizers/extensive metabolizers (PM/EM) ~ 8-fold

What are exposure changes with various CYP inhibitors in subjects with different CYP2D6 genotypes?

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf

Eliglustat Label – Section 7.1

Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Drug Interaction Studies or on Predicted Interaction in EMs and IMs

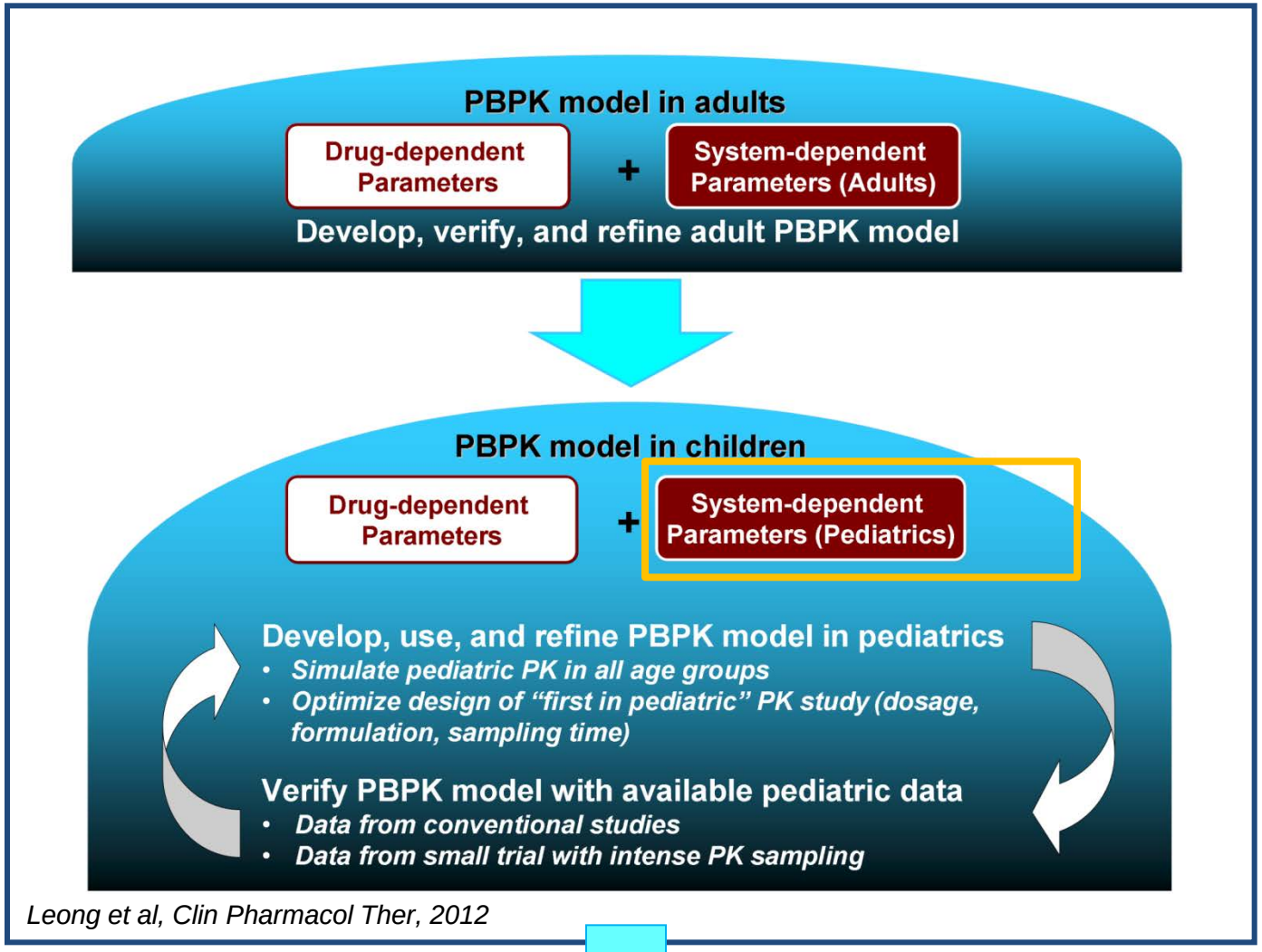
		Recommended CERDLEGA Dosage, by CYP2D6 Metabolizer Status		Simulated conditions
	CYP450 Inhibitors	EM	IM	
√	Strong or Moderate CYP2D6 inhibitors concomitantly with Strong or Moderate CYP3A inhibitors	Contraindicated	Contraindicated	2x2x2=8
	Strong CYP2D6 inhibitors e.g., paroxetine	84 mg once daily	84 mg once daily	Obs
√	Moderate CYP2D6 inhibitors e.g., terbinafine	84 mg once daily	84 mg once daily	1x2=2
	Strong CYP3A inhibitors e.g., ketoconazole	84 mg once daily	Contraindicated	Obs
√	Moderate CYP3A inhibitors e.g., fluconazole	84 mg once daily	Not recommended	1x2=2

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Predicted Interaction in PMs

	CYP450 Inhibitors	Recommended CERDELGA Dosage for PMs	Simulated conditions
√	Strong CYP3A inhibitors e.g., ketoconazole	Contraindicated	1
√	Moderate CYP3A inhibitors e.g., fluconazole	Not recommended	1
√	Weak CYP3A inhibitors e.g., ranitidine	Not recommended	1

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

Pediatrics: Is current workflow adequate?



Leong et al, Clin Pharmacol Ther, 2012

Inform dosing in pediatrics in lieu of PK study

Valganciclovir hydrochloride (Valcyte) Efficacy Supplement (2015)

cytomegalovirus (CMV) nucleoside analogue DNA polymerase inhibitor

Label update (Sec 8.4): "…A physiologically based pharmacokinetic (PBPK) model was developed based on the available pharmacokinetic data from pediatric and adult patients to support dosing in heart transplant patients less than 1 month of age. However, due to uncertainty in model predictions for neonates, VALCYTE is not indicated for prophylaxis in this age group."

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022257s005,021304s011lbl.pdf

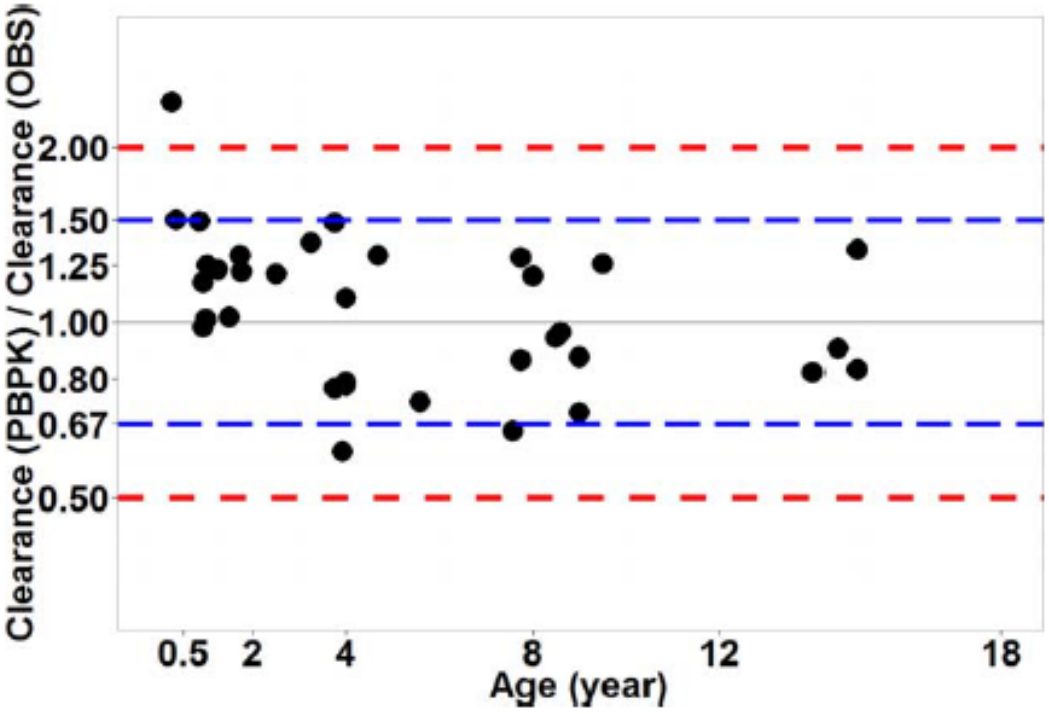
Pediatric PK: predictive performance?

Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 00, 00; doi:10.1002/psp4.12101

ORIGINAL ARTICLE

Predictive Performance of Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling of Renally Cleared Drugs in Children

W Zhou[1], TN Johnson[2], H Xu[1], SYA Cheung[3], KH Bui[1], J Li[1], N Al-Huniti[1] and D Zhou[1]*



+/- 50%
+/- 100%

Summary

- **PBPK analyses are routinely submitted to the FDA**
- **Confidence varies, depending on predictive performance for intended purposes**
- **Establishing confidence in physiology (drug independent) model is crucial for effective use of PBPK**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