The Use of Physiologically based Pharmacokinetic Modeling and Simulation to Address Clinical Pharmacology Questions in Regulatory Reviews

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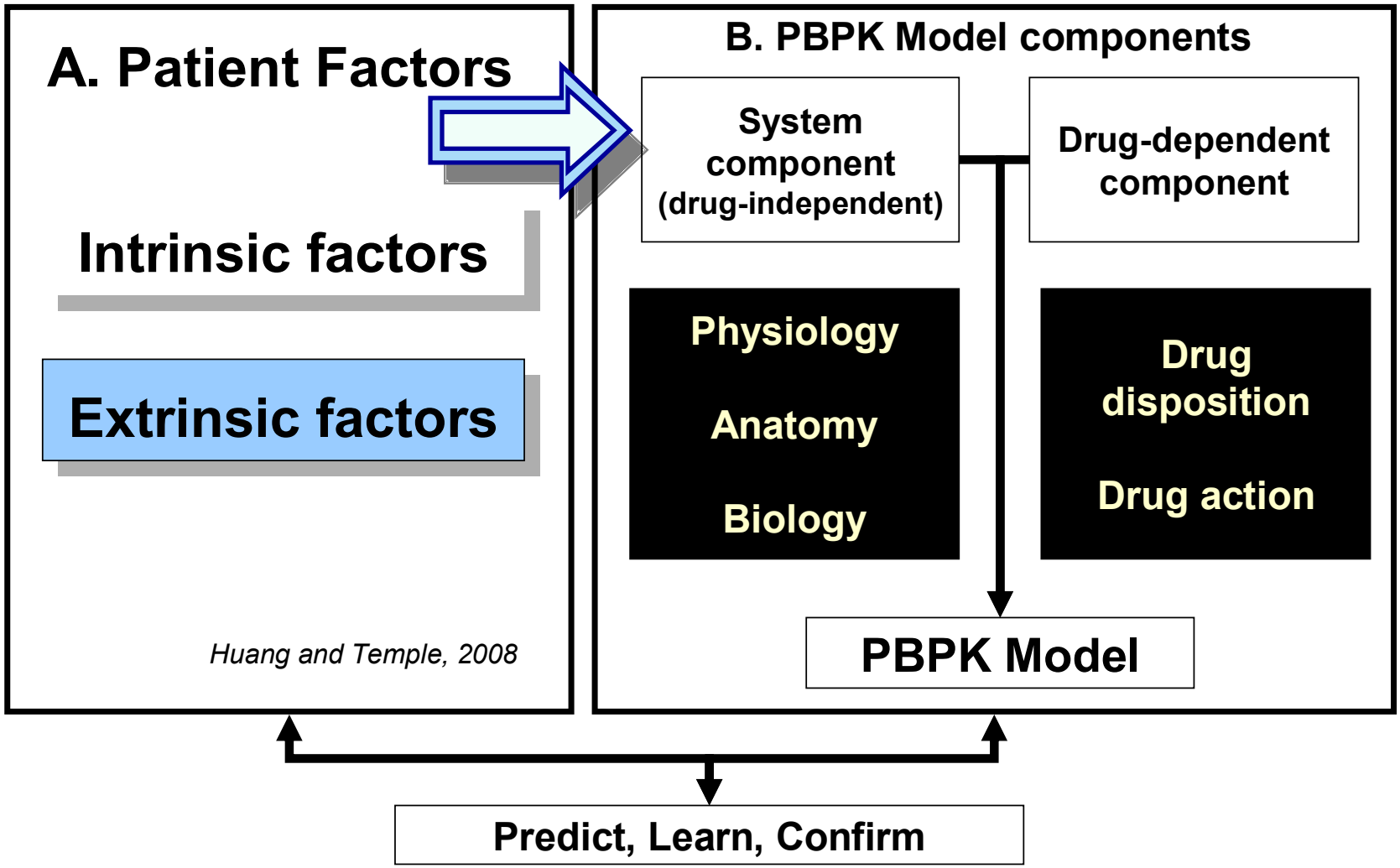
Webinar presentation at Pharmaceutical Users Software Exchange (PhUSE) Meeting, Boston, June 20, 2013

PBPK today

- Broader recognition in addressing complex drug development issues
- Significant advancements in the methodology and tools that integrate system- and drug-dependent information
- Increased applications to support decision making on whether, when and how to conduct study
- Increased submission of PBPK analyses to the FDA and the use by reviewers to support reviews

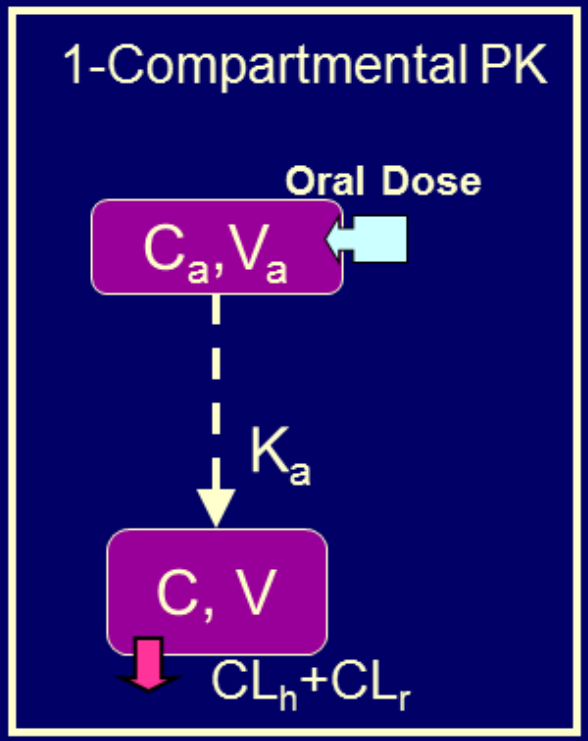
Rowland, 2011, Zhao, 2012, Huang, 2013

PBPK: Predict, learn, and confirm



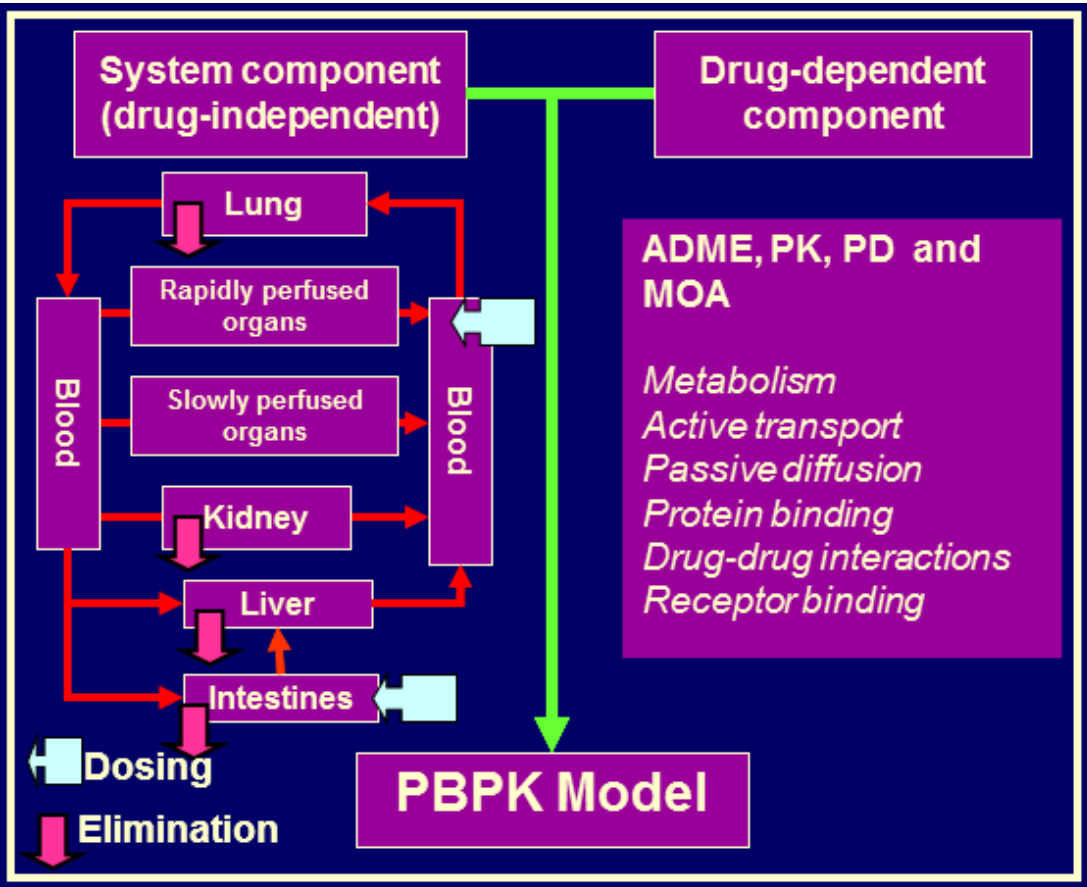
Adapted from Zhao P, Clin Pharmacol Ther 2011

Why PBPK? To PREDICT unknown



$V*dC/dt = K_a*V_a*C_a-(CL_h+CL_r)*C$

$V_a*dC_a/dt = - K_a*V_a*C_a$



$$C = \frac{K_a * Dose}{V * (Ka - \frac{CL_h + CL_r}{V})} * (e^{-\frac{(CL_h+CL_r)}{V}*t} - e^{-K_a*t})$$

C_{plasma}
C_{liver}
C_{kidney}
C_{muscle} … …

And…

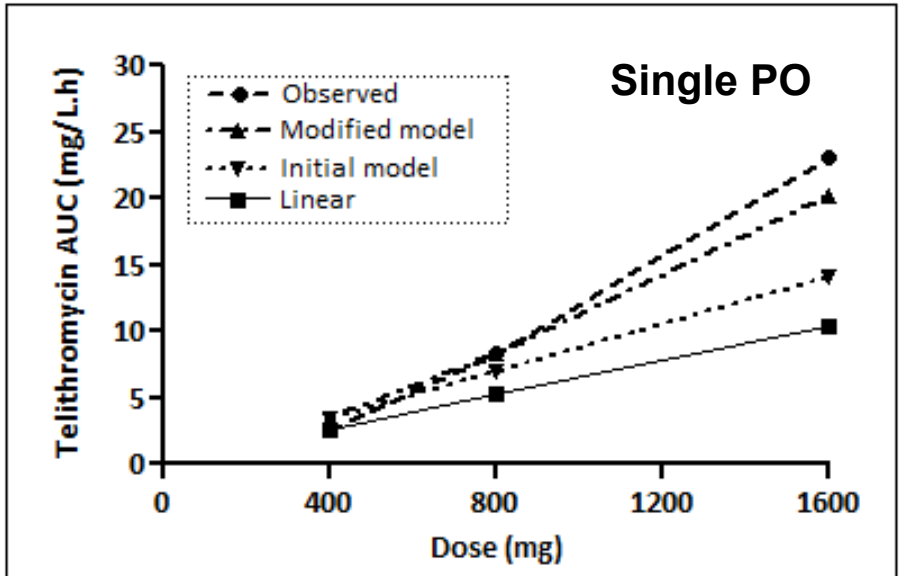
PK Non-linearity

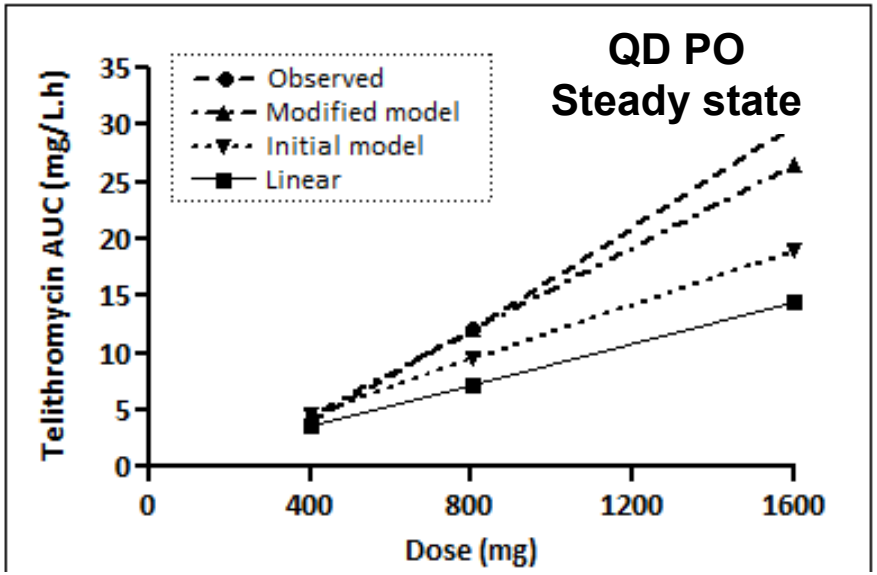
Can we LEARN nonlinear PK through PBPK modeling?

Can PBPK model integrating auto-inhibition PREDICT DDI ?

Vieira, Clin Pharmacol Ther, 2012

LEARNING nonlinear PK through PBPK



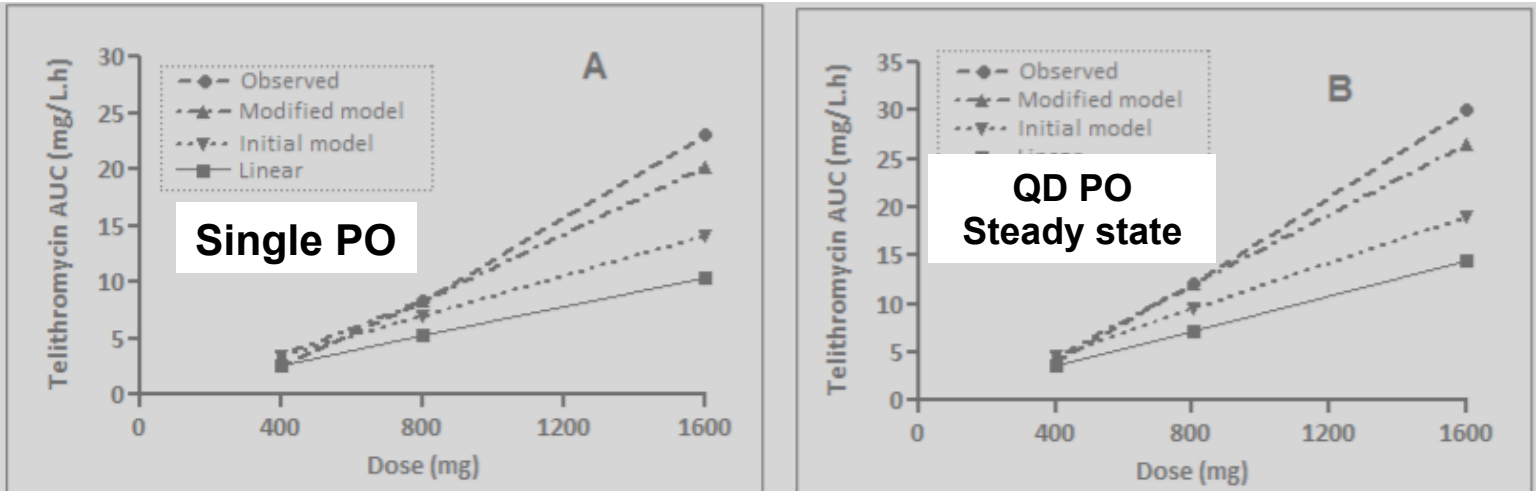


Vieira et al, Clin Pharmacol Ther, 2012

Evaluation of sources of nonlinearity using PBPK

- × **Absorption: Saturation of P-gp**
- × **Metabolism: Saturation**
- × **Excretion: Saturation**
- ✓ **Metabolism: Auto-inhibition (via time-dependent inhibition, TDI)**

PBPK model with autoinhibition PREDICTED DDI

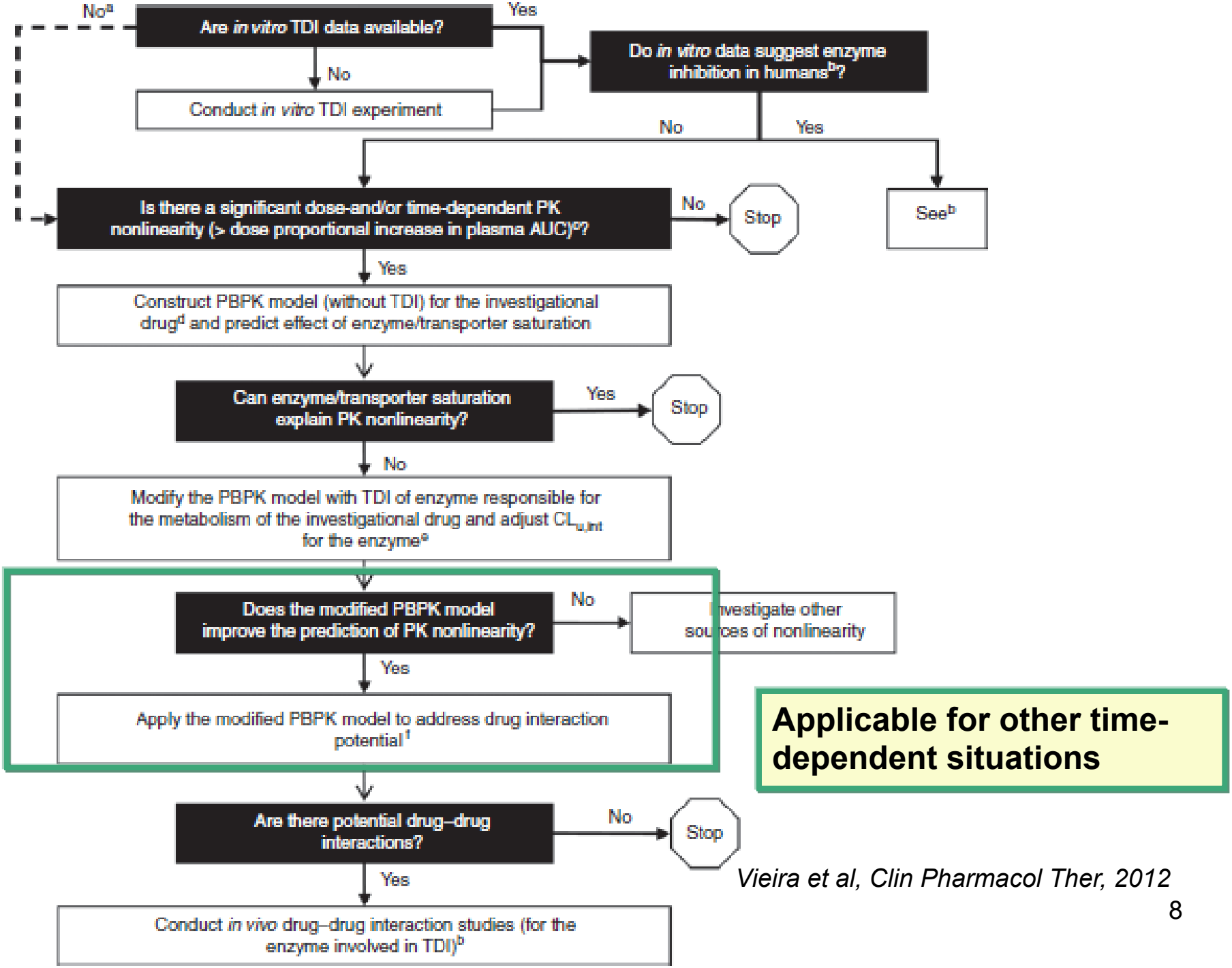


Vieira et al, Clin Pharmacol Ther, 2012

Effect of telithromycin (p.o. 800 mg once daily)

	IV midazolam		PO midazolam	
	Observed	**PBPK Predicted**	**Observed**	**PBPK Predicted**
C_{max} Ratio	1.05	1.13	2.62	2.39
AUC Ratio	**2.20**	**3.26**	**6.11**	**6.72**
Ratio of F_G	-	-	1.92	1.59
Ratio of F_H	-	-	1.45	1.63
AUC ratio (Model without TDI)		***<1.25***		***<1.25***

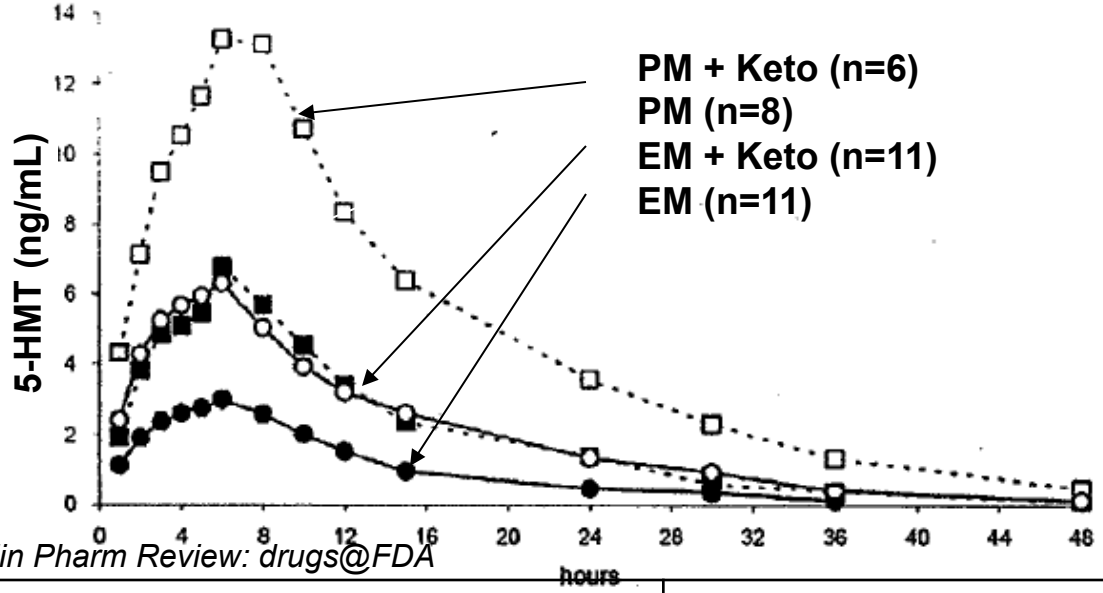
Observed data was not used to inform model



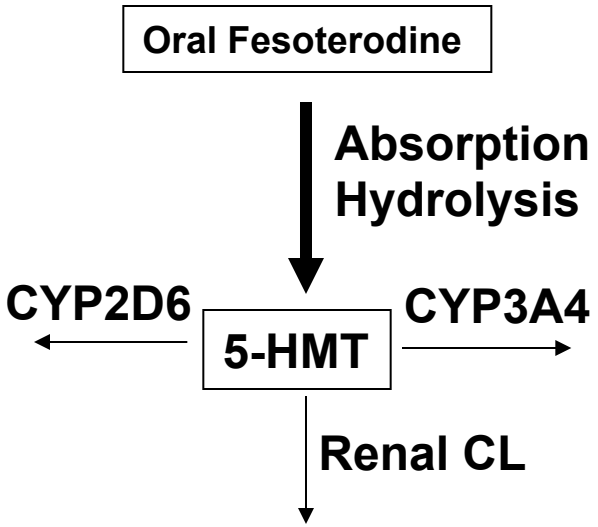
Applicable for other time-dependent situations

Vieira et al, Clin Pharmacol Ther, 2012

Extrapolating effect of CYP2D6 PM + CYP3A4 moderate inhibitor when data on PGx with strong inhibitor are available



Clin Pharm Review: drugs@FDA



	Observed		Predicted	
	AUCR	CmaxR	**AUCR**	**CmaxR**
EM +/- Ketoconazole	2.3 [a]	2.0 [a]	**1.9**	**1.8**
PM +/- Ketoconazole	2.5 [a]	2.1 [a]	**3.3**	**2.4**
PM / EM	2.3	2.1	**1.6**	**1.5**
PM + Keto / EM - Keto	5.7 [a]	4.5 [a]	**5.4**	**3.6**
EM +/- Fluconazole	1.3 [b]	1.2 [b]	**1.3**	**1.2**
PM + Fluconazole / EM - flucoazole	-	-	**2.6**	**2.1**

[a] Clinical Pharmacology Review (drugs@fda); [b] Malhotra et al (2001) B J Clin Pharmacol 72:226-234.

In the absence of ANY DDI or PGx study, can we PREDICT the effects?

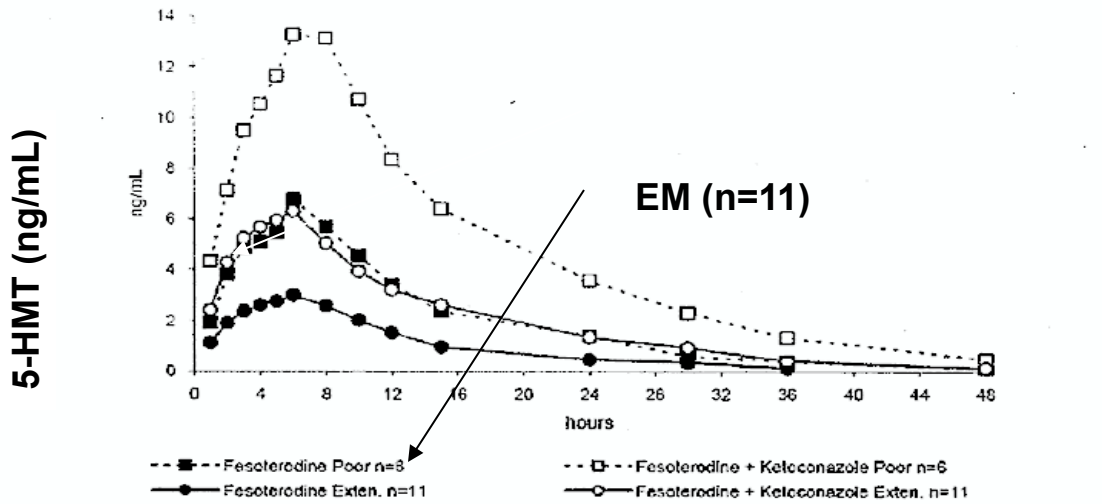
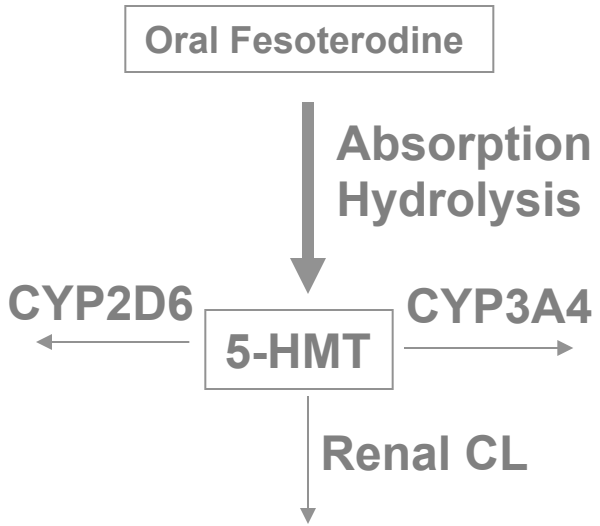


Figure 1. Plasma concentrations of SPM 7605 (arithmetic mean, study SP684) in CYP 2D6 EM and PM in the present or absent of ketoconazole 200mg twice daily*

*Original NDA review by Doanh Tran (DPS - December 5, 2006)

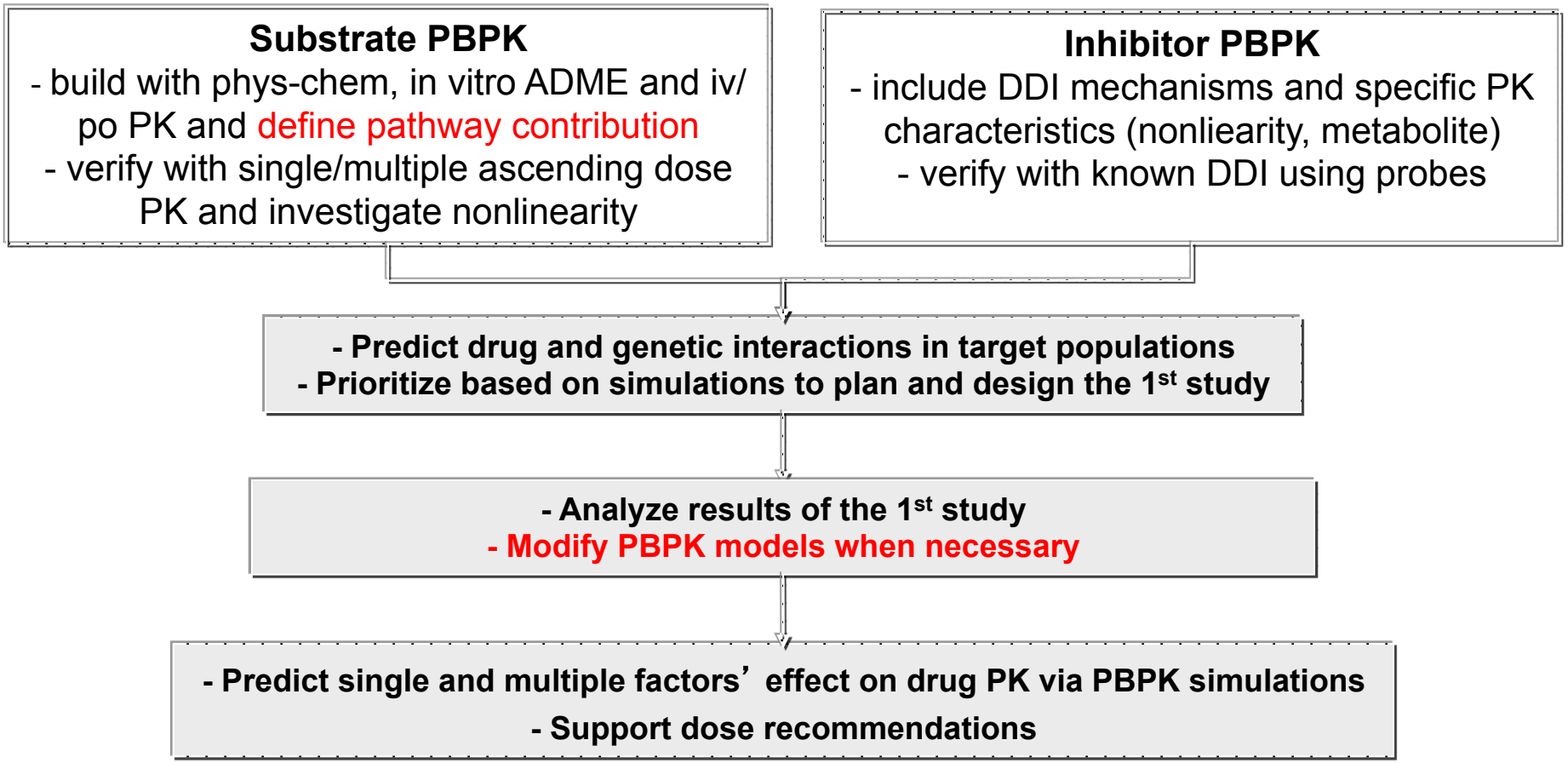
CYP 2D6 Review/Drugs@FDA



	Observed		Predicted	
	AUCR	CmaxR	**AUCR**	**CmaxR**
EM +/- Ketoconazole	?	?	**1.9**	**1.8**
PM +/- Ketoconazole	?	?	**3.3**	**2.4**
PM / EM	?	?	**1.6**	**1.5**
PM + Keto / EM - Keto	?	?	**5.4**	**3.6**
EM +/- Fluconazole	?	?	**1.3**	**1.2**
PM + Fluconazole / EM - Fluconazole	?	?	**2.6**	**2.1**

[a] Clinical Pharmacology Review (drugs@fda); [b] Malhotra et al (2001) B J Clin Pharmacol 72:226-234.

Proposal of using PBPK to prioritize clinical interaction studies for substrate drugs



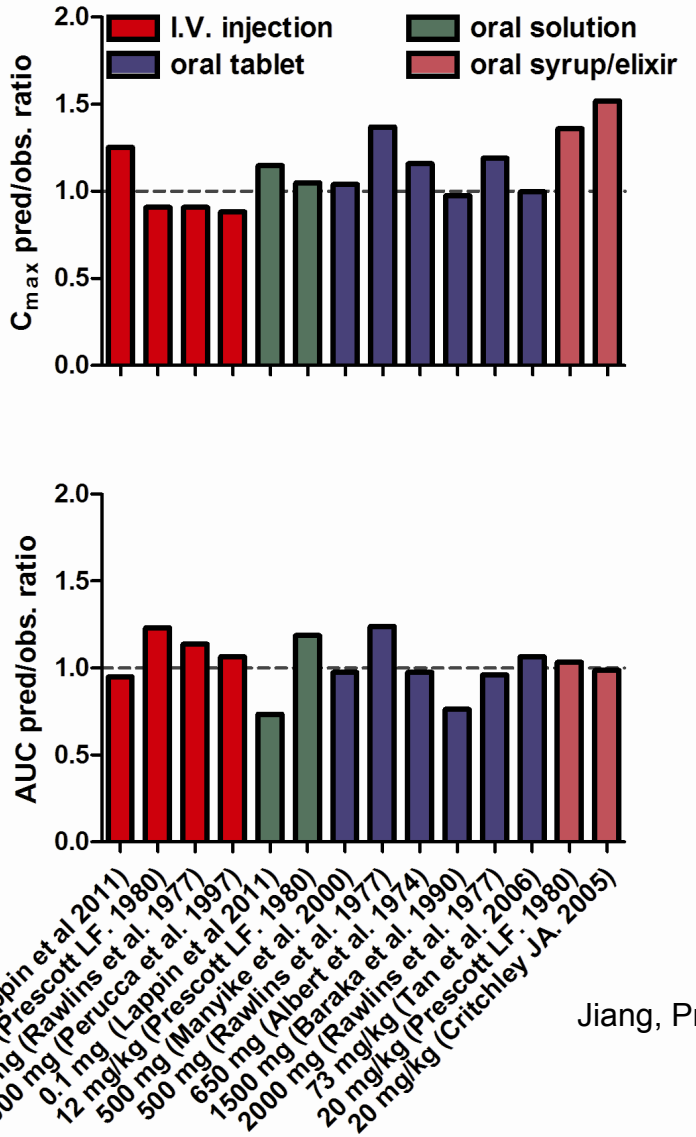
Zhao, Clin Pharmcol Ther, 2011

Vieira, manuscript in preparation

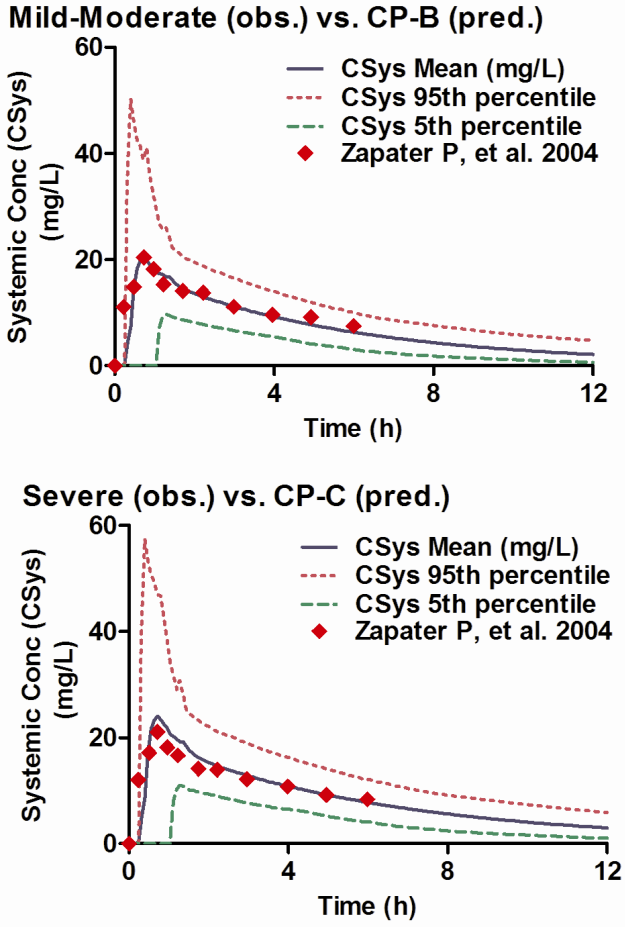
Can pediatric PK be PREDICTED using PBPK model derived from adult data?

PREDICTING APAP PK in adults

Healthy Adults

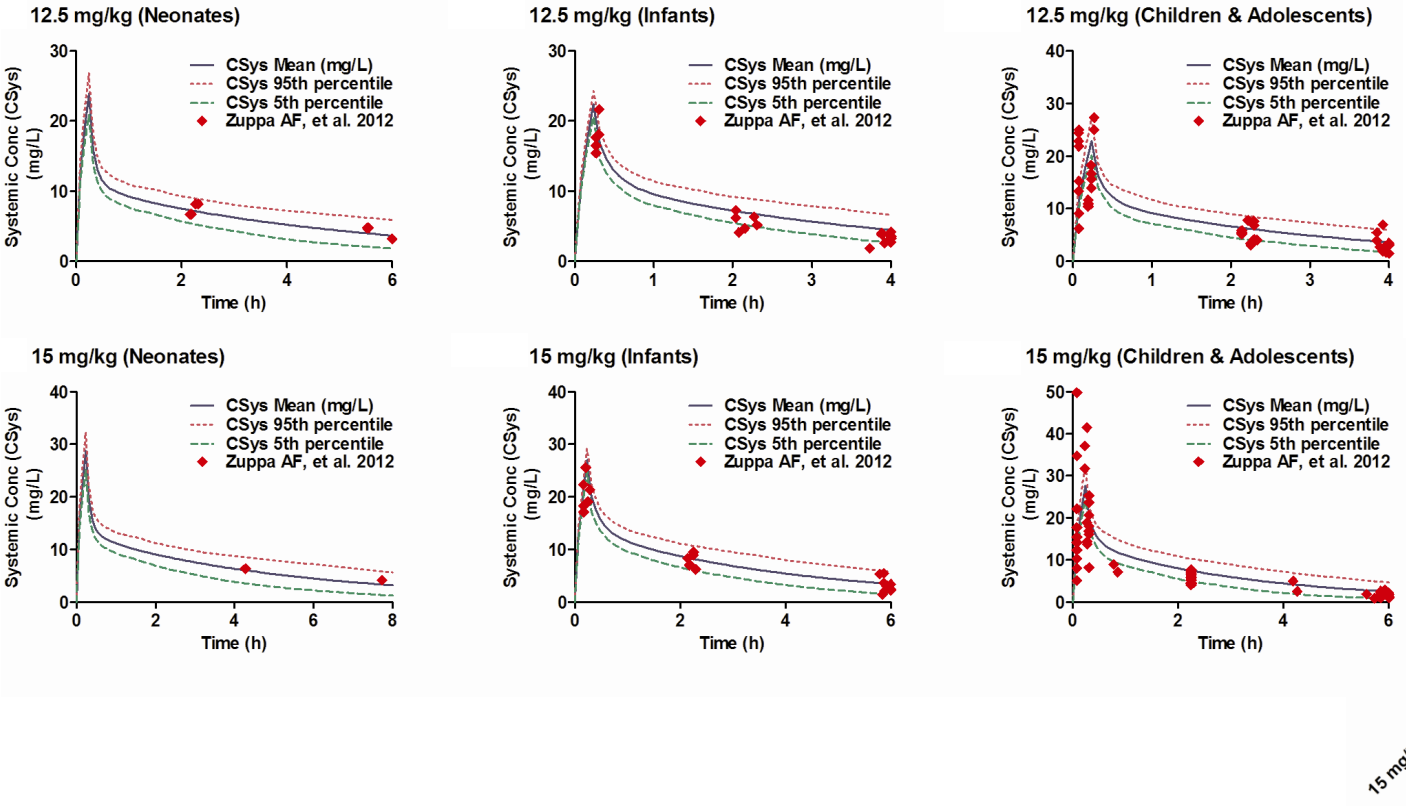


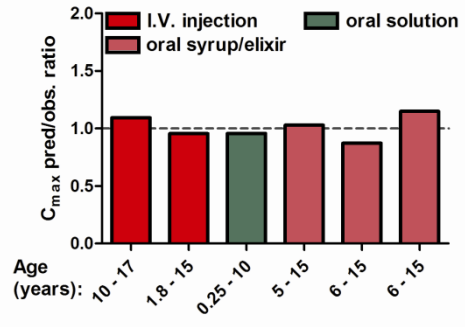
Cirrhosis Patients

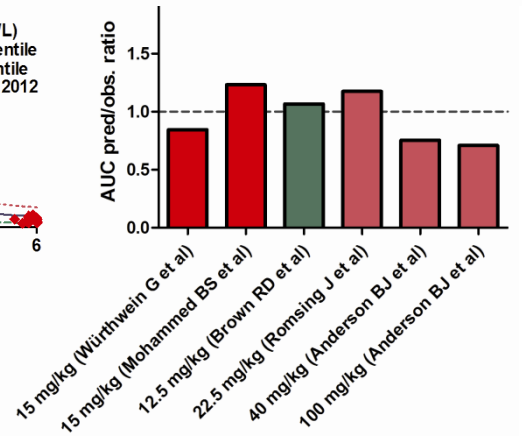


Jiang, President Trainee Award presentation, ASCPT Annual Meeting, 2013

PREDICTING APAP PK in children



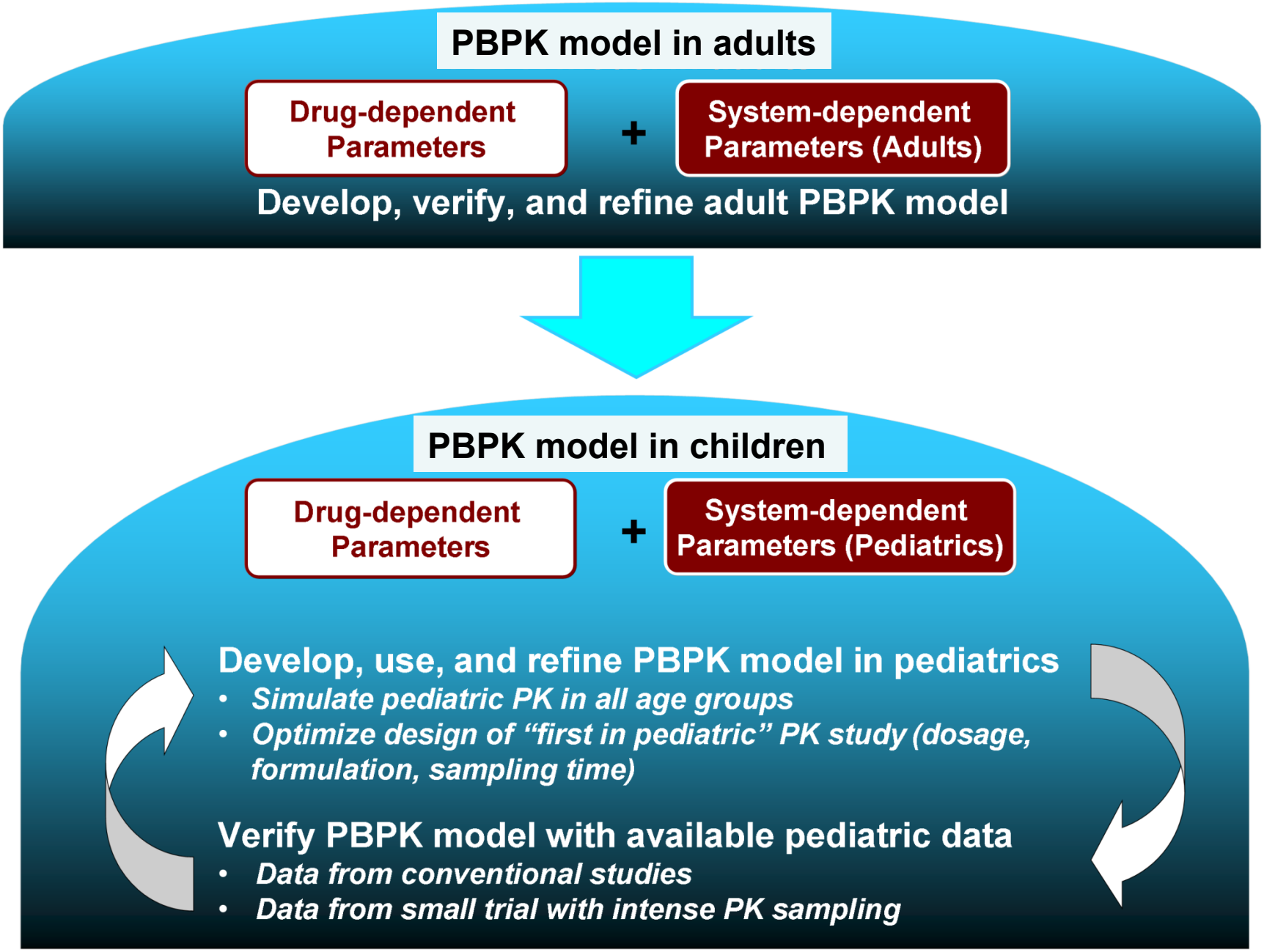




Age Groups		Urinary APAP-Glucuronide/APAP-Sulfate Ratio (Steady State)		
		(12.5 and 15 mg/kg)	Model Prediction (12.5 mg/kg)	Model Prediction (15 mg/kg)
Neonates	(0 – 0.08 year)	0.603 (N = 2)	0.566 (N = 100)	0.570 (N = 100)
Infants	(0.08 – 2 years)	0.970 (N = 13)	1.12 (N = 100)	1.11 (N = 100)
Children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

(Zuppa AF, et al. 2011)

Jiang, President Trainee Award presentation, ASCPT Annual Meeting, 2013

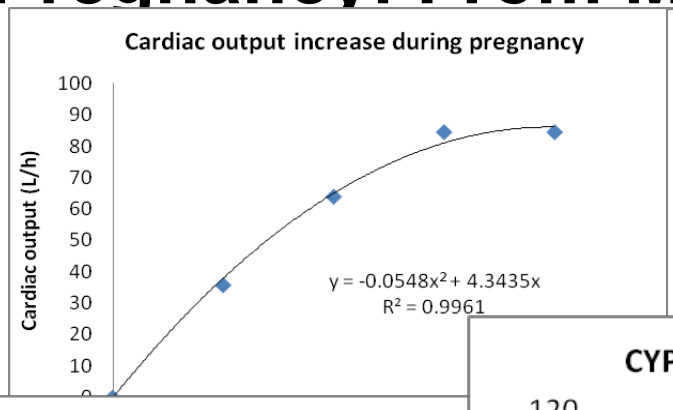


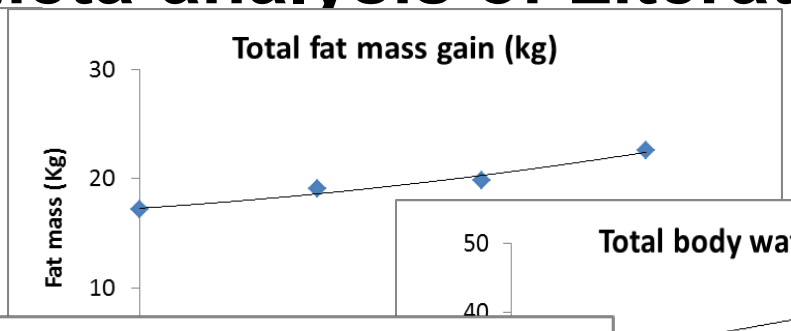
Leong et al, Clin Pharmacol Ther, 2012

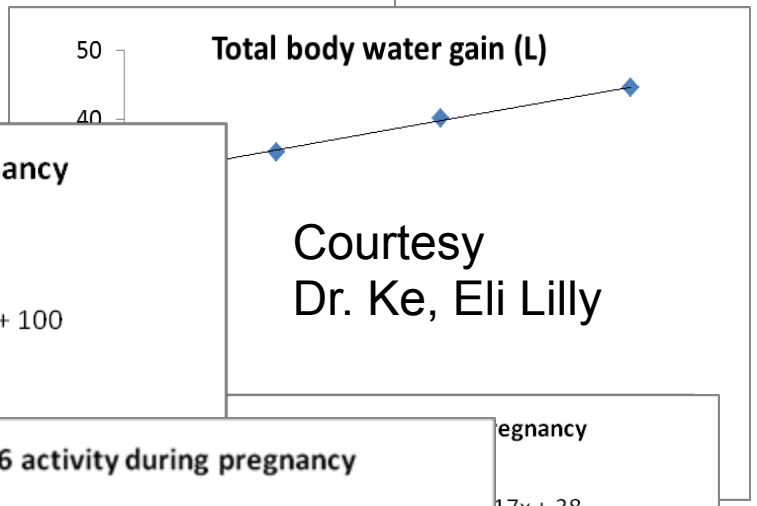
Other patient factors?

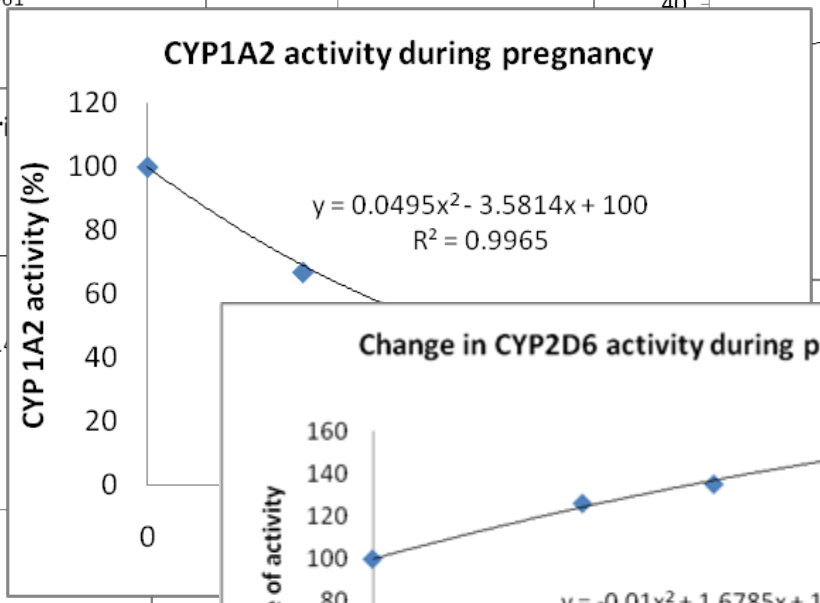
LEARNING the system through PBPK modeling

Prior Knowledge of Physiological Changes during Pregnancy: From Meta-analysis of Literature Data

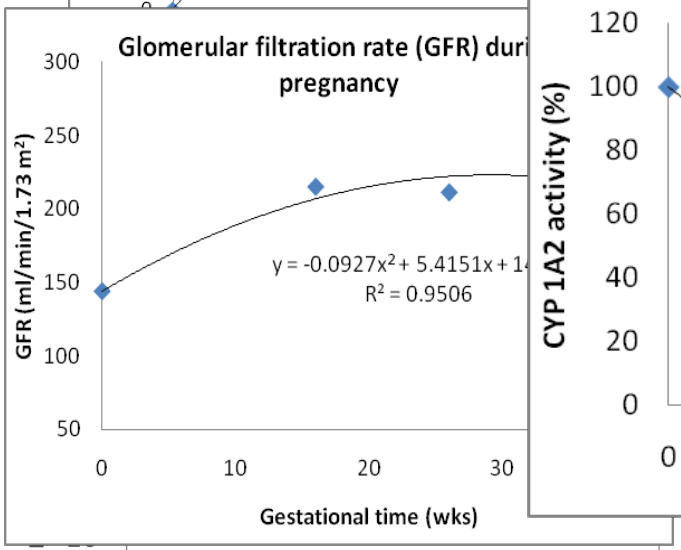


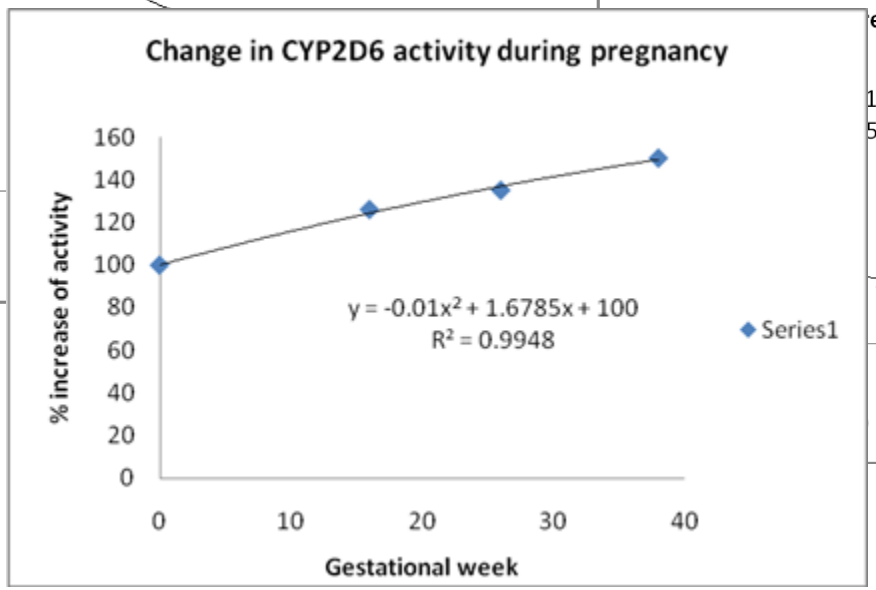


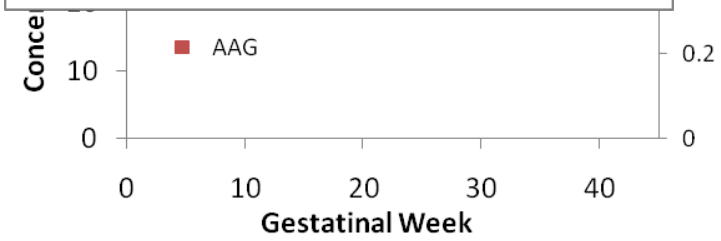


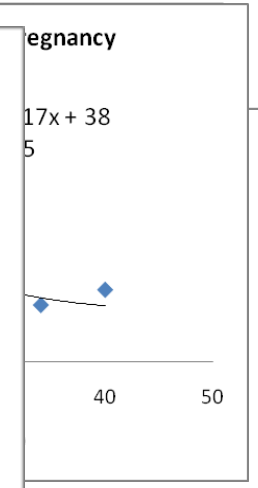


Courtesy
Dr. Ke, Eli Lilly



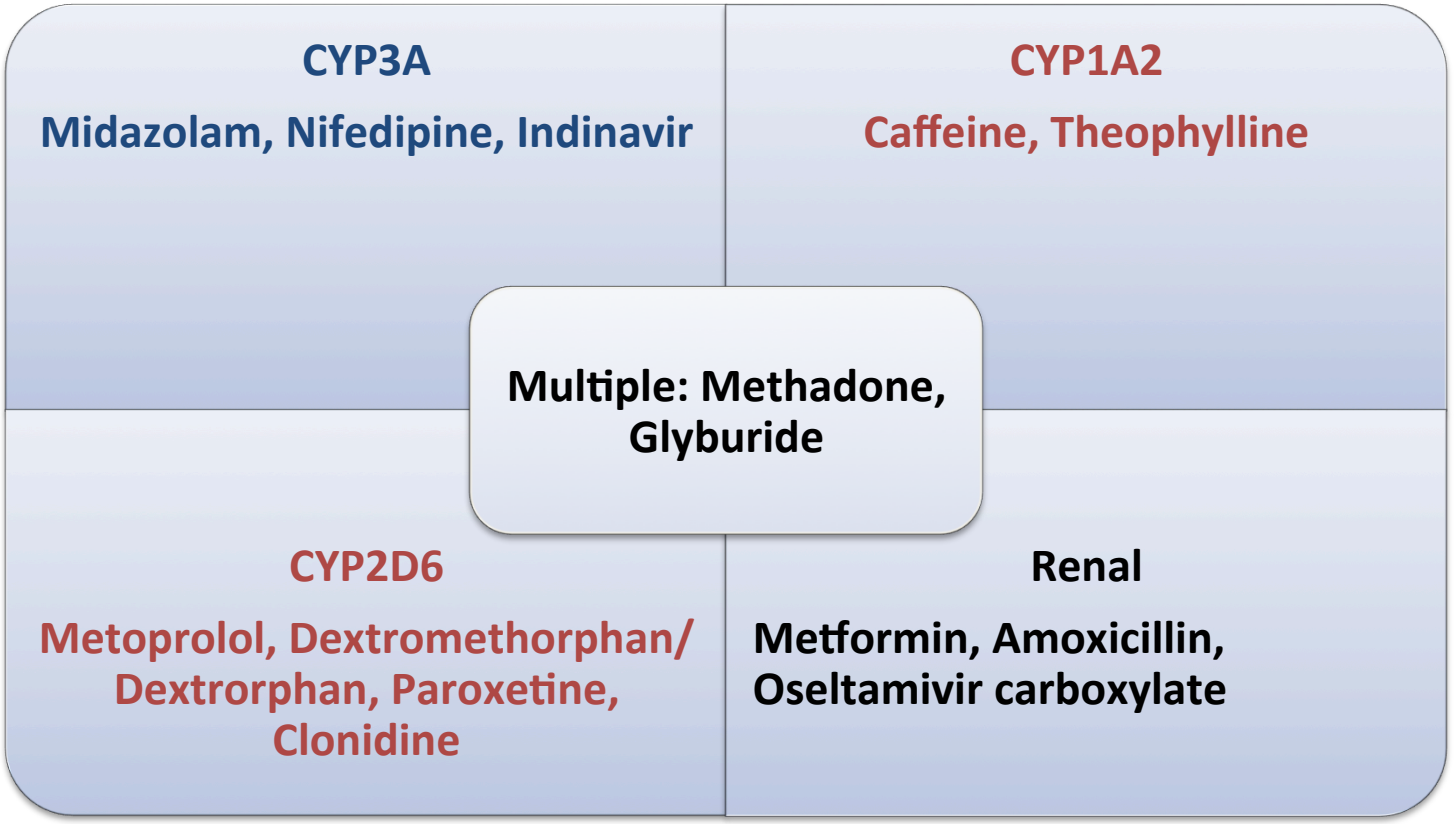






Abduljalil et al., Clinical Pharmacokinetics, 2012

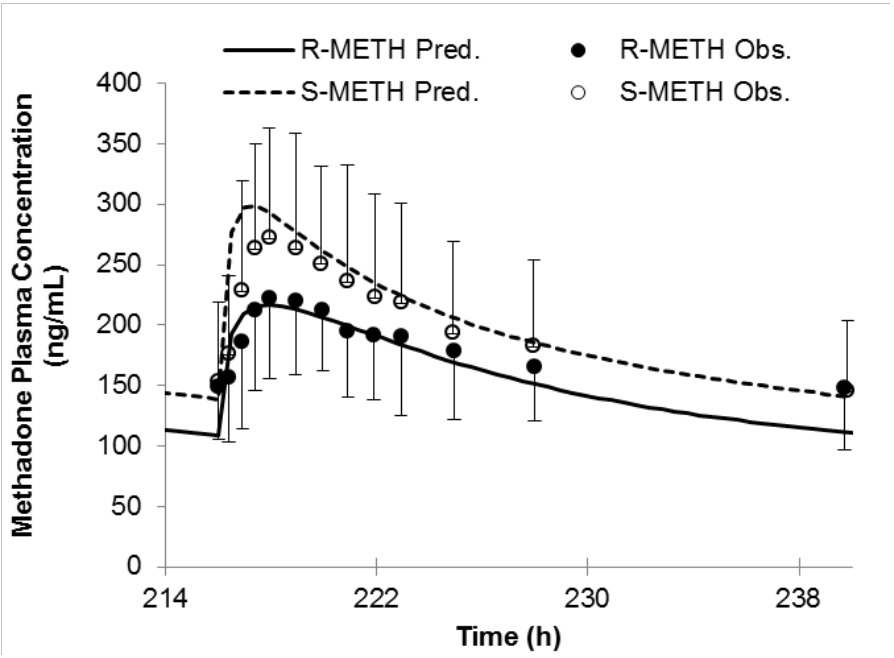
LEARNING the effect of pregnancy on CYPs using probes COMFIRMING the model with other drugs

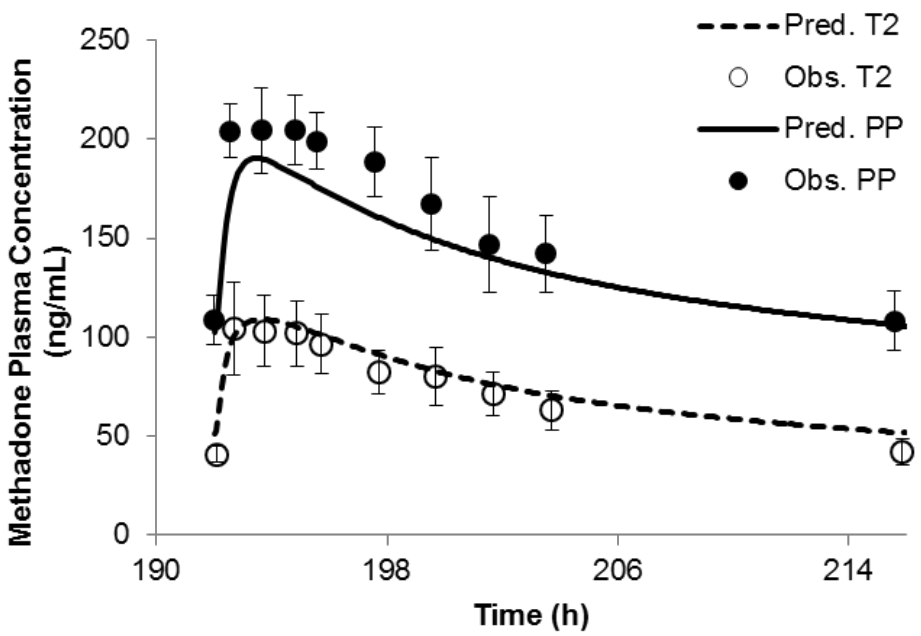


Ke, Clin Pharmcol Ther: Pharmacometrics & Systems Pharmacology, 2012

Ke,. Drug Metab Dispos. 2013

PREDICTING methadone PK during pregnancy [CYP2B6 (35-50%), CYP3A4 (27-37%) and CYP2C19 (~7%)]

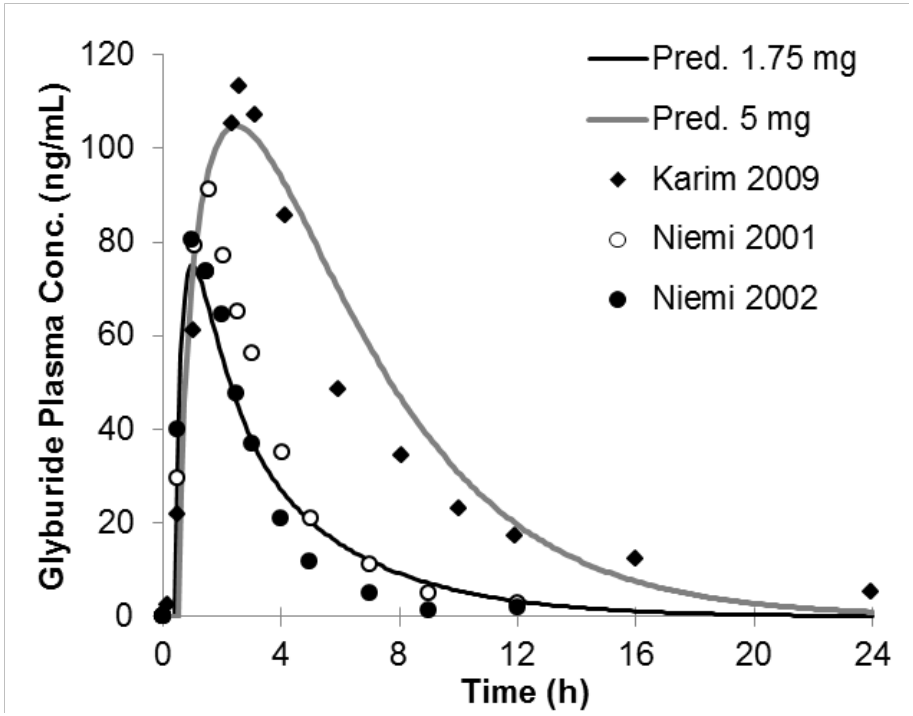


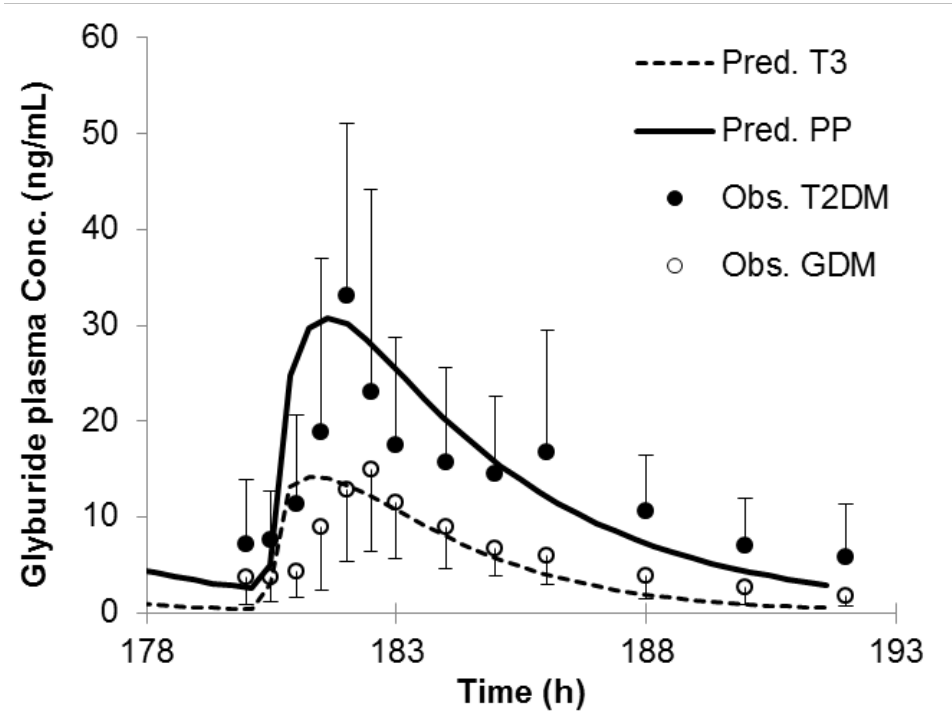


- **Hepatic CYP2B6 in vitro data; CYP2C19 proguanil PK.**
- **T2 second trimester; pp: postpartum**

Ke, Brit J Clin Pharmaco: submitted, 2013

PREDICTING glyburide PK during pregnancy [CYP3A4 (~50%), CYP2C9 (~30%) and CYP2C19 (~20%)]





- **Hepatic OATPs were assumed constant throughout pregnancy.**
- **T3: third trimester; PP: postpartum**

Ke, Brit J Clin Pharmaco: submitted, 2013

Organ dysfunction: the interplay

Effect of liver impairment on renal clearance

Table I. Physiological changes associated with liver cirrhosis

Parameter	Child-Pugh class		
	A	B	C
Blood flow			
portal[a]	0.40	0.36	0.04
hepatic arterial[b]	1.3	2.3	3.4
renal[c]	0.88	0.65	0.48
other organs[d]	1.75	2.25	2.75
Cardiac index[e]	1.11	1.27	1.36
Albumin[f]	0.81	0.68	0.50
α_1-Acid glycoprotein[g]	0.60	0.56	0.30
Haematocrit value[h]	0.39	0.37	0.35
Functional liver mass[i]	0.69	0.55	0.28
Hepatic enzymes[j]			
CYP3A4	1	0.4	0.4
CYP1A2	1	0.1	0.1
CYP2E1	1	0.83	0.83
GFR[k]	1	0.70	0.36

Edginton, Clin Pharmacokinet, 2008

Table III. Physiological and biochemical parameter changes associated with liver cirrhosis

Parameter	Control	Child-Pugh score		
		A	B	C
Liver volume fraction	1.0	0.81	0.65	0.53
CYP (pmol/mg)				
1A2	52	32.9	13.6	6.10
2A6	20	17.7	12.3	6.40
2B6	17	17.0	15.3	13.6
2C8	24	16.6	12.5	7.90
2C9	73	50.4	38.0	24.1
2C18	1.0	0.32	0.26	0.12
2C19	14	4.50	3.60	1.70
2D6	8.0	6.10	2.60	0.84
2E1	61	45.1	29.3	6.71
3A4	137	80.8	53.2	34.2
Gut CYP3A4 (nmol per total gut)	70	59	40	25
Albumin (g/L)	44.7	41.1	33.9	26.3
α_1-acid glycoprotein (g/L)	0.80	0.57	0.52	0.46
Haematocrit (%)	40.9	36.6	32.9	31.9
Cardiac output (L/h)	306	355	403	431
Portal blood flow (L/h)				
males	58.2	52.9	36.9	32.2
females	65.8	59.9	41.7	36.4
Hepatic arterial blood flow (L/h)	19.9	28	32.3	38.1
Q_{vill} (L/h)	18.4	23.7	28.0	36.6
GFR (mL/min)	120	83.7	69.9	66.5

CYP = cytochrome P450; **GFR** = glomerular filtration rate; Q_{villi} = villous blood flow.

Johnson, Clin Pharmacokinet, 2010

Organ dysfunction: the interplay

Effect of renal impairment on hepatic pathways

Table 1. Key physiological and biochemical parameter changes associated with differing degrees of renal impairment.

Parameter	Control	GFR (ml/min/1.73 m²)	
		30–59	<30
CYP1A2 (pmol/mg)	52 [58]	33 [63,129–131]	24 [129–131]
CYP2C8 (pmol/mg)	24 [58]	20 [64]	13 [64]
CYP2C9 (pmol/mg)	73 [58]	63 [65]	29 [65]
CYP2C19 (pmol/mg)	14 [58]	5.5 [66]	2.3 [66]
CYP2D6 (pmol/mg)	8.0 [58]	4.6 [67,132,133]	2.1 [132,133]
CYP3A4 (pmol/mg)	137 [58]	73 [68,134,135]	62 [68,135]
Albumin ($g.l^{-1}$) M F	44.9 [205] 41.8 [205]	41.6 [136,137,205] 38.8 [136,137,205]	37.6 [136,137,205] 35.0 [136,137,205]
Hematocrit (%) M F	43.0 [43] 38.0 [43]	39.7 [43] 33.2 [43]	36.5 [43] 31.3 [43]
Gastric emptying time (h)	0.40 [35]	0.55 [19]	0.65 [19]

F: Female; GFR: Glomerular filtration rate; M: Male.

Yeo, Exp Op Clin Pharmacol, 2011

PBPK Simulation: Renal Impairment + Moderate Enzyme Inhibitor in Elderly

Rivaroxaban AUC Ratio	Renal functions			
	Normal	Mild	Moderate	Severe
No Erythromycin	**1.0** [a]	**1.4** [a]	**1.5** [a]	**1.6** [a]
With Erythromycin	1.6 [b]	**2.5** [b]	**2.9** [b]	**3.0** [b]

[a] Observed with in older subjects

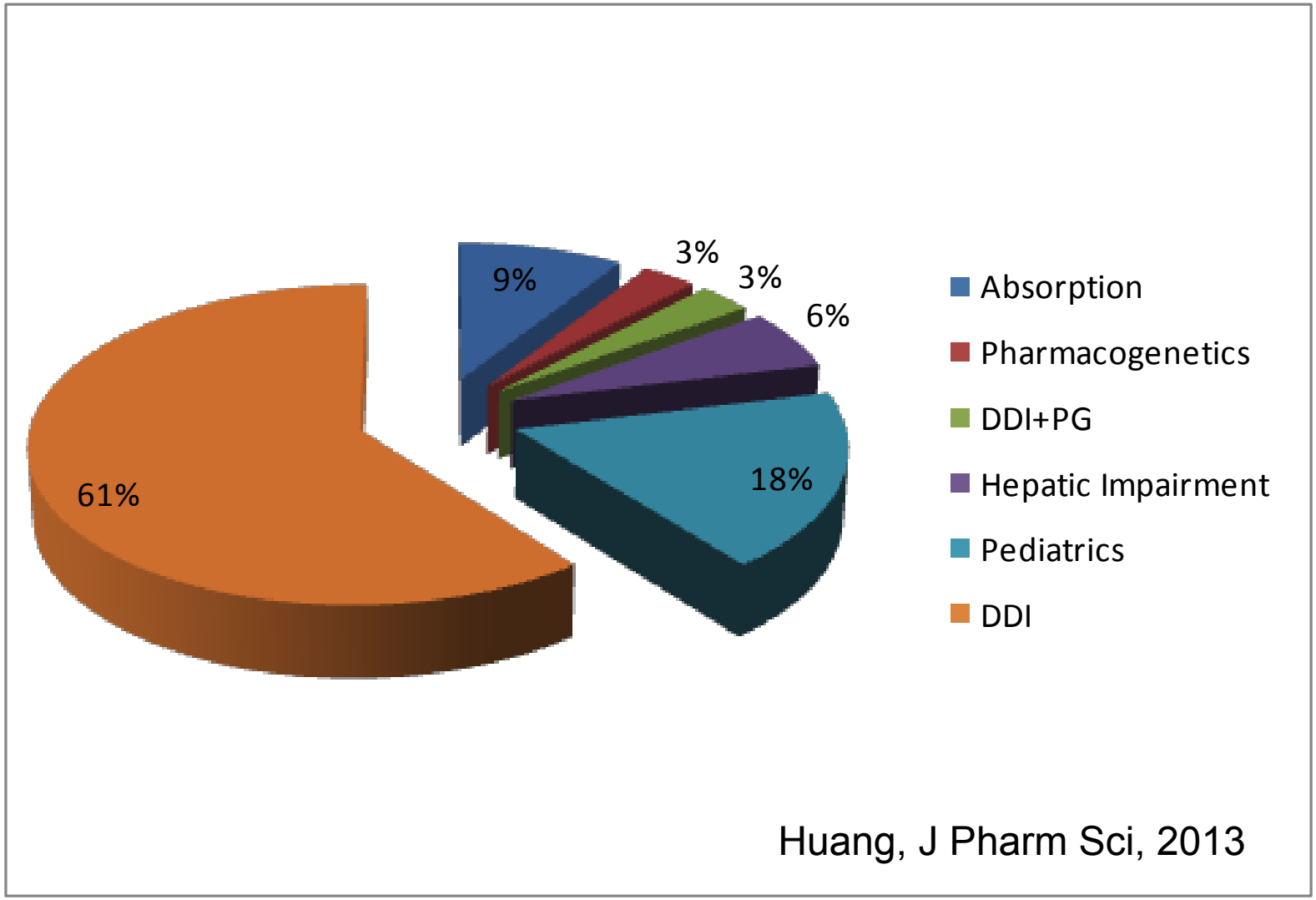
[b] **Simulated using younger subjects with normal renal function as baseline**

More than 2-fold AUC Ratio is considered clinically significant

Sponsor studied the combined effect as a post marketing requirement

Grillo , Biopharm Drug Dispo, 2012

PBPK submissions by clin pharm categories (2008-2012)



Basic steps for PBPK analyses

0. Determine Questions that may be addressed by PBPK

Zhao, Clin Pharmacol Ther, 2012

1. Determine Clearance Pathways (e.g., f_m)

2. Build PBPK Model (Drug- and System- parameters)

3. Compare simulated profiles with in vivo data

4. Refine model

5. Predict (unlimited # of) **unknown clinical settings**

Zhao, Clin Pharmacol Ther, 2011

Summary

- **Unknown situations can be predicted by PBPK**
- **Utility depends on the level of confidence**

✓ Support design: ALL

✓ Serve as platform to learn physiology and drug attributes: ALL

✓ Support decision making: ALL

✓ Support dosing recommendations: SOME

Recently published PBPK work by OCP

Concept, perspective, and best practice	Huang SM, Abernethy DR, Wang Y, et al. The utility of modeling and simulation in drug development and regulatory review. *J Pharm Sci*. 2013 Huang S-M, Rowland M, Application of Physiologically-based pharmacokinetics Modeling in Regulatory Review, *Clin Pharmacol Ther, 2012* Huang SM. PBPK as a tool in regulatory review. *Biopharm Drug Dispos. 2012* Zhao P, Rowland M, Huang S-M, Best practice in the use of physiologically based pharmacokinetic modeling and simulation to address clinical pharmacology regulatory questions. *Clin Pharmacol Ther, 2012* Zhao P, Zhang L, Grillo JA, et al, Application of Physiologically-based pharmacokinetics (PBPK) Modeling and Simulation During Regulatory Science**.** *Clin Pharmacol Ther, 2011*
Study design	Duan JZ, Jackson AJ, Zhao P. Bioavailability Considerations in Evaluating Drug-Drug Interactions Using the Population Pharmacokinetic Approach. *J Clin Pharmacol. 2011* Zhao P, Ragueneau-Majlessi I, Zhang L, et al. Quantitative evaluation of pharmacokinetic inhibition of CYP3A substrates by ketoconazole: a simulation study. *J Clin Pharmacol. 2009*
Organ impairment	Grillo JA, Zhao P, Bullock J, et al, Utility of a physiologically–based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug–drug–disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice, *Biopharm Drug Dispo, 2012* Zhao P, de LT Vierira M, Grillo J, et al, Evaluation of Exposure Change of Non-renally Eliminated Drugs in Patients with Chronic Kidney Disease Using Physiologically-based Pharmacokinetic Modeling and Simulation. *J Clin Pharmacol, 2012*
Non-linear PK, DDI prediction	De LT Vieira M, Zhao P, Gil Berglund E, et al, Predicting Drug Interaction Potential by Using a Physiologically-based pharmacokinetics (PBPK) Model: Case Study of Telithromycin, a Time-Dependent CYP3A inhibitor. *Clin Pharmacol Ther, 2012*
Pediatrics	Leong R, Vieira ML, Zhao P, et al. Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. *Clin Pharmacol Ther 2012*
Pregnancy	Ke AB, Nallani S, Zhao P, et al. A PBPK Model to Predict Disposition of CYP3A-metabolized Drugs in Pregnant Women: Verification and Discerning the Site of CYP3A Induction. *Clin Pharmcol Ther: Pharmacometrics & Systems Pharmacology, 2012* Ke AB, Nallani SC, Zhao P, Rostami-Hodjegan A, Isoherranen N, Unadkat JD. A Physiologically Based Pharmacokinetic Model to Predict Disposition of CYP2D6 and CYP1A2 Metabolized Drugs in Pregnant Women. *Drug Metab Dispos*. 41:801-13. *2013*

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