Use of PBPK in Clinical Pharmacology Reviews

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Sep 18, 2012 2nd AIMBE/NIH Summit on Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process

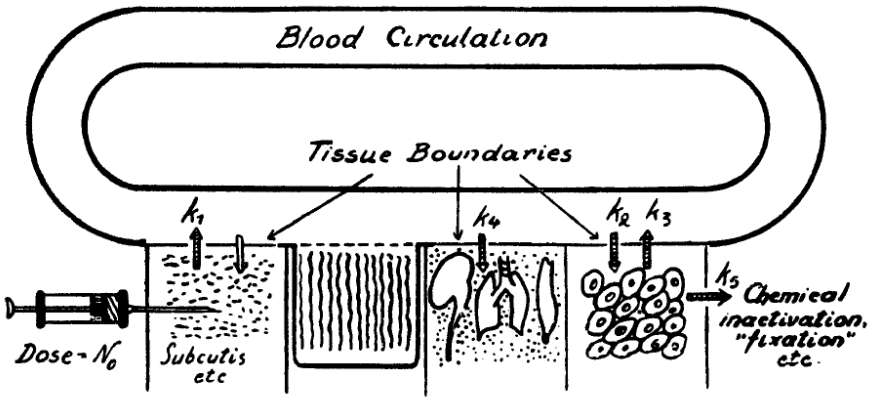
The Views expressed in this presentation do not reflect the official policy of the FDA

Outline

- Why PBPK
- Application of PBPK in clinical pharmacology review
- Verification of PBPK models through predict-learn-confirm processes

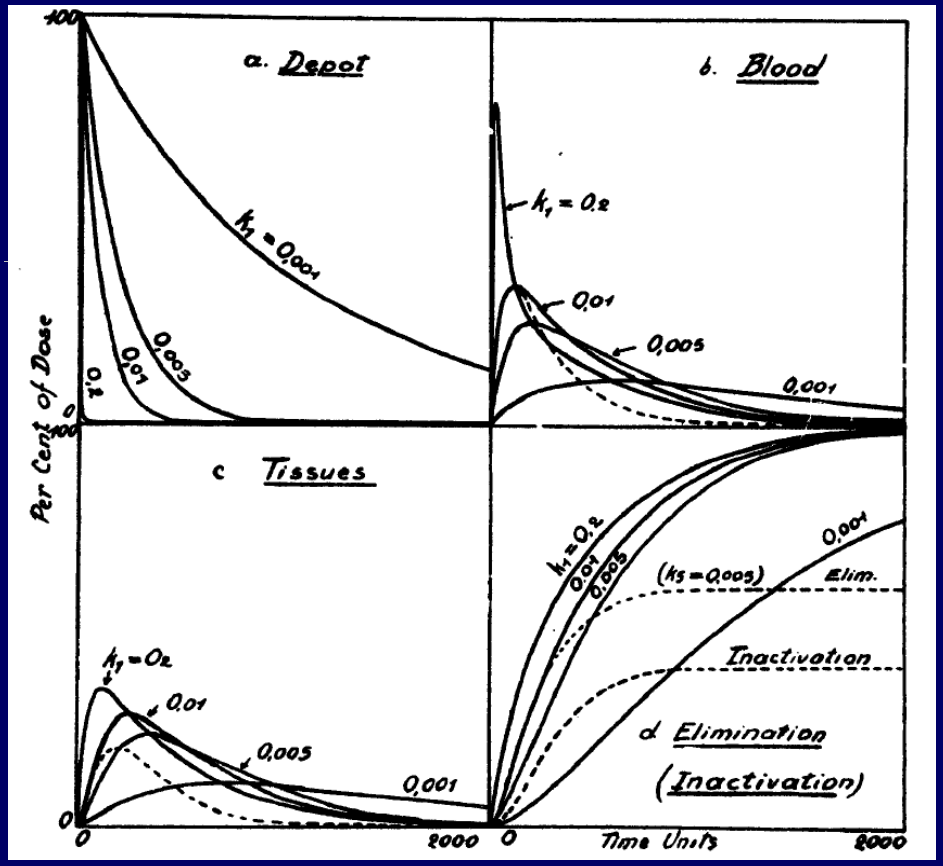
Physiologically-based Pharmacokinetic models (PBPK)

The model



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	—	V_3	—
Concentration	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff	k_1'	—	k_4'	k_2'	—
Velocity constant out	$k_1 = k_1'/V_1$	—	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	—	not existing	$k_2 = k_2'/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take up -"- output	Inactivation

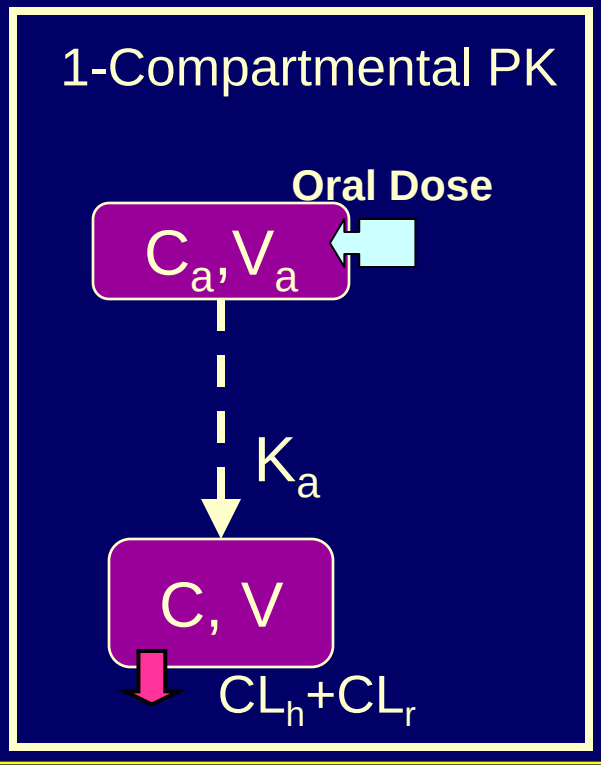
Effect of absorption kinetics



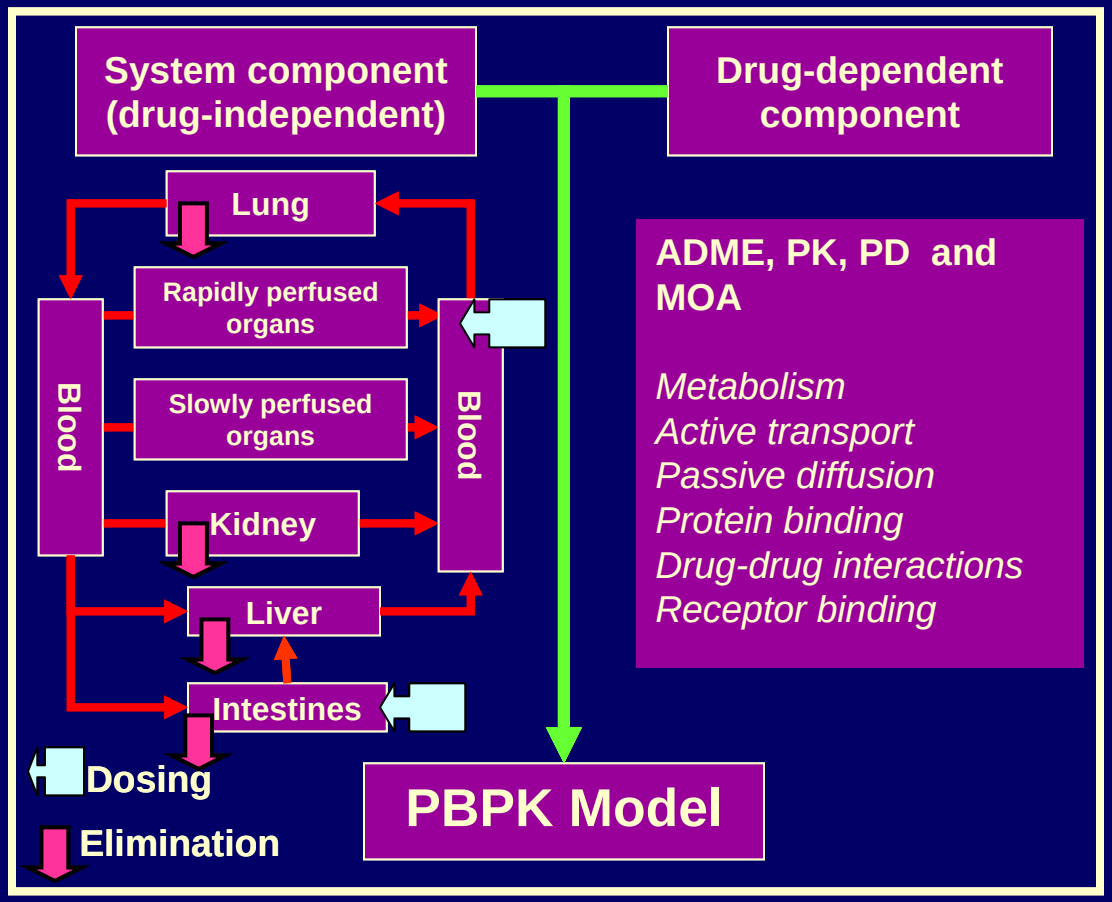
Teorell, Arch Intern Pharmacodyn, 1937

History: One of the Earliest PK Models "Was a PBPK Model"

Can Model Provide Desired Insights?



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



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

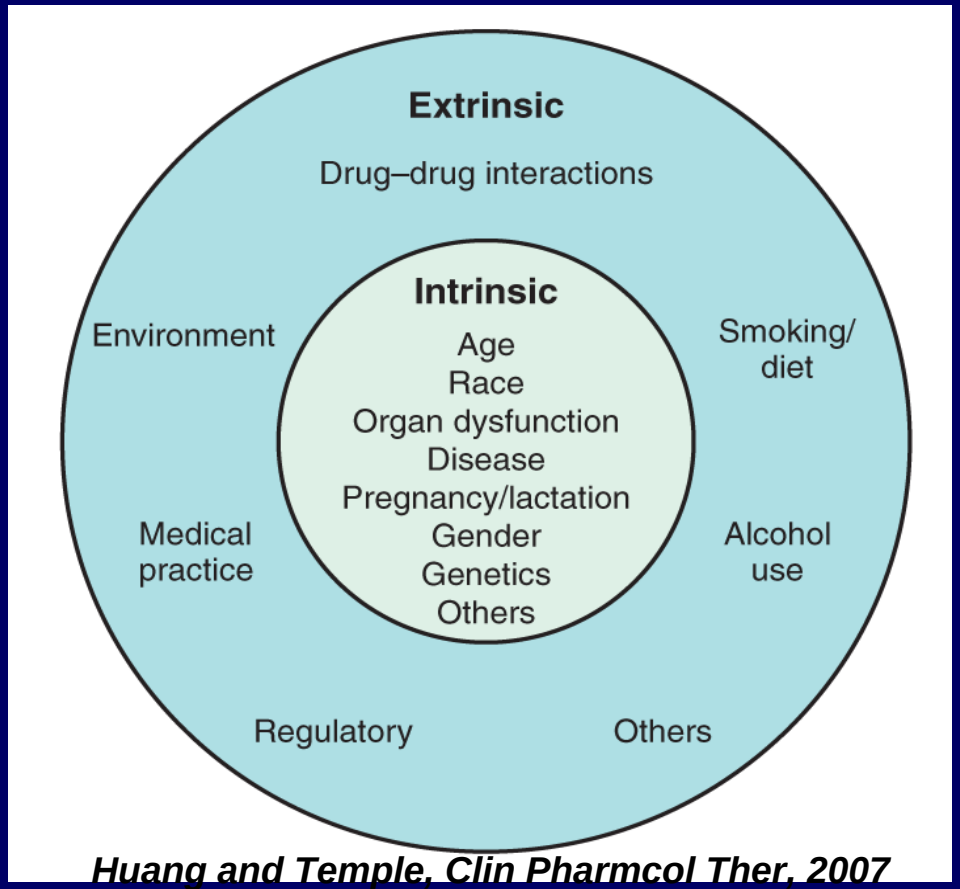
C_{plasma}
C_{liver}
C_{kidney}
C_{muscle} … …

And…

Clinical Pharmacology

- Central role: to assess PKPD in specific patient groups

- To make more informed decision on drug dosing



Huang and Temple, Clin Pharmcol Ther, 2007

- To guide our decisions:
  - *In theory, all situations can be <u>tested</u> clinically. However, ethical and practical issues may limit the numbers of studies one can conduct*
  - *Can some situations be <u>predicted</u> using current knowledge?*

PBPK: Predict, Learn, and Confirm

A. Patient Factors

Intrinsic factors

Extrinsic factors

Huang and Temple, 2008

B. PBPK Model components

System component (drug-independent)

Drug-dependent component

Physiology

Anatomy

Biology

Drug disposition

Drug action

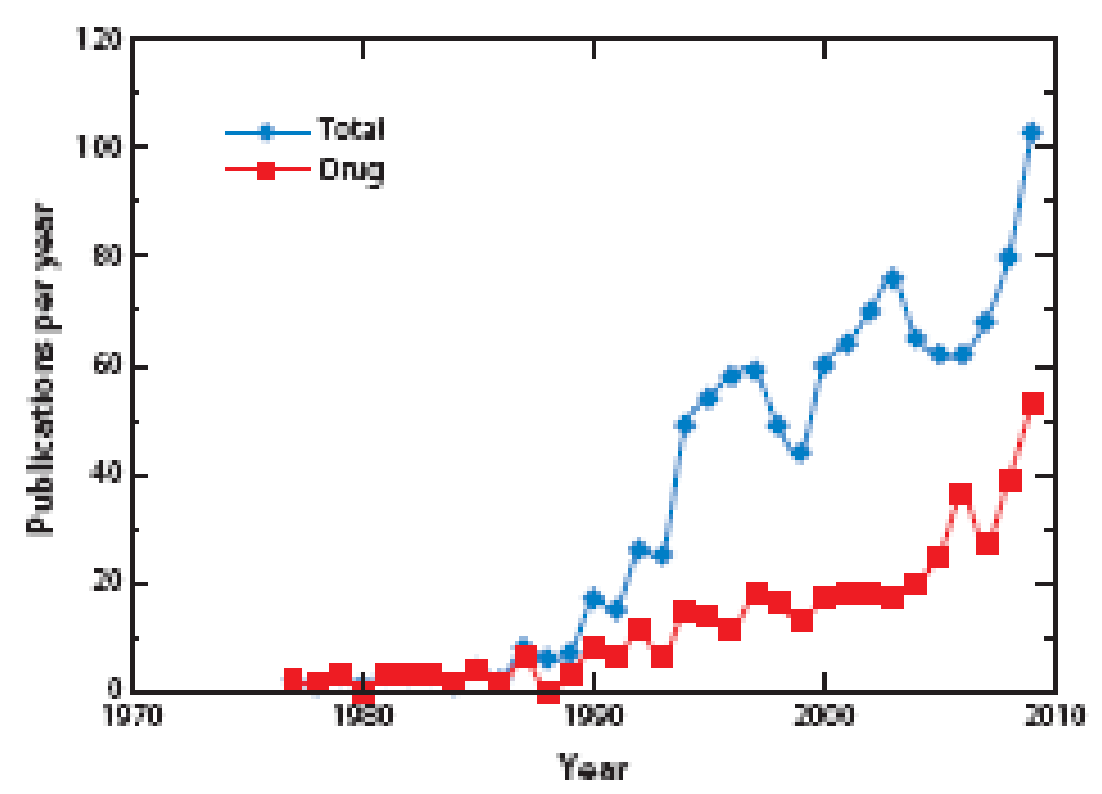
PBPK Model

Predict, Learn, Confirm

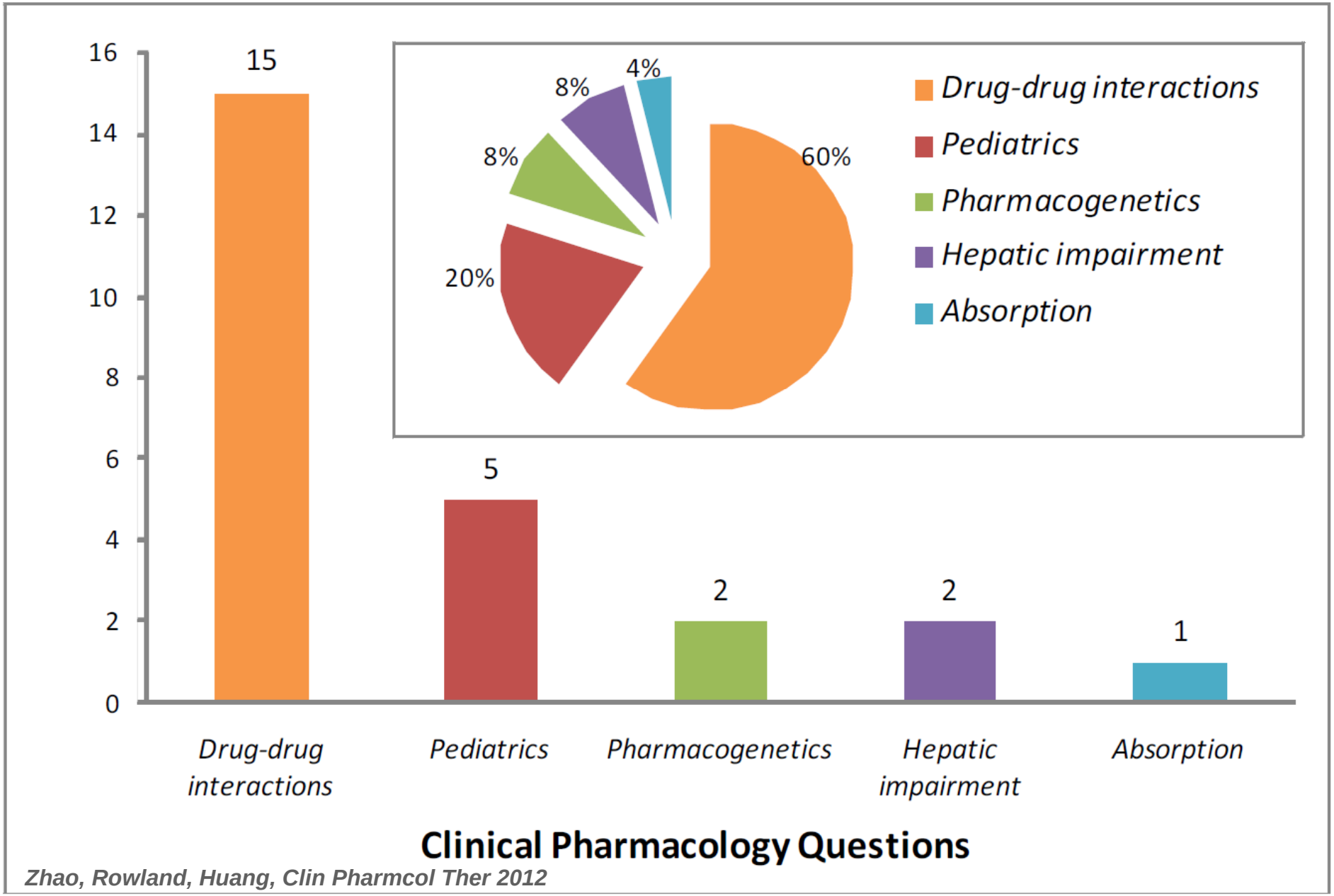
Adapted from Zhao P, et al Clin Pharmacol Ther 2011

Increased Interest in Using PBPK

Rowland M, Peck C, Tucker G,
Physiologically-based pharmacokinetics in Drug Development and Regulatory Science
Annu Rev Pharmcol Toxicol, 2011



Supplementary Figure 1: Distribution of clinical pharmacology questions addressed by PBPK among submissions over the period between Jun 2008 and December 2011



Zhao, Rowland, Huang, Clin Pharmcol Ther 2012

Recently published PBPK work by OCP

Concept, perspective, best practice

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

Zhao P, Zhang L, Grillo JA, et al, Application of Physiologically-based pharmacokinetics (PBPK) Modeling and Simulation During Regulatory Science. *Clin Pharmacol Ther, 2011*

Huang S-M, Rowland M, Application of Physiologically-based pharmacokinetics Modeling in Regulatory Review, *Clin Pharmacol Ther, 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*

Renal impairment, metabolite PK, transporter-enzyme

Grillo JA, Zhao P 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 Vieira 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*

Nonlinear PK and time-dependent inhibition

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 and pregnancy

Leong R, De LT Vieira M et al, , Regulatory Experience with Physiologically-Based Pharmacokinetic Modeling for Pediatric Drug Trials, *Clin Pharmacol Ther, 2012*

Ke AB, Nallani S, 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: in press

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Multiple Factors

Situations requiring mechanistic models

Investigational drug

- is a substrate of CYP3A4 AND (polymorphic) CYP2D6, what exposure change can be expected when a moderate CYP3A4 inhibitor is used in CYP2D6 PM?
- is renally AND hepatically cleared, what exposure change can be expected when a CYP inhibitor is used in patients with decreased renal function?
- forms an active/toxic metabolite whose exposure was increased in subjects with renal impairment, what are the effect of renal impairment AND drug interactions on the exposure of this metabolite?
- has dose- and time- dependent PK, what is its potential as an enzyme inhibitor?

❖ ***How much do we know about the compound***

DDI Prediction

Interacting drug

System component (drug-independent)

Substrate

ADME, PK, PD and MOA

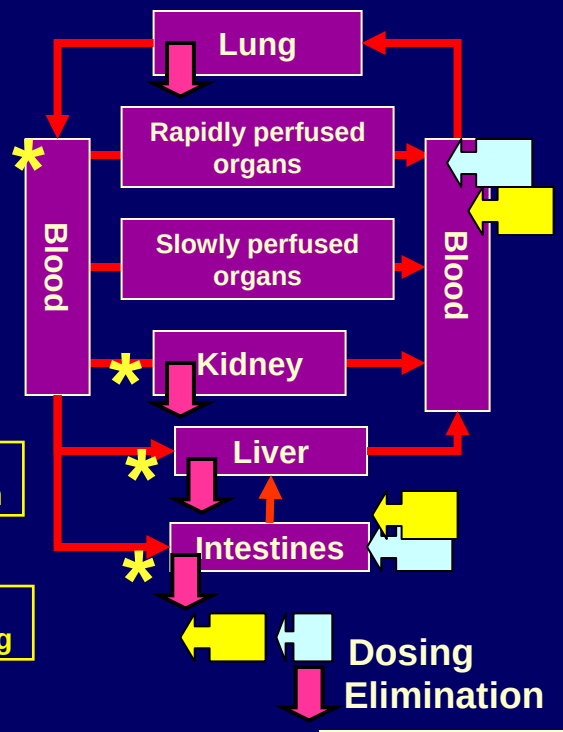
Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

f_p
B/P
Vss

CL_r

F_h, CL_h

F_g



ADME, PK, PD and MOA

Metabolism
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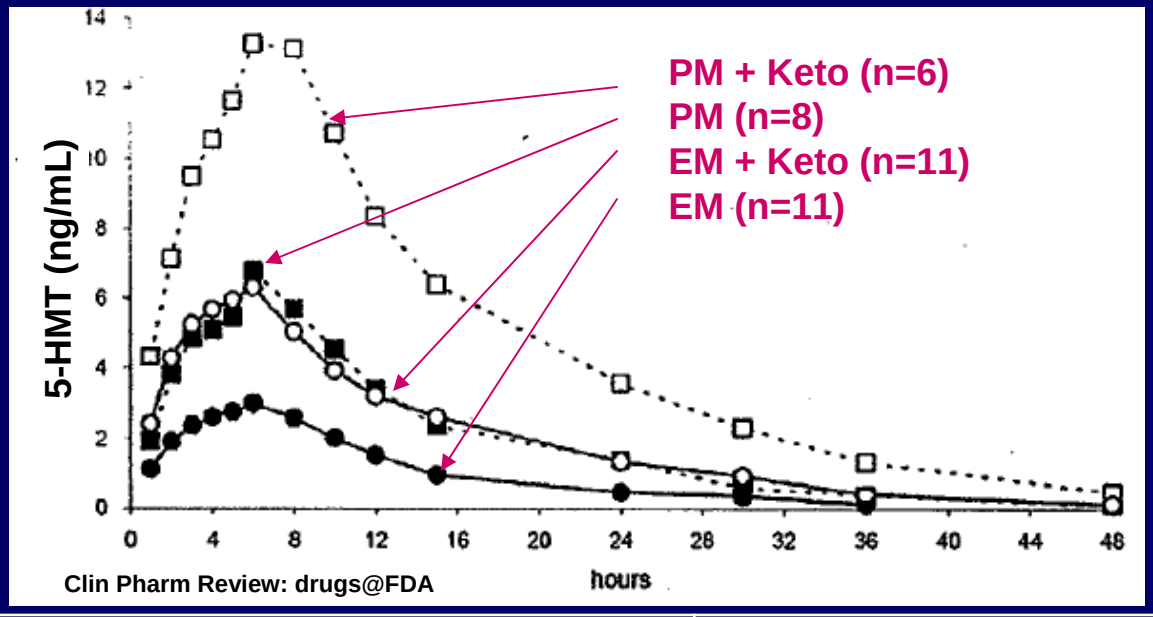
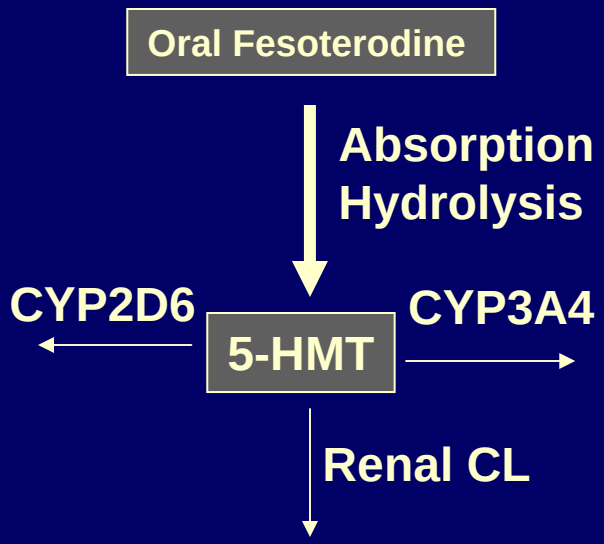
PBPK Model: Interacting Drug

PBPK Model: Substrate

Parameters can be altered by DDI

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



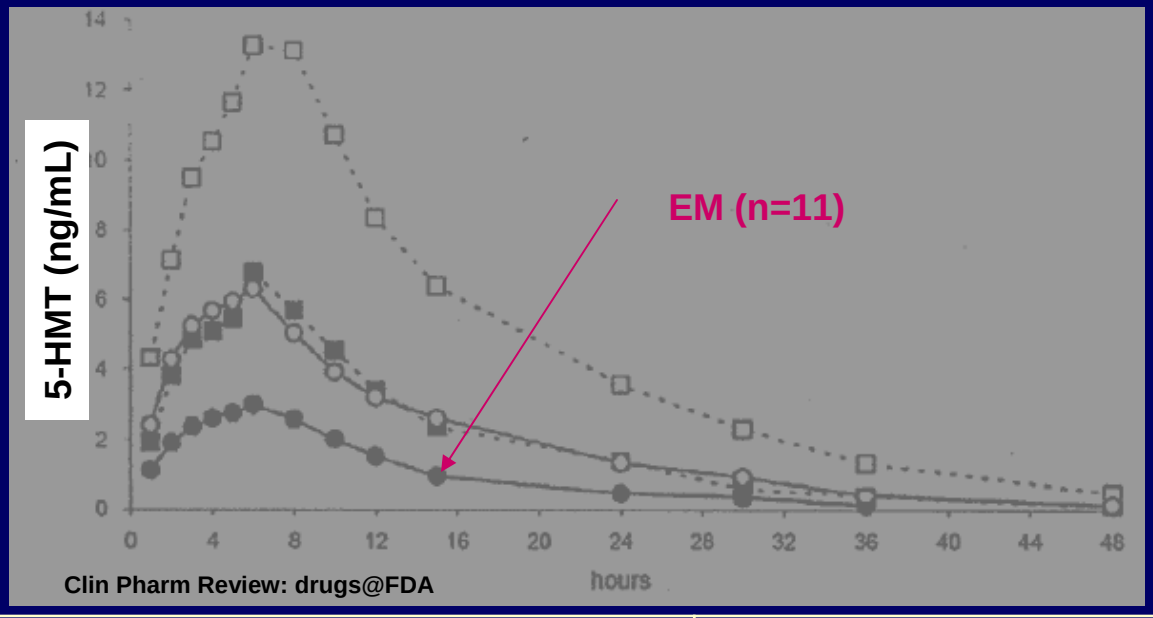


	Observed		Predicted	
	AUCR	CmaxR	AUCR	CmaxR
EM +/- Ketoconazole	2.3 [a]	2.0 [a]	1.9	1.8
PM +/- Ketoconazole	2.5 [a]	2.1 [a]	3.3	2.4
PM / EM	2.3	2.1	1.6	1.5
PM + Keto / EM	5.7 [a]	4.5 [a]	5.4	3.6
EM +/- Fluconazole	1.3 [b]	1.2 [b]	1.3	1.2
PM + Fluconazole / EM	-	-	2.57	2.09

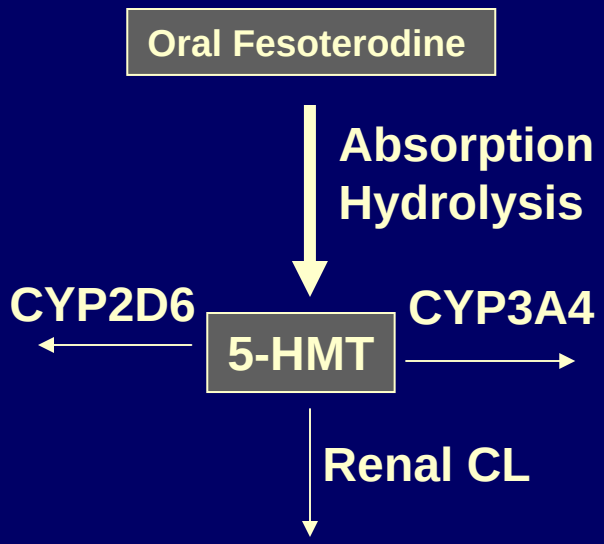
[a] Clinical Pharmacology Review (drugs@fda); [b] Malhotra et al (2001) B J Clin Pharmacol 72:226-234.

Vieira et al, ASCPT Annual Meeting, National Harbor, MD, March 2012

Or, can we PREDICT DDI BEFORE any DDI/PG study is conducted? Which one to do first? Which one can be waived?



Clin Pharm Review: drugs@FDA



	Observed		Predicted	
			AUCR	CmaxR
EM +/- Ketoconazole			1.9	1.8
PM +/- Ketoconazole			3.3	2.4
PM / EM			1.6	1.5
PM + Keto / EM			5.4	3.6
EM +/- Fluconazole			1.3	1.2
PM + Fluconazole / EM			2.57	2.09

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Huang and Temple, 2008

B. PBPK Model components

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Biology

Drug disposition

Drug action

PBPK Model

Predict, Learn, Confirm

Adapted from Zhao P, et al Clin Pharmacol Ther 2011

How “valid” is a PBPK model ?

- **Multiple solutions due to numerous system- and drug-dependent parameters**

Vieira et al, Clin Pharmacol Ther 2012; Zhao et al, J Clin Pharmacol, 2012

- **It is equally important to demonstrate**
  - **Model plausibility with regard to physiology and drug ADME**

    sources, justifications, assumptions
  - **visual inspection of the simulation results against observed data**

    curve shape, match of profiles from multiple studies with population simulations

Verification of PBPK Models through Predict-learn-confirm: An Ongoing Process for Both Drug and System Components

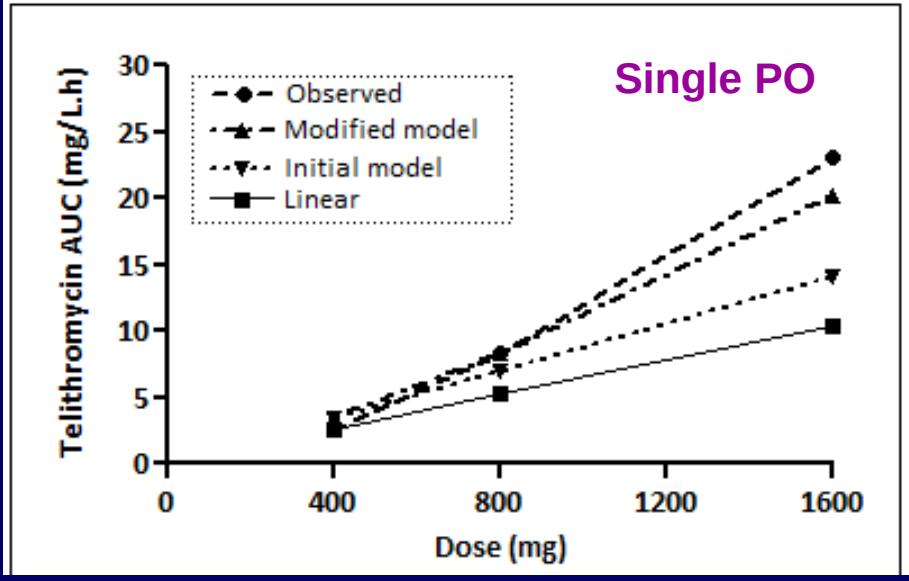
- ✓ Like any model, PBPK is built for purpose
- ✓ Comparing plasma PK profiles is not sufficient to validate a drug PBPK model

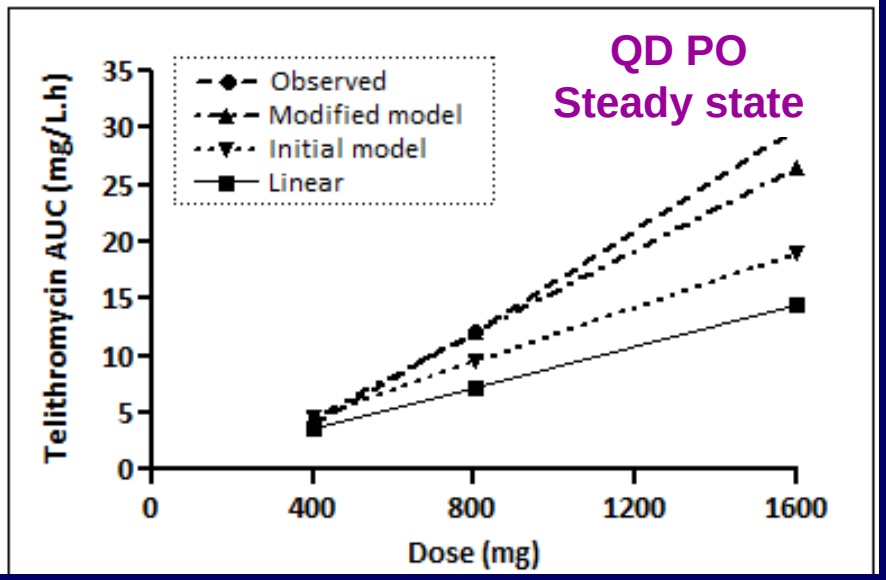
PK Non-linearity

*What can we **LEARN** from nonlinear PK?*

*Can PBPK model integrating nonlinear PK **PREDICT** DDI?*

LEARNING Nonlinear PK through PBPK



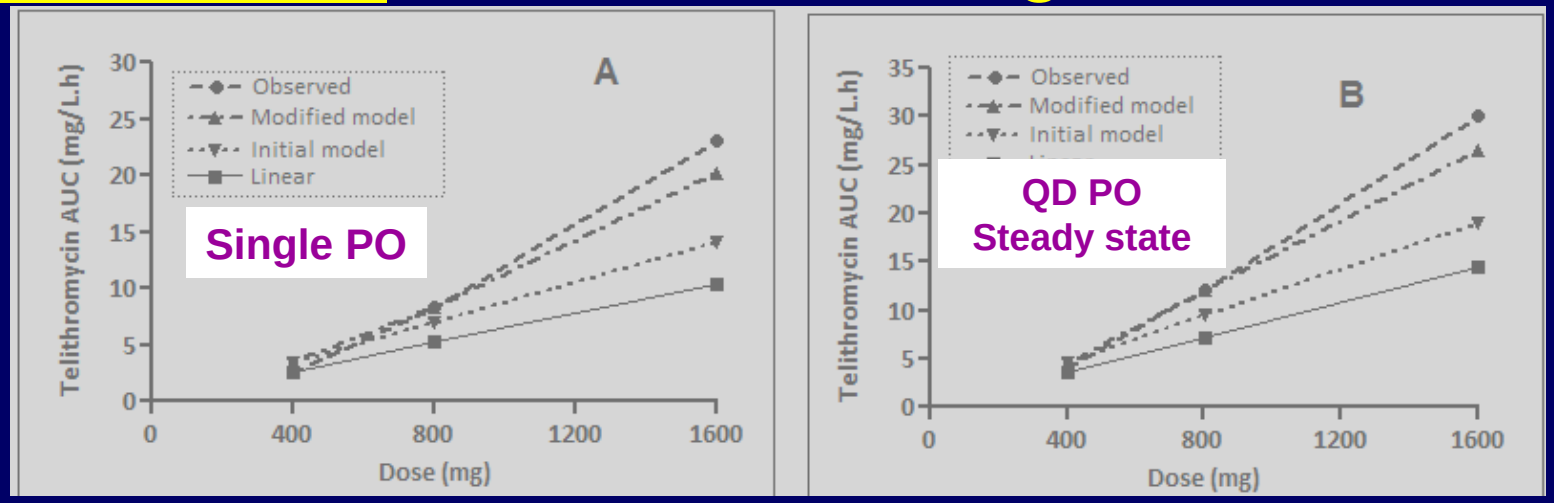


Vieira et al, Clin Pharmacol Ther, 2012

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 Integrating Nonlinear PK
PREDICTED DDI Without Using Known DDI Data

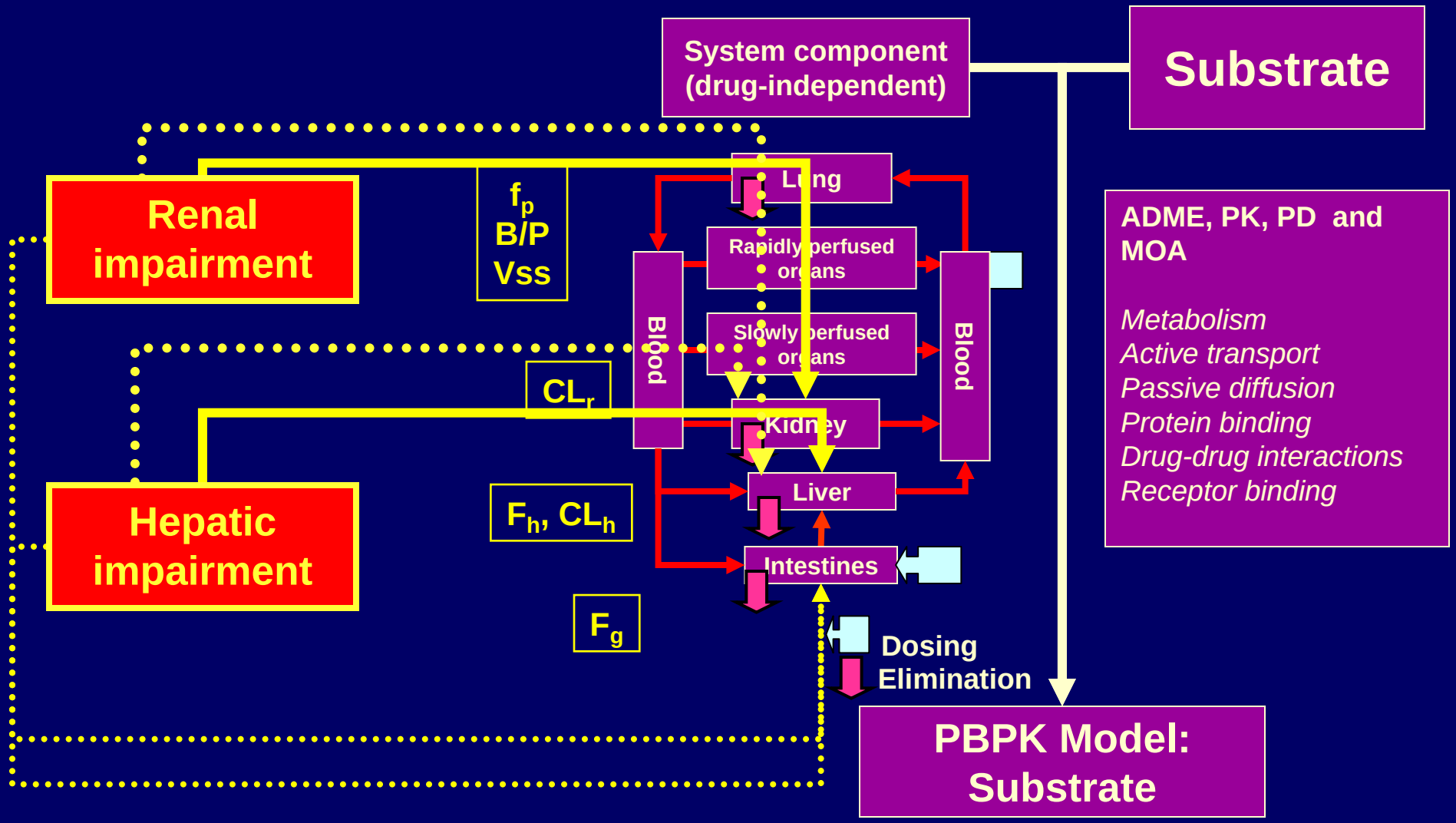


Vieira et al, Clin Pharmacol Ther, 2012

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*

Organ Impairments



Parameters altered by Organ impairment: importance of "INTERPLAY"

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 m^2)	
		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	44.9 [205]	41.6 [136,137,205]	37.6 [136,137,205]
F	41.8 [205]	38.8 [136,137,205]	35.0 [136,137,205]
Hematocrit (%) M	43.0 [43]	39.7 [43]	36.5 [43]
F	38.0 [43]	33.2 [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

CONFIRMING the Effect of Renal Impairment on Hepatic Pathways via PBPK

Compound (% CL by kidney)	Observed $AUCR_{Severe\ RI/Normal}$	PBPK[a] Predicted $AUCR_{Severe\ RI/Normal}$
Sildenafil (<1%)	**2.0[b]** (Mild: 0.9; Moderate: 1.2)	**2.2**
Repaglinide (<1%)	**SD: 2.7; MD: 3.0[c]** (Mild/Moderate: SD: 1.8; MD1.6)	**SD: 2.5; MD: 2.3**
Telithromycin (~20%)	**1.9[d]** (Mild: 1.4; Moderate: 1.2)	**1.6**

a. SimCYPV10.10; b. Muirhead. *Br. J.Clin.Pharmacol.* 2002; c. Marbury. *Clin.Pharmacol.Ther.* 2000; d. Shi, *Int.J.Clin.Pharmacol.Ther.* 2005

Zhao P, et al, J Clin Pharmacol 2012

PREDICTING Effect of Renal Impairment And DDI in The 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

Grillo et al, Biopharm Drug Dispo, 2012

LEARNING time-dependency through PBPK

Pediatrics

Geriatrics

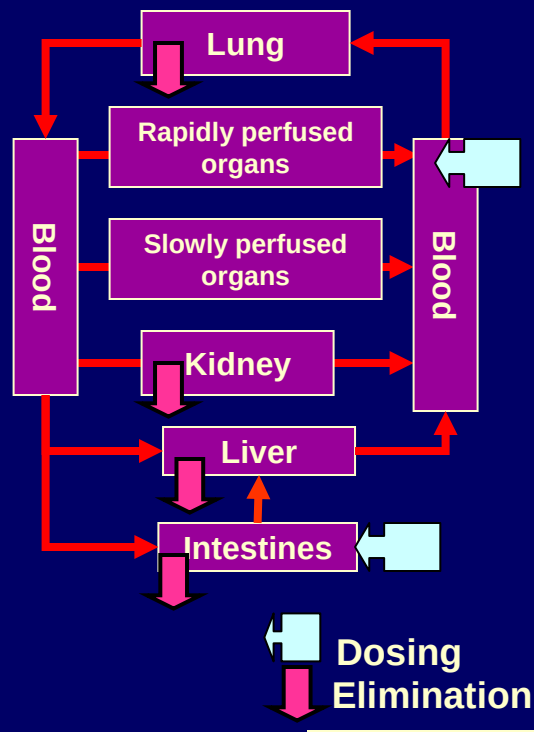
Pregnancy

f_p
B/P
Vss

CL_r

F_h, CL_h

F_g

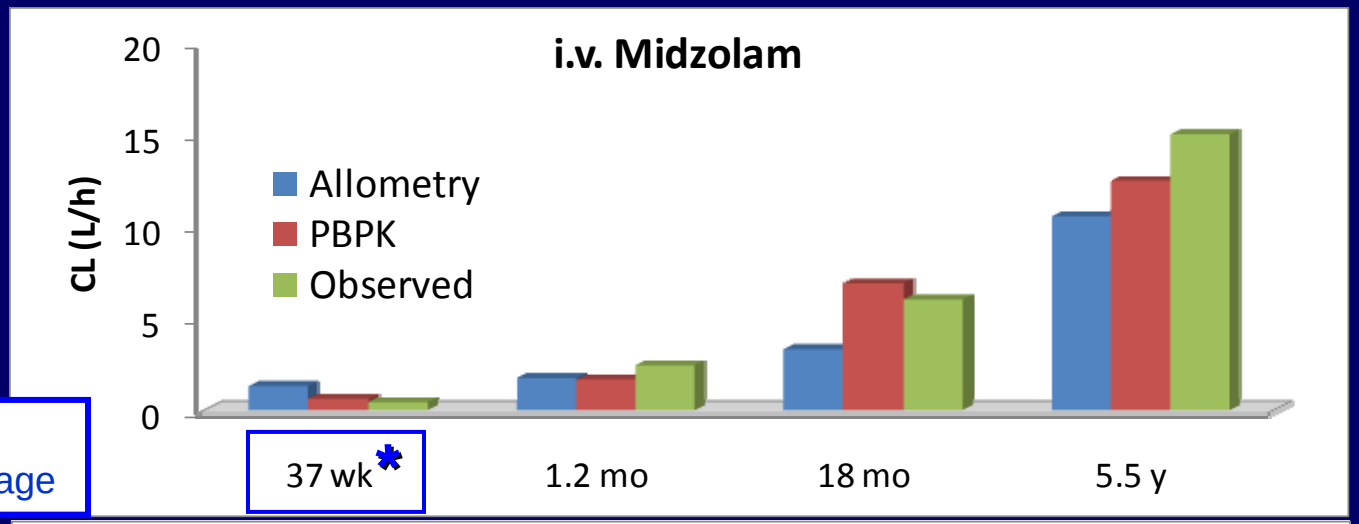


ADME, PK, PD and MOA

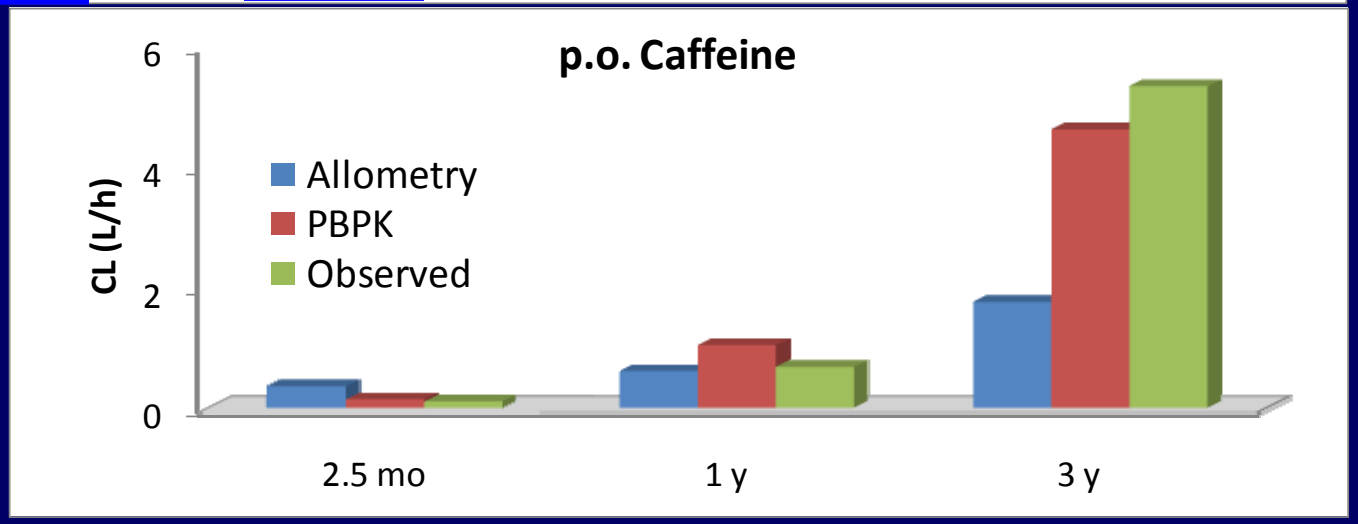
Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

Parameters altered longitudinally

Clearance Prediction Needs To Be Tailored To Individual Drug



* Post-conceptional age



Modified from Johnson et al, Clin Pharmacokinet, 2006

Conclusions

- PBPK model integrates knowledge in drug disposition, DDI mechanisms, and the effect of patient factors (disease, age, genetics), and can be applied to quantitatively evaluate intrinsic and/or extrinsic factors

- For PBPK of each drug, “predict-learn-confirm” verifies the approach in general, and improves our understanding of the interaction between the drug molecule and the system

- PBPK model should be continuously updated for enhanced model confidence in predicting <u>unknown</u> clinical situations

Acknowledgements

FDA Office of Clinical Pharmacology

Scientific Interest Group (PBPK-SIG)

- Formed March 2009
- Steering committee:, Drs. Joe Grillo, Lei Zhang, Ping Zhao
- Dr. Manuela Vieira (University of Florida, FDA Critical Path Fellow)
- Mentors: Drs. Shiew-Mei Huang and Larry Lesko

External collaborators

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