Experience In Using PBPK Models in Clinical Pharmacology Reviews

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Mar 19, 2012 AIMBE/NIH Summit on Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process

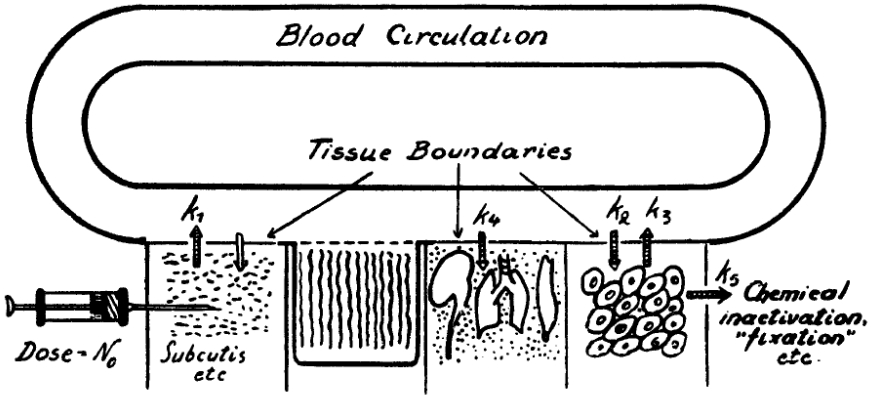
The Views expressed in this presentation do not reflect the official policy of the FDA

Outline

- Why PBPK
- Application of PBPK in clinical pharmacology review

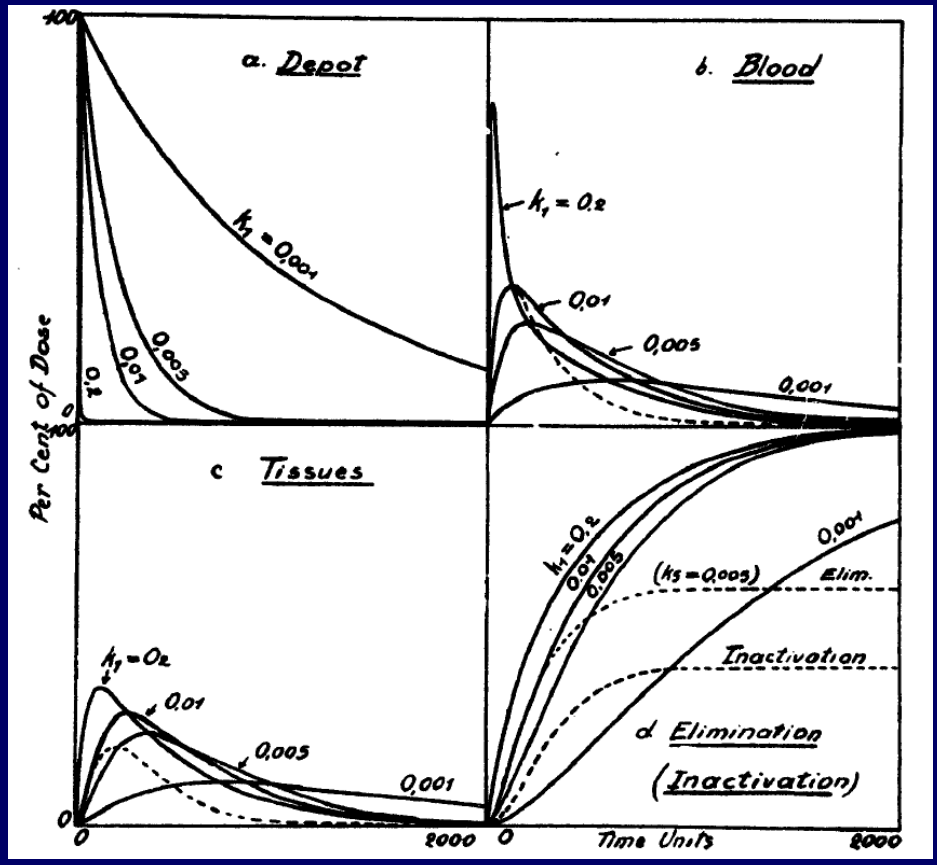
Physiologically-based Pharmacokinetic models (PBPK)

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

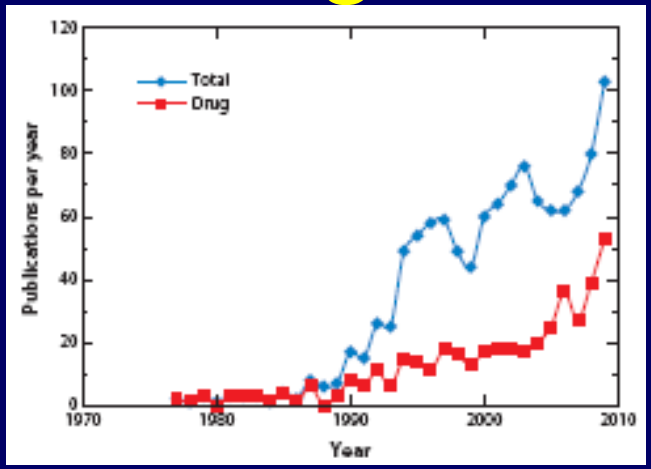
Effect of absorption kinetics



Teorell, Arch Intern Pharmacodyn, 1937

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

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*

From the Office of Clinical Pharmacology, FDA--

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

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*

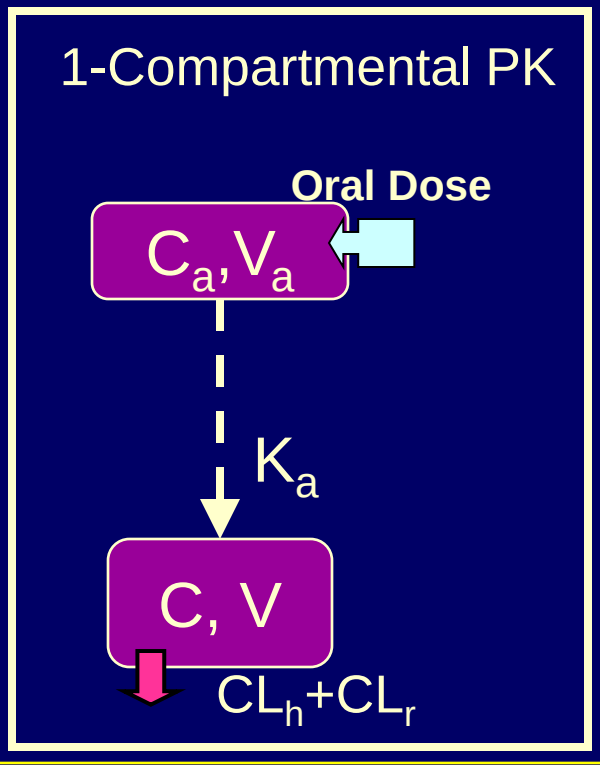
De LT Vieira M, Zhao P, Gil Berglund E, et al, Predicting Drug Interaction Potential by Using a Physiologically-based pharmacokinetics (PBPK) Model: Case Study of Telithromycin, a Time-Dependent CYP3A inhibitor. *Clin Pharmacol Ther, (in press)*

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

Huang S-M, Rowland M, Application of Physiologically-based pharmacokinetics Modeling in Regulatory Review, *Clin Pharmacol Ther, 2012*

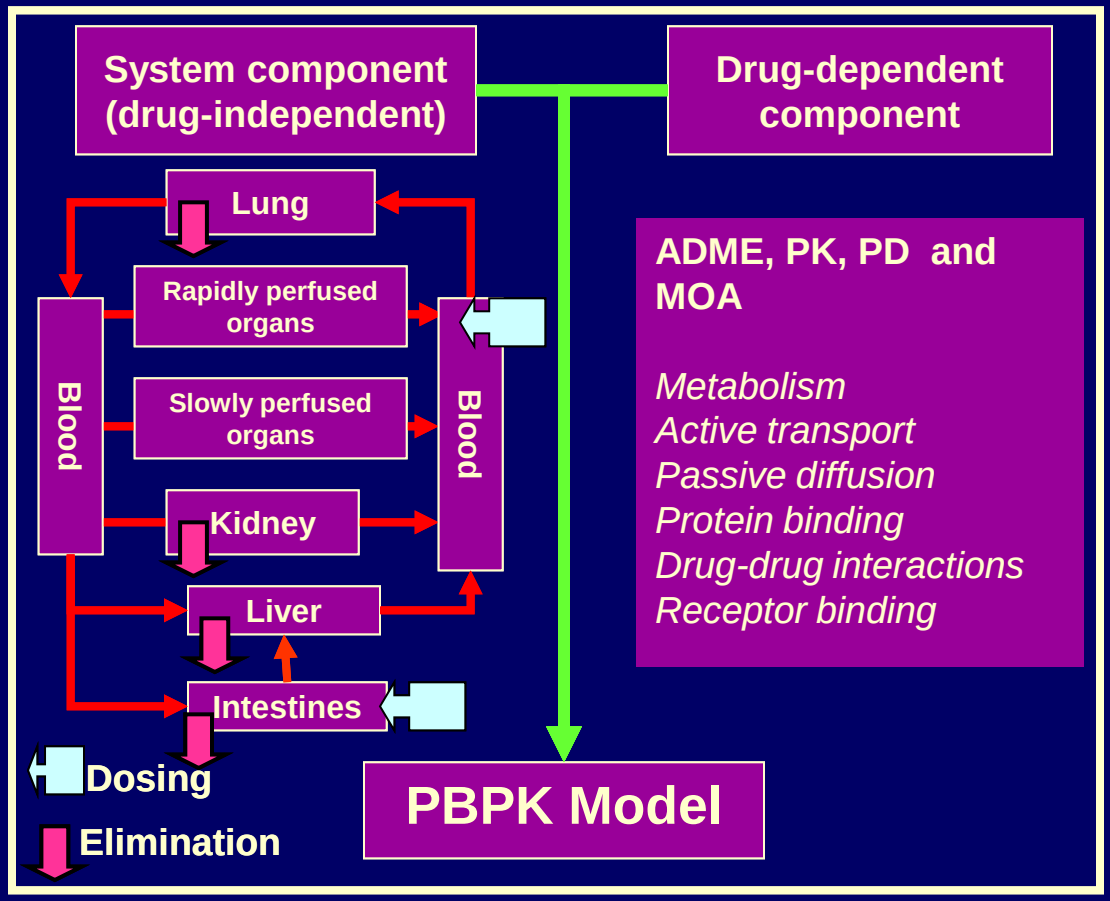
Grillo JA, Zhao P et al, Utility of a physiologically–based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug–drug–disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice, *Biopharm Drug Dispo, 2012*

Can Model Provide Desired Insights?



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

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

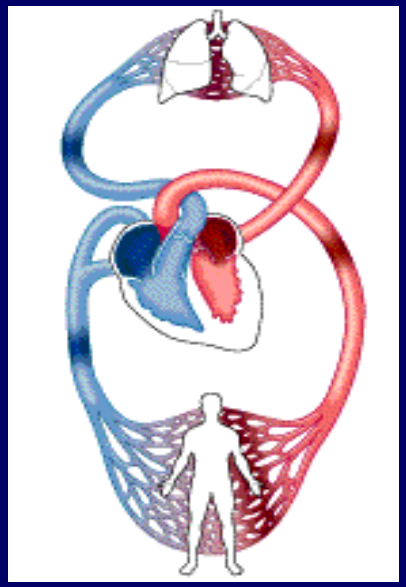


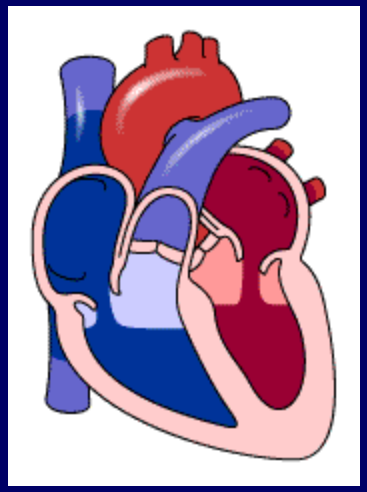
$$C = \frac{K_a * Dose}{V * (Ka - \frac{CL_h + CL_r}{V})} * (e^{-\frac{(CL_h+CL_r)}{V}*t} - e^{-K_a*t})$$

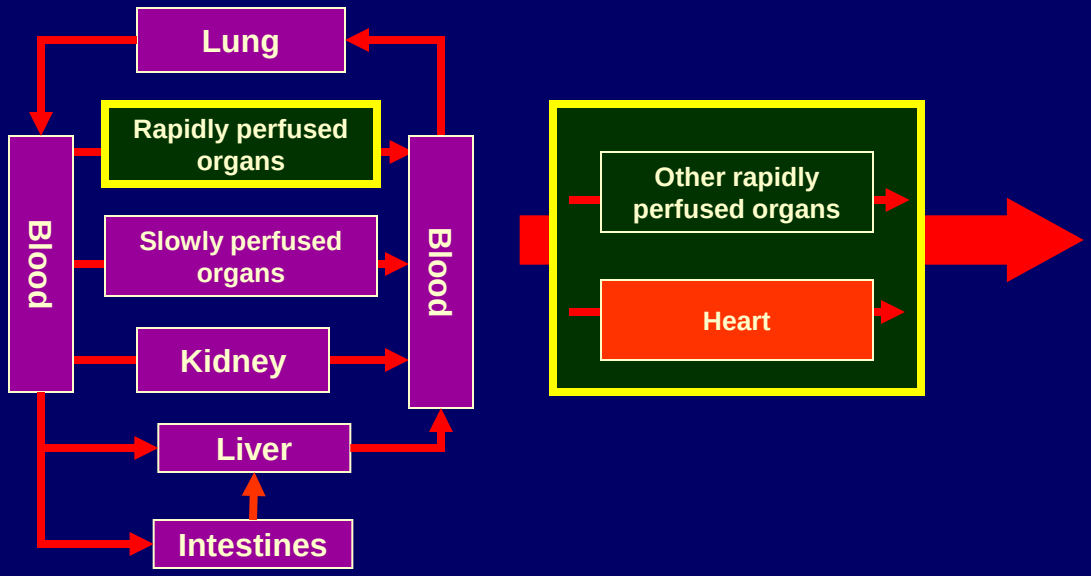
C_{plasma}
C_{liver}
C_{kidney}
C_{muscle} … …

And…

PBPK: Systems Clinical Pharmacology

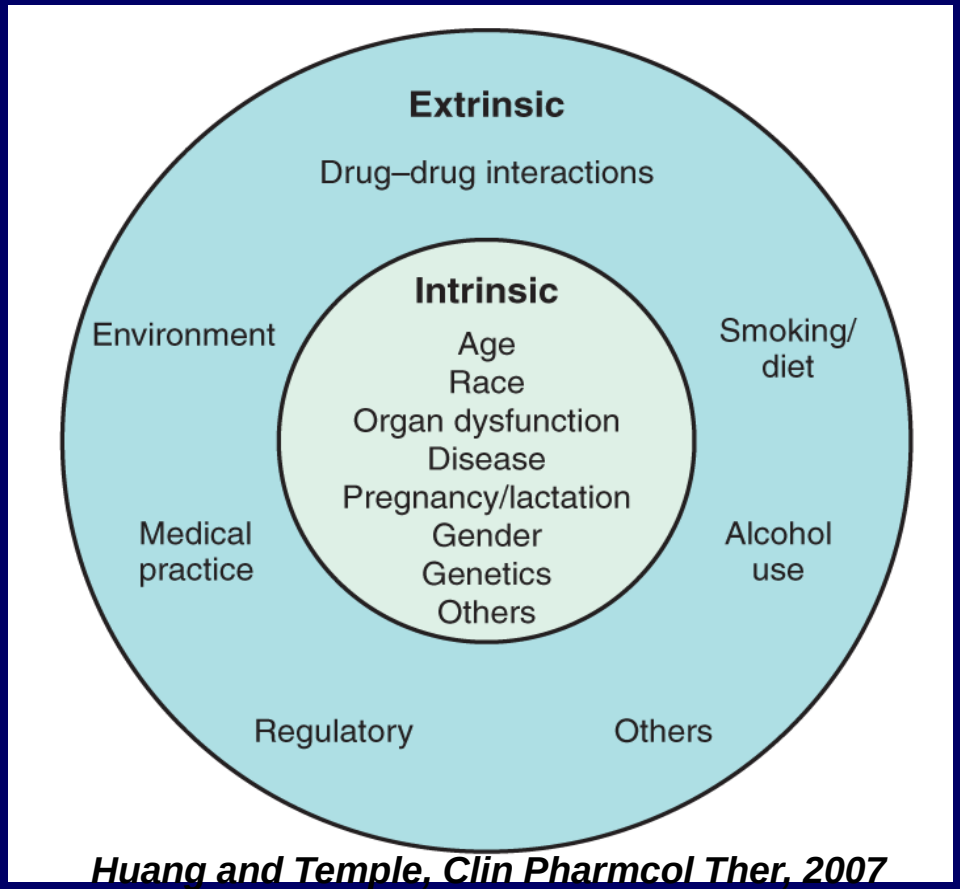






Clinical Pharmacology

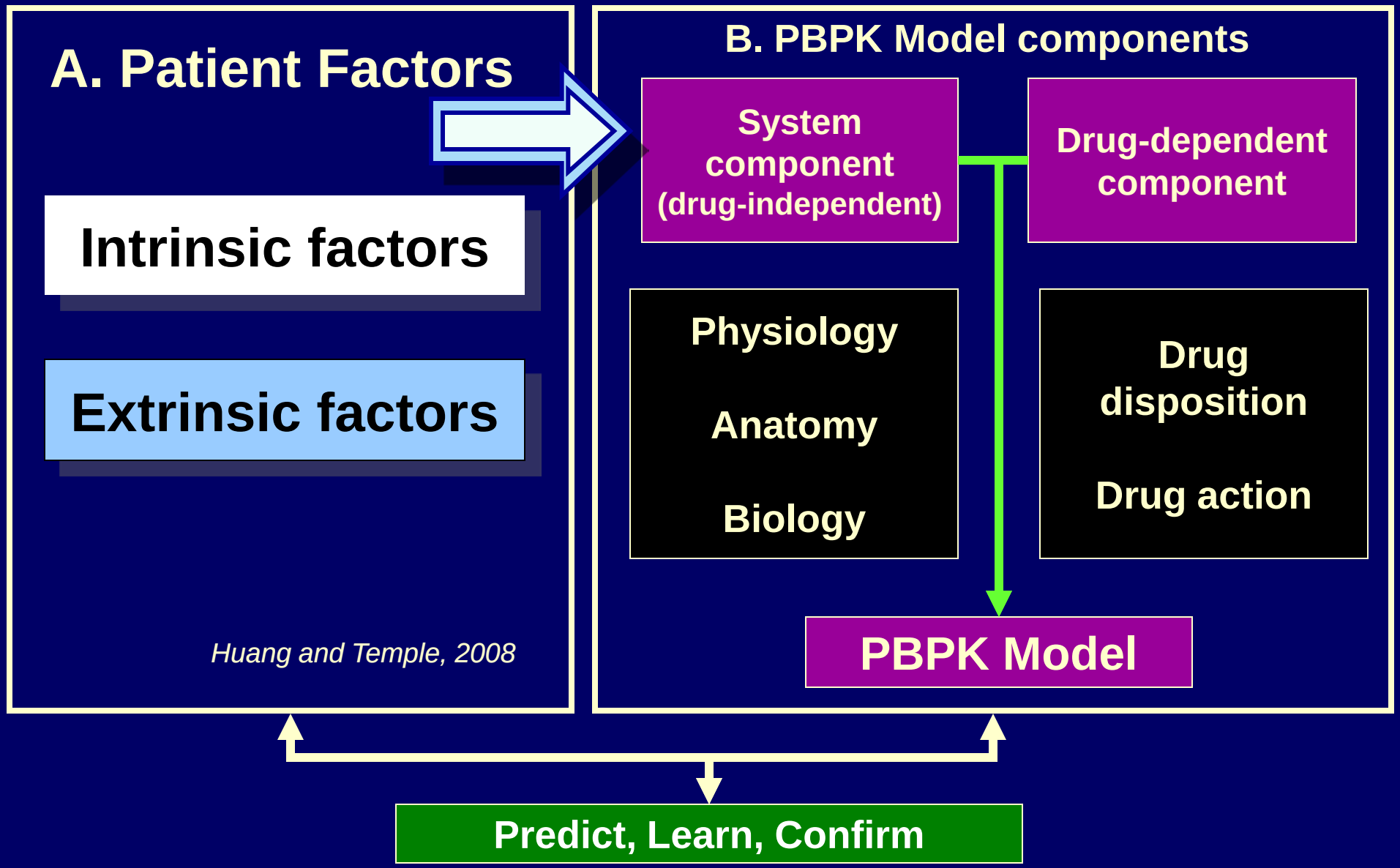
- Central role: to assess PKPD in specific patient groups
- To make more informed decision on drug dosing
- To guide our decisions:



Huang and Temple, Clin Pharmcol Ther, 2007

- ***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



Adapted from Zhao P, et al Clin Pharmacol Ther 2011

Outline

- Why PBPK
- Application of PBPK in clinical pharmacology review

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

ADME, PK, PD and MOA

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

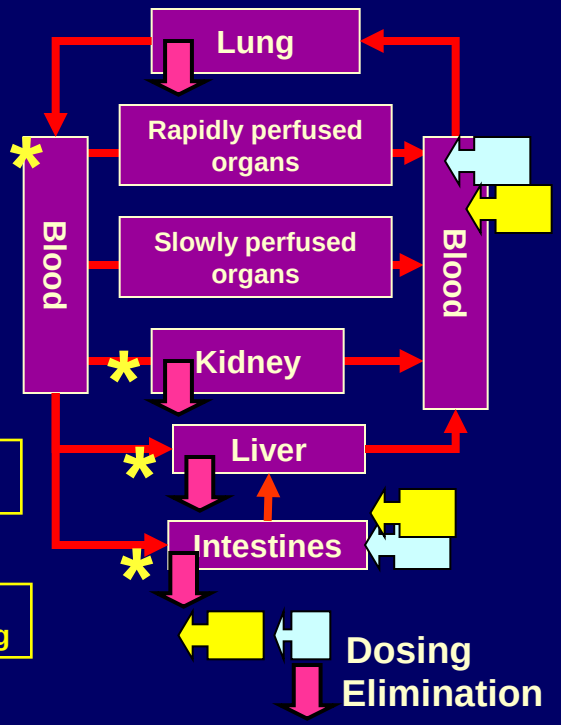
System component (drug-independent)

f_p
B/P
Vss

CL_r

F_h, CL_h

F_g



Substrate

ADME, PK, PD and MOA

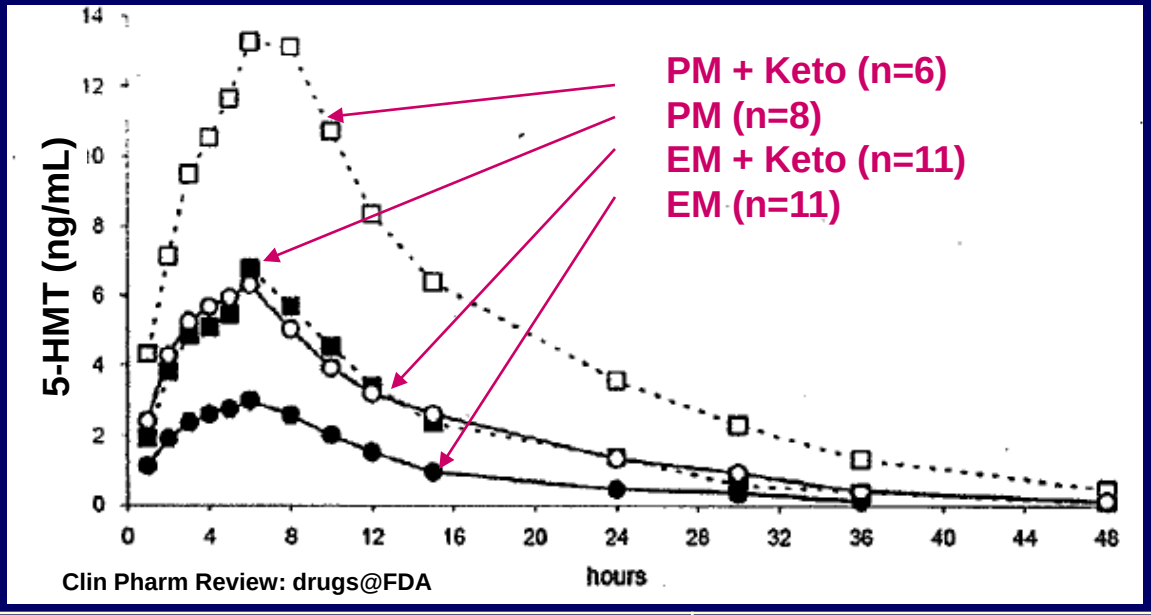
Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

PBPK Model: Interacting Drug

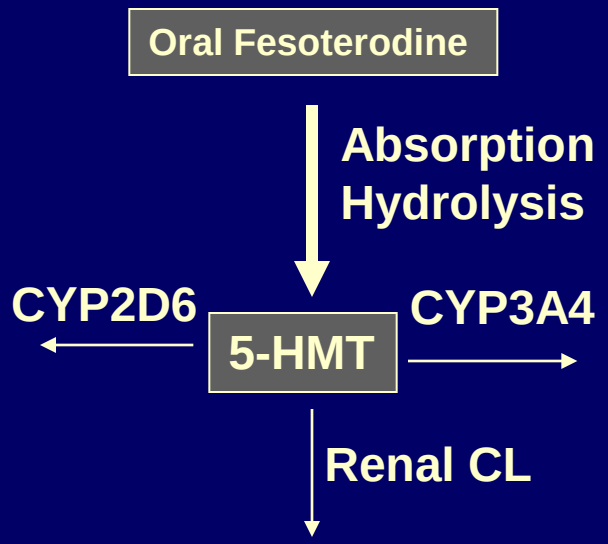
PBPK Model: Substrate

Parameters can be altered by DDI

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



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	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.

Apparaju et al, DCP3; Vieira et al, ASCPT Annual Meeting, National Harbor, MD, March 2012

Fesoterodine case
Polymorphic vs Non-polymorphic enzyme ~ 1:1

Each contributes > 25% CLs
Question #1 for Audience, with available clinical data, can PM + fluconazole be predicted?

No. Clinical study should be conducted _____
Yes. Prediction can be used to design clinical study _____
Yes. Clinical study is not necessary _____

	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

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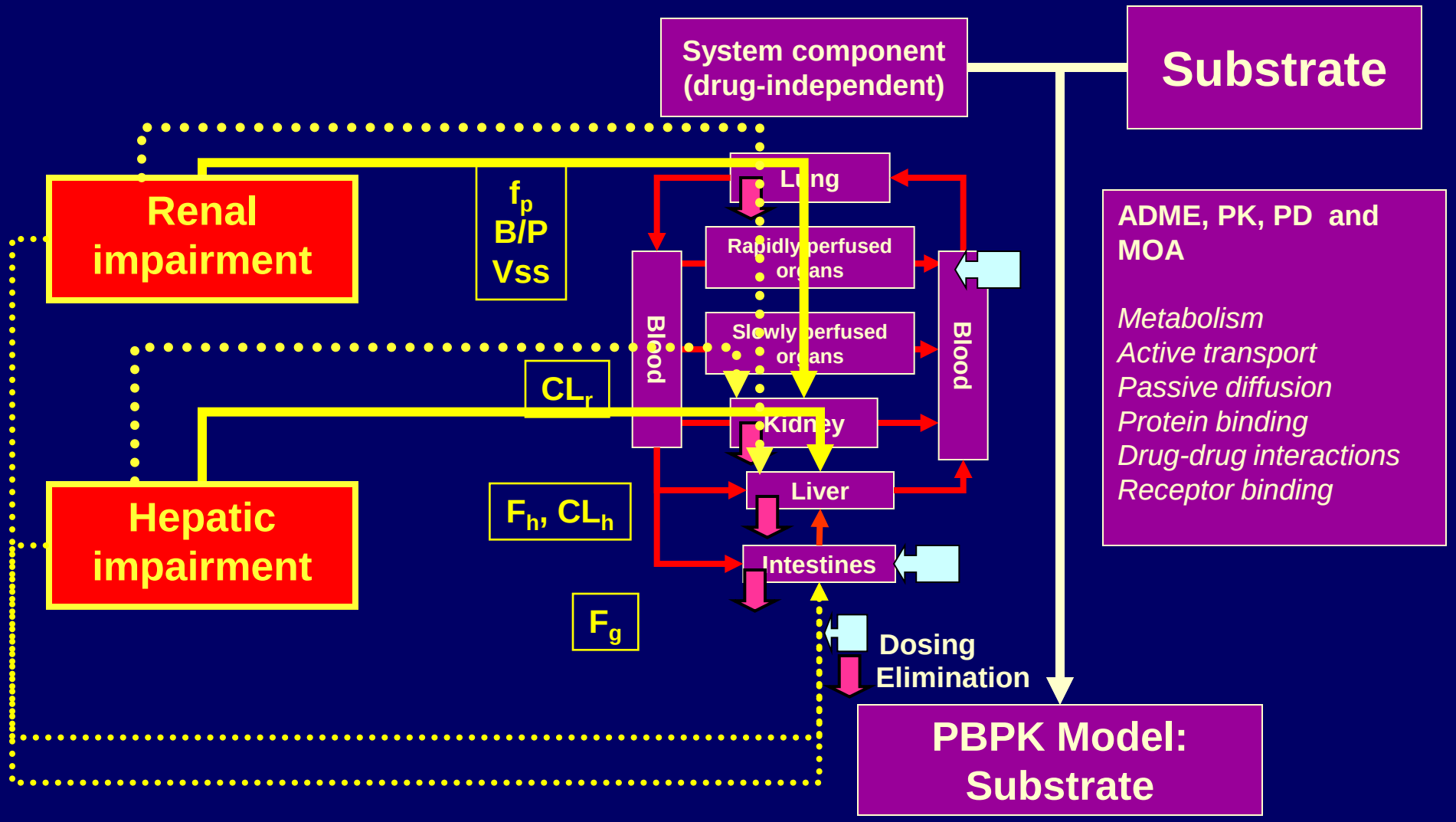
Organ Impairments



Parameters altered by Organ impairment: importance of "INTERPLAY"

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

Johnson, Clin Pharmacokinet, 2010

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_{villi} (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.

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 chose to study the combined effect (on-going)

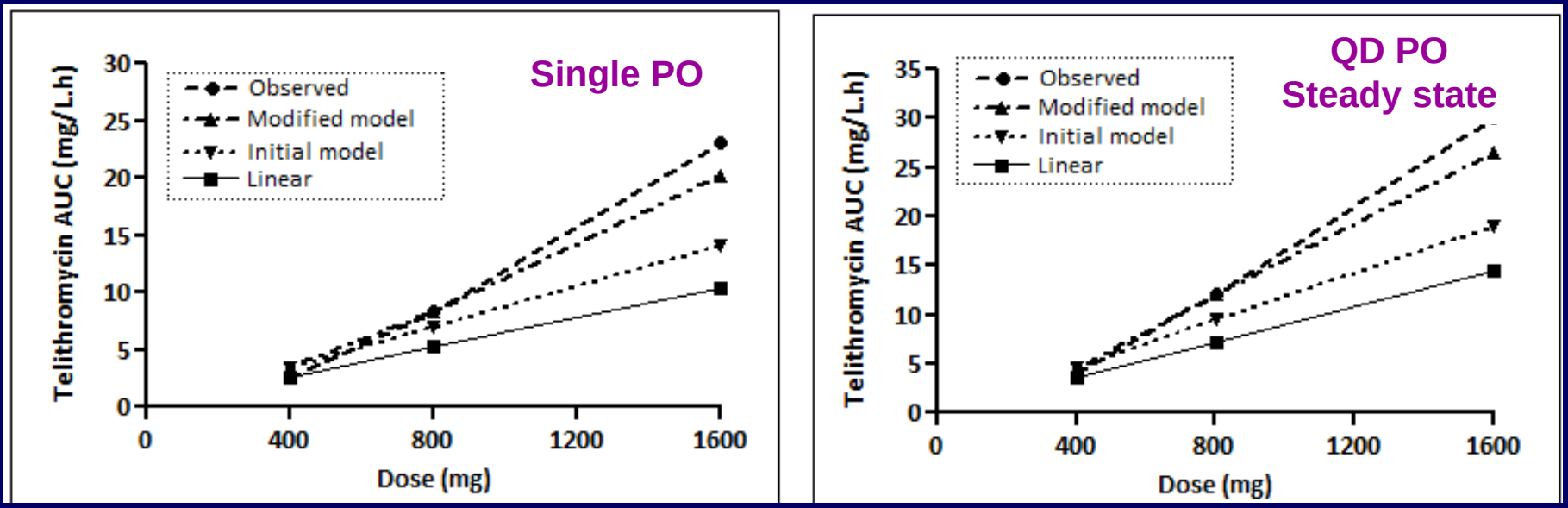
Grillo et al, DCP5

Grillo et al, Biopharm Drug Dispo, 2012

PK Non-linearity

What is the drug-drug interaction potential of an investigational drug that demonstrates dose and time dependent PK?

DDI Caused by Dose- and Time-dependent PK

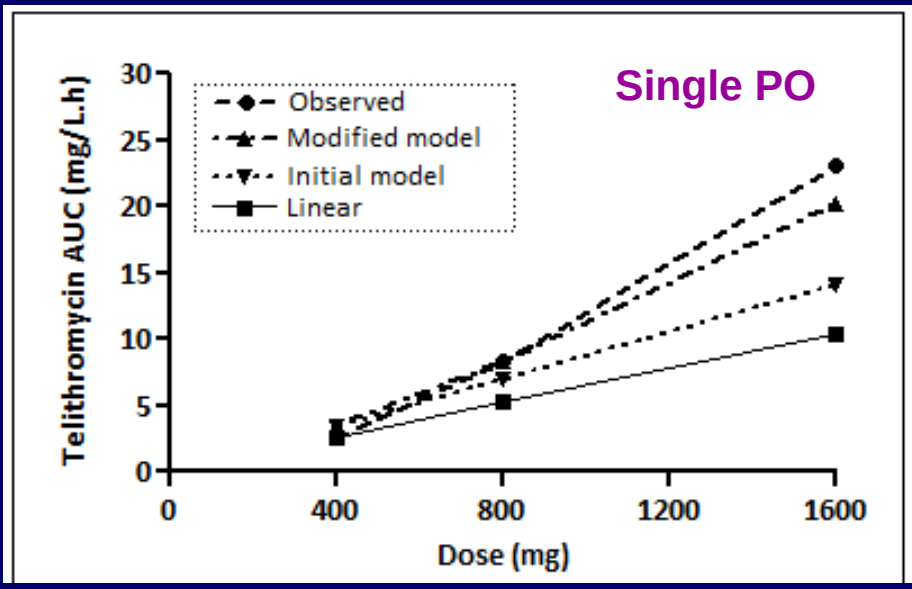


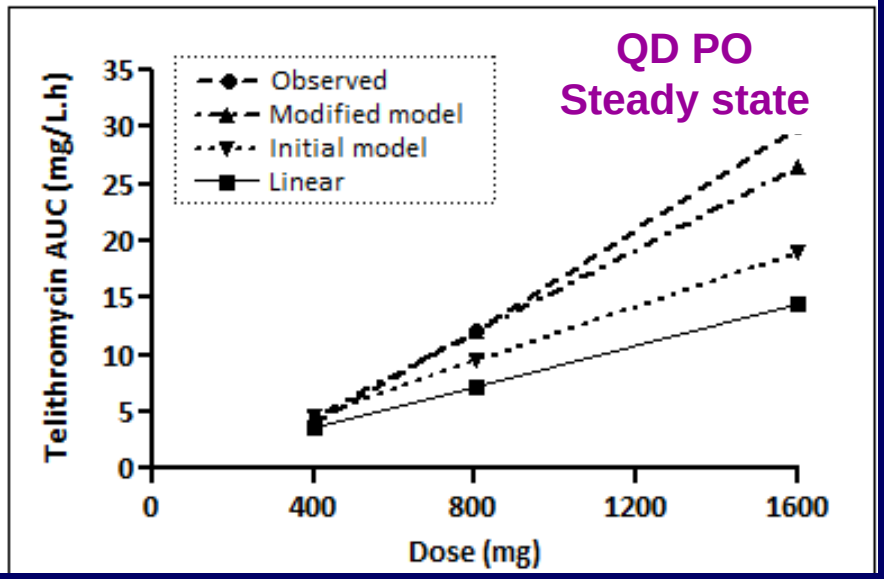
Vieira et al, Clin Pharmacol Ther, In press

Evaluation of sources of nonlinearity using PBPK

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

DDI Caused by Dose- and Time-dependent PK





Vieira et al, Clin Pharmacol Ther, In press

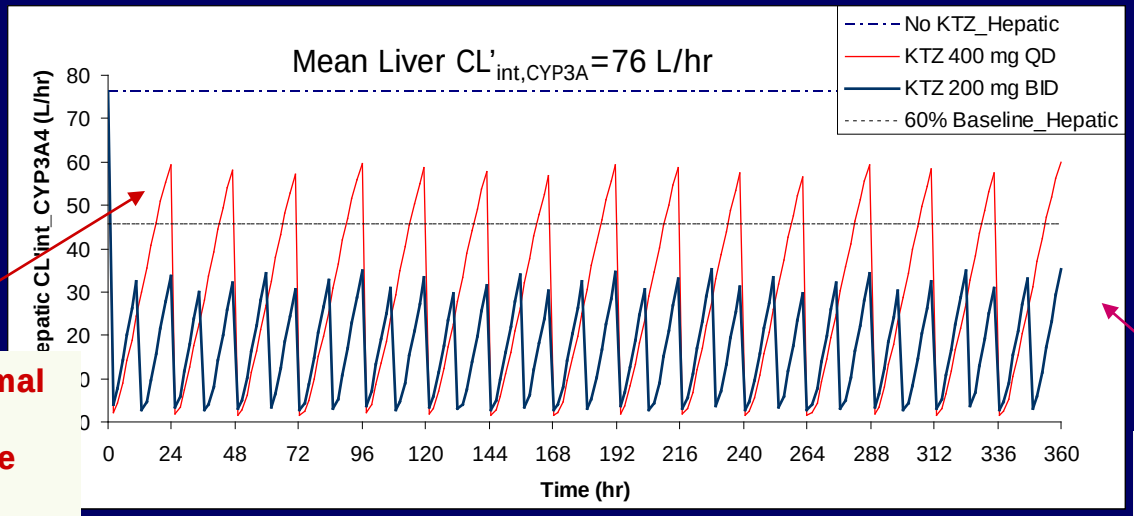
Effect of telithromycin (p.o. 800 mg once daily)

	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*

Study Design

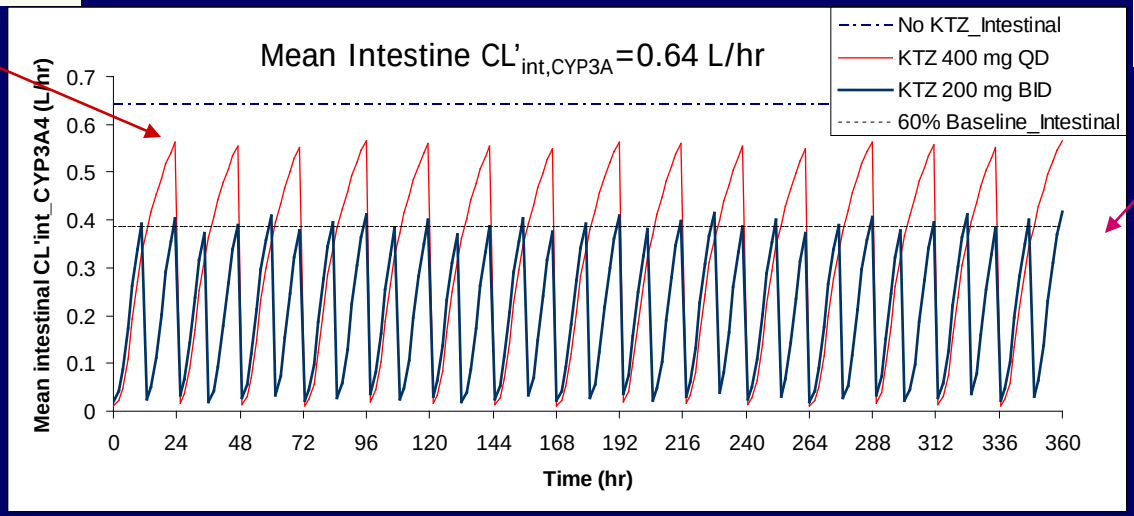
Should inhibitor and substrate be given together?
How does drug-drug interaction or organ impairment affect metabolite exposure?

PBPK Provides Insights of Mechanism and Time-variation



QD400 achieved maximal inhibition but returned close to baseline before the next dose

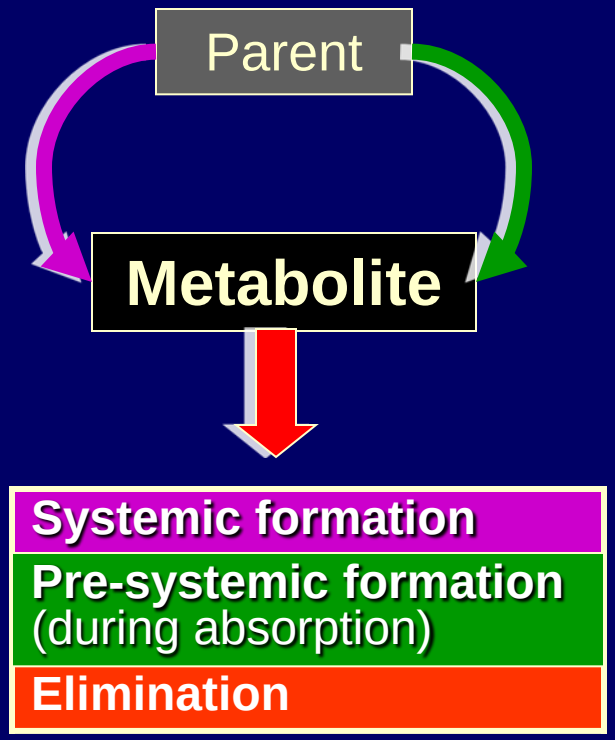
BID200 generally maintained >40% inhibition

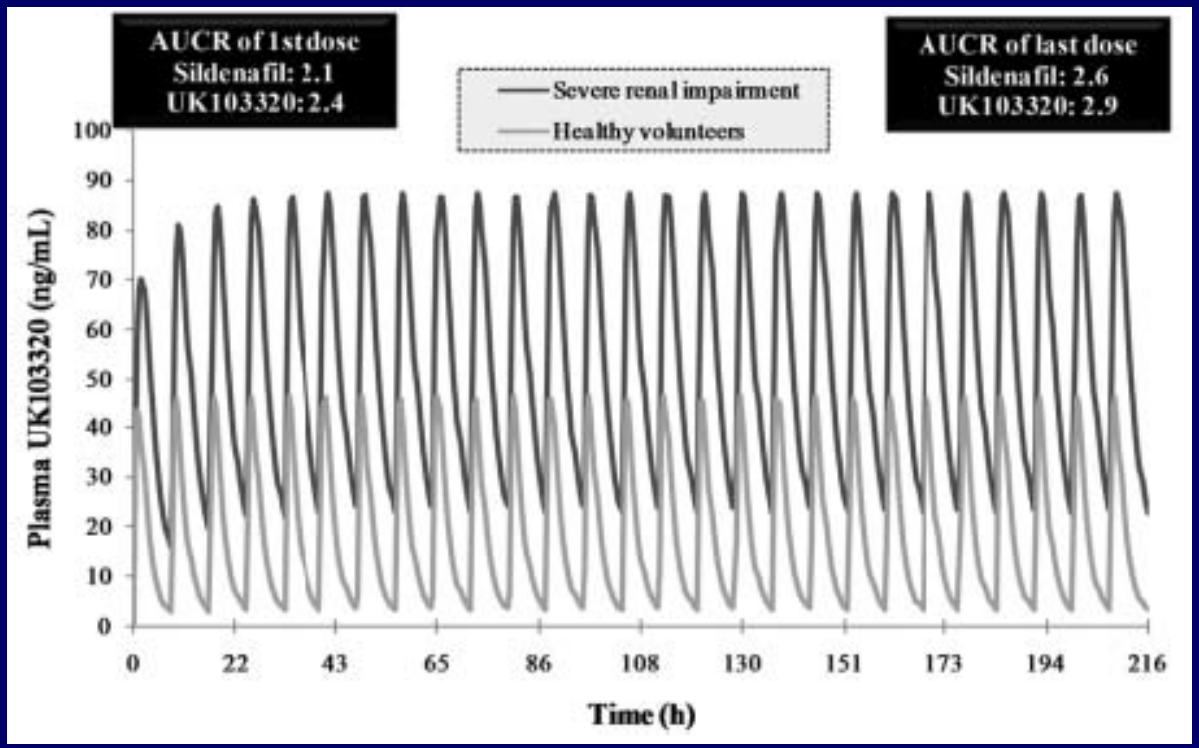


Zhao et al, J Clin Pharmacol, 2009

❖ ***Should ketoconazole be administered 400 mg QD or 200 mg BID?***

Model-based Design of Clinical PK Studies

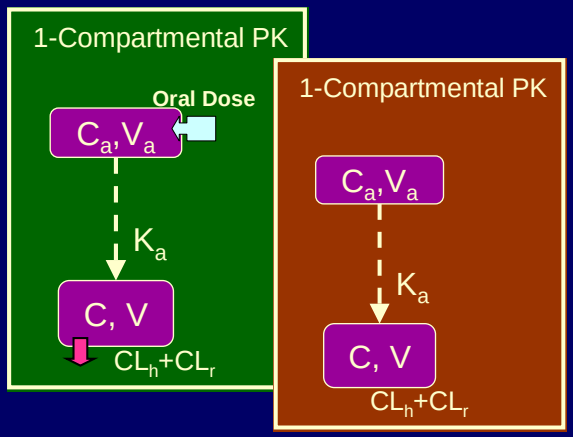


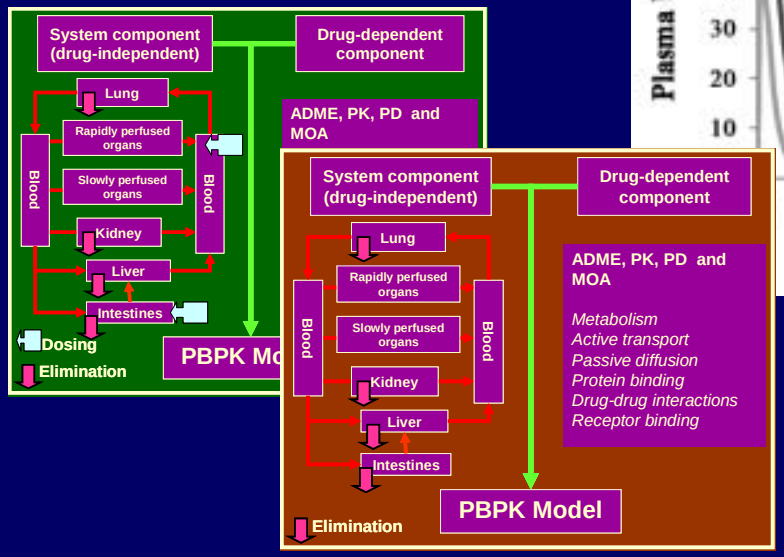


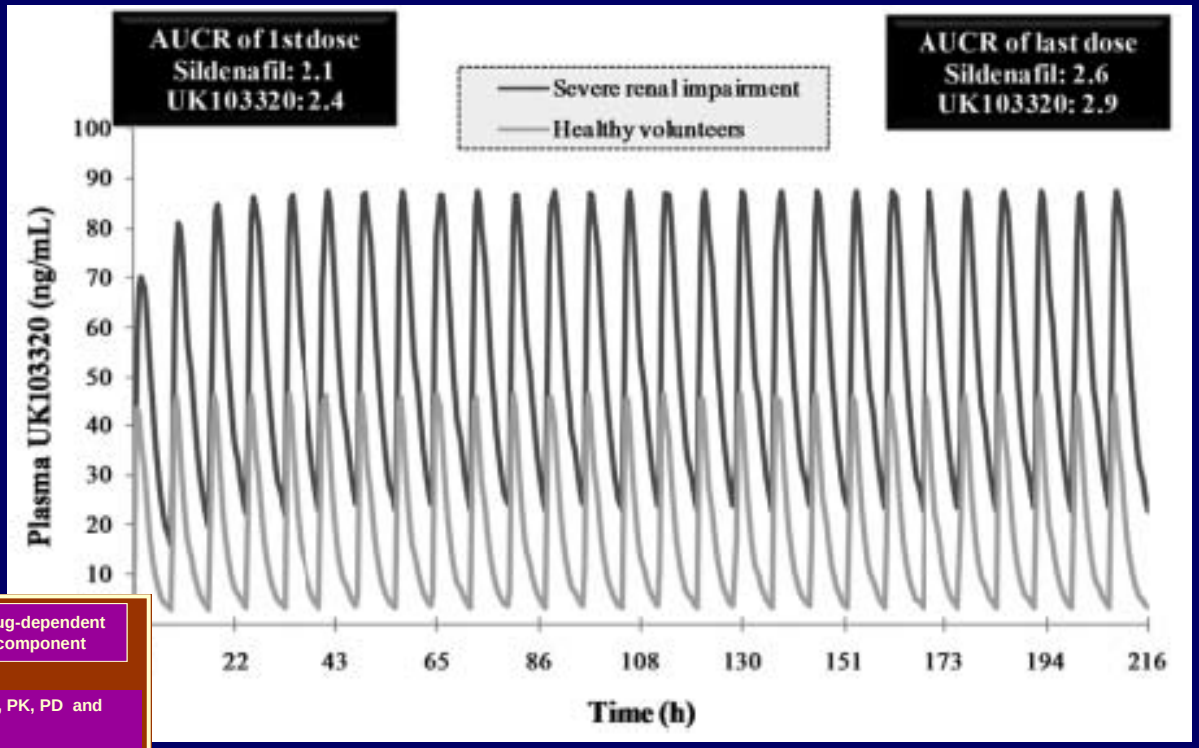
Zhao et al, J Clin Pharmacol, 2012

- ***How metabolite exposure changes when multiple pathways are affected by multiple patient factors?***
- ***What if***  ***becomes*** ***?***
- ***Distribution of metabolite?***

Model-based Design of Clinical PK Studies







Zhao et al, J Clin Pharmacol, 2012

Parent model

Metabolite model

❖ ***PBPK model generates PK profiles of interested species with greater mechanistic insights***

The Longitudinal Dimension

Pediatrics

Geriatrics

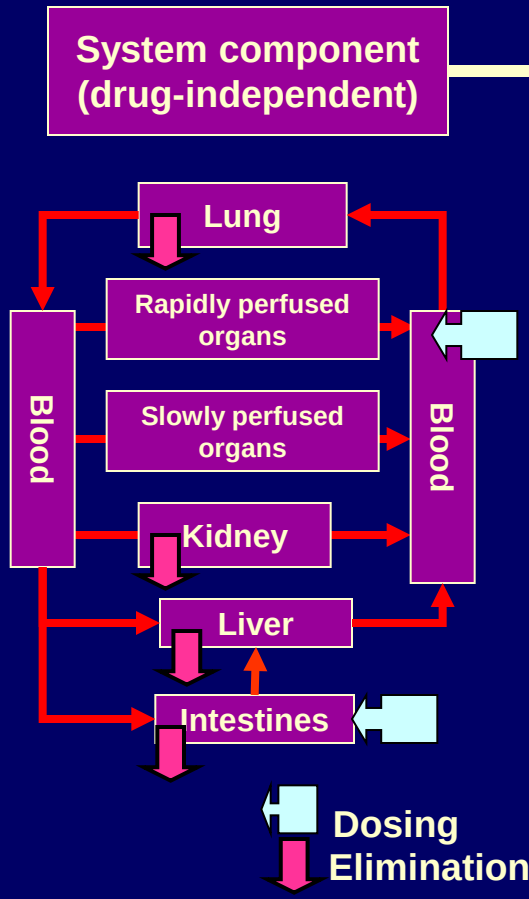
Pregnancy

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

PBPK Model: Substrate

Parameters altered longitudinally

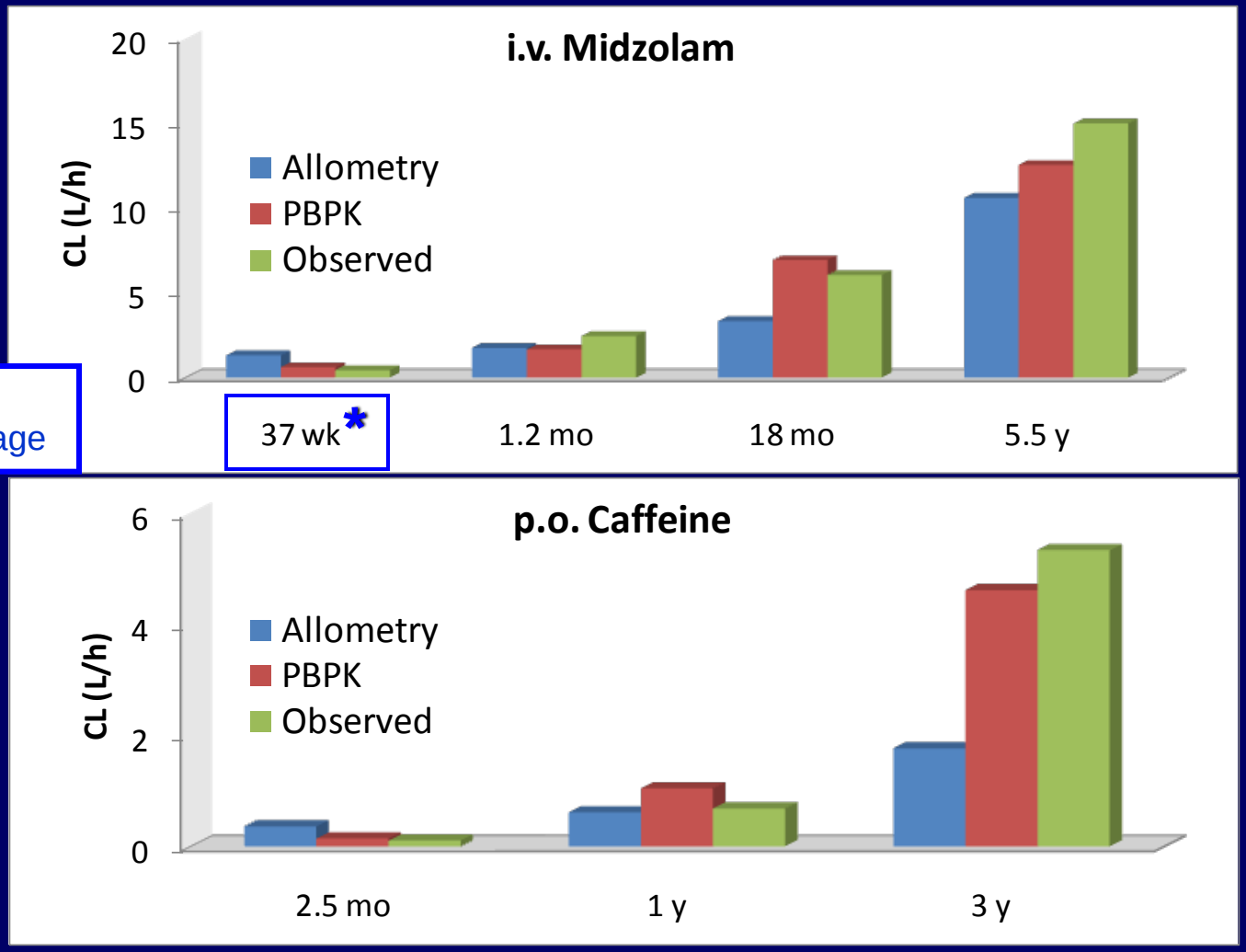
When is PBPK Needed in Pediatric Drug Development?

- **Can we predict PK of an investigational drug in an age group that has NOT been exposed to the drug? (First in Pediatric PK Prediction)**

- **Can the effect of patient factor(s) on drug PK be assumed the same as that in adults?**

  - *Diseases (including organ impairments)*
  - *Drug-drug interactions*
  - *Pharmacogenetics*

Clearance Prediction Needs To Be Tailored To Individual Drug



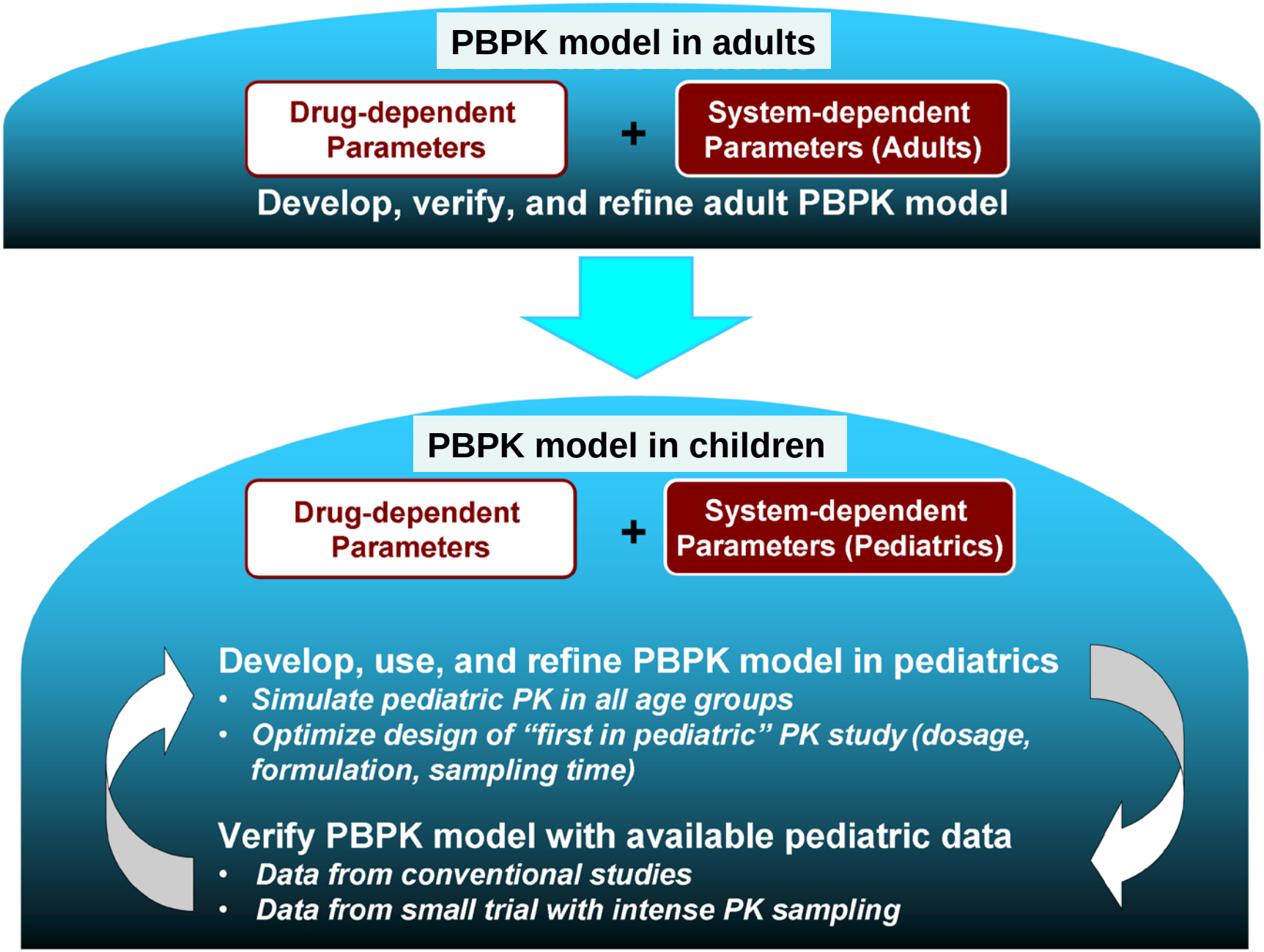
* Post-conceptional age

Modified from Johnson et al, Clin Pharmacokinet, 2006

Pediatric submissions containing PBPK (2009-2011)

	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, In Press



Leong et al, Clin Pharmacol Ther, In Press

Summary: Pediatric PBPK

- PBPK model building requires knowledge of physiology (system) and drug disposition
- Application of a pediatric PBPK model should use existing adult model and integrate/update with current knowledge in ontogeny of physiological processes
- PBPK model should be continuously updated for enhanced model confidence in predicting unknown clinical situations

Basic steps for PBPK analyses

0. Determine Questions that may be addressed by PBPK

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 P, et al, Clin Pharmacol Ther, 2011>

Conclusions

- **PBPK models can be applied to quantitatively evaluate intrinsic and/or extrinsic factors**

  - *Provide full PK profiles of substrate and interacting drug - DDI*
  - *Assess effect of multiple factors*
  - *Optimize study design and data analysis*
  - *Identify knowledge gaps*
  - *Generate hypotheses (for further studies)*

- **It is important to integrate knowledge in mechanisms of DDI and drug disposition, and the effect of organ impairment**

- **It is important to understand the interplay of the intrinsic/extrinsic factors**

- **PBPK model can be continuously updated for enhanced model confidence in predicting unknown 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

Professors Sandy Pang (Toronto), Amin Rostami-Hodjegan (Manchester), Yuichi Sugiyama (Tokyo), and Malcolm Rowland (Manchester); Dr. Eva Gil Berglund (EMA-MPA); Drs. Karen Rowland-Yeo and Masoud Jamei (SimCYP)

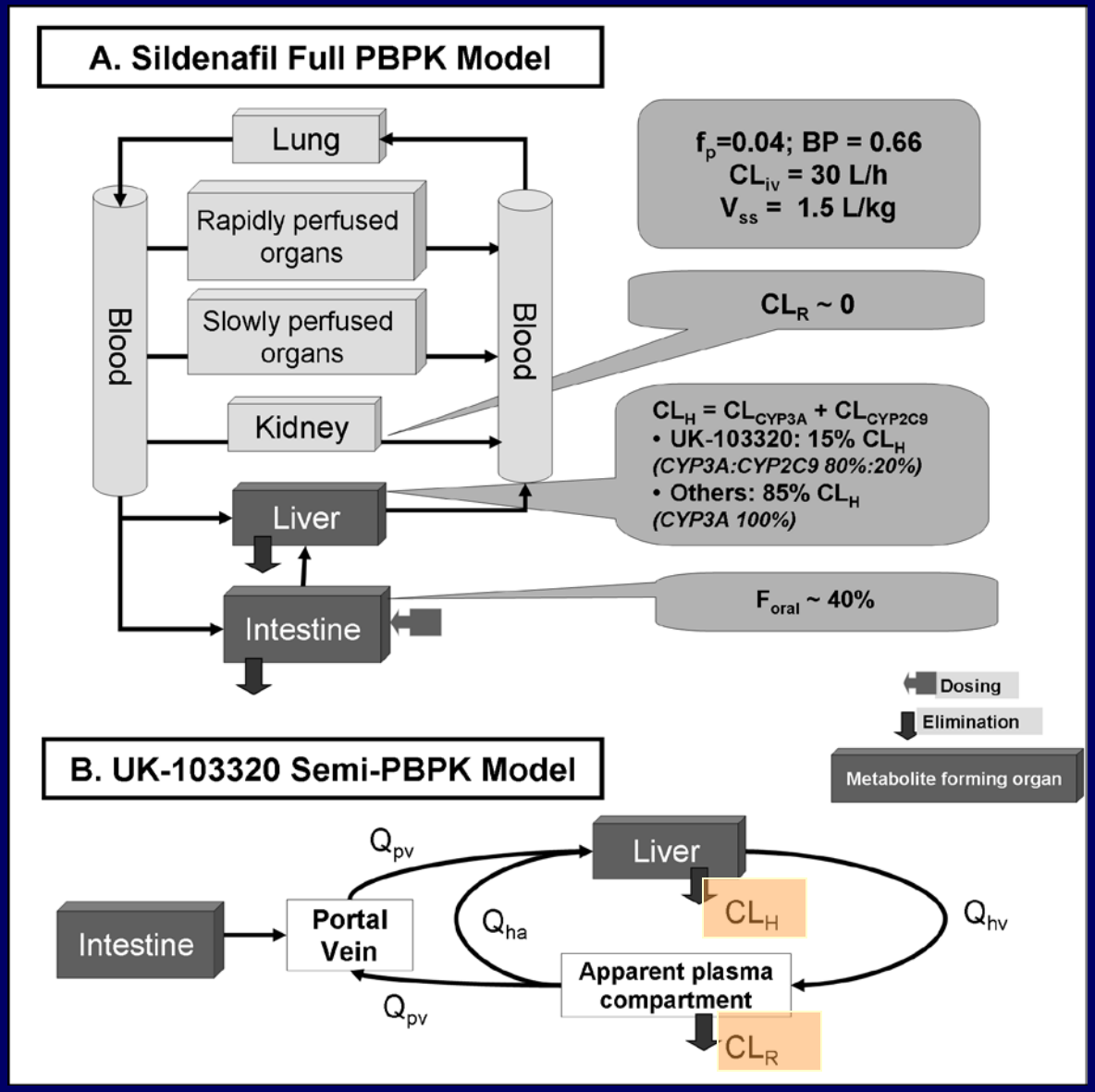
Renal Impairment on Non-renally Eliminated Drugs

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

The Need to Consider Metabolites in RI or DDI



Targeted by RI?

Assuming UK103320 is solely metabolized by CYP3A4

	AUCR of UK103320	
	Severe RI	Inhibition
Obs.	3.0[a]	1.4[b]
Pred.	2.5	5.2

[a]. Muirhead. *Br. J.Clin.Pharmacol.* 2002, with renal impairment

[b]. Muirhead. *Br.J.Clin.Pharmacol.* 2002, using erythromycin

Zhao P, et al, J Clin Pharmacol, 2012

❖ ***Over-predicted DDI: knowledge gap in metabolite disposition?***