Predicting Transporter Drug-Drug Interaction Using PBPK: Impact of Variability in In Vitro Data

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Disclaimer

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

Outline

- Update of DDI guidance on model-based predictions
- Why PBPK
- “Top-down” aspect of PBPK
- Evaluating transporter DDI using PBPK, a process of predict-learn-confirm

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 June 2012
CPMP/EWP/560/95/Rev. 1
Committee for Human Medicinal Products (CHMP)

Guideline on the Investigation of Drug Interactions

Final

Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

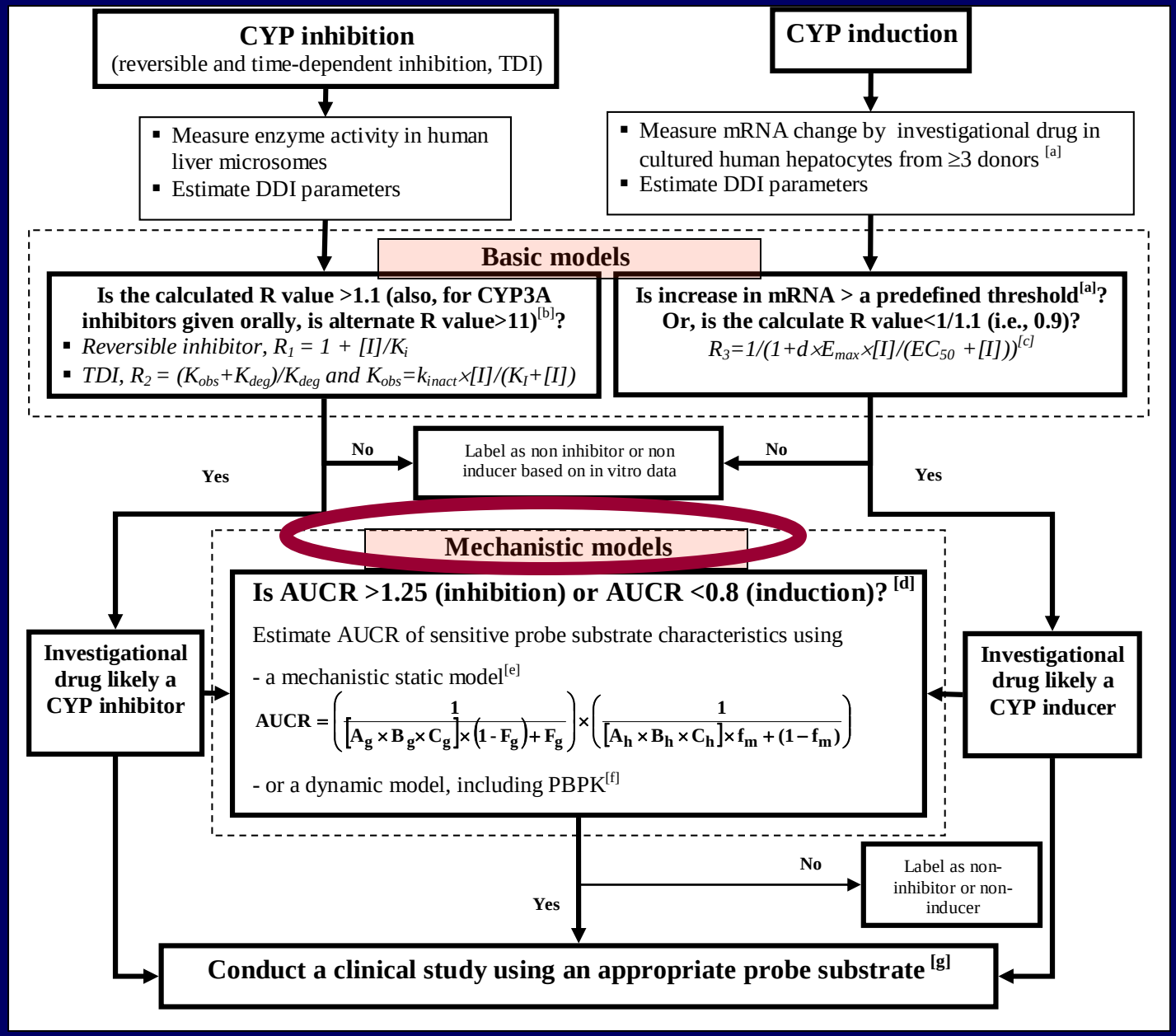
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or Lei Zhang, 301-796-1635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2012
Clinical Pharmacology

General Scheme of Model-Based Prediction: The Investigational Drug (and Metabolite Present at ≥25% of Parent Drug AUC) as an Interacting Drug of CYP Enzymes



Model-based Prediction of DDI for Drug Transporters

- Multiple decision trees provided for major transporters (P-gp, OATP1B1/3, OAT1/3, OCT2, and BCRP) using basic and mechanistic static models
- Complexity recognized in "Complex drug interactions" section, which proposes the use of physiologically-based pharmacokinetic modeling (PBPK)

Complex Drug-drug Interactions

Such "complex drug interaction" scenarios include, but are not limited to:

- Concurrent inhibition and induction of one enzyme or concurrent **inhibition of enzyme and transporter by a drug**
- Increased inhibition of drug elimination by the use of more than one inhibitor of the same enzyme that metabolizes the drug
- Increased inhibition of drug elimination by use of inhibitors of more than one enzyme that metabolizes the drug
- Inhibition by a drug and its metabolite or metabolites, both of which inhibit the enzyme that metabolizes the substrate drug
- Inhibition of an enzyme other than the genetic polymorphic enzyme in poor metabolizers taking substrate that is metabolized by both enzymes
- Use of **enzyme/transporter inhibitors in subjects with varying degrees of impairment of drug eliminating organs** (e.g., liver or kidney)

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- Update of DDI guidance on model-based predictions
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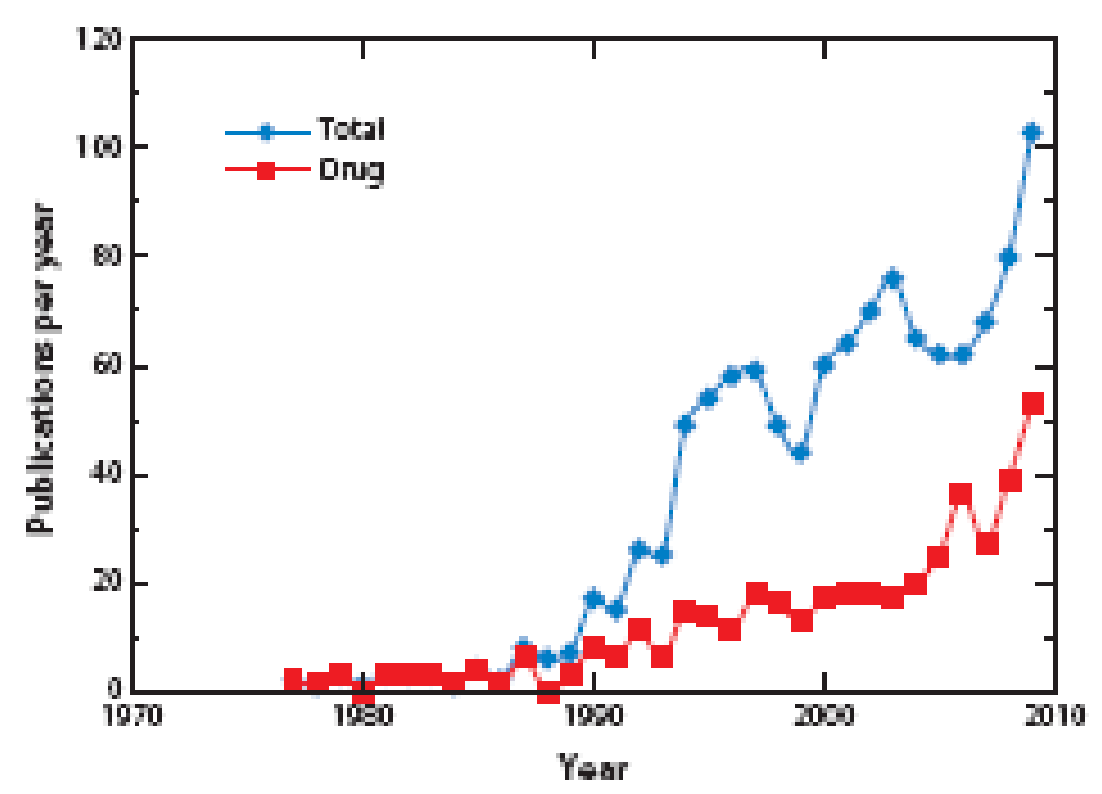
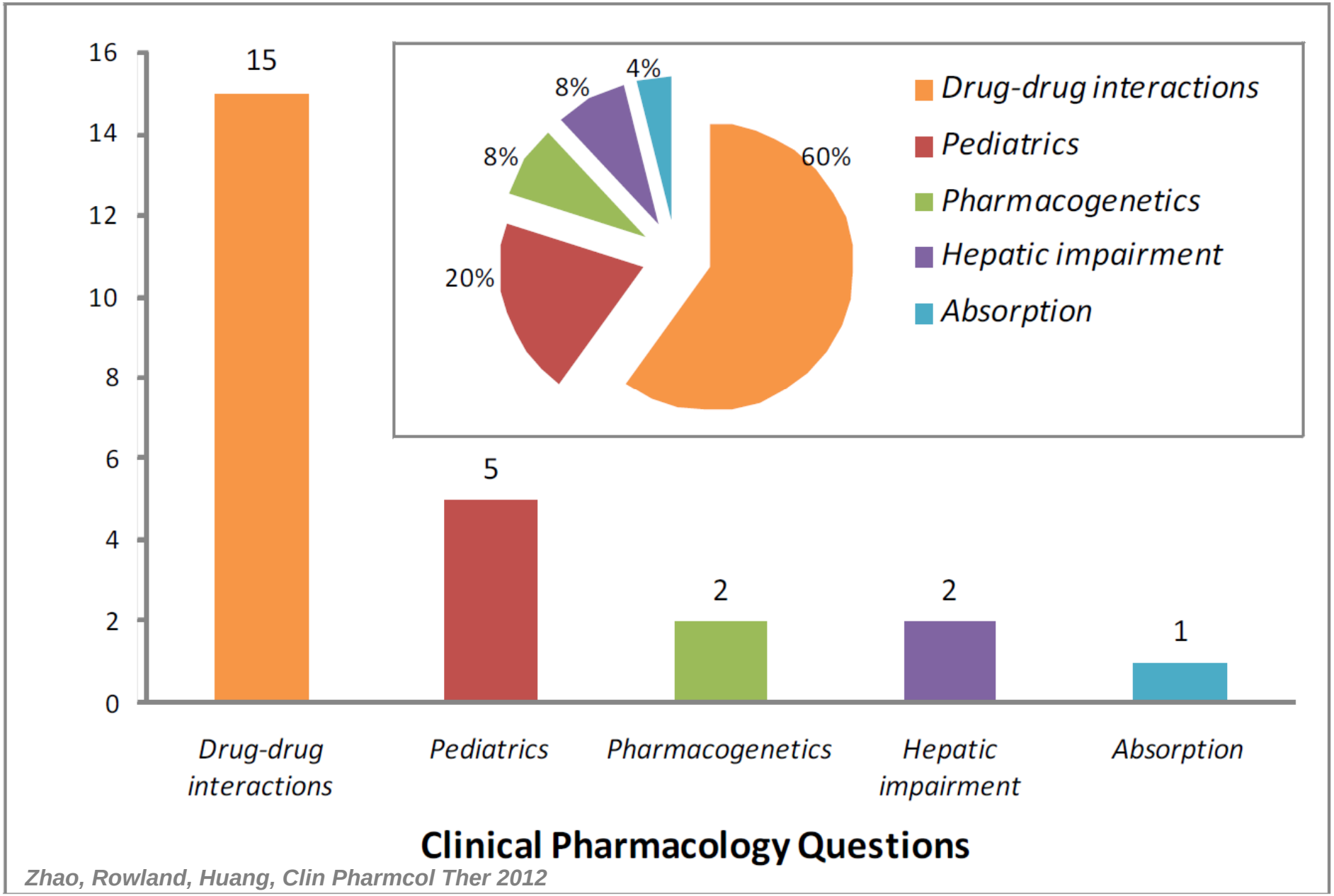
- “Top-down” aspect of PBPK
- Evaluating transporter DDI using PBPK

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

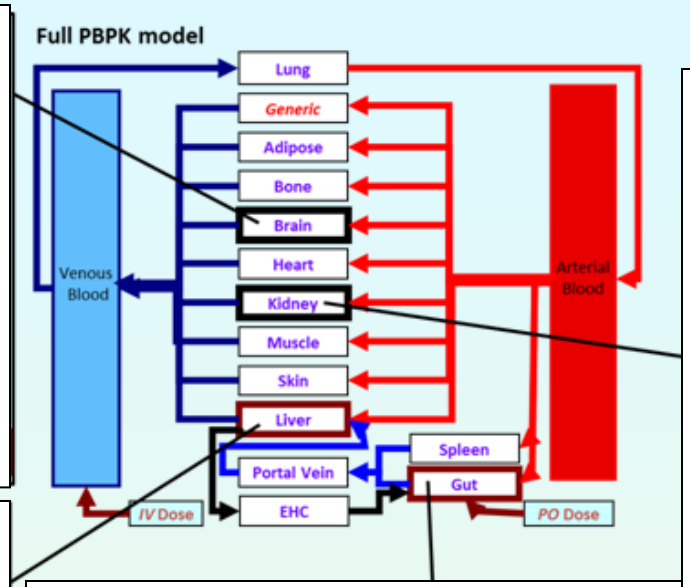


Zhao, Rowland, Huang, Clin Pharmcol Ther 2012

Pre-defined Permeability-Limited Models

MANCHESTER 1824

Brain



Kidney

Liver

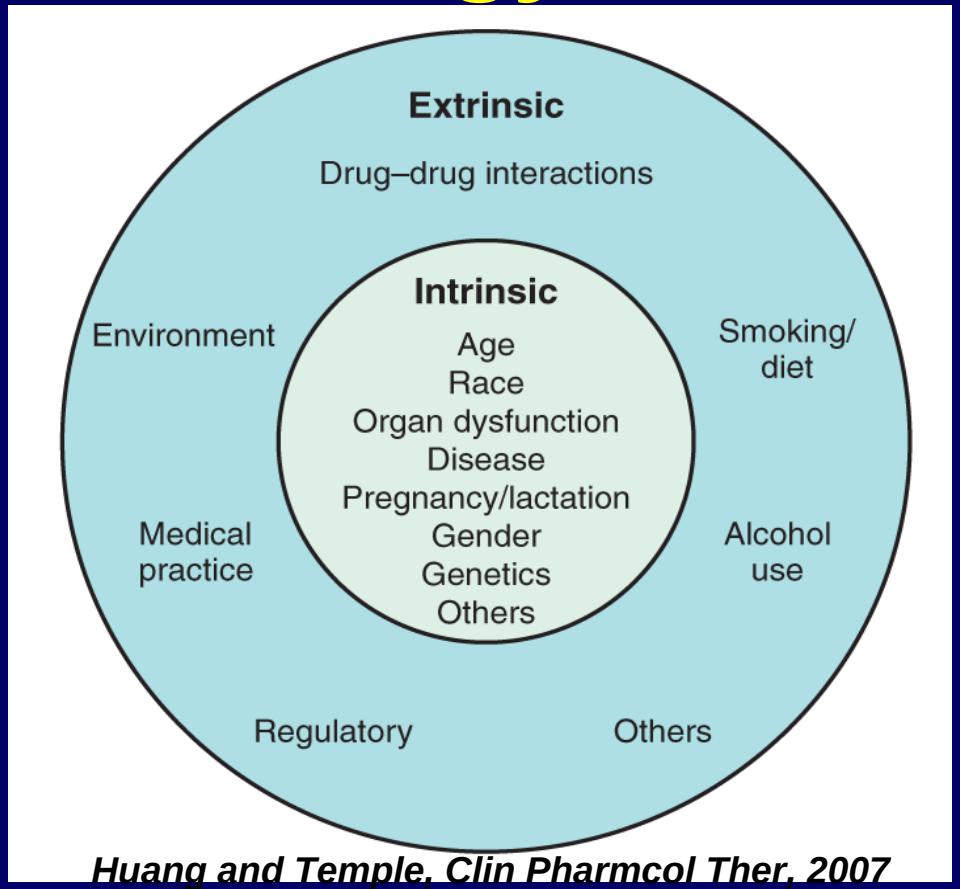
Gut

Courtesy Prof. Rostami-Hodjegan (U Manchester)

Permeability-limited model are available for the intestine, liver, kidney and brain.

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

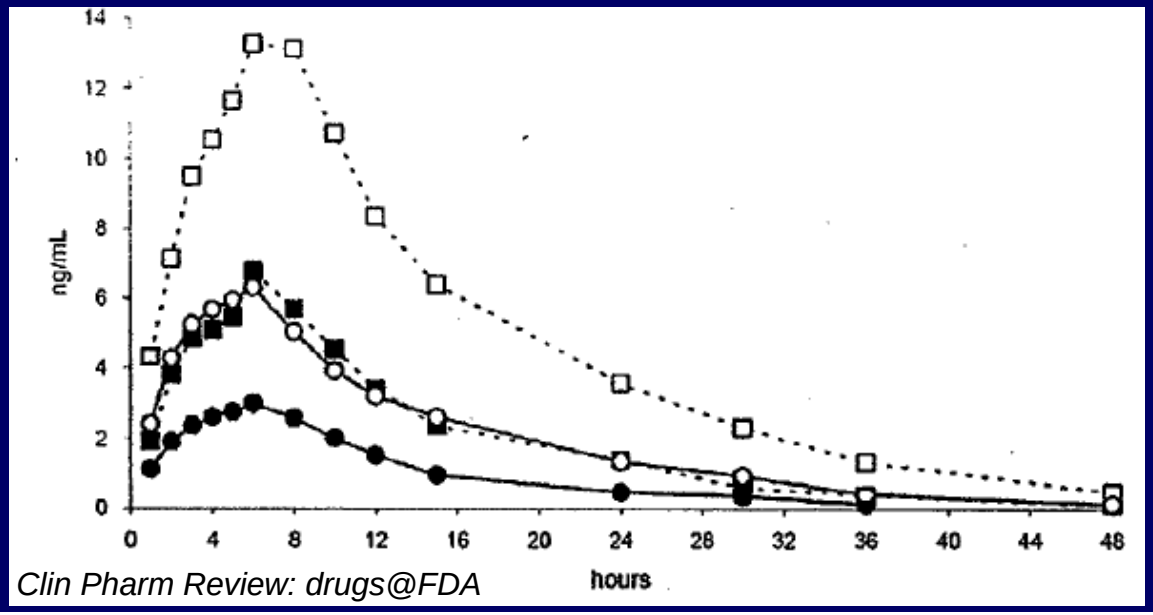
Drug action

PBPK Model

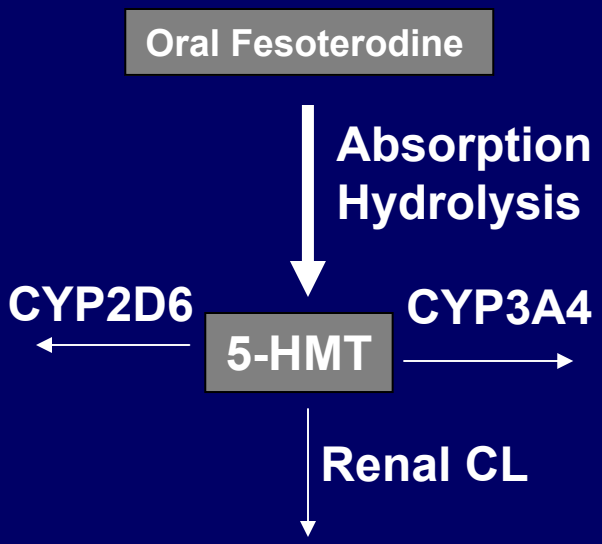
Predict, Learn, Confirm

Adapted from Zhao P, et al Clin Pharmacol Ther 2011

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



Clin Pharm Review: drugs@FDA

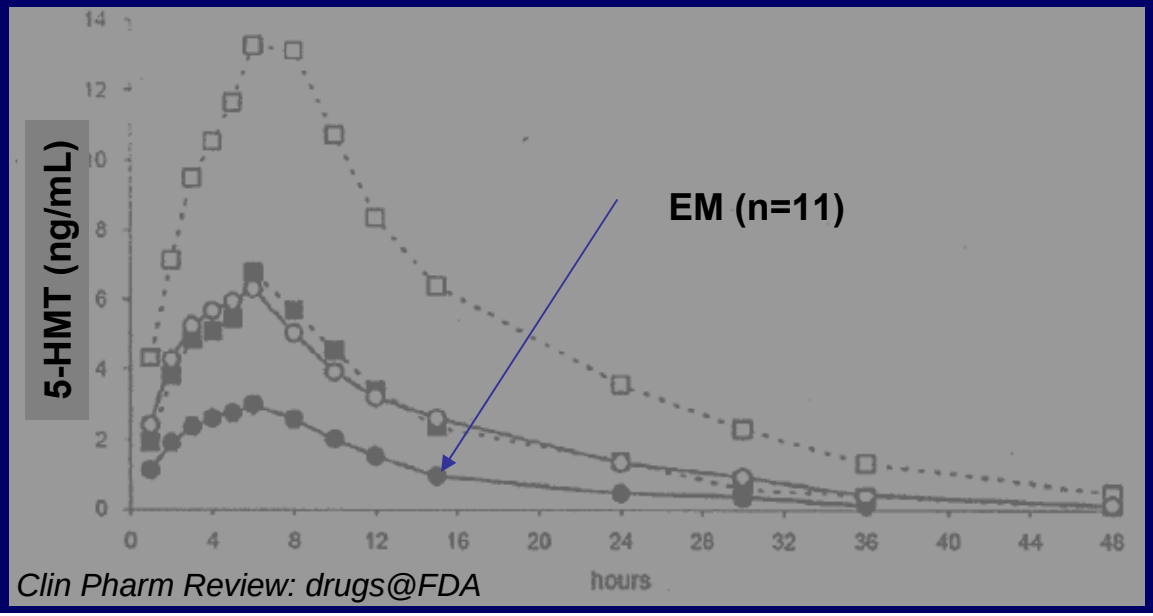


	Observed		Predicted	
	AUCR	CmaxR	AUCR	CmaxR
EM +/- Ketoconazole	2.3 [a]	2.0 [a]	1.9	1.8
PM +/- Ketoconazole	2.5 [a]	2.1 [a]	3.3	2.4
PM / EM	2.3	2.1	1.6	1.5
PM + Keto / EM	5.7 [a]	4.5 [a]	5.4	3.6
EM +/- Fluconazole	1.3 [b]	1.2 [b]	1.3	1.2
PM + Fluconazole / EM	-	-	2.6	

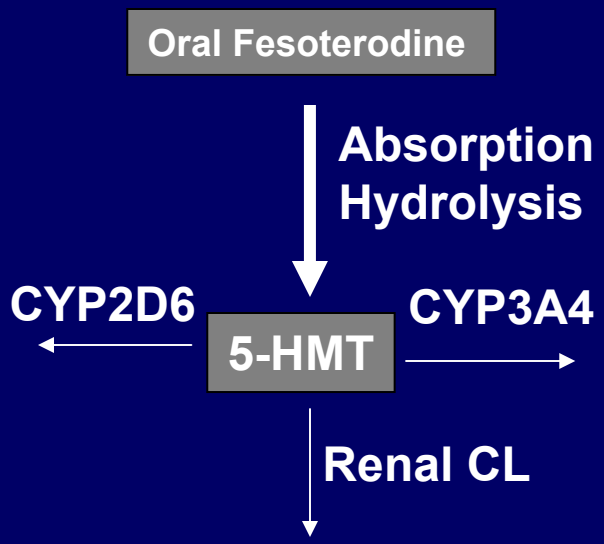
[a] Clinical Pharmacology Review (drugs@fda); [b] Malhotra et al (2001) B J Clin Pharmacol 72:226-234.

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	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	?	?	2.6	2.1

[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

Complexity of Transporter DDI

- **Associated with both drug ADME and DDI potential**
  - *PK of substrate and interacting drug*
  - *DDI mechanism(s) of interacting drug*
- **At all levels of physiology**
  - *Organ/tissue level (more than 1 transporters, in more than 1 organ)*
  - *Cell level (differential expression, uptake and efflux, more than 1 cell type)*
  - *Subcellular system*
- **Enzyme-transporter-(permeability) interplay**

Need knowledge integration and mechanistic modeling of local as well as whole body kinetic events

Outline

- Update of DDI guidance on model-based predictions
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- “Top-down” aspect of PBPK
- Evaluating transporter DDI using PBPK

Modeling of Local And Whole Body Kinetics: “Bottom-up”+ “Top-down”

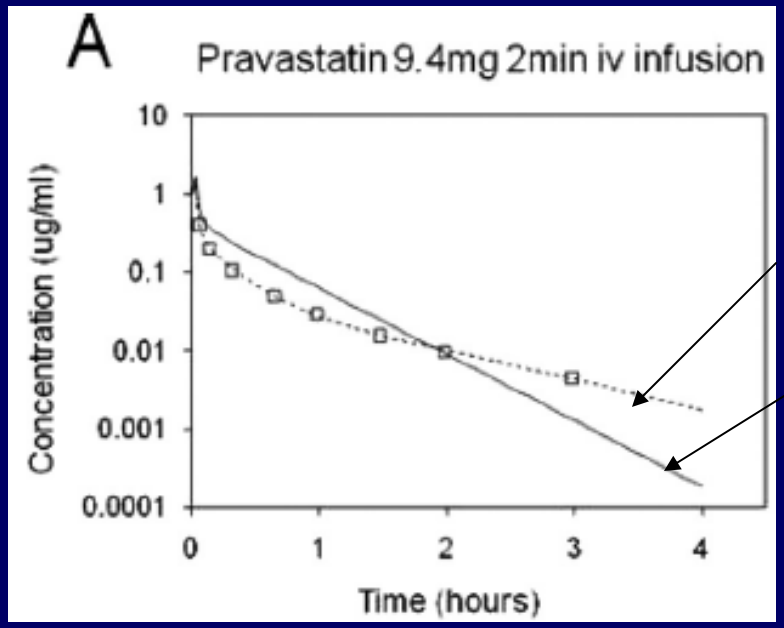
- Obtaining parameters in a complex in vitro system
- Integrating in vitro parameters in PBPK
- Refining model parameters using in vivo PK data

Predict, Learn, Confirm

LEARNING Active and Passive Processes Using PBPK: Scaling Factors (SF) for Pravastatin

	$CL_{int, u, act.}$	$CL_{int, u, pass.}$	$CL_{int, u, bile}$
In vitro (uL/min/10^6 cells)	1.8	0.1	1.2
Organ level (ml/min/kg?)			
No SF	19	1.1	12
+ SF from i.v. data (SF)	**406 (21)**	**4.2 (3.9)**	**1.5 (0.12)**

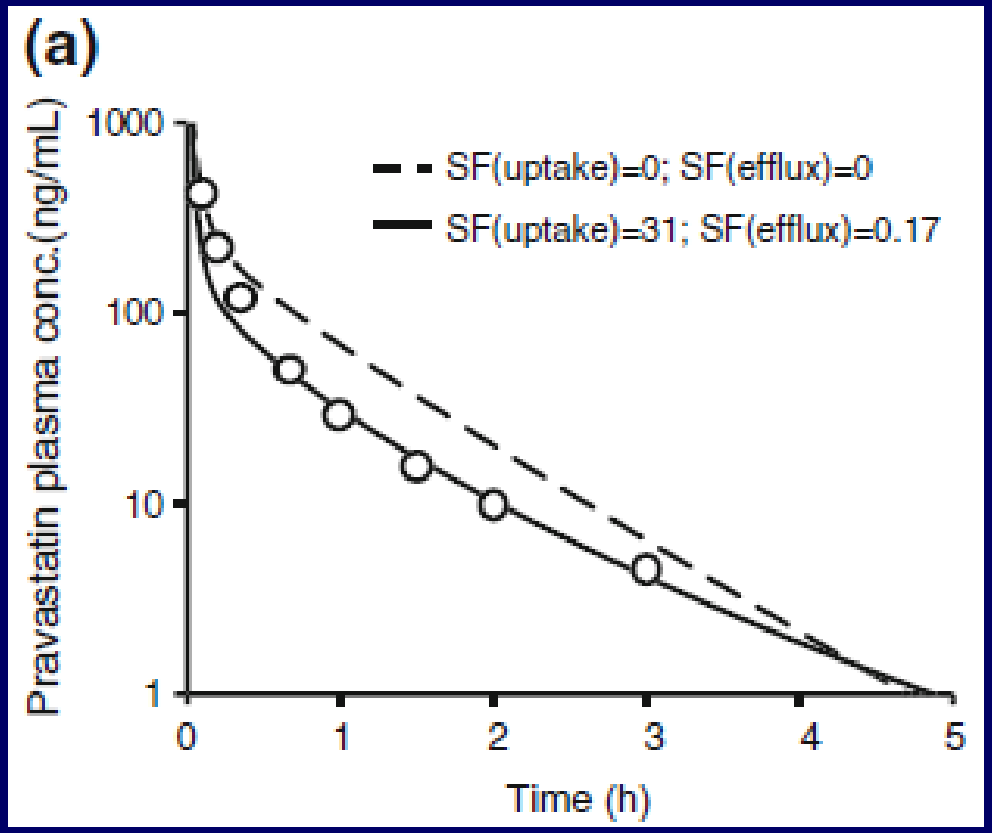
Jones et al, Drug Metabo Dispo, 2012



+ SF from fitting i.v. data

- SF

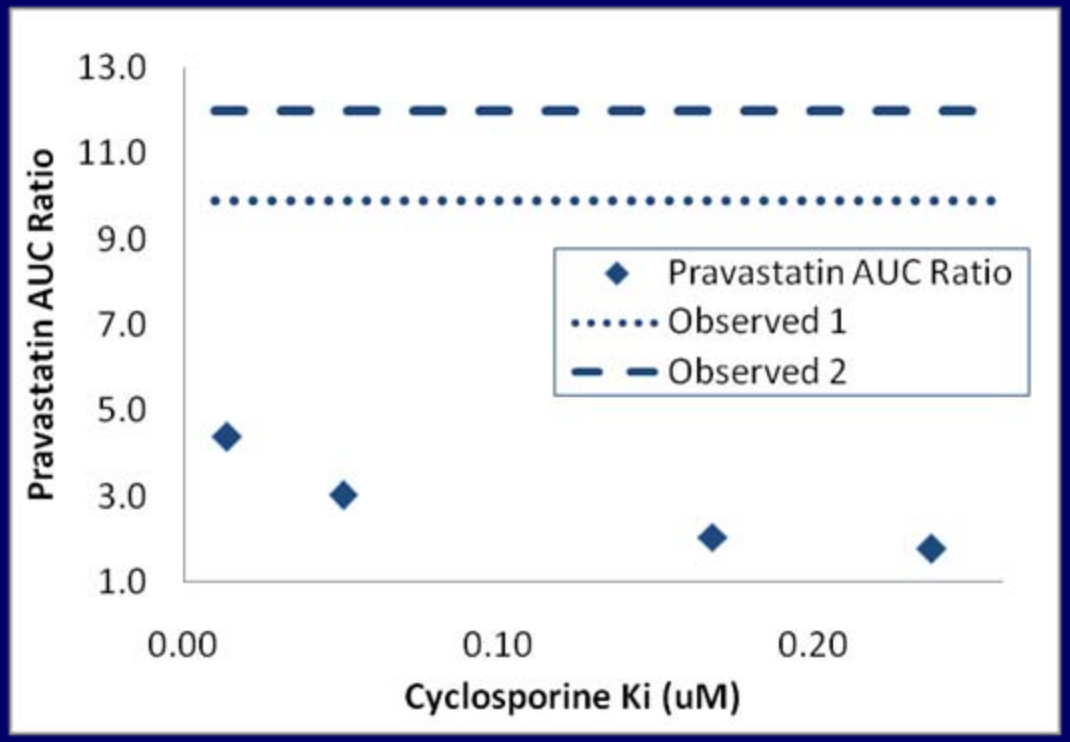
Pravastatin DDI: Liver Specific?



Scaling factors for both liver uptake and biliary efflux are needed

Varma et al, Pharm Res, 2012

Pravastatin DDI: Liver Specific?



PBPK simulation underestimated pravastatin AUC increase by cyclosporine over the reported range of Ki for OATP1B1

Varma et al, Pharm Res, 2012

Effect on extrahepatic pathway(s)?

Handling Multiple Active Processes Using PBPK - Pravastatin

Database on expression data were used to parameterize pravastatin human PBPK model

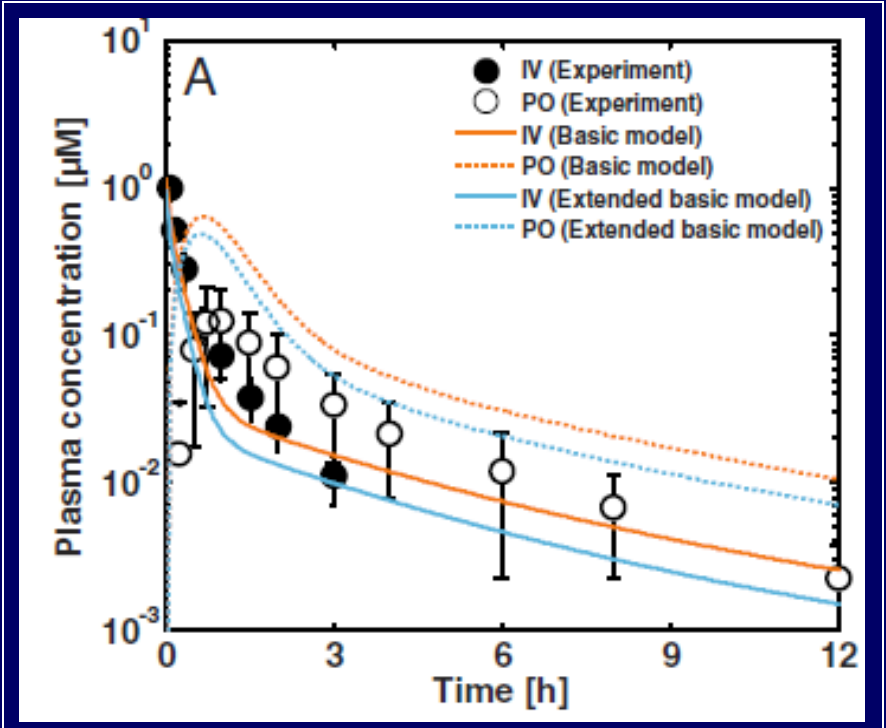
k^*_{cat} as an organ-independent parameter for each active (transport or metabolism) process

$$V_{max}^{Organ,i} = k_{cat} \cdot SF \cdot e_{Rel}^{Organ,i} = k_{cat}^{*} \cdot e_{Rel}^{Organ,i}$$

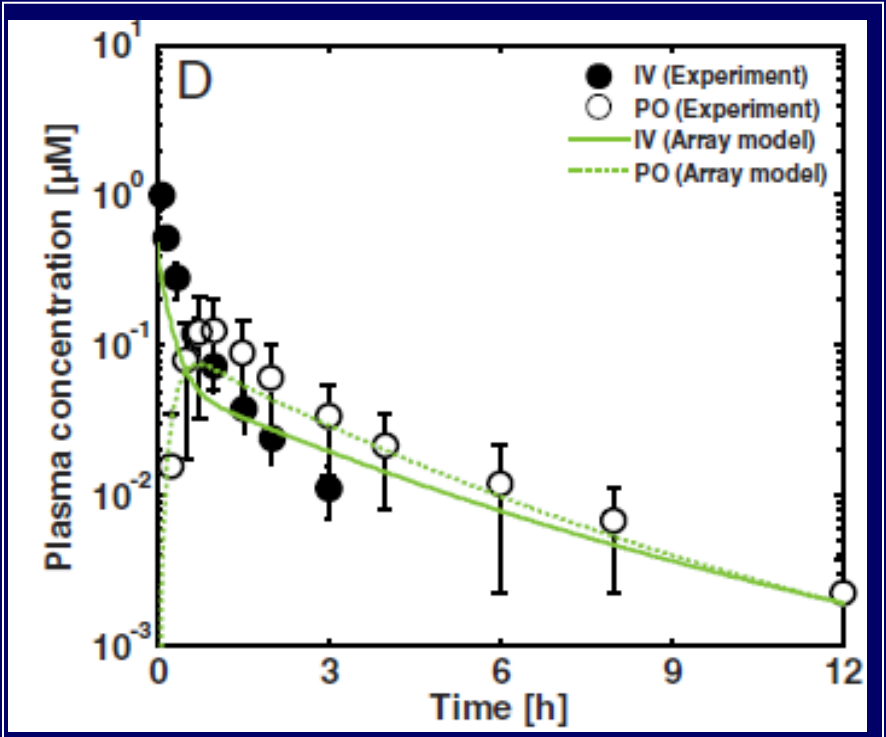
Meyer et al, Drug Metabo Dispo, 2012

Liver	Kidney	Intestine
• OATP1B1 • OAT3 • MRP2 • Sulfotransferase	. • OAT3 • MRP2 • Sulfotransferase	. . • MRP2 • Sulfotransferase

Handling Multiple Active Processes Using PBPK - Pravastatin



Basic model: general CL_H and CL_R
Extended basic model: integration of known mechanisms: GI degradation and OATP1B1 in the liver



Model integrating experimental expression data (array database for example)

Meyer et al, Drug Metabo Dispo, 2012

Improved fit with model considering expression data for all tissues

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Renal Dysfunction: The Interplay

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	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 (RI) on Hepatic Pathways

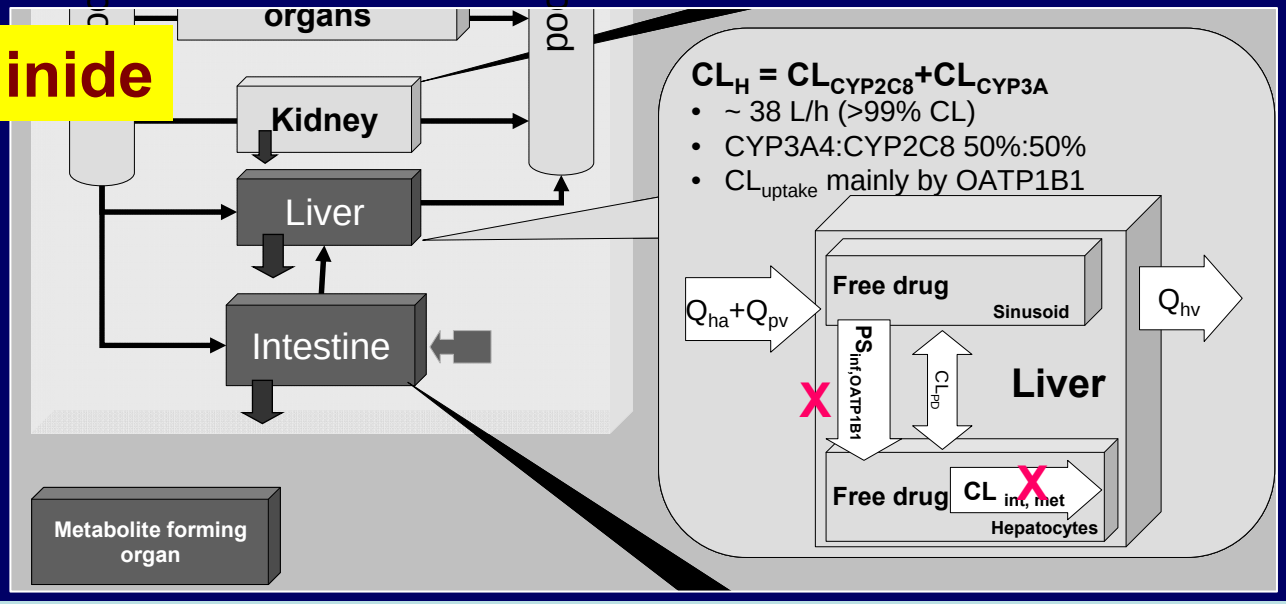
Compound (% CL by kidney)	Observed AUCR Severe RI/Normal	PBPK[a] Predicted AUCR Severe RI/Normal
Sildenafil (<1%)	2.0[b] **(Mild: 0.9; Moderate: 1.2)**	2.2
Repaglinide (<1%)	SD: 2.7; MD: 3.0[c] **(Mild/Moderate: SD: 1.8; MD1.6)**	SD: 2.5; MD: 2.3
Telithromycin (~20%)	1.9[d] **(Mild: 1.4; Moderate: 1.2)**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

LEARNING the Effect of Renal Impairment on CL_h

Repaglinide



X: Effect of renal impairment on OATP and CYPs

	Assumption on $PS_{inf,OATP1B1}$	Repaglinide AUC Ratio by Severe Renal Impairment	
		Single dose	Multiple doses
Obs [a]		**2.7**	**3.0**
Pred.	No change	1.3	1.2
Pred.	**▼ 52%**	**2.5**	**2.3**

Zhao et al, J Clin Pharmacol, 2012

[a]. Marbury. Clin.Pharmacol.Ther. 2000

Hepatic uptake (OATP) is likely to be affected by renal impairment

Gemfibrozil: Multiple DDI Mechanisms

In Vitro Inhibition Parameters

SIMCYP

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Competitive Inhibition

- Gemfibrozil mean **CYP2C8 Ki** = 27 μM
- Substrate-dependent: range **7.2 μM** – 58 μM

  (repaglinide < amodiaquine < montelukast < rosiglitazone < cerivastatin < paclitaxel)
- Gemfibrozil 1-*O*-β glucuronide mean **CYP2C8 Ki** = 3.2 μM (**0.8 μM** – 4.8 μM)
- Gemfibrozil mean **OATP1B1 Ki** = 29 μM (12 μM – 65 μM)

  (Estradiol 17-β-*D* glucuronide and pitavastatin)
- Gemfibrozil 1-*O*-β glucuronide mean **OATP1B1 Ki** = 19 μM (8 μM – 22 μM)

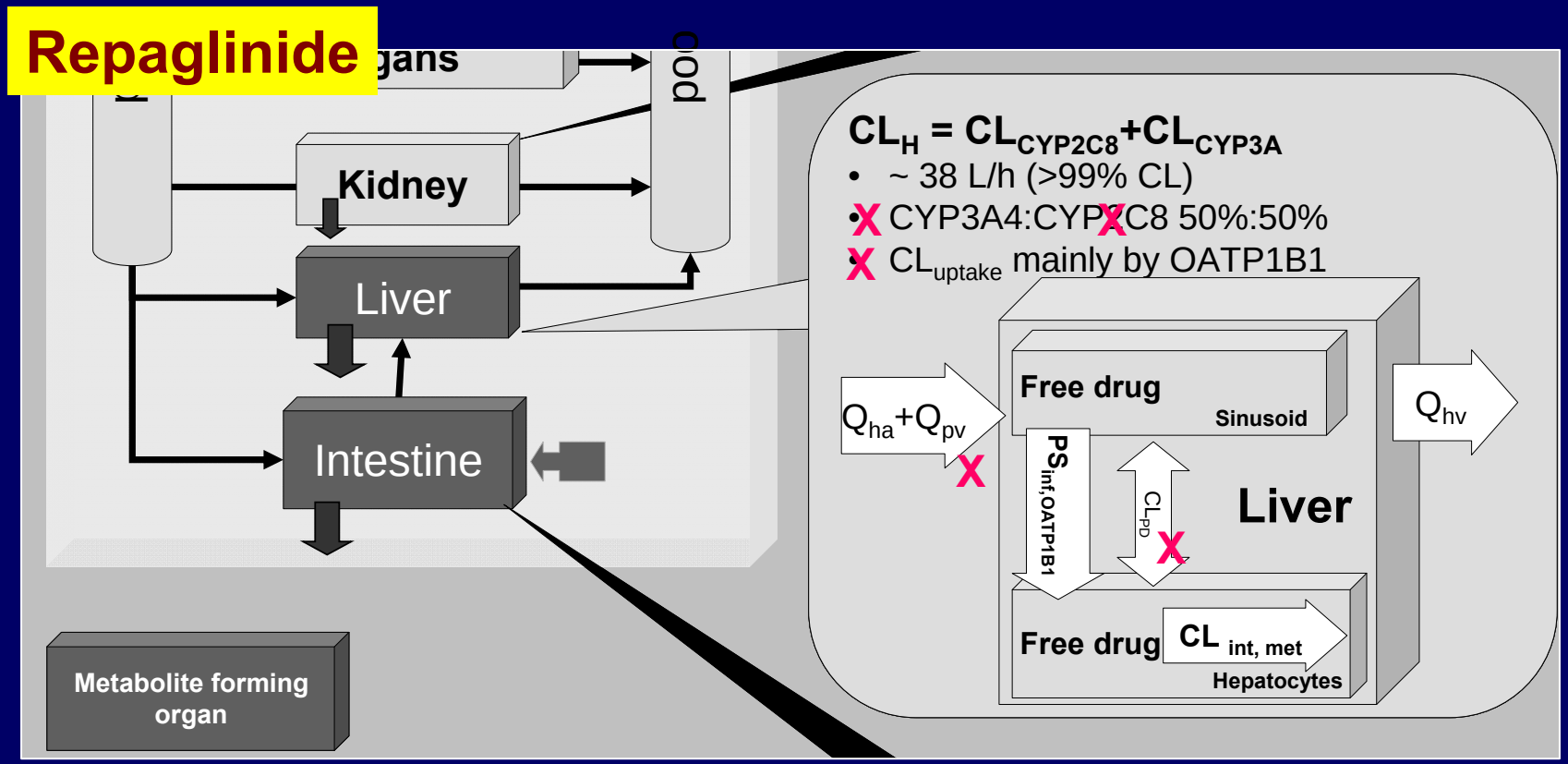
Mechanism-Based Inhibition

- Gemfibrozil 1-*O*-β glucuronide

  Range **CYP2C8** Kinact/Kapp: 0.1 - 0.67

  (rosiglitazone < repaglinide < montelukast < pioglitazone < amodiaquine < paclitaxel)
- **CYP2C8 Kapp = 19 μM** **Kinact = 13 /h** **Kinact/Kapp** = 0.67

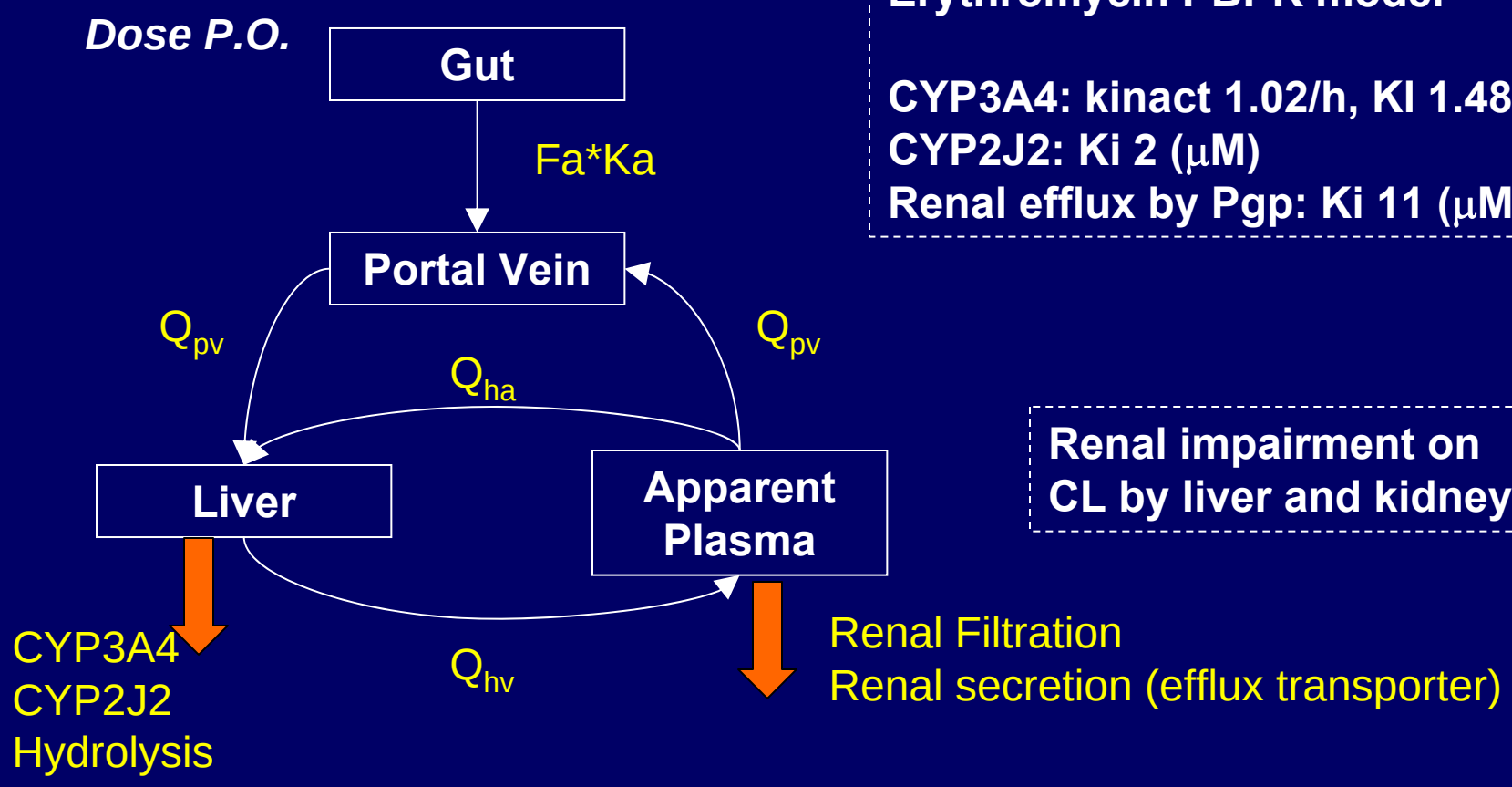
Complex DDI of Gemfibrozil – Repaglinide



X: Multiple processes by parent and metabolite

Rivaroxaban: PREDICTING Effect of Renal Impairment And DDI in The Elderly

Rivaroxaban PBPK model



Erythromycin PBPK model

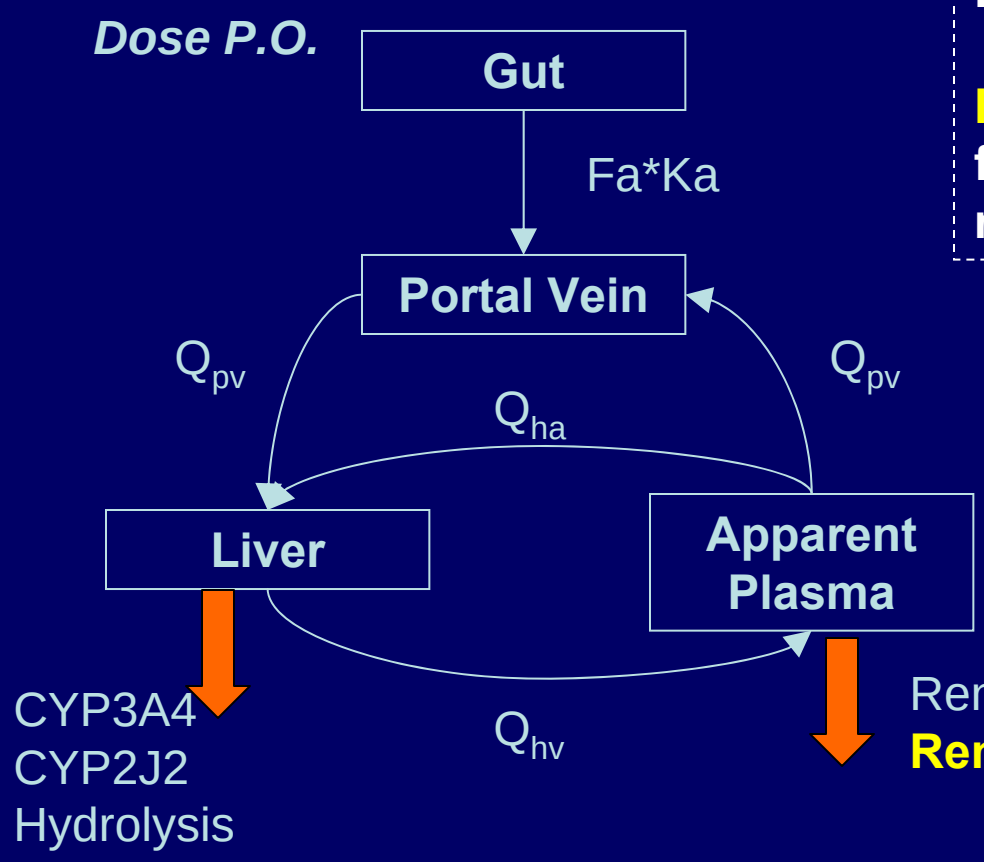
CYP3A4: kinact 1.02/h, KI 1.48 μM
CYP2J2: Ki 2 (μM)
Renal efflux by Pgp: Ki 11 (μM)

Renal impairment on CL by liver and kidney

Grillo et al, Biopharm Drug Dispo, 2012

Rivaroxaban: PREDICTING Effect of Renal Impairment And DDI in The Elderly

Rivaroxaban PBPK model



Erythromycin PBPK model

Renal efflux by Pgp: Ki 11 (μM) from in vitro study using rivaroxaban as substrate

Renal impairment: Decrease in secretion calculated from CLr and GFR data

Grillo et al, Biopharm Drug Dispo, 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

Conclusions

- Transporter-based DDIs are often highly complex
- PBPK can be used to evaluate complex DDI, because the model integrates knowledge in drug absorption, disposition, DDI mechanisms, and the effect of patient factors (disease, age, genetics) for both substrate and interacting drugs
- Clinical pharmacokinetic data are valuable for PBPK model modification
- PBPK model should be constantly updated with new data for improved predictability of untested situations

Acknowledgements

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Pharma IQC DDI Prediction Groups

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*

Huang SM. PBPK as a tool in regulatory review. Biopharm Drug Dispos. 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 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*

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*

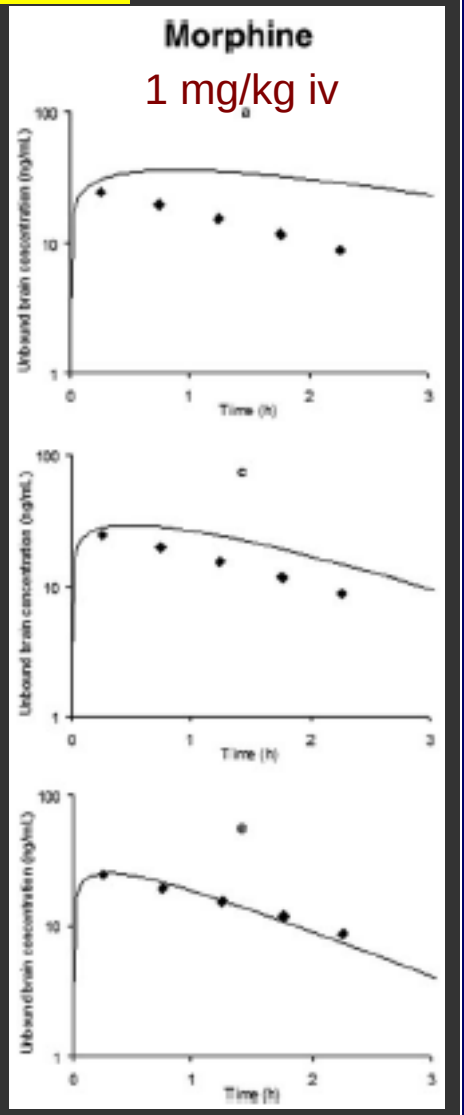
Ke AB, Nallani S, et al. A PBPK Model to Predict Disposition of CYP3A-metabolized Drugs in Pregnant Women: Verification and Discerning the Site of CYP3A Induction. Clin Pharmcol Ther: Pharmacometrics & Systems Pharmacology, 2012

LEARNING

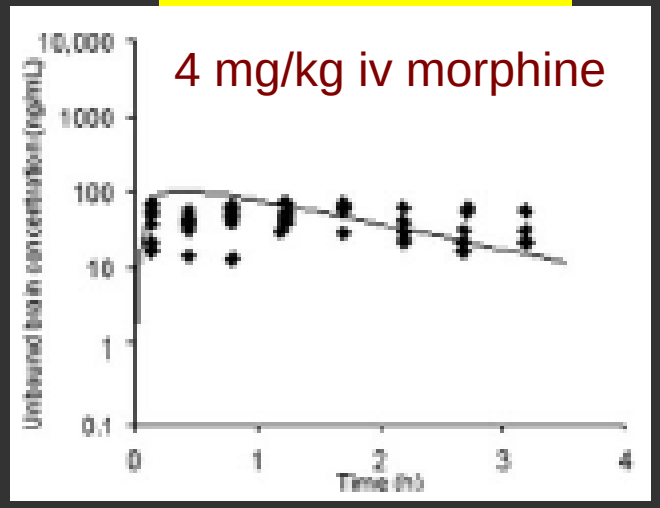
Passive only

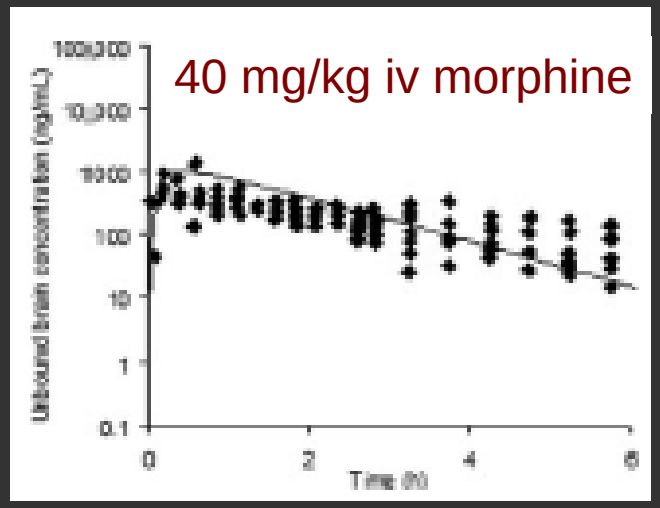
Passive
+
in vitro efflux

Passive
+
in vitro efflux
+
RAF



CONFIRMING

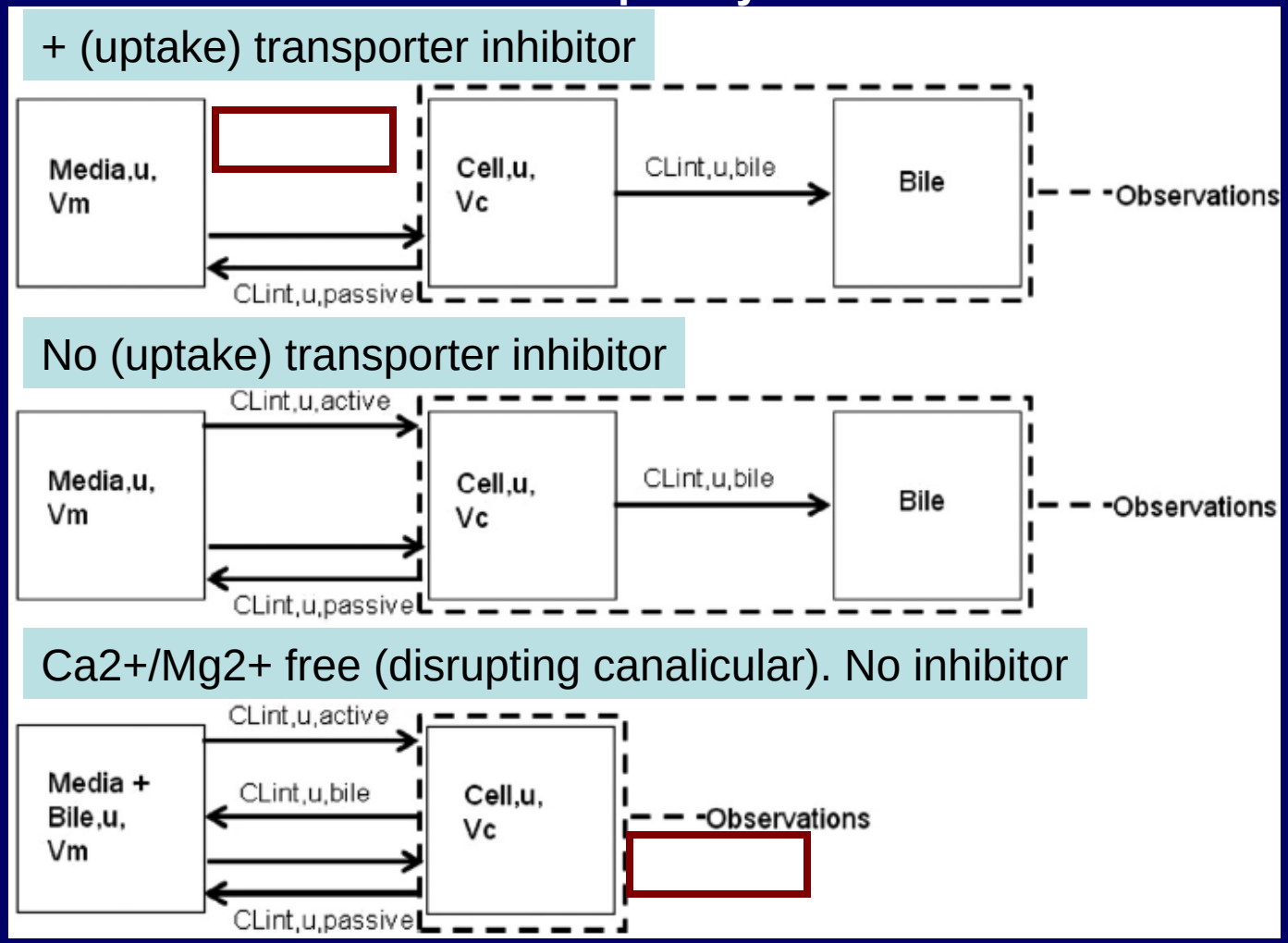




Ball et al, J Pharm Sci, 2012

Obtaining In Vitro Parameters Using Mechanistic Models

Sandwich Culture Human Hepatocytes



CL_{ints} →PBPK

Jones et al, Drug Metabo Dispo, 2012