# Model-based Evaluation of Drug Disposition and Drug-drug Interaction Potential of Metabolites

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**Food and Drug Administration**

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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 metabolites
- Why PBPK
- Application of PBPK in evaluating metabolite disposition and DDI potential

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*DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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**

# Regulatory Requirements for Testing DDI Potential of Drug Metabolites

## FDA

The potential for drug interactions with metabolites of investigational drugs (metabolites present at >25% of parent drug AUC) should be considered (see section IV.A.3).

## EMA

… the effects of other medicinal products on the exposure of clinically relevant pharmacologically active metabolites should always be considered

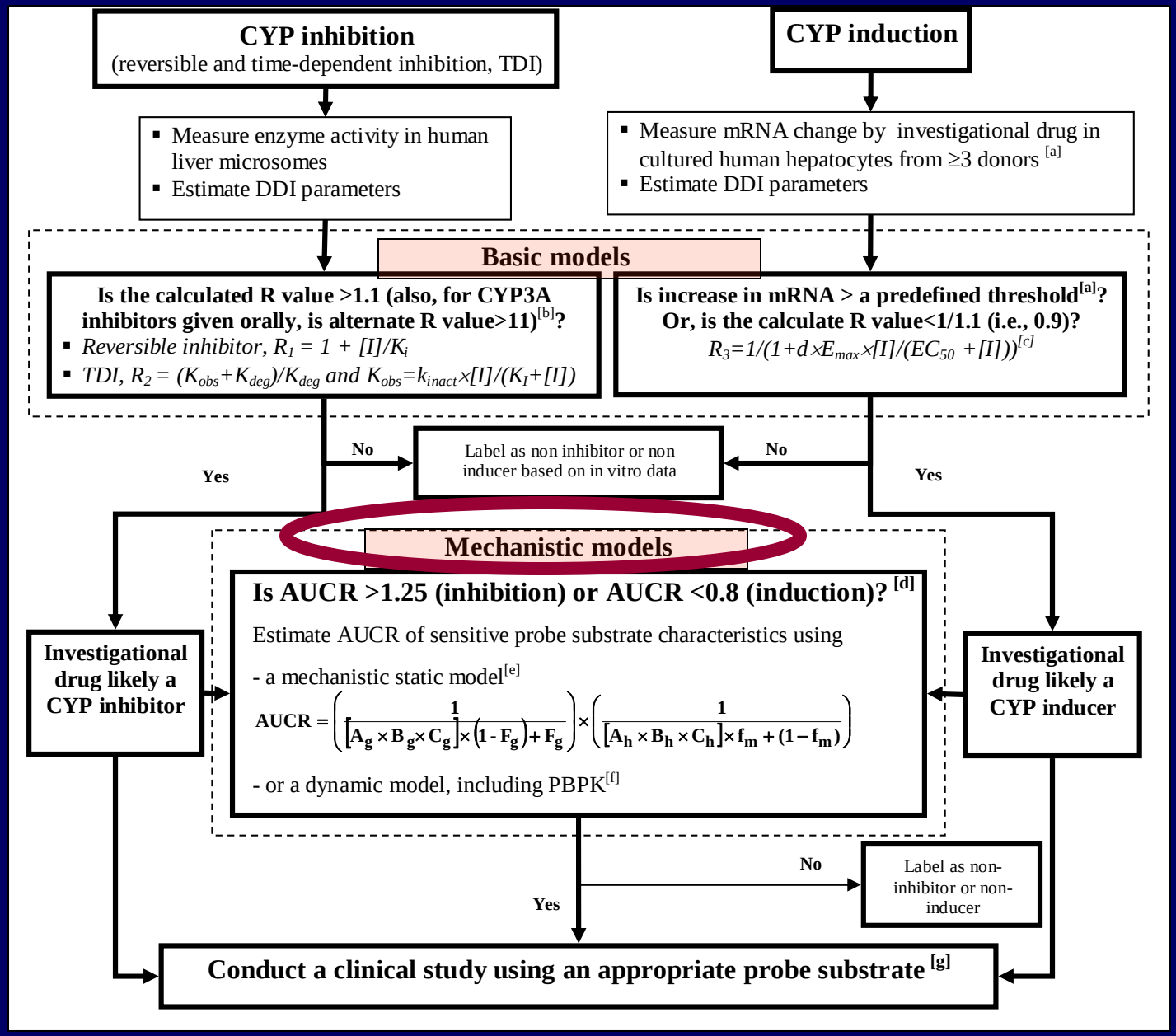
… as metabolites may inhibit drug metabolising enzymes, the effect of metabolites with a moderate to high exposure should be investigated (see section 5.3.3).

# IV-A-3. Considerations of the Metabolites of Investigational Drugs (FDA)

Metabolites formed in vivo may reach significant exposure (e.g., ≥ 25% of the parent drug) and elicit pharmacological and/or toxicological effects. Therefore, the same considerations on further metabolism, transport, and drug interaction studies described above should be considered for relevant metabolites of the investigational drugs. The decision on which metabolite(s) should be investigated depends on multiple factors, including the knowledge in pharmacological/toxicological activities (from in vitro human cell line data and/or in vivo animal data) and the knowledge in metabolites' disposition kinetics. For example, metabolites deemed insignificant after a single dose of the parent drug may accumulate to appreciable exposure after multiple dosing if they have long half-lives. Unexpected high exposure of metabolites may be attained in subjects with decreased function of organs responsible for their elimination and in the event of drug interactions affecting the disposition of the parent drug. Appropriate assays for metabolites should be in place to monitor the metabolite levels along with the parent. Given the complexity of the kinetics and interaction mechanisms of formed metabolites, modeling and simulation integrating knowledge of drug disposition kinetics of both parent investigational drug and metabolites may provide a useful tool to facilitate the evaluation of drug interaction potential of metabolites (see earlier sections).

- **Significant exposure: ≥25% of parent drug**
- **Treated as parent drug regarding metabolism, transport, DDI**
- **Decision also depends on multiple factors:**
  - ✓ ***Knowledge in activity (pharmacological or toxic)***
  - ✓ ***Significance in situations not represented by single dose studies in healthy volunteers (accumulation after multiple dosing, decreased elimination of metabolites by patient factors)***
- **Modeling and simulation integrating both parent and metabolite(s) data are useful**

# 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



# Metabolite as a victim or a perpetrator (EMA)

**Victim**

… if there are pharmacologically active metabolites estimated based on **unbound systemic exposure** whose **in vitro activity** contributes to **≥ 50% of the in vivo target** pharmacological effect, enzymes contributing to main formation and elimination pathways of these metabolites should be identified.

→ *Plasma protein binding, in vitro EC50, metabolite PK*

**Perpetrator**

… metabolites with an AUC **both larger than one fourth of the AUC of parent drug and larger than 10% of the drug-related exposure**

→ *Plasma protein binding, in vitro DDI, metabolite PK*

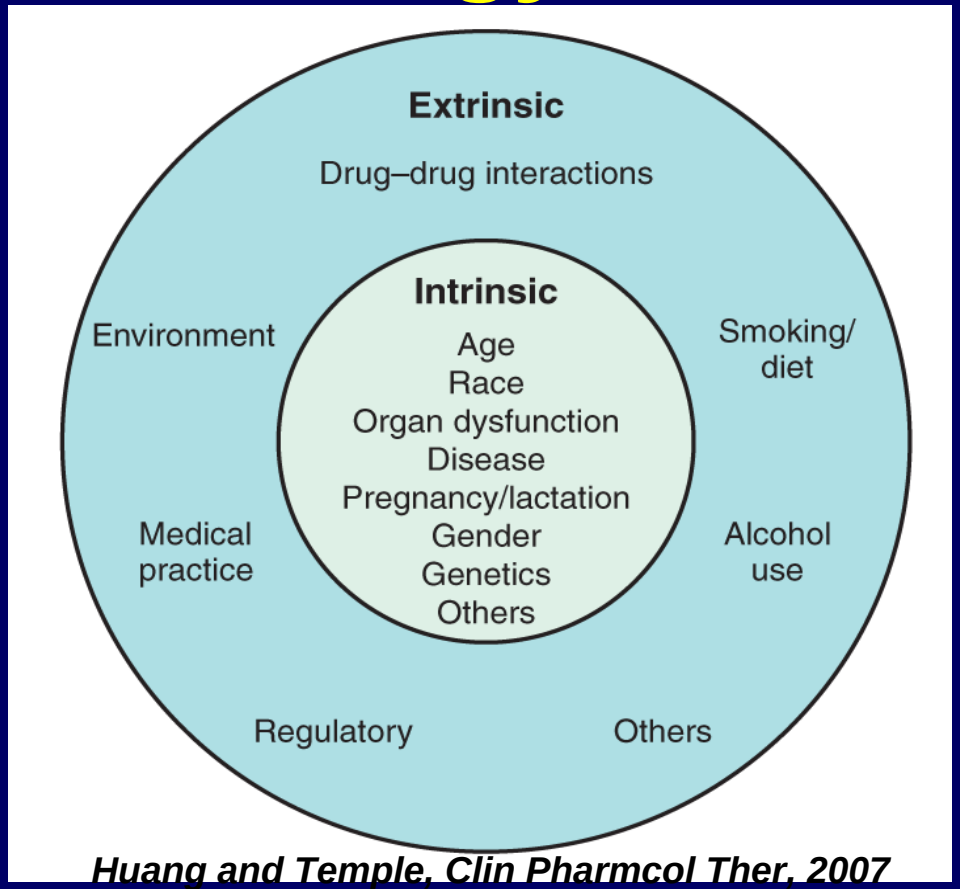
… Due to the difficulties in predicting the concentration of inhibitory metabolite at the site(s) of the enzyme, **PBPK modelling and simulations are encouraged** to support the evaluation.

# Outline

- Update of DDI guidance on metabolites
- Why PBPK
- Application of PBPK in evaluating metabolite disposition and DDI potential

# 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

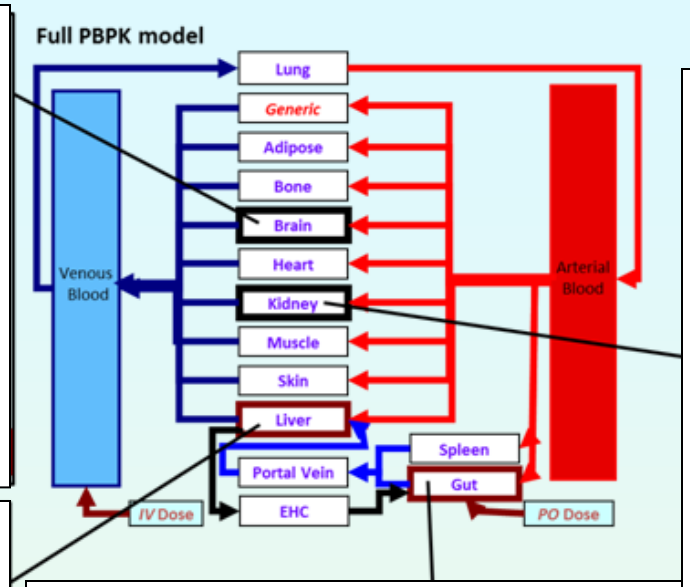


Adapted from Zhao P, et al Clin Pharmacol Ther 2011

# Pre-defined Permeability-Limited Models

MANCHESTER 1824

Brain




Kidney

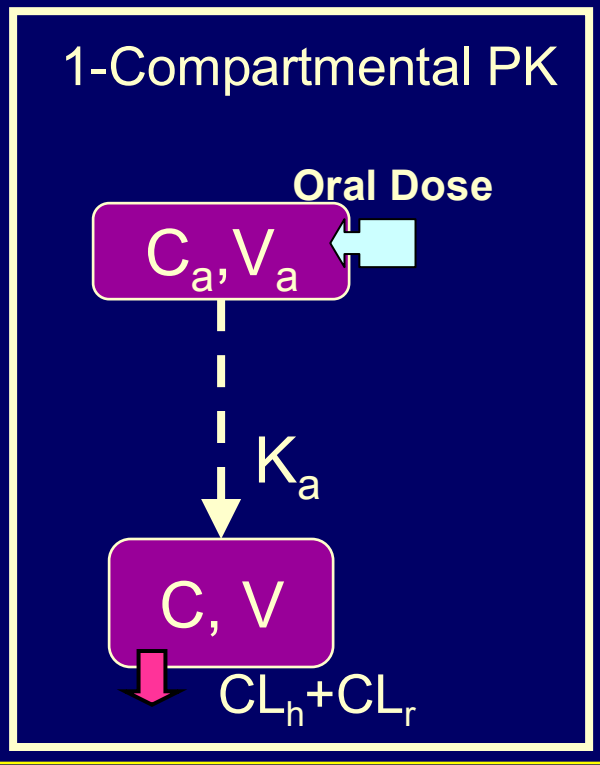
Liver

Gut

Courtesy Prof. Rostami-Hodjegan (U Manchester)

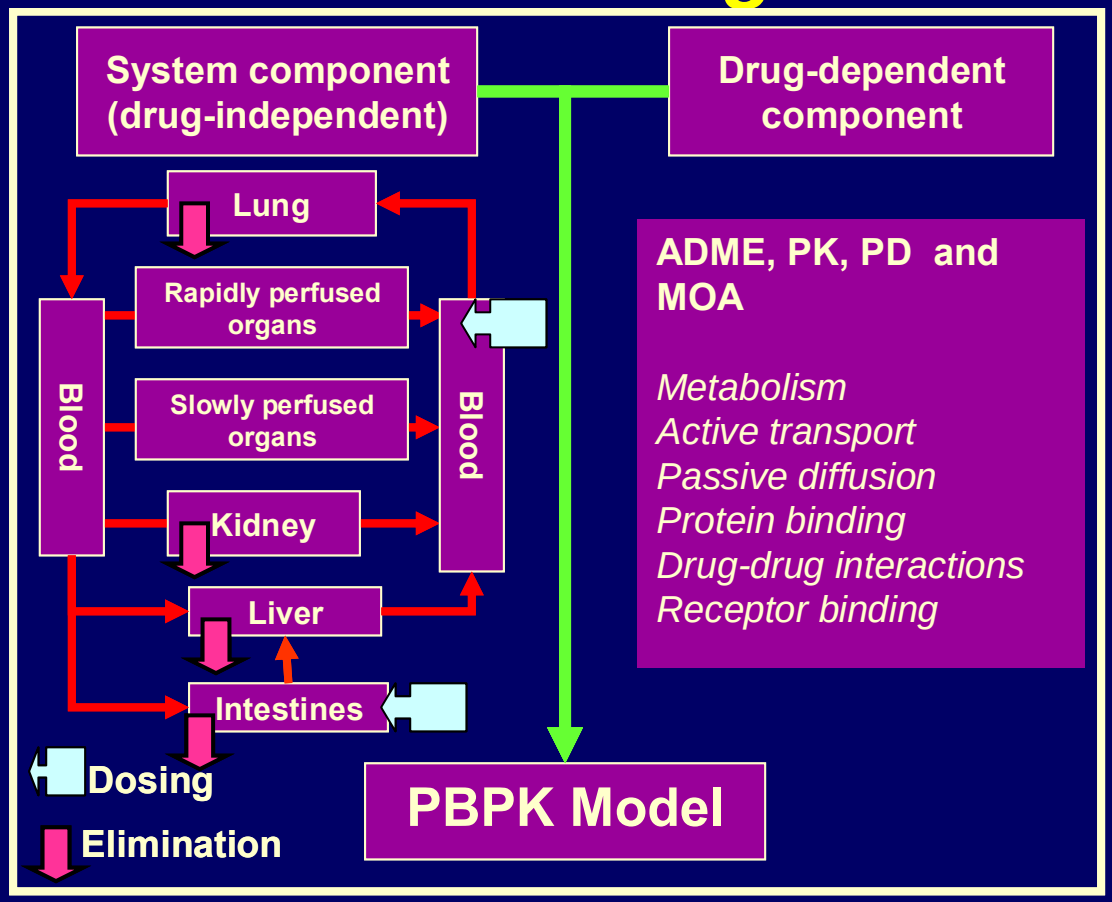
Permeability-limited model are available for the intestine, liver, kidney and brain.

# Can Model Provide Desired Insights?




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

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

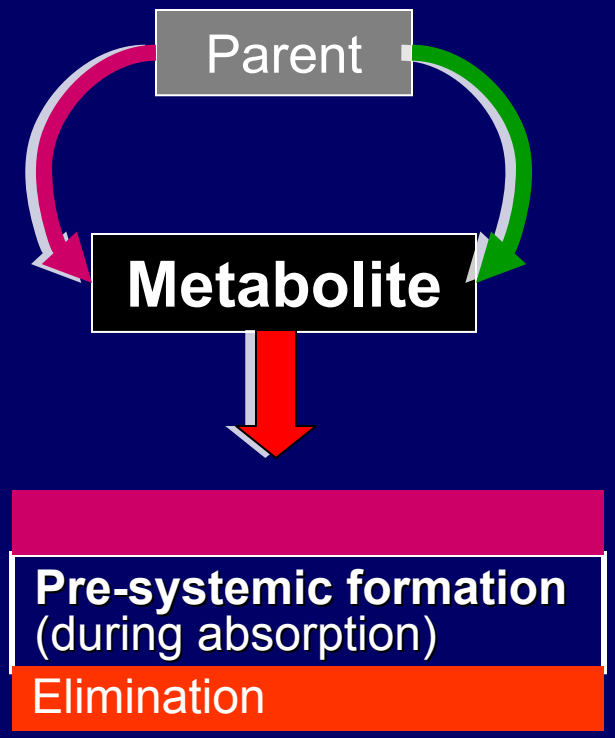


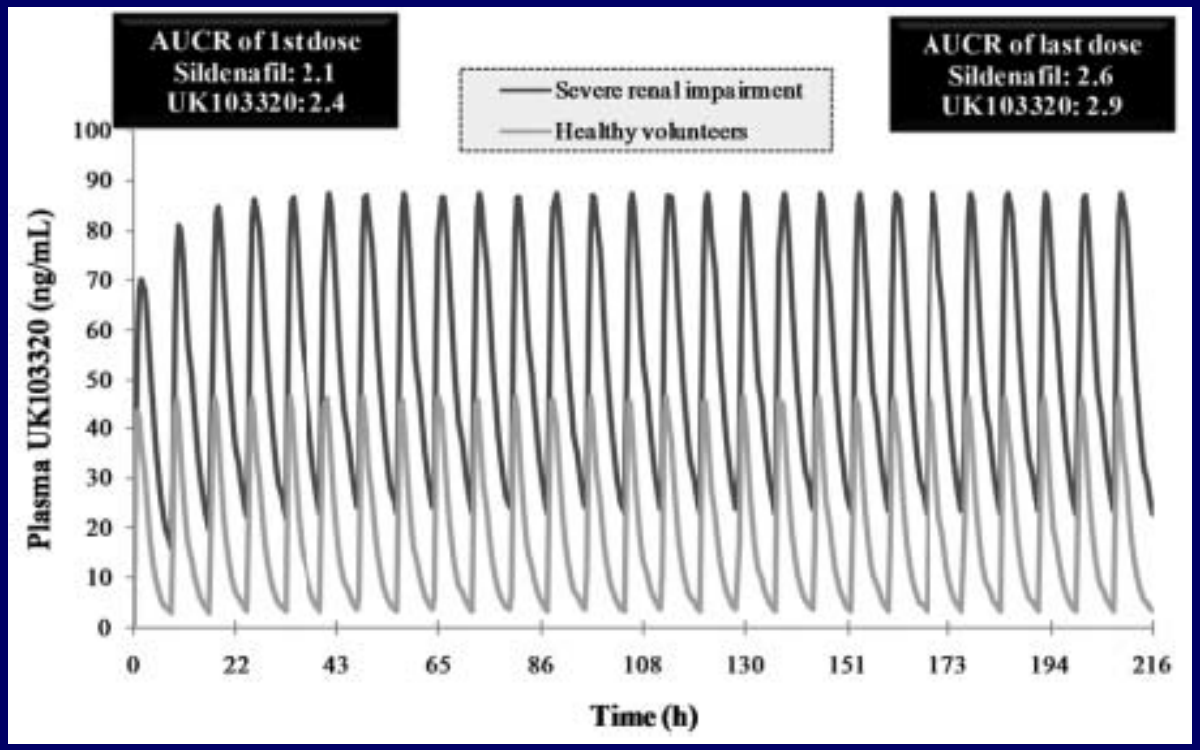

$$C = \frac{K_a * Dose}{V * (Ka - \frac{CL_h + CL_r}{V})} * (e^{-\frac{(CL_h + CL_r)}{V} * t} - e^{-K_a * t})$$

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

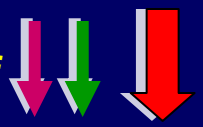
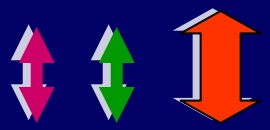
**And…**

# Model-based Design of Clinical PK Studies

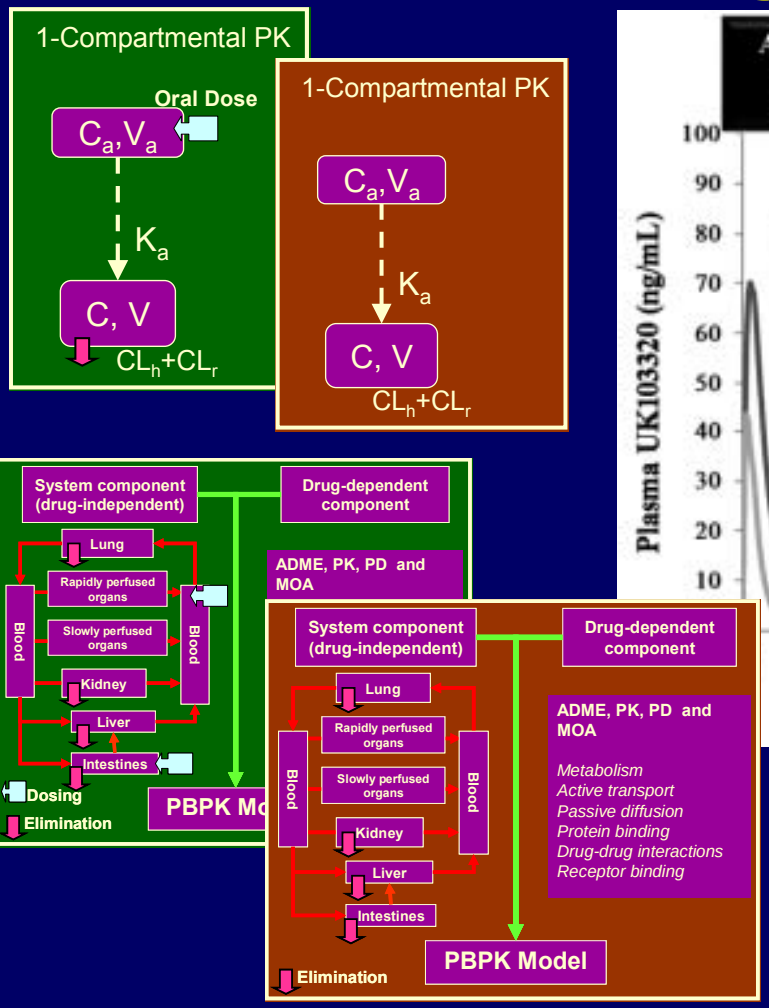


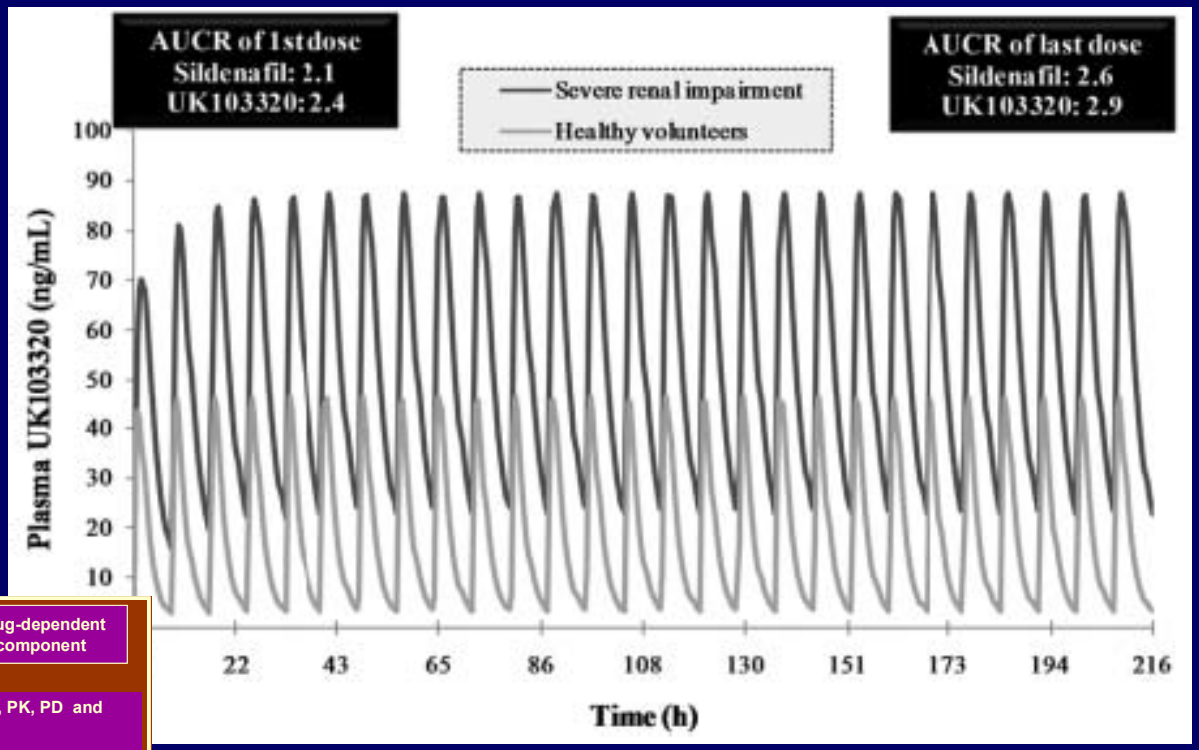




*Zhao et al, J Clin Pharmacol, 2012*

- ***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

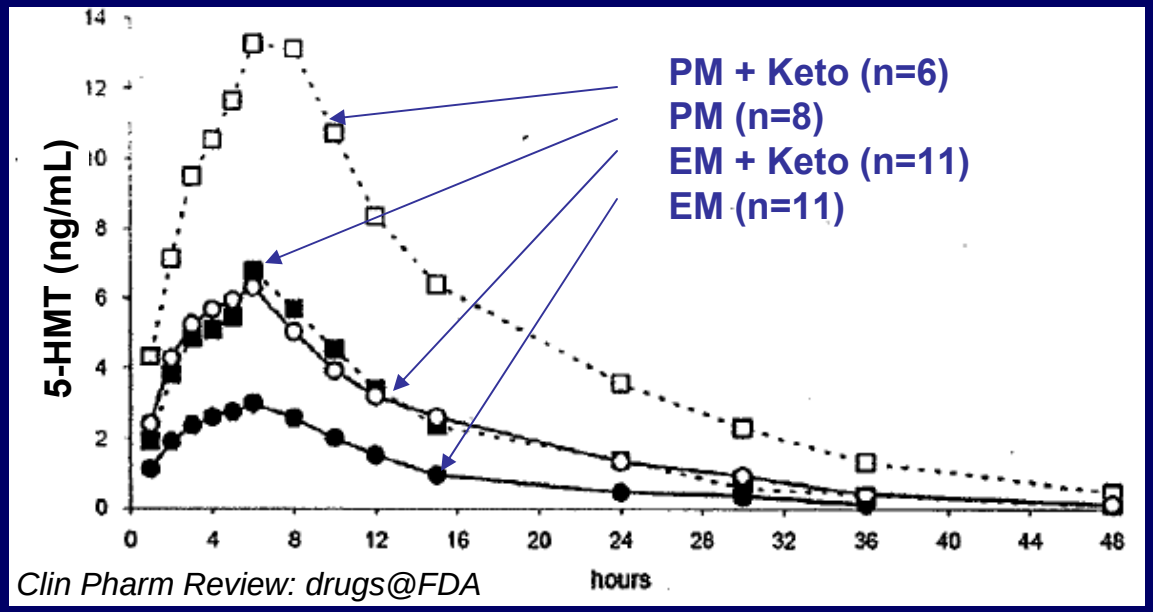
***PBPK model generates PK profiles of interested species with greater mechanistic insights***

# Complex Drug-drug Interactions

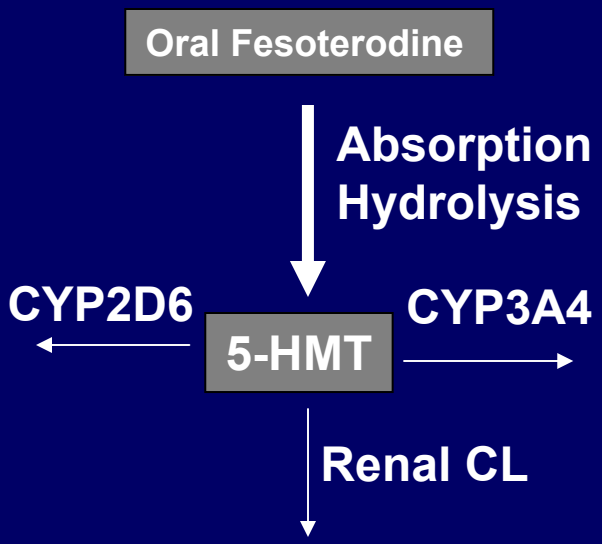
Such “complex drug interaction” scenarios include, but are not limited to:

- 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)

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




*Clin Pharm Review: drugs@FDA*

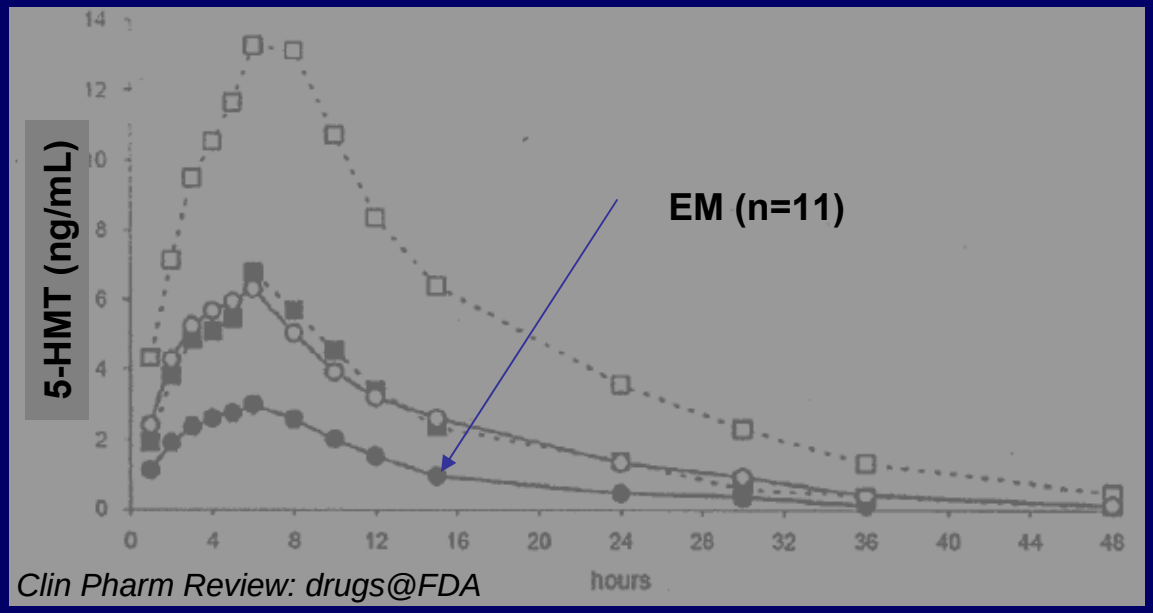



| | Observed | | Predicted | |
|---|---|---|---|---|
| | AUCR | CmaxR | AUCR | CmaxR |
| EM +/- Ketoconazole | 2.3 [a] | 2.0 [a] | 1.9 | 1.8 |
| PM +/- Ketoconazole | 2.5 [a] | 2.1 [a] | 3.3 | 2.4 |
| PM / EM | 2.3 | 2.1 | 1.6 | 1.5 |
| PM + Keto / EM | 5.7 [a] | 4.5 [a] | 5.4 | 3.6 |
| EM +/- Fluconazole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

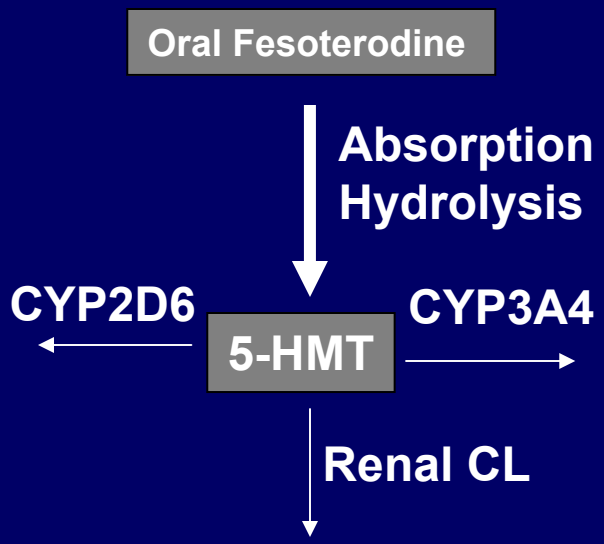
*[a] Clinical Pharmacology Review (drugs@fda); [b] Malhotra et al (2001) B J Clin Pharmacol 72:226-234.*

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

# 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.*

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# Outline

- Update of DDI guidance on metabolites
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# LEARNING and CONFIRMING the DDI of Metabolites

## Example (I): Triazolam, Diltiazem and N-desmethyldiltiazem (MA)

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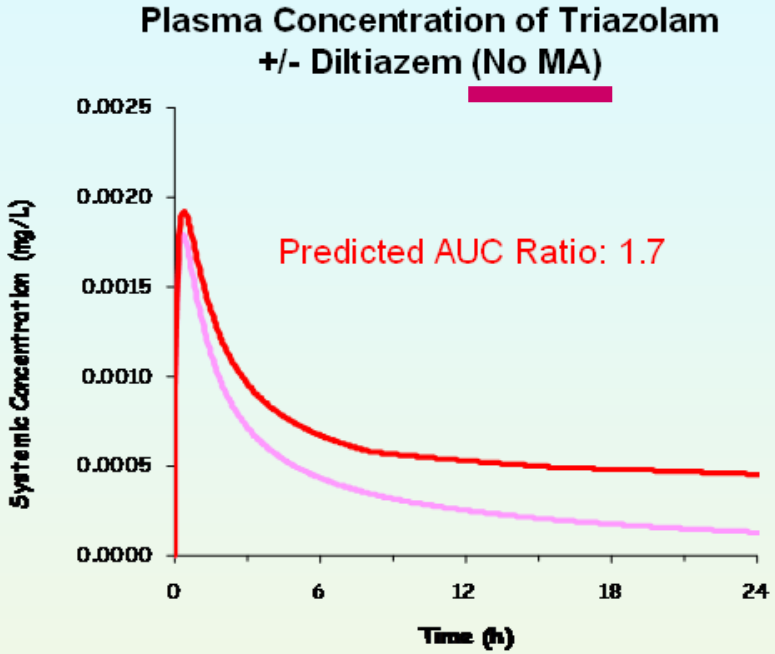
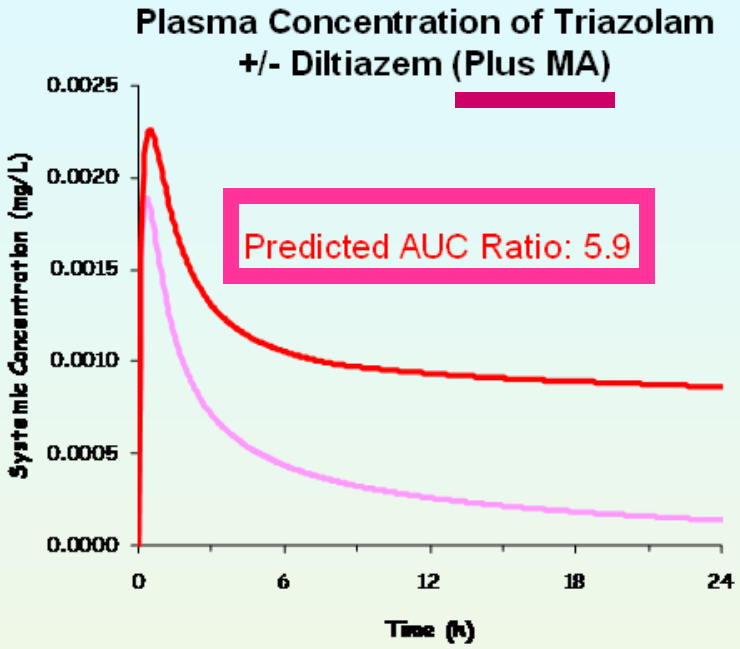
**Observed AUCi/AUC Ratio: 4.4**




CSys Triazolam only — CSys Triazolam plus Diltiazem (MA)

*Courtesy of Dr. Karen Yeo*

Rowland Yeo *et al.* EJPS 2010



*Courtesy of Dr. Yeo (SimCYP)*

# Evaluate Cyclosporin (CsA) Metabolite (AM1) as Transporter Inhibitor Using PBPK

## Summary of CsA and AM1 $IC_{50}$ data

| | $IC_{50}$ ±SD (μM) | | $IC_{50}$ shift (fold) |
|---|---|---|---|
| **Cyclosporine** | | | |
| OATP1B1 | 0.198 ±0.069 | **0.019 ±0.007** | 12 (5.3-21) |
| OATP1B3 | 0.162 ±0.056 | **0.032 ±0.003** | 5.2 (3.8-6.7) |
| **AM1** | | | |
| OATP1B1 | 0.411 ±0.161 | **0.093 ±0.023** | 4.8 (2.9-9.5) |
| OATP1B3 | 0.191 ±0.062 | **0.059 ±0.015** | 3.3 (1.6-4.3) |

- Up to 12-fold increase in CsA potency following pre-incubation (OATP1B1)
- Comparable CsA potencies for OATP1B1 and -1B3
- AM1 less potent than cyclosporine; 'time-dependent' effect as for CsA

**Courtesy Dr. Galetin (U Manchester)**

**Poster # T2292**

*Gelatin: Symposium of Transporter Modeling at AAPS Meeting*

# 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*

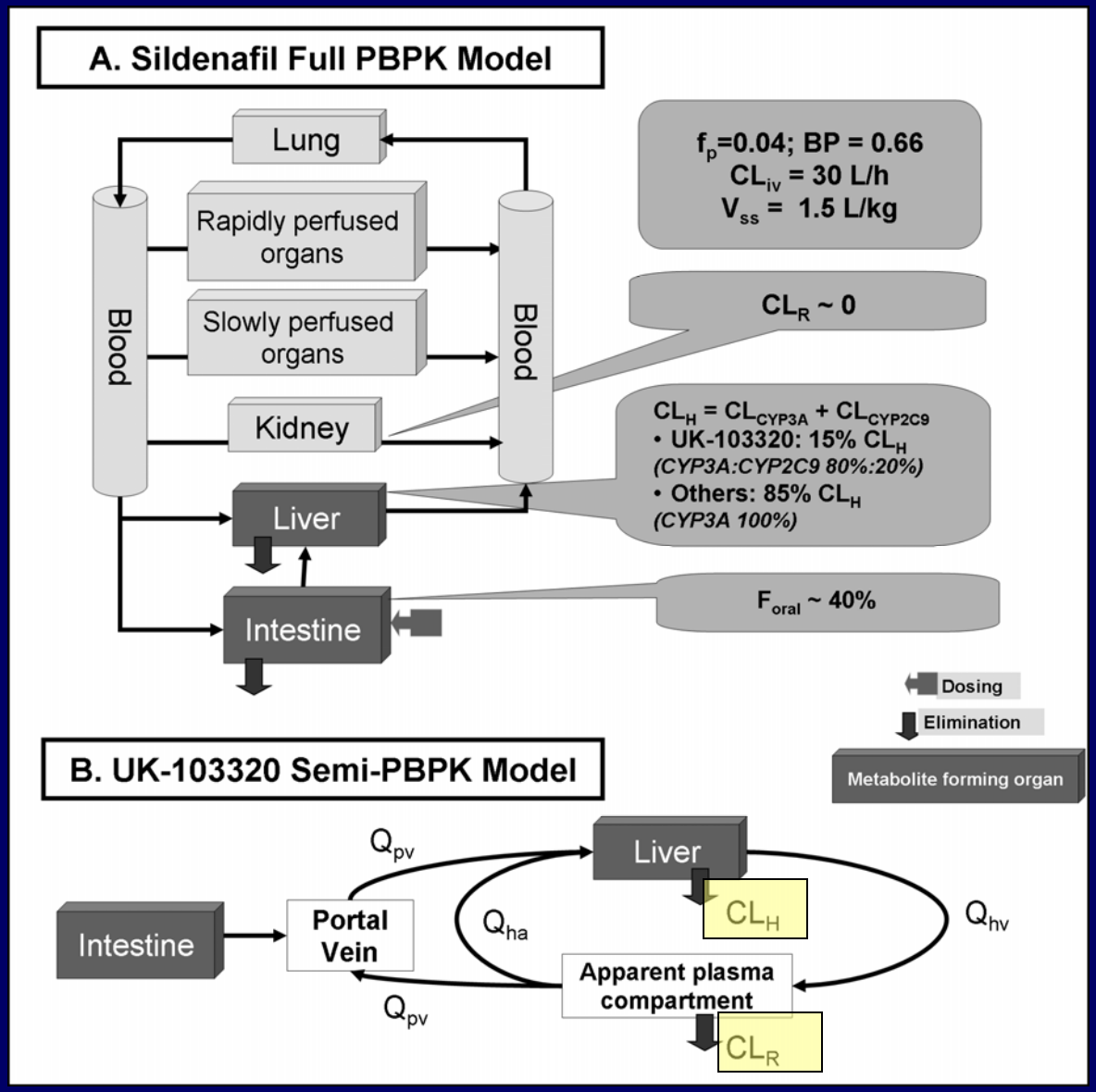
# CONFIRMING the Effect of Renal Impairment (RI) on Hepatic Pathways

| 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*

# Metabolite Considerations: Renal Impairment (RI) or DDI




**Targeted by RI?**

**Assuming UK103320 is solely metabolized by CYP3A4**

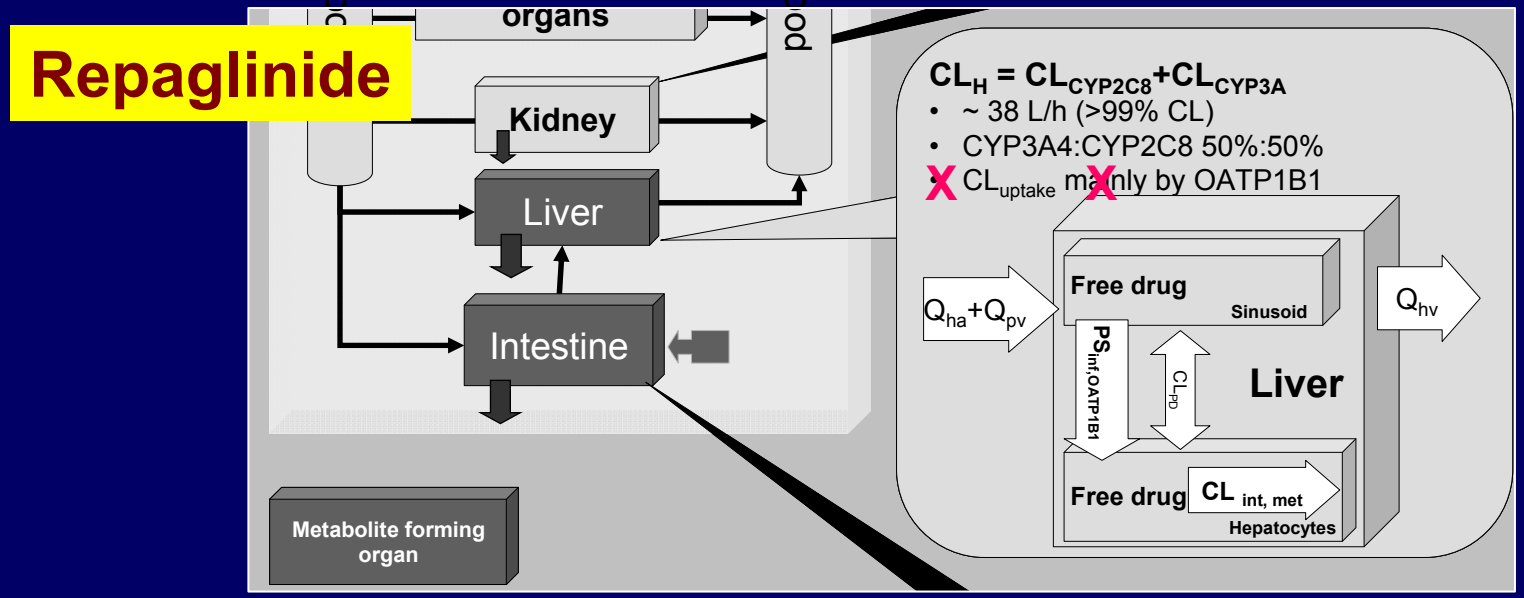
| | AUCR of UK103320 | |
|---|---|---|
| | Severe RI | Inhibition |
| Obs. | 3.0[a] | 1.4[b] |
| Pred. | 2.5 | 5.2 |

[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?***

# Complex DDI of Repaglinide




**X: Inhibition of CYP3A4 and/or CYP2C8**

**AUC Ratio of repaglinide (Niemi et al, Diabetologia. 2003)**

| Gemfibrozil (CYP2C8) | Itraconazole (CYP3A) | Combined |
|---|---|---|
| 8.1 | 1.4 | 19.3 |

# 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

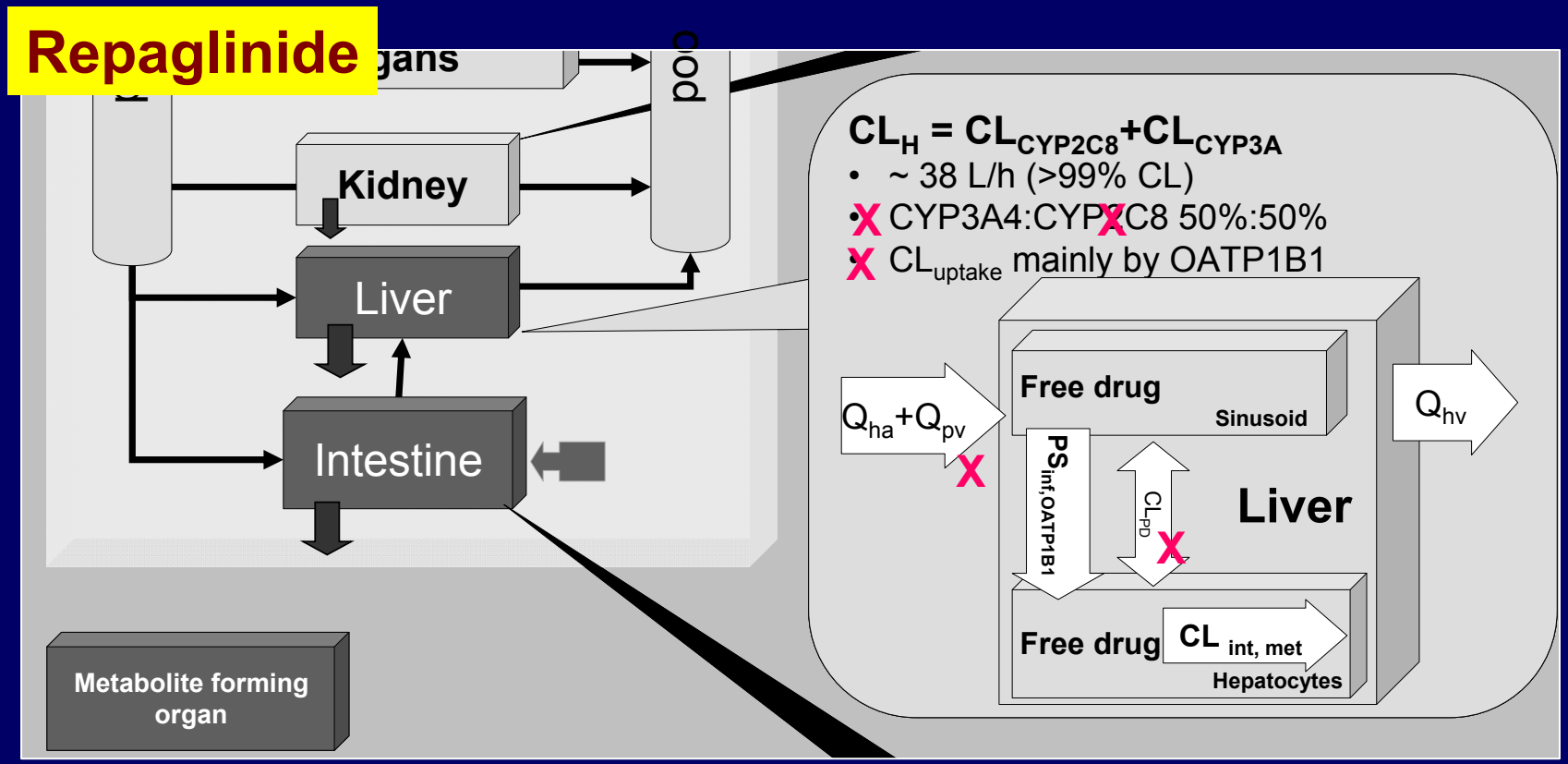
  Range **CYP2C8** Kinact/Kapp: 0.1 - 0.67

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



*Courtesy of Dr. Yeo (SimCYP)*

# Complex DDI of Gemfibrozil – Repaglinide




**X: Multiple processes by parent and metabolite**

# Drug - X

- **Indication: oncology**
- **[I]/$K_i$ for CYP2C9 ~2 (>0.1) or $R_1$ ~3 (2012 FDA draft guidance)**

- **Sponsor requested not to conduct a DDI study with S-warfamin because:**

- *Drug-X has short $t_{1/2}$ (~0.5 hr)*
- *Highly protein bound (fu 0.07)*
- *Negative PBPK predicted DDI (warfarin AUCR ~1.0)*
- *No safety signal in patients taking Drug-X and warfamin (note at a dose lower than clinical dose)*



*Zhao et al, Clin Pharmacol Ther 2011 (Case No 1)*

# Drug - X

- ***However, AUC values of several metabolites are greater than 25% of that of the parent drug.***

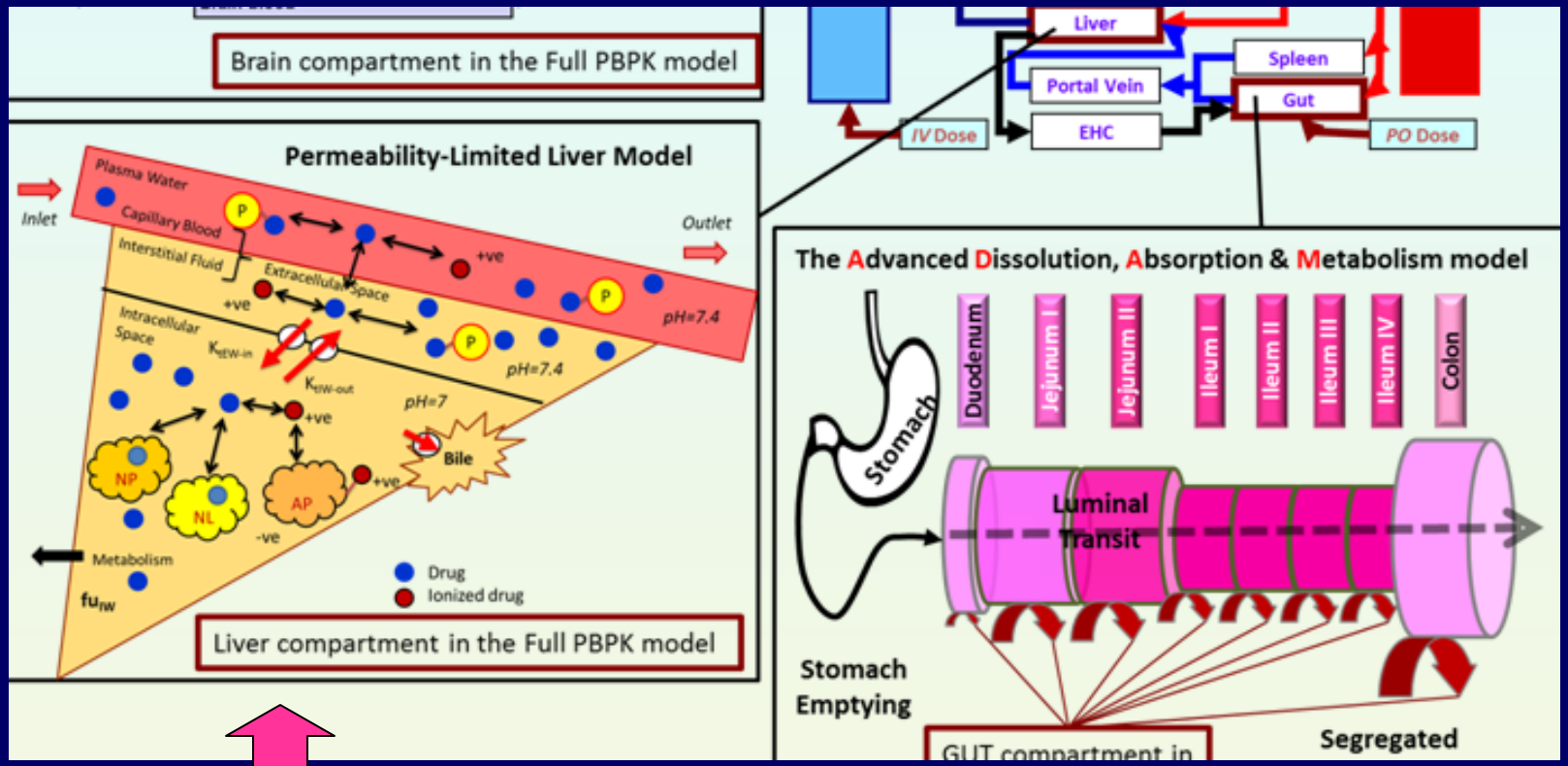
- ***Reviewer's PBPK simulation showed more than 25% increase (AUCR>1.25) in warfarin exposure assuming similar or 10x more potent Ki, and recommended sponsor to obtain in vitro inhibition data for Drug-X metabolites.***

- ***In vitro data suggested that one metabolite had comparable R1 as parent, and sponsor decided to conduct CYP2C9 clinical DDI study***

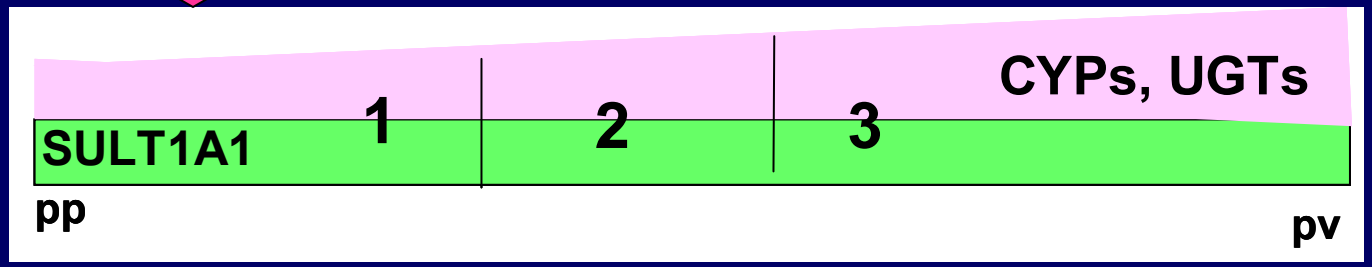


*Zhao et al, Clin Pharmacol Ther 2011 (Case No 1)*

# Future: Integration of Heterogeneity




*Courtesy of Prof. Rostami-Hodjegan (U Manchester)*




*Courtesy of Prof. Pang (U Toronto)*

# Conclusions

- **Drug metabolites may be involved with clinically significant drug-drug interactions, and the significance depends on:**
  - *Metabolite exposure and disposition after parent drug administration*
  - *Pharmacological/toxicological relevance*
  - *Enzyme/transporter inhibition/induction mechanisms*

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

# Acknowledgements

**FDA**

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**External**

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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*

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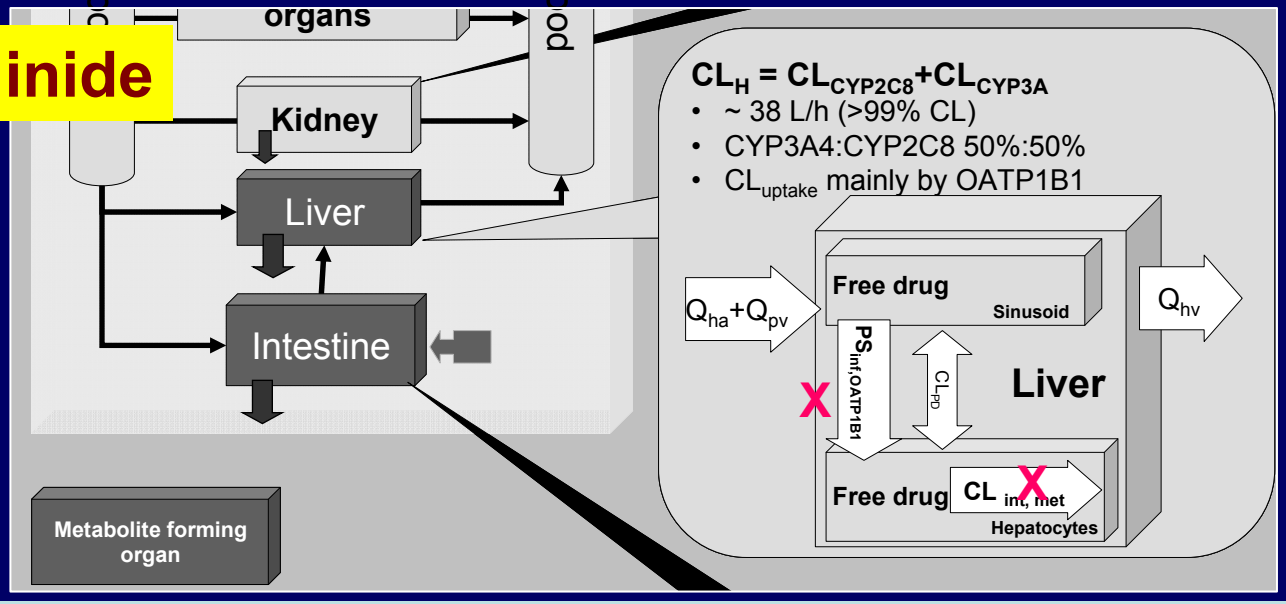
# LEARNING the Effect of Renal Impairment on $CL_h$

**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**