AAPS Annual Meeting
"Emerging Transporters and Topics Beyond the ITC White Paper"
Chicago, IL
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A US Regulator's Perspective on Evaluation of Transporters

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Drugs

Guidance, Compliance & Regulatory Information

- Guidances (Drugs)
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- International Conference on

Clinical Pharmacology

Below is a sortable listing of Clinical Pharmacology Guidances

Category	Title	Type	Date
Clinical Pharmacology	Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling (PDF - 363KB)	Draft Guidance	02/08/05
Clinical Pharmacology	Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies (PDF - 531KB)	Draft Guidance	02/17/11
Clinical Pharmacology	Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (PDF - 221KB)	Final Guidance	05/05/03
Clinical Pharmacology	Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application (PDF - 519KB)	Final Guidance	02/01/87
Clinical Pharmacology	General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (PDF - 37KB)	Draft Guidance	11/01/98
Clinical Pharmacology	Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (PDF - 319KB)	Draft Guidance	03/22/10
Clinical Pharmacology	Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (PDF - 222KB)	Final Guidance	05/30/03
Clinical Pharmacology	Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling (PDF - 324KB)	Draft Guidance	11/01/04
Clinical Pharmacology	Population Pharmacokinetics (PDF - 135KB)	Final Guidance	02/01/99
Clinical Pharmacology	Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (PDF - 827KB)	Draft Guidance	02/17/12

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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

What is New?

Draft Guidance Published in February 2012

- Many decision trees and tables
- Model-based evaluation of metabolism-based interactions
  - basic and mechanistic models, including PBPK
  - consideration of metabolites
- Transporter-based interactions
- Therapeutic protein-drug interactions
- Other enzymes (e.g., UGT)
- Labeling section

Public Comments Received (by May 2012)

- Twenty seven sets of comments received (PhRMA, BIO, IQC, 22 individual companies, 2 individuals)
- Other comments via emails, informal meetings
- Various research collaborations
- Revision is ongoing

Why Evaluate Transporter-based Interactions?

Transport-based Interactions

Gene	Aliases	Tissue	Function	Interacting drug	Substrate (affected drug)	Changes in substrate plasma AUC (AUC ratios)
ABC transporters of clinical importance in the absorption, disposition, and excretion of drugs						
ABCB1	P-gp, MDR1	Intestinal enterocyte, kidney proximal tubule, hepatocyte (canalicular), brain endothelia	Efflux	Dronedarone	Digoxin	2.6-fold
				Quinidine	Digoxin	1.7-fold
				Ranolazine	Digoxin	1.6-fold
				Tipranavir/ritonavir	Loperamide	0.5-fold
				Tipranavir/Ritonavir	Saquinavir/ ritonavir	0.2-fold
ABCG2	BCRP	Intestinal enterocyte, hepatocyte (canalicular), kidney proximal tubule, brain endothelia, placenta, stem cells, mammary gland (lactating)	Efflux	GF120918	Topotecan	2.4-fold
SLC transporters of clinical importance in the disposition and excretion of drugs						
SLCO1B1	OATP1B1, OATP-C, OATP2, LST-1	Hepatocyte (sinusoidal)	Uptake	Lopinavir/ritonavir	Bosentan	5-48 fold[a]
				Cyclosporine	Pravastatin	9.9-fold
				Rifampin (single dose)	Glyburide	2.3-fold
				Cyclosporine	Rosuvastatin	7.1-fold[b]
				Cyclosporine	Pitavastatin	4.6-fold
SLCO1B3	OATP1B3, OATP-8			Lopinavir/ritonavir	Rosuvastatin	2.1-fold
SLC22A2	OCT2	Kidney proximal tubule	Uptake	Cimetidine	Dofetilide	1.5-fold
				Cimetidine	Pindolol	1.5-fold
				Cimetidine	Metformin	1.4-fold
SLC22A6	OAT1	Kidney proximal tubule, placenta	Uptake	Probenecid	Cephradine	3.6-fold
				Probenecid	Cidofovir	1.5-fold
				Probenecid	Acyclovir	1.4-fold
SLC22A8	OAT3	Kidney proximal tubule, choroid plexus, brain endothelia	Uptake	Probenecid	Furosemide	2.9-fold

The transporters listed are the likely transporters; however, because the studies are *in vivo*, it is not possible to assign definitively specific transporters to these interactions. ABC, adenosine triphosphate–binding cassette; AUC, area under the curve; BCRP, breast cancer resistance protein; LST, liver-specific transporter; MDR, multidrug resistance; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; P-gp, p-glycoprotein; SLC, solute carrier.

[a]Minimum predose plasma level (C_{Trough}) data from day 4 (48-fold), day 10 (fivefold) after coadministration. [b]Interaction could be partly mediated by BCRP.

Modified from ref. 2 and other sources.

Zhang, Huang, Lesko, Clin Pharmacol Ther, 89, 481-484 (2011)

U.S. Department of Health & Human Services www.hhs.gov

U.S. Food and Drug Administration

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For Consumers

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FDA: Limit Use of 80 mg Simvastatin

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The Food and Drug Administration is recommending that the use of drugs containing 80 mg of simvastatin—the highest approved dose of the popular cholesterol-lowering statin—be sharply curtailed because of the risk of muscle injury.

FDA says this dose should only be used by patients who have been taking it for 12 months or longer without ill effect.

"Our overall goal is to get doctors to not start patients on 80 mg of simvastatin," says Eric Colman, M.D., deputy director of FDA's Division of Metabolism and Endocrinology Products.

And if health care professionals find that patients now taking 40 mg of simvastatin aren't meeting their LDL cholesterol goal, FDA is advising them to choose a different statin rather than raising the simvastatin dose to 80 mg, says Amy Egan, M.D., deputy director for safety in the FDA division.

All statins, despite their proven benefit in lowering the risk of heart attacks and strokes, carry some risk of an injury called myopathy, characterized by unexplained muscle weakness or pain.

But the risk is greater for patients who take the 80 mg doses of simvastatin, especially in the first year of treatment. Colman says the muscle damage is often caused by interactions with other medications. And some people are genetically predisposed towards simvastatin-related myopathy, he says.

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm257884.htm

(2)

DRUG INTERACTIONS

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.3, 4, 5.1, 7.1, 7.2, 7.3, 12.3)

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with simvastatin
Amiodarone, verapamil, diltiazem	Do not exceed 10 mg simvastatin daily
Amlodipine, ranolazine	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- Coumarin anticoagulants: Concomitant use with ZOCOR prolongs INR. Achieve stable INR prior to starting ZOCOR. Monitor INR frequently until stable upon initiation or alteration of ZOCOR therapy. (7.6)

USE IN SPECIFIC POPULATIONS

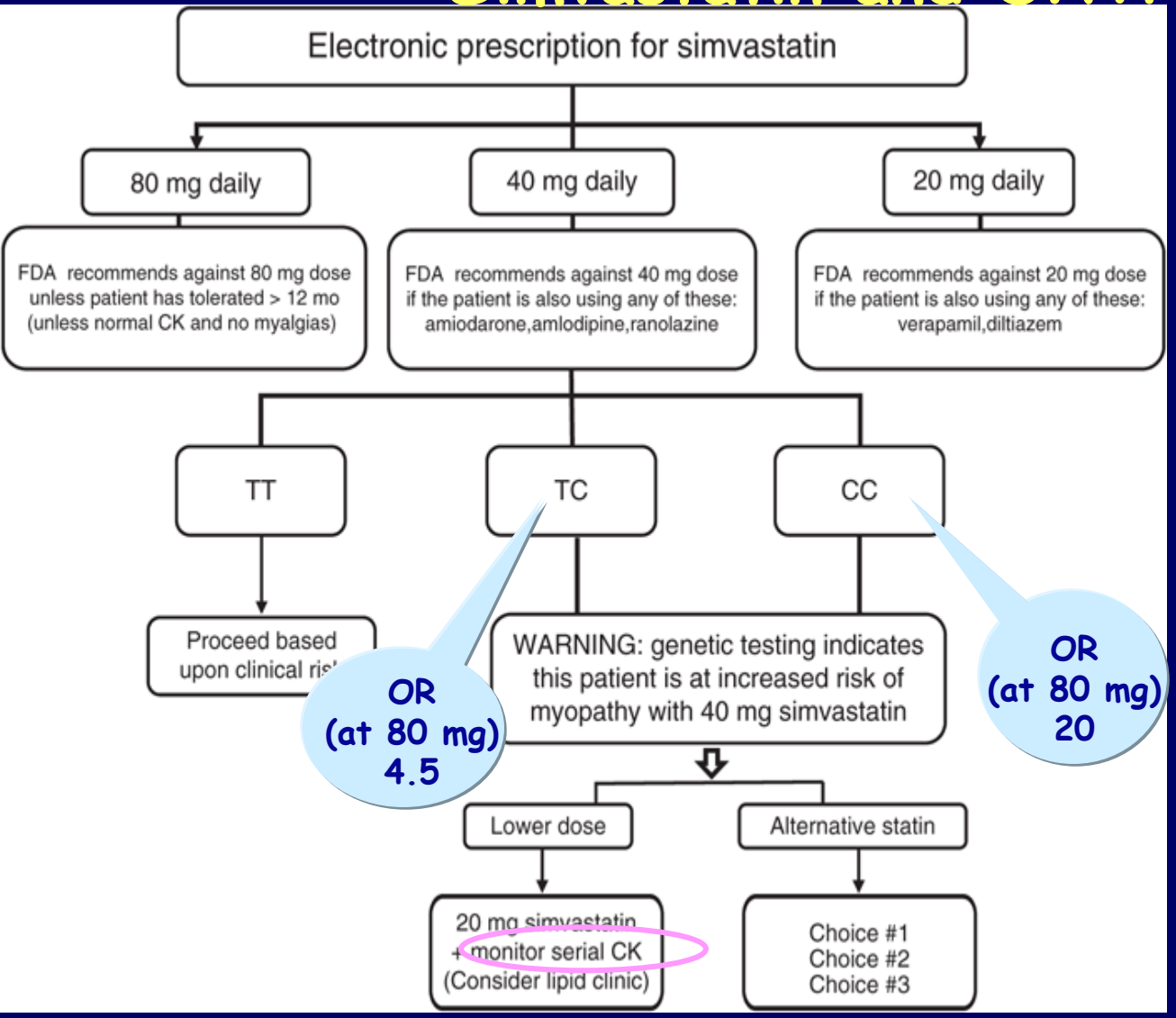
- Severe renal impairment: patients should be started at 5 mg/day and be closely monitored. (2.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2011

Drugs at the FDA (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/
(http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019766s077s082lbl.pdf
Highlights section of Simvastatin labeling (Zocor)

Clinical Pharmacogenomics Implementation Consortium Recommendation - Simvastatin and OATP1B1-



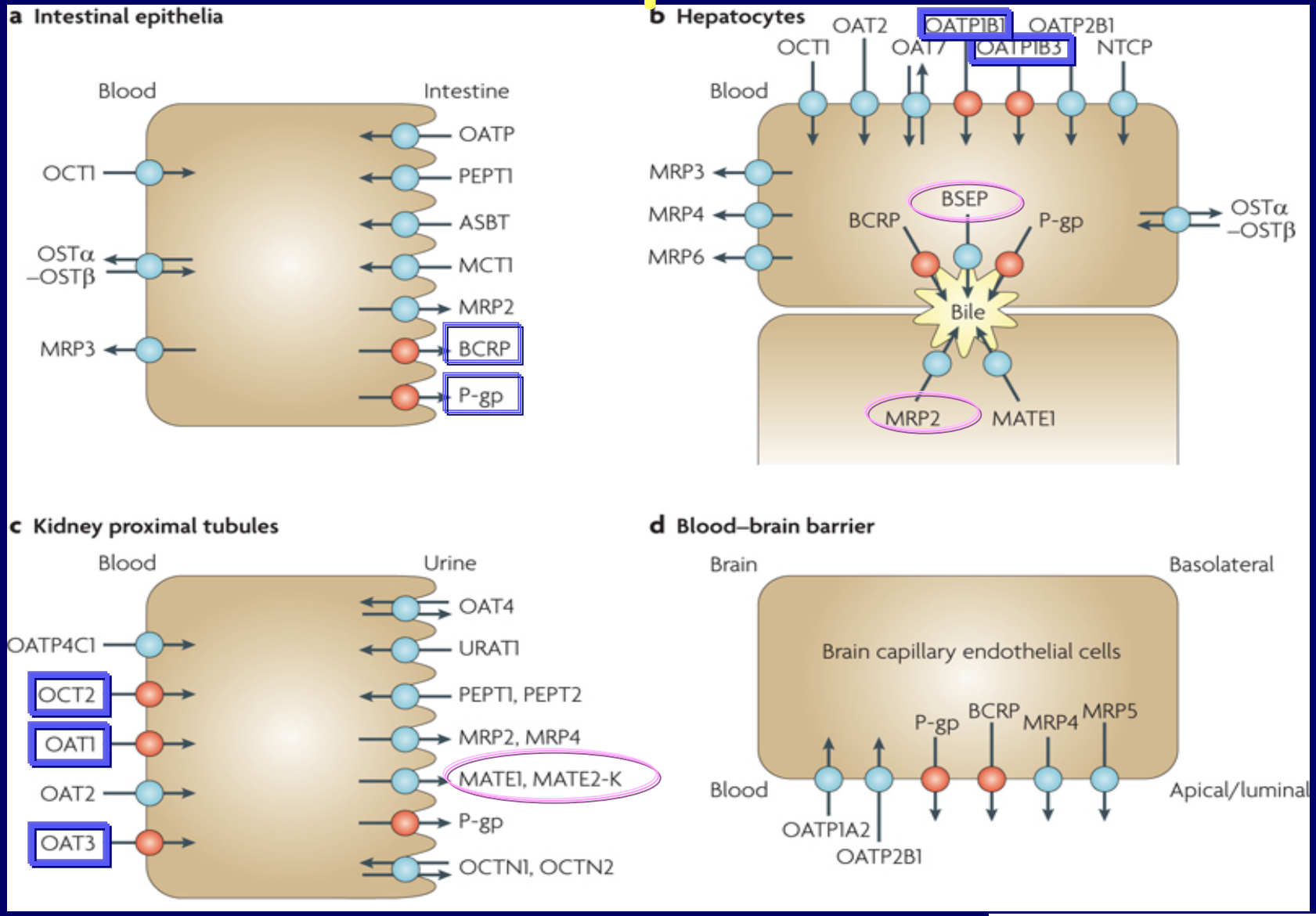
PREDICT (Pharmacogenomics Resource for Enhanced Decisions in Clinical Care and Treatment) decision support algorithm for simvastatin.

Algorithm activated by provider selection of any simvastatin dose during the process of electronic prescribing at Vanderbilt University Medical Center. CK, creatine kinase.

RA Wilke, et al, Clin Pharmacol Ther July 2012

What transporter to Evaluate in Drug Development?

Human Transport Proteins



International Transporter Consortium, Nature Reviews Drug Discovery, 9, 215 - 236, (2010)

Nature Reviews | Drug Discovery

When to Evaluate Transporter-based Interactions?

Evaluation of NME as a Substrate for Transporters—Other Drugs' Effect on NME

All NMEs

Hepatic or biliary Secretion major? e.g., ≥ 25% total clearance?

s

Determine whether NME is an OATP1B1 or OATP1B3 Substrate*

Refer to OATP1B1/1B3 decision tree** for the need to conduct *in Vivo* studies

Renal active secretion major? e.g., ≥ 25% total clearance?

es

Determine whether NME is an OAT1, OAT3 or OCT2 substrate*

Refer to OAT1/3 and OCT2 decision tree** for the need to conduct *in vivo* studies

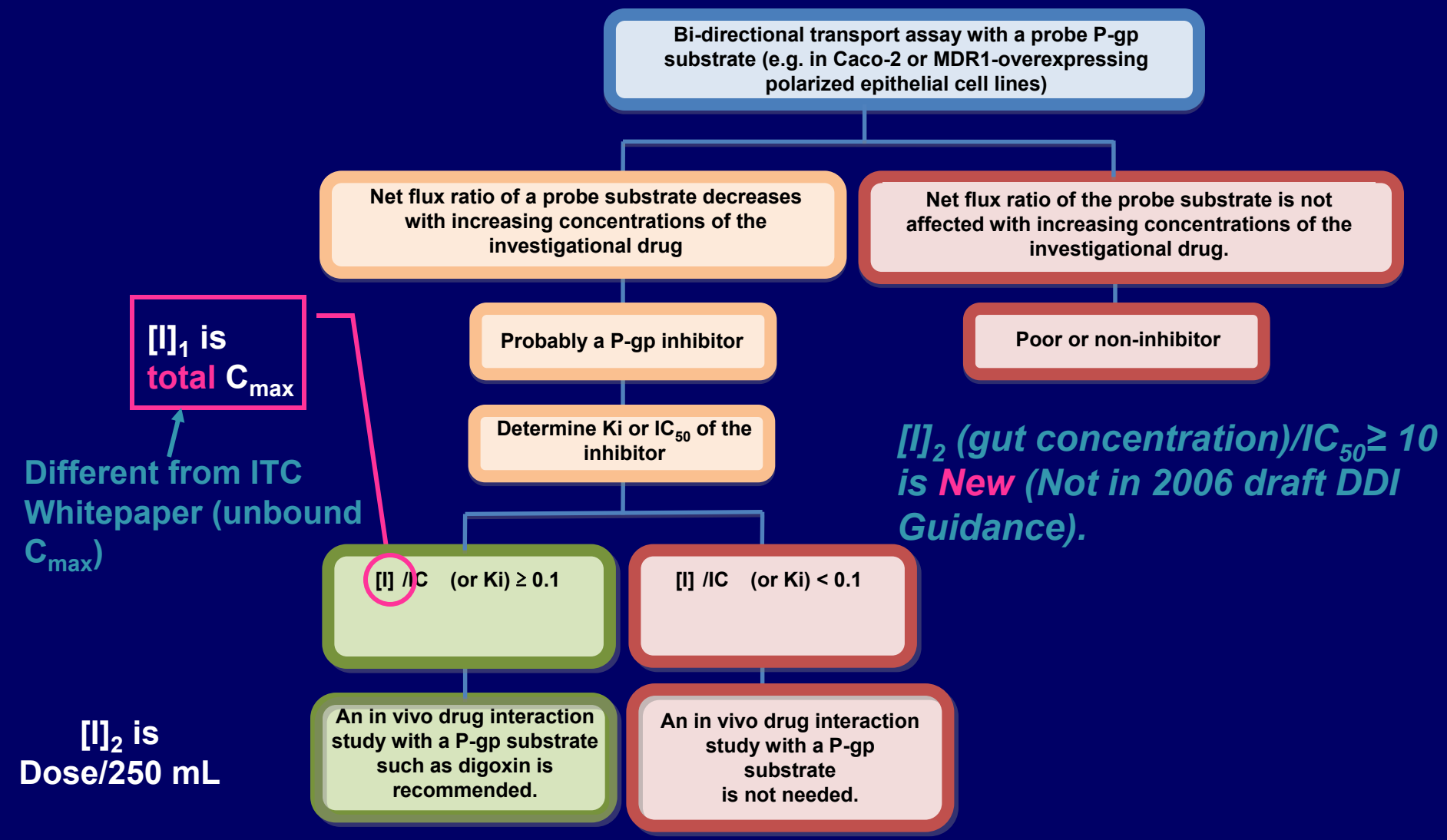
Determine whether NME is a P-gp and/or BCRP substrate *

Refer to P-gp and BCRP decision tree** for the need to conduct *in vivo* studies

* The sponsor has the option to use *in vitro* tools first for the evaluation.

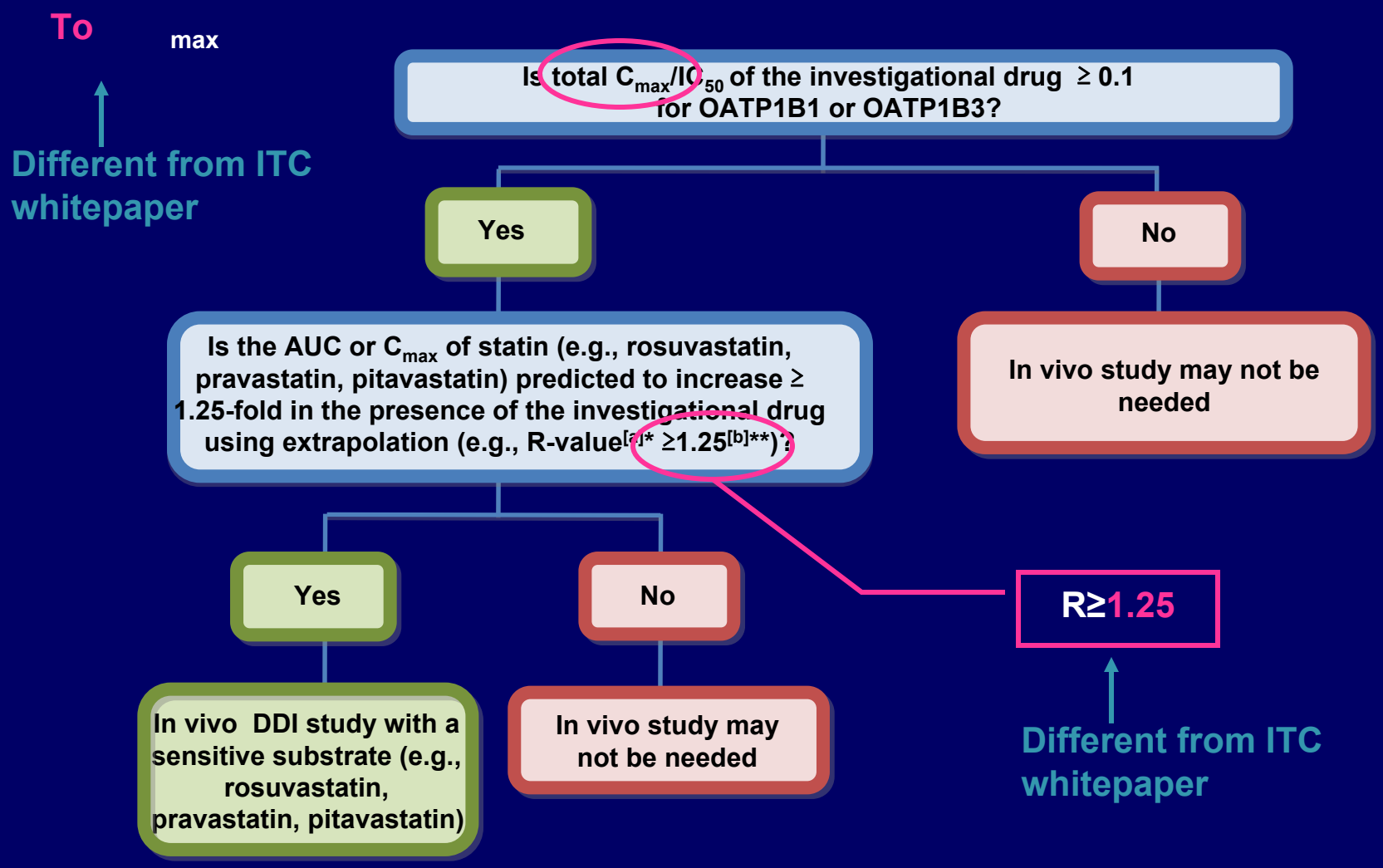
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter

P-gp Inhibition Decision Tree



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

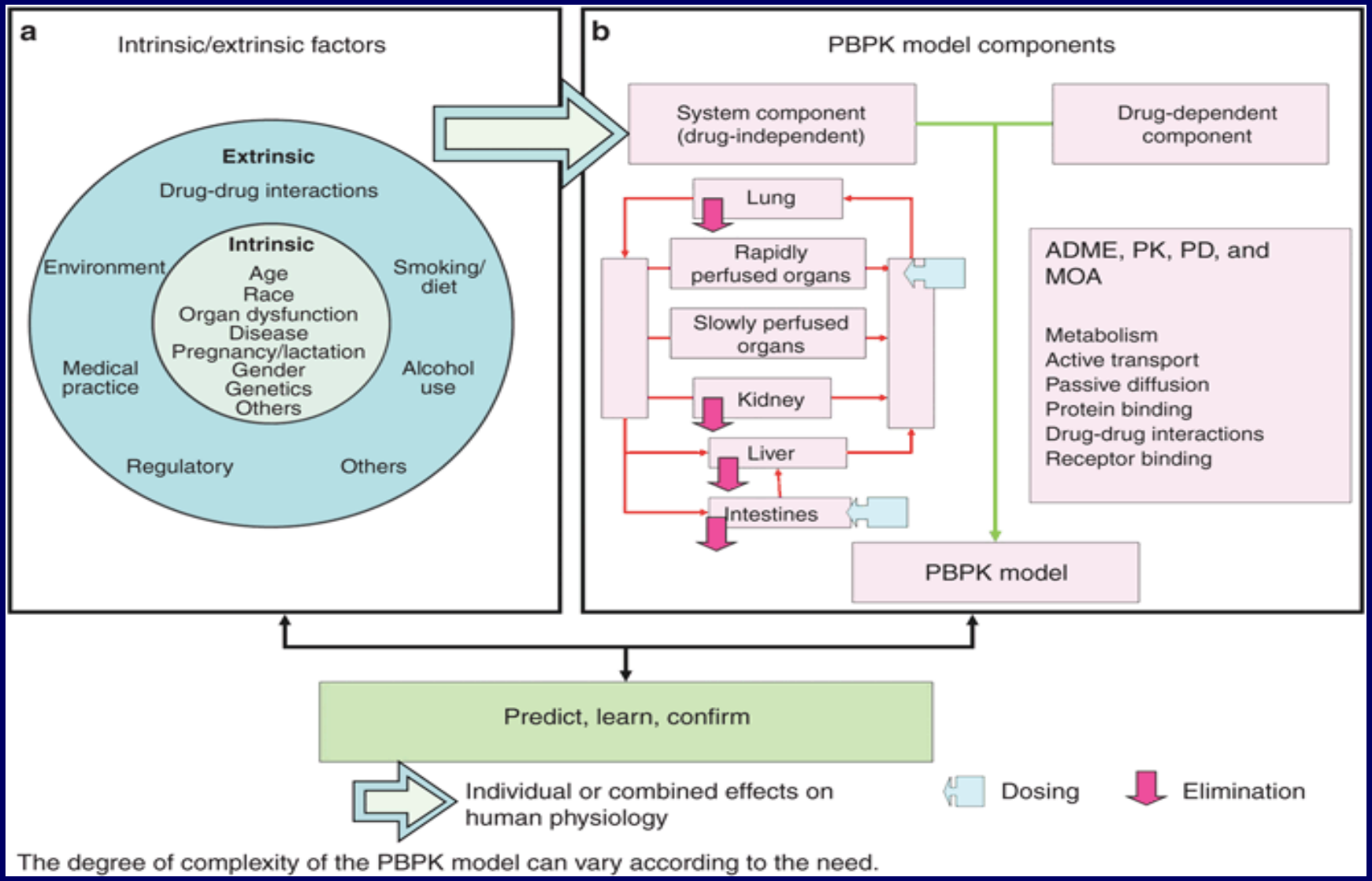
OATP Inhibition Decision Tree



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResource/DrugInteractionsLabeling/ucm093583.htm

Utility of Physiologically-Based Pharmacokinetic (PBPK) Modeling

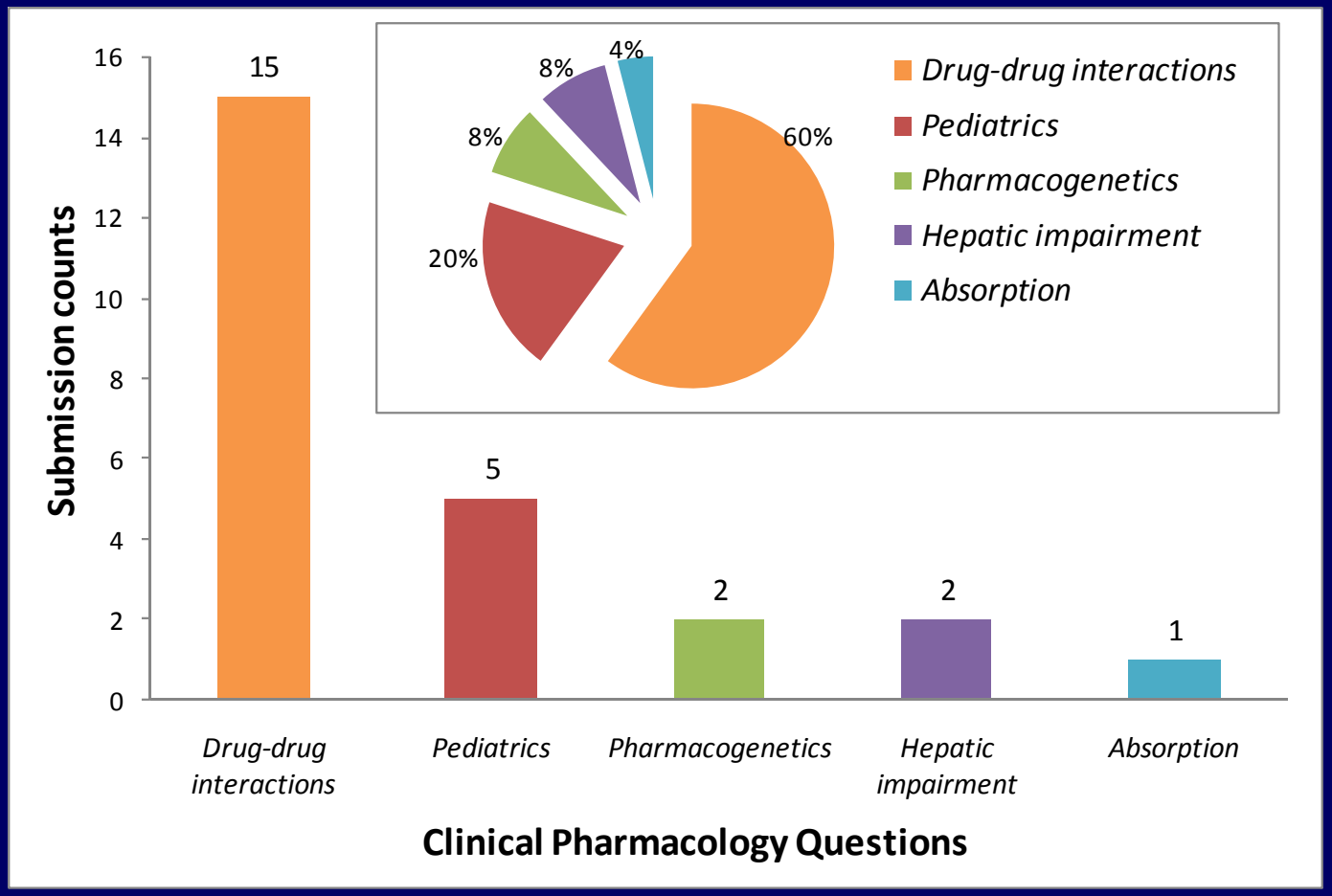
Application of Physiologically-based Pharmacokinetic (PBPK) Modeling



The degree of complexity of the PBPK model can vary according to the need.

<Huang S-M, Rowland M, Clin Pharmacol Ther, 91:542-549 (March, 2012)>
<Zhao P, et al, Clin Pharmacol Ther, 89:259-267 (February, 2011)>

Regulatory Submissions with PBPK Data



2008-July 2010 (2011 CPT): 7 IND, 6 NDA
July 2010-Dec 2011: 7 IND, 5 NDA

<Zhao P, Rowland M, Huang S-M. Clin Pharmacol Ther, July 2012 (supplementary file)>

PBPK Publications by the Office of Clinical Pharmacology

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, Utility of Physiologically-based pharmacokinetics Modeling in Regulatory Review, *Biopharm Drug Dispo, 2012*

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 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

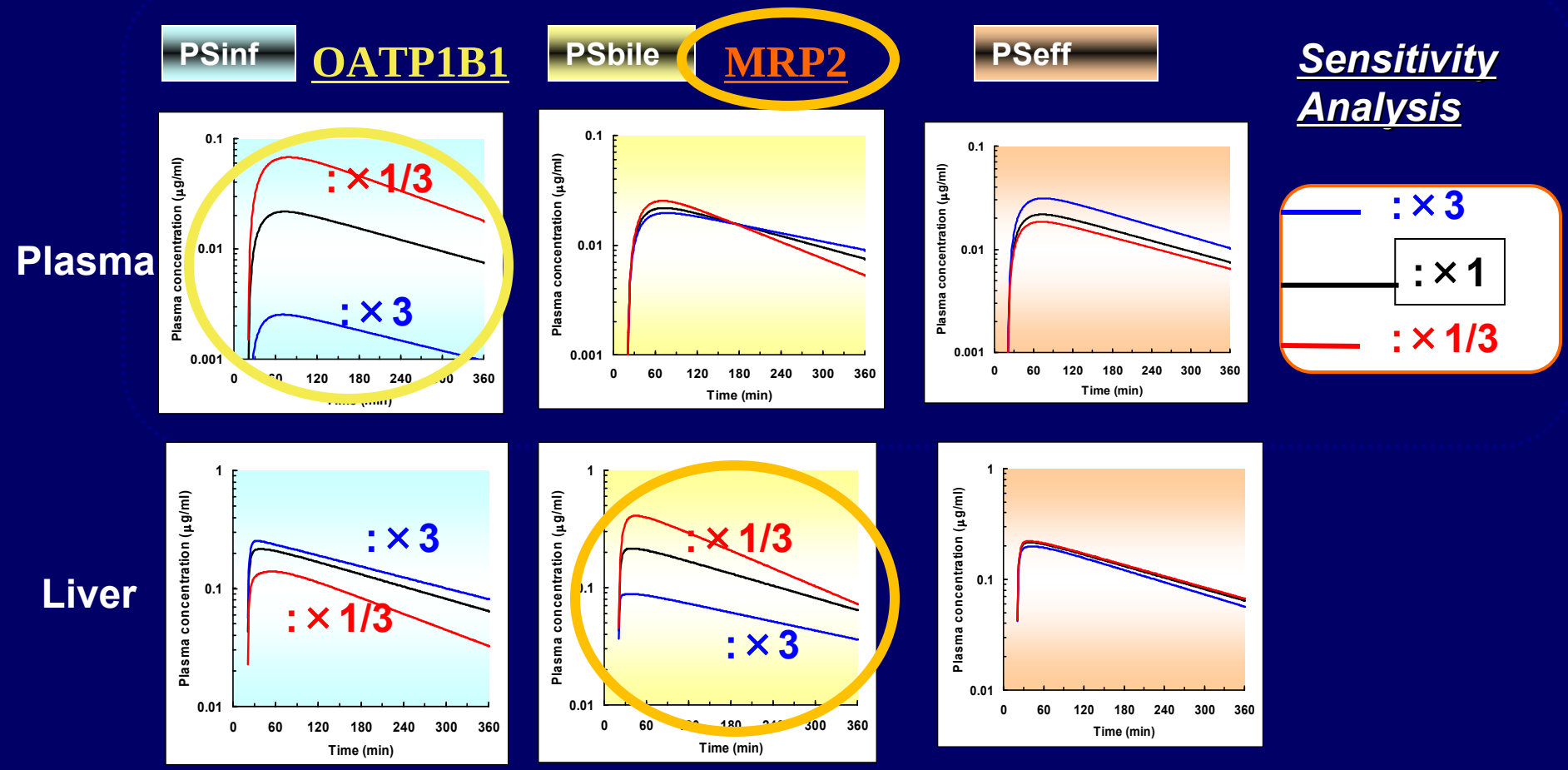
De LT Vieira M, Zhao P, Gil Berglund E, et al, Predicting Drug Interaction Potential by Using a Physiologically-based pharmacokinetics (PBPK) Model: Case Study of Telithromycin, a Time-Dependent CYP3A inhibitor. *Clin Pharmacol Ther, 2012*

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: in press

Application of PBPK
- Pravastatin -



Courtesy of Dr. Yuichi Sugiyama

Modified from Yuichi Sugiyama, Optivia webinar, July 2010
< Watanabe T, et al, JPET, 328:652, 2009>

Summary (1)

- FDA has issued for public comments another draft drug interaction guidance to include recommendations related to the evaluation of transporter-based drug interactions, in addition to CYP & non-CYP based interactions, interactions involving therapeutic proteins, and the use of various mechanistic models (static and dynamic, including PBPK models) to assess combined effect of various patient factors

Summary (2)

- Continual discussion on how best to use various models in the prediction of drug interaction potential is critical

- FDA(OCP)/PhRMA (IQC) groups
- OCP sabbatical scientists
- Consortia such as International transporter Consortium
- Other regulatory agencies (e.g., EMA, MPA)
- Public workshop
- Others

References

FDA Drug Development and Drug Interactions Website;
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

Genomics at the FDA:
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm

Drugs@FDA;
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Clinical Pharmacology Guidance for industry:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

For Consumers:
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm212747.htm