AAPS Annual Meeting
Clinical Pharmacology & Translational Research (CPTR) Open Forum
Chicago, IL
October 16, 2012

Whither Transporters in Drug Development -A US Regulator's View-

Shiew-Mei Huang, Ph.D.
Deputy Director
Office of Clinical Pharmacology
OTS, CDER, FDA

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

A to Z Index Follow FDA FDA V

Most Popular Searches

Home | Food | Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Prod

Drugs

Home Drugs Guidance, Compliance & Regulatory Information Guidances (Drugs)

Guidance, Compliance & Regulatory Information

- Guidances (Drugs)
- Advertising
- Bioequivalence Recommendations for Specific Products
- Biopharmaceutics
- Biosimilarity
- CMC - Microbiology (Chemistry, Manufacturing, and Controls)
- Chemistry, Manufacturing, and Controls (CMC)
- Clinical / Antimicrobial
- Clinical / Medical
- Clinical Pharmacology
- Combination Products
- Concept Papers
- Current Good Manufacturing Practices (CGMPs)/Compliance
- Drug Safety
- Electronic Submissions
- FDAAA (Food and Drug Administration Amendments Act)
- Generics
- Good Review Practices
- Industry Letters
- International Conference on Harmonisation - Efficacy
- 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Pharmacology	Clinical Lactation Studies--Study Design, Data Analysis, and Recommendations for Labeling (PDF - 363KB)	Draft Guidance	02/08/05
Clinical Pharmacology	Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies (PDF - 531KB)	Draft Guidance	02/17/11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General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (PDF - 37KB)	Draft Guidance	11/01/98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in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (PDF - 319KB)	Draft Guidance	03/22/10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

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)

Members of the International Transporter Consortium (2007)

Academia

Leslie Z. Benet:
University of California, San Francisco
Kim L.R. Brouwer:
University of North Carolina at Chapel Hill
Kathleen M. Giacomini:
University of California, San Francisco*
Toshihisa Ishikawa: RIKEN Yokohama Institute*
Dietrich Keppler: German Cancer Research Center
Richard B. Kim: University of Western Ontario
Mikko Niemi: University of Helsinki
Yuichi Sugiyama: University of Tokyo
Peter. W. Swaan: University of Maryland
Stephen H. Wright: University of Arizona

FDA

Shiew Mei Huang:
Food and Drug Administration*
Lei Zhuang:
Food and Drug Administration

Industry

Xiaoyan Chu: Merck
Raymond Evers: Merck
Volker Fischer: Abbott
Katheen M. Hillgren: Lilly Research Laboratories
Keith A. Hoffmaster: Novartis
Caroline A. Lee: Pfizer
Joseph W. Polli: GlaxoSmithKline
Donald J. Tweedie:
Boehringer Ingelheim Pharmaceuticals*
Joseph A. Ware: Genentech
Maciej Zamek-Gliszczynski:
Lilly Research Laboratories

Huang S-M, Zhang L, Giacomini K, Clin Pharmacol Ther 87: 32-36, 2010

White Paper

From the "International Transporter Consortium"

1. **Overview of Transporters**

   Overview, MDR1, BCRP, OAT/OCT, OATP

2. **Methods for Studying Transporters**

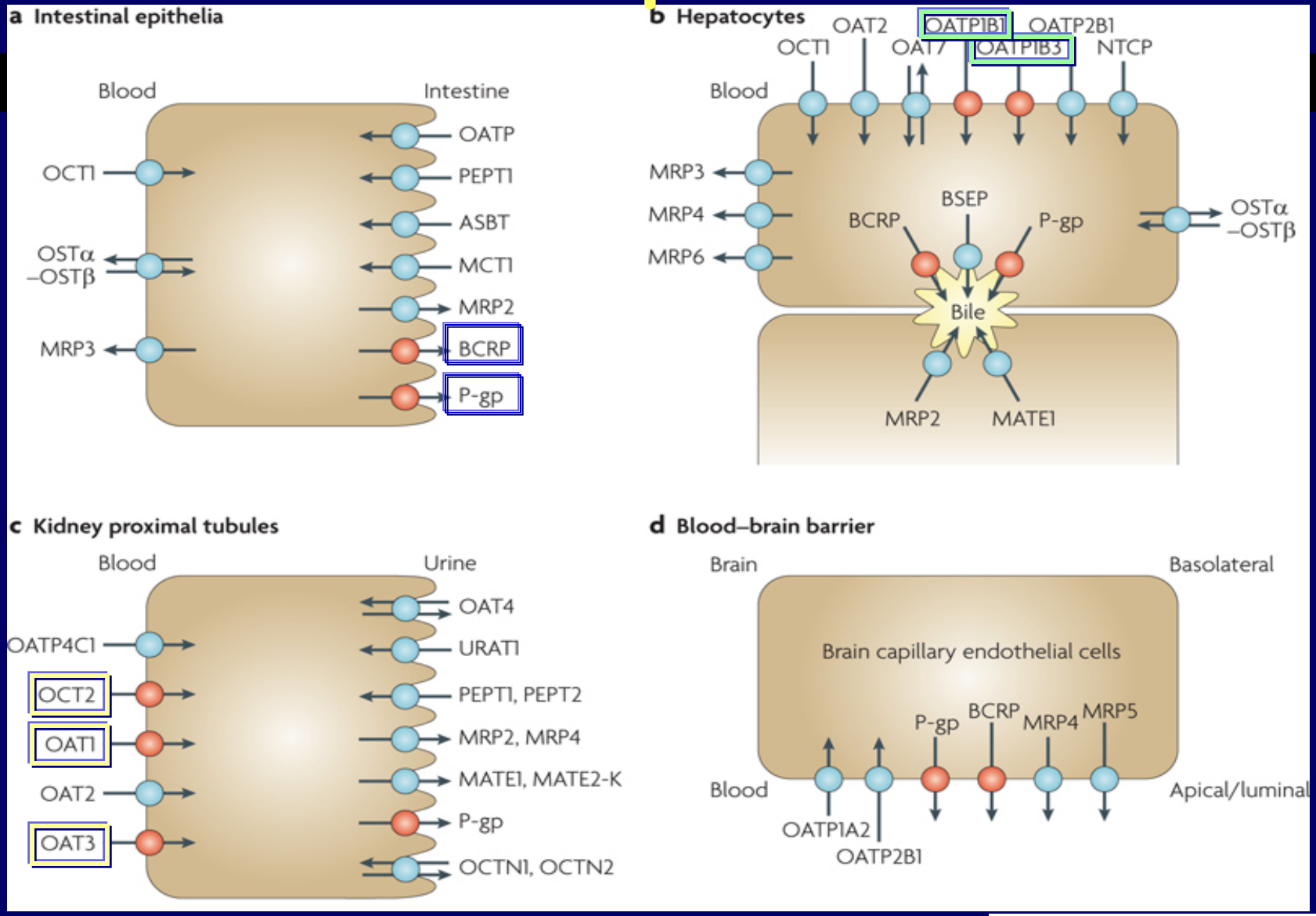
   Cell/membrane models, intact organ/in vivo models; modeling/imaging tools, enzyme/transporter interplay

3. **Drug Development Issues**

   Overview/example cases; decision trees

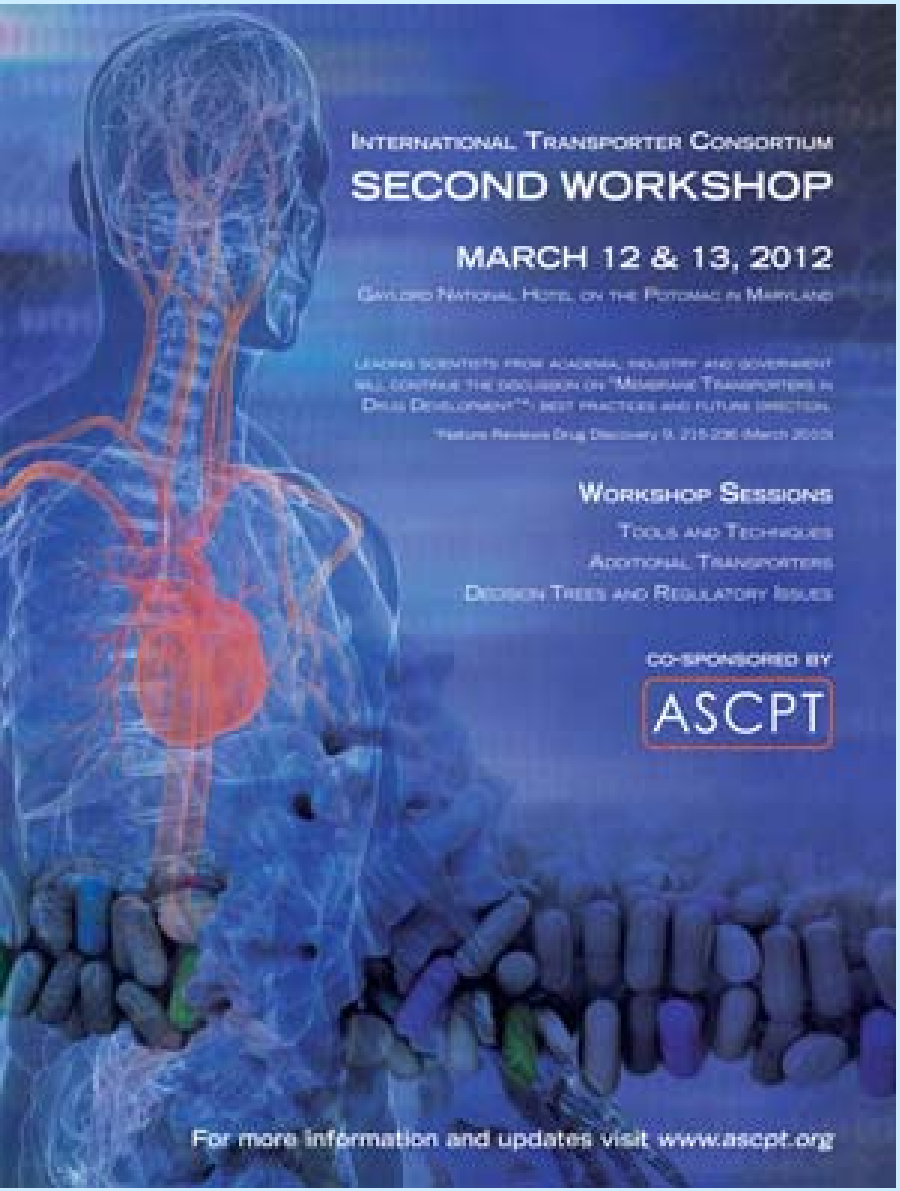
1. International Transporter Consortium, Nature Reviews Drug Discovery, March 2010
2. Huang S-M, Woodcock J, Nature Reviews Drug Discovery, March 2010

Human Transport Proteins



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

Nature Reviews | Drug Discovery



March 12-13, 2012
National Harbor/Washington DC

Papers to be published in Clin Pharmacol Ther November 2012 (Zamek-Gliszczynski et al) and July 2013 issues

Current Executive Committee:
KLR Brouwer, KM Giacomini, S-M Huang, DJ Tweedie, M Zamek-Gliszczynski

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?

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

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

Determine whether NME is an OATP1B1 or OATP1B3 Substrate*

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

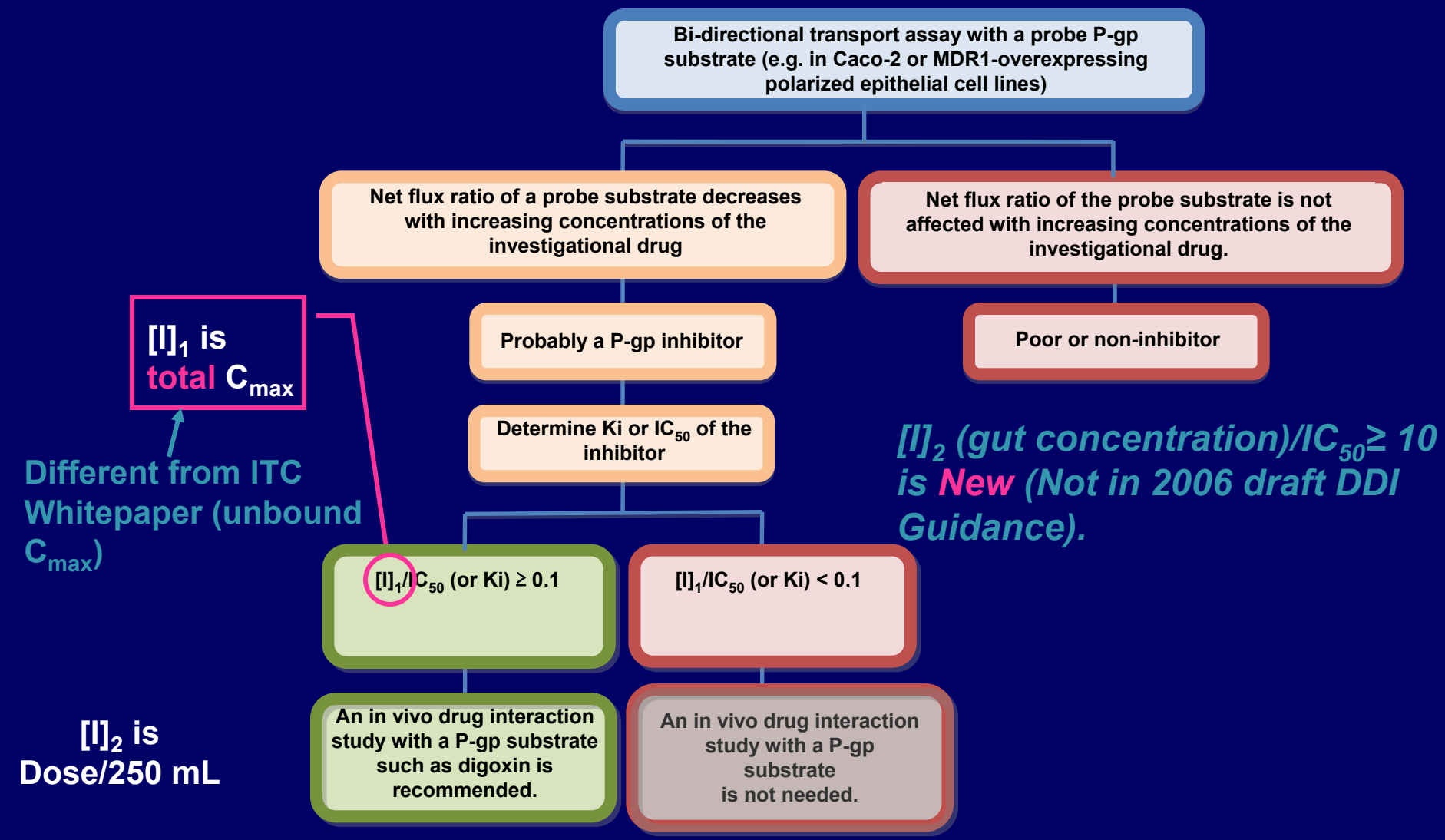
Refer to P-gp and BCRP decision tree for the need to conduct *in vivo* studies**

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

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

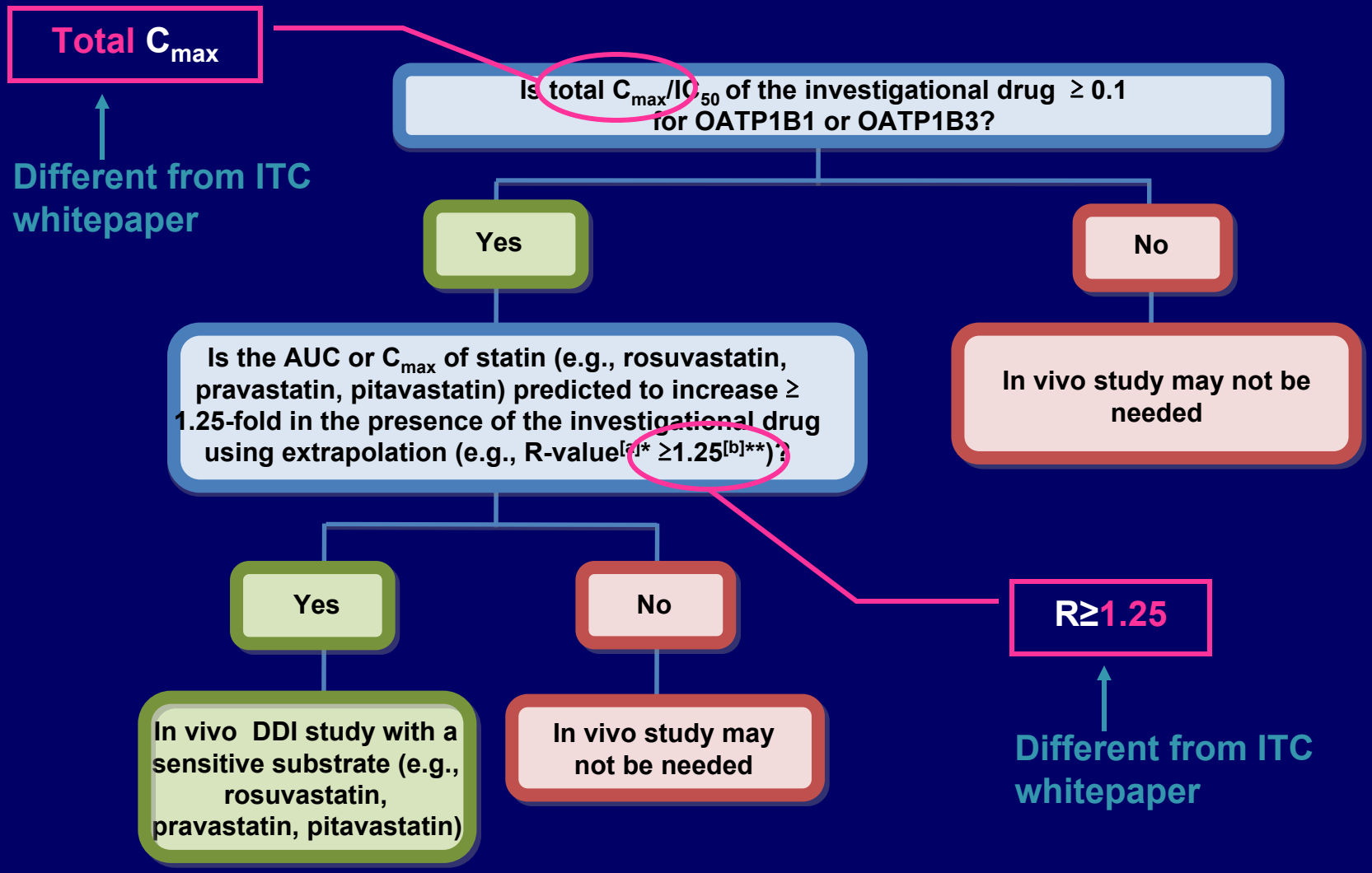
* The sponsor has the option to use *in vitro* tools first for the evaluation.
** Refer to the Transporter Whitepaper (ITC, Nature Reviews Drug Discovery, March 2010) for the decision tree for each transporter

P-gp Inhibition Decision Tree



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

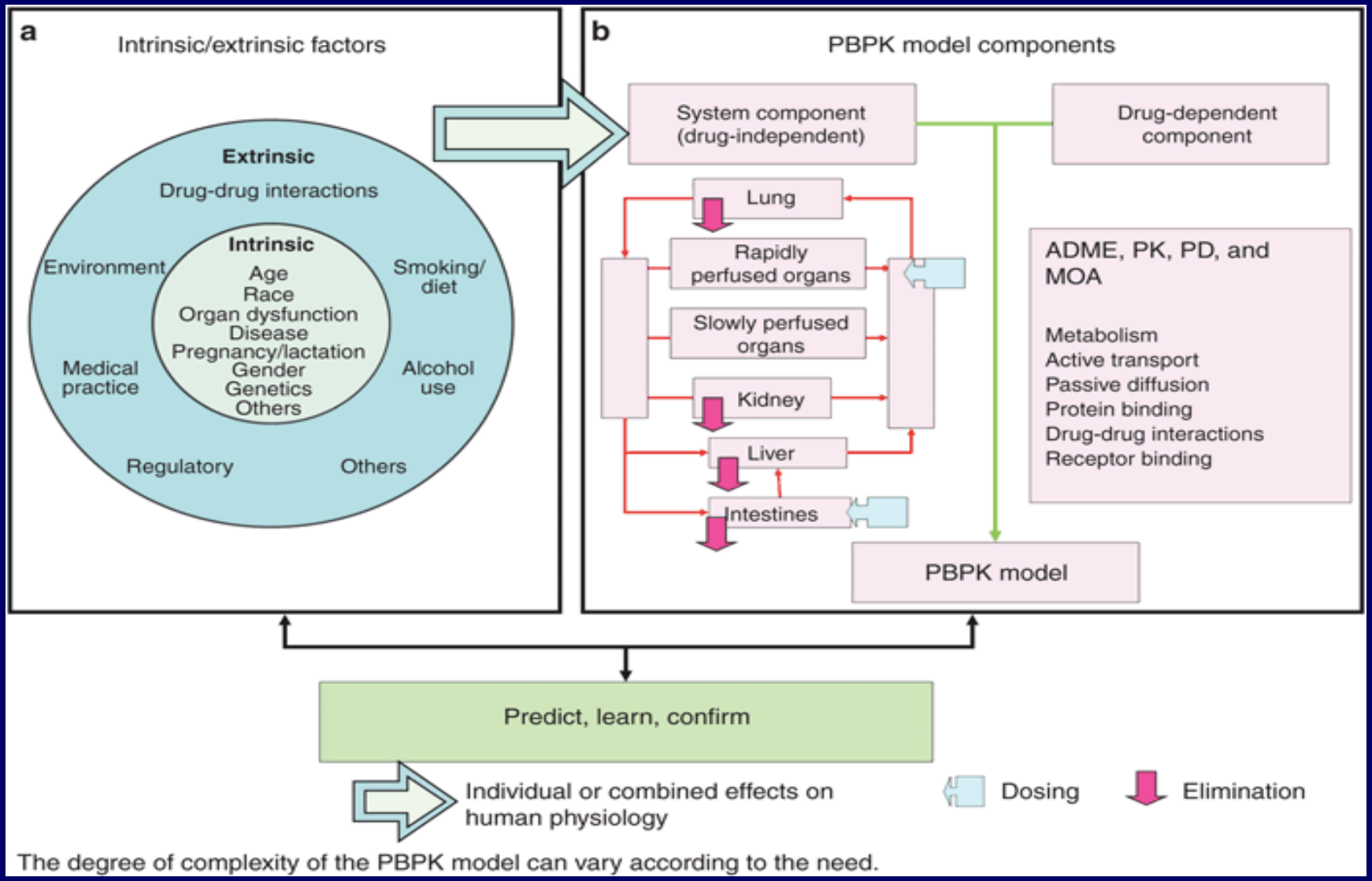
OATP Inhibition Decision Tree



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

Utility of Physiologically-Based Pharmacokinetic (PBPK) Modeling

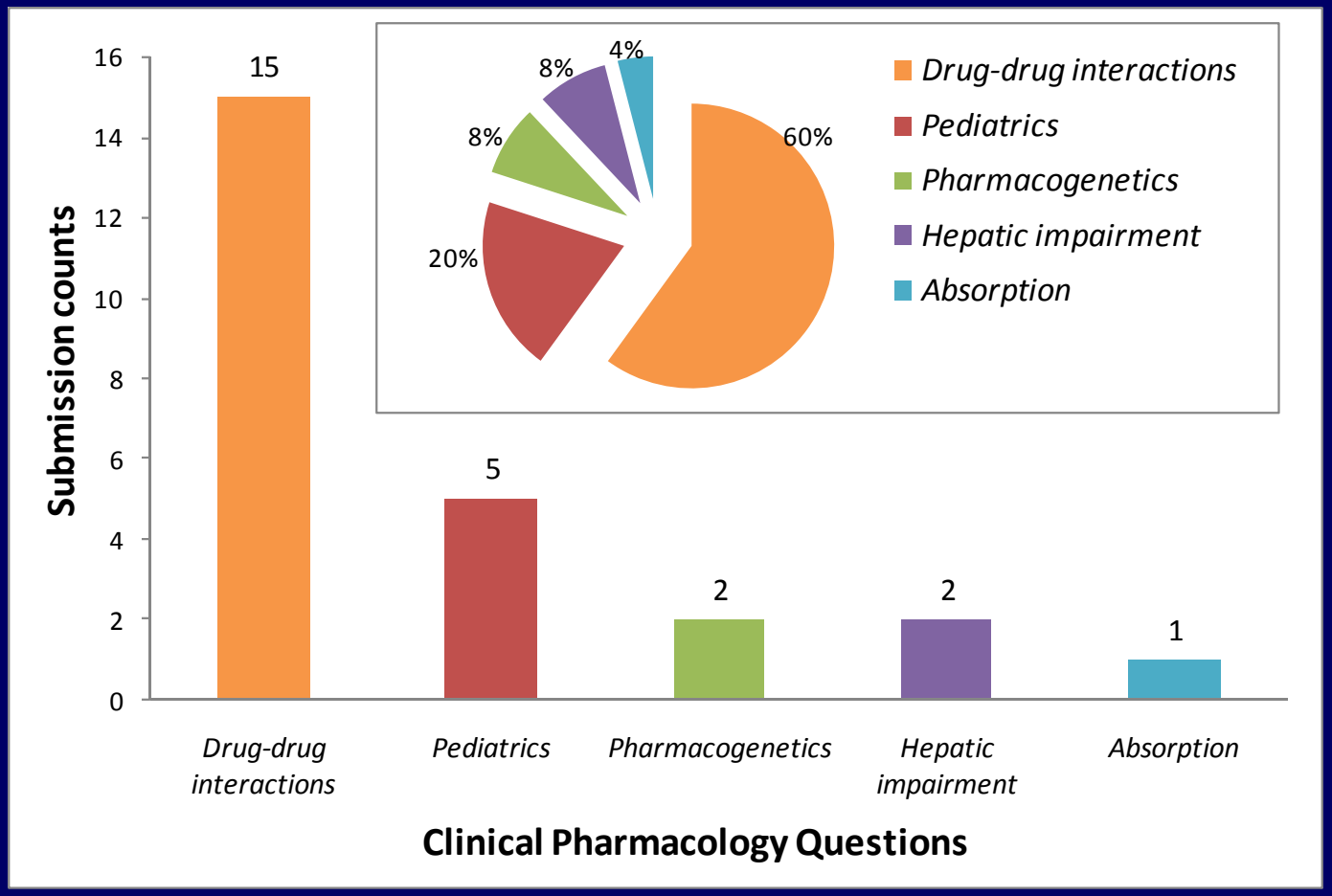
Application of Physiologically-based Pharmacokinetic (PBPK) Modeling



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)>

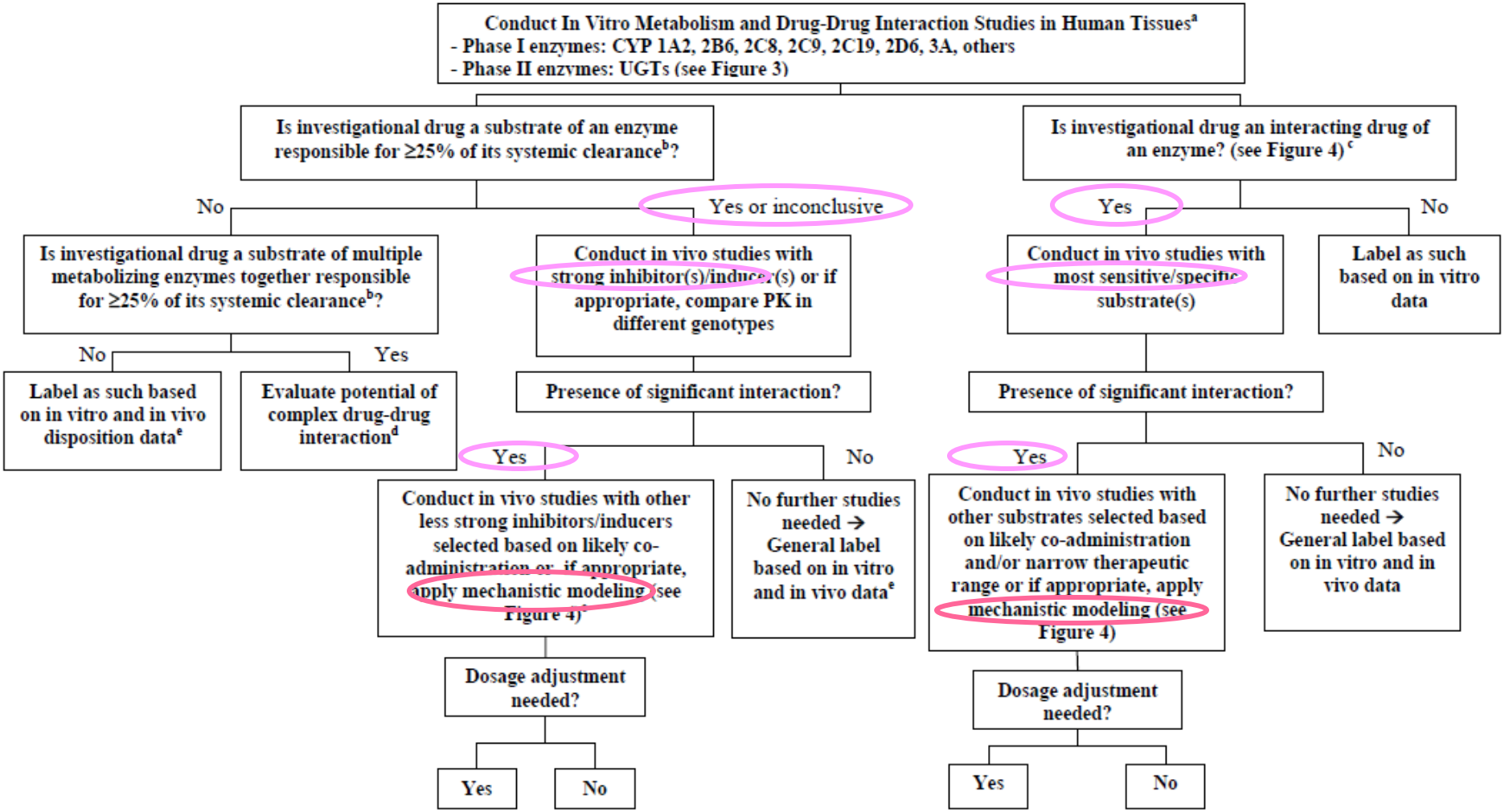
Regulatory Submissions with PBPK Data



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)>

Metabolism-Based Drug-Drug Interaction Studies- Decision Tree



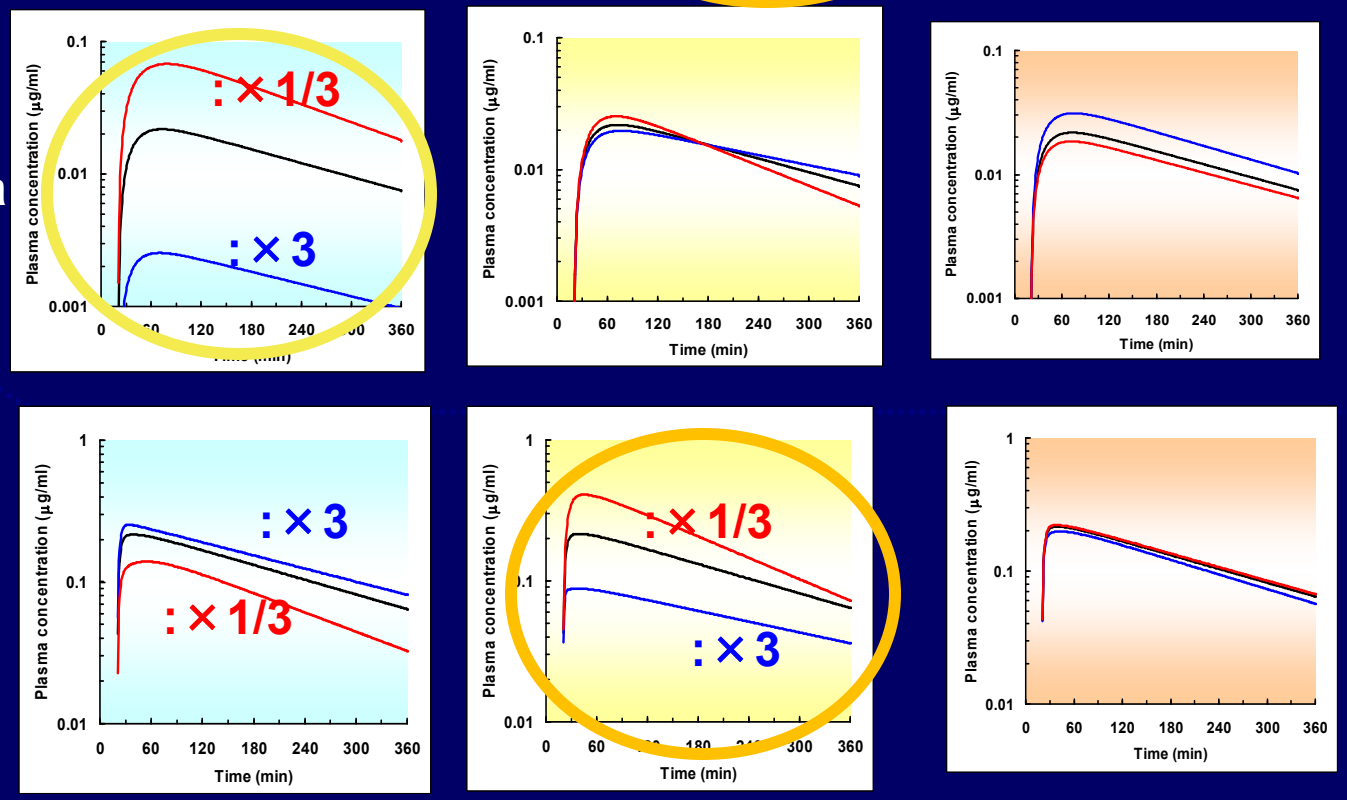
→ Conduct in vivo studies with other less strong inhibitors/inducers selected based on likely co-administration or if appropriate, apply mechanistic modeling

Application of PBPK
- Pravastatin -

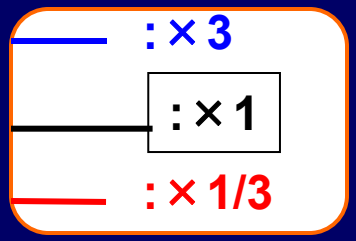
PSinf OATP1B1 PSbile MRP2 PSeff

Plasma

Liver



Sensitivity Analysis



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