PPDM Symposium:
Transporter Proteins III: Clinical Relevance and Applications
FIP Pharmaceutical Sciences World Congress- American Association of Pharmaceutical Scientists Annual meeting, November 18, 2010
New Orleans, LA

The Role of Drug Transporters in Drug Safety - Perspective from the FDA-

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Office of Clinical Pharmacology, OTS
Center for Drug Evaluation and Research, FDA
Shiewmei.huang@fda.hhs.gov

Drugs Withdrawn from the US Market due to Safety Reasons

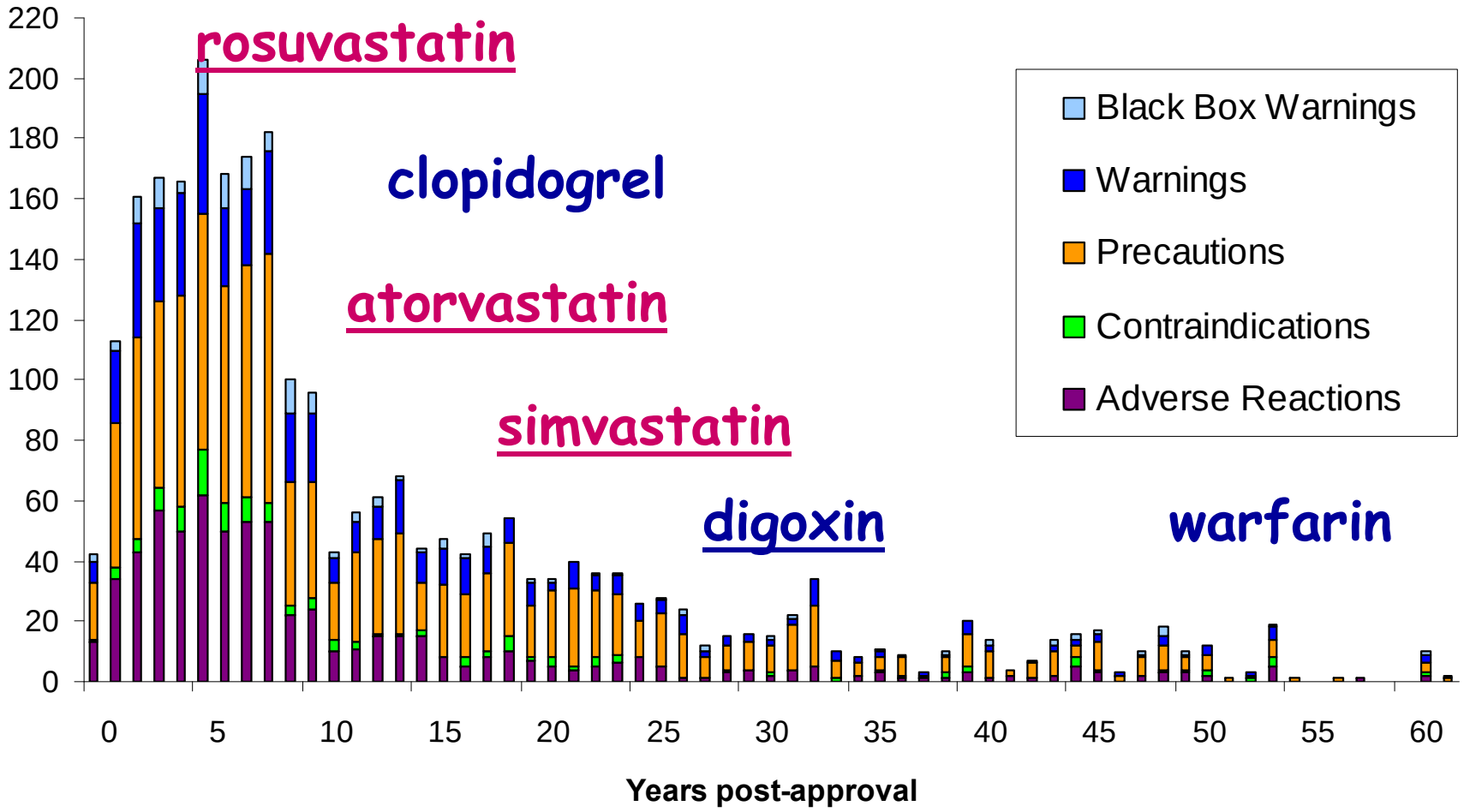
Withdrawn	Approv	Drug name	Use	Risk
1998	1997	Mibefradil	High blood pressure/Chronic stable angina	Torsades de Pointes; Drug-drug interactions
1998	1997	Bromfenac	NSAID	Acute liver failure
1998	1985	Terfenadine	Antihistamine	Torsades de Pointes; Drug-drug interactions
1999	1988	Astemizole	Antihistamine	Torsades de Pointes; Drug-drug interactions
1999	1997	Grepafloxacin	Antibiotics	Torsades de Pointes
2000(2002)*	2000	Alosetron*	Irritable bowel syndrome in women	Ischemic colitis; complications of constipation
2000	1993	Cisapride	Heartburn	Torsades de Pointes; Drug-drug interactions
2000	1997	Troglitazone	Diabetes	Acute liver failure
2001	1997	Cerivastatin	Cholesterol lowering	Rhabdomyolysis; Drug-drug interactions
2001	1999	Rapacuronium	Anesthesia	Bronchospasm
2003	1993	Levomethadyl	Opiate dependence	Fatal arrhythmia
2004	1999	Rofexocib	Pain relief	
2005	2001	Valdecoxib	Pain relief	Skin reactions (SJS)
2005(2006)*	2004	Natalizumab*	Multiple sclerosis	Brain infection
2005	2004	99m Tc**	Diagnostic aid	Cardiopulmonary arrest
2005	1975	Pemoline	ADHD	Liver failure

CYP/transporter inhibitor

CYP/transporter substrate

Composition of Safety-Related Labeling Changes for All Drug Products

(changes made Oct 2002-Aug 2005, n=2645 label changes for 1601 NDA/BLA entries)

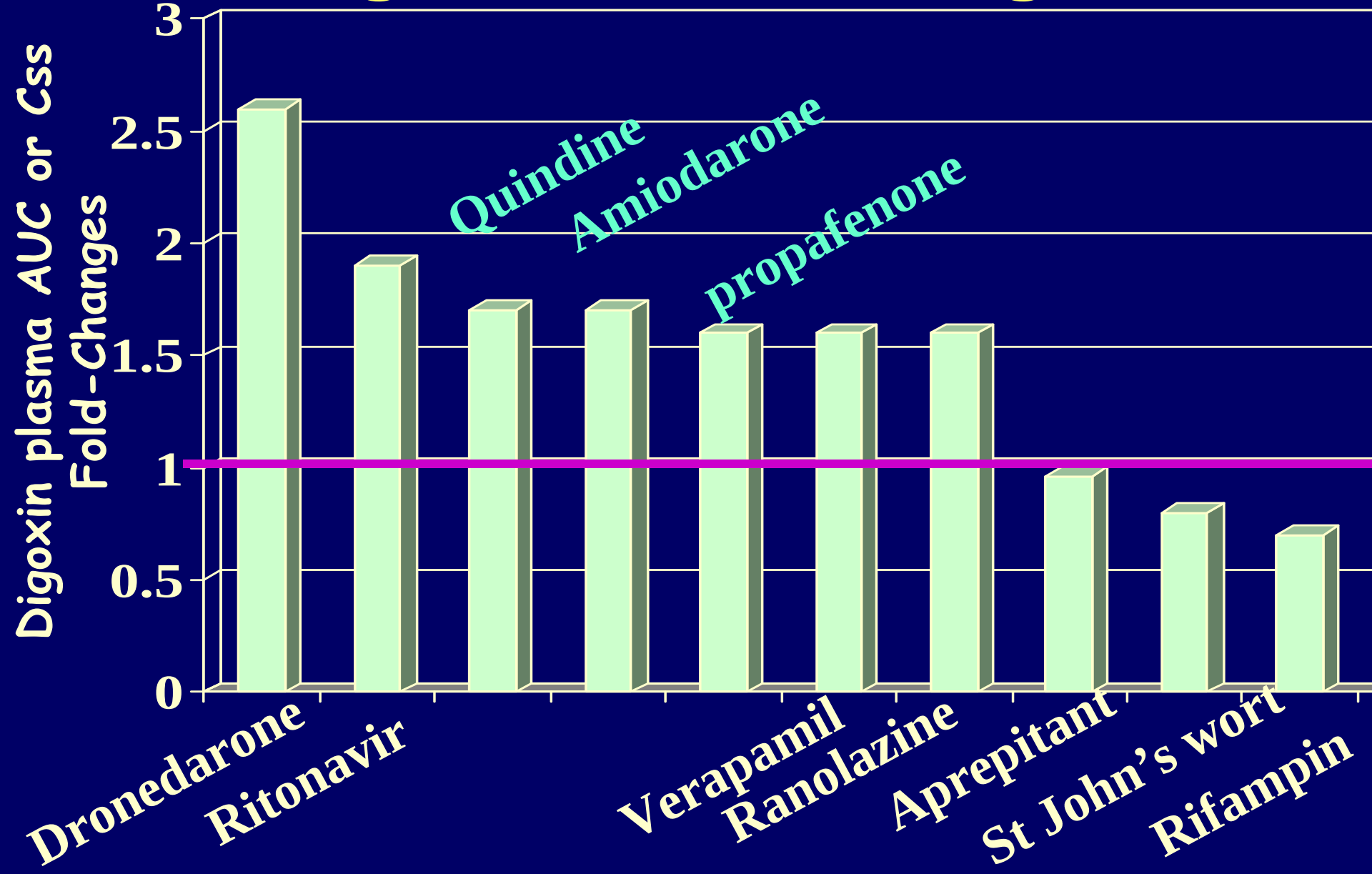


Modified from: T Mullin, CDER, Office of Planning and Analysis, OTS presentation, May 2009

P-gp & Digoxin

- NTR (narrow therapeutic range) drug
- Drug Interactions

Digoxin AUC Changes



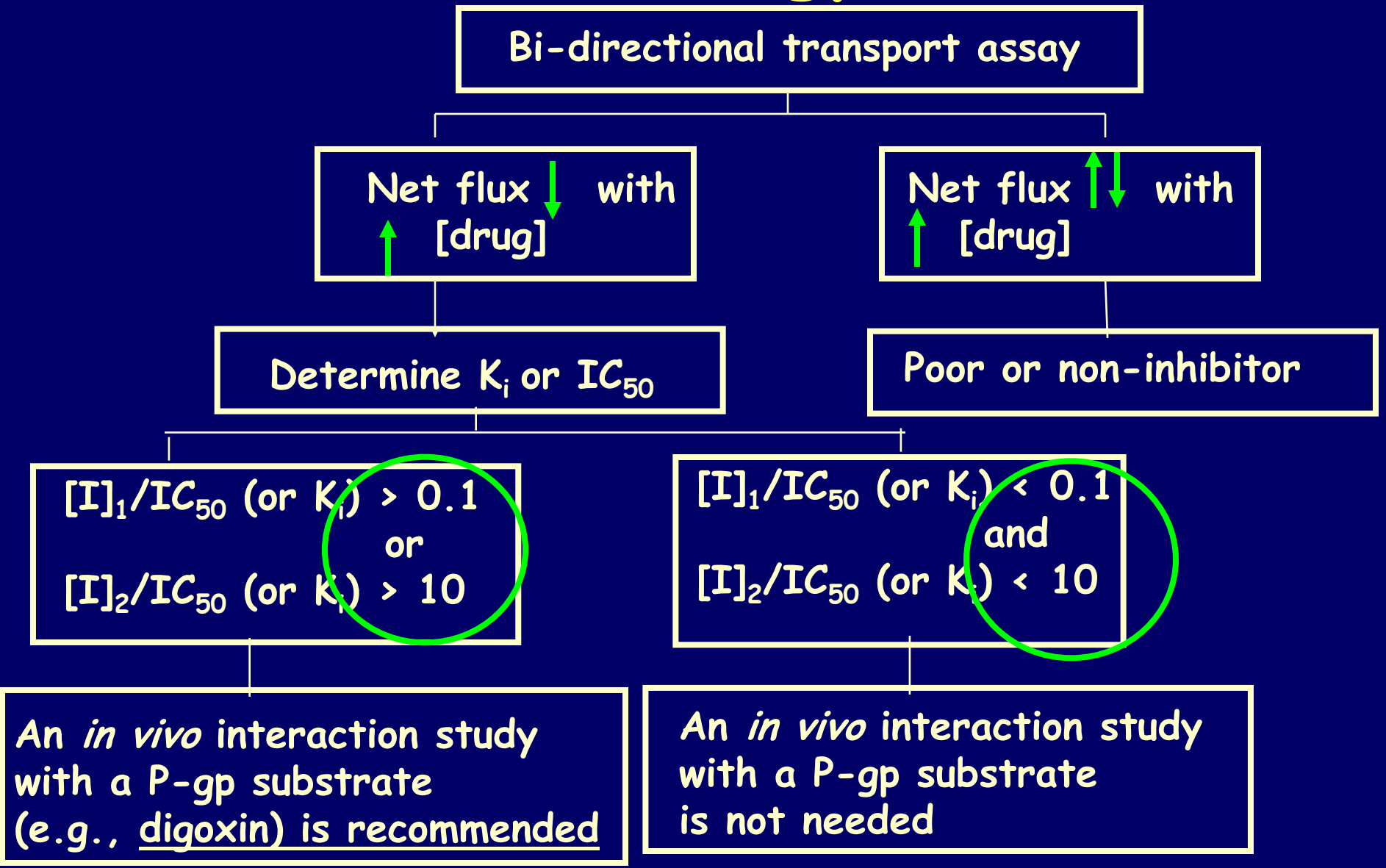
Labeling (2004)

"Drugs that induce/inhibit P-glycoprotein in intestine or kidney have the potential to alter digoxin pharmacokinetics"
recommendation of dosing adjustments and/or monitoring of digoxin levels when "amiodarone, propafenone and quinidine" are to be used with digoxin.

"No significant changes in digoxin pharmacokinetics have been reported with disopyramide, dofetilide, flecainide, moricizine, mexilitine, procainamide,or sotalol"

Drugs at the FDA (digoxin, "PRECAUTIONS-Drug Interactions- Antiarrythmics)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/21648lbl.pdf
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

Is the NME a P-gp Inhibitor?



Is digoxin the only clinically relevant P-gp substrate?

Dabigatran

PRADAXA® (dabigatran etexilate mesylate) capsules for oral use
Initial U.S. Approval: 2010

----------INDICATIONS AND USAGE----------

PRADAXA is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (1)

----------WARNINGS AND PRECAUTIONS----------

- Risk of bleeding: PRADAXA can cause serious and, sometimes, fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.1)
- Temporary discontinuation: Avoid lapses in therapy to minimize risk of stroke (5.2)
- P-gp inducers and inhibitors: Avoid coadministration of rifampin with PRADAXA because of effects on dabigatran exposure (5.3)

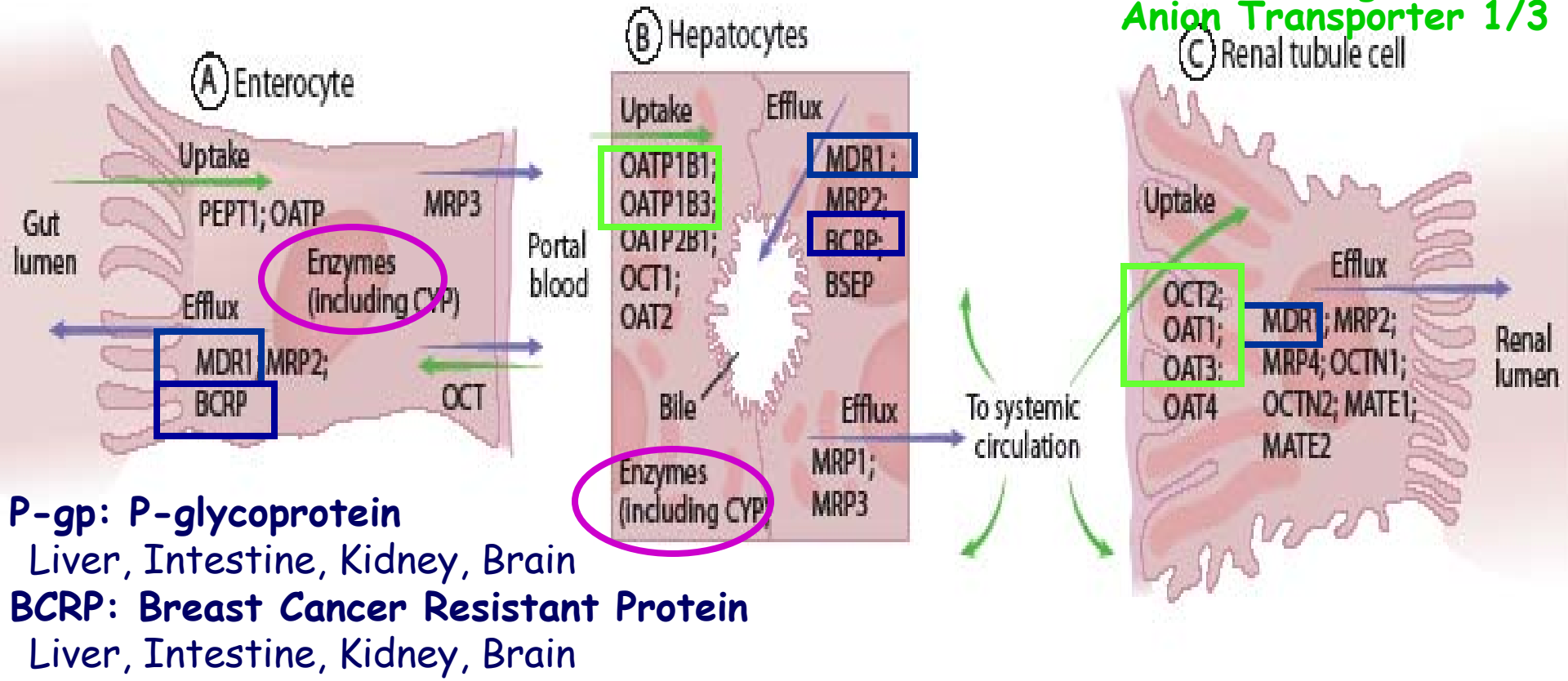
Drugs at the FDA (dabigatran- HIGHLIGHTS) , October 19, 2010
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022512s000lbl.pdf
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

Other transporters?

Selected efflux & uptake transporters in the gut wall (a), liver (b), and kidneys (c)

OATP: Organic Anion Transporting Polypeptide

- OCT2: Organic Cation Transporter 2
- OAT1/3: Organic Anion Transporter 1/3



P-gp: P-glycoprotein
Liver, Intestine, Kidney, Brain

BCRP: Breast Cancer Resistant Protein
Liver, Intestine, Kidney, Brain

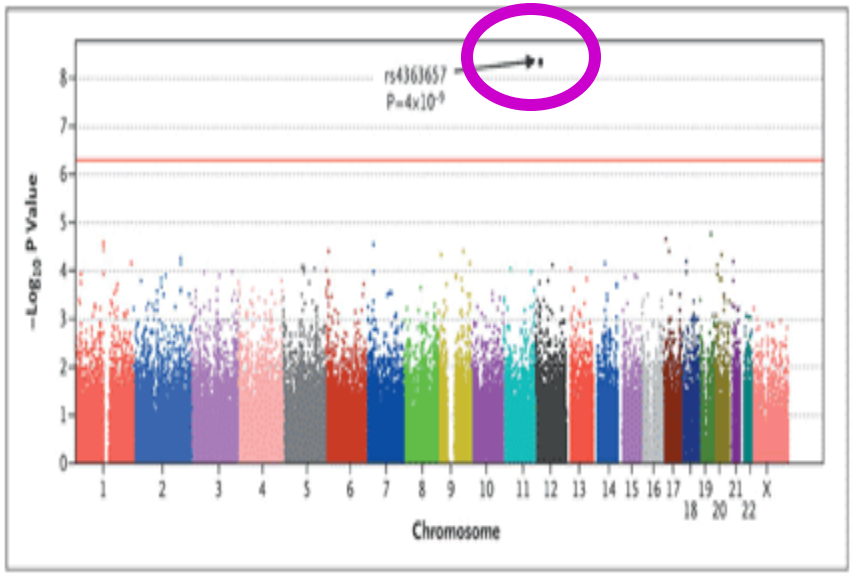
Huang S-M, Lesko LJ, and Temple R, "Adverse Drug Reactions and Pharmacokinetic Drug Interactions", Chapter 21, Adverse Drug Reactions and Drug Interactions in Part 4, FUNDAMENTAL PRINCIPLES: Clinical Pharmacology, "Pharmacology and Therapeutics: Principles to Practice," Ed. Waldman & Terzic, Elsevier, 2009

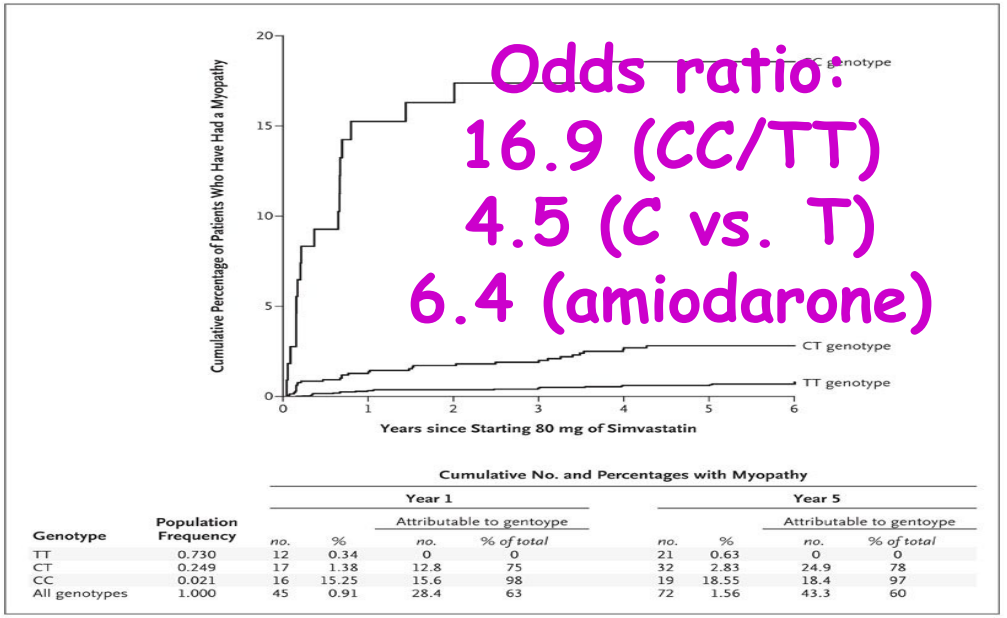
OATP, BCRP, P-gp
&
Statins

- Drug Interactions
- Pharmacogenetics

Pharmacogenetics (simvastatin)
-Myopathy-

Genomewide Association





Cumulative No. and Percentages with Myopathy

Genotype	Population Frequency	Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	no.	% of total	no.	%	no.	% of total
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

1. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype (c.521T>C)
2. Association replicated in another 40 mg group

The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-799 (UK)

Labeling of Simvastatin

TABLE 1 Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

- Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone

→ Avoid simvastatin

- Gemfibrozil Cyclosporine Danazol

→ Do not exceed 10 mg simvastatin daily

- Amiodarone Verapamil

→ Do not exceed 20 mg simvastatin daily

- Diltiazem

→ Do not exceed 40 mg simvastatin daily

Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-containing Products

→Do not take 80 mg

- Grapefruit juice

→ Avoid large quantities of grapefruit juice (>1 quart daily)

Simvastatin labeling (Zocor), May 2010: HIGHLIGHTS
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019766s080lbl.pdf

Comparative exposure and dose recommendation in subgroups with various patient factors

Group	Ethnic factor	Fold change in exposure (AUC)	Initial dose (mg)	Daily dose (mg)
1	Control	1-fold	10–20	5–40
2	Hepatic impairment	1.1-fold (mild) 1.2-fold (moderate)	10–20 10–20	5–40 5–40
3	Renal impairment	1-fold (mild) 1-fold (moderate) 3-fold (severe)	10–20 10–20 5	5–40 5–40 ≤10
4	Race	2-fold (Asians)	5	5–20
5	Cyclosporine	7-fold		5
6	Gemfibrozil	1.9-fold		10
7	Lopinavir/ ritonavir	5-fold		10

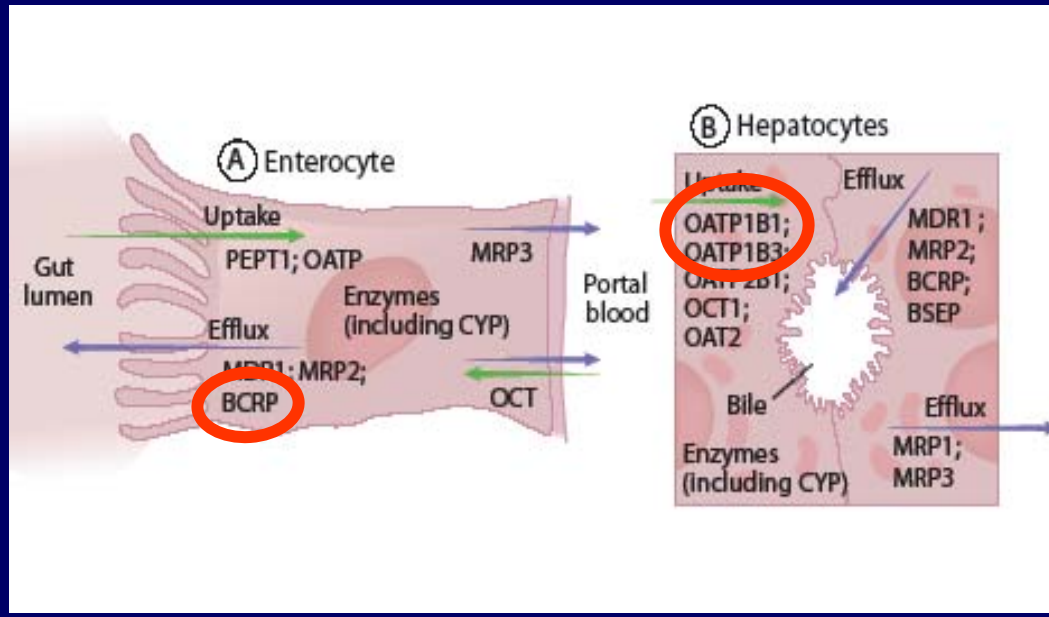
(Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); Labeling from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.); **November 2007 labeling**

<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>

Rosuvastatin

- Rosuvastatin is not extensively metabolized; ~ 10% of a radiolabeled dose is recovered as metabolite.
- No drug interactions with ketoconazole, erythromycin, itraconazole, known CYP3A4/P-gp inhibitors

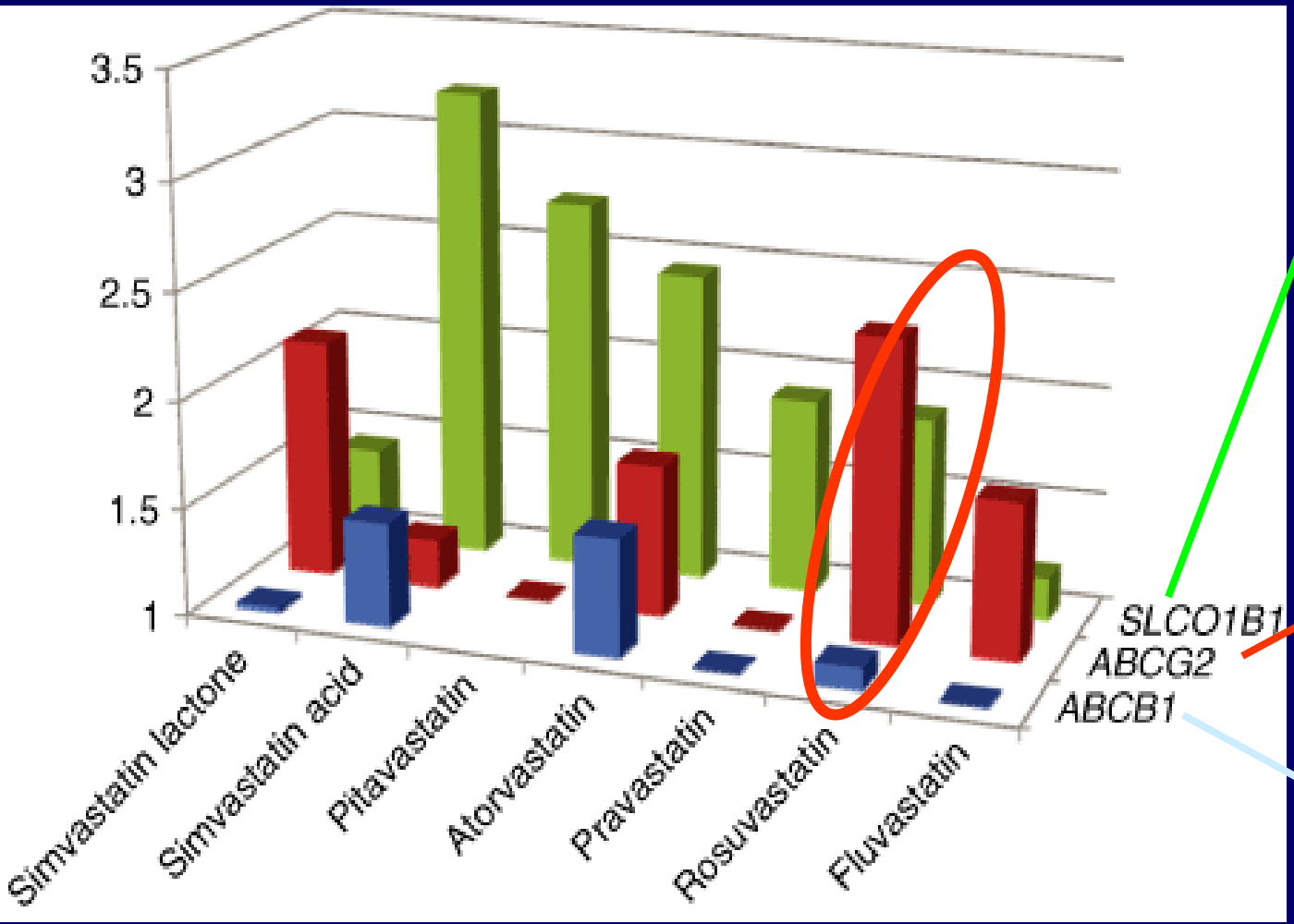
→ Possible mechanism- cyclosporine inhibition of BCRP (efflux transporter) & OATP1B1 (uptake transporter)



Crestor Labeling (AstraZeneca); htttp://www.accessdata.fda.gov/scripts/cder/drugsatfda

Simonson SG, et al. Clin Pharmacol Ther. 2004; 76(2):167; Kesjutaki JE, et al, Clini Pharmacol Ther 2009; 86:197; Tomlinson B, Clin Pharmacol Ther 2010

Fold-Change in Plasma AUC
- Effect of Transporter Genetics -



(OATP1B1)
c.521CC/TT

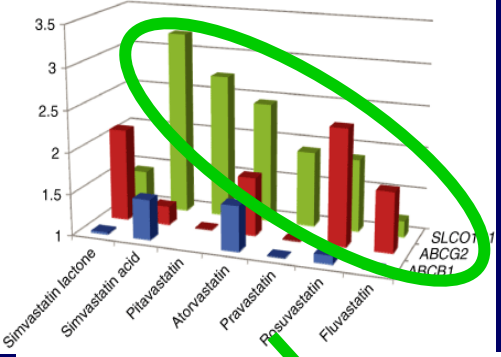
c.521T>C
White: Black: Asian
15-20: 2 : 10-15%

(BCRP)
c.421AA/CC

c.421 C>A
White: Black: Asian
15-20: 0-5 : 25-35%

(P-gp)
c.1236TT/CC
c.2677TT/GG
c.3435TT/CC

Data from Niemi M, Clin Pharmacol Ther 87:130, January 2010



Dosing Based on Transporter Genetics?

- Are We Ready?-

SLCO1B1 c.521T>C genotype

	TT	TC	CC	Normal dose range*
Simvastatin	80 mg	40 mg	20 mg	5–80 mg/day
Pitavastatin	4 mg	2 mg	1 mg	1–4 mg/day
Atorvastatin	80 mg	40 mg	20 mg	10–80 mg/day
Pravastatin	80 mg	40 mg	40 mg	10–80 mg/day
Rosuvastatin	40 mg	20 mg	20 mg	5–40 mg/day
Fluvastatin	80 mg	80 mg	80 mg	20–80 mg/day

Data from Niemi M, Clin Pharmacol Ther 87:130, January 2010

→Other metabolic pathways?

→Other transport pathways?

Transporter Information in Drug Labeling

	2004-2006	2007-2009
# of Approved NMEs	67	56
# (%) with transporter information in the labelings	11 (16%)	21 (38%)
# on P-glycoprotein	6	20
# in vitro	10	16
# in vivo	14	9
# on other transporters	1	6
# in 'Highlights' section	1	7
# of PMRs/PMCs related to transporters	3	10

NME: new molecular entity;
<Modified from Agarwal et.al, ACCP 2010 Abstract>

Transporter Information in Drug Labeling

Transporter	Drug Names*
P-gp	Aliskiren, ambrisentan, [aprepitant], *clarithromycin*, colchicine, [dexvenafaxine], *dronedarone*, [eltrombopag], *everolimus*, fexofenadine, [fosaprepitant], [ixabepilone], *lapatinib*, *maraviroc*, *nilotinib*, *paliperidone*, posaconazole, [prasugrel], [[propafenone]], propranolol, *ranolazine*, saxagliptin, silodosin, sirolimus, sitagliptin, *tipranavir***, *tolvaptan*, topotecan, [vorinostat]
OATP1B1	Atorvastatin, *cyclosporine*, *eltrombopag****, *lapatinib*, valsartan
OATP	Ambrisentan
OAT	Sitagliptin (OAT3)
OCT	Metformin, pramipexole, [saxagliptin], [sitagliptin], varenicline (OCT2)
BCRP	Lapatinib, topotecan
MRP	Mycophenolate (MRP2), [ixabepilone] (MRP1),valsartan (MRP2)

HIGHLIGHTS

*Not an extensive list: data based on a preliminary survey of electronic PDR and Drugs@FDA on September 18, 2009. They are substrates, *inhibitors*, ***both substrates and inhibitors***, [not a substrate or an inhibitor], or [[not studies as a substrate or an inhibitor]]; **:Tipranavir is also a P-gp inducer *** an inhibitor; its labeling contains a list of OATP1B1 substrates

<Huang, SM, Zhang L, Giacomini KM, Clin Pharmacol Ther January 2010>

OATP1B1

"Eltrombopag is an inhibitor of OATP1B1 transporter. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 (e.g., rosuvastatin) and consider reduction of the dose of these drugs."

The following were listed as OATP1B1 substrates: "benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin"

Drugs at the FDA (Promacta, November 2008, "Highlights" and "Drug Interactions")
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

Members of the International Transporter Consortium

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FDA

Industry

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*
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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
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Food and Drug Administration*
Lei Zhuang:
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Xiaoyan Chu: Merck
Raymond Evers: Merck
Volker Fischer: Abbott
Katheen M. Hillgren: Lilly Research Laboratories
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Donald J. Tweedie:
Boehringer Ingelheim Pharmaceuticals*
Joseph A. Ware: Genentech
Maciej Zamek-Gliszczynski:
Lilly Research Laboratories

*Co-chairs

<Huang, SM, Zhang L, Giacomini KM, Clin Pharmacol Ther January 2010>

Co-sponsored by DIA Drug Information Association FDA

FDA Critical Path Transporter Workshop

in collaboration with PhRMA aaps American Association of Pharmaceutical Scientists ISSX

October 2-3, 2008 | Marriott Bethesda North Hotel & Conference Center, Bethesda MD, USA

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

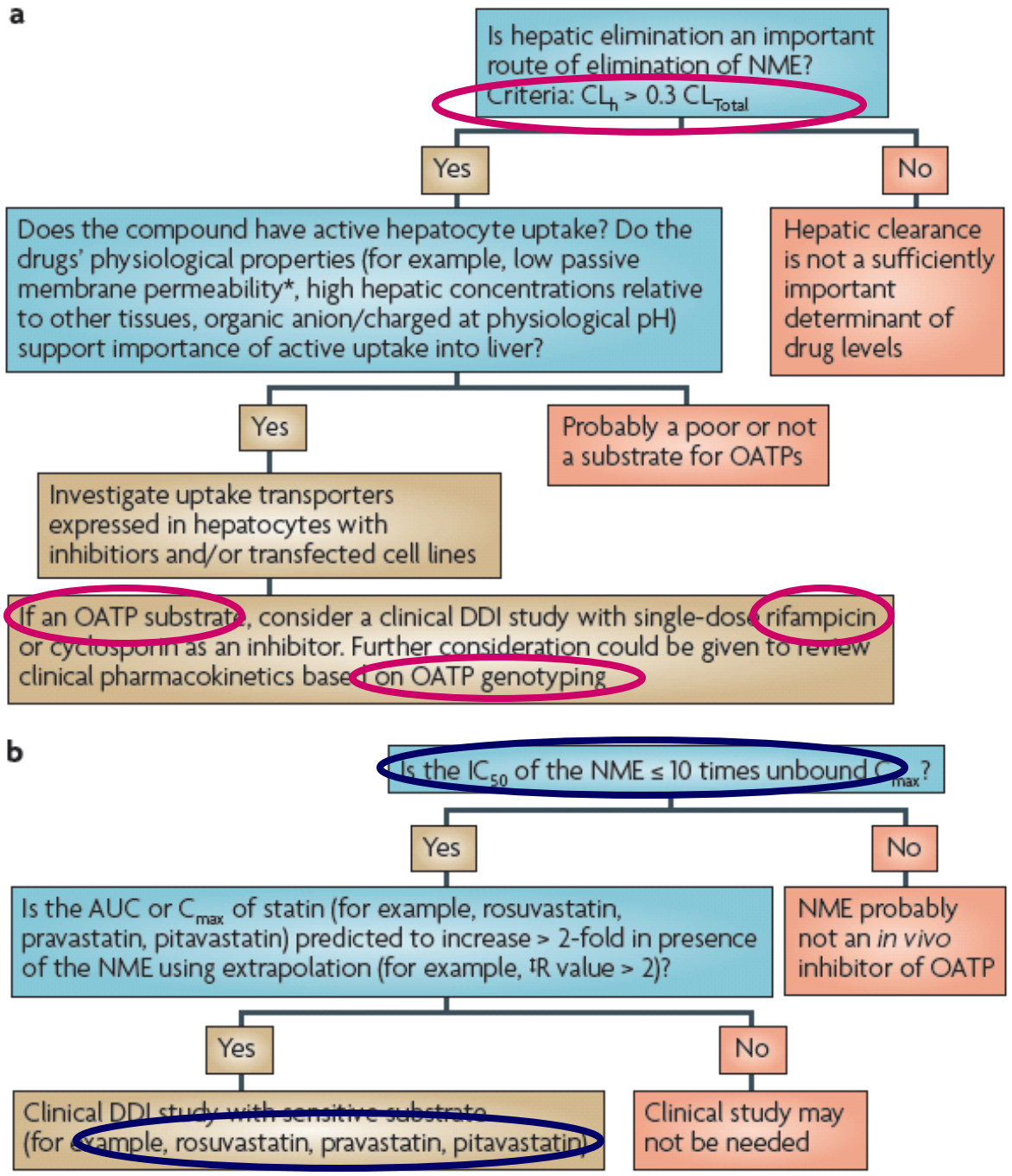
2. Huang S-M, Woodcock J, Nature Reviews Drug Discovery, March 2010

OATP Decision Trees-

(a) substrate

(b) inhibitor

International Transporter Consortium, Nature Reviews Drug Discovery, March 2010



INTERNATIONAL TRANSPORTER CONSORTIUM SECOND WORKSHOP

March, 2012
Bethesda/Washington DC

Preliminary Notice

Updates will be provided on the AAPS Transporter Website

www.aapspharmaceutica.com/ITCwhitepaper

-**Leading scientists from academia, the FDA and industry will extend discussions arising from the ITC white paper:**

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

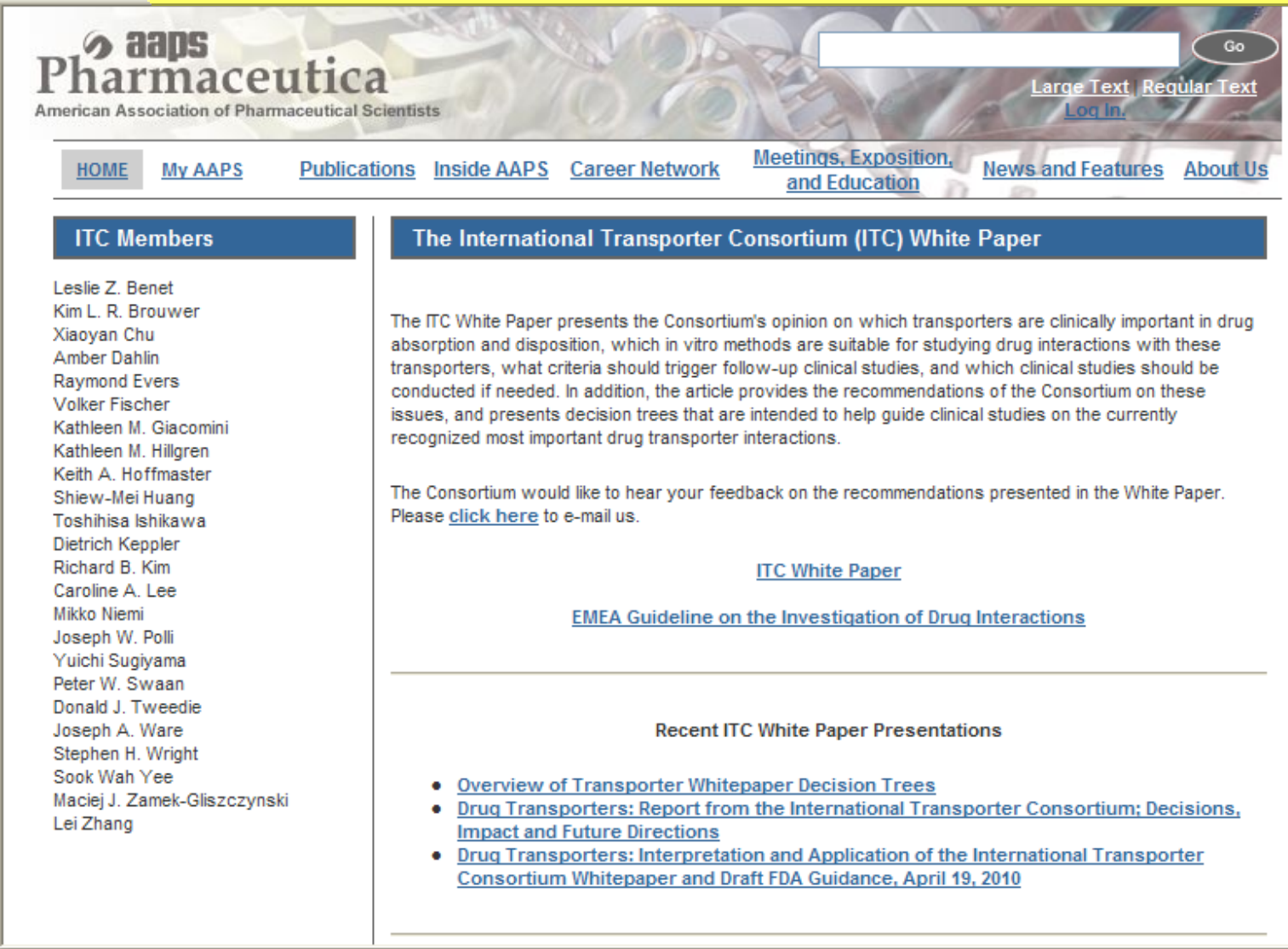
-**As with the first workshop, participants will be encouraged to join discussions on best practices and future directions.**

WORKSHOP SESSIONS

- **Tools and Techniques**
- **Additional Transporters**
- **Decision Trees and Regulatory Issues**

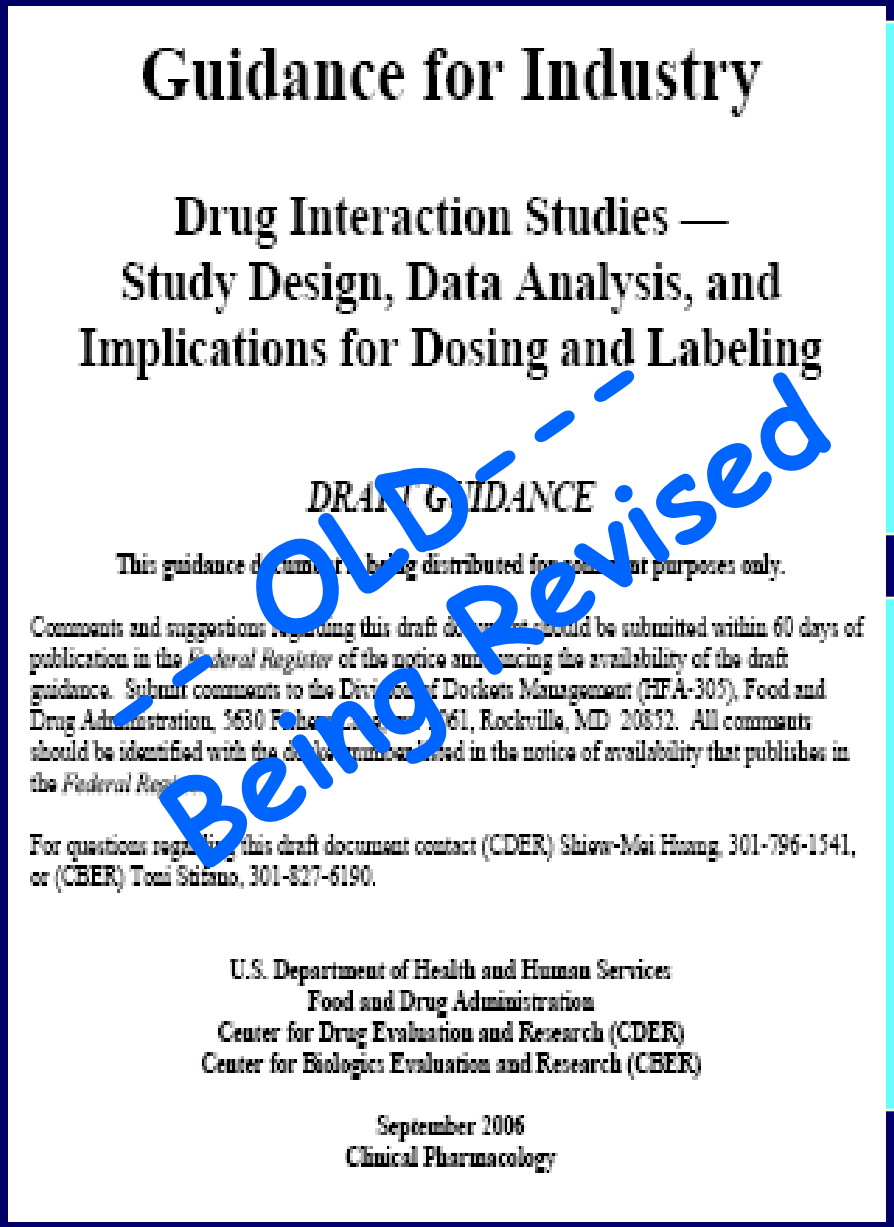
ITC Whitepaper Web Page

http://www.aaps.org/inside/focus_groups/DrugTrans/ITCwhitepaper.asp



Dr. Maciej J. Zamek-Gliszczynski

Revision of Guidance



Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 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 (CBER) Toni Stiles, 301-827-6190.

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

September 2006
Clinical Pharmacology

OLD – Being Revised

Draft published for public comment September 11, 2006

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf

OLD

FDA Drug Development & Drug Interaction website

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

Development & Approval Process (Drugs)

Development Resources

Drug Interactions & Labeling

- Drug Development and Drug Interactions
- Drug Development and Drug Interactions: Possible Models for Decision-Making
- Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers
- Drug Development and Drug Interactions: Advisory Committee Meetings
- Drug Development and Drug Interactions: Meetings

Drug Development and Drug Interactions

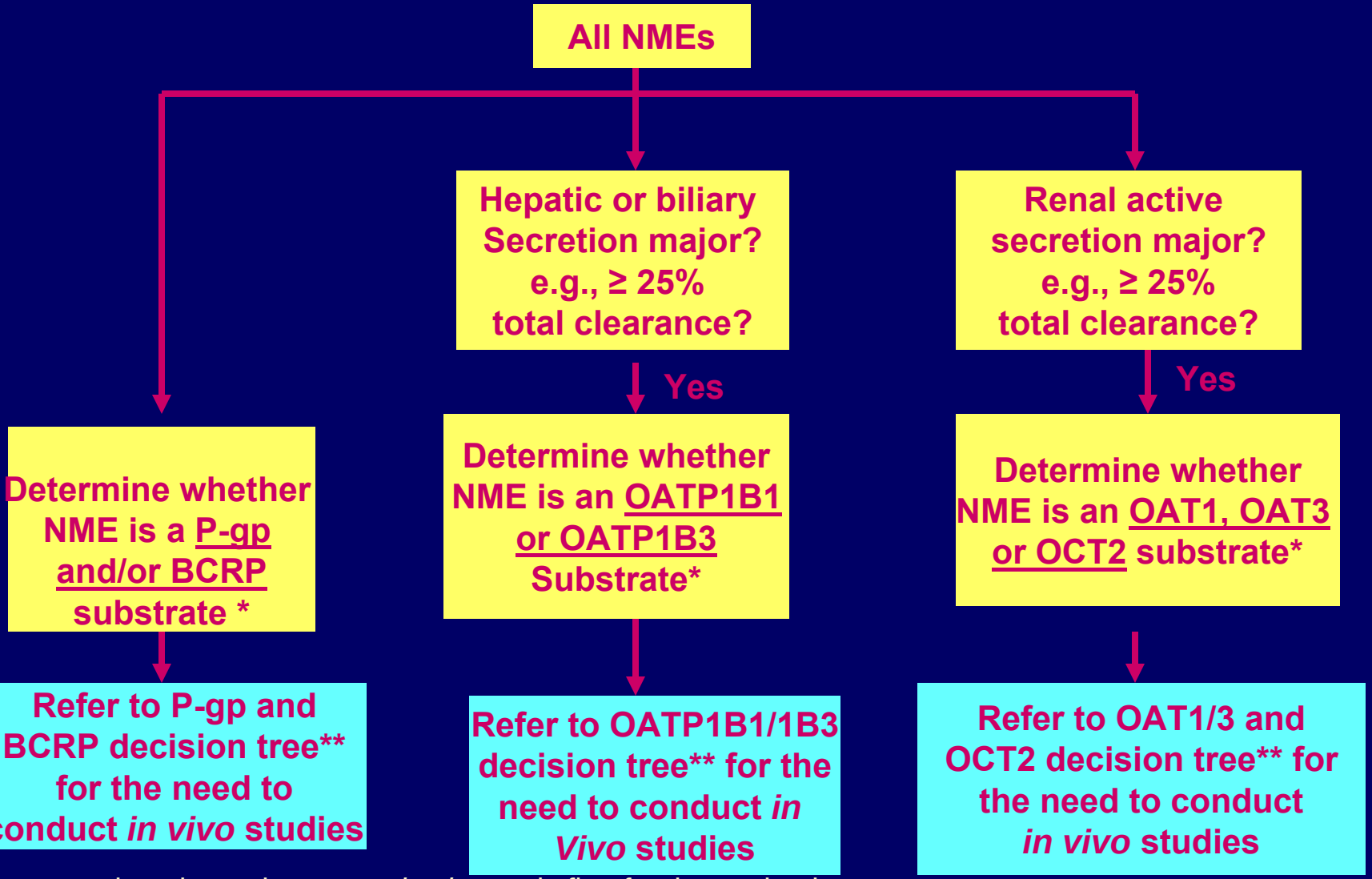
- Overview
- Background Information
- Tables of Substrates, Inhibitors and Inducers
  - CYP Enzymes
    - In vitro
    - In vivo
      - Examples of in Vivo Substrate, Inhibitor, and Inducer for Specific CYP Enzymes
      - Classification of Inhibitors
      - Classification of Substrates
  - P-gp Transporters
  - Major Human Transporters
- Possible Models for Decision-Making
  - CYP-Based Drug-Drug Interaction Studies
  - P-gp-Based Drug-Drug Interaction Studies (updated 9/25/2006)

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

New Draft Guidance
- Key Messages -

- The need to understand metabolism, transport, and drug-drug interaction (DDI) in order to assess benefit/risk
- Application of mechanistic models in DDI prediction (static and dynamic models, including PBPK)
- The need to evaluate therapeutic protein-drug interactions
- The need to have exposure-response info to determine clinical significance of exposure changes due to drug interactions

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



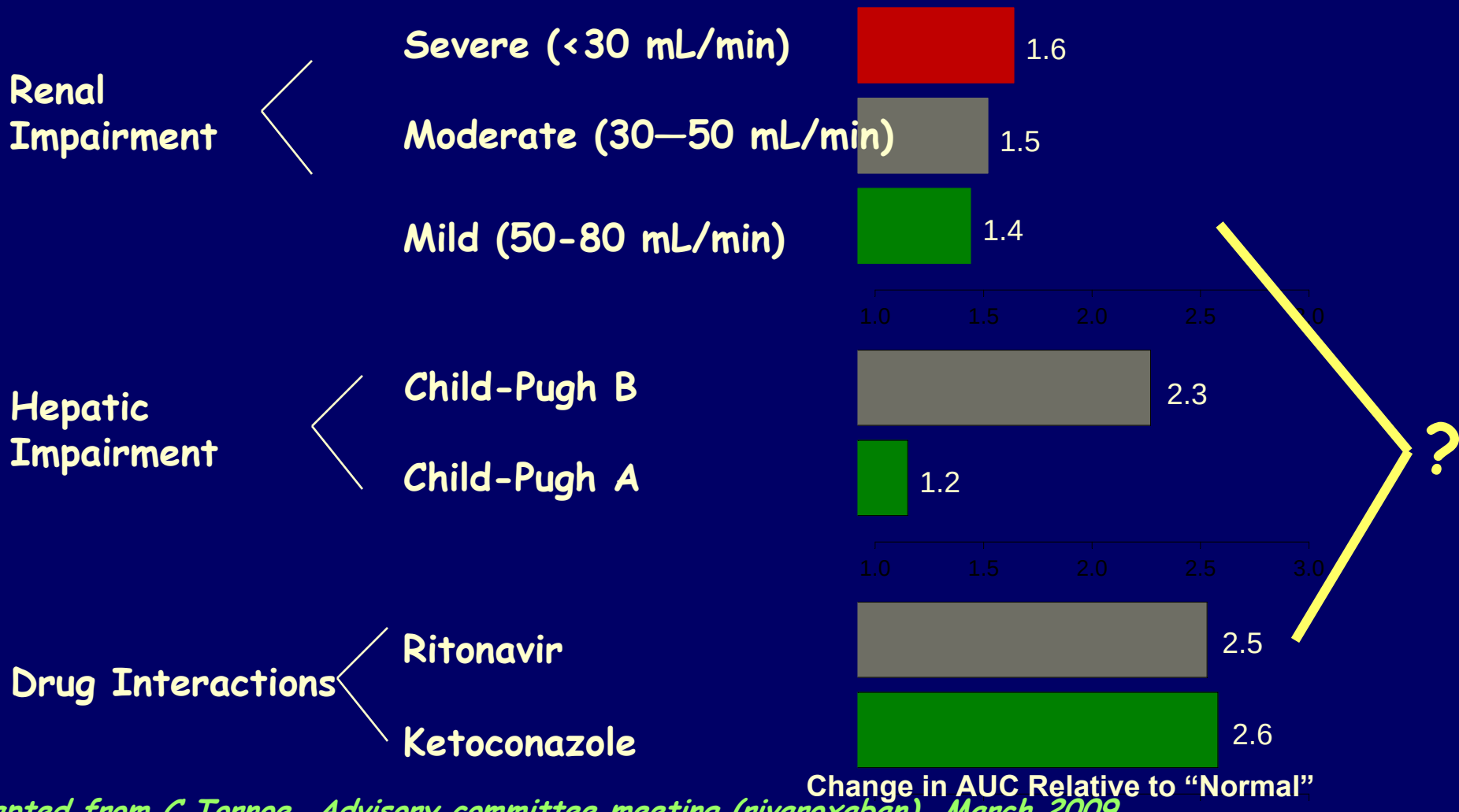
* The sponsor has the option to use *in vitro* tools first for the evaluation.

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

*

Source: FDA Clinical Pharmacology Advisory Committee Meeting, 3/17/10.

Moderate Hepatic Impairment and Strong CYP3A4/ P-gp Inhibitors have >2-fold Increase in Exposure

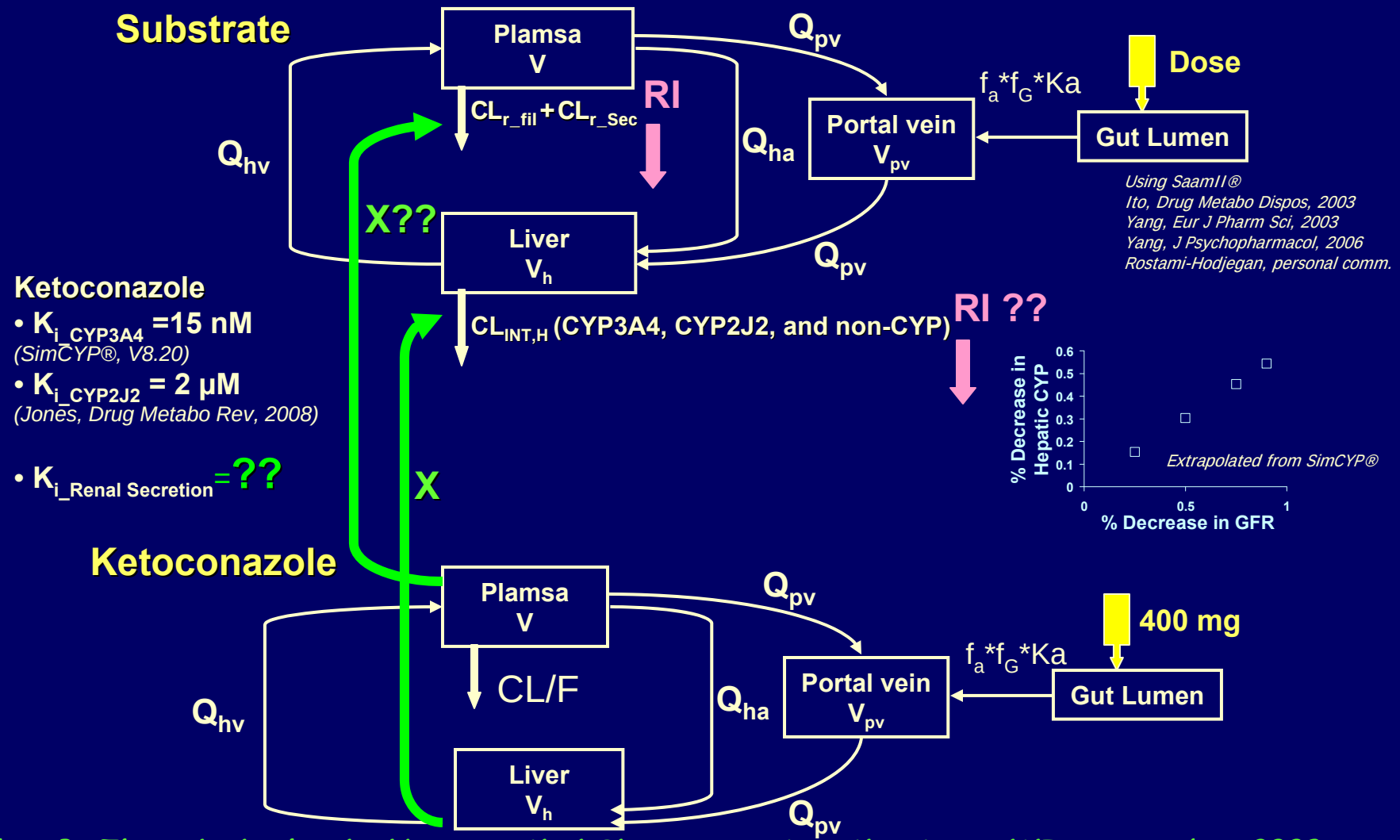


Adapted from C Tornoe, Advisory committee meeting (rivaroxaban), March 2009
http://www.fda.gov/ohrms/dockets/ac/09/slides/2009-4418s1-06-FDA-Tornoe.pdf

→Follow up PBPK modeling on multiple impairments: Zhao P, et al, presentation at the annual meeting of American Society for Clinical Pharmacology and Therapeutics, Atlanta, GA, March 2010

Drug Interaction and Renal Impairment

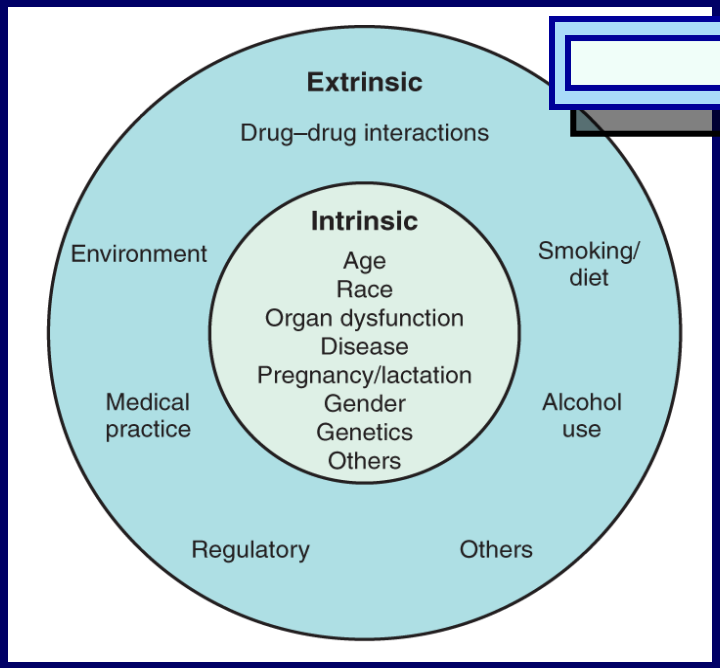
A semi-PBPK simulation



<Zhao P, Zhang L, Lesko, L, Huang S-M, LOL presentation, Merrimac, WI, September 2009>
<Zhao P, et al, presentation at ASCPT, Atlanta, GA, March 2010>

PBPK: Application of PBPK in Clinical Pharmacology Evaluation

A. Intrinsic/extrinsic Factors



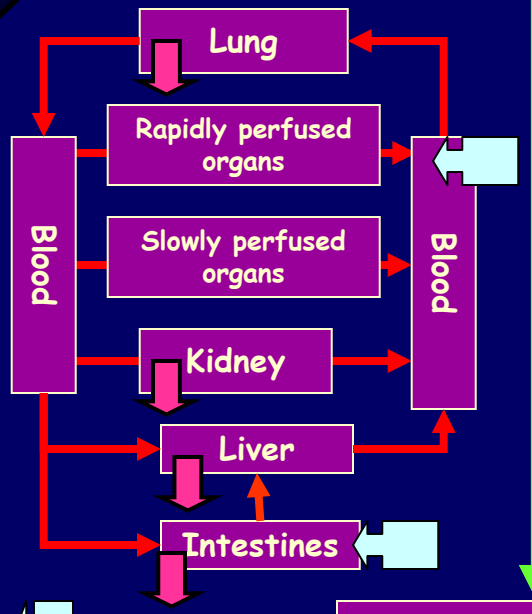
Huang and Temple, 2008

Individual or combined effects on human physiology

B. PBPK Model components

System component (drug-independent)

Drug-dependent component



Dosing

Elimination

ADME, PK, PD and MOA

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

PBPK Model

Predict, Learn, Confirm

<Zhao P, et al, Clin Pharmacol Ther, in press>

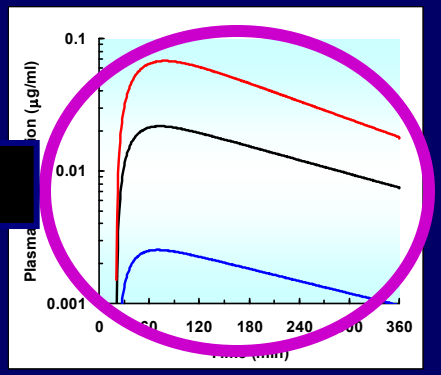
PBPK Modeling
- Pravastatin in Humans -

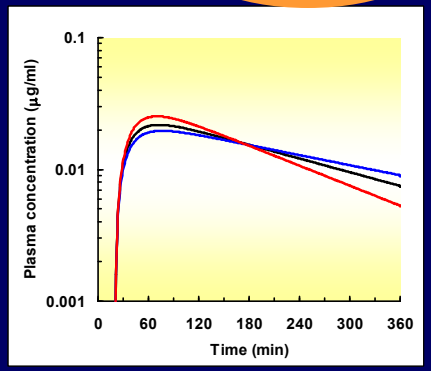
PSinf | OATP1B1 | PSbile | MRP2 | PSeff

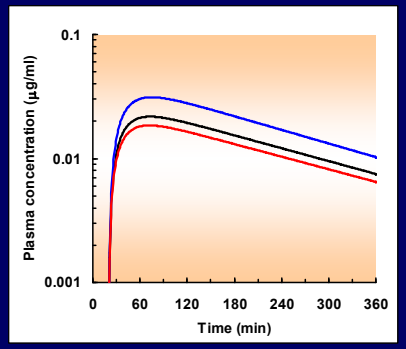
Sensitivity Analysis

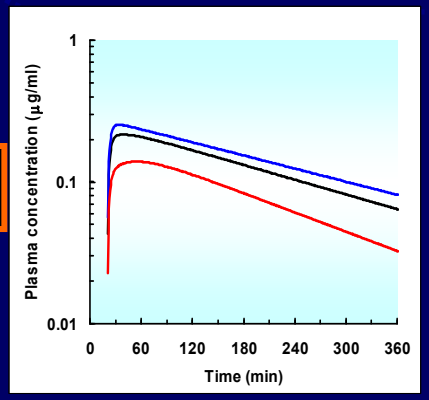
: × 3
: × 1
: × 1/3

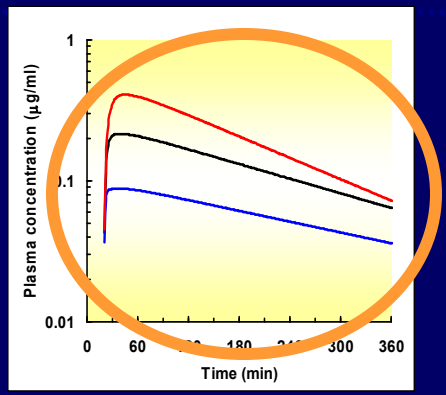
Liver

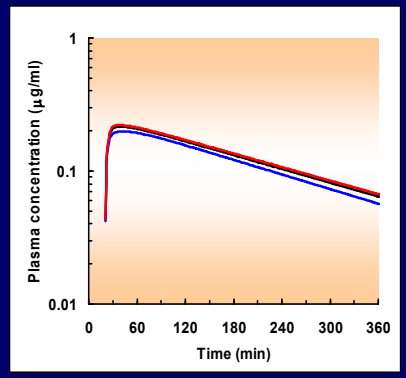












Courtesy of Dr. Yuichi Sugiyama

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

Interactions of HIV Protease Inhibitors with OATP

Table 1. Comparison of IC_{50} and K_i-values of HIV PI for inhibition of OATP1B1 and OATP1B3-mediated CGamF (1 μM) accumulation with unbound plasma concentrations.

Inhibitors	Maximum inhibition (% of control)		IC_{50} (μM)		K_i (μM)		Plasma protein binding (%)[a]	C_{max} corrected for plasma protein binding (μM)[a]
	OATP1B1	OATP1B3	OATP1B1	OATP1B3	OATP1B1	OATP1B3		
Amprenavir	61±9	75±2	14.4±3.8	19.1±2.0	12.8	13.1	90	1.0–3.2
Atazanavir	72±8	87±7	1.7±0.2	3.0±1.0	1.5	2.0	86	0.6–1.3
Darunavir	66±3	83±2	3.5±1.1	4.8±0.8	3.1	3.3	93	0.3–1.1
Indinavir	63±4	76±2	12.2±4.2	12.3±1.1	10.8	8.5	65	1.7–4.4
Lopinavir	76±3	89±2	0.5±0.1	2.0±0.1	0.5	1.4	98	0.3
Nelfinavir[b]	38±9	34±6	n.d.	n.d.	n.d.	n.d.	98	0.10
Ritonavir	73±1	86±4	1.6±0.3	3.6±1.1	1.4	2.5	99	0.16
Saquinavir	74±0.3	80±4	2.1±1.2	4.1±1.0	1,8	2.8	98	0.11–0.30
Rifampicin	79±5	94±3	1.8±0.3	1.3±0.7	1.6	0.9	–	–
Digoxin	38±7	54±9	7.9±2.1	1.0±0.4	7.0	0.7	–	–
Bromosulphophthalein	74±9	92±3	0.7±0.4	1.4±0.4	0.6	1.0	–	–

Notes:n.d., Not determined.

[a]From Williams & Sinko (1999), Hoetelmans et al. (2003), Perry et al. (2005), Swainston Harrison & Scott (2005), Marin-Niebla et al. (2007), Ruane et al. (2007) and Chandwani & Shuter (2008).

[b]Due to solubility limitations, nelfinavir could only be tested up to a concentration of 20 μM.

IC_{50}-values were calculated according to the sigmoid inhibitory effect model as described in the Materials and Methods section.

Annaert P, et al, Xenobiotica, 40(3): 163-176, 2010

→Can the drug interaction data from ritonavir/ lopinavir extrapolated to other PIs?

Summary

- As drug development science advances and additional info becomes available, drug labels have continued to be updated

- The role of transporter in drug efficacy & safety have been increasingly evaluated

  [P-gp-based interactions are among the most evaluated; others include OATP, OCT, OAT, BCRP]

Summary (2)

- Collaborations among academia, industry, government agencies, (and consumers) are key to success in developing useful information for the safe and effective use of drug products

- Various decision trees have been developed to guide clinical studies based on in vitro data

Summary (3)

- Pharmacogenetic tools are available and critical in identifying important pathways and potential drug interactions (both genome-wide association and candidate gene approaches)
- Modeling/simulation tools (e.g., PBPK based) are critical and increasingly being used to optimize study design and to address issues related to multiple inhibitors/multiple patient factors

Summary (4)

FDA plans to issue for public comments another draft drug interaction guidance, which will include recommendations related to evaluation of transporter-based drug interactions, in addition to 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

Acknowledgement

- 2006 Guidance Working Group members
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