

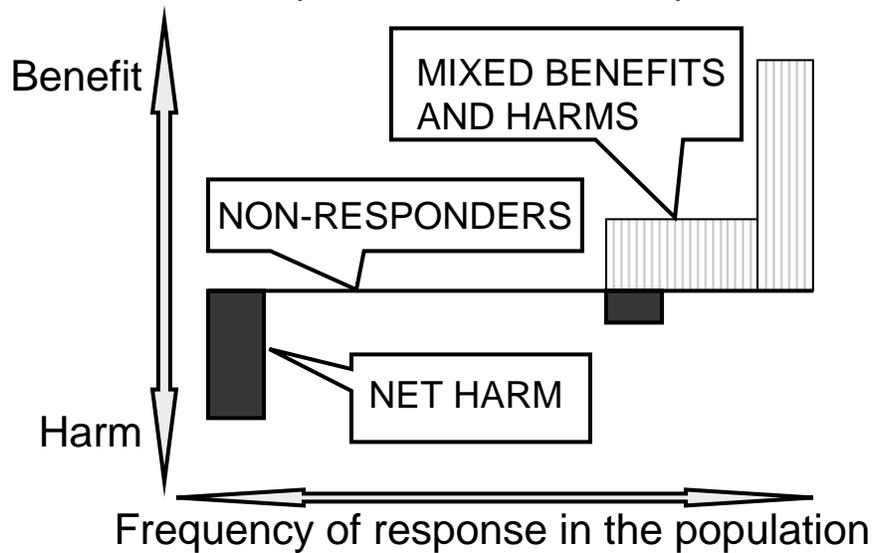
OARSA Seminar  
Center for Food Safety and Applied Nutrition  
March 17, 2011  
Laurel, MD

## Recent Advances in Transporter and CYP-based Interactions including the Interactions of Dietary Supplements and Drugs

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Office of Clinical Pharmacology, OTS  
Center for Drug Evaluation and Research, FDA  
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### Variability of Patient Response



Barbara Evans, *Notre Dame Law Review* 85(2):419-524, 2010  
[http://www.nd.edu/~ndlrev/archive\\_public/85ndlr2/Evans.pdf](http://www.nd.edu/~ndlrev/archive_public/85ndlr2/Evans.pdf)

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### Many Factors Affect Drug Exposure/Response

**It is critical to evaluate how these factors affect drug exposure/response**

**Ultimate goal → Optimal dosing for patients with these individual factors**

*Huang S-M, Temple R, Is this the Drug or Dose for you? Clin Pharmacol Ther 84: 287-294, 2008*

*<FDA Clinical Pharmacology guidance documents:  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>*

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### Dose Adjustment in Patients with Various Factors

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### 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

→ Current practice: Adjust the dose to achieve similar systemic exposure → Only the first step

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

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### Use of Prescription/ OTC/Supplements



- 80% of individuals > 57 YO takes at least 1 medical product (prescription, OTC, supplement)
- 50% takes at least 5 medical products
- 30% takes at least 5 prescription drugs

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## Interactions- Dietary Supplements, Food, Juices-



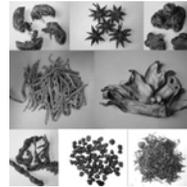
St John's Wort



Grapefruit Juice



Curcumin



Chinese Herbs?

<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm096386.htm>  
<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm182745.htm>

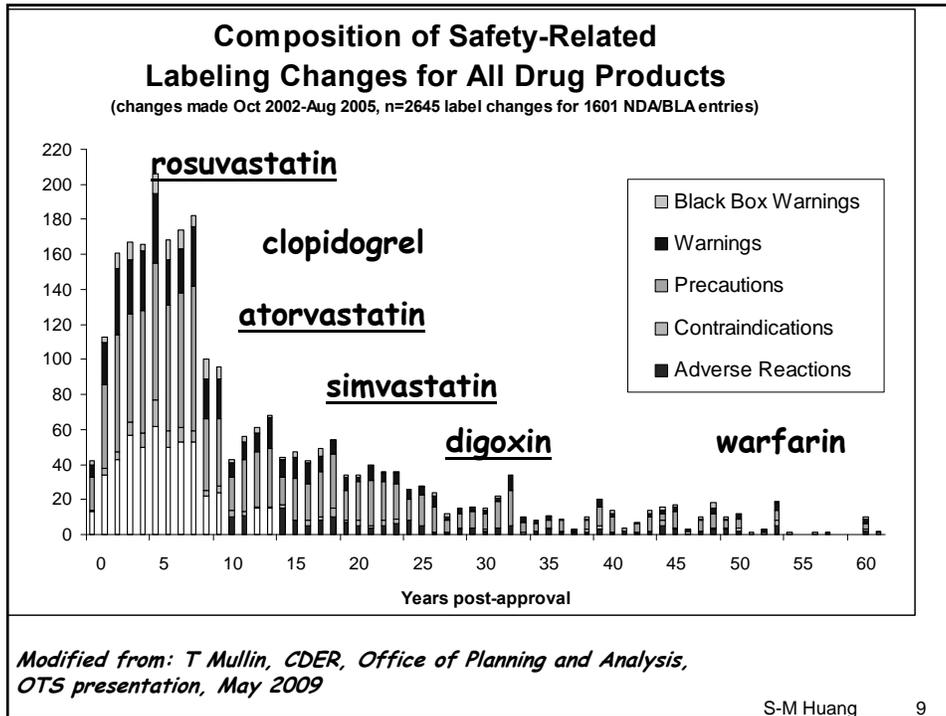
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## Drugs Withdrawn from the US Market due to Safety Reasons

Withdrawn	Approved	Drug name	Use	Risk
			<b>CYP/transporter inhibitor</b>	
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	Amphetamine	ADHD	Liver failure
			<b>CYP/transporter substrate</b>	

Huang, S-M, et al, "Principles of Gender-Specific Medicine", Ed., Legato M, Academic Press, 2004, pp 848-859 ; Huang, S-M, et al, Toxicology Mechanisms and Methods, 16: 89-99, 2006

Recent advances in transporter and CYP-based Interactions including the interactions of dietary supplements and drugs  
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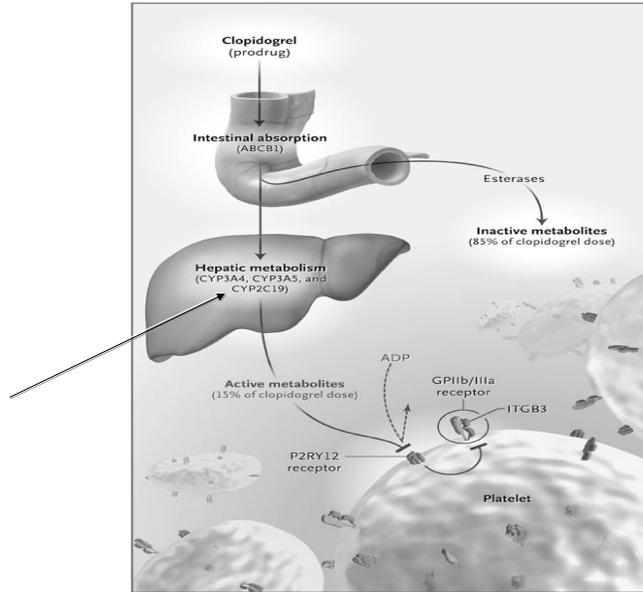
# Labeling Example (1)

## CYP2C19 & Clopidogrel

Updating labeling  
Genetic Data ↔  
Drug Interaction warning

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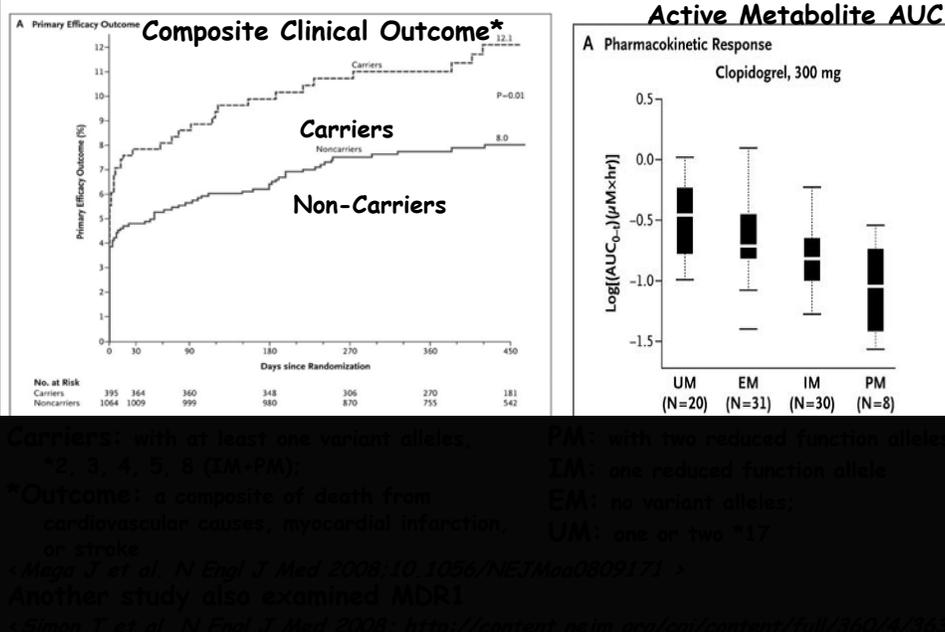
### Roles in Clopidogrel Activity of Proteins with Known Genetic Polymorphisms

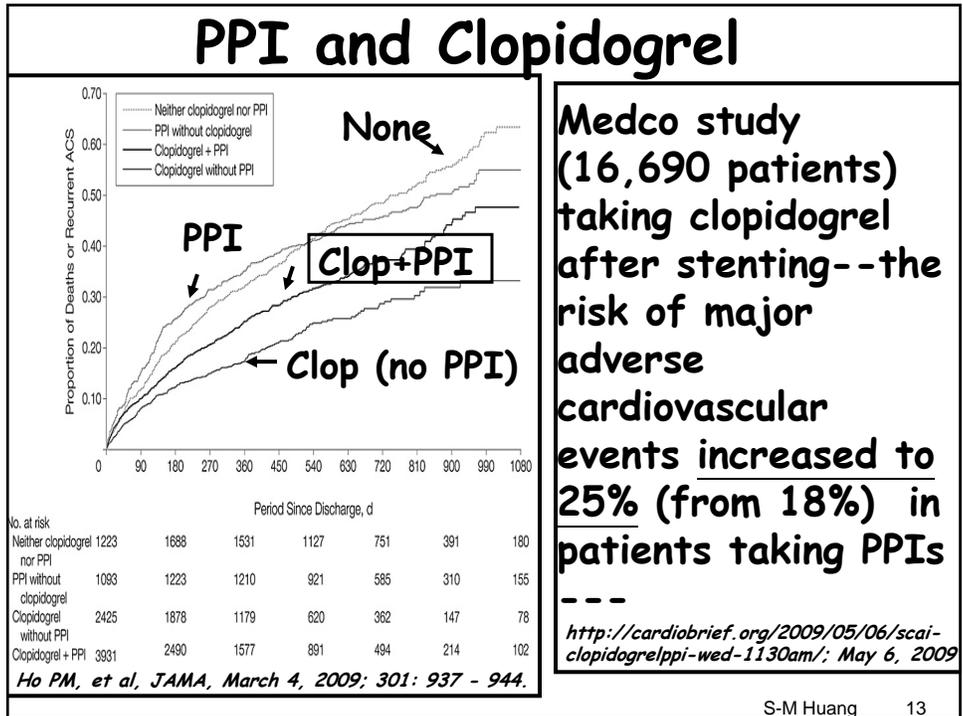


<Simon et al. N Engl J Med:360:363-375, January 2009 >

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## CYP2C19 and Clopidogrel





## FDA Actions

**January 2009: Early communication**  
 Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel.....

*January 26, 2009*  
[http://www.fda.gov/cder/drug/early\\_comm/clopidogrel\\_bisulfate.htm](http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm)

**May 2009: Labeling changes**  
 CYP2C19 poor metabolizer status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolizers has yet to be determined

*Drugs at the FDA (Plavix, "DOSAGE and ADMINISTRATION-Pharmacogenetics", & "PRECAUTIONS- Drug Interactions")*  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/020839s040lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020839s040lbl.pdf)  
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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**MedWatch The FDA Safety Information and Adverse Event Reporting Program**

**Safety Information**

**Safety Alerts for Human Medical Products**

- 2009 Safety Alerts for Human Medical Products
- 2008 Safety Alerts for Human Medical Products
- 2007 Safety Alerts for Human Medical Products
- 2006 Safety Alerts for Human Medical Products
- 2005 Safety Alerts for Human Medical Products
- 2004 Safety Alerts for Human Medical Products
- 2003 Safety Alerts for Human Medical Products
- 2002 Safety Alerts for Human Medical Products
- 2001 Safety Alerts for Human Medical Products

### Clopidogrel (marketed as Plavix) and Omeprazole (marketed as Prilosec) - Drug Interaction

**Audience:** Cardiovascular healthcare professionals, pharmacists

[Posted 11/17/2009] FDA notified healthcare professionals of new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole. Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

Other drugs that are expected to have a similar effect and should be avoided in combination with clopidogrel include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

Recommendations for healthcare professionals are provided in the "Information for Healthcare Professionals" sheet.

[11/17/2009 - Information for Healthcare Professionals - FDA]  
 [11/17/2009 - Public Health Advisory - FDA]  
 [11/17/2009 - Follow-Up to January 2009 Early Communication - FDA]

Previous Medwatch Alert:  
 [01/26/2009] Clopidogrel bisulfate (marketed as Plavix) Early Communication

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## March 2010 Relabeling

**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

- Effectiveness of Plavix depends on activation ... by ... CYP2C19
- Poor metabolizers .... exhibit higher cardiovascular event rates following ... acute coronary syndrome (ACS). or ... percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify .. CYP2C19 genotype ...
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

**WARNINGS AND PRECAUTIONS**

- Avoid concomitant use with drugs that inhibit CYP2C19 (e.g., omeprazole)

*Drugs at the FDA (Plavix, "HIGHLIGHTS")*  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020839s042lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf)  
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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## August 2010 Relabeling

### 2.3 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response [see *Clinical Pharmacology (12.5)*], an appropriate dose regimen for this patient population has not been established.

### 2.4 Use with Proton Pump Inhibitors (PPI)

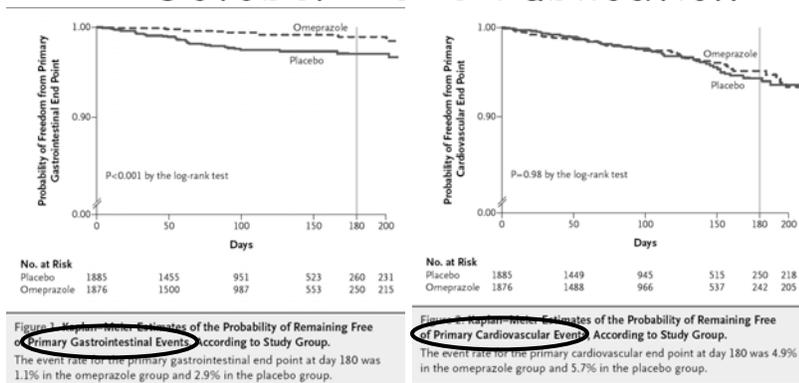
Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of Plavix. Avoid using omeprazole concomitantly or 12 hours apart with Plavix. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.1)* and *Clinical Pharmacology (12.5)*].

#### Drugs at the FDA

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020839s048lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s048lbl.pdf)  
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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## October 2010 Publication



→ Among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper gastrointestinal bleeding. There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but our results do not rule out a clinically meaningful difference in cardiovascular events due to use of a PPI.

*D.L. Bhatt et al, COGENT trial | October 6, 2010 | (DOI: 10.1056/NEJMoa1007964)*

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## Clopidogrel and Pharmacogenetic Test in Clinical Practice (one example)

- Vanderbilt University Medical Center joins Scripps Clinic, starting to routinely test for variations in CYP2C19 gene before antiplatelet therapy
- Test for \*1 (wild), 2, 3 (loss-of-function), 17 (gain-of-function)
- Individual clinicians to decide treatment options
  - If homozygous for loss-of-function  
→ prasugrel
  - If contraindications for prasugrel  
→ increase the dose from 75 to 150 mg  
or ticagrelor when it is available

<http://www.theheart.org/article/1139495.do> (October 21, 2010)

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# Clinical Utility

## Editorial

*Clinical Pharmacology & Therapeutics* (2010) **88** 6, 729-733. doi:10.1038/clpt.2010.229

### What Is Clinical Utility and Why Should We Care?

L J Lesko<sup>1</sup>, I Zineh<sup>1</sup> and S-M Huang<sup>1</sup>

<sup>1</sup>Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

Correspondence: L Lesko, ([lawrence.lesko@fda.hhs.gov](mailto:lawrence.lesko@fda.hhs.gov)); I Zineh, ([Issam.Zineh@fda.hhs.gov](mailto:Issam.Zineh@fda.hhs.gov)); S-M Huang, ([ShiewMei.Huang@fda.hhs.gov](mailto:ShiewMei.Huang@fda.hhs.gov))

## State of the Art

*Clinical Pharmacology & Therapeutics* (2010) **88** 6, 765-773. doi:10.1038/clpt.2010.230

### Assessing the Clinical Utility of Diagnostics Used in Drug Therapy

J Woodcock<sup>1</sup>

<sup>1</sup>Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA

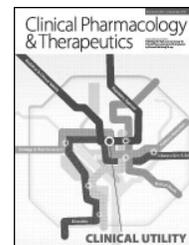
## State of the Art

*Clinical Pharmacology & Therapeutics* (2010) **88** 6, 774-778. doi:10.1038/clpt.2010.233

### Enrichment of Clinical Study Populations

R Temple<sup>1</sup>

<sup>1</sup>Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA



December 2010

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# Labeling Example (2)

## CYP3A & Dasatinib

### Classification of Inhibitors

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

FDA U.S. Food and Drug Administration A-Z Index Search

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Drugs

Home > Drugs > Development & Approval Process (Drugs) > Development Resources

**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>

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Recent advances in transporter and CYP-based Interactions including the interactions of dietary supplements and drugs  
CFSAN OARSA Seminar, March 17, 2011, Laurel, MD

<b>Classification of Inhibitor/Inducers*</b>			
<u>CYP Enzymes</u>	<b>Strong Inhibitors</b>	<b>Moderate inhibitors</b>	<b>Weak inhibitors</b>
	$\geq 5$ -fold increase in AUC	$\geq 2$ but $<5$ -fold increase in AUC	$\geq 1.25$ but $<2$ -fold increase in AUC
<u>CYP Enzymes</u>	<b>Strong Inducers</b>	<b>Moderate Inducers</b>	<b>Weak Inducers</b>
	$\geq 80\%$ decrease in AUC	50- 80% decrease in AUC	20-50% decrease in AUC

\*Possible models  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>;  
 the U Washington drug interaction database  
<http://www.druginteractioninfo.org/>

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**Dasatinib** (May 2009 labeling)

**Concomitant Strong CYP3A4 inhibitors:** CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) may increase dasatinib plasma concentrations. Grapefruit juice should be avoided.

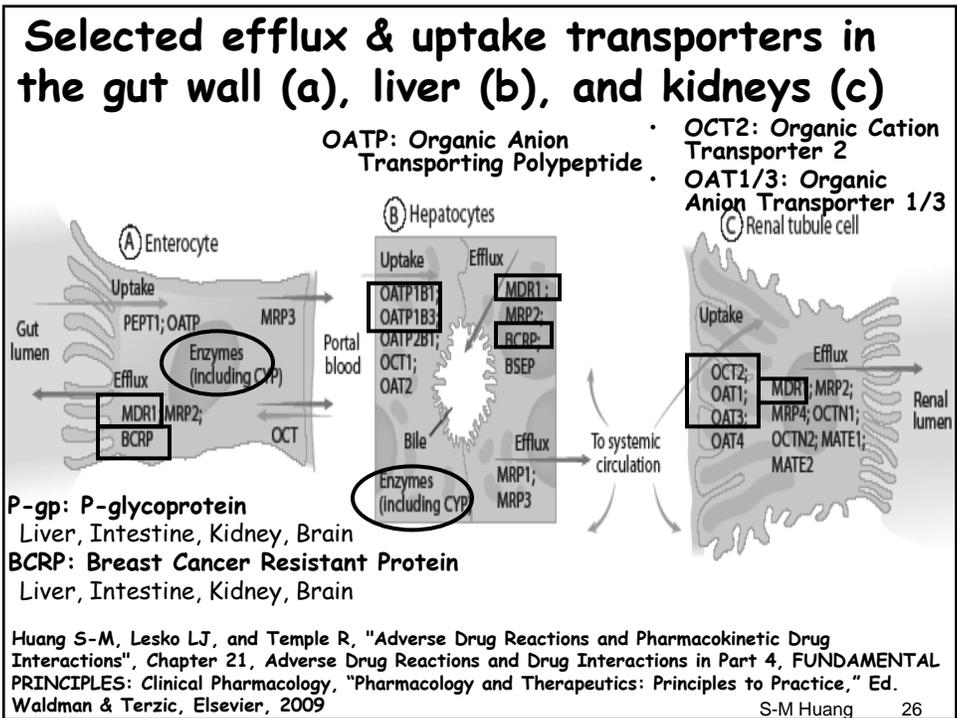
**Concomitant Strong CYP3A4 inducers:** The use of concomitant strong CYP3A4 inducers .....should be avoided (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital). St. John's Wort .....should be avoided.

*Drugs at the FDA (Sprycel, "DOSAGE and ADMINISTRATION")*  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/021986s004lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021986s004lbl.pdf)  
<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>

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# What Do We Know about Transporters?

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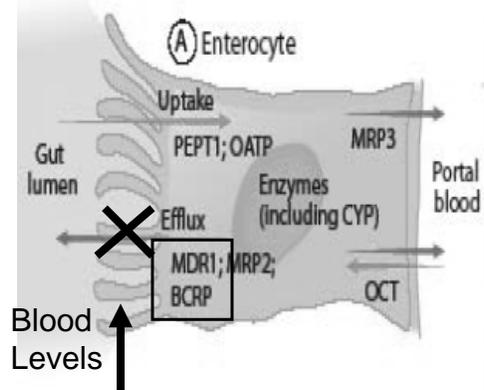
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## Important Intestine Transporters

### Efflux

(to intestinal lumen):

- P-glycoprotein (P-gp, MDR1, ABCB1)
- Breast Cancer Resistance Protein (BCRP, ABCG2)



Inhibitors	Substrates	Consequence	AUC
Quinidine	Digoxin	Digoxin Exposure ↑	1.7-fold ↑
GF120918	Topotecan	Topotecan Exposure ↑	2.4-fold ↑

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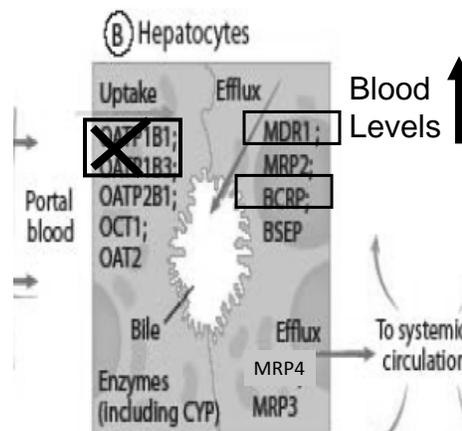
## Important Liver Transporters

Uptake  
(from blood to hepatocytes):

- OATP1B1
- OATP1B3

Efflux  
(excretion to bile):

- P-gp
- BCRP



Inhibitors	Substrates	Consequence	AUC
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure ↑	7-fold ↑
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure ↑	2-fold ↑

### Important Kidney Transporters

**Uptake**  
(from blood to kidney):

- OCT2
- OAT1
- OAT3

**Efflux**  
(secretion to urine)

- P-gp (MDR1)

Inhibitors	substrates	Consequence	AUC
Probenecid	Cephadrine	Cephadrine Exposure ↑	3.6-fold ↑
Cimetidine	Metformin	Metformin Exposure ↑	1.4-fold ↑

## Labeling Example (3)

### OATP, BCRP, P-gp & Statins

- Drug Interactions
- Pharmacogenetics

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### Comparative exposure and dose recommendation in subgroups with various patient factors

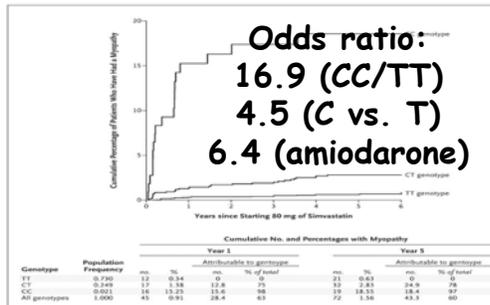
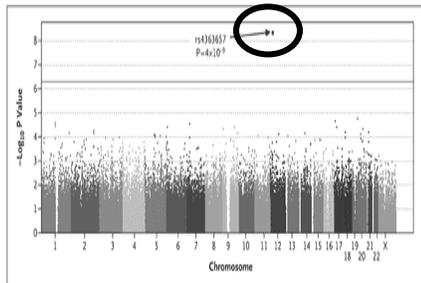
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4	Race	2-fold (Asians)	5	5-20
5	Cyclosporine	7-fold		5
6	Gemfibrozil	1.9-fold		10
7	Lopinavir/ritonavir	5-fold		10

(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> S-M Huang 31

## Pharmacogenetics (simvastatin) - Myopathy -

### Genomewide Association



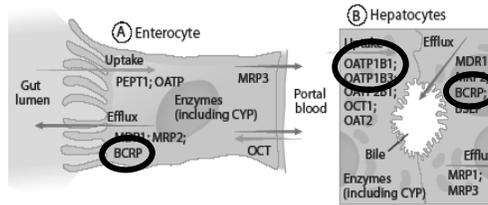
1. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype (c.521T>C)
2. Association replicated in another 40 mg group

The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-799 (UK) S-M Huang 32

## 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)

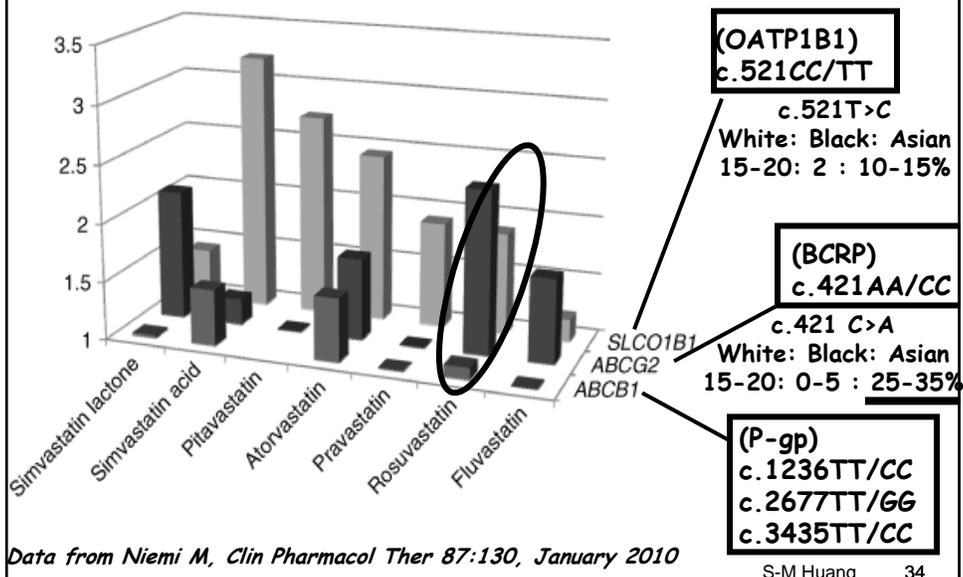


Crestor Labeling (AstraZeneca); <http://www.accessdata.fda.gov/scripts/cder/drugsatfda>

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

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



## OATP1B1 inhibitors

"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"

*Eltrombopag: for for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura*

*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/index.cfm?fuseaction=Search.Label_ApprovalHistory)*

*<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>*

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## Labeling Example (4)

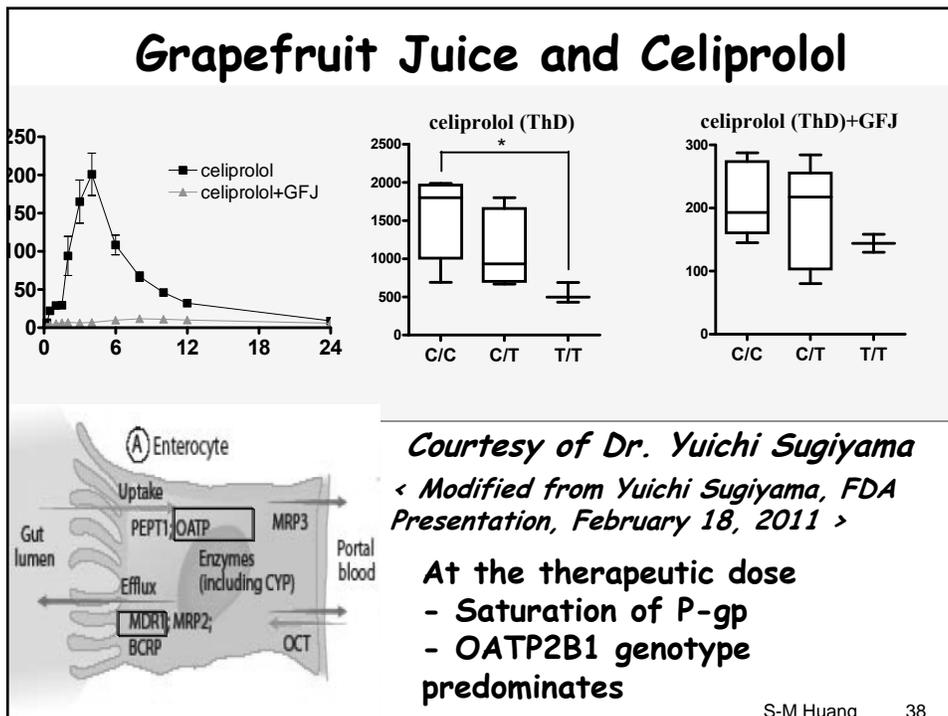
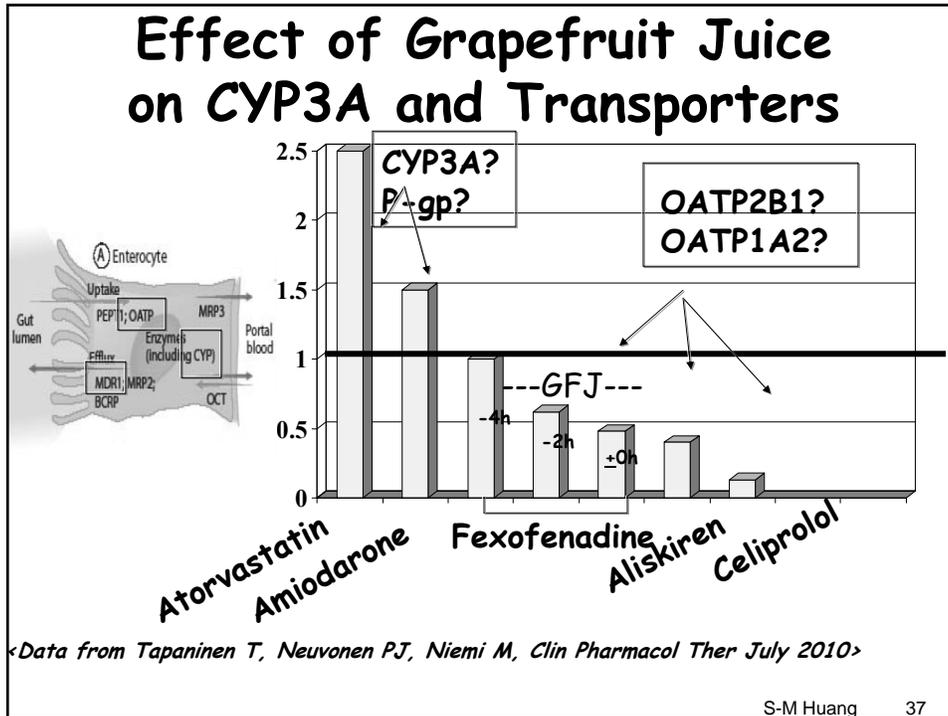
OATP, BCRP, P-gp

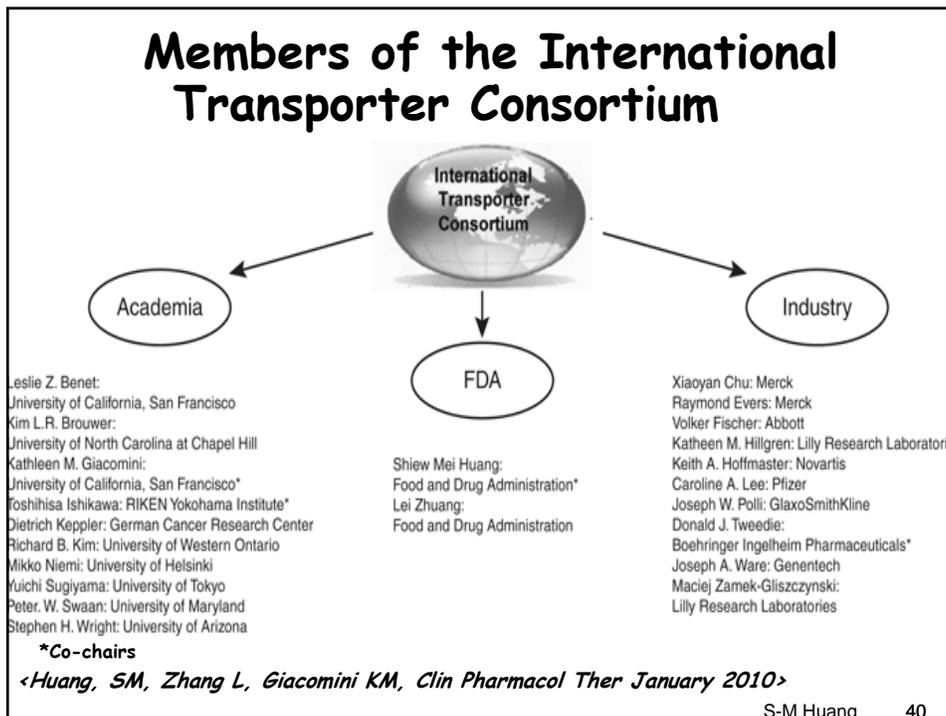
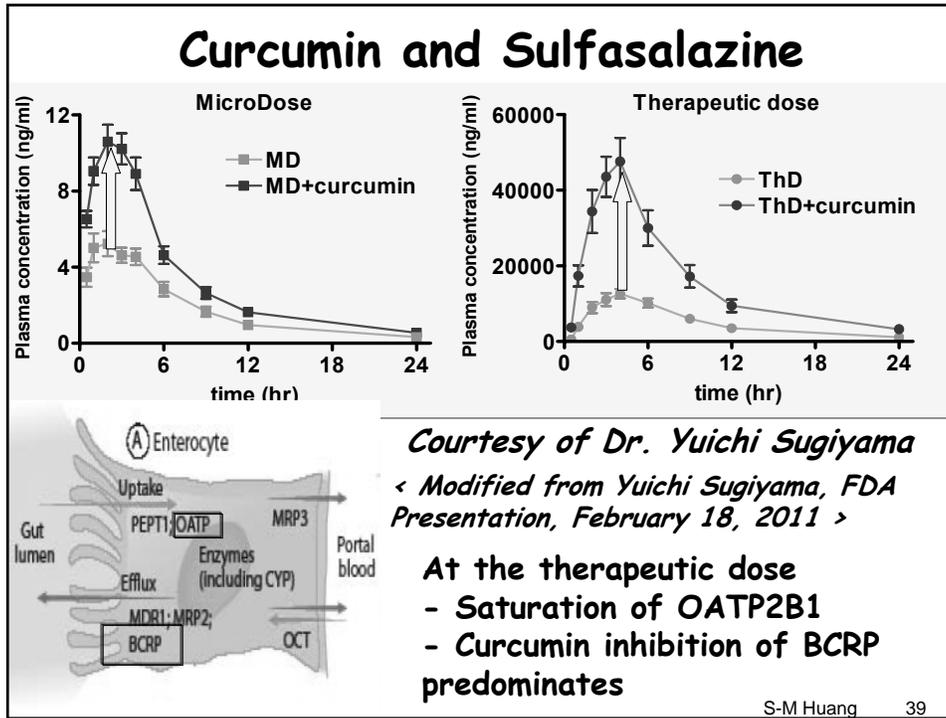
&

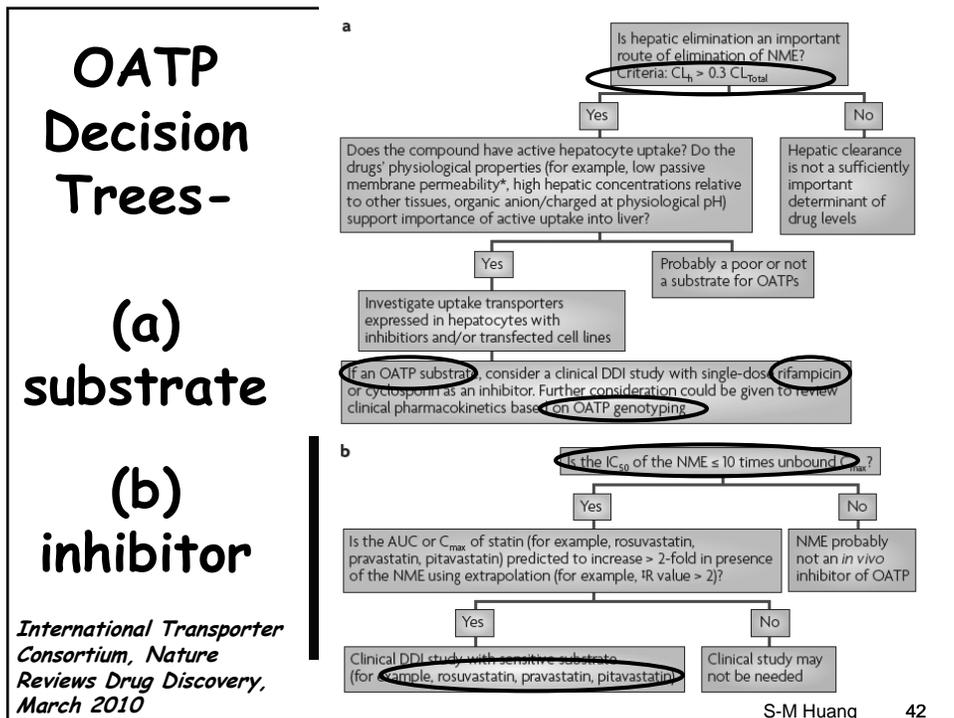
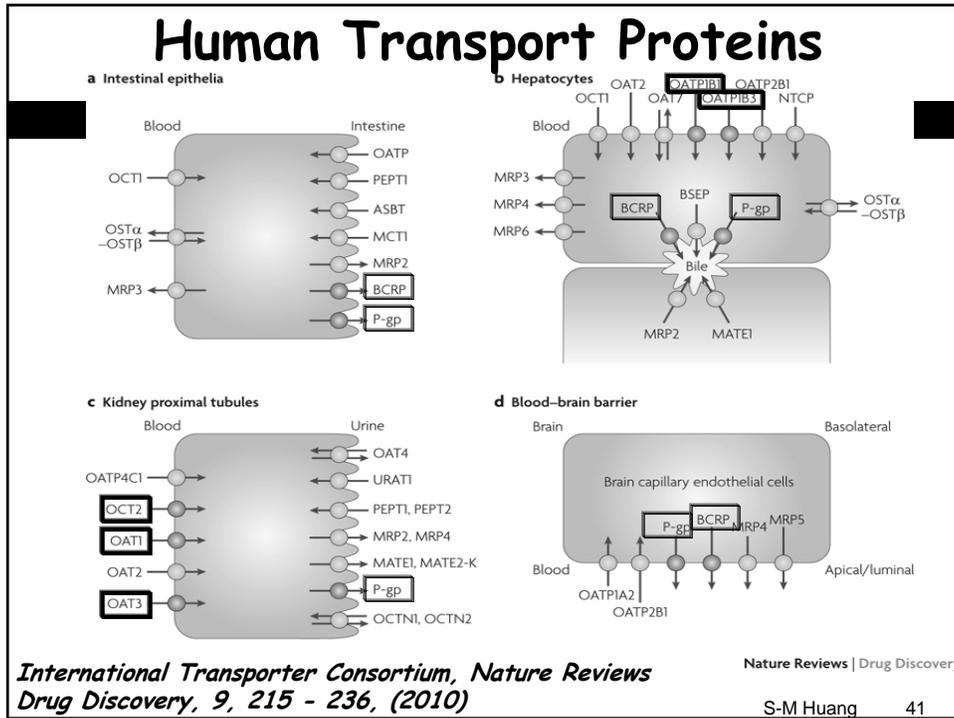
Other drugs

- Drug Interactions
- Pharmacogenetics

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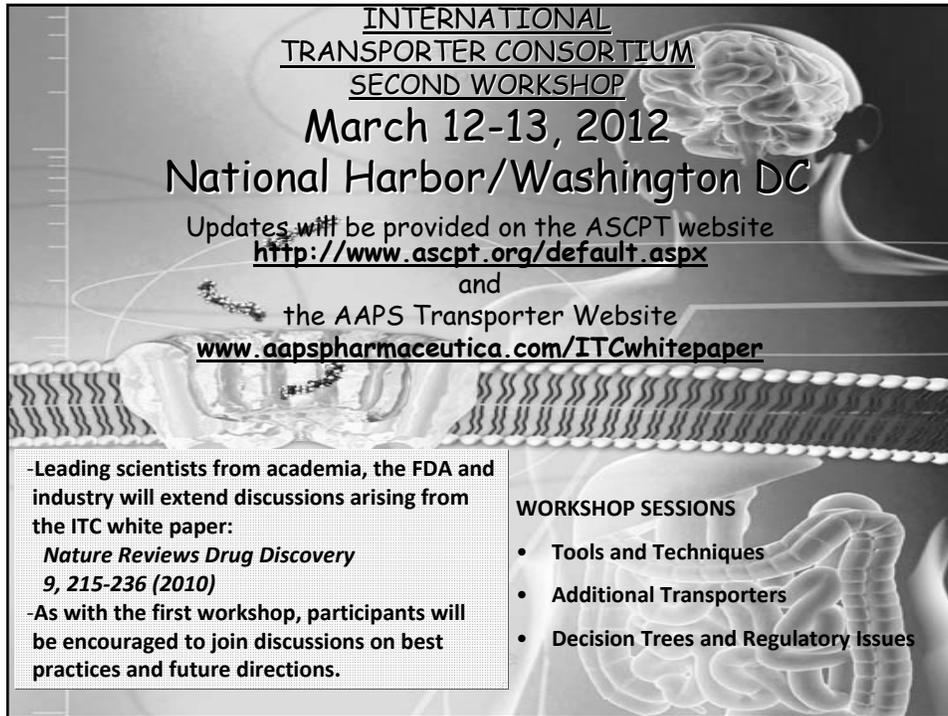
INTERNATIONAL  
TRANSPORTER CONSORTIUM  
SECOND WORKSHOP  
March 12-13, 2012  
National Harbor/Washington DC

Updates will be provided on the ASCPT website  
<http://www.ascpt.org/default.aspx>  
and  
the AAPS Transporter Website  
[www.aapspharmaceutica.com/ITCwhitepaper](http://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



**FDA Guidance**

**Guidance for Industry**

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

**Has been  
Revised**

DRAFT GUIDANCE

This guidance document is for informational 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) Tomi Stefano, 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

*Draft 2006 Guidance:*  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>

**Revision to be published  
in 2011 as a draft for  
public comment**

*Clinical Pharmacology Guidance Documents:*  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm>

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**Recent advances in transporter and CYP-based Interactions including the interactions of dietary supplements and drugs  
CFSAN OARSA Seminar, March 17, 2011, Laurel, MD**

**FDA Guidance for Industry**

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**Guidance for Industry**

**Clinical Pharmacogenomics:  
Premarketing Evaluation in Early Phase  
Clinical Studies**

*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-301), 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) Laurence LeBlanc at 301-796-1565 or Shiew-Mei Huang at 301-796-1541, or (CDER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800, or Changning Handenschield at 301-827-3947, or (CDRH) Frances Kahush at 301-796-5408.

**Published for public  
comment in February  
2011**

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

**Send in your comments**

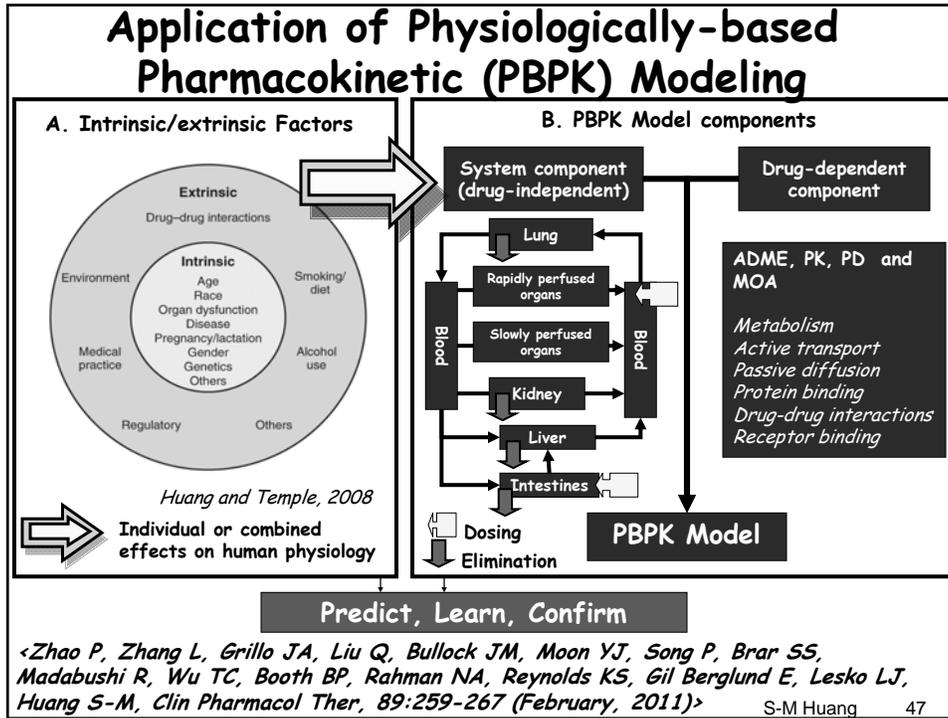
U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)

February 2011  
Clinical Pharmacology

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**Utility of Physiologically-  
Based Pharmacokinetic (PBPK)  
Modeling**

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### PBPK: Application of PBPK in Clinical Pharmacology Evaluation (2)- Rivaroxaban

Factors	Rivaroxaban AUC Change	Recommendations (EMA)
Ritonavir or ketoconazole	<b>2.5-2.6x</b>	<b>Co-administration not recommended</b>
Erythromycin or clarithromycin	<b>1.3-1.5x</b>	-- No dosage change
Renal impairment (CL <sub>cr</sub> in mL/min)		
50-80	<b>1.4-1.6x</b>	-- No dosage change
30-49	<b>1.4-1.6x</b>	Use with caution, if also on drugs increasing plasma levels
15-29	Limited data	Use with caution
<15	---	Not recommended

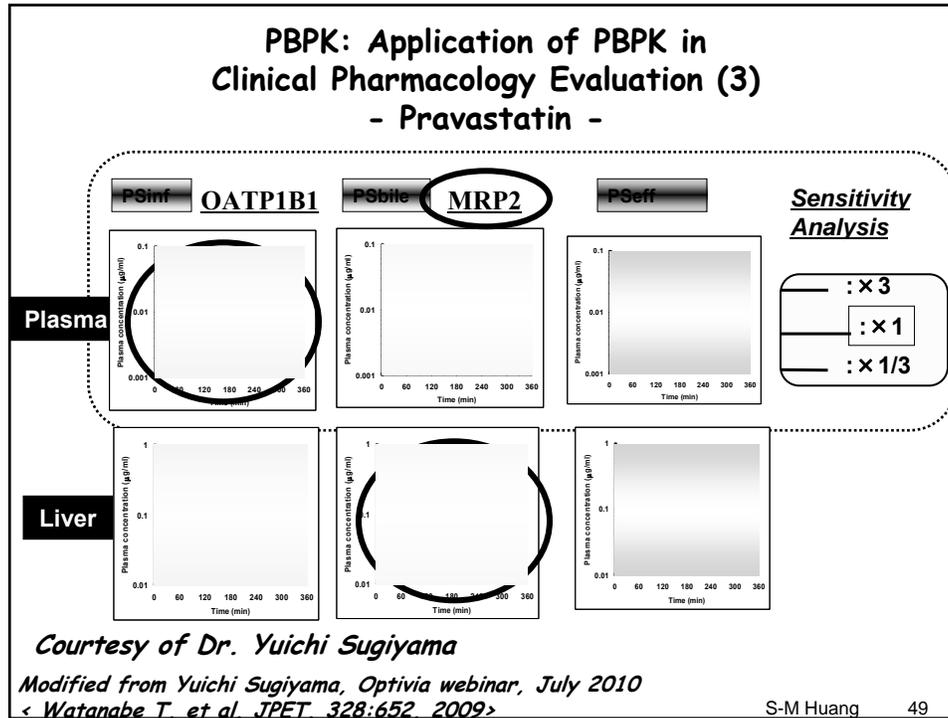
Rivaroxaban: 36% renal, metabolism (18% CYP3A, 14% CYP2J2).

**What happens when renal impaired patients also take inhibitors?**

→ Simulations can help evaluate “what if” scenarios and determine the path forward (studies or labeling).

- [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000944/WC500057108.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf)
- Zhao P, et al, Clin Pharmacol Ther, 89:259-267 (February, 2011)

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### PBPK: Application of PBPK in Clinical Pharmacology Evaluation (4) - HIV Protease Inhibitors -

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

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

Inhibitors	Maximum inhibition (% of control)		$IC_{50}$ ( $\mu$ M)		$K_i$ ( $\mu$ M)		Plasma protein binding (%) <sup>b</sup>	$C_{max}$ corrected for plasma protein binding ( $\mu$ M) <sup>a</sup>
	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 <sup>b</sup>	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	-	-
Bromosulphthalein	74 ± 9	92 ± 3	0.7 ± 0.4	1.4 ± 0.4	0.6	1.0	-	-

Notes: n.d., Not determined.  
<sup>a</sup>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).  
<sup>b</sup>Due to solubility limitations, nelfinavir could only be tested up to a concentration of 20  $\mu$ M.  
 $IC_{50}$ -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*

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## 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]**

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## 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**

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## 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

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## 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

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## Acknowledgement

- Office of Clinical Pharmacology (OCP)/OTS



- OCP Transporter Scientific Interest Group
- OCP PBPK Scientific Interest Group
- Lei Zhang      Kellie Reynolds      Ping Zhao  
Larry Lesko      Bob Temple
- International Transporter Consortium
- Janet Woodcock/Critical Path Initiative
- Academic/industry scientists- discussions

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## 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>

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