Regulatory Guidance on Drug-Drug Interactions: Comparing Draft Guideline/Guidance Documents by EMA and FDA
American Society for Clinical Pharmacology & Therapeutics
Annual Meeting, Dallas, TX
March 4, 2011

FDA Perspective - Evaluation of Drug Interactions

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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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 Stifano, 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)

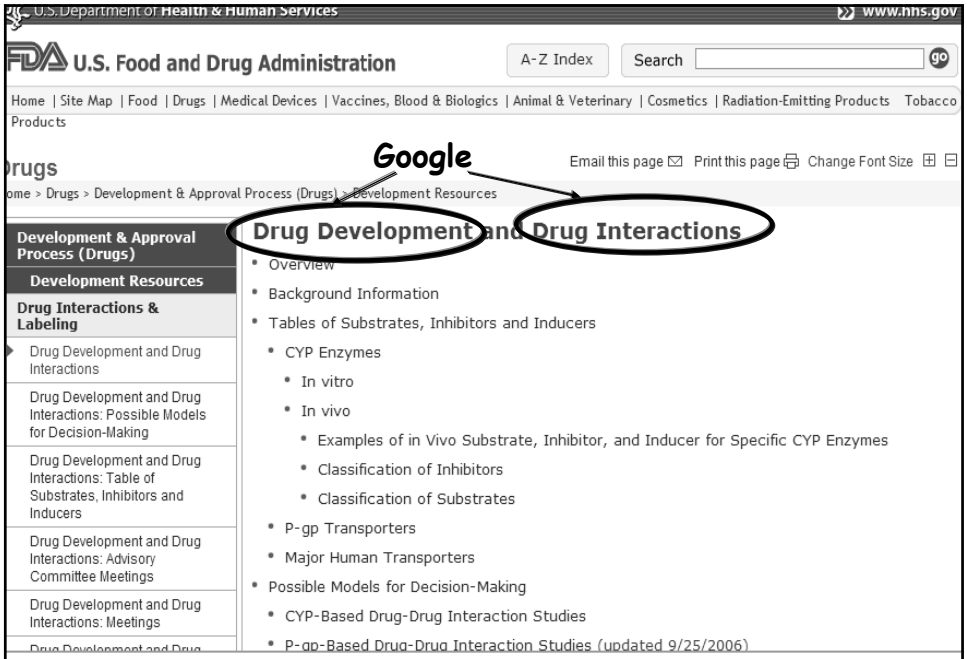
September 2006
Clinical Pharmacology

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

S-M Huang 2



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

S-M Huang 3

New Draft Guidance
- Key Messages -

- The need to understand metabolism, transport, and drug-drug interaction (DDI) in order to assess benefit/risk
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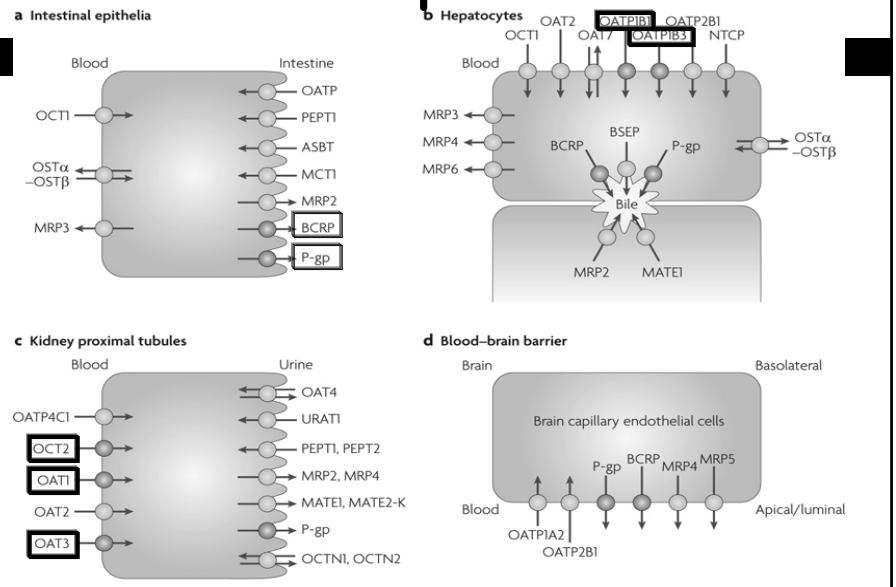
S-M Huang 4

Human Transport Proteins

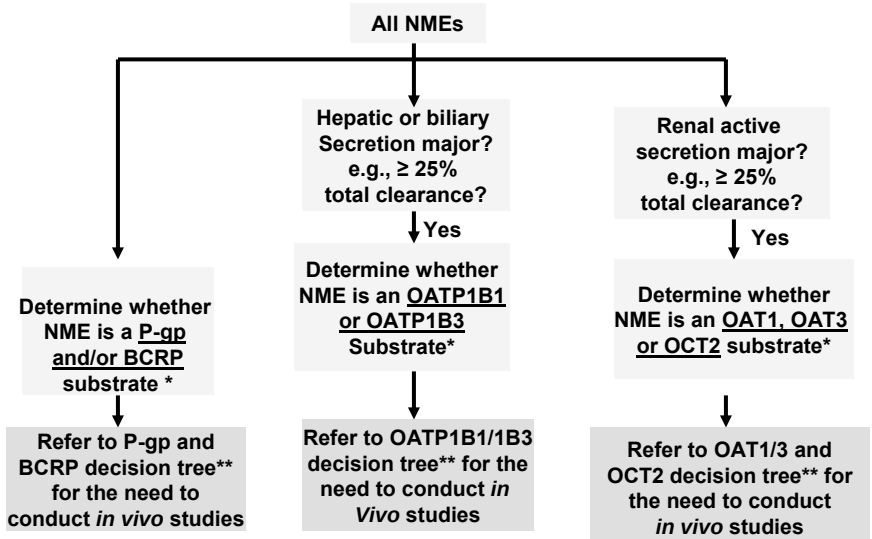


International Transporter Consortium, Nature Reviews Drug Discovery, 9, 215 - 236, (2010)

Nature Reviews | Drug Discovery

S-M Huang 5

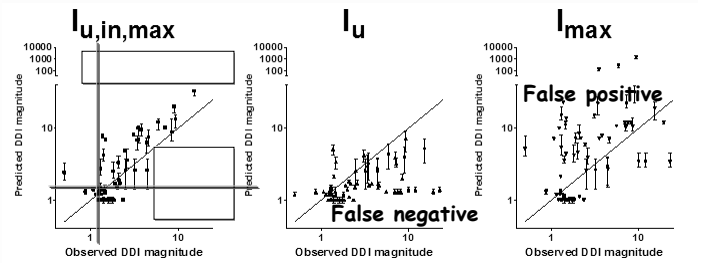
Evaluation of NME as a Substrate for Transporters—Other Drugs' Effect on NME



* 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
* *FDA Clinical Pharmacology Advisory Committee Meeting, 3/17/10*

S-M Huang 6

OATP Decision Trees-

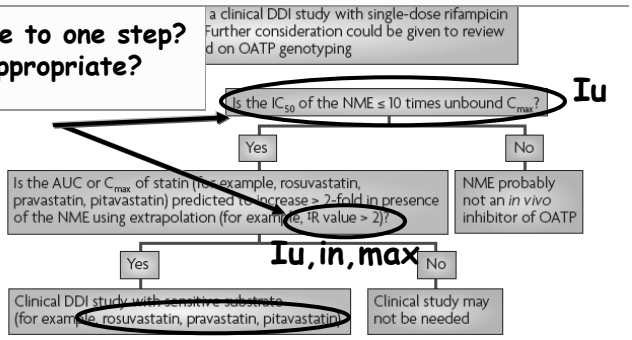


Courtesy: Dr. Yuichi Sugiyama, Feb 2011

→Should we modify these to one step?
→ Is the R value of 2 appropriate?

(b) inhibitor

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



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/

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;
1. Modified from Agarwal et.al, ACCP Annual Meeting, September 2010, Baltimore, MD
2. PMC/PMR survey-- Fan Y, et al, Clin Pharmacol Ther 89(1): S37, February 2011 (presentation at OII-B-1, 445 pm, Reunion ABC, Friday, March 4, ASCPT meeting, Dallas, TX) S-M Huang 9

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/ S-M Huang 10

New Draft Guidance
- Key Messages -

- The need to understand metabolism, transport, and drug-drug interaction (DDI) in order to assess benefit/risk
- <u>Application of mechanistic models in DDI prediction (static and dynamic models, including PBPK)</u>
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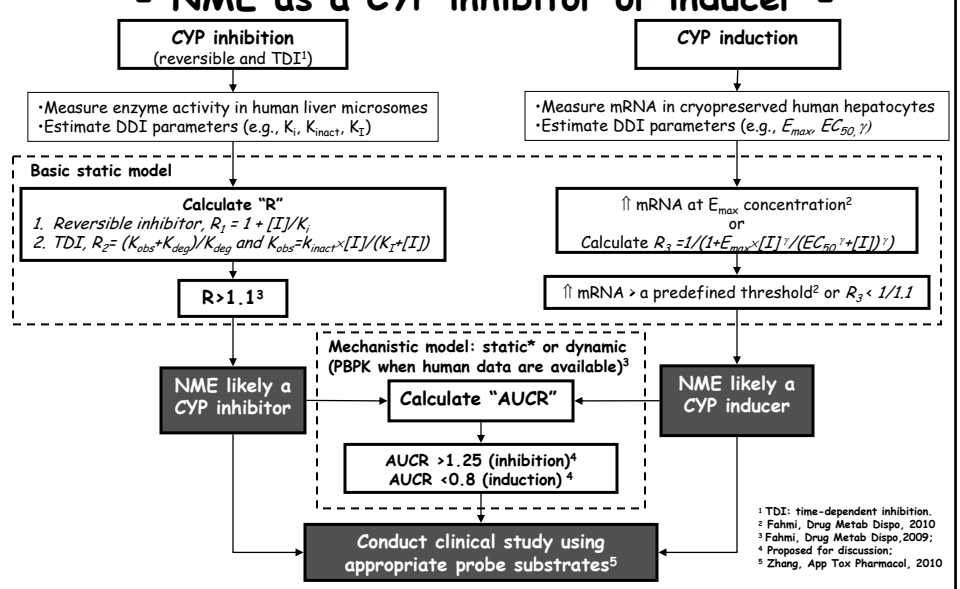
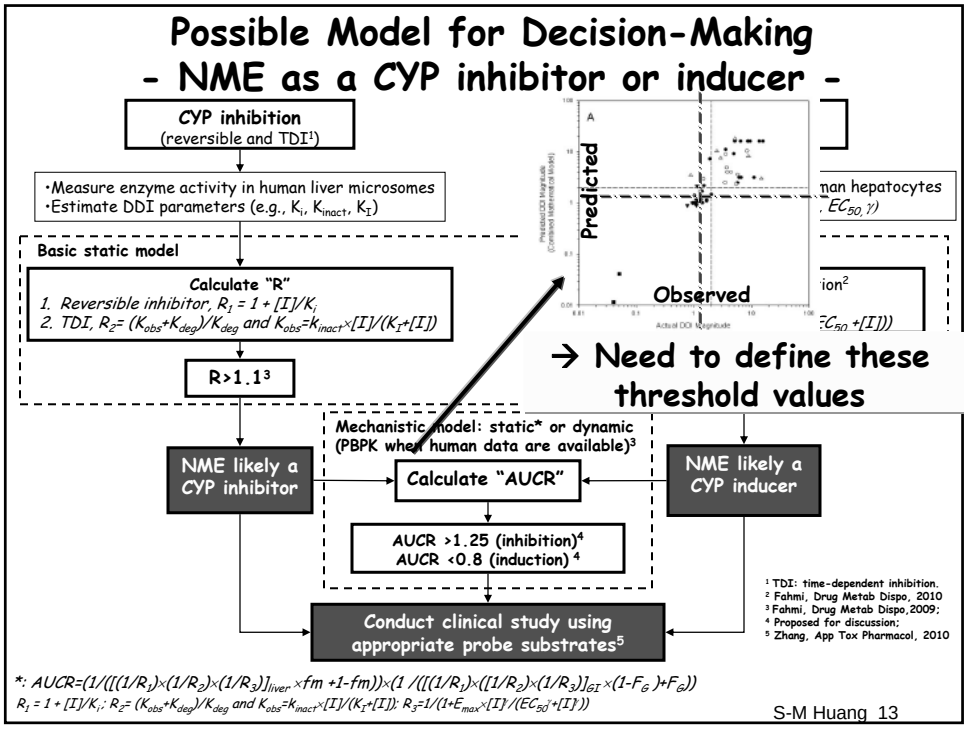
S-M Huang 11

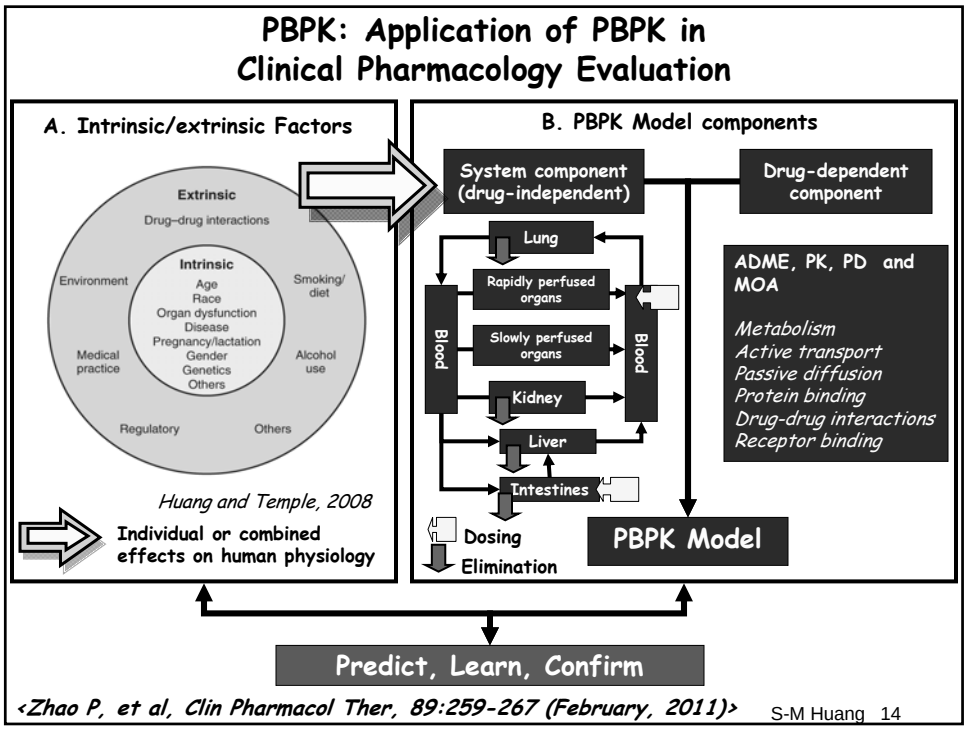
Possible Model for Decision-Making
- NME as a CYP inhibitor or inducer -



*: $AUCR=(1/([(1/R_1)\times(1/R_2)\times(1/R_3)]_{liver}\times fm + 1 - fm))\times(1/([(1/R_1)\times([1/R_2)\times(1/R_3)]_{GI}\times(1-F_G)+F_G))$
$R_1 = 1 + [I]/K_i$; $R_2 = (K_{obs}+K_{deg})/K_{deg}$ and $K_{obs}=k_{inact}\times[I]/(K_I+[I])$; $R_3=1/(1+E_{max}\times[I]^{\gamma}/(EC_{50}^{\gamma}+[I]^{\gamma}))$

S-M Huang 12


Possible Model for Decision-Making
- NME as a CYP inhibitor or inducer -
CYP inhibition
(reversible and TDI[1])
•Measure enzyme activity in human liver microsomes
•Estimate DDI parameters (e.g., K_i, K_{inact}, K_I)
Basic static model
Calculate "R"
1. Reversible inhibitor, $R_1 = 1 + [I]/K_i$
2. TDI, $R_2 = (K_{obs}+K_{deg})/K_{deg}$ and $K_{obs}=k_{inact}\times[I]/(K_I+[I])$
R>1.1[3]
Predicted
Observed
→ Need to define these threshold values
Mechanistic model: static* or dynamic (PBPK when human data are available)[3]
NME likely a CYP inhibitor
Calculate "AUCR"
NME likely a CYP inducer
AUCR >1.25 (inhibition)[4]
AUCR <0.8 (induction)[4]
Conduct clinical study using appropriate probe substrates[5]
[1] TDI: time-dependent inhibition.
[2] Fahmi, Drug Metab Dispo, 2010
[3] Fahmi, Drug Metab Dispo,2009;
[4] Proposed for discussion;
[5] Zhang, App Tox Pharmacol, 2010
*: $AUCR=(1/([(1/R_1)\times(1/R_2)\times(1/R_3)]_{liver}\times fm + 1-fm))\times(1/([(1/R_1)\times([1/R_2)\times(1/R_3)]_{GI}\times(1-F_G)+F_G))$
$R_1 = 1 + [I]/K_i$; $R_2 = (K_{obs}+K_{deg})/K_{deg}$ and $K_{obs}=k_{inact}\times[I]/(K_I+[I])$; $R_3=1/(1+E_{max}\times[I]/(EC_{50}+[I]))$
S-M Huang 13

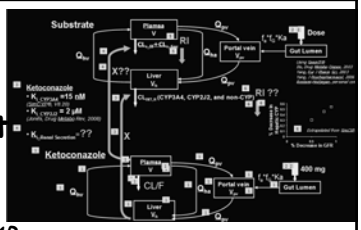

PBPK: Application of PBPK in Clinical Pharmacology Evaluation
A. Intrinsic/extrinsic Factors
Extrinsic
Drug–drug interactions
Intrinsic
Age
Race
Organ dysfunction
Disease
Pregnancy/lactation
Gender
Genetics
Others
Environment
Smoking/ diet
Medical practice
Alcohol use
Regulatory
Others
Huang and Temple, 2008
Individual or combined effects on human physiology
B. PBPK Model components
System component (drug-independent)
Drug-dependent component
Lung
Rapidly perfused organs
Slowly perfused organs
Kidney
Liver
Intestines
Blood
Blood
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, 89:259-267 (February, 2011)>
S-M Huang 14

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

Factors	Rivaroxaban AUC Change	Recommendations (EMA)
Ritonavir or ketoconazole	2.5-2.6x	Co-administration not recommended
Erythromycin or clarithromycin	1.3-1.5x	-- No dosage change
Renal impairment (CLcr in mL/min)		
50-80	1.4-1.6x	-- No dosage change
30-49	1.4-1.6x	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,

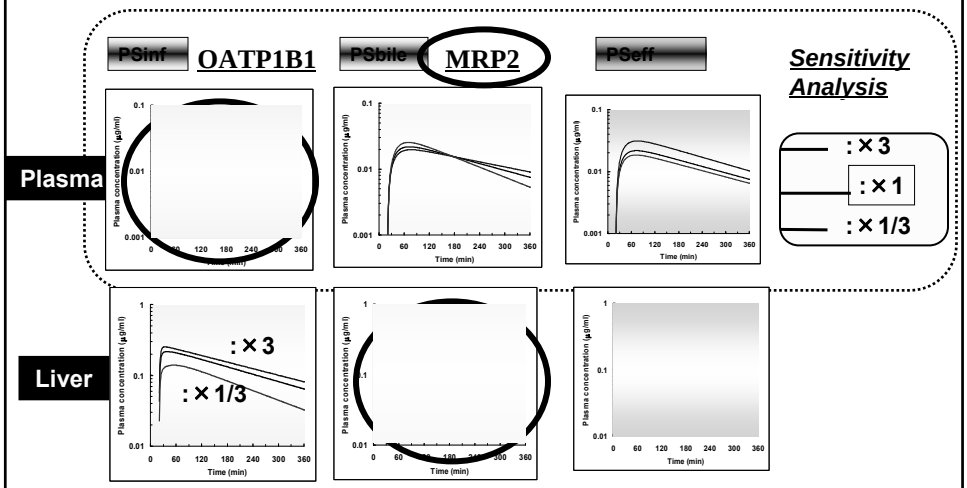
What happens when renal impaired patients also take inhibitors?
→ Simulations can help evaluate "what if" scenarios and determine the path forward (studies or labeling).



1. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf
2. Zhao P, et al, Clin Pharmacol Ther, 89:259-267 (February, 2011)

S-M Huang 15

PBPK: Application of PBPK in Clinical Pharmacology Evaluation (3) - Pravastatin -



Courtesy of Dr. Yuichi Sugiyama

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

S-M Huang 16

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 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

S-M Huang 17

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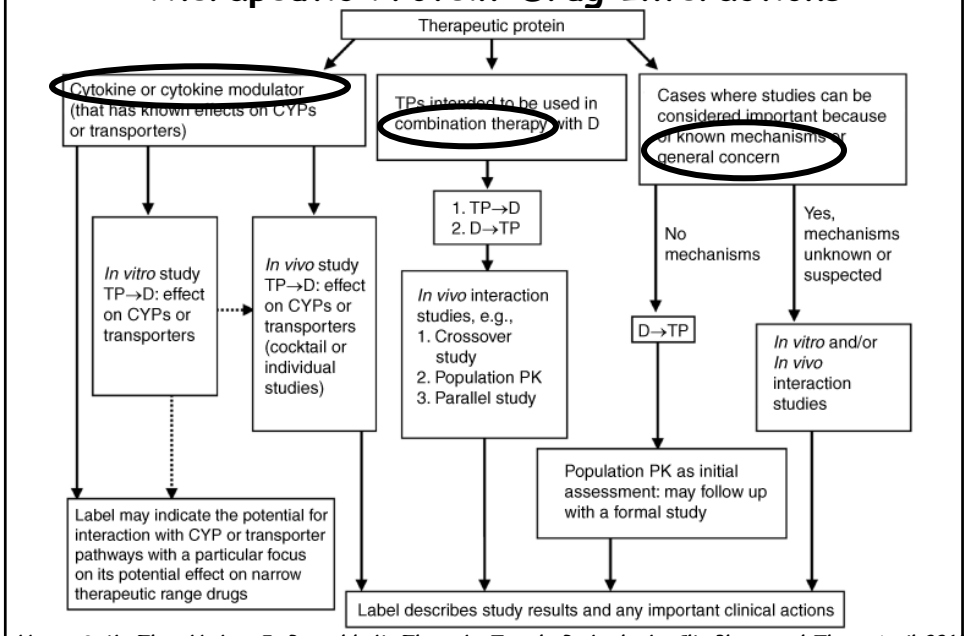
Therapeutic Protein-Drug Interactions



Huang S-M, Zhao H, Lee J, Reynolds K, Zhang L, Temple R, Lesko L, Clin Pharmacol Ther, April 2010

<Girish S, et al, report from the AAPS/NBC workshop meeting, June 2010>

S-M Huang 19

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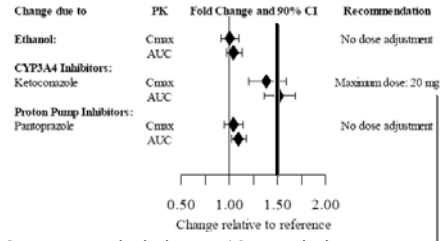
S-M Huang 20

- Labeling Examples -

Clinical Pharmacology

7.3 Potential for Other Drugs to Affect Vilazodone

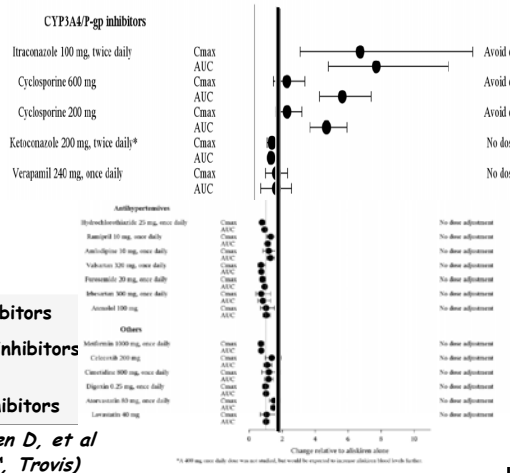
Figure 1. Impact of other drugs on Vilazodone PK



Recommended dose: 40 mg daily

- Reduce to 20 mg, if co-admin with strong inhibitors
- Reduce to 20 mg, if co-admin with moderate inhibitors for patients with intolerable adverse event
- No dose adjustment, if co-admin with mild inhibitors

Impact of co-administered drugs on the pharmacokinetics (PK) of aliskiren



OCP reviews - 1. Yu B, et al; 2.Menon-Andersen D, et al

1. January 2011 vilazodone labeling (VIIBRYD™, Trovis)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s000lbl.pdf

2. February 2011 aliskiren labeling (Tekturna®, Novartis)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021985s014lbl.pdf

S-M Huang 21

Summary

- FDA will be issuing <u>for public comments</u> another draft drug interaction guidance to include recommendations related to the evaluation of <u>transporter-based drug interactions</u>, in addition to CYP & <u>non-CYP based interactions</u>, interactions involving <u>therapeutic proteins</u>, and the use of various <u>mechanistic models</u> (static and dynamic, including PBPK models) to assess combined effect of various patient factors
- Discussion with EMA is planned

S-M Huang 22

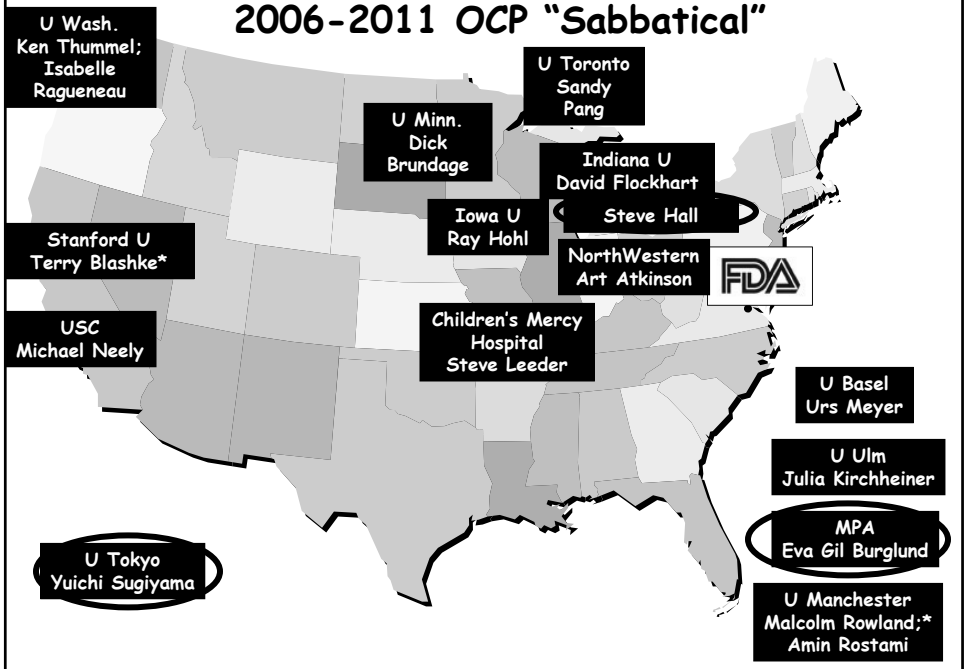
Acknowledgement

- 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

S-M Huang 23

2006-2011 OCP "Sabbatical"



S-M Huang 25

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

-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**

International Consortium for
Innovation and Quality
in Pharmaceutical Development

IQ/FDA Drug-Drug Interaction Prediction Workshop

Silver Spring, Maryland
Monday, June 06, 2011 - Tuesday, June 07, 2011

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About this Event

Drug-Drug Interaction Prediction Workshop

Co-sponsored by FDA and the Drug Metabolism Leadership Group of the IQ Consortium

Hosted by the FDA

Focus on model based DDI predictions

Regulatory update: SM Huang (FDA) and E Gil Berglund (EMA)
Academic update: K Maeda (Japan), J Unadkat (US), and A Gelatin (UK)
Industry experiences: 8 cases from different companies

Workgroup update: H Einolf (Novartis), RS Obach (Pfizer), P Zhao and L Zhang (FDA)

S-M Huang 26