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

Shiew-Mei Huang, Ph.D.
Deputy Director
Office of Clinical Pharmacology
OTS, CDER, FDA
<table>
<thead>
<tr>
<th>Category</th>
<th>Title</th>
<th>Type</th>
<th>Date</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Lumination Studies—Study Design, Data Analysis, and Recommendations for Labeling (PDF - 066KB)</td>
<td>Draft Guidance</td>
<td>02/05/05</td>
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<tr>
<td>Pharmacology</td>
<td>Clinical Pharmacogenomics, Premarking Evaluation in Early Phase Clinical Studies (PDF - 051KB)</td>
<td>Draft Guidance</td>
<td>02/17/11</td>
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<td>Clinical</td>
<td>Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (PDF - 272KB)</td>
<td>Final Guidance</td>
<td>05/05/03</td>
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<td>Pharmacology</td>
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<td>Drug Interaction Studies—Study Design, Data Analysis, and Recommendations for Dosing, and Labeling Requirements (PDF - 827KB)</td>
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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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance.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
• 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Aliases</th>
<th>Tissue</th>
<th>Function</th>
<th>Interacting drug</th>
<th>Substrate (affected drug)</th>
<th>Changes in substrate plasma AUC (AUCratios)</th>
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</thead>
</table>
| ABC transporter of clinical importance in the absorption, disposition, and excretion of drugs

<table>
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<tr>
<th>Gene</th>
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<th>Changes in substrate plasma AUC (AUCratios)</th>
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<tbody>
<tr>
<td>ABCB1</td>
<td>P-gp, MDR1</td>
<td>Intestinal enterocyte, kidney proximal tubule, hepatocyte (canalicular), brain endothelia</td>
<td>Efflux</td>
<td>Dronedarone</td>
<td>Digoxin</td>
<td>2.6-fold</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quinidine</td>
<td>Digoxin</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Ranolazine</td>
<td>Digoxin</td>
<td>1.6-fold</td>
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<td></td>
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<td></td>
<td></td>
<td>Tipranavir/ritonavir</td>
<td>Lopeamide</td>
<td>0.5-fold</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tipranavir/ritonavir</td>
<td>Saquinavir/ritonavir</td>
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<tr>
<td>ABCG2</td>
<td>BCRP</td>
<td>Intestinal enterocyte, hepatocyte (canalicular), kidney proximal tubule, brain endothelia, placenta, stem cells, mammary gland (lactating)</td>
<td>Efflux</td>
<td>GF120918</td>
<td>Topotecan</td>
<td>2.4-fold</td>
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| SLC transporter of clinical importance in the disposition and excretion of drugs

<table>
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<tr>
<th>Gene</th>
<th>Aliases</th>
<th>Tissue</th>
<th>Function</th>
<th>Interacting drug</th>
<th>Substrate (affected drug)</th>
<th>Changes in substrate plasma AUC (AUCratios)</th>
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<tbody>
<tr>
<td>SLC10A1</td>
<td>OATP1B1, OATP-C, OATP2, LST-1</td>
<td>Hepatocyte ( sinusoidal)</td>
<td>Uptake</td>
<td>Lopinavir/ritonavir</td>
<td>Bosentan</td>
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<td>Cyclosporine</td>
<td>Pravastatin</td>
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<td></td>
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<td></td>
<td>Rifampin (single dose)</td>
<td>Glyburide</td>
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<td></td>
<td>Cyclosporine</td>
<td>Rosuvastatin</td>
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<td></td>
<td>Cyclosporine</td>
<td>Pitavastatin</td>
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<td>SLC10A3</td>
<td>OATP1B3, OATP-8</td>
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<td>Lopinavir/ritonavir</td>
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<td>SLC22A2</td>
<td>OCT2</td>
<td>Kidney proximal tubule</td>
<td>Uptake</td>
<td>Cimetidine</td>
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<td></td>
<td></td>
<td>Cimetidine</td>
<td>Pindolol</td>
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<tr>
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<td></td>
<td></td>
<td>Cimetidine</td>
<td>Metformin</td>
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<tr>
<td>SLC22A6</td>
<td>OAT1</td>
<td>Kidney proximal tubule, placenta</td>
<td>Uptake</td>
<td>Probencid</td>
<td>Cephradine</td>
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<td>Probencid</td>
<td>Cidofovir</td>
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<td>Probencid</td>
<td>Acyclovir</td>
<td>1.4-fold</td>
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<td>SLC22A8</td>
<td>OAT3</td>
<td>Kidney proximal tubule, choroid plexus, brain endothelia</td>
<td>Uptake</td>
<td>Probencid</td>
<td>Furosemide</td>
<td>2.9-fold</td>
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</tbody>
</table>

*The transporters listed are the likely transporters; however, because the studies are in vitro, 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.

*Minimum predose plasma level (C_{\text{predose}}) data from day 4 (48-fold), day 10 (fivefold) after coadministration. Interaction could be partly mediated by BCRP.

Modified from ref. 2 and other sources.
Members of the International Transporter Consortium (2007)

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

Human Transport Proteins

a Intestinal epithelia

Blood → Intestine
- OATP
- PEPT1
- ASBT
- MCT1
- MRP2
- BCRP
- P-gp

b Hepatocytes

Blood → Bile
- OATP1B1
- OATP2B1
- OCT1
- OAT7
- OATP1B3
- NTCP
- MRP3
- MRP4
- MRP6
- BCRP
- BSEP
- P-gp
- OSTA
- OSTβ

C Kidney proximal tubules

Blood → Urine
- OAT4
- URAT1
- PEPT1, PEPT2
- MRP2, MRP4
- MATE1, MATE2-K
- P-gp
- OCTN1, OCTN2

D Blood–brain barrier

Brain capillary endothelial cells
- P-gp
- BCRP
- MRP4
- MRP5

Brain
- Blood
- Apical/luminal
- Basolateral

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?

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

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

Determining whether NME is an OATP1B1 or OATP1B3 Substrate *

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

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

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

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

* 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.
**P-gp Inhibition Decision Tree**

- **Bi-directional transport assay with a probe P-gp substrate (e.g. in Caco-2 or MDR1-overexpressing polarized epithelial cell lines)**
  - Net flux ratio of a probe substrate decreases with increasing concentrations of the investigational drug
    - Probably a P-gp inhibitor
    - Determine Ki or IC$_{50}$ of the inhibitor
      - $[I]_1/IC_{50}$ (or Ki) $\geq 0.1$
        - An in vivo drug interaction study with a P-gp substrate such as digoxin is recommended.
      - $[I]_1/IC_{50}$ (or Ki) $< 0.1$
        - An in vivo drug interaction study with a P-gp substrate is not needed.
    - Net flux ratio of the probe substrate is not affected with increasing concentrations of the investigational drug.
      - Poor or non-inhibitor

- $[I]_1$ is total $C_{\text{max}}$

- $[I]_2$ is Dose/250 mL

- $[I]_2$ (gut concentration)/IC$_{50}$ $\geq 10$ is New (Not in 2006 draft DDI Guidance).

Different from ITC Whitepaper (unbound $C_{\text{max}}$)

OATP Inhibition Decision Tree

Total $C_{\text{max}}$

Is $C_{\text{max}}/IC_{50}$ of the investigational drug ≥ 0.1 for OATP1B1 or OATP1B3?

Yes

Is the AUC or $C_{\text{max}}$ of statin (e.g., rosuvastatin, pravastatin, pitavastatin) predicted to increase ≥ 1.25-fold in the presence of the investigational drug using extrapolation (e.g., $R$-value $\geq 1.25^{[b][c]}$)?

Yes

In vivo DDI study with a sensitive substrate (e.g., rosuvastatin, pravastatin, pitavastatin)

No

In vivo study may not be needed

No

In vivo study may not be needed

Different from ITC whitepaper

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.

Regulatory Submissions with PBPK Data

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

Metabolism-Based Drug-Drug Interaction Studies - Decision Tree

Conduct In Vitro Metabolism and Drug-Drug Interaction Studies in Human Tissues
- Phase I enzymes: CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A, others
- Phase II enzymes: UGTs (see Figure 3)

Is investigational drug a substrate of an enzyme responsible for ≥25% of its systemic clearance?

- No
  - Is investigational drug a substrate of multiple metabolizing enzymes together responsible for ≥25% of its systemic clearance?
    - No
      - Label as such based on in vitro and in vivo disposition data
    - Yes
      - Evaluate potential of complex drug-drug interaction

- Yes or inconclusive

Presence of significant interaction?

- Yes
  - Conduct in vivo studies with other less strong inhibitors/inducers selected based on likely co-administration or if appropriate, apply mechanistic modeling (see Figure 4)
    - Dosage adjustment needed?
      - Yes
      - No

- No
  - Conduct in vivo studies with strong inhibitor(s)/inducer(s) or if appropriate, compare PK in different genotypes
    - Presence of significant interaction?
      - Yes
      - Conduct in vivo studies with other substrates selected based on likely co-administration and/or narrow therapeutic range or if appropriate, apply mechanistic modeling (see Figure 4)
        - Dosage adjustment needed?
          - Yes
          - No
      - No further studies needed → General label based on in vitro and in vivo data

- Is investigational drug an interacting drug of an enzyme? (see Figure 4)
  - Yes
  - Conduct in vivo studies with most sensitive/specific substrate(s)
  - Label as such based on in vitro data

- No

→ 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 -

**Sensitivity Analysis**

**OATP1B1**

- Plasma: × 3
- Liver: × 1/3

**MRP2**

- Plasma: × 1
- Liver: × 1/3

**PSinf**

- Plasma: × 1/3
- Liver: × 1/3

**PSbile**

- Plasma: × 1/3
- Liver: × 3

**PSeff**

- Plasma: × 3
- Liver: × 1

**Plasma concentration (μg/ml)**

0 60 120 180 240 300 360

*Courtesy of Dr. Yuichi Sugiyama*

*Modified from Yuichi Sugiyama, Optivia webinar, July 2010*<br>*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:

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