Overview of 2012 FDA draft guidance on drug interactions

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New Draft Guidance for Industry

• Drug Interaction Studies- Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations
• Published February 2012
• As of 6/22/2012: 27 sets of comments (PhRMA, BIO, IQC, 22 companies, 2 individuals)
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)

The NEW draft guidance on evaluation of drug-drug interactions

- What’s new??
  - Application of mechanistic models (including PBPK) in drug interaction prediction
  - Much more information about transporter based interactions
  - Decision tree for evaluation of therapeutic protein-drug interactions
  - Updated labeling information
Outline

• Evaluation of new drug as inhibitor or inducer of CYPs (Figure 4)
  – Includes PBPK
• In vivo interaction topics
  – Cocktail studies
  – Population PK
• Transporter mediated drug interactions
• Complex drug interactions
• Therapeutic protein – drug interactions
• Drug interaction information in labeling
Evaluation of Drug as an Inhibitor or Inducer of CYP enzymes

• Use figure 4 to determine whether an in vivo inhibition or induction study is needed based on in vitro data for various CYPs.

• CYPs of primary interest: 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4
CYP inhibition
(reversible and time-dependent inhibition, TDI)
- Measure enzyme activity in human liver microsomes
- Estimate DDI parameters

CYP induction
- Measure mRNA change by investigational drug in cultured human hepatocytes from ≥3 donors
- Estimate DDI parameters

Basic models

Is the calculated R value >1.1 (also, for CYP3A inhibitors given orally, is alternate R value>1)\(^{[b]}\)?
- Reversible inhibitor, \(R_1 = 1 + [I]/K_i\)
- TDI, \(R_2 = (K_{obs} + K_{deg})/K_{deg} \text{ and } K_{obs} = k_{inac} \times [I]/(K_i + [I])\)

Is increase in mRNA > a predefined threshold\(^{[a]}\)?
Or, is the calculate R value<1/1.1 (i.e., 0.9)?
\[R_3 = 1/(1+d \times E_{max} \times [I]/(EC_{50} + [I]))^{[c]}\]

No
Label as non inhibitor or non inducer based on in vitro data

Mechanistic models

Investigational drug likely a CYP inhibitor

Is AUCR >1.25 (inhibition) or AUCR <0.8 (induction)?\(^{[d]}\)
- a mechanistic static model\(^{[c]}\)
\[\text{AUCR} = \left(\frac{1}{A_g \times B_g \times C_g \times (1 - E_g) + E_g}\right) \times \left(\frac{1}{A_h \times B_h \times C_h \times f_m + (1 - f_m)}\right)\]
- or a dynamic model, including PBPK\(^{[f]}\)

No
Investigational drug likely a CYP inducer

Yes
Conduct a clinical study using an appropriate probe substrate\(^{[g]}\)

No
Label as non-inhibitor or non-inducer
Ig

substrate needs to be developed and drug interaction mechanisms should be appropriately defined by data interaction using both in vitro drug disposition data (e.g., protein/tissue binding, metabolism, transport, and drug-drug interaction) and physicochemical properties. The model should be refined when human pharmacokinetic data become available. The model can then be used to evaluate the drug-drug interaction potential with a sensitive substrate of the CYP enzymes of interest (Rostami-Hodjegan and Tucker 2007). The model of the substrate needs to be developed and drug interaction mechanisms should be appropriately defined by linking the models of the substrate and the interacting drug (see section IV.A.1.b-3 and Figure 5 for more details). If a metabolite is involved in a drug-drug interaction, a model for the metabolite can be established and linked to the parent drug to evaluate its inhibition/induction potential.

Note that these cutoff values may vary among different laboratories because of the variability among hepatocyte lots.

Equations are as described in Bjornsson et al. 2003. \( [I] \) can be estimated by the maximal total (free and bound) systemic inhibitor concentration in plasma and the cutoff for R is 1.1. In addition, for CYP3A inhibitors that are dosed orally, \([I]=Dose/250\ mL\) and the cutoff for this alternate R is 11 (Zhang et al. 2008). \( k_{deg} \) is the apparent first order degradation rate constant of the affected enzyme; \( K_i \) is the unbound reversible inhibition constant determined in vitro; \( k_{inact} \) and \( K_i \) are maximal inactivation rate constant and apparent inactivation constant, respectively; \( k_{deg} \) is the apparent inactivation rate constant and \( K_{inh} = k_{deg}[I]/(K_i[I]) \), and R is the ratio of intrinsic clearance by metabolizing enzyme in the absence and in the presence of inhibitor.

Equation is described in Fahmi et al. 2009. \( EC_{50} \) is the concentration causing half maximal effect; \( E_{max} \) is the maximum induction effect; and \([I] \) is maximal total (free and bound) systemic inducer concentration in plasma; d is a scaling factor that is assumed as 1 for the basic model.

These are suggested values according to the lower and upper limit of equivalence range. However, we are open to discussion based on sponsors’ interpretation. If the calculated AUCR using a mechanistic static model is outside the equivalence range, the sponsor has the option to use a dynamic model (e.g., a PBPK model) supported by available clinical pharmacokinetic data to calculate AUCR and determine whether or not there is a need to conduct clinical drug-drug interaction studies.

A mechanistic static model (or a “net effect model”) is modified from that reported by Fahmi et al. 2009.

<table>
<thead>
<tr>
<th>Reversible inhibition</th>
<th>Time-dependent inhibition</th>
<th>Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_g = \frac{1}{1 + \frac{[I]_g}{K_i}} )</td>
<td>( B_g = \frac{k_{deg,g} k_{deg,h} [I]<em>g \times [I]<em>h \times k</em>{inh} }{k</em>{deg,g} + k_{deg,h} + [I]_g \times K_i + [I]_h + K_i} )</td>
<td>( C_g = 1 + \frac{d \times E_{max} \times [I]_g}{[I]<em>g + EC</em>{50}} )</td>
</tr>
<tr>
<td>( A_h = \frac{1}{1 + \frac{[I]_h}{K_i}} )</td>
<td>( B_h = \frac{k_{deg,h} k_{deg,g} [I]<em>h \times [I]<em>g \times k</em>{inh} }{k</em>{deg,g} + k_{deg,h} + [I]_g \times K_i + [I]_h + K_i} )</td>
<td>( C_h = 1 + \frac{d \times E_{max} \times [I]_h}{[I]<em>h + EC</em>{50}} )</td>
</tr>
</tbody>
</table>

Where \( F_a \) is the fraction available after intestinal metabolism; \( f_{inh} \) is the fraction of systemic clearance of the substrate mediated by the CYP enzyme that is subject to inhibition/induction; subscripts “h” and “g” denote liver and gut, respectively; \([I]_b = f_{inh} \cdot ([I]_{inh, max} + F_{a}\times K_i \times Dose/Q_h) \) (Ito et al. 2002); \([I]_b = F_{a}\times K_i \times Dose/Q_a \) (Rostami-Hodjegan and Tucker 2004). In these equations, \( f_{inh} \) is the unbound fraction in blood, \([I]_{inh, max} \) is the maximal total (free and bound) inhibitor concentration in the blood at steady state; \( K_i \) is the first order absorption rate constant in vivo (e.g. 0.1/min, Ito et al. 1998); and \( Q_a \) and \( Q_h \) are blood flow through enterocytes (e.g., 18 L/hr/70 kg, Yang et al. 2007 (a)) and hepatic blood flow (e.g., 97 L/hr/70 kg, Yang et al. 2007 (b)), respectively.

Dynamic models, including physiologically-based pharmacokinetic (PBPK) models, can be developed using both in vitro drug disposition data (e.g., protein/tissue binding, metabolism, transport, and drug-drug interaction) and physicochemical properties. The model should be refined when human pharmacokinetic data become available. The model can then be used to evaluate the drug-drug interaction potential with a sensitive substrate of the CYP enzymes of interest (Rostami-Hodjegan and Tucker 2007). The model of the substrate needs to be developed and drug interaction mechanisms should be appropriately defined by linking the models of the substrate and the interacting drug (see section IV.A.1.b-3 and Figure 5 for more details). If a metabolite is involved in a drug-drug interaction, a model for the metabolite can be established and linked to the parent drug to evaluate its inhibition/induction potential.

See Table 5 (section V.C below) and Zhang et al. 2010.
Why does Figure 4 have so many footnotes??

- More than a page of footnotes?
- Footnotes with equations?
- Are you kidding me???
Inhibition- Basic Model

Evaluate reversible and time-dependent inhibition (TDI) for all investigational drugs
CYP inhibition
(reversible and time-dependent inhibition, TDI)

- Measure enzyme activity in human liver microsomes
- Estimate DDI parameters

Basic models

Is the calculated R value >1.1 (also, for CYP3A inhibitors given orally, is alternate R value >11)\(^b\)？
- Reversible inhibitor, \(R_1 = 1 + [I]/K_i\)
- TDI, \(R_2 = (K_{obs} + K_{deg})/K_{deg}\) and \(K_{obs} = k_{inact} \times [I]/(K_I + [I])\)

Investigational drug likely a CYP inhibitor

Mechanistic models

Is AUCR >1.25 (inhibition) or AUCR

Estimate AUCR of sensitive probe substrate ch - a mechanistic static model\(^c\)

\[
AUCR = \left( \frac{1}{A_g \times B_g \times C_g} \times \left( 1 - F_g \right) + F_g \right) \times \left( \frac{A_h \times B_h}{A_g \times B_g} \right)
\]
Inhibition- Basic Model

• Is the calculated R value >1.1 (also for CYP3A inhibitors given orally, is alternate R value >11)?
  – R > 1.1 is the same as previous [I]/Ki > 0.1

• What is [I]?
  – Maximal total (free and bound) systemic inhibitor concentration (R cutoff is 1.1)
  – For CYP3A inhibitors given orally: [I]=Igut=Molar dose/250 mL (R cutoff is 11)

• CYP3A inhibitors given orally- determine R value for systemic and gut inhibition. The answer is “yes” if either criterion is met.
Reversible inhibition

• If the calculated R value >1.1 for multiple CYPs
  – Rank ordering of R value for the next step (do not include CYP3A in the rank order evaluation)
Time-dependent inhibition

- Inhibitory effect increases over time
- Not promptly reversible
- In vivo consequence:
  - interaction is greater over time with multiple dosing
  - interaction is not immediately reversible after the inhibitor is stopped
In vitro inhibition
Conclusion of basic model

• “No inhibition”
  – No in vivo study needed
  – Label- indicate lack of potential interaction

• “Yes, inhibition is possible”
  – Option 1: conduct in vivo study with appropriate probe substrate (no change from previous practice)
  – New Option 2: evaluate further using a mechanistic model (static or dynamic)
CYP Induction-Basic Model
What are the Key Recommendations for CYP Induction in 2012 Guidance?

- Human hepatocytes
  - Cyropreserved (≥3 donors)
- mRNA level is recommended as endpoint
- Study CYP1A2, CYP2B6, and CYP3A initially
CYP induction

- Measure mRNA change by investigational drug in cultured human hepatocytes from ≥3 donors [a]
- Estimate DDI parameters

**Basic models**

Is increase in mRNA > a predefined threshold[a]?  
Or, is the calculate R value<1/1.1 (i.e., 0.9)?  
\[ R_3 = \frac{1}{1 + d \times E_{max} \times [I] / (EC_{50} + [I])} \]

Label as non inhibitor or non inducer based on in vitro data

**Mechanistic models**

(inhibition) or AUCR <0.8 (induction)? [d]

Sensitive probe substrate characteristics using mechanistic model[e]

\[ \frac{1}{C_g \times (1 - F_g) + F_g} \times \left( \frac{1}{A_h \times B_h \times C_h} \times f_m + (1 - f_m) \right) \]
CYP Induction

• Evaluate induction for all investigational drugs

• Measure mRNA levels relative to vehicle controls in human hepatocytes (lots from \( \geq 3 \) donors)

• Or estimate drug interaction parameters
  – \( E_{\text{max}}, EC_{50} \)
Why do We Recommend mRNA as Endpoint for Induction Basic Model in 2012 Guidance?

• 40% enzyme activity increase relative to positive control is not discriminative
  – In particular, high false negative rate (see next slide)
  – Relative induction ratio to that of positive control (i.e., rifampin) was not consistent among different hepatocyte lots.

• Enzyme induction activity may be confounded by concurrent inhibition or inactivation; mRNA assay does not have this confounding factor

• mRNA level has a greater dynamic range than CYP activity
  – More sensitive to detect induction
  – More sensitive to generate a response curve for Emax and EC50 determination
Use 40% to positive control as the cutoff:
- 31% tests with potent inducers missed the "40%" cutoff (false negatives).
- 44% tests with mild/moderate inducers missed the 40% cutoff (false negatives).
- All negatives showed as negative based on 40% cutoff (0% false positive).
- There is an overlap of % rifampin response between non-inducers and inducers, a clear cutoff based on % to positive control seems not possible (e.g, a 20% cutoff still has false negatives and introduces false positives).

A Survey Dataset:
- 46 compounds (for CYP3A induction)
- 12 potent inducers, 19 weak/mild inducers, 15 non-inducers.
- % induction relative to Rifampin at various concentrations.
Induction Basic Model-NEW
Algorithm and Criteria (1)

• Measure mRNA change in human hepatocytes from ≥ 3 donors

• Criteria: mRNA> a predefinded theresold relative to vehicle control
  – How is this threshold* determined?
    • Fahmi, et al, DMD, 2010 (for details)

(* A lab and hepatocyte lot-specific threshold; Need to qualify the hepatocyte lots with positive, negative and vehicle controls)
Induction Basic Model-NEW Algorithm and Criteria (2)

\[ R_3 = \frac{1}{1 + d \times E_{\text{max}} \times [I] / (\text{EC}_{50} + [I])} \]

- \( E_{\text{max}} \) is the maximum induction effect
- \( \text{EC}_{50} \) is the concentration causing half maximal effect
- “d” is a scaling factor. Use \( d=1 \) as the default for the basic induction model
- What is [I]?
  - Maximal total (free and bound) systemic concentration
  - Criteria: \( R_3 \) of 1/1.1 (i.e., 0.9) as the cutoff
    - \( \leq 0.9 \) → predicted positive induction
    - \( >0.9 \) → predicted negative induction

- Data from recent Pharma/IQ-FDA-Academia collaboration demonstrated that this cutoff is reasonable for the basic model
CYP Co-Induction?

• Can we use negative CYP3A induction data to “waive” induction studies for other CYP enzyme?
  – 1A2? No. (Different nuclear receptor, e.g., AhR, than CYP3A)
  – 2B6? Need more data to prove (some overlap with CYP3A but CAR may have more influence)
  – 2C (8, 9,19)? Yes. (Overlap with CYP3A)
  – 2D6: Non-inducible
In Vitro Induction
Conclusion of Basic Model

• “No induction” (based on either mRNA fold change relative to vehicle controls or R₃)
  – No in vivo study needed
  – Label- indicate lack of potential interaction

• “Yes, induction is possible”
  – Option 1: conduct in vivo study with appropriate probe substrate (no change from previous practice)
  – New Option 2: evaluate further using a mechanistic model (static or dynamic)
Mechanistic Models
(Static or Dynamic)
CYP inhibition
(reversible and time-dependent inhibition, TDI)

- Measure enzyme activity in human liver microsomes
- Estimate DDI parameters

CYP induction

- Measure mRNA change by investigational drug in cultured human hepatocytes from ≥3 donors[a]
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Is the calculated R value >1.1 (also, for CYP3A inhibitors given orally, alternate R value>11) [b]?
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- TDI, \( R_2 = (K_{obs}+K_{deg})/K_{deg} \) and \( K_{obs}=k_{inac}\times[I]/(K_I+[I]) \)

Basic models

Investigational drug likely a CYP inhibitor

Yes

Investigational drug likely a CYP inducer

Yes

No

Conduct a clinical study using an appropriate probe substrate [g]

No

Label as non-inhibitor or non-inducer based on in vitro data

Mechanistic models

Is AUCR >1.25 (inhibition) or AUCR <0.8 (induction)? [d]

Estimate AUCR of sensitive probe substrate characteristics using
- a mechanistic static model[e]
\[
AUCR = \left( \frac{1}{A_g \times B_g \times C_g \times (1 - E_g_1) + E_g} \right) \times \left( \frac{1}{A_h \times B_h \times C_h \times f_m + (1 - f_m)} \right)
\]
- or a dynamic model, including PBPK[f]

Yes

No

Label as non-inhibitor or non-inducer
Mechanistic models

Is AUCR >1.25 (inhibition) or AUCR <0.8 (induction)? \[[d]\]

Estimate AUCR of sensitive probe substrate characteristics using

- a mechanistic static model \[[e]\]

\[
\text{AUCR} = \left( \frac{1}{[A_g \times B_g \times C_g] \times (1 - F_g) + F_g} \right) \times \left( \frac{1}{[A_h \times B_h \times C_h] \times f_m + (1 - f_m)} \right)
\]

- or a dynamic model, including PBPK \[[f]\]

Investigational drug likely a CYP inhibitor

Investigational drug likely a CYP inducer

Conduct a clinical study using an appropriate probe substrate \[[g]\]

Yes

No

Label as non-inhibitor or non-inducer

Gut

Liver

<table>
<thead>
<tr>
<th>Reversible inhibition</th>
<th>( A_g = \frac{1}{1 + \frac{[I]_g}{K_i}} )</th>
<th>( A_h = \frac{1}{1 + \frac{[I]_h}{K_i}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-dependent inhibition</td>
<td>( B_g = \frac{k_{\text{deg},g}}{k_{\text{deg},g} + \frac{[I]<em>g \times k</em>{\text{inact}}}{[I]_g + K_i}} )</td>
<td>( B_h = \frac{k_{\text{deg},h}}{k_{\text{deg},h} + \frac{[I]<em>h \times k</em>{\text{inact}}}{[I]_h + K_i}} )</td>
</tr>
<tr>
<td>Induction</td>
<td>( C_g = 1 + \frac{d \times E_{max} \times [I]_g}{[I]<em>g + EC</em>{50}} )</td>
<td>( C_h = 1 + \frac{d \times E_{max} \times [I]_h}{[I]<em>h + EC</em>{50}} )</td>
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</tbody>
</table>

Modified from Fahmi et al, 2009

\([I]_h = f_{u,b} \times ([I]_{max,b} + F_a \times K_a \times \text{Dose/Q}_h)\) (Ito et al. 2002); \([I]_g = F_a \times K_a \times \text{Dose/Q}_n\) (Rostami-Hodjegan and Tucker 2004)
Dynamic model: Full PBPK

Interacting drug

ADME, PK, PD and MOA
Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

System component (drug-independent)

Substrate

ADME, PK, PD and MOA
Metabolism
Active transport
Passive diffusion
Protein binding
Drug-drug interactions
Receptor binding

Parameters can be altered by DDI
Cabazitaxel

- Approved in 2010 for prostate cancer
- 25 mg/m² once every 3 weeks, IV infusion over 1 hr

$I/K_i = 0.14$ on CYP3A

Basic model $R_1 = 1.14$

Song et al, DCP5; Zhao et al, Clin Pharmacol Ther 2011 (Case No 4)
Simulation: Cabazitaxel as a CYP3A inhibitor (Midazolam as a substrate)

Trial Results for 3 Groups of 10 Individuals out of a Population of 30 for a PK Profile Simulation

- No significant change in midazolam AUC

\[ K_i,CYP3A4 = 1.66 \mu M \]
\[ [I]/K_i = 0.14 \]
\[ R_1 = 1.14 \]

Song et al, DCP5; Zhao et al, Clin Pharmacol Ther 2011 (Case No 4)
Simulation: Cabazitaxel as a CYP3A inhibitor (Midazolam as a substrate)

- Sensitivity analysis on $K_i$: No significant change in midazolam AUC ratios, even with a wide $[I]/K_i$ range

Song et al, DCP5; Zhao et al, Clin Pharmacol Ther 2011 (Case No 4)
Comments on the draft guidance

- Inhibition: use of total Cmax and unbound Ki is not supported by literature and leads to F+
- Gut CYP3A inhibition: alt R of 11 for $[I] = I_{gut} = \text{dose}/250$, not validated for enzymes.
- Induction: allow enzyme activity as endpoint if drug is not an inhibitor.
- Provide guidance for situations when Emax and EC$_{50}$ cannot be calculated because of weak induction profile.
Comments on the draft guidance

• PBPK and Mechanistic Modeling-
  – Concern regarding timing, feasibility, and complexity
  – Criteria for assessing “equivalence” (predicted AUC ratio of 0.8 to 1.25) is too narrow.
In vivo drug interaction studies
In vivo drug interaction studies

• All aspects of study design: consider the objective of the study.
  – Define potential for an interaction
  – Extrapolate results to other drugs
  – Determine specific dose adjustments
Cocktail studies

- Simultaneous administration of a mixture of substrates of multiple CYP enzymes and transporters
  - substrates are specific for enzyme or transporter
  - substrates do not interact with each other
  - sufficient sample size

- No interaction - eliminate need for further evaluation of the CYP or transporter

- Interaction observed - can provide definitive result if exposure changes (AUC, Cmax) are evaluated

- Label can include the results; does not have to indicate results are from a cocktail study

(Comment - what are the criteria for “negative” and “positive”)
Population PK

• Utility (effect on new drug):
  – help characterize impact of previously identified interaction
  – detect unsuspected interaction
    • valuable benefit when complex interactions are possible
  – confirm absence of interaction

• Usually cannot
  – persuasively show absence of interaction observed in DDI study
  – evaluate effect on co-administered drugs

• Include sparse or intensive blood sampling

• Need carefully designed study procedures and sample collection

• Document dose, time of administration, time of food consumption (when relevant)
Transporter-Mediated Drug Interactions
## Examples of Transporter-Mediated Drug Interactions

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Affected Drug</th>
<th>Consequence</th>
<th>Fold Changes in Substrate Plasma AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Digoxin</td>
<td>Digoxin Exposure 1.7-fold ↑</td>
<td>P-glycoprotein (P-gp, MDR1) Inhibition</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Digoxin</td>
<td>Digoxin Exposure 30% ↓</td>
<td>P-gp Induction</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Digoxin</td>
<td>Digoxin Exposure 2.6-fold ↑</td>
<td>P-gp Inhibition</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Cephradine</td>
<td>Cephradine Exposure 3.6-fold ↑</td>
<td>Organic Anion Transporter (OAT) Inhibition</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Metformin</td>
<td>Metformin Exposure 1.4-fold ↑</td>
<td>Organic Cation Transporter (OCT) Inhibition &amp; Multidrug and Toxin Extrusion (MATE) Inhibition</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Rosuvastatin</td>
<td>Rosuvastatin Exposure 7-fold ↑</td>
<td>Organic Anion Transporting Polypeptide (OATP) Inhibition &amp; Breast Cancer Resistance Protein (BCRP) Inhibition</td>
</tr>
<tr>
<td>Lopinavir/ Ritonavir</td>
<td>Rosuvastatin</td>
<td>Rosuvastatin Exposure 2-fold ↑</td>
<td>OATP Inhibition</td>
</tr>
</tbody>
</table>
Evaluation of NME as a Substrate for Transporters—Other Drugs’ Effect on NME (Figure 6)

All NMEs

Hepatic or biliary secretion major? e.g., ≥ 25% total clearance?

Yes or unknown

Determine whether NME is an OATP1B1 or OATP1B3 Substrate*

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

Determine 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?

Yes or unknown

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

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

P-gp/BCRP Substrate Decision Tree (Figure A1)

In bi-directional transporter assay (e.g., in Caco-2 or MDR1-overexpressing polarized epithelial cell lines) is the net flux ratio of an investigational drug ≥ 2?

Net flux ratio ≥ 2 (a)

Is efflux significantly inhibited by one or more P-gp inhibitors? (b)

Yes

Probably a P-gp substrate (c)

Complete an assessment of nonclinical and clinical information to determine whether an in vivo DDI study is warranted (d)

No

Net flux ratio < 2

Poor or non-P-gp substrate

Other efflux transporters are responsible for observed data (e)

BCRP is new.

Zhang, L et. al., Xenobiotica, 38: 709–724, 2008
Selection of Inhibitors for In Vivo Transporter Mediated Interaction Studies

- Overlap of P-gp and CYP3A inhibitors
  - Inhibition potency for either P-gp or CYP3A may not be equal
- If an NME is a dual substrate
  - Select potent/strong inhibitors for both for worst case scenario
  - Select a strong inhibitor for one pathway but not the other to understand the relative contribution of each pathway.
OATP1B1/OATP1B3 Substrate Decision Tree (Figure A3) - New

Does the compound have active hepatocyte uptake, do the drug’s physiological properties (e.g., low passive membrane permeability, high hepatic concentrations relative to other tissues, organic anion/charged at physiological pH) support importance of active uptake into liver?

Yes

Investigate uptake in OATP1B1- or OATP1B3-overexpressing cell lines compared to that in empty vector cells. (b)

If an OATP substrate, consider an in vivo drug interaction study with single dose rifampin or cyclosporine as perpetrator. Comparative PK study in subjects with various genotypes of OATP1B1 can help identify the importance of this pathway.

No

Likely a poor or not a substrate for OATPs
OCT2/OAT1/OAT3 Substrate Decision Tree (Figure A5) - New

Is uptake of the investigational drug in the OCT2-, OAT1- or OAT3-overexpressing cells greater than that in empty vector cells\(^{(a)}\)?

- **Yes**
  - Likely a substrate. In vivo DDI study with cimetidine for OCT2 and with probenecid for OAT1, OAT3 as perpetrators

- **No**
  - Poor or not a substrate of OCT2, OAT1, or OAT3

May need to consider other renal transporters. The emerging ones include MATE-1 and MATE2-K.
New Drug as a Transporter Inhibitor
P-gp/BCRP Inhibition Decision Tree (Figure A2) - New

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
    - \([I_1]/IC_{50} (or Ki) \geq 0.1\) or \([I_2]/IC_{50} (or Ki) \geq 10\)
      - An in vivo drug interaction study with a P-gp substrate such as digoxin is recommended.
    - \([I_1]/IC_{50} (or Ki) < 0.1\) and \([I_2]/IC_{50} (or Ki) < 10\)
      - 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

\([I_2] (gut concentration)/IC_{50}\) is New

Initially proposed in Zhang L et al., Xenobiotica, 38(7–8): 709–724, 2008
In Vitro and In Vivo Digoxin Data
Recent NDA approvals (2003-2010)

- The proposed $[I]_1/IC_{50}$ and the $[I]_2/IC_{50}$ criteria accurately predicted the in vivo DDI outcomes for 9 out of 11 NMEs (82%) that were reviewed in our study.

- The two false positives (i.e., etravirine and maraviroc)
  - Partially may be attributed to potential P-gp induction effects that may off-set their inhibition effects
    - Etravirine is a PXR activator and CYP3A inducer
    - Maraviroc also induce P-gp in vitro (although weak compared to rifampin)

Agarwal S, Zhang L, Huang, S-M, Clin Pharmacol Ther 89(1): February 2011 (poster presentation at the annual ASCPT meeting, Dallas, TX, March 2-5, 2011);
Limitations

• Only considers P-gp inhibition. No interplay between metabolism and P-gp or induction could be projected.

• *In vitro* IC$_{50}$ determination may be different from different labs which could impact the I/IC$_{50}$ ratios.

• Applies only for immediate-release formulations.

• May not work for investigational drugs that are prodrugs.
OATP Inhibition Decision Tree (Figure A4)-New

1. Is total $C_{\text{max}}/IC_{50}$ of the investigational drug $\geq 0.1$ for OATP1B1 or OATP1B3?
   - Yes
     - Is the AUC or $C_{\text{max}}$ of statin (e.g., rosuvastatin, pravastatin, pitavastatin) predicted to increase $\geq 1.25$-fold in the presence of the investigational drug using extrapolation (e.g., $R$-value$^{[a]*} \geq 1.25^{[b]**}$)?
       - 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

OCT/OAT Inhibition Decision Tree (Figure A6) - New

Is the investigational drug an inhibitor of OCT2, OAT1, or OAT3?
Criteria: Uptake of model substrates (e.g., MPP+, for OCT2; PAH for OAT1, or ES for OAT3) decreases with increased concentrations of the investigational drug.

Yes
- Determine the IC₅₀

- Unbound Cmax/IC₅₀ of the investigational drug ≥ 0.1
  - In vivo DDI study with a sensitive substrate (a)

- Unbound Cmax/IC₅₀ of the investigational drug < 0.1
  - In vivo DDI study is not needed

No
- Poor or not an inhibitor of OCT2, OAT1, or OAT3

MPP⁺, 1-methyl-4-phenylpyridinium; PAH, para-aminohippuric acid; ES, estrone-3-sulfate.
(a) For the investigational drug that is an OCT2 inhibitor, metformin may be used as the substrate for the clinical drug interaction study.
For investigational drugs that are OAT1 or OAT3 inhibitors, multiple OAT1 or OAT3 substrates could be used in clinical DDI studies, including zidovudine, acyclovir, ciprofloxacin, tenofovir, or methotrexate.

**May need to consider other renal transporters. The emerging ones include MATE-1 and MATE2-K.
Summary

• Transporter-based drug interactions are being increasingly evaluated during drug development.

• *In vitro* transporter studies are useful to predict the potential for interactions and aid in the development of clinical drug interaction strategies.

• Clinical DDI studies can provide informed recommendation on the proper use of the drug.
Comments on the Draft Guidance

- Little evidence of clinically relevant BCRP interactions
- Exclude BCS class 2 (in addition to class 1) from Pgp and BCRP substrate evaluation.
- Allow model systems other than bidirectional studies in CaCo-2 cells (for Pgp and BCRP)
- Substrate studies: cut-off values of 2 are too prescriptive, may vary by systems and labs.
- $I_2$ for poorly soluble drugs should be maximum soluble dose in simulated gastric fluid
Complex Drug Interactions
Multiple Factor Scenarios

Investigational drug

- is a substrate of CYP3A4 AND (polymorphic) CYP2D6, what exposure change can be expected when a moderate CYP3A4 inhibitor is used in CYP2D6 PM?

- is renally AND hepatically cleared, what exposure change can be expected when a CYP inhibitor is used in patients with decreased renal function?

- forms an active/toxic metabolite whose exposure was increased in subjects with renal impairment, what are the effect of renal impairment AND drug interactions on the exposure of this metabolite?
Multiple Factor Considerations

- A thorough understanding of the drug disposition of an investigational drug is critical for the evaluation and prediction of drug interaction potential.
- Minor pathways in one population may play significant roles in a different population.
- Modeling and simulations are helpful in evaluating drug interaction potential under different clinical scenarios.
Therapeutic Protein-Drug Interactions
Therapeutic Protein (TP)-Drug (D) Interaction Potential -Possible Mechanisms

• PK Interaction
  – CYP enzyme modulation (TP→D)
  – Competitive binding
  – Immunosuppression (D→TP)
  – Mechanisms to be elucidated

• PD interaction
  – Antagonism of PD effects
  – Synergistic myelotoxicity, infections, etc.
  – Mechanisms to be elucidated

Source: Zhao H
Differential effect of cytokines and cytokine modulators, on CYP enzyme activities (decreased, unless noted a)

<table>
<thead>
<tr>
<th>CYP enzyme</th>
<th>Cytokines/cytokine modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>IFNα, IFNα-2b, IFNβ, IL2, IL-6</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>IL-1</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>IL2, IL-10</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Tocilizumab\textsuperscript{a}, IFNα-2b, FNβ, IL2, TNFα, IL-6</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>IFNα-2b</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>IL-2, IFNα-2b,</td>
</tr>
<tr>
<td>CYP3A</td>
<td>Basiliximab, muromonab-CD3, \textit{tocilizumab}\textsuperscript{a}, IL-1, IL-2, IL-6, IL-10</td>
</tr>
</tbody>
</table>

Data were from in vitro and/or in vivo studies.
\textsuperscript{a}The effect of tocilizumab, an IL-6 receptor inhibitor, is increase in activity

Morgan et al DMD 2008; Lee et al, Clin Pharmacokinetics 2010; Huang et al, CPT 2010
Figure 7-Summarizes the Thought Process to Consider TP-DDI Evaluation (Section IV.B.2.)

Therapeutic Protein (TP)

Cytokine or cytokine modulator (that has known effects on CYPs or transporters)

In vitro study
TP→D: effect on CYPs or transporters

Label may indicate the potential for interaction with CYP or transporter pathways with a particular focus on its potential effect on narrow therapeutic range drugs (e.g., warfarin)

TPs intended to be used in combination therapy with D

1. TP→D
2. D→TP

In vivo study
TP→D: effect on CYPs or transporters (cocktail or individual studies)

In vivo interaction studies, e.g., crossover study, population PK, or parallel study

Cases where studies can be considered important because of known mechanisms or general concerns other than its possible effect on CYPs or transporters

No known or suspected mechanisms

Yes, known or suspected mechanism; or potential for mechanism unknown

D→TP

In vitro or in vivo interaction studies

Population PK as initial assessment; may follow up with a formal study

Label describes study results and any important clinical actions
Some comments related to TP-DDI…

- “Cytokine or cytokine modulator” too broad → limit to “proinflammatory…”
- “In vitro box evaluation” in Figure 7
  - Remove
  - On a case by case basis, appropriate in vitro assays can guide clinical DDI decision
  - Clarify whether required
- Oncology (chemotherapy) should be made as an exception
- How to interpret the 3rd box on the right?
- Include a table of known TP-DDI with reported magnitude of changes
- Should not recommend TP-DDI until preclinical methodology is ready
- Timing of TP-DDI
- Provide guidance on TP-DDI study design
Incorporating Drug Interaction Information into the Label
Relevant Labeling Sections

- Highlights
- Full Prescribing Information
  - 2 Dosage and Administration
  - 4 Contraindications
  - 5 Warnings and Precautions
  - 7 Drug Interactions
  - 12 Clinical Pharmacology
7 Drug Interactions

• Description of clinically significant interactions and practical instructions for preventing or managing them
  – Order of list: severity, relevant groups (ex: CYP3A inhibitors), alphabetical
• Can mention notable negative interactions (for example-if the interaction is observed with most other drugs in the same class)
• Brief description of mechanism, if known (CYP3A inhibitor, P-gp inhibitor)
• Interactions noted under Contraindications or Warnings & Precautions can be discussed in more detail here (not many examples of this)
• Details of PK studies from “12 Clinical Pharmacology” should not be repeated here
12.3 Pharmacokinetics

- Includes more detail about the drug interaction studies
- Can include negative results of drug interaction studies
- Can include clinically relevant nonclinical data
- Format- organized and understandable
  - Forest Plot
  - Table
  - Any organized, understandable format
  - Consider level of detail for negative results
General Comments on Draft Guidance

• In some cases the guidance has extended beyond the current state of the art
• Need more FDA and EMA harmonization
• Too many false positive results- predictive framework was developed to account for even the slightest risk of false negative prediction
• Need to define “no effect” boundary and “not clinically significant”