Regulatory Science Perspectives on Transporter -Mediated Drug-Drug Interactions

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– Transporters in Drug Development Pre-conference

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Drug Transporters: Contribute to variability in drug concentration and response

- Pharmacokinetic determinant
  - **Absorption**
  - **Distribution**
  - **Metabolism**
    - by controlling drug’s access to the enzymes
  - **Excretion**

- Pharmacodynamic determinant
  - Delivery to site of action
  - Control of tissue concentrations
  - Therapeutic targets
    - Sodium-glucose co-transporter 2 (SGLT2) inhibitor for the treatment of Type 2 diabetes (e.g., canagliflozin, dapagliflozin, empagliflozin)
    - Urate transporter (URAT1) inhibitor in combination with an XO inhibitor for the treatment of gout (e.g., lesinurad)

Which transporters are clinically important and should be considered for evaluation during drug development?

Drug-Drug Interactions (DDI)

Genetic Variation

Disease State

Safety, Efficacy
Transporter Mediated Drug-Drug Interaction Discussion

2006  FDA published a draft drug-drug interaction (DDI) guidance (P-gp)
2006  FDA Clinical Pharmacology Advisory Committee Meeting
2007  Formation of International Transporter Consortium (ITC)
2008  DIA/FDA Critical Path Transporter Workshop (1st ITC Transporter Workshop)
2010  ITC Transporter White Paper (Nature Reviews Drug Discovery)
       (In addition to P-gp)
2010  FDA Clinical Pharmacology Advisory Committee Meeting
2012  FDA published the revised draft DDI guidance (expanded transporter section)
2013  2nd ITC Transporter Workshop (in conjunction with ASCPT Annual Meeting)
2013  Seven ITC transporter whitepapers (Clinical Pharmacology & Therapeutics July 2013 Issue)
2013  EMA finalized their DDI guideline
2014  PMDA published their DDI guideline
2015  AAPS/FDA/ITC Joint Transporter Workshop
2016  AAPS/FDA/ITC Joint Transporter Workshop (will occur on even years)
2017  3rd ITC Transporter Workshop (in conjunction with ASCPT Annual Meeting)
2017  FDA will publish its revised draft DDI guidance
2018  More whitepapers following ITCW3

AAPS: American Association of Pharmaceutical Scientists; DIA: Drug Information Association; EMA: European Medicines Agency; FDA: Food and Drug Administration; PMDA: Pharmaceuticals and Medical Devices Agency of Japan
Red: Critical transporter proteins to evaluate prospectively
Green: additional one to evaluate prospectively
Yellow: retrospective evaluation
Regulatory Recommendations for Assessing Transporter-Mediated DDIs

Compared to previous versions, added recommendations for additional transporters besides P-gp (BCRP, OATP1B1/3, OAT1/3, OCT2, MATEs, etc.) and decision framework.
Since 2007, 40-60% of NME drug labels contain transporter information (N=183).

P-gp is the most frequently studied transporter (2003-2011) (N=74)
Transporters are Commonly Studied During Drug Development (2013-2015)

Summary of Transporter and Metabolism information Contained in the Submissions for NME New Drug Applications (NDAs) Recently Approved by the FDA.

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transporter evaluated in vitro (% of NDAs)</td>
<td>80% (20/25)</td>
<td>73% (22/30)</td>
<td>76% (25/33)</td>
</tr>
<tr>
<td># of Transporter assays</td>
<td>120</td>
<td>450</td>
<td>~400</td>
</tr>
<tr>
<td># of Transporters tested*</td>
<td>16</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Metabolism evaluated in vitro (% of NDAs)</td>
<td>88% (22/25)</td>
<td>100% (30/30)</td>
<td>91% (30/33)</td>
</tr>
</tbody>
</table>

*P-gp is the most frequently evaluated transporter. Other transporters included BCRP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT2, OAT3, OAT4, OCT1, OCT2, OCT3, MATE1 and MATE2-K, BSEP, MRP2, MRP4, etc.

Yu, et. al., DMD, 2014; Yu, et. al., DMD, 2016; Yu, et. al., DMD, 2017
Evaluation of Drug-Drug Interactions

<table>
<thead>
<tr>
<th>In Vitro DDI Assessment</th>
<th>Clinical DDI Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>How to assess the DDI potential?</td>
<td>When to conduct needed clinical DDI studies?</td>
</tr>
<tr>
<td>What should be my clinical DDI assessment strategy?</td>
<td>How should clinical DDI studies be conducted?</td>
</tr>
<tr>
<td>Which clinical DDI studies should I conduct?</td>
<td>How should results from clinical DDI studies be analyzed, interpreted, managed and communicated?</td>
</tr>
</tbody>
</table>

Focuses on enzyme- and transporter-based DDI

Model-based DDI Prediction and Simulation

Modified from Dinko Rekić, ASCPT 2016
General Approaches for Evaluation of Transporter-Mediated DDI

• Understand the clinical question
• Assess NME as a substrate or inhibitor of various enzymes and transporters to understand its DDI potential
  – An integrated approach (in vitro, in vivo, in silico)
    • Decision models
      – Consider all mechanisms to understand clearance pathways and describe variability and/or DDI
      – Basic → Mechanistic (static or PBPK)
    – Follow up studies
• Translate results into labeling
Investigational Drug as a Substrate of Transporters (1)

*Does the drug level depend on a given transporter?*

- In vitro assessments—Which transporters?
  - Route of elimination
  - Rate-limiting step
  - Other (physicochemical properties and structure)

- In vivo transporter DDI evaluation may be relevant
  - P-gp and BCRP
    - knowledge about tissue penetration is critical (safety or efficacy reasons)
    - intestinal absorption may lead to variability in drug response
  - OATP1B1 and OATP1B3
    - hepatic uptake is needed for effect
    - hepatic elimination is significant
  - OAT1, OAT3, OCT2, MATE
    - active renal secretion or concerns about renal toxicity
Investigational Drug as a Substrate of Transporters (2)

- Conduct DDI study with a known inhibitor
- Select inhibitor based on the goal of the study
- Usually select inhibitor based on likelihood of co-administration (lack of index inhibitors)
- Possible worst case evaluation
  - Cyclosporine inhibits multiple transporters (P-gp, OATP, BCRP)
  - If positive, use inhibitor that is more selective
- Another approach- begin with more selective inhibitors
- Studies are not easily extrapolated to other drugs

Courtesy: K Reynolds
<table>
<thead>
<tr>
<th>Drug Interactions &amp; Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Development and Drug Interactions</td>
</tr>
<tr>
<td>Drug Development and Drug Interactions: Possible Models for Decision-Making</td>
</tr>
<tr>
<td>Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers</td>
</tr>
<tr>
<td>Drug Development and Drug Interactions: Advisory Committee Meetings</td>
</tr>
<tr>
<td>Drug Development and Drug Interactions: Publications</td>
</tr>
<tr>
<td>Drug Development and Drug Interactions: Related Links</td>
</tr>
<tr>
<td>Drug Development and Drug Interactions: Working Group Members</td>
</tr>
</tbody>
</table>

**Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers**

- **CYP Enzymes**
  - In vitro
    - In vitro marker reactions
    - In vitro selective inhibitors
    - In vitro inducers
  - Clinical index drugs
    - Clinical index substrates
    - Clinical index inhibitors
    - Clinical index inducers
  - Examples of clinical substrates, inhibitors, and inducers
    - Clinical substrates
    - Clinical inhibitors
    - Clinical inducers

- **Transporters**
  - In vitro
    - In vitro substrates
    - In vitro inhibitors
    - Examples of clinical substrates, inhibitors and inducers

Investigational Drug as an Inhibitor of Transporters

Does the drug affect a given transporter?

In vitro assessment--Basic Models for Predicting NME as Transporter Inhibitors

– Relevant inhibitor concentrations \([I]/\text{in vitro IC}_{50} \geq \text{cutoff value?}\)
  • Yes, predict positive
  • No, predict negative

Relevant Inhibitor Concentration

**P-gp, BCRP:** Gut concentration

\[ [I]_2 = \frac{\text{Dose}}{250 \, \text{mL}} \]

**OATP1B:** Free hepatic inlet concentration

\[ I_{u,\text{in,\text{max}}} = f_{u,p} \times \left( \frac{(C_{\text{max}} + (F_a F_g \times k_a \times \text{Dose}))}{Q_h/R_B} \right) \]

**OAT/OCT:** Free systemic concentration

\[ I_u = C_{\text{max,u}} \]

**MATE:** Free systemic concentration

\[ I_u = C_{\text{max,u}} \]

(as a “surrogate” and a different cutoff may be warranted)
Evaluation of Proposed Decision Criteria for Various Transporters (FDA Transporter Scientific Interest Group)

Objectives:
• To compare the prediction performance of various criteria for transporter-mediated DDIs proposed by FDA, EMA and PMDA.
• To provide scientific support to reach harmonized criteria

Methodology:
• Consider the specificity and sensitivity of substrates
  – In vitro
  – In vivo DDI with a known inhibitor
  – Polymorphism
• Minimize drug pairs that may have confounding interaction mechanisms (e.g., via enzymes or other transporters).
• Data sources
  – University of Washington Drug Interaction Database (UW DIDB)
  – Drugs@FDA
  – Internal data
### P-gp: Comparison of prediction performance with different cut-off criteria

<table>
<thead>
<tr>
<th></th>
<th>EMA(^1)</th>
<th>PMDA&amp; FDA(^2)</th>
<th>(I_2/IC_{50}) alone (#1)</th>
<th>(I_2/IC_{50}) ≥45 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I_{1u}/IC_{50} ≥ 0.02) OR (I_2/IC_{50} ≥ 10)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>(I_1/IC_{50} ≥ 0.1) OR (I_2/IC_{50} ≥ 10)</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>TN (#)</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>TP (#)</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>TPV (%)</td>
<td>61</td>
<td>61</td>
<td>63</td>
<td>71</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>73</td>
<td>73</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Likelihood ratio positive (LR+)</td>
<td>1.77</td>
<td>1.77</td>
<td>1.94</td>
<td>2.72</td>
</tr>
<tr>
<td>Likelihood ratio negative (LR-)</td>
<td>0.420</td>
<td>0.420</td>
<td>0.395</td>
<td>0.427</td>
</tr>
</tbody>
</table>

\(^{1}\) 2012 EMA DDI guideline; \(^{2}\) 2014 PMDA draft DDI guideline and 2012 FDA draft DDI guidance. \(I_2=\text{gut concentration.}\)

All methods showed similar results. When considering \(I_2/IC_{50}\) alone, \(I_2/IC_{50} ≥ 10\) (#1) showed a slightly better numerical result with the lowest likelihood of false negative predictions as compared to other criteria (lowest LR-);


**V Arya, et al, ASCPT 2017, PI-007**
OATP1B1: Comparison of prediction performance with different methods and cutoff criteria

<table>
<thead>
<tr>
<th>Method</th>
<th>1: $I_{\text{max}}/K_i \geq 0.1$</th>
<th>2: $I_{\text{u,max}}/K_i \geq 0.02$</th>
<th>3: $R \geq 1.04$ (EMA)</th>
<th>4: $R \geq 1.1$</th>
<th>5: $R \geq 1.25$ (PMDA)</th>
<th>6: $I_{\text{max}}/K_i \geq 0.1$ and $R \geq 1.25$ (FDA 2-step)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN</td>
<td>12</td>
<td>17</td>
<td>8</td>
<td>12</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>FP</td>
<td>27</td>
<td>16</td>
<td>33</td>
<td>22</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>TN</td>
<td>28</td>
<td>39</td>
<td>22</td>
<td>33</td>
<td>39</td>
<td>42</td>
</tr>
<tr>
<td>TP</td>
<td>40</td>
<td>35</td>
<td>44</td>
<td>40</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>PPV</td>
<td>60%</td>
<td>69%</td>
<td>57%</td>
<td>65%</td>
<td>70%</td>
<td>73%</td>
</tr>
<tr>
<td>NPV</td>
<td>70%</td>
<td>70%</td>
<td>73%</td>
<td>73%</td>
<td>72%</td>
<td>71%</td>
</tr>
<tr>
<td>Likelihood ratio positive (LR+)</td>
<td>1.57</td>
<td>2.31</td>
<td>1.41</td>
<td>1.92</td>
<td>2.45</td>
<td>2.85</td>
</tr>
<tr>
<td>Likelihood ratio negative (LR-)</td>
<td>0.453</td>
<td>0.461</td>
<td>0.385</td>
<td>0.385</td>
<td>0.407</td>
<td>0.428</td>
</tr>
</tbody>
</table>

1 2012 EMA DDI guideline; 2 2014 PMDA draft DDI guideline; 3 2012 FDA draft DDI guidance.

$R \geq 1.04$ (Criterion #3) and $R \geq 1.1$ (Criterion #4) had the lowest likelihood of false negative predictions as compared to other criteria (lowest LR-). Criterion #4 appears to be reasonable with a lower false positive prediction (higher LR+).
OAT1/OAT3: Comparison of prediction performance with different cut-off criteria

<table>
<thead>
<tr>
<th>$C_{\text{max,u}}/ IC_{50}$</th>
<th>All substrates (59 DDI Studies)</th>
<th>OAT1-specific substrates (13 DDI Studies)</th>
<th>OAT3-specific substrate (32 DDI Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA $\geq 0.02^a$</td>
<td>FDA $\geq 0.1^b$</td>
<td>PMDA $\geq 0.25^c$</td>
<td>EMA $\geq 0.02^a$</td>
</tr>
<tr>
<td>FN</td>
<td>0</td>
<td>1$^d$</td>
<td>1$^d$</td>
</tr>
<tr>
<td>FP</td>
<td>20</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>TP</td>
<td>22</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>TN</td>
<td>17</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>PPV</td>
<td>52%</td>
<td>64%</td>
<td>72%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>96%</td>
<td>97%</td>
</tr>
</tbody>
</table>

$^a$ Criteria suggested in 2012 EMA DDI guideline. $^b$ Criteria suggested in 2012 FDA draft DDI guidance. $^c$ Criteria suggested in 2014 PMDA draft DDI guideline. $^d$ The false negative prediction using 0.1 (also 0.25) as a cut-off was for a study between etoricoxib and methotrexate (MTX) where AUC of MTX increased by 27% with etoricoxib. In another study conducted by the same authors, AUC of MTX was only increased by 4.9% with etoricoxib (*J Clin Pharmacol*. 49(10):1202-1209, 2009). The 27% increase may reflect cross study variability because the study design between the 2 studies was very similar.

## OCT2/MATEs: Comparison of prediction performance of different cut-off criteria

<table>
<thead>
<tr>
<th></th>
<th>EMA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ITC&lt;sup&gt;b&lt;/sup&gt;</th>
<th>PMDA&lt;sup&gt;c&lt;/sup&gt;</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
<th>#8</th>
<th>#9</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max,u&lt;/sub&gt;/&lt;IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>OCT2 ≥ 0.02 OR</td>
<td>OCT2 ≥ 0.1 OR</td>
<td>OCT2 ≥ 0.25 OR</td>
<td>OCT2 ≥0.02 OR</td>
<td>OCT2 ≥0.1 OR</td>
<td>OCT2 ≥ 0.25 OR</td>
<td>MATEs ≥0.02</td>
<td>MATEs ≥0.25</td>
<td>MATEs ≥0.02</td>
</tr>
<tr>
<td>FN</td>
<td>0</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>FP</td>
<td>10</td>
<td>9</td>
<td>5</td>
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<td>10</td>
<td>10</td>
<td>6</td>
<td>9</td>
<td>8</td>
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<tr>
<td>TP</td>
<td>18</td>
<td>16</td>
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<td>18</td>
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<tr>
<td>TN</td>
<td>5</td>
<td>6</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>PPV</td>
<td>64%</td>
<td>64%</td>
<td>75%</td>
<td>64%</td>
<td>64%</td>
<td>64%</td>
<td>73%</td>
<td>67%</td>
<td>65%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>75%</td>
<td>77%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>82%</td>
<td>100%</td>
<td>70%</td>
</tr>
</tbody>
</table>

a A cut-off of 0.02 applied to unbound C<sub>max</sub>/IC<sub>50</sub> for OCT2 or for MATEs was suggested in 2012 EMA DDI guideline;
b A cut-off of 0.1 for OCT2 or for MATEs was suggested in ITC paper (Hillgren KM, et. al, *Clin Pharm Ther*, 94(1):52-63, 2013). As of note, 2012 FDA’s draft DDI guidance has a cutoff of 0.1 only for OCT2; c A cut-off of 0.25 was suggested in 2014 PMDA draft DDI guideline. d Among these false negatives, two DDI records were between ranolazine (inhibitor, different doses) and metformin (substrate) (Zack J, *Clin Pharm in Drug Develop*, 4(2) 121–129, 2015). The other DDI study was between isavuconazole and metformin (Clinical Pharmacology and Biopharmaceutical review for NDA 207-500 from Drugs@FDA).

Investigational Drug as an Inhibitor of Transporters

Does the drug affect a given transporter?

In vivo evaluation

• Determine whether studies are relevant
  – likely concomitant medications and their safety profile

• Select substrate for DDI study
  – Most transporter substrates are not selective
  – Can select based on likely concomitant drugs
Which Stain to Select for DDI?

- Relative contribution of various transporters/enzymes on the disposition of statin drugs is different, e.g.,
  - OATP1B1, BCRP, P-gp, MRP2, etc.
  - CYP3A4, CYP2C8, CYP2C9, etc.
- Depending on inhibitor specificity on these transporters/enzymes, interaction with different statins may be different.

Niemi M, Clin Pharmacol Ther, Jan 2010
# ZEPATIER (Elbasvir and Grazoprevir) and Statin DDI

Approved 2016; For the treatment of HCV

<table>
<thead>
<tr>
<th>In Vitro (As Inhibitor)</th>
<th>Elbasvir</th>
<th>Grazoprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A</td>
<td>No</td>
<td>Yes, weak inhibitor</td>
</tr>
<tr>
<td>P-gp</td>
<td>Yes, little effect on digoxin</td>
<td>No</td>
</tr>
<tr>
<td>BCRP</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>OATP</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

In Vivo DDI studies with 4 Statin Drugs

<table>
<thead>
<tr>
<th>Co- Administered Drug</th>
<th>Regimen of Co- Administered Drug</th>
<th>EBR or/and GZR Administration</th>
<th>EBR or/and GZR Regimen</th>
<th>N</th>
<th>AUC*</th>
<th>C_max</th>
<th>C_trough†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Atorvastatin 10 mg single-dose</td>
<td>EBR + GZR</td>
<td>50 mg + 200 mg once daily</td>
<td>16</td>
<td>1.94 (1.63, 2.33)</td>
<td>4.34 (3.10, 6.07)</td>
<td>0.21 (0.17, 0.26)</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Pitavastatin 1 mg single-dose</td>
<td>GZR</td>
<td>200 mg once daily</td>
<td>9</td>
<td>1.11 (0.91, 1.34)</td>
<td>1.27 (1.07, 1.52)</td>
<td>--</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Pravastatin 40 mg single-dose</td>
<td>EBR + GZR</td>
<td>5 mg + 200 mg once daily</td>
<td>12</td>
<td>1.64†</td>
<td>1.55</td>
<td>--</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Rosuvastatin 10 mg single-dose</td>
<td>EBR + GZR</td>
<td>50 mg + 200 mg once daily</td>
<td>12</td>
<td>2.26 (1.89, 2.69)</td>
<td>5.49 (4.29, 7.04)</td>
<td>0.98 (0.84, 1.13)</td>
</tr>
</tbody>
</table>

How about effect on other statin drugs?

Drugs@ FDA and Zepatier® USPI label
Mechanistic static models for predicting DDIs risk of statins

• Mechanistic static models were built for 7 statins currently marketed in the U.S.
  – Atorvastatin, fluvastatin, lovastatin, simvastatin, pitavastatin, pravastatin, and rosuvastatin
• Model performance:
  – Among 57 in vivo DDI studies, 33 (~60%) were predicted within 80-125% of clinically observed AUCR and 48 (~84%) were within 50-200% of clinically observed AUCR.

*Duan P, et al, AAPS 2013; Manuscript in Preparation.*
## Predicted DDIs for a Hypothetical Drug

### Assumptions
- Assume Ki for all pathways are 0.1 μM.

### Potential use of these models:
- Guide inclusion/exclusion of certain stains in clinical trials
- Select relevant statins for further clinical DDI assessment
- Support labeling recommendation for proper co-medication of specific statins with an NME in patient populations

### Table: Fold change in AUCR

<table>
<thead>
<tr>
<th>Affected pathway Statins</th>
<th>CYP3A4 inhibition only</th>
<th>OATP1B1 inhibition only</th>
<th>BCRP or MRP2 only</th>
<th>All pathways including enzymes and transporter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>2.6</td>
<td>2.3</td>
<td>1.7</td>
<td>11</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>1.0</td>
<td>1.2</td>
<td>1.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>11</td>
<td>1.5</td>
<td>1.0</td>
<td>13</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1.0</td>
<td>2.5</td>
<td>1.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>1.0</td>
<td>1.8</td>
<td>3.0</td>
<td>9.7</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>1.0</td>
<td>1.6</td>
<td>2.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>25</td>
<td>2.7</td>
<td>1.0</td>
<td>31</td>
</tr>
</tbody>
</table>

*Duan P, et al, AAPS 2013; Manuscript in Preparation.*
Need More Mechanistic Models

- Transporters are important for tissue distribution.
- The consequence of the interaction mediated by transporters may not always be apparent if an in vivo human DDI study only measures systemic exposure.
  - PK may not change in the same direction as PD
- Determining whether the NME is a substrate or inhibitor of key transporters can help to build mechanistic models to understand the underlying clinical consequences, such as increased toxicity signal or altered efficacy markers due to altered tissue distribution of a substrate drug.

Adapted from Zhao P, et al
Clin Pharmacol Ther 2011
# PBPK applications: current status

<table>
<thead>
<tr>
<th>Applications</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug-drug Interactions</strong></td>
<td></td>
</tr>
<tr>
<td>Drug as enzyme substrate</td>
<td>• Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling</td>
</tr>
<tr>
<td>Drug as enzyme perpetrator</td>
<td>• Use to confirm the lack of enzyme inhibition • Additional evidence needed to confirm predictive performance for positive interactions</td>
</tr>
<tr>
<td>Transporter-based</td>
<td>• In vitro-in vivo extrapolation not mature • Complicated by transporter-enzyme interplay • Predictive performance yet to be demonstrated</td>
</tr>
<tr>
<td><strong>Specific populations</strong></td>
<td></td>
</tr>
<tr>
<td>Organ impairments (hepatic and renal)</td>
<td>• Predictive performance yet to be improved • System component needs an update</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>• Allometry is reasonable for PK down to 2 years old • Less than 2 years old ontogeny and maturation need to be considered</td>
</tr>
<tr>
<td><strong>Others with limited experience</strong></td>
<td></td>
</tr>
<tr>
<td>Pregnancy, ethnicity, geriatrics, obesity, disease states</td>
<td></td>
</tr>
<tr>
<td>Food effect, formulation change, pH effect (including DDIs on gastric pH)</td>
<td></td>
</tr>
<tr>
<td>Tissue concentration, drug delivery for locally-acting products</td>
<td></td>
</tr>
</tbody>
</table>

*Updated from Wagner, CPT-PSP, 2015*

*Courtesy: P Zhao*
### Examples of PBPK models submitted to FDA by drug developers to address questions related to drug transporters

<table>
<thead>
<tr>
<th>Drug names</th>
<th>Transporters</th>
<th>Applications of PBPK modeling</th>
<th>Potential Regulatory implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxegol</td>
<td>Intestinal P-gp</td>
<td>Predicting the effect of P-gp inhibitor</td>
<td>No clinically significant effect of co-administered drug that only inhibits P-gp</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Intestinal P-gp</td>
<td>Predicting the role of P-gp on oral absorption</td>
<td>P-gp plays minimal role on oral absorption</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Intestinal P-gp</td>
<td>Predicting the inhibition effect on intestinal P-gp</td>
<td>Potential inhibition may be minimized if a P-gp substrate with narrow therapeutic window is not co-administered with ibrutinib simultaneously</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Hepatic OATPs</td>
<td>Predicting the role of OATP on drug disposition and DDI</td>
<td>Both OATP and CYP3A saturation contributed to observed nonlinearity of simeprevir. Strong and moderate CYP3A inhibitors can significantly increase simeprevir exposure, and coadministration with these inhibitors should be avoided</td>
</tr>
</tbody>
</table>

*Y Pan, et. al. JCP 2016; Drugs@FDA*
Emerging Areas

• Altered drug concentrations in tissues
  – Knowledge of drug as transporter substrate or inhibitor may help to explain some observed clinical effect
    • Liver: Statins, Metformin
    • Kidney: Tenofovir, Cisplatin

• Altered endogenous substance concentrations
  – Increased serum creatinine by a drug may not represent renal toxicity; PMR for QSYMIA (phentermine and topiramate); As a biomarker for transporter inhibition
  – Bile salts and conjugated bilirubin are transported by BSEP and MRPs. Nonclinical and clinical experiences during drug development will dictate whether to evaluate these transporters
  – Coproporphyrins (CP-I and CP-III) are transported by OATP1B1 and OATP1B3 in the liver. Recent animal and clinical data suggested that they may be used as potential hepatic OATP1B markers

Summary

• Alterations in transporter activities contribute to variability in PK, PD, efficacy, and safety.
• *In vitro* transporter studies increase our ability to predict occurrence of *in vivo* DDIs and aid in development of clinical DDI strategies.
• Decision criteria proposed are being used to predict DDI potential and need to be further evaluated and refined when more data are available.
• *In silico* methods (e.g., PBPK) have potential utility and require continued collaborative efforts to fill the knowledge gaps.
• Transporter research is evolving.
  – Emerging transporters with clinical importance may need to be considered.
  – Transporter's role in toxicity or efficacy needs to be understood (e.g., OCT1)
  – Biomarkers for transporters
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    • U of Maryland
    • U of Washington
FDA
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