Updates on FDA’s DDI Guidance for Transporter-Mediated DDIs: Considerations and Perspectives

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Disclaimer: The contents of this presentation are my personal opinions and do not necessarily reflect the views and/or policies of the U.S. Food and Drug Administration
• Background

• DDIs for a drug as substrate of transporters
  -- P-gp and BCRP
  -- OATP1B1/1B3
  -- OAT1/3, OCT2, MATEs

• DDIs for a drug as inducer of Transporters

• DDIs for a drug as inhibitor of Transporters
  -- P-gp and BCRP
  -- OATP1B1/1B3
  -- OAT1/3
  -- OCT2/MATEs

• Case Example

• Summary
Many Factors Affect Drug Exposure and Response

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

Ultimate goal → Optimal dosing for patients with these individual factors


History of DDI Guidance

1997: In vitro

1999: In vivo

2006: In vitro and In vivo Combined

2012: In vitro and In vivo Combined

2017: Today’s discussion

Categorization for perpetrators and substrates
Included Transporters
Model-based predictions
More Transporters
Therapeutic Proteins

Therapeutic Proteins

Transporters
• Made 2 separate guidance documents (In Vitro & Clinical)
• Introduced concept of index drugs/index studies (for CYPs)
• Effort to harmonize with EMA/PMDA on certain prediction methods/criteria from in vitro to in vivo
• Removed tables of substrates and perpetrators (hosted on FDA’s DDI website for ease of update)
• Removed decision trees (might be saved on website)
• Under clearance → final guidances
Topics not Covered in 2017 Guidance

- Therapeutic protein DDI (part of 2012 draft)*
- Non-CYP enzymes (e.g., UGT, part of 2012 draft)
- Gastric pH change mediated DDI*
- Oral contraceptive (OC) DDI
- Detailed Section 7 (DDI) labeling recommendation
- Protein displacement
- Pharmacodynamic interactions

* Federal Registry notice issued in 2018 to collect feedback for future stand-alone guidances
Investigational Drug as a Substrate of Transporters

- P-gp and BCRP (efflux transporters) considering an in vivo study with P-gp and/or BCRP inhibitor for a substrate drug when

  -- Intestinal absorption is likely to be a major cause of the variability in drug PK and response.

  -- Biliary excretion/renal active secretion may also contribute to DDI, AUC of digoxin administered intravenously increased by 40% - 170% with quinidine, ritonavir, and verapamil

Investigational Drug as a Substrate of Transporters

- OATP1B1 and OATP1B3 (hepatic uptake transporters)
  - Hepatic/biliary elimination is significant
  - May consider properties suggesting the importance of active uptake into liver, e.g.,
    - Anion or zwitter ion at physiological pH,
    - High hepatic concentrations relative to other tissues (e.g., from animal studies),
    - Low passive permeability
      - Any cut-off of Papp? The importance of OATP1B1/3 depends on the relative rate of active uptake to passive transport in vivo.
      - Statin drugs affected by OATP1B inhibitors have different permeability (e.g., simvastatin, atorvastatin, rosuvastatin, pitavastatin)

Note: not all the substrates of OATP1B1/3 are anions or zwitter ions.

Investigational Drug as a Substrate of Transporters

- OAT1, OAT3, OCT2, MATE1, MATE2/K (renal uptake or efflux transporters)
  
  Significant active renal secretion ($\geq 25\%$ of systemic clearance of the drug) or concerns about renal toxicity

  \[
  \text{Active secretion} = \text{CL}_r - (f_{u,p} \times \text{GFR}), \quad \text{assuming there is no re-absorption (e.g., no active re-absorption and passive re-absorption is equal to passive secretion).}
  \]

- For a drug which is a transporter substrate, the decision on conducting clinical DDI studies is also affected by: likely concomitant drugs, safety considerations, route of elimination, etc.
Outline

• Background
• DDIs for a drug as substrate of transporters
  -- P-gp and BCRP
  -- OATP1B1/1B3
  -- OAT1/3, OCT2, MATEs
• DDIs for a drug as inducer of Transporters
• DDIs for a drug as inhibitor of Transporters
  -- P-gp and BCRP
  -- OATP1B1/1B3
  -- OAT1/3
  -- OCT2/MATEs
• Case Example
• Summary
- Current knowledge about transporter induction is limited; consider evaluating P-gp induction if CYP3A induction is observed.
- OATP1B1/3 may also be induced by some CYP3A inducers (e.g., rifampin, carbamazepine).

Investigational Drug as an Inhibitor of Transporters

- Evaluate an NME as an inhibitor for
  - P-gp, BCRP;
    OATP1B1, OATP1B3;
    OAT1, OAT3, OCT2, MATE1, MATE-2K
  - Applicable for most drugs (a drug not as a substrate of a transporter doesn’t mean it cannot be an inhibitor)

- Basic Models for predicting in vivo inhibition potential of transporters by the NME
  Is relevant inhibitor concentration compared to inhibitory potency \([I]/IC_{50} \geq \text{cutoff value}\)? If yes, in vivo inhibition is possible.
### Criteria for In Vitro to In Vivo Extrapolation for Transporter inhibition mediated-DDIs

<table>
<thead>
<tr>
<th>Transporters</th>
<th>2012 Draft guidance</th>
<th>2017 Draft Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P-gp</strong></td>
<td>$I_1/IC_{50} \geq 0.1$ or $I_2/IC_{50} \geq 10$</td>
<td>$I_2/IC_{50} \geq 10$ (for oral drugs)</td>
</tr>
<tr>
<td><strong>OATP1B1/ OATP1B3</strong></td>
<td>Step 1: $I_{total, max}/IC_{50} \geq 0.1$</td>
<td>$I_{unbound, inlet, max}/IC_{50} \geq 0.1$</td>
</tr>
<tr>
<td></td>
<td>Step 2: $I_{unbound, max}/IC_{50} \geq 0.25$</td>
<td></td>
</tr>
<tr>
<td><strong>OAT1/OAT3</strong></td>
<td>$I_{unbound, max}/IC_{50} \geq 0.1$</td>
<td>Remained the same</td>
</tr>
<tr>
<td><strong>OCT2/MATE1/ MATE2-K</strong></td>
<td>$I_{unbound, max}/IC_{50} \geq 0.1$ (only for OCT2)</td>
<td>$I_u, max/IC_{50} \geq 0.1$ for OCT2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$OR$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$I_u, max/IC_{50} \geq 0.02$ for MATEs</td>
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</tbody>
</table>

- The sponsor should consider whether to conduct an in vivo study based on whether the likely concomitant medications used in the indicated patient populations are known substrates of these.
- Sponsors may calibrate their internal in vitro systems with known inhibitors and non-inhibitors of these transporter and propose a specific cutoff value with proper justification.
# P-gp: Comparison of Prediction Performance with Different Cut-off Criteria

<table>
<thead>
<tr>
<th></th>
<th>EMA¹</th>
<th>PMDA&amp; FDA²</th>
<th>( I_2/IC_{50} ) alone (#1)</th>
<th>( I_2/IC_{50} ) alone (#2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN (#)</td>
<td>6 (11%)</td>
<td>6 (11%)</td>
<td>6 (11%)</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>FP (#)</td>
<td>12 (23%)</td>
<td>12 (23%)</td>
<td>11 (21%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>TN (#)</td>
<td>16 (30%)</td>
<td>16 (30%)</td>
<td>17 (32%)</td>
<td>21 (40%)</td>
</tr>
<tr>
<td>TP (#)</td>
<td>19 (36%)</td>
<td>19 (36%)</td>
<td>19 (36%)</td>
<td>17 (32%)</td>
</tr>
</tbody>
</table>

<p>| | | | | |</p>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV</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>
</tbody>
</table>

- \( I_2/IC_{50} \geq 10 \text{ alone} \) (\( I_2 = \text{Dose/250 mL, reflecting inhibitor concentration in gut lumen} \)) seems sufficient for reasonable prediction of P-gp mediated DDIs for oral drugs.

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

P-gp or BCRP Inhibition-Mediated DDIs

- BCS Class II or IV drugs: the dose given won’t be dissolved in 250 mL. → Possible false positive.

  No optimal solution yet. Need further research. Caveat with aqueous solubility – impact of bile acid and/or excipients. Ketoconazole or itraconazole has very low solubility at neutral pH. Yet, these drugs ↑ digoxin and/or dabigatran AUC

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose regimen</th>
<th>IC₅₀ (µM)ᵃ</th>
<th>I₂/IC₅₀ for DE</th>
<th>% Change of dabigatran AUCᵇ, ᶜ</th>
<th>% Change of digoxin AUCᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>200-mg capsule, q.d., for 5 days</td>
<td>0.41</td>
<td>1,100</td>
<td>117ᵈ, 592ᵉ</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>200 mg, q.d., for 5 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400 mg, s.d., or 400 mg, q.d., for 8 days</td>
<td>3.4</td>
<td>880</td>
<td>138–153</td>
<td>NRᶠ</td>
</tr>
</tbody>
</table>

What about drugs given parentally or metabolite that are the inhibitors of P-gp and/or BCRP?

\[ \frac{I_1}{IC_{50}} \geq 0.1 \quad (I_1 = \text{total Cmax}) \text{ might be utilized.} \]

Or \[ \frac{I_1}{IC_{50}} \geq 0.02? \quad (I_1 = \text{unbound Cmax}) \]

There are very limited data. Need further evaluation.
# OATP1B1: Comparison of Prediction Performance with Different Cutoff Criteria

<table>
<thead>
<tr>
<th>Method</th>
<th>1: $I_{\text{max}}/K_i \geq 0.1$</th>
<th>2: $I_{u,\text{max}}/K_i \geq 0.02$</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 (11%)</td>
<td>17 (16%)</td>
<td>8 (7%)</td>
<td>12 (11%)</td>
<td>15 (14%)</td>
<td>17 (16%)</td>
</tr>
<tr>
<td>FP</td>
<td>27 (25%)</td>
<td>16 (15%)</td>
<td>33 (31%)</td>
<td>22 (21%)</td>
<td>16 (15%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>TN</td>
<td>28 (26%)</td>
<td>39 (36%)</td>
<td>22 (21%)</td>
<td>33 (31%)</td>
<td>39 (36%)</td>
<td>42 (39%)</td>
</tr>
<tr>
<td>TP</td>
<td>40 (37%)</td>
<td>35 (33%)</td>
<td>44 (41%)</td>
<td>40 (37%)</td>
<td>37 (35%)</td>
<td>35 (33%)</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>
</tbody>
</table>

**$R \geq 1.1$** ($I_{u,\text{inlet,}\text{max}}/IC_{50} \geq 0.1$), unbound liver inlet concentrations of inhibitor) seems providing a reasonable balance between false negative and false positive predictions.


OATP1B1/3 Inhibition-Mediated DDIs

• IC$_{50}$ or Ki determined with pre-incubation

Shift of IC$_{50}$ or Ki after pre-incubation observed (e.g., cyclosporine, rifampin)

Better predication of in vivo DDI with lower Ki of cyclosporine

Limited experience so far. Need further research.
  Assay: pre-incubation time varies among labs

  Clinical relevance: qualitative and/or quantitative prediction performance of IC$_{50}$ or Ki with pre-incubation vs. not.

• Utility of endogenous biomarkers →

Utility of Endogenous Biomarkers for OATP1B1/3 Inhibition-Mediated DDIs

Coproporphyrins in Plasma and Urine Can Be Appropriate Clinical Biomarkers to Recapitulate Drug-Drug Interactions Mediated by Organic Anion Transporting Polypeptide Inhibition

Comparative Evaluation of Plasma Bile Acids, Dehydroepiandrosterone Sulfate, Hexadecanedioate, and Tetradecanedioate with Coproporphyrins I and III as Markers of OATP Inhibition in Healthy Subjects

Further Studies to Support the Use of Coproporphyrin I and III as Novel Clinical Biomarkers for Evaluating the Potential for Organic Anion Transporting Polypeptide 1B1 and OATP1B3 Inhibition
Utility of Endogenous Biomarkers for OATP1B1/3 Inhibition-Mediated DDIs

- In Vivo DDI studies with model compound or investigational drugs incorporating coproporphyrin I (CP I) and/or CP III e.g., rifampin, simeprevir, JNJ-A, GDC-0810, Drug X with different extent of DDI effects on various OATP1B1/3 substrates

- Modeling approach to predict DDI effect of a drug on OATP1B1/3 substrates based on the drug’s effect on CP I
  - Population PK
  - PBPK
  - Combined popPK and PBPK

The cut-off value 0.02 (EMA) yielded more false positives. The value 0.1 (FDA) or even 0.25 (PMDA) seems to be a reasonable cut-off.

### 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><strong>C&lt;sub&gt;max,u&lt;/sub&gt;/IC&lt;sub&gt;50&lt;/sub&gt;</strong></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>MATEs ≥0.02</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>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>
</tr>
<tr>
<td>MATEs ≥0.1</td>
<td>10</td>
<td>9</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>MATEs ≥0.25</td>
<td>18</td>
<td>16</td>
<td>15</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>16</td>
<td>18</td>
<td>15</td>
</tr>
<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>100%</td>
<td>82%</td>
<td>70%</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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).

Case Example - Dolutegravir

• An anti-HIV drug. Cmax ~4 μg/mL at 50 mg b.i.d. Plasma protein bound ≥ 98.9%. IC_{50} value for OCT2 was 1.93 μM (or 0.8 μg/mL).

• Is there a potential for dolutegravir to inhibit OCT2 in vivo and cause clinically significant drug interactions? Is there a need to further conduct an in vivo DDI study with OCT2 substrate(s)?

• Cmax,u/IC_{50} = 0.05 < 0.1 thus, it would be concluded that dolutegravir won’t cause clinically relevant DDIs mediated by inhibition of OCT2 in humans. → No further DDI assessment is needed.

NDA 204790 Clinical Pharmacology review at Drugs@FDA; TIVICAY USPI (labeling)
**Case Example - Dolutegravir**

Later literature reported a lower IC\(_{50}\) 0.11 \(\mu\text{M}\). Confirmed by another source (0.21 \(\mu\text{M}\)). Using the new data, \(\text{Cmax,u}/\text{IC}_{50} = 0.89 > 0.1\), it would be concluded that dolutegravir may cause clinically relevant DDI.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 2 (Dolutegravir 50 mg q12h)</th>
<th></th>
<th>GLS Mean Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Mean (CV%)</td>
<td>Period 2 vs Period 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Period 1 Metformin Alone (n = 15)</td>
<td>Period 2 Metformin Plus Dolutegravir (n = 14)</td>
<td>Period 3 Metformin Alone (n = 13)</td>
</tr>
<tr>
<td>AUC(0–(\tau)), (\mu\text{g} \cdot \text{h/mL})</td>
<td>6.49 (16.0)</td>
<td>15.9 (15.9)</td>
<td>6.69 (16.4)</td>
</tr>
<tr>
<td>Cmax, (\mu\text{g/mL})</td>
<td>0.875 (24.3)</td>
<td>1.85 (13.1)</td>
<td>0.872 (14.8)</td>
</tr>
<tr>
<td>tmax, h*</td>
<td>4.00 (1.50, 8.00)</td>
<td>4.00 (1.00, 6.00)</td>
<td>4.00 (2.00, 8.00)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>77.2 (16.6)†</td>
<td>31.4 (15.9)</td>
<td>74.8 (16.4)</td>
</tr>
<tr>
<td>t(1/2), h</td>
<td>4.27 (26.5)†</td>
<td>4.89 (19.6)</td>
<td>4.48 (24.3)†</td>
</tr>
</tbody>
</table>

USPI of TIVICAY: With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or TIVICAY. When stopping TIVICAY, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of TIVICAY is recommended.

Note: Other mechanism may also be involved besides renal transporter inhibition (see back-up slide).

Chu X, et al. Drug Metab Dispos. 2016 Sep;44(9):1498-509
Song IH, et. al. J Acquir Immune Defic Syndr. 2016 Aug 1;72(4):400-7
Why there was discrepancy? – Non-Specific Binding

Dolutegravir OCT2 IC50 Assessment

<table>
<thead>
<tr>
<th>Assay model</th>
<th>Polarized MDCK-OCT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>Metformin, 10uM</td>
</tr>
</tbody>
</table>

- 18 fold difference (1.9uM vs. 110nM) in previously reported IC50s using metformin as substrate (at diff. conc.)
- IC50 based on nominal concentration is close to one source: 3.1uM vs. 1.9 uM
- After recovery adjustment, IC50 dropped to 0.54uM, closer to 110nM [Lepist, et. al. 2014]

\[\rightarrow\text{still much higher than calculated DTG } C_{\text{max,u}} (<100\text{nM})\]

From Dr. Yong Huang, Optivia Biotechnology Inc. April 2015
Summary

• Drug interactions are one critical factor in determining the drug and dose for individual patients.

• An integrated approach can be used to leverage available in vitro/in vivo information to evaluate DDI potential (e.g., simple model, mechanistic static and/or PBPK model, validated biomarkers).

• The criteria of simple models (the matrix, the cut-off values) will be continuously evaluated for their prediction performance with more data becoming available and may be periodically updated.

• Standardize and validate in vitro assay conditions to ensure data with good quality (e.g., including proper controls, check recovery/mass balance, pay attention to potential non-specific binding).
Acknowledgements

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Zhongqi Dong*
Tian Zhou
Dinko Rekic*
Kenta Yoshida*

*former FDA colleagues
Similar t1/2 of metformin when given alone or with dolutegravir and differences between pre-dose steady-state concentrations may indicate possibility that metformin absorption was increased by dolutegravir, although the authors didn’t find dolutegravir altering metformin absorption in CaCo2 cells and no inhibition of PMAT, OCT1, or OCT3 by dolutegravir.

Metformin urine samples were not collected in the study. Therefore, it remains unknown whether and how much metformin renal clearance was affected by dolutegravir. This case also highlights the importance to collect urine PK samples for renal transporters-mediated DDI studies.