Prediction of Metabolite-Mediated DDIs Using PBPK

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Outline

• Background and Context
  o Physiologically-Based Pharmacokinetic (PBPK) Modeling and Simulation
  o DMLG Metabolite Drug-Drug Interaction (DDI) PBPK Working Group

• Real-World Application of PBPK
  o How to Incorporate Metabolite Data
  o Metabolite Kinetics
  o Issues and Assumptions

• Case Example- Inhibitory Metabolite Impact on Inhibitory Parent DDI
  o Identifying Major CYPs In Vitro
  o Metabolite Impact on Intrinsic Clearance
  o Metabolite Impact on Parent DDIs (as Perpetrator or Victim)

• Conclusions and Final Thoughts
Physiologically-Based PK Models

- PBPK models incorporate a drug-independent physiological model and a drug-dependent PK model

Zhao et al. CPT 2011
The Innovation & Quality Consortium

- Pharmaceutical company led initiative to evaluate the utility of PBPK in describing metabolite contribution to observed DDIs
Metabolite ADME Scholarship Group

- 18 members, familiar with issues of ADME and DDI, representing 18 pharmaceutical companies

- **Objectives** of the group:
  - **Assess the contribution of metabolites** to DDI; focused on inhibition of CYP enzymes by parent and metabolites (based on recent literature reviews)
  - **Provided recommendations to IQ DMLG** on how to assess the contributions of metabolites to DDI in drug development

- Why were we concerned about metabolites?
  - **Draft DDI Guidance (FDA, EMA) recommended metabolite evaluation** when abundance is high relative to parent – led to working group formation
  - **The magnitude of DDI depends inhibitor exposure and potency (I/Ki)** – such a dynamic environment is poorly represented by a single concentration estimate \( (C_{ave}, C_{max}, C_{hepatic\ inlet}, \text{etc}) \) – PBPK models are more mechanistic and more relevant
Metabolite Role in DDI – The Papers That Started it All


1323 marketed drugs (US)

130 CYP inhibitors identified (UW DIDB)

106 inhibitors with circulating metabolites

34 metabolites with in vitro and in vivo data

19 reversible inhibitors

15 MBIs

11 drugs with DDI data (n=56 datasets)
In the past, DDI risk assessments have been based on *in vivo* and *in vitro* parent data \((I/K_i)\), which often leads to over-prediction of DDI (worst-case scenario).

However, there has been concern that PBPK modeling may lead to a failure to catch “surprise” DDIs caused by inhibitory metabolites.

Therefore, an assessment of the utility of PBPK modeling in capturing drugs with “surprise” DDIs was needed.

A PBPK sub team was formed to respond to this request, and characterize metabolite contribution to DDI for CYP inhibitors.

However, it is important to remember that risk of metabolite contribution to DDI is expected to be low (2% of 144 most prescribed; 0.2% of US market).
Sub Team Co-Leads:
Manthena Varma (Pfizer)* & Ian Templeton (Janssen)

Chris MacLauchlin (GSK)  Jin Zhou (BI)
Chuang Lu (MPI)          Jian Lin (Pfizer)*
Edgard Schuck (Eisai)    Yuan Chen (Genentech)*
Grant Generaux (GSK)*     Susanna Tse (Pfizer)
Guanfa Gan (BI)          Sheila Peters (AZ)
Hongbin Yu (BI)          Mohamad Shebley (Abbvie)
Jialin Mao (Genentech)   

*Model Developers

Main Objectives:

• Design PBPK models, based on available *in vitro* and *in vivo* data, to assess utility of PBPK approach in predicting “surprise” interactions

• Use PBPK models to determine critical information required for relevant predictive models

• Publish results to provide recommendations for industry

Templeton et al. CPT:PSP 2016
Metabolite DDI PBPK Sub-Team Case Examples

• The following in vivo DDIs were greater than expected (parent inhibition alone):
  • **Amiodarone (n-desethyl-amiodarone); (s)-Warfarin (CYP2C9) AUC_R ~2**
    - Parent CL predicted based on *in vitro* data
    - Parent V<sub>SS</sub> estimated based on IV dose PK
    - Metabolite formation and distribution optimized from PO dose PK (P&M)
  • **Bupropion (hydroxy-bupropion + 2); Desipramine (CYP2D6) AUC_R ~5.2**
    - Metabolite V<sub>SS</sub> predicted based on phys-chem data
    - Metabolite clearance based on CL<sub>IV,Parent</sub> and PO metabolite PK
  • **Gemfibrozil; Repaglinide (CYP2C8) AUC_R ~8**
    - Parent PBPK model based on available *in vitro* and clinical data
    - Metabolite formation rate from parent elimination
    - Metabolite CL and V<sub>SS</sub> based on PO dose PK model fitting
  • **Sertraline; Pimozide (CYP3A4) AUC_R ~1.4; Desipramine (CYP2D6) AUC_R ~1.5**
    - Metabolite formation rate from parent elimination
    - Metabolite CL based on PO dose PK model fitting
    - Metabolite V<sub>SS</sub> predicted based on phys-chem data

*Chen et al. DMD 2015
Varma et al. Pharm Res 2013*
Itraconazole, Another Example of Metabolite DDI

- Azole anti-fungal which inhibits a vital fungal CYP
- Potent inhibitor of human CYP3A4 *in vitro* and *in vivo*
- Also a substrate of CYP3A4; metabolized to form at least three sequential metabolites: hydroxy-, keto- and ND-ITZ (all inhibit CYP3A4)
- ITZ becoming more relevant as a result of KTZ prohibition in DDI studies

ISOHERRANEN ET AL. DMD 2004
ITZ & Metabolites; Single v. Multiple Dose

- Metabolite/Parent ratio changes as a function of time
- Relative role of ITZ and metabolites in DDI is a function of dose and time
- PBPK more likely to capture these dynamic effects vs. static model

Templeton et al. CPT 2008
Templeton et al. CPT 2010
PBPK Model of ITZ and OH-ITZ Impact on MDZ DDI

- ITZ and primary metabolite, OH-ITZ, PBPK models were developed to evaluate metabolite contribution to CYP3A DDI and to design optimal DDI studies.
- ITZ CL and $V_{ss}$ were based on *in vitro* and phys-chem data and optimized based on IV data.
- OH-ITZ $V_{ss}$ were based on *in vitro* and phys-chem data and optimized based on PO data.
- Incorporation of OH-ITZ improved prediction accuracy, but still some under-prediction.

**Figure 2** Predictive performance of the modified SimCYPitraconazole model, in which the major modification to the input parameters was reduction of hydroxyitraconazole volume at steady state ($V_{ss}$). (a) The black bars represent the observed mean AUC ratio; the white bars represent the predicted median AUC ratio for the respective trial (trials 1–9). (b) The black bars represent the observed mean $C_{max}$ ratio; the white bars represent the predicted median $C_{max}$ ratio for the respective trial. See Supplementary Table S2 for details of dosing regimens. q.d., once daily; SD, single dose.

*Ke et al. CPT 2014*
Observations & Recommendations of the WG

• Metabolite contribution to “surprise” DDI is the exception, rather than the rule

• PBPK is a useful tool for evaluating the role of metabolites in the clinical DDI based on *in vitro* data

• Modeling metabolite contribution to inhibition DDI in vivo requires a large amount of additional data which is not typically collected a priori

• **While PBPK is not likely to provide an early warning of metabolite role in DDI *in vivo*, this tool is very useful in describing the time- and dose-dependent mechanisms responsible for observed *in vitro-in vivo* disconnects**

• However, if sufficient metabolite data are collected during development, PBPK may be applied for early risk assessments as well
Real-World Application of Metabolite PBPK

- **Fit-For-Purpose vs. mechanistic metabolite PBPK models**

- The extent of metabolite data, available to support PBPK model development, will depend on the stage, and the company – often minimal data for model verification

- **Fit-For-Purpose**
  - Requires minimal *in vitro* and *in vivo* data
  - Unable to capture impact of parent or metabolite on metabolite formation
  - Unable to capture non-linearity (single vs. multiple dose, different doses or schedules)

- **Mechanistic**
  - Requires more intensive metabolite data for model development and verification
  - Formation clearance and elimination predicted based on *in vitro* data or optimized based on *in vivo* data
  - Distribution volume predicted based on phys-chem data in the absence of IV metabolite data
How to Incorporate Metabolite Data

• **Fit-For-Purpose**
  
  o Simple first order absorption kinetics derived from clinical data (e.g. $f_a$, $k_a$)
  
  o Observed oral clearance used to derive parent elimination
  
  o Assign metabolite formation to a specific pathway (e.g. CYP3A4) and elimination to a global clearance parameter based on parent elimination
  
  o Optimize metabolite distribution volume based on observed *in vivo* metabolite data
  
  o Assign DDI parameters based on in vitro data

• **Mechanistic**
  
  o Use *in vitro* parent permeability data to predict absorption profile
  
  o Scale *in vitro* parent and metabolite elimination to derive *in vivo* clearance
  
  o Use *in vitro* metabolite formation via specific pathway to drive *in vivo* metabolite formation
  
  o Measure physchem properties (e.g. logP, $f_u$, B/P), or IV metabolite data, to predict metabolite $V_{SS}$

• **Both**
  
  o Assume missing data similar to parent (e.g. protein binding)
  
  o Investigate any uncertainty associated with model parameters using sensitivity analysis
Metabolite Kinetics Principles

- Under FRL conditions, metabolite clearance may be extrapolated from *in vivo* parent data.
- Dose-dependent changes in metabolite/parent ratio may be due to changes in metabolite formation or elimination (or *usually* some combination of the two!)

\[
\frac{AUC_{\text{metabolite}}}{AUC_{\text{parent}}} = \frac{CL_{\text{formation}}}{AUC_{\text{metabolite}}} \quad \text{where,} \quad CL_{\text{formation}} = CL_{\text{parent}} \times f_{\text{parent} \rightarrow \text{metabolite}}
\]
Issues and Assumptions

• Typically, phys-chem and protein binding data are not collected for metabolite
  - **IMPACT**: prediction of permeability, distribution volume, binding

• Parent and metabolite *in vitro* data collected in different experiments
  - **IMPACT**: relative protein binding or DDI potency

• Metabolite is rarely administered IV
  - **IMPACT**: prediction of elimination clearance and distribution volume

• Minimal metabolite data collected in clinical studies; generally just one or two time points and one dose
  - **IMPACT**: retrograde model development or model verification
Case Example: Metabolite Impact DDI

- Ph 2 development compound with a primary metabolite (M1) found to circulate at levels approximately 20% of parent total exposure
- *In vitro* studies indicated that M1 was primarily formed by CYP3A4 and CYP2C9; with the major contribution by CYP3A4 \( \text{fm}_{\text{CYP3A4}} > 80\% \)
- Both parent and M1 were potent inhibitors of CYP3A4 *in vitro* \( \text{IC}_{50} < 0.3 \, \mu\text{M} \)
- Sponsor interested in DDI risk as victim (inhibition, induction) and perpetrator (inhibition) of CYP3A4-mediated DDI to support label negotiations with the FDA regarding dosing guidelines (conmeds)
Identifying Major CYPs In Vitro (Metabolite Formation)

- Recombinant systems used to identify major CYPs forming metabolite
- Specific CYP inhibitors used in HLM systems to confirm role of CYPs in metabolite formation
- In this case, CYP3A4 was identified as the major CYP leading to formation of M1

<table>
<thead>
<tr>
<th>CYP</th>
<th>Specific Inhibitor</th>
<th>Relative Mean Metabolite (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>no MBI</td>
<td>100 ± 1.6</td>
</tr>
<tr>
<td>Control</td>
<td>no Competitive</td>
<td>100 ± 3.7</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>furafylline</td>
<td>95 ± 2.6</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>quinidine</td>
<td>96 ± 3.4</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>montelukast</td>
<td>97 ± 2.2</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>1-O-b-glucuronide</td>
<td>99 ± 1.5</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>N-benzylnirvanol</td>
<td>92 ± 3.2</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>sulfaphenazole</td>
<td>86 ± 2.5</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>troleandomycin</td>
<td>30 ± 3.7</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>ketoconazole</td>
<td>9.5 ± 4.1</td>
</tr>
</tbody>
</table>
Characterizing Major CYPs with Recombinant Systems (Parent Depletion)

- Recombinant data must be scaled (e.g. intersystem extrapolation factors) to predict \textit{in vivo} clearance
- These data may be used to predict $\text{CL}_{\text{int}}$ and $f_{m,CYP}$

### CYP3A4

- $y = -0.0109x + 0.8427$

### CYP2C9

- $y = -0.0071x + 0.1528$

<table>
<thead>
<tr>
<th></th>
<th>$k$ (1/min)</th>
<th>$V$ (mL)</th>
<th>$S$ (pmol)</th>
<th>$\text{CL}_{\text{int}}$ (µL/min/pmol)</th>
<th>Abundance (pmol/mg)</th>
<th>ISEF (Cypex HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>0.0109</td>
<td>0.05</td>
<td>2.5</td>
<td>0.2174</td>
<td>137</td>
<td>0.25</td>
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<tr>
<td>CYP2C9</td>
<td>0.0071</td>
<td>0.05</td>
<td>1.25</td>
<td>0.2822</td>
<td>73</td>
<td>0.09</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>$\text{CL}_{\text{int}}$ (µL/min/mg)</th>
<th>ISEF $\text{CL}_{\text{int}}$ (µL/min/mg)</th>
<th>$\text{CL}_{\text{int}}$ (L/h)</th>
<th>ISEF $\text{CL}_{\text{int}}$ (L/h)</th>
<th>$f_{m,CYP}$</th>
<th>ISEF $f_{m,CYP}$</th>
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<tbody>
<tr>
<td>CYP3A4</td>
<td>29.79</td>
<td>7.45</td>
<td>35.21</td>
<td>8.80</td>
<td>0.59</td>
<td>0.80</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>20.60</td>
<td>1.85</td>
<td>24.35</td>
<td>2.19</td>
<td>0.41</td>
<td>0.20</td>
</tr>
<tr>
<td>Total</td>
<td>50.39</td>
<td>9.30</td>
<td>59.56</td>
<td>10.99</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
ISEF Scaling of Recombinant Data

- Recombinant systems express a single drug metabolizing enzyme in
  - Baculovirus-insect cells (BD Supersomes™)
  - Yeast
  - E. coli
  - Mammalian cells
- Accessory proteins (OR, b5), and CYPs, are generally “over-expressed” relative to HLM, producing higher activity in rCYP systems vs. the same CYP in HLM
- ISEF accounts for differences in CYP (and cofactor) abundance in rCYP vs. HLM

\[
ISEF = \frac{V_{\text{max or CL (probe: HLM pool)}}}{V_{\text{max or CL (probe: rCYP)}} \times \text{CYP abundance in HLM pool}}
\]

- ISEF should be consistent across all probe substrates for given CYP
- ISEF allows for population variability to be brought into the model (ethnicity, age or disease state) by providing link to population specific CYP abundance
Qualification of ISEF Method

- The ISEF method allows for quantitative extrapolation of HLM intrinsic clearance from rCYP phenotyping data
- Validation of ISEFs was conducted using 10 marketed drugs by comparing the extrapolated data with published data
- The enzyme kinetics ($K_m$ and $V_{max}$) of selected probe substrates for CYPs 1A2, 2C9, 2D6, and 3A4 were determined in HLM and rP450s
- When enzyme kinetics of metabolite formation for CYPs 1A2, 2C9, 2D6, and 3A4 were used, the ISEFs determined were generally within 2-fold of that determined on the basis of substrate depletion
- Optimally, ISEF values should be determined concurrently with candidate drug, but ISEF values for many systems are available

Chen et al. DMD 2011
Hepatic and intestinal $\text{CL}_{\text{int}}$ decrease over time as a function of inhibitory parent accumulation and inhibitory metabolite formation.

Time-dependent and dose-dependent impact of metabolite captured by PBPK.
Impact of Metabolite on MDZ DDI (perpetrator)

- Parent inhibitor dosed QD for 14 days; MDZ single dose on Day 7
- 10 trials (n=10); age 20-50; 50% female; healthy volunteers
- Formation of inhibitory metabolite exacerbates the observed CYP3A4 DDI

### Geometric Mean (%CV) DDI

<table>
<thead>
<tr>
<th></th>
<th>Parent Only</th>
<th>Parent &amp; Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$C_{\text{max}}$ Ratio</strong></td>
<td>1.9 (17)</td>
<td>2.2 (19)</td>
</tr>
<tr>
<td><strong>AUC$_{0-\text{inf}}$ Ratio</strong></td>
<td>2.8 (26)</td>
<td>3.8 (37)</td>
</tr>
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Impact of Metabolite on RIF DDI (victim)

- Rifampin dosed 600mg QD for 7 days followed by 7 days concurrent administration with 200mg QD test drug
- 10 trials (n=10); age 20-50; 50% female; healthy volunteers
- Formation of inhibitory metabolite overcomes rifampin induction of CYP3A4

### Geometric Mean (%CV)

<table>
<thead>
<tr>
<th></th>
<th>Parent Only</th>
<th>Parent &amp; Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/mL)</td>
<td>2.5 (55)</td>
<td>4.9 (54)</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (h*mg/mL)</td>
<td>50 (60)</td>
<td>111 (56)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>4.0 (68)</td>
<td>1.8 (67)</td>
</tr>
</tbody>
</table>
Impact of Metabolite on CLA DDI (victim)

- Clarithromycin dosed 500mg BID for 7 days followed by 7 days concurrent administration with 200mg QD test drug
- 10 trials (n=10); age 20-50; 50% female; healthy volunteers
- Metabolite contribution to DDI was minimal due to potent CLA inhibition of CYP3A4

<table>
<thead>
<tr>
<th></th>
<th>Parent Only</th>
<th>Parent &amp; Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/mL)</td>
<td>6.8 (45)</td>
<td>7.0 (45)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (h*mg/mL)</td>
<td>162 (45)</td>
<td>167 (45)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>1.2 (42)</td>
<td>1.2 (43)</td>
</tr>
</tbody>
</table>
Case Example Summary

• **Midazolam DDI (perpetrator)**
  o failure to account for the contribution of metabolite lead to an under-prediction of the DDI potential

• **Rifampin DDI (victim)**
  o when metabolite contribution was accounted for there was a marked reduction in the predicted DDI potential – almost no apparent DDI at steady-state

• **Clarithromycin DDI (victim)**
  o the impact of the metabolite was reduced as a result of the potent synergistic inhibition achieved already by parent compound and clarithromycin

<table>
<thead>
<tr>
<th>DDI</th>
<th>Classification</th>
<th>Apparent Metabolite Impact on DDI</th>
<th>Apparent Change in CYP3A4 CL_int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Perpetrator</td>
<td>Increased inhibition</td>
<td>decreased</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Victim</td>
<td>Reduced induction</td>
<td>No change</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Victim</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>
Conclusions

• While PBPK is **not likely to provide an early warning** of metabolite role in DDI *in vivo*, PBPK is very useful in describing the mechanisms responsible for observed *in vitro-in vivo* disconnects

• Careful design of *in vitro* and early clinical studies will allow for development of a **mechanistic, and useful**, metabolite PBPK model

• **Once developed, a PBPK model, which describes both parent and metabolite kinetics, can be a powerful tool in predicting DDI risk; to support regulatory interactions and ultimately label wording**