Biomarkers of CYP3A activity: What have we learned and are we ready to utilize biomarkers to replace clinical DDI studies?

Perspectives and case examples from industry

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Compound A

Complex *in vitro* DDI properties: CYP3A4 substrate, mixed time-dependent inhibition, reversible inhibition and induction of CYP3A

**Question:** What is the net effect of parent + metabolites on midazolam exposure at steady-state in patients?
An integrated PBPK approach

**Model development**

<table>
<thead>
<tr>
<th>Compound A</th>
<th>M1</th>
<th>M2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) In vitro phenotyping; 2) Human ADME; 3) Clinical studies SD and MD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Model performance verification**

- DDI studies with SD of **Compound A** + MD of CYP3A4 modulators
- Midazolam DDI study after 4 daily doses of **Compound A**

**Model simulations**

- The effect of **Compound A** and metabolites on midazolam exposure at steady-state
  - 4βHC data up to 28 days (n=10)

**Confirmation**
Assessment of net effect

Simulated PK profiles

Time course of plasma 4βHC

<table>
<thead>
<tr>
<th>Time [Days]</th>
<th>3</th>
<th>8</th>
<th>15</th>
<th>22</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted midazolam AUC GMR</td>
<td>0.84</td>
<td>0.60</td>
<td>0.55</td>
<td>0.54</td>
<td>0.54</td>
</tr>
<tr>
<td>Median Plasma 4βHC ratio relative to baseline (n=10)</td>
<td>1.2</td>
<td>1.4</td>
<td>1.8</td>
<td>1.9</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Best case = weak induction (FDA, 2012)

Worst case = moderate induction (Mangold et al 2016)

Limitation of 4βHC to differentiate weak and moderate induction given the complexity of TDI/induction by parent + metabolites
Compound A conclusions

• PBPK model predicted a weak induction of CYP3A (best case scenario).

• Inducer classification based on model predicted 4βHC changes classified Compound A as moderate CYP3A inducer (worst case scenario).

• An integrated approach increased our confidence in DDI predictions.
Compound B: available data

• *In vitro* studies
  – CYP3A4-mediated metabolism
  – Weak CYP3A4 inducer

• Clinical PK and DDI studies
  – Study with itraconazole: fmCYP3A4 of ~0.8
  – Long t$_{1/2}$ (~160 hr); 28 days to steady-state
  – Plasma 4βHC levels (multiple ascending dosing, 90 days)

**Question:** Is it possible to determine the CYP3A4 induction potential clinically using 4βHC data from FIH study?
**Method**

**Application of plasma 4\(\beta\)HC data**

A dynamic model (Yang et al., 2010)

- Bottom-up approach using in vitro EC\(_{50}\) predicted midazolam AUC GMR of 1
- Top-down approach used to calculate optimized EC\(_{50}\) (~13-fold reduction)

**PBPK model**

Optimized PBPK model predicted that **Compound B** would result in midazolam AUC GMR of 0.66 (weak)

<table>
<thead>
<tr>
<th>Days</th>
<th>Regulatory CYP3A inducer classification based on model-predicted 4(\beta)HC increase (MDZ AUC GMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mechanism–based PK/PD (Leil et al., 2014)</td>
</tr>
<tr>
<td>90</td>
<td>Moderate</td>
</tr>
<tr>
<td>14</td>
<td>Weak (0.62)</td>
</tr>
</tbody>
</table>
Compound B conclusions

• PBPK model predicted MDZ AUC ratio of 0.66 (weak)
• The prediction was confirmed by biomarker data quantitatively.
• Compound B advanced to POC testing without the need of midazolam DDI study.
• Is it important to measure 4βHC levels at late time point (after 2-week) for compounds with long $t_{1/2}$ to capture PK steady state of perpetrator as well as 4βHC?
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