Evaluation of New Chemical Entities as Victims of Metabolic Drug Drug Interactions

Presented by Tonika Bohnert on Behalf of IQ DDI Victim Working Group
IQ Annual Symposium
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Victim(Affected Drug) DDI : The Issue

Victim DDI Risk Assessment is Critical for:
- Early clinical risk assessment to guide *Safe* First in Human
- Certain exclusion criteria (DDI/Polymorphism)

**Ensure Patient safety** → drug development, registration, and post-marketing phases

Definitive studies not commonly done till POC/Ph2

*Currently no recommended integrated strategy for victim DDI risk assessment in the clinic*

FIH: First in Human; POC: Proof of Concept
Collaboration of 21 IQ companies to: Integrate existing best industry practices of use of in vitro methods, in vivo preclinical studies, modeling and simulation, to recommend strategy to evaluate NCEs to be *victim of metabolic DDIs* in the clinic → To be published as White Paper (Q4 2014)
Three Critical Areas of Focus of WG

De-risking Victim Drug DDI potential

- $f_{\text{CL}}$
  - How best to estimate contribution of metabolism vs renal/biliary excretion to NCE CL
  - Perspective & Recommendations

- $f_{\text{m}}$
  - Guidelines to estimate fractional contribution of CYPs & non-CYPs towards NCE metabolism
  - Current status & future needs

- Modelling & Simulation (M&S)
  - Key input information for victim drug DDI prediction
  - Recommend M&S strategy to influence decision-making at different stages of drug development

WG: Working Group; CL: Clearance; NCE: New Chemical Entity
\( f_{\text{CL}} \) and \( f_m \)

\( f_{\text{CL}} \): Fraction of drug *cleared by a pathway*: Route of Clearance

\[
f_{\text{CL,metabolism}} + f_{\text{CL,renal}} + f_{\text{CL,biliary}} = 1
\]

\( f_m \): Fraction of drug *metabolized* by an enzyme (i.e. \( f_m, \text{CYP3A4} \))

Potential severe ramifications when \( f_m \times f_{\text{CL,metabolism}} > 0.5 \)

\( f_m \) and \( f_{\text{CL}} \) assessments commonly not done till Ph2

*With Competitive inhibitor with [I]/Ki of 15* (Ref: Rowland Matin equn)
Approaches to Estimate $f_{CL}$
Understanding role of metabolism in humans is critical to making an accurate prediction of victim DDI potential
**$f_{CL}$ Determination in Humans**

- Clinical DDI study with CYP-selective (or appropriate DME) inhibitor

\[
f_{m,CYP} \approx f_{i,CYP} = 1 - \frac{AUC_{control}}{AUC_{inhibited}}
\]

- assumes complete inhibition of the CYP enzyme
- for CYP3A4, assumes $F_g^{inhibited} = F_g^{control}$

- Radiolabeled human ADME study

- $f_{CL,metabolism}, f_{CL, renal}$ quantitatively determined
- Elimination pathways defined (in excreta), e.g. metabolic, parent drug secretion, etc.

*Caveats: unstable metabolites in excreta (e.g. glucuronides converted back to parent in feces), non-absorbed parent drug vs. secreted parent, estimations of enzyme involved in the primary reaction(s) when secondary/tertiary metabolites formed*

$F_G$: Fraction escaping gut metabolism
The sequence, timing, & nature of a common set of in vitro & in vivo studies that companies routinely rely on, to estimate \( f_{\text{CL,metabolism}} \) in humans depends on case by case approach.

In absence of definitive \( f_{\text{CL}} \) data in humans, thoroughly assess available information of NCE (BCS class, confidence in human IVIVE based on animal IVIVE, \( f_{\text{CL,metabolism}} \) vs \( f_{\text{CL,renal/biliary}} \) in animals, in vitro human transporter data) before risk assessment based on worst case scenario (assume \( f_{\text{CL,metabolism}} = 1 \)).
Estimating $f_m$ In Vitro
Estimation of $f_m$

- Identify which metabolizing enzyme(s) involved
- Estimate “What is Fraction” metabolized by DME: $f_m$

Structure of NCE and Metabolite Profiling generally gives good idea of what to look for:
- Oxidative vs Direct Conjugation vs other metabolic pathways
- NADPH-dependent or not

When contribution by a metabolizing enzyme is $\geq 25\%$ then determine $f_m$
**fm Determination - Recommended Guidelines**

- Identification of DME and fm estimation in NCE metabolism most sensitive when monitoring major metabolite(s) formed

- Quantitative metabolite assessment best done with 14C-NCE. When not available, ‘relative’ assessments can be made utilizing UV or LC/MS/MS

- When NCE has multiple metabolites, or 14C NCE &/or metabolite standards not available, monitoring NCE disappearance has yielded reasonable success (*caveat: parent needs to be moderate to high CL*)

- Common approaches for fm estimation: RAF/ISEF, selective enzyme inhibition (monitoring inhibitor cross-reactivity)

NCE: New Chemical Entity; DME: Drug Metabolizing Enzyme
### f_m - Current Status: Quantitative or Qualitative?

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Tools available for RAF or ISEF</th>
<th>fm (from in vitro studies)</th>
<th>Clinical Victim DDI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recombinant Enzyme</td>
<td>Probe substrates</td>
<td>Tissue abundance</td>
</tr>
<tr>
<td>CYP</td>
<td>Yes (various)</td>
<td>Yes^a</td>
<td>Yes^a</td>
</tr>
<tr>
<td>FMO</td>
<td>Yes (1, 3, 5)</td>
<td>Yes^b</td>
<td>Yes^c</td>
</tr>
<tr>
<td>AO/XO</td>
<td>Emerging^d</td>
<td>Yes</td>
<td>Emerging^d</td>
</tr>
<tr>
<td>MAO</td>
<td>Yes (A &amp; B)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>UGT</td>
<td>Yes (Various)</td>
<td>Yes^e</td>
<td>Emerging^f</td>
</tr>
<tr>
<td>SULT</td>
<td>Yes (Various)</td>
<td>Yes^h</td>
<td>Emerging^h</td>
</tr>
<tr>
<td>NAT</td>
<td>Yes (1 &amp; 2)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>GST</td>
<td>Yes (Various)</td>
<td>No</td>
<td>Yes^l</td>
</tr>
<tr>
<td>CES</td>
<td>Yes (1 &amp; 2)</td>
<td>Yes^j</td>
<td>No</td>
</tr>
</tbody>
</table>

- **a**: For major isoforms
- **b**: Non-isoform selective
- **c**: mRNA-based abundance reported
- **d**: In liver
- **e**: For e.g. 1A1, 1A4, 1A6, 1A9, 2B7
- **f**: For e.g. 1A1, 1A3, 1A4, 1A5, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, 2B17- liver, intestine, & kidney
- **g**: For some isoforms – e.g. 1A1, 1A4, 1A6, 1A9, 2B7
- **h**: For e.g. 1A1, 1A3/4, 1B1, 1E1, 2A1- Liver, intestine, kidney, lung (relative abundance)
- **i**: Limited reports
- **j**: Limited e.g GSTA1, A2, M1, M2, M3 and P1
- **k**: UV & fluorescent probe metabolic pathways

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**High**: Several Reported
**Moderate**: Few/Occasional Reported
**Low**: None Reported
Perspectives of $f_m$ Approaches

Areas we feel confident in:
- Identification of DMEs involved
- $f_{m,CYP}$, $f_{m,UGT}$ (select)
- Contribution of CYP vs other oxidative DMEs when pathways overlap
- Contribution of Conjugative DMEs
  - semi-quantitative (cold NCE) or quantitative (radiolabeled NCE) metabolite profiling in vitro human matrices &/or Ph1 studies

Areas we are gaining confidence in:
- $f_m$ non-CYP enzymes
  - The “CYP” journey has helped demonstrate what we need- scaling of non-CYPs emerging
  - Scaling of CYPs & non-CYPs in extrahepatic tissues
  - $f_m$ of low CL compounds

When quantitative $f_m$ of a DME is not available, thoroughly assess known risk → incidence & magnitude of clinical DDI reported via that DME, before best/worst case scenario assumptions (e.g. $f_m \geq 0.5$)

DME: Drug Metabolizing Enzyme; NCE: New Chemical Entity
Modeling & Simulation in Victim Drug DDI Predictions
## Models & Data Required Depends on Timing & Objective

<table>
<thead>
<tr>
<th>Common Models Used</th>
<th>Study/Data</th>
<th>Question to address/stage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple Static</strong></td>
<td>In vitro human metabolism study – met ID and profile</td>
<td>Involvement of metabolic CL and CYP enzyme</td>
</tr>
<tr>
<td><strong>Mechanistic Static</strong></td>
<td>Reaction phenotyping</td>
<td>Contribution of CYP in metabolic CL ($f_m$)</td>
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<tr>
<td><strong>Mechanistic Dynamic</strong></td>
<td>In silico &amp; in vitro (logP, pKa, $f_{u,p}$, B/P, $P_{app}$, $CL_{int}$ etc.)</td>
<td>Human PK ($f_a$, $k_a$, $V_{ss}$, CL) prediction</td>
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<tr>
<td></td>
<td>Preclinical mass balance study</td>
<td>Route(s) of CL</td>
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<tr>
<td></td>
<td>Clinical PK (oral)</td>
<td>Refine model and guide clinical DDI study design</td>
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<tr>
<td></td>
<td>Clinical PK (IV), human mass balance study</td>
<td>Disposition in human, estimate $f_{m\text{CYP}}$, $F_G$, $f_a$, $F_{oral}$, biliary or renal CL</td>
</tr>
<tr>
<td></td>
<td>Clinical DDI w/ strong inhibitor</td>
<td>confirm in vivo $f_{m\text{CYP}}$, predict other DDIs</td>
</tr>
</tbody>
</table>

- **Late / Discovery / Pre-FIH**
- **Clinical**
M&S Recommendations

Select a fit-for-purpose model, based on specific application and stage of drug discovery/development

Utilize sensitivity analysis to help identify uncertainty & its impact on DDI risk assessment thoroughly

• Recommend additional key experimental data
• Common parameters for sensitivity analysis: $f_{m\text{CYP}}, f_{u,gut}/F_g$

Consider other factors when leveraging DDI predictions for decision-making and clinical study plan (i.e. safety margin of victim drugs, co-meds, special populations & dose regimens)

Modelling is only as good as data provided so use caution with parameters & approximations to avoid poor & misleading outcomes
**Integrated Strategy of Victim DDI Assessment**

*Majority of NCEs have the potential to be a victim of some DDI since they all have to be cleared by some pathway*

Victim DDI risk assessment should be made at all stages with focus on $f_{CL}$, $f_m$, M&S

- Make best estimate of $f_{CL,\text{metabolism/renal/(biliary)}}$ (preclinical in vivo & IVIVE) & $f_m$ (in vitro)
- Integrate all data via M&S for worst case scenario with assumption that all metabolism by major enzyme(s) identified in vitro
  - Informs whether clinical exclusion required (DDI/polymorphism) in FIH
  - Guides Safe Starting Dose for Victim DDI Study in Clinic

- Learn any additional information to refine DDI predictions from FIH studies
- Determine $f_{CL,\text{metabolism/renal/(biliary)}} \to ^{14}$C-Human ADME study
- Determine $f_m \to$ Clinical Victim DDI Study
- Refine DDI model to predict additional DDIs
- Support dose selection, labelling, justification of delay/waiver of clinical DDI studies