A Clinical Reviewer’s Perspective on CIVM For Drug Development

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Disclaimer and Disclosures

• The views and opinions in this presentation are my own and do not represent guidance or recommendations from the FDA.

• I have no disclosures, financial or otherwise, pertinent to this talk.
Outline

• Introduce the DILI Team
• Why non-clinical information matters to our team
• How we use non-clinical information now
The DILI Team Workspace
Interdisciplinary Division of Hepatology and Nutrition DILI Team

Office of Surveillance and Epidemiology

Pre-market Post-market
The DILI Team

DILI Team
- Paul H. Hayashi, MD, MPH
  - Team Lead
- Eileen Navarro, MD
  - Team Lead
- Ling Lan, MD, PhD
  - Clinical analyst
- Edwige Chiogo-Vouffo, PharmD, PhD
  - Non-clinical analyst

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Minjun Chen, PhD
National Center for Toxicological Research (NCTR)

Frederick Moulin, PhD, DVM
Office of New Drugs
Division of Pharmacology
Workload for DILI Team through first quarter 2023

- NDA + BLA
- IND
- Other
- AC
- Total (not including ACs)
Overview

NON-CLINICAL (IN VITRO & ANIMAL STUDIES)

CLINICAL TRIALS

APPROVAL PROCESS

POST-MARKET ASSESSMENTS
Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH)

“Finding one Hy’s Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population.”

FDA Guidance for Industry: DILI (2009)
Causality Scores: Body of Evidence

<table>
<thead>
<tr>
<th>Causality score</th>
<th>Likelihood (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = definite</td>
<td>&gt;95</td>
<td>Liver injury is typical for the drug or herbal product ('signature' or pattern of injury, timing of onset, recovery). The evidence for causality is 'beyond a reasonable doubt'</td>
</tr>
<tr>
<td>2 = highly likely</td>
<td>75–95</td>
<td>The evidence for causality is 'clear and convincing' but not definite</td>
</tr>
<tr>
<td>3 = probable</td>
<td>50–74</td>
<td>The causality is supported by 'the preponderance of evidence' as implicating the drug but the evidence cannot be considered definite or highly likely</td>
</tr>
<tr>
<td>4 = possible</td>
<td>25–49</td>
<td>The causality is not supported by 'the preponderance of evidence'; however, one cannot definitively exclude the possibility</td>
</tr>
<tr>
<td>5 = unlikely</td>
<td>&lt;25</td>
<td>The evidence for causality is 'highly unlikely' based upon the available information</td>
</tr>
<tr>
<td>6 = insufficient data</td>
<td>Not applicable</td>
<td>Key elements of the drug exposure history, initial presentation, alternative diagnoses and/or diagnostic evaluation prevent one from determining a causality score</td>
</tr>
</tbody>
</table>

Diagnosis of DILI in clinical practice versus pre-market development

- Timing
- Pattern of Injury
- Exclusion of other causes
- Pre-event Risk of DILI

Expert opinion: Causality Score
How we use pre-test probability?

- **Pre-event likelihood**
  - High (amoxicillin-clavulanate)
  - Low (amlodipine)

- **Post-event data**
  - Timing
  - Pattern of injury
  - Exclusion of other causes

- **Predictive value of data**
  - High
  - Low

- **Highly likely amoxicillin clavulanate DILI**
- **Possible or unlikely DILI**
Can we use CIVM to inform pre-test probability?

Pre-event likelihood

Non-clinical/CIVM data

Post-event data

Timing

Pattern of injury

Exclusion of other causes

Predictive value of data

High

Low

+ -
Diagnosis of DILI in clinical practice versus pre-market development
Our Consults

Consultation Sections:
Section 1.0 Target Disease and Rationale
Section 2.0 ADME and DDI pertinent to DILI risk
Section 3.0 Non-clinical data pertinent to DILI
Section 4.0 Clinical data
Section 5.0 Assessment & Recommendations

3.0 Non-clinical Data

3.1 In vitro data:

3.2 Animal / Toxicology data

3.3 Summary of Non-clinical data

High level summary of non-clinical findings related to DILI risk is in Table 3.

Table 3: Summary of non-clinical data pertaining to DILI risk

<table>
<thead>
<tr>
<th>Item</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major CYPs or UGTs</td>
<td></td>
</tr>
<tr>
<td>Reactive metabolites (i.e., glutathione trapping)</td>
<td></td>
</tr>
<tr>
<td>Mitochondria studies/inhibition</td>
<td></td>
</tr>
<tr>
<td>Time dependent inhibition</td>
<td></td>
</tr>
<tr>
<td>LogP (lipophilicity) values &gt;3 associated with increased DILI risk</td>
<td></td>
</tr>
<tr>
<td>Covalent binding</td>
<td></td>
</tr>
<tr>
<td>Transporter (BSEP or MRP2 inhibition)</td>
<td></td>
</tr>
<tr>
<td>Elevation in liver analytes (e.g., ALT, AP, TB)</td>
<td>Animal Studies</td>
</tr>
<tr>
<td>Liver histopathology findings (animal species)</td>
<td></td>
</tr>
</tbody>
</table>
A Model to Predict Severity of Drug-Induced Liver Injury in Humans

Minjun Chen, Jürgen Borlak, and Weida Tong

National Center for Toxicological Research (NCTR)

Predictors: Drug properties

- Daily drug dose
- Lipophilicity
- Reactive metabolites

Outcome: DILI risk based on labeling

- Most concern
  - Withdrawn
  - Box warning
  - W/P: Risk of severe liver injury
- Less concern
  - Less than severe liver injury risk
- No concern
  - No mention of liver injury risk

DILI score = 0.608*\log(\text{daily dose/mg}) + 0.227*\log P + 2.833*(\text{RM formation})
DILI Score Performance

Dose-based DILI Score

Most Less No

DILI risk category by labeling

High risk
Moderate risk
Low risk

P < 0.001

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>In clinical trials</td>
<td>In clinical trials</td>
<td>In clinical trials</td>
</tr>
<tr>
<td>Target disease/Indication</td>
<td>Disease X</td>
<td>Disease Z</td>
<td>Disease X</td>
</tr>
<tr>
<td>Daily dose (mg/day)</td>
<td>150</td>
<td>200</td>
<td>150</td>
</tr>
<tr>
<td>LogP (lipophilicity)</td>
<td>3.8</td>
<td>2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Reactive metabolite &amp; Time dependent inhibition of CYP</td>
<td>(+) time-dependent inhibitor of CYP3A4/5</td>
<td>(-) time dependent inhibition</td>
<td>(+) time dependent inhibition of CYP2C8 and CYP2C9</td>
</tr>
<tr>
<td>Metabolite covalent-binding or glutathione trapping</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>DILI score</td>
<td>6.54 (RM = yes)</td>
<td>3.17 (RM = no)</td>
<td>6.75 (RM = yes)</td>
</tr>
</tbody>
</table>
Summary

- CIVM data could directly or indirectly inform clinical diagnoses of DILI pre- and post-market.
- The DILI Team is supportive of CIVM development.
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