Clinical liver safety assessment: update on best practices workshop Nov 9, 2012, Boston

FDA/C-Path Conference on Drug-Induced Liver Injury, March 21, 2013
Michael Merz, Novartis Institutes for BioMedical Research
Outline

- Background, objectives, deliverables
- Key topics and agenda
- Attendees
- Consensus points
- Status white paper, next steps
Background

- Only two regulatory guidances on Drug-Induced Liver Injury available (FDA, HC), focusing on clinical safety assessment and risk management
- Neither of these does address some important questions e.g.
  - Assessment of liver safety signals in special populations, e.g. oncology or hepatitis patients
  - Appropriate methods for causality assessment

Objective:

- Seek consensus among clinicians, regulators, academic experts, and industry representatives on what may be considered current best practices in terms of detecting, analyzing, and interpreting liver safety signals in clinical drug development.
- Initiate alignment of liver safety assessment and management across ICH regions.

Deliverable

- White paper describing best practices that might finally serve as an entry point for a formal ICH procedure on harmonization of liver safety assessment.
Key topics and agenda

Key focus areas:
- Causality assessment
- Data elements and data standards
- Methodology of liver safety assessment
- Considerations for special populations

Introductions, opening statements and presentations

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction, expectations towards liver safety best practices</td>
<td>Paul Watkins, Hamner IDSS</td>
</tr>
<tr>
<td></td>
<td>Michael Merz, Novartis</td>
</tr>
<tr>
<td>FDA’s approach to liver safety assessment: current status and</td>
<td>John Senior, FDA</td>
</tr>
<tr>
<td>challenges</td>
<td>Mark Avigan, FDA</td>
</tr>
<tr>
<td>Comments from the FDA Guidance on DILI</td>
<td>Arie Regev, Eli Lilly</td>
</tr>
<tr>
<td>Liver injury causality assessment: US and European perspectives</td>
<td>Leonard Searf, FDA</td>
</tr>
<tr>
<td></td>
<td>Guru Aimthal, Nottingham U</td>
</tr>
<tr>
<td>Linking phenotypes to biosamples: biobanking issues</td>
<td>Paul Watkins, Hamner IDSS</td>
</tr>
<tr>
<td>Introduction to breakout groups</td>
<td>Michael Merz, Novartis</td>
</tr>
</tbody>
</table>

Coffee break

Parallel breakout sessions

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data elements essential to assess clinical liver safety, data</td>
<td>Paul Watkins, Hamner IDSS</td>
</tr>
<tr>
<td>standards, data acquisition</td>
<td>Michael Merz, Novartis</td>
</tr>
<tr>
<td>Methodology to manage liver safety data (eDiSH, others)</td>
<td>Paul Watkins, Hamner IDSS</td>
</tr>
<tr>
<td>Methodology to assess liver safety from data with special</td>
<td>Paul Watkins, Hamner IDSS</td>
</tr>
<tr>
<td>considerations (cancer, hepatitis trials)</td>
<td>Michael Merz, Novartis</td>
</tr>
<tr>
<td>Chairs: Neil Kaplowitz, UCSF</td>
<td></td>
</tr>
<tr>
<td>Chairs: Einar Ejörnsson, Reykjavik U</td>
<td></td>
</tr>
<tr>
<td>Chairs: Paul Watkins, Hamner IDSS</td>
<td></td>
</tr>
<tr>
<td>Chairs: Dominique Larrey, Montpellier U</td>
<td></td>
</tr>
</tbody>
</table>

Lunch break

Report from breakouts, discussion, next steps                          | All                                               |
| Closing remarks                                                      | Paul Watkins, Hamner IDSS                         |
|                                                                      | Michael Merz, Novartis                            |

Chair: Paul Watkins, Hamner IDSS
Workshop attendees

Academia, 16 (30.8%)

Regulators, 9 (17.3%)

Industry, 27 (51.9%)

Academia:
- Thierry POYNARD, Pitié-Salpêtrière Hospital - AP-HP Paris
- Hugo Perazzo, Pitié-Salpêtrie
- Herbert L. Bonkovsky, Carolinas Med
- James H. Lewis, Georgetown U
- Paul Watkins, Hamner/UNC
- Cheng-wei Chen, Shanghai No.
- Yimin Mao, Shanghai Renj
- Hajime Takikawa, Teikyo Univers
- Raul J. Andrade, University of N
- Dominique Larrey, St Eloi Hospit:
- Guruprasad Padur Aithal, University of N
- Einar S. Bjornsson, The National L
- Jack Utrecht, University of T:
- Neil Kaplowitz, University of C
- Willis Maddrey, University of T
- Gerd Kullak-Ublick, University of Z

Regulators:
- Beatriz da Silva Lima, University of Li
- Elmer Schabel, BfArM, Gemna
- John R. Senior, FDA
- Charles Cooper, FDA
- Mark Avigan, FDA
- Leonard B. Seeff, FDA
- Gordon James Gallivan, Health Canada
- Yoshiro Saito, National Institute of Health Sciences, Japan
- Keiko Maekawa, National Institute of Health Sciences, Japan

Industry:
- Holly Read
- Abbott Laboratories
- eneca
- Ingelheim Pharmaceuticals, Inc
- Ingelheim Pharmaceuticals, Inc & Co.
- mthKline
- mthKline
- cck LLC
- um Pharmaceuticals

MD Organization
- Michele Bortolini
- Hoffmann-La Roche
- UCB BioSciences, Inc.

Best Practice discussions - M Merz - March 21, 2013 - FDA DILI conference
Causality assessment (though not a breakout session)

Topic leads: Arie Regev, Eli Lilly; Leonard Seeff, FDA; Guru Aithal, Nottingham U

(Some) discussion points:

- Structured classification
  - Three vs five categories

- Standardized instruments
  - RUCAM: still useful?
  - What modifications may be required?
  - Do we need an entirely new instrument?

- What about Bayesian methods?
  - Drug specific vs generic

- How reliable are “drug signatures”?

- How to identify autoimmune hepatitis unmasked by drugs?

- How to include and assess alcohol consumption?
(Some) discussion points:

Data elements:
- Definition of DILI phenotype
  - ALT 5 x vs ALT 3 x ULN; different definitions by population, e.g. oncology patients?
- Baseline definition: two measurements?
- Use fold ULN, fold baseline, or IU for liver test assessment?
- Inclusion of data from local labs
- Liver test monitoring intervals: recommendation in FDA guidance sufficient, or do we need a more data driven approach?
- Use of archived samples
- Need to capture alcohol consumption?
- AlkPhos and/or or GGT to assess cholestatic injury?

Data standards:
- CDISC standards
- Need for standardized vocabularies

Data acquisition:
- Standardized liver safety CRF pages: prerequisite to establish a liver safety data warehouse?
- Standardized liver safety questionnaire to guide investigators and ensure proper data collection
Methodology to assess/manage liver safety data

Chairs: Paul Watkins, Hamner IDSS; Michael Merz, Novartis

(Some) discussion points:

- **Tabular summaries**
  - Incidence tables
  - Shift tables
  - Descriptive statistics

- **Graphics**
  - Which graphs are useful?
  - What is the most efficient workflow?
  - Include R ratio into assessment?

- **Statistical approaches**
  - Outlier detection
  - Modeling approaches
    - PK/PD models to assess exposure response relationship?
    - Are PBPK models useful/required to estimate liver exposure?
    - In silico models
(Some) discussion points:

- Which populations deserve special attention?
  - Heart failure?

- Inclusion criteria
  - <10 x ULN?
  - ULN vs multiples of individual baseline

- Stopping rules
  - >20 x ULN?
  - ULN vs multiples of individual baseline

- Causality assessment:
  - Factor in changes in viral load?

- How take into account standard of care effects?
Some consensus (?) points

- **Causality assessment:**
  - There is currently no suitable causality assessment instrument available for DILI in clinical development.
  - Expert assessment cannot generally be performed in real time.
  - A clinical trial specific tool may have to be developed; may have to be modified to development stage.

- **Data elements and data standards**
  - Need to systematically train investigators on proper data collection for DILI cases.
  - Need for using standard nomenclature, defining phenotype and practices to characterize severity/course.
  - Need to standardize data capture and handling, using agreed-upon CRF pages and questionnaires.

- **Methodology:**
  - A graphical workflow using a set of standard graph templates including the FDA’s eDISH plot and Kaplan-Meier plots is adding value to tabular summaries and narratives.
  - Statistical approaches should be explored to define appropriate quadrant boundaries for eDISH plots.

- **Special populations:**
  - Critical analysis of available data is required to better define specific inclusion criteria and stopping rules.
  - An appropriate “baseline” value for liver chemistries may be the nadir reached during viral clearance.
  - Pooling liver safety data across a range of different target populations will improve understanding, assessment, and management of DILI in clinical drug development.
White paper status and next steps

- **Status:** subteams currently working on individual chapters
  - **Lead-/co-authors:**
    - Introduction: Paul Watkins, John Senior, Marc Avigan, Michael Merz
    - Causality assessment: Arie Regev, Leonard Seeff, Guru Aithal
    - Data elements: Mark Avigan, Einar Bjoernsson
    - Methodology: Michael Merz, Paul Watkins
    - Special populations: Gerd Kullak-Ublick, Neil Kaplowitz

- **Next steps**
  - Incorporate feedback received as yet and input from conference attendees
  - Submit manuscript to Drug Safety for publication in Supplement Edition
  - Consider involvement of CIOMS/ICH to work towards harmonization process