Referral concerning:

Draft Guidance for Industry:
Drug-induced liver injury: Premarketing Clinical Evaluation
FDA, 25 October 2007 (Docket 2007D-0396)

Rec'd 12/26/07

From: Swedish MPA Staff and consultants, 19 December 2007

Summary of comments of draft guidance document:

This draft is mainly devoted to clinical assessment, thus **not** preclinical assessment, action and documentation on premarketing signs of Drug-Induced Liver Injuries, DILIs.

It is pointed out that drugs which cause elevated AT as well as bilirubin levels or impaired function such as inhibition of synthesis of clotting factor are those at risk to cause severe DILI. It is also stated that drugs with, in retrospect, clear hepatotoxic potential have not shown any signal at all in animal studies, not shown dose-related toxicity and show a very low rate in humans, usually 1/5000-1/10000, all suggesting to reflect host specific factors.

Another problem pointed at is that some drugs do not show any hepatotoxicity by elevation of AT. The frequency of AT elevation of a drug in a population is not predictive either, the degree of elevation and liver function tests may be better predictors. ALT is considered more liver specific, although expressed in other tissues. Increased bilirubin levels is an indicator of severed liver function, especially accompanied with increased AT.

Hy's law is presented as the fundamental rule of thumb when assessing liver specific lab parameters (points summarized):

1. Suspected liver toxic drug shows more frequent 3-fold or greater ULN of ALT or AST than control or placebo.

2. Among these subjects as in 1), if they also show elevation of TBL more than 2xULN, without initial findings of cholestasis.

3. No other explanation, clinical condition, for increased AT and TBL.

One case which fulfills the criteria of Hy's Law in a trial is ominous, two or more cases highly predictive of potential DILI.

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The document further outlines clinical evaluation of DILI, by "General considerations", "Case Report Forms", "Interpretations of Signals of DILI or Acute Liver Failure", and "Analysis of Signals of DILI". Lastly, several illustrative cases of DILI are assembled in the Appendix A.

General comments:

The scope of the guidance document is clincal assessment/evaluation of possible occurence of liver injury and their predictive value for severe DILI. It is a conscientiously and well written document with several practical and useful rules of thumb and suggestions on how to investigate, differentiate, document and act on signs of hepatotoxicity in patients on study drug. It reflects the current thinking in the field of drug-induced liver injury and can be considered the state-of-the art for guidance of the management of DILI.

It is recognized that the discussion on preclinical hepatotoxicity and its relevance to clinical hepatotoxicity lies outside the scope of the draft. However, it would have been interesting with some overview of the preclinical-clinical bridging information related to liver toxicity. Even though it is recognized that preclinical tests do not predict rare drug-induced hepatotoxicity in humans, they sometimes need to be revisited and/or extended when clinical signals occur. We suggest future update and inclusion of any new preclinical information which may be of relevance to the diagnosis or prevention of DILI. (See also European Draft guideline "Detection of early signals of hepatotoxicity from non-clinical data" EMEA/CHMP/SWP/150115/2006).

Please find minor points to consider related to structure and clarifications below.

Specific comment 1:

On p. 2, line 62: Suggested addition: "....gather, *apart from detailed information of treatment with other drug(s)*, additional clinical and laboratory information::"

On p. 2, line 79: Proposed addition: "...thousand subjects were studied. *In addition, often patients with underlying risk factors for liver injury were excluded in the clinical trials".*

Specific comment 2:

The wording on p.5, line 183, could be further clarified:

Current wording:

"As a rule of thumb, based on Zimmerman's original estimate of 10-50 percent mortality associated with hepatocellular injury sufficient to impair the liver bilirubin excretory function, severe DILI can be estimated to occur at a rate of at least one-thenth the rate of so-called Hy's Law cases (Temple 2001)".

Proposed wording:

"As a rule of thumb, since hepatocellular damage causing impaired liver bilirubin excretory function is associated with 10-50% mortality, based on Zimmerman's original estimate, the rate of severe DILI may be at least one tenth of the rate of so-called Hy's Law cases (Temple 2001).

Specific comment 3:

On p.5, line 201. Insert subtitle, e.g. "Major findings" and number the bullet points in bold text (1, 2, 3) on p. 5 and 6.

Specific comment 4:

On page 6, line 234 it is stated: " We are not aware of false positive Hy's Law findings".

The authors should explain what they really mean by this. Do the authors mean that when a patient is found to have ALT≥3 ULN and bilirubin ≥2 ULN that the drug is going to give severe hepatotoxicity or any hepatotoxicity? In the paper by Bjornsson and Olsson in Hepatology 2005, there were a total of 32 cases with erythromycin suspected liver injury (with concomitant jaundice) whereas no cases resulted in death or liver transplantation. Erythromycin has very rarely on its own been associated with a fatal outcome.

Specific comment 5:

On p. 6, line 239: Proposed addition: " The degree of assurance depends on the population exposed for a long enough time, *how discontinuation criteria were set in the clinical trials regarding liver test abnormalities* and on the rate of severe DILI that would be of interest."

Specific comment 6:

On page 10, concerning elevations of aminotransferases (AT) in ischemic hepatitis it is stated that AT >10,000, it is perhaps better to keep on mentioning the multiples of the upper limit normal (e.g. >25xULN).

Specific comment 7:

On p.8, section 5. "Decision to Stop Drug Administration":

The first sentence is suggested to be further clarified to avoid misunderstanding:

Current writing:

"It has been observed that *dechallenge* (stopping drug administration) does not always, or even usually, result in immediate improvement in abnormal lab values."

Proposed writing:

" Stopping drug administration, *dechallenge*, does not always result in immediate improvement in abnormal lab values".

Specific comment 8:

On p 9 & 10, section 6 . "Evaluating Data for Alternative Causes":

Although probably rare outside oncology trials, malignancy should be mentioned, as a possible cause for liver enzyme elevation.

Proposed change p. 10, line 404:
Current wording: "Biliary tract disorders", Proposed wording: *Hepatobiliary disorders.*

Proposed change p.10, line 406:
Current wording: "Malignant interruption of the biliary tract also should be considered."
Proposed wording: "*Malignant infiltration of the liver and biliary tract should also be considered.*"

Specific comment 9:

The possible role of eosinophilia in assessment of the aetiology and severity of DILI could be further clarified somewhere in the draft.

For example, on p. 9, line 374, eosinophilia is mentioned (as a co-finding with other symptoms and AT-elevations) suggestive of discontinuation of study drug. Also, eosinophilia is mentioned on p. 10, line 441, as suggestive of immunological mechanism and if present speaks against rechallenge.

Specific comment 10:

On the top of page 14, line 505, it is mentioned that "several in vitro methods are available to detect and quantify binding for a drug or its metabolites to liver proteins, including radiochemical and immunological methods".

Perhaps it should be acknowledged that unfortunately these methods are very rarely useful in prediction of hepatotoxicity or useful in diagnosing DILI. It would though be of interest to mention in which rare instances this can be of use, such as in treatment with isoniazid, where analysis of acetylation status is potentially useful.

Program

Detecting and Investigating Drug-Induced Liver Injury During Clinical Trials

What should we be doing about uncommon but potentially serious adverse events (e.g., DILI, Stevens-Johnson syndrome, rhabdomyolysis, prolonged QT interval, etc.) found during controlled clinical trials?

A national/international discussion and debate on issues raised by the draft guidance of 25 October 2007 (Docket No. 2007D-0396) toward building consensus among interested parties of the pharmaceutical industry, regulatory bodies, academic investigators and consultants, and public groups or individuals.

The program is being co-sponsored by the Food and Drug Administration/Center for Drug Evaluation and Research (FDA/CDER), the Pharmaceutical Research and Manufacturers of America (PhRMA), and the American Association for the Study of Liver Disease (AASLD).

National Labor College, Silver Spring MD, 26-27 March 2008
10000 New Hampshire Avenue at Powder Mill Road, Silver Spring MD 20903

Wednesday, 26 March

7:30	*Continental Breakfast*	
8:00	Introductions and Brief (5') Opening Statements	Janet Woodcock, FDA/CDER Alan Goldhammer, PhRMA John Vierling, AASLD

Session I: When should an investigational drug be stopped during a trial?

Moderator, Paul Watkins, U NC

8:15	Clinical meaning of elevated aminotransferase activity?	Naga Chalasani, IN U
8:45	Liver test elevations seen in patients on placebo.	Robert Tipping, Merck
9:15	Lessons from isoniazid – would it be approved today?	John Senior, FDA/CDER
9:45	*Break*	
10:15	A simple tool for finding important cases in a clinical trial	Kate Gelperin, FDA/CDER
10:45	Hy's Law explained	Adrian Reuben, MU SC
11:15	Was it the drug, or a disease? How to determine it.	Don Rockey, UT SW
11:45	General discussion	All
12:15	*Lunch*	

Moderator, Paul Seligman, FDA/CDER

Session IIA: Should rechallenge be used to prove the drug caused the reaction?

1:30	Immune-allergic sensitization to a xenobiotic	Jack Uetrecht, U Toronto
2:00	Hierarchy of evidence – how much do we need to know?	Leonard Seeff, NIH
2:30	Balancing the risks and benefits of rechallenge	Christine Hunt, GSK
3:00-3:30	General discussion –speakers and audience	All
	Break	

Session IIB: Can we find a truly predictive biomarker to prevent serious adverse reactions?

4:00	What kind of a biomarker do we need?	Mark Avigan, FDA/CDER
4:30	How might we find one?	Jack Bloom, Lilly
5:00	Role of clinical trials in cracking the nut	Arthur Holden, SAEC*
5:30	General discussion –speakers and audience	All
6:00 – 6:45	*Reception: wine and cheese, mingle and relax ---*	*Serious Adverse Event Consortium
7:30	*Reassemble for dinner: serve soup, salad, main course*	
	Discuss ethical, management, political issues	
	Ethical perspectives	Dave Wendler, NIH
	Industry perspectives	Jay Barth, Merck
	International regulatory perspectives	(to be confirmed)
	Dessert, coffee	

Thursday, 27 March

7:30	*Continental Breakfast*	
Session III:	**Should patients with stable underlying liver disease be incuded?**	
	Moderator, John Pears, AstraZeneca	
8:00	Study the patients who will be treated	Robert Temple, FDA/CDER
8:30	Would this increase the risk of DILI?	William Lee, UT SW
9:00	Case for continuing to exclude them	Arie Regev, Lilly
9:30	General discussion, panelists and audience	
10:00	*Break*	
10:30	Breakout groups I, II, and III Each group to formulate and specify the questions to be asked for consensus building	
12:00	*Lunch*	
1:00	Public statements: Brief 5' statements (arguments, questions, comments) from interested persons, groups	
2:00	Asking the questions and discussion of each 1) What should be the stopping rules for study drug administration? 2) When should rechallenge be done/not done? 3) Should patients with preexisting liver disease be studied? 4) Other questions, issues	
3:00	*Adjourn*	

For details and changes follow information posted at website: www.fda.gov/cder/livertox
Registration by AASLD: $350 for industry; $175 for government or academia
Lodging reservations on your own at NLC or in Silver Spring