



Date: December 12, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2007D-0396
Response to FDA Call for Comments
Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical
Evaluation

Dear Sir or Madam:

Reference is made to the October 25, 2007 Federal Register notice announcing the request for comments on Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation.

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Cathie Schumaker, Executive Director- US Regulatory Policy & Intelligence, at 301-770-4479.

Sincerely,

A handwritten signature in cursive script that reads "Donna Dea". To the right of the signature is a large, stylized checkmark or flourish.

Donna Dea
VP, Regulatory Policy, Intelligence & Labeling
Telephone: 302-885-1978
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Enclosure

Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation

General Comments:

The document is concise, well written, well organised, and easy to read.

Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation		
Section	Page or Line Number	Comment or proposed replacement text
III	p. 4, line 130	<p><i>“The degree of AT elevation may be a better indicator of potential for severe DILI....”</i></p> <p>Comment: This phrase is vague and it addresses an issue that is discussed in detail further on in the text (pages 5 and 6). Proposed replacement text is: <i>“The most specific indicator is evidence of altered liver function.”</i></p>
III	p. 4, line 153	<p><i>“The liver has a large excess of bilirubin-excreting capacity; injury to hepatocytes sufficient to cause jaundice or near jaundice (i.e., a bilirubin >2 mg/dL) represents an extent of damage so great that recovery may not be possible in some patients.”</i></p> <p>Comment: “Near jaundice” has no real clinical relevance and is arguably a poor choice of terms. Suggest replacing “near jaundice” with “mild hyperbilirubinemia” which may be clinically undetectable, but measurable. Jaundice usually becomes clinically evident at plasma bilirubin concentrations of 3 to 4 mg/dL.</p>
III	p.5, line 175	<p><i>“.....finding two is highly predictive of a potential for severe DILI”.</i></p> <p>Comment: This statement is too strong, since it implies that a rigorous and objective analysis has been undertaken and subjected to independent peer review. This is not the case. Proposed rewording is: <i>“.....finding two is considered highly predictive of a potential for severe DILI”.</i></p>
III	p.5, lines 183-189	<p><i>“...Zimmerman’s original estimate of 10 to 50 percent mortality associated with.....”</i></p> <p>Comment: Zimmerman’s experience was based on analysis of patients who had developed marked symptomatic liver dysfunction that required clinical investigation, and such cases form the basis of the large retrospective analyses undertaken in Spain and Sweden. It has not been established that 10 to 50 per cent mortality occurs in cases where relatively modest impairment of liver function (i.e. asymptomatic ≥ 3 fold elevations in ALT plus ≥ 2 fold elevation in</p>

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		<p>bilirubin) has been observed in clinical trials, and intuitively this seems extremely unlikely.</p> <p>Proposed rewording: The text needs to be altered to make this distinction explicit.</p>
III	p.5, line 206	<p><i>"...severely hepatotoxic at relatively high rates (1/10,000)".</i></p> <p>Comment: This value is a low incidence, albeit one that is clinically significant in a large treated patient population. Suggested wording is <i>"...severely hepatotoxic in a large treated patient population (i.e. incidence ≥ 1/10,000)".</i></p>
III	p. 6, line 235	<p><i>"Therefore, the finding of two Hy's Law cases, and probably even one, is a strong predictor of a significant rate of severe liver injury."</i></p> <p>Comment: Do not agree that one Hy's Law case translates into a <i>"significant rate of severe liver injury"</i> without knowing how many subjects were exposed to the offending agent. Suggest replacing <i>"rate"</i> with <i>"risk"</i>.</p>
IV. A. 6.	p. 10, lines 409 - 413	<p>In order to better distinguish this situation from DILI, replace:</p> <p>"Cardiovascular causes. Cardiovascular disease, especially right heart failure and hypotension, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with spectacular increases of serum AT (e.g., AT >10,000). Cardiovascular dysfunction, including hypotension or right heart failure, should be assessed by physical examination and history."</p> <p>With:</p> <p>"Cardio-respiratory causes. Cardiovascular disease, especially with right heart failure and hypotension, and any cause of impaired oxygenation of the liver such as shock or acute hypoxic episodes, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and occasionally spectacular increases of serum AT (e.g., AT >10,000) where AST > ALT. Recovery is usual provided the underlying cause is successfully treated and occurs over 12-15 days. Cardiovascular dysfunction, including hypotension or right heart failure, and any cause of hypoxaemia should be assessed by physical examination and history and treated promptly."</p>

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IV.B.	p. 12, lines 514 - 517	<p>FDA has added: <i>"Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to FDA promptly."</i></p> <p>Comment: The definition of Hy's law is in part contingent upon the following criterion: <i>"No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury."</i> Therefore, it would be appropriate to remove the word "potential. Proposed rewording is: <i>"Any Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to FDA promptly."</i></p>
IV.C.	p. 13, lines 568-571	<p><i>"This calculation would then suggest a rate of expected severe liver injury <1 per 10,000 exposed patients, assuming that the rate of severe injury when AT and TBL are both elevated is about 10 percent....."</i></p> <p>Comment: The assumption is unjustified, for reasons given above (Comment on p. 5, lines 183-189). Therefore more cautious wording is appropriate.</p> <p>Proposed rewording is <i>"This calculation would then suggest that the rate of expected severe liver injury could be as high as 1 per 10,000 exposed patients, assuming that the rate of severe injury when AT and TBL is up to 10 percent....."</i></p>
Appendix A	Overall Comments	<p>Examples, particularly for the pre-marketing data, should include the frequency of ALT and/or bilirubin elevations on comparators/placebo. The fact that there were 5 cases of ALT > 3 x ULN and Tbili > 2 x ULN on comparator in the ximelagatran NDA should be included in the ximelagatran example.</p> <p></p> <p>DILI Examples in Draft Guidanc...</p> <p>Examples should explicitly state how many ALT > 3 x ULN and Tbili > 2 x ULN had no alternative explanations. This is perhaps implied in the bromfenac and troglitazone cases but should be stated directly.</p>
Appendix	p. 23, lines 939-	<i>"In fact, at least one death occurred among the 7,000 exposed</i>

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A	941	<p><i>patients subsequent liver toxicity, further supporting such an estimate”.</i></p> <p>Comment: The meaning of this sentence is unclear. It needs to be reworded.</p>