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

Comments to: **Docket No. 2007D-0396**
Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

From: **Eli-Lilly and Company**

The Liver Safety Committee at Eli Lilly & Company has read the ***Guidance for Industry on Drug-Induced Liver Injury*** and generally feels it is a very comprehensive and practical document that has improved significantly in its recent version.

The following are comments and suggestions related to the current version.

1. The ***Guidance*** generally supports enrollment of patients with abnormal baseline liver tests. However, there are no recommendations regarding qualifications for this recommendation. The document should clarify the following topics in relation to patients with underlying liver diseases:

    a. **Inclusion and exclusion criteria:** the document should discuss which levels of aminotransferases and which disease states should be considered protocol exclusion criteria. For example the following questions should be addressed:
        i. Should patients with ALT>5X ULN be enrolled in a clinical trial? We recommend excluding them unless the drug is given to treat the liver disease.
        ii. Should patients with Hy's rule levels be enrolled? We recommend excluding such patients.
        iii. Should evidence of synthetic liver dysfunction be considered an exclusion criterion? We favor excluding patients with synthetic dysfunction unless the study directly addresses patients with hepatic impairment.

iv. Should a patient with acute icteric viral hepatitis (A,B,C,D or E), active autoimmune hepatitis, or acute alcoholic hepatitis be enrolled? We suggest excluding these patients unless the drug is given to treat these conditions.

b. **Screening tests:** the ***Guidance*** document should specify which tests ought to be performed during screening phase in patients who are enrolled with abnormal liver tests. We recommend screening these patients for hepatitis A,B and C, autoimmune hepatitis and possibly additional tests dependent on the clinical circumstances.

2. It may be beneficial to mention specific groups of patients who may have altered risk-benefit ratios. For example: clinical trials of anti-cancer drugs in patients with advanced malignancy. In these cases even high levels of bilirubin (related to hepatic metastases) would not be considered an exclusion criterion. Another unique example is patients who are active alcohol drinkers and are treated with anti psychotic, anti-relapse or other essential medications.

3. The term "rechallenge" is mentioned several times (lines 436-454); however, it is not defined in this document. Since there is significant confusion regarding this term it should be clearly defined, including the amount of drug and the length of treatment that constitutes rechallenge.

4. The word "sensitivity" (line 233) is probably a typo. Should be "specificity".

5. In line 508 the text suggests indirectly that AST>2XALT is a diagnostic test for acute alcoholic hepatitis. Unfortunately AST>2XALT is not a specific finding and may also occur in a few other conditions (e.g. ischemic hepatopathy). We therefore suggest changing the text in the parenthesis as follows: "history of recent drinking and AST>2XALT are supportive finding."

6. For the sake of consistency we suggest adding the words "*or increased PT-INR*" after the words ..."*evidence of reduced overall liver function in one or more subjects, manifested by increased serum total bilirubin (TBL)*"... (line145).

7. Since eosinophil count may be an important factor in the decision to discontinue a drug the term "eosinophilia" should be accurately defined (line 374).

8. Eosinophilia is a common finding in several African and South American countries. Since many pharmaceutical companies perform clinical trial in these countries, it should be mentioned that eosinophilia in these countries may be unrelated to the drug and should not be used as a single reason for drug discontinuation in patients with ALT>3XULN (line 374).

9. The acronym "NDA" is spelled out on line 71 but "BLA" (Biologic License Application) is not spelled out anywhere in this document. It should be spelled out when it is first mentioned (line 133).

Please feel free to contact me for any questions or comments.

Sincerely,

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