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Wyeth



Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Docket No. 2007D–0396, October 25, 2007 (72 FR, 60681-60682)**

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the following comments on the FDA's draft guidance for industry entitled, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation."

Wyeth is one of the largest research based pharmaceutical and healthcare products companies and is a leading developer, manufacturer, and marketer of prescription drugs, biopharmaceuticals, vaccines, and over the counter medications. Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance; our comments are provided below.

## GENERAL COMMENTS

We support the Agency's initiative to develop a comprehensive guidance aimed at improving the assessment of a drug to cause severe liver injury. However, we believe the guidance would be more useful if additional clarification was added as suggested herein.

In general, we recommend that as a result of FDA's ability to review confidential data across various therapeutic areas, any advances in predicting severe drug induced liver injury (DILI) promptly be made available in the public domain.

## SPECIFIC COMMENTS

### I. Hy's Law Clarification

(i) The guidance states (line 154) that injury to hepatocytes sufficient to cause jaundice or near jaundice (i.e., a bilirubin >2 mg/dL *or 1.5xULN*) represents an extent of damage so great that recovery may not be possible. However, the guidance (line 169) also a Hy's Law case (point #2) includes elevation of TBL to >2xULN as one of the criterion. We note that the criteria as presented could lead to confusion.

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*We recommend that FDA revise the guidance for clarity and furthermore we recommend that the FDA present >2X ULN as the criterion for elevation of bilirubin (rather than mg/dL) to ensure consistency and evaluation of data collected from various laboratories.*

(ii) The guidance (line 163 – 173) provides criteria for identification of Hy's Law cases. However, we believe that as presented, it is unclear if the components are applicable to an individual or to the entire database. In addition, we believe that use of "more frequent" (line 165) is too ambiguous to provide clear guidance for sponsors.

*We recommend that line 163, 165-167, and 168-169 be revised as follows to clarify that the Hy's Law components apply to an individual rather than the entire database:*

*~~Briefly~~, A Hy's Law case~~s have~~ has the following three components:*

1. *~~The drug causes h~~ Hepatocellular injury, generally shown by ~~more frequent~~ 3-fold or greater elevations above the ULN of ALT or AST ~~than the (nonhepatotoxic) control agent or placebo~~.*
2. *~~Among~~ A subject~~s~~ showing such AT elevations, often with ATs much greater than 3xULN, ~~some subjects also show~~ with also an elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).*
3. *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.*

(iii) The guidance (line 514) also refers to any "potential Hy's Law case". However, it is unclear when a case would be identified as a "potential" Hy's Law case (vs. a Hy's Law case that meets the criteria provided in lines 165 – 173) that subsequently require prompt reporting as a serious unexpected adverse event as stated in lines 514 - 517.

*We recommend that the term "potential Hy's Law case" be defined in the context of this guidance and that an example of a potential Hy's Law case be included (e.g., the criteria for points one and two of a Hy's Law case have been met however, the assessment for point three has not yet been completed).*

## II. Clinical Evaluation of DILI – Patients with Liver Abnormalities or Disease

The guidance (lines 267-271) states "Patients are sometimes excluded from clinical trials because of baseline liver test abnormalities or a history of liver disease, but there is no well-established reason to do this, ... These patients should generally be included in at least Phase 3 trials because ..." While it is implied

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(lines 274-277) that patients with decompensated, unstable acute or chronic liver disease be excluded from clinical trials except where specific treatment of these disorders is under study, we believe that this point should be strengthened. For clarity, the guidance should specify that only patients with well-characterized liver disease should be initially included in clinical trials as unexplained elevations may introduce an undefined risk and could potentially hinder the trial.

*We recommend that the text (lines 267-277) be revised to clearly state that patients with decompensated or unstable acute or chronic liver disease should be excluded from clinical trials except where specific treatment of these disorders is being studied.*

**III. Signals of DILI and Hy's Law - Patients with Elevated LFTs and Pre-existing Liver Abnormalities**

While recommendations are provided (e.g., lines 313-314) for patients with elevated liver function tests (LFTs), it would be helpful if a separate section were included for the evaluation of patients with elevated LFTs at baseline. In addition, this section should clearly distinguish between patients with pre-existing liver abnormalities and the identification of subjects with laboratory abnormalities that are new (i.e. treatment-emergent). This would be particularly useful since this guidance encourages sponsors to include individuals with pre-existing liver disease in clinical trials. As such, distinction between on-therapy increases in laboratory results and natural history of underlying disease can present a unique challenge.

Also, the addition of guidance regarding the interpretation of elevated total bilirubin in the context of hemolysis or underlying chronic liver disease would be helpful. The guidance should reflect the need to differentiate the presence of direct bilirubin elevations from indirect bilirubin elevations, by obtaining both total and direct bilirubin levels. For example, the guidance (lines 241-244) could be clarified when stating, "The implications of these three findings may be different in patients with existing liver disease such as fatty liver disease, NASH, or chronic hepatitis C or B, with bilirubin metabolism abnormalities...."

*We recommend that a separate section be added to specifically address assessment of patients with elevated LFTs at baseline. Additionally we recommend that this section emphasize the need to differentiate the presence of direct bilirubin elevations from indirect bilirubin elevations, by obtaining both total and direct bilirubin levels.*

**IV. Clinical Evaluation of DILI – Decision to Stop Drug Administration**

(i) Clinical judgement is a critical factor when considering the stopping of treatment. There are instances where application of the suggested stopping rules

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could result in inappropriate termination, and there are instances where subjects who do not meet these criteria would still benefit from suspension of therapy. The guidance (lines 364-367) notes that a decision to stop treatment is based on a variety of factors however we believe the role of clinical judgement should be strengthened when making this decision.

*We recommend that the guidance (line 367) be revised from "In general, treatment should be stopped if:" to "In addition to clinical judgement, discontinuation of treatment should be considered if:"*

(ii) The guidance (lines 370 and 372) states that treatment should be stopped if "ALT or AST >8xULN" and "ALT or AST>3xULN and (TBL>2xULN or INR >1.5.)"

*Please provide a reference to support the ">8xULN" and "INR" criteria presented in lines 370 and 372.*

**VI. Clinical Evaluation of DILI – Case Report Forms**

(i) Section B (lines 494 – 512) is entitled, "Case Report Form" however we believe the information recommended for inclusion when liver injury is found would be more appropriately located in the patient narrative of the clinical study report.

*We recommend that the section title (line 494) be revised to "Patient Narrative" to better identify the intent and location for submission of the information to be included when liver injury is found.*

(ii) The guidance (line 500 and 501) recommends that the "Time" as well as the date be provided for (a) the start of drug administration to start of illness and for (b) of the cessation of drug, or interruption of drug administration. While we believe that obtaining the time of these activities may provide useful information in a database, obtaining the exact time is generally not feasible or practical when monitoring patients in the trial.

*We recommend that "Time" be removed from the information to be provided in cases in which liver injury is found (i.e., lines 500 and 501).*

**VII. Clinical Evaluation of DILI – Interpretation of Signals of DILI or Acute Liver Failure**

(i) The guidance (lines 523 – 524) states, "The presence of even a single case of severe liver failure resulting from treatment in the premarketing clinical trials database is an indicator of a high level of hepatotoxic risk." Clarification is recommended to ensure that causes other than the drug have been considered.

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*We recommend that this be clarified by adding the following to the beginning of the statement on line 523, "When other causes of hepatic failure have been excluded, the presence of even a single case ..."*

(ii) It is unclear how "severe liver failure" is defined in this guidance. The guidance would benefit from more background information relevant to drug induced liver injury including definitions of standard terms (e.g., ULN), and their interpretation. Furthermore, a standardized DILI nomenclature would assist sponsors in the interpretation of signals and trending.

*We recommend that a glossary of terms be included to provide consistency in the understanding and interpretation of terms and nomenclature used in the guidance.*

(iii) The guidance, (lines 537-538) states, "Therefore these greater AT elevations can be examined in the whole clinical trials database, not just in the controlled trials." There are significant methodological issues when combining data from controlled and uncontrolled studies in a comparative analysis of laboratory data. Subjects in open-label extension studies are typically exposed to the investigational drug for longer periods of time and simple incidence rates can be misleading in this setting. We believe that while data from uncontrolled trials can be useful, this data should be analyzed separately from the controlled data.

*We recommend that lines 537 – 538 be revised to* "Therefore these greater AT elevations can be examined in the whole clinical trials database, ~~not just in the controlled trials~~; uncontrolled trials should be evaluated separately."

**VIII. Clinical Evaluation of DILI – Analysis of Signals of DILI**

(i) When assessing Hy's Law Cases in the clinical trial database, the guidance (lines 629 – 630) recommends that, "A narrative summary for each Hy's Law case should be provided." To better assist the sponsors in appropriately providing this information and to ensure consistency when submitting, we recommend that this statement be revised to clarify that this information be included in the Patient Narrative. Please also refer to comment VI (i).

*We recommend that lines 629 –630 be revised to "A narrative summary for each Hy's Law case should be provided in the Patient Narrative."*

(ii) During the overall assessment of a drug's potential to cause DILI, the guidance (lines 688 - 690) recommends that the sponsor should consider various questions including "Will some form of monitoring, by symptoms or serum testing be needed?" Usually this would be considered only if there was evidence

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of severe liver injury or the potential for it. If so, effectiveness of monitoring in the NDA database should be discussed."

We recommend that this point be revised to focus on obtaining pertinent information and reduce the burden on the patients. It is recognized that monitoring of LFTs outside of clinical trials has not been very successful in reducing DILI. Not only does this type of monitoring become a burden for patients, monitoring for potential idiosyncratic reactions may not result in valuable information since many patients will be tested to detect a rare event. Furthermore, efforts should be made to identify high-risk patients via screening tests or other risk factors to monitor LFTs in a planned manner. Increased awareness of clinical symptoms associated with DILI that would trigger obtaining LFTs and guidance regarding drug discontinuation might be more effective with clinicians than widespread monitoring.

*We recommend that line 688 – 690 (beginning with "Usually, this...") be revised to clarify that efforts should be made to identify high risk patients via screening tests or other risk factors so that monitoring of LFTs can be done in a focused manner.*

We are submitting the above comments in duplicate. Wyeth trusts that the Agency will take these comments into consideration when finalizing this draft guidance.

Sincerely,

Roy J. Baranello, Jr.
Assistant Vice President
Regulatory Policy and Operations
Global Regulatory Affairs