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PhRMA

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Division of Dockets Management
HFA-306
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2007D-0396; Draft Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation; 72 Federal Register 60681; October 25, 2007

Dear Sir/Madam:

The following comments on the above noted draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives.

PhRMA complements the Agency for drafting a concise and well written guidance on this subject. The guidance is thoughtful and appropriately educational. Drug-induced Liver Injury (DILI) is a major issue in the development of new products and accounts for a significant number of program delays and discontinuations. PhRMA supports finalizing this draft guidance as it will help sponsors recognize liver safety signals early in clinical development, thus contributing to increased patient safety. PhRMA welcomes the establishment of criteria for evaluating DILI in clinical trials using Hy's Law and other assessments as familiar and well validated criteria. PhRMA also welcomes the efforts of the agency to draw clear distinctions between different types and mechanisms of DILI, and to appropriately recognize that different types of DILI carry different levels of risk to patients. Importantly, the draft guidance recognizes that this understanding of the type and severity of DILI is fundamental to any subsequent informed risk-benefit based decision.

The guidance also includes many practical and medically sound recommendations such as: (1) not excluding patients with pre-existing liver disease from pivotal studies, (2) not automatically stopping drug after an initial observation 3xULN (or even 5xULN) in the absence of biochemical or symptomatic indication of liver function impairment, (3) monitoring frequency, and (4) recommendations for workup of patients following an elevation.

An item of frequent confusion around the application of Hy's Law is the need for a causality assessment for the reports. The guideline clearly states (lines 143-147) that to be a reasonable predictor for potential severe hepatotoxicity, reports not only need to meet the liver function test alteration criteria, but also to not be explained by another cause, and be seen together with an increase rate of AT elevations compared to an appropriate control population. The concept of

causality is also nicely covered under item the third component (criteria) for Hy's Law cases (lines 171-173). A possible relevant illustration of this could be provided in the Exanta (ximelagatran) example included in the guidance, where a number of cases meeting at least some of Hy's Law criteria in the comparator arm (enoxaprin-warfarin) were reported, without this being generally believed to indicate severe hepatotoxicity of this comparator arm.

A possible further helpful clarification would be to clearly differentiate in the guidance document cases that only meet the "biological" or "laboratory" criteria for Hy's law (concurrent elevation of AT >3xULN and total bilirubin >2xULN) from cases seen with a drug, which meet the "full" criteria (including the causality aspects), by the use of a qualifying statements such as "laboratory criteria for Hy's Law" vs. "full" Hy's Law cases.

In addition to the above general comments, and in order to improve the usefulness of the guidance document, PhRMA would like to offer the following more specific comments. Whenever possible, specific suggestions or alternative wording are provided together with the comments.

Specific comments

1. Section III starting on page 3 – Line 123:

   This section describes Hy's Law and other measure of DILI in terms of sensitivity and specificity relative to detection of liver injury. These terms are appropriate for the description of performance of laboratory assays. It would also be valuable to cover in this section the performance of the assays and tests in terms of positive and negative predictive values.

   Sulfa drugs could be added as an example of common alternate etiology for liver injury.

2. Page 3 – Line 125:

   PhRMA suggests removing "(AT elevations)" after "hepatocellular injury" as it could be construed from this statement that the Agency consider AT elevations and hepatocellular injury as synonymous.

3. Page 4 – Line 145:

   We recommend the inclusion in the guidance of wording to further clarify or define the time interval implied with the wording "in conjunction". Due to the importance of a Hy's Law finding, the temporal association of ALT and bilirubin elevations (with bilirubin elevations synchronous or following peak ALT) should be clarified, to avoid erroneous interpretation of event to be termed Hy's Law cases.

   Questions that are often asked regarding the application of Hy's Law criteria include: How to handle cases where of AT and bilirubin elevations occur during the course of treatment but not concurrently. Are total bilirubin and AT elevations expected to occur at the same time, all of the time, or is it expected that there may be a delayed increase in bilirubin that follows AT elevation, at least in some cases? How should cases of delayed bilirubin elevations be

handled if AT elevations have resolved (i.e., are these not expected to meet the criteria for Hy's Law)? Similarly, events of bilirubin elevations preceding ALT elevations (e.g., hyperbilirubinemia with blood transfusions, etc. followed by subsequent ALT elevations) should be clarified as not meeting Hy's Law criteria. Additional wording to clarify the above would be of significant help.

4. Page 4 – Line 154:

   Jaundice is described as "i.e., a bilirubin >2 mg/dl", however, the Hy's Law description on line 169 and elsewhere refers to significance of bilirubin changes relative to ULN. To promote consistency in the comparison of values to relative to their normal ranges, we recommend removing the parenthetical "(i.e., a bilirubin >2 mg/dl)" from line 154.

5. Page 4 – Line 169:

   There are examples of drugs with likely transporter interactions resulting in increased total bilirubin, which is predominantly indirect, transient, and occasionally associated with ALT elevations. To differentiate these likely drug-related and clinically innocuous events from events of serious liver injury, bilirubin fractionation is valuable (i.e. in serious liver injury, direct bilirubin typically exceeds 35% of total bilirubin) (Oxford Textbook of Hepatology)

   We suggest that the guidance include recommendations for bilirubin fraction testing when total bilirubin exceeding 2xULN to assess whether hyperbilirubinemia is predominantly direct or indirect. It would also be helpful for the guidance to clarify whether a clinical event of ALT>3xULN and total bilirubin >2xULN (80% indirect bilirubin) in a subject with Gilbert's syndrome is considered a potential Hy's Law event.

6. Page 5 – Line 175:

   The draft guidance states that "Finding one Hy's Law case in clinical trials is ominous; finding two is highly predictive of a potential for severe DILI". We note that this statement is only appropriate given the proper context, i.e., cases which meet the "full" criteria for Hy's Law and if "in clinical trials" is understood to mean "in most clinical development programs, where a total of roughly 3000 patients are exposed." Although this is explained elsewhere in the guidance, the use of the term "ominous" without the proper context may be inappropriately misinterpreted. PhRMA suggests not using this word.

7. Pages 5-6 – Starting on line 202:

   The Agency makes a good case for the levels of abnormality they propose for ALT/AST as being meaningful. However, the ranges for ALT are different from the Common Toxicity Criteria for Grades 1-4. It would be certainly be important to recommend the use of similar grading systems in summarizing laboratory data in NDA/BLAs.

8. Page 6 – Section IV. starting on Line 247 (Clinical Evaluation of DILI):

   The guidance should highlight the fact that acute viral co-infection (Hepatitis A thru E) should be ruled out in the evaluation of DILI and this evaluation for other potential causes should be done early based on the clinical picture.

9. Page 6 – Line 258:

   The draft guidance states: "The following general recommendations for evaluating and monitoring potential drug-induced hepatotoxicity may not be suitable for all situations and should be modified for special populations, such as people with preexisting liver disease or malignancies, and in light of accumulating data." Evidence-based safety guidelines for those with pre-existing liver disease or malignancies would be highly beneficial.

   An internal FDA Hepatotoxicity Advisory Team could most effectively develop liver chemistry subject stopping criteria for preexisting liver disease or malignancies to guide reviewing divisions, rather than having individual FDA reviewing divisions create liver safety recommendations for each area.

10. Page 7 – Lines 267-277 – Section IV.A.1. "Patients with Liver Abnormalities or Disease" and Pages 9-10 – Lines 378-426 – Section IV.A.6. "Evaluating Data for Alternative Causes":

    The draft guidance sections identify preexisting disease as a potentially confounding factor for the detection of DILI, and encourage sponsors to include patients with preexisting liver disease in some clinical trials. While we agree with the concept of including patients with preexisting liver disease in clinical trials, the draft guidance would benefit from the inclusion of clear guidance on the circumstances under which this can be done safely and appropriately.

    The guidance should be more explicit about the distinction between "baseline liver abnormalities" and "history of liver disease" - the latter could include established cirrhosis, which can increase the risk of hepatic decompensation from a toxic drug. The paragraph does mention "diminished liver reserve", but in the context that this could confound the interpretation of whether a Hy's Law case has occurred, rather than to clarify the distinct safety issues. Based on the experience of various PhRMA companies, Hy's Law criteria may not be fully suitable in studies of Patients with Liver Abnormalities, due at least in part to the reliance of Hy's Law on fold increases of laboratory measures over the "Upper Limit of Normal". We propose that the sections describing Hy's Law and the section dealing with Evaluating Data for Alternate Causes be updated to contain specific language noting this limitation of Hy's Law.

    Clear guidance on how DILI might be detected in the presence of non-drug induced liver impairment would also be very important. Similarly, additional clarity/guidance on how best to assess possible cases of DILI caused by an investigational drug that is administered concomitantly with other drugs with independent and possibly synergistic potential to produce DILI would be welcomed.

Guidance could be given on how to recognize patients with compensated cirrhosis without performing invasive procedures. Medical History, clinical features, historical abdominal ultrasound and platelet counts could be used to identify such compensated cirrhotic patients.

The guidance might also mention that certain disease populations have more common TA elevations, either because of the underlying disease or other drugs that are commonly prescribed. For example, unexpectedly high TA variability and elevation rates have been observed in asthmatics treated with usual care during long-term safety studies. PhRMA would also welcome additional guidance from the Agency or examples to describe "best practices" for inclusion of patients with preexisting AT elevations in clinical trials.

11. Page 7 – Lines 279-297, Section IV.A.2. "Detection of DILI":

    The Agency should consider adding whether testing for Gilbert's syndrome should be recommended for any observation of TA>3xULN, with or without TBL>2xULN as learning whether drug-related TA elevations commonly occur in Gilbert's carriers without concomitant or subsequent TBL elevation may be valuable.

12. Page 7 – Lines 299-316, Section IV.A.3. "Confirmation" and page 8 – Lines 318-339, Section IV.A.4 "Close Observation":

    Although the recommendations in these sections seem reasonable, it is unclear as to whether these are based on the Agency's staff medical experience or on specific publications/studies or data sets. Clarification of the source of these recommendations would be helpful.

    The wording in the sections may also benefit from further clarification that these are general guidelines which not need to be applied literally or in a prescriptive fashion, otherwise these could potentially be in conflict or interfere with medical standard of care.

    For example, a repeat testing within 48 to 72 hours (lines 301-303) may not be required for asymptomatic subjects with ALT<5xULN and normal bilirubin, where a longer interval may be acceptable.

13. Page 7 – Line 307:

    PhRMA requests the Agency clarify whether prompt retesting recommended should be conducted if **either** of these conditions is observed (even in the absence of the other).

14. Page 7 – Lines 308-312:

    Although appropriately pragmatic, the provision for use of local laboratory data for follow-up introduces a source of variance that is potentially problematic to the overall interpretation of laboratory data. PhRMA would welcome comments from the Agency on the acceptability of appropriate methods to compute changes from baseline and correction factors which may be used for normalization or summarization of the data or as part of decision rules (retesting

or discontinuation) when the repeat tests are done locally rather than at the laboratory which processed the original baseline sample.

15. Page 8 – Lines 312-316:

    It would be helpful if the Agency could clarify if the recommendation regarding 2-fold increases holds regardless of the degree of elevation prior to treatment.

16. Page 8 – Lines 318-339:

    The definition of Close Observation provided in lines may be too specific and prescriptive. We suggest that line 320 be revised to "*Close Observation Endpoints and Assessments May Include (but are not limited to):*."

17. Page 8 – Line 330-331:

    Use of the International Normalized Ratio (INR) to assess liver function: INR as a measure for the assessment of liver function is mentioned only briefly in the guidance document, without any context or discussion of its use and limitations. We would welcome additional comments/guidance in Section IV.A.3 and/or 4 to describe INR and its purpose, appropriate use and limitations, in the context of DILI.

18. Page 9 – Line 374:

    Since eosinophil count may be an important factor in the decision to discontinue a drug, the term "eosinophilia" should be accurately defined. Eosinophilia is a common finding in several African and South American countries. Since many pharmaceutical companies perform clinical trials 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.

19. Page 9 – Line 402:

    The guidance states: "Alcoholic and autoimmune hepatitis should be assessed by history and serologic testing (e.g., antinuclear antibodies)." However, the International Group on Autoimmune Hepatitis (AIH) suggests use of ANA & ASMA (titers typically >1:80) to evaluate Type 1 AIH and anti-LKM1 (where titers may be <1:80) to evaluate Type 2 AIH (Alvarez F. Journal of Hepatology 1999; 31: 929-938). Autoantibodies can also occur in drug-induced liver injury (Watkins PB. Hepatol 2006; 43: 618-631). Rather than specifically mentioning the use of the relatively nonspecific antinuclear antibody alone, it is suggested that a more open-ended statement such as "Consider autoantibodies" would be more appropriate (to examine possible autoantibodies appearing with drug-induced liver injury vs. preceding autoimmune hepatitis).

20. Page 11 – Lines 370-373:

    Starting on line 137, the guidance states: "Generally, ALT is considered a more liver-specific aminotransferase than AST, although it also occurs in many tissues (Green and

Flamm 2002)." However, in section IV.A.5 (Decision to Stop Drug Administration), ALT and AST are treated similarly in the guidance section on stopping criteria, despite AST's lower specificity for liver injury. We recommend that subject discontinuation criteria focus more on ALT than AST.

21. Page 10 – Section IV.A.8:

    The term "rechallange" is mentioned several times, however it is not accurately defined. 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.

22. Page 11 – Section IV.A.9 starting with line 456 (Research Opportunities):

    The call for action for research is an important and valuable section, but may not belong in a guidance document. If retained in the final document, it could include a call for analysis and research into the relative sensitivity and specificity of geometric v. arithmetic TA elevations. The normal range of baseline TA values is wide (~10-fold). "Normal" ALT for different people might be a stable value of ~5 IU, a stable value of ~50 IU, or highly variable but mainly within the normal range. It's not known whether an elevation from 50 to 150 IU or an elevation from 5 to 75 IU is a better indicator of hepatocellular injury. The latter sort of elevation might turn out to be a DILI signal that has been missed to date (or it might be meaningless - which would also be valuable to learn). It could be mentioned that other markers, such as GGT, are not useful due to high variability and lack of specificity.

    The Agency may also consider commenting on the current status of toxicokinetic models and their predictive value in assessing liver toxicity.

23. Page 11 – Lines 459-466:

    The guidance states that there's interest in evaluating genetic, "genomic, proteomic, and metabolomic methods to determine how subjects differ, and to seek biomarkers that identify the susceptible persons". Use of these tests requires the subject's informed consent. It may be helpful to mention the value of a prespecified informed consent including possible exploratory analyses to assure successful completion of these tests following safety events.

24. Page 10 – Lines 494-512:

    The draft guidance provides very specific reference to Case Report Forms (CRF) and what information should be recorded in the CRF for cases in which liver injury is found. We believe that this wording is too specific and prescriptive, and recommend that the existing text on lines 497-498 be revised to read "*…hepatic illness, the following information should be captured in case report forms or other appropriate safety database for cases in which liver injury is found…*"

    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). PhRMA suggests changing the text

in parenthesis as follows: "history of recent drinking and AST>2XALT are supportive finding."

25. Page 12 – Lines 514-517:

Consistent with the suggestion included in our general comments regarding differentiation of cases meeting the "biological" or "laboratory" criteria for Hy's law vs. "full" Hy's Law cases, clarification from the FDA as to expectations for expedited reporting of such cases is requested.

PhRMA assumes that cases which meet the laboratory criteria, but in the presence of reasonable alternative causes would not automatically qualify as requiring expedited reporting, however, clarification from the Agency on this point would be most welcome. Additionally, a possible alternative to the current wording would be to delete the word "potential" in the sentence "*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 the FDA promptly*." and focus on "clearly identified" or "full" Hy's Law cases.

Additionally, clarity as to whether all potential Hy's Law cases are expected to be unblinded by the sponsor would be helpful.

26. Page 12 – Section C, starting on line 519:

Guidance/recommendations from the Agency on how to monitor and interpret transient early changes in LFTs which do not meet Hy's law criteria would greatly improve the usefulness of the guidance document. Data from the FDA experience supporting the recommendations for such activities would also be extremely helpful.

27. Page 12 – Line 530:

For consistency we suggest the replacement of "*…AT values ≥ 3x-…*" with "*…AT values >3x-…*".

28. Page 13 – Lines 573-690 – Section IV.D. "Analysis of Signals of DILI":

While this section provides a very thorough discussion of the evaluation of clinical data for evidence of DILI, there is very little mention of the use of preclinical data to help inform clinical observations and data (limited to reference to "Several in vitro methods…" in line 585 of page 14). For a more complete assessment of DILI, we suggest that the guidance include knowledge of the drug target, mechanism, and primary and secondary pharmacology as well as any and all relevant evidence from preclinical toxicology studies.

29. Page 13-14 – Lines 579-586 – Section IV.D.1. "Assessment of Drug Metabolism":

The agency may consider providing other examples of potentially relevant enzyme systems beyond CYP 450, such as N-acetyltransferase or glutathione synthetase enzymes which have been associated with metabolism-related DILI.

30. Page 14 – Lines 585-586:

    Although the draft guidance states that in vitro assessment of drug or metabolite protein binding potential is possible, it does not provide a perspective on the value or limitations of such data. Additional guidance from the Agency on this topic will be welcomed.

31. Page 14 – Lines 588-612 Section IV.D.2:

    We would welcome additional guidance from the Agency on how to analyze LFTs across clinical trials in an NDA or BLA (i.e., pooled vs. meta-analyses methodologies). Additionally, providing further clarity on the differences between "Hy's Law cases" and "possible Hy's Law Cases" or cases meeting the "biological" or "laboratory" criteria for Hy's Law would be extremely helpful in conducting and interpreting analyses.

32. Page 14 – Line 622:

    PhRMA recommends the addition of "concomitant medications" to the sentence ("*The contribution of sex, age, drug dose or regimen and* ***concomitant medications*** *to the abnormalities seen should be explored*").

33. Page 16 – Lines 688-690:

    PhRMA requests further clarity/guidance from the Agency with regards to monitoring. Guidance would be particularly appreciated on the circumstances where monitoring would be expected/needed. It would also be of help if the Agency could clarify what is meant by "effectiveness of monitoring in the NDA database" and how this could be assessed.

34. Other Comments:

    - Although the title of the guidance contains the general term "DILI", the document particularly focuses on the evaluation of hepatocellular injury (as opposed to cholestatic injury, where AP is elevated). The document should address these other issues more fully or it should specify more clearly that it is limited to severe DILI presenting as acute hepatitis.

    - We would welcome the addition in the document of guidance on patient eligibility - hospitalization criteria and stopping rules for drugs that are known or likely to have liver toxicity.

    - Additional information from the Agency regarding the specificity of "marked" AT elevations, e.g., >10xULN, 15x, 20x, 30x would also be helpful.

    - Additional information about the implications of dose-related increases in AT that FDA might include in the guidance document would be useful to Sponsors.

    - Finally, PhRMA would also welcome getting further clarity on the Agency's perspective on how to reflect the findings from the clinical trials in the package insert, particularly

relative to monitoring of liver function and the various sections of the package insert than may be affected by those findings.

PhRMA trusts these comments will be useful to the Agency as FDA moves forward to finalize this important guidance.

Sincerely,