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January 14, 2008

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

Subject: Comments for Docket 2007D-0396, Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation

Dear Sir/Madam,

The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) draft guidance *Drug-Induced Liver Injury: Premarketing Clinical Evaluation.* BIO represents more than 1,150 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products.

We have and will continue to support FDA's efforts to advance our collective knowledge of the mechanisms and signs of drug-induced liver injury (DILI). We applaud FDA's efforts in publishing this draft guidance document to discuss current tools available to predict DILI and provide practical recommendations to consider in monitoring for and interpreting signals of potential DILI in a clinical development program. Our comments on the proposed guidance follow below.

Please note that these materials were reviewed when compiling our comments:

- FDA Guidance for Industry on "General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products"; http://www.fda.gov/cder/guidance/1970dft.pdf
- Evans DC et al., *Chem Res Toxicol.* 2004; 17:3-16
- Park BK et al., *Annu Rev Pharmacol Toxicol.* 2005;45:177-202
- Day SH et al., *J Pharmacol Toxicol Methods.* 2005 Sep-Oct;52(2):278-85

General Comments

Universal Utility of Hy's Law

In this draft Guidance, FDA suggests that one or two absolute cases that follow the conditions of Hy's Law can be highly predictive of hepatotoxicity associated with the drug. In a database of 3,000 patients, one Hy's Law case is highly predictive of a true incidence rate for severe DILI of one in 10,000. However, in the case of ximelagatran referenced in this Guidance, there were five Hy's Law cases in the comparator arm (enoxaprin-warfarin). In such a controlled and limited patient population, this would seem to indicate that the comparator was extremely hepatotoxic, and yet it is not generally believed to be so. These findings seem to weaken the argument that Hy's Law can universally predict a significant incidence of severe DILI. While we acknowledge that most experience to date does support the validity of Hy's Law, we would like FDA to consider and further discuss the findings in the ximelagatran case.

Discussion of Benefit/Risk Arguments

In the draft Guidance, FDA seems to indicate that a Hy's Law case in a database of 3,000 patients, which would predict an incidence of severe DILI of one in 10,000 in a general population, would ultimately render the drug not approvable in any circumstance. There may be other limited circumstances where FDA may still consider approving such a drug (for instance, if no alternative safer therapy exists and the drug may reduce morbidity and/or mortality in a certain patient population). We ask FDA to consider including a brief discussion of how these laboratory findings, especially in the absence of any observed DILI in the clinical trial database, would factor in to a regulatory decision that must weigh demonstrated benefit against potential risk.

Addressing More Ambiguous Findings

This document clarifies how FDA may view a drug with clear potential to cause serious DILI, but does not adequately address more ambiguous cases. For instance, how would FDA view a significantly increased incidence of alanine aminotransferase (ALT) elevations without any definitive Hy's Law cases in a database that meets International Conference on Harmonisation (ICH) standards for short- and long-term exposure? The guidance could include a call for analysis and research into the relative sensitivity and specificity of geometric v. arithmetic transaminase (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 is 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).

Specific Comments

Section I, Introduction, p.1, line 23: FDA makes it clear that this draft guidance focuses on identifying drugs that may cause severe DILI. There is a potential for a drug to cause "mild or moderate" DILI (e.g., injury that does not result in transplantation or death but may have long-term consequences to the liver function or predispose an individual to chronic liver disease)? The guidance does not address this issue. For completeness, we recommend the FDA discuss mild or moderate DILI in this guidance or in another forum.

Section II, Background: Hepatotoxicity, p.2, line 53: We caution FDA against using the abbreviation "AT" for aminotransferase, as this is not a routinely used abbreviation and may be misinterpreted. We recommend FDA use the standard abbreviation.

Section III, Signals of DILI and Hy's Law, p.3, line 123: This section reviews which abnormal laboratory findings may be signals of severe DILI. Hy's Law appears to be the only algorithm with good specificity. Two other situations are discussed in the Guidance: an excess of aminotransferase elevations over comparator rates, and marked absolute elevations of 5-, 10- and 20-fold or more from baseline, but predictive value for each of these conditions is limited. No other potential biomarkers are discussed. As stated in our General Comments, we would prefer to see FDA address the more ambiguous situations and how these situations should be handled in the clinical development program and regulatory proposal. It would be useful to see a more expansive list of investigational drugs that have had some ambiguous signal that may have raised questions of the potential for DILI, and what respective outcomes were seen in the clinical trials and/or the postapproval safety database.

Section III, Signals of DILI and Hy's Law, p.4, line 142: By "marked peak AT elevations", we assume FDA is referring to either ALT or aspartate aminotransferase (AST), but not necessarily both. It would be helpful to clarify this, and include a discussion of the potential for a rise in the ALT level independent of AST or vice versa. Also, we assume that these marked peak elevations are considered a more specific signal of relation to drug in the absence of any other explanation, but we would like FDA to clarify if this assumption is true.

Section III, Signals of DILI and Hy's Law, p.4, line 144: FDA suggests that evidence for impaired liver function in "one or more subjects", manifested by increased serum total bilirubin (TBL) and aminotransferase elevation, is the single clearest predictor of the drug's potential for severe hepatotoxicity when paired with a higher overall incidence of aminotransferase elevations compared to placebo. This seems to suggest that the overall size of the clinical database is irrelevant, and that one absolute case is all that may matter to identify a drug as a severe hepatotoxin. We believe that that denominator should be considered, especially if comparable numbers of cases are observed in the control groups. For example, in the ximelagatran clinical database, five Hy's Law cases were observed in the enoxaparin-warfarin control group, suggesting an idiosyncratic reaction in the population that was studied.

Section III, Signals of DILI and Hy's Law, p.4, line 145: FDA states that the single clearest predictor is reduced overall liver function, manifested by increased serum total bilirubin **in conjunction** with AT elevation (emphasis added). We request that FDA more clearly define the time interval implied with the phrase "in conjunction". It is not clear whether total bilirubin and AT elevation are expected to occur at the same time, or whether there may be a delayed increase in bilirubin that follows AT elevation.

Section III, Signals of DILI and Hy's Law, p.4, line 166: The first condition requires a "more frequent" increase of 3x the upper limit of normal (ULN) for ALT or AST in comparison to placebo or nonhepatotoxic control agent. Since AST can be a less specific indicator, we ask FDA to include the option of measuring ALT only.

Section III, Signals of DILI and Hy's Law, p.4, line 169: The second condition requires that some subjects show an increase in TBL of >2x ULN in addition to serum transaminase elevations. We believe consideration should also be given to the direct to indirect bilirubin ratio and how this may be used to further define cases of interest.

Section III, Signals of DILI and Hy's Law, p.5, line 176: The cases observed in the warfarin arm of the ximelegatran studies need to be addressed in this discussion.

Section III, Signals of DILI and Hy's Law, p.5, line 202: This section should discuss the relative specificity of ALT versus AST. We ask FDA to consider whether AST needs to be measured, as we believe that AST is less specific than ALT in signaling potential liver injury or changes to liver function.

Section III, Signals of DILI and Hy's Law, p.6, line 222: We ask FDA to address the relevance of the denominator in the overall clinical database in relation to a single Hy's Law case, and the relative rates in (non-hepatotoxic) comparator groups, as seen with ximelegatran. (See our comments regarding line 144.)

Section III, Signals of DILI and Hy's Law, p.6, line 223: We request guidance regarding assessment of development of DILI in patients with elevated bilirubin due to obstructive disease, including malignancy.

Section III, Signals of DILI and Hy's Law, p.6, line 223: We suggest adding the phrase "with or without metastatic disease" after the word "malignancy".

Section IV, Clinical Evaluation of DILI, p.7, line 267: FDA recommends that patients with "baseline liver test abnormalities or a history of liver disease" be included in clinical trials to better measure the effects of the drug in this population. We also ask FDA to discuss whether there is a certain population that should be excluded. For instance, should a patient with a baseline ALT >10x ULN be included in a clinical trial? Are there any disease populations or subsets of those populations that should be excluded because of extreme vulnerability?

Section IV, Clinical Evaluation of DILI, p.7, line 271: Patients with severe liver disease should be excluded from Phase 3 clinical trials if the candidate drug would not be prescribed to them. Therefore, we suggest adding the following sentence "Subjects meeting Hy's Law should not be enrolled in clinical trials except in studies of drugs intended to be prescribed to such patients after approval."

Section IV, Clinical Evaluation of DILI, p.7, line 276: Is a typically sized Phase 1 program (in subjects with normal liver function) sufficiently robust in terms of safety to proceed to controlled clinical trials in patients with "stable chronic liver disease"?

Section IV, Clinical Evaluation of DILI, p.7, line 287: FDA recommends intense monitoring for DILI in the first 3 months of exposure in early trials of longer duration. We believe that many cases of DILI are observed in the 3-6 month period of a long-term exposure, and FDA should consider changing this to 6 months before relaxing the monitoring intervals.

Section IV, Clinical Evaluation of DILI, p.7, line 308: FDA states that prompt retesting is necessary if "AT is much greater than 3xULN or TBL is greater than 2xULN". We suggest

that FDA consider whether retesting is necessary if TBL is elevated but aminotransferase levels are stable.

Section IV, Clinical Evaluation of DILI, p.7, line 299: The document should make explicit 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.

Section IV, Clinical Evaluation of DILI, p.7, line 316: Line 624 on Page 15 mentions the biopsy data and reports; however, no other reference of any biopsy is made in Section IV A 3: Confirmation or in Section IV A 4: Close Observation. Therefore, we suggest adding the following language at the end of the paragraph "if indicated, a liver biopsy should be considered."

Section IV, Clinical Evaluation of DILI, p.8, line 322: We suggest rewording the first sentence of this bullet to read, "Repeating liver tests two or more times weekly."

Section IV, Clinical Evaluation of DILI, p.8, line 332: We suggest adding the following language to the end of this bullet, "with consideration for liver biopsy."

Section IV, Clinical Evaluation of DILI, p.8, line 337: FDA recommends that sponsors include any additional laboratory test values in the case report forms and/or database. FDA should include guidance on how to handle additional testing results coming from a local (non-protocol mandated) laboratory that may use different units or reference ranges than the central laboratories specified in the protocol.

Section IV, Clinical Evaluation of DILI, p.9, line 370: FDA should clarify whether these stopping rules are to be applied upon **initial** observation of the value or upon **confirmation** of the value.

Section IV, Clinical Evaluation of DILI, p.9, line 370: We suggest updating AST> 8X ULN to AST> 10ULN.

Section IV, Clinical Evaluation of DILI, p.9, line 372: We recommend that the TBL criterion be restricted to situations where the direct:total bilirubin ratio > 50%.

Section IV, Clinical Evaluation of DILI, p.9, line 372: The international normalized ratio (INR) criterion of >1.5 should be caveated with the phrase "in the absence of oral anticoagulant medications".

Section IV, Clinical Evaluation of DILI, p.9, line 391: Clarification on the definition of "adolescent" and "young adult" may also be helpful to ensure consistency in reporting of data. Per the FDA Guidance for Industry on "General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products", the following definitions are used for pediatric populations:

- Neonate: birth to 1 month
- Infant: 1 month to 2 years

- Child: 2 – 12 years
- Adolescent: 12 - < 16 years
- Adult: 16 years or older (the pharmacokinetics of a drug in children 16 years and older is expected to be similar to that of adults).

Various sources may have differing definitions for these subpopulations.

Section IV, Clinical Evaluation of DILI, p.9, line 392: Please clarify whether Epstein-Barr virus (EBV) testing is required for all adolescent and young adult patients, and what are the inclusive age ranges. Please note that EBV testing may not be available for all sites.

Section IV, Clinical Evaluation of DILI, p.9, lines 401-402: Serologic testing may not be readily available at all sites. Requirement for autoimmune hepatitis assessment may be difficult to implement. We suggest that serologic testing be recommended rather than required.

Section IV, Clinical Evaluation of DILI, p.12, line 504: We suggest that FDA add use of herbal supplements and exposure to environmental hazards to this list.

Section IV, Clinical Evaluation of DILI, p.12, lines 494-512: The guidance appears to require a specific case report form (CRF) for DILIs in addition to the CRFs already included in the study that contain much of the information indicated in this section. We ask FDA to clarify that no separate CRF is needed.

Section IV, Clinical Evaluation of DILI, p.12, line 505: We suggest deleting the phrase "whether drug is known to be hepatotoxic".

Section IV, Clinical Evaluation of DILI, p.12, line 509: The guidance doesn't specifically address metastasis in oncology patients. Therefore, we suggest adding the phrase "metastatic disease" in between "congestive heart failure," and "underlying other viral disease".

Section IV, Clinical Evaluation of DILI, p.12, line 514: We request that FDA clarify whether all potential Hy's Law cases are to be unblinded by the sponsor.

Section IV, Clinical Evaluation of DILI, p.12, line 514: The phrase "Potential Hy's Law case" is too broad and ambiguous. We suggest deleting the word "Potential".

Section IV, Clinical Evaluation of DILI, p.12, line 514: According to the definition of Hy's Law presented in this draft guidance, sponsors are only to treat events that could not be explained by any other cause (see line 171) as serious unexpected adverse events. If FDA would like any case meeting the first two criteria of Hy's Law (i.e., ALT/AST >3x ULN and TBL >2x ULN) to be treated as serious and unexpected adverse events, this should be clarified in this paragraph.

Section IV, Clinical Evaluation of DILI, p.12, line 523: We ask FDA to rephrase this sentence to include "even a single **unexplained** case" [emphasis added], as a case of liver failure that is clearly due to another cause would not be indicative of a high level of hepatotoxic risk.

Section IV, Clinical Evaluation of DILI, p.12, line 533: FDA recommends that rate of transaminase elevations in the experimental drug arm be compared to the rates observed in the control arm. However in some cases, the comparator may not have the potential to cause significant liver injury (e.g., statins) yet they may cause transaminase elevations. We request that FDA provide recommendations for handling this situation.

Section IV, Clinical Evaluation of DILI, p.13, line 553: The guidance appears to imply that elevations of transaminases and bilirubin have to occur simultaneously in order to represent a signal. Because this may not be the case and we ask that FDA provide guidance on the appropriate window of time between an increase in one and an increase in the other that may also signal potential severe DILI.

Section IV, Clinical Evaluation of DILI, p.13, line 579: Can FDA provide comments on the sensitivity or specificity of drug metabolism studies to detect a potential hepatotoxin?

Section IV, Clinical Evaluation of DILI, p.13, line 579: We suggest the drug metabolism section should focus on enzyme systems in addition to the CYPs.

Section IV, Clinical Evaluation of DILI, p.14, line 600: We believe the focus should be on ALT elevations as AST is not liver-specific and could be misleading in this situation.

Section IV, Clinical Evaluation of DILI, p.14, line 601: We question the value of summarizing results based on bilirubin elevations in the absence of concurrent transaminase elevations.

Section IV, Clinical Evaluation of DILI, p.14, line 602: If FDA is interested primarily in hepatocellular injury, it should be clarified that bilirubin and alkaline phosphatase abnormalities are only supplemental to rule out biliary disease in cases of interest.

Section IV, Clinical Evaluation of DILI, p.14, line 603: We ask FDA to clarify whether "accompanied by" indicates observations only occurring at the same time or within some defined window of time in relation to each other. (Please see our comment on line 553.)

Section IV, Clinical Evaluation of DILI, p.14, line 614: We ask FDA to consider whether and when there is value in analyzing rates of liver-related adverse events per patient-year of exposure.

Section IV, Clinical Evaluation of DILI, p.14, line 627: We ask FDA to be consistent in the terminology "Hy's Law cases" versus "possible Hy's Law cases". If FDA is using one term vs. the other intentionally, the reasons should be defined at the beginning of the guidance.

Section IV, Clinical Evaluation of DILI, p.14, line 627: The phrase "Possible Hy's Law cases" is too broad. We recommend deleting the word "possible".

Section IV, Clinical Evaluation of DILI, p.14, line 677: We ask FDA to clearly define the boundaries of mild, moderate, and severe DILI.

Appendix A, p.21: This appendix provides a detailed understanding of three examples of drugs that were found via the premarketing clinical database or in the postmarketing period to

cause idiosyncratic hepatotoxicity. It would be useful for FDA to add examples of drugs where premarketing signals were more ambiguous and for which there may or may not have been an eventual emergence of a true hepatotoxic concern in the postmarketing period.

Appendix A, Exanta (ximelagatran), p.22, line 927: The cases of increases in ALT and TBL in the warfarin arm should be discussed in this section.

Conclusion

We appreciate the FDA's diligence in driving a common understanding of the state of the science of hepatotoxicity and its application in drug development programs. If there are any questions regarding these comments, please feel free to contact us.

Sincerely,

/s/

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