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Dockets Management Branch
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Re: NAS; Not Product Specific
General Correspondence: Comments on Draft Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation
[Docket No. 2007D-0396]

Dear Sir or Madam:

Reference is made to the notice published by FDA in the Federal Register on October 25, 2007 to invite written comments on the draft "Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation." The purpose of this submission is to provide comments from GlaxoSmithKline (GSK) on this document.

GSK is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture and distribution of medicines and vaccines that enable people to lead longer, healthier and more productive lives. We appreciate the opportunity to comment on this draft guidance document on an important aspect of the evaluation of drug safety.

By way of introduction, we provide over-arching comments on the draft guidance as a whole. Thereafter, GSK's comments track the draft guidance sections.

General Comments on the Draft Guidance

The FDA draft guidance is excellent and will be a user-friendly tool when finalized. The October 2007 draft guidance has further sharpened and clarified the January 2007 concept paper prepared by the Hepatotoxicity Working Group comprising staff from the CDER and CBER.

Comments on Draft Guidance Sections

III. Signals of DILI and Hy's Law [Page 4, Line 138]

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, ALT and AST are treated similarly in FDA's liver chemistry subject stopping criteria, despite AST's lower specificity for liver injury (e.g. may be markedly increased with muscle injury, in greater proportion than ALT).

As ALT is a more liver-specific and accurate measure of liver injury than AST, we suggest ALT should be utilized in subject stopping criteria and references to AST should be removed.

III. Signals of DILI and Hy's Law [Page 4, Line 169]

FDA has heightened attention to Hy's Law. However, GSK has examples of non-HIV 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 needed (i.e. in serious liver injury, direct bilirubin typically exceeds 35% of total bilirubin [Oxford Textbook of Hepatology]).

- For all Hy's Law cases, the guidance should recommend fractionating total bilirubin exceeding 2xULN to assess whether hyperbilirubinemia is predominantly direct or indirect. Increasingly, drugs in development inhibit OATP1B1, UGT1A1, etc., resulting in total bilirubin elevations, which are primarily indirect bilirubin (e.g. direct bilirubin <35%).
- It would be helpful for FDA 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 Hy's Law event.

III. Signals of DILI and Hy's Law [Page 4, Line 171]

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 hyperbilirubinemia with blood transfusions, etc. with subsequent ALT elevations to be termed a Hy's Law event. Events of bilirubin elevations preceding ALT elevations should be excluded from Hy's Law events.

IV. Clinical Evaluation of DILI, A. General Considerations [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 these areas.

IV. Clinical Evaluation of DILI, A. General Considerations, 3. Confirmation [Page 7, Line 301]

The draft guidance states: "In general, an increase of serum AT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing." This short interval for return doesn't appear merited for asymptomatic subjects with ALT<5xULN and normal bilirubin.

In asymptomatic subjects with ALT>3xULN and <5xULN, repeat testing within 7 days is both clinically appropriate and reasonable, rather than current recommendation for repeat liver chemistries within 48-72 hrs, due to modest clinical severity of this finding and pragmatic realities, including labs drawn on Friday with results arriving after the weekend, subject's difficulty in returning to clinics within 24hrs of lab test return, etc.

IV. Clinical Evaluation of DILI, A. General Considerations, 6. Evaluating Data for Alternative Causes [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 suggesting use of the relatively nonspecific antinuclear antibody alone, it is recommended that the more open-ended "Consider autoantibodies..." is appropriate (to examine possible autoantibodies appearing with drug-induced liver injury vs. preceding autoimmune hepatitis).

IV. Clinical Evaluation of DILI, A. General Considerations, 9. Research Opportunities [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.

IV. Clinical Evaluation of DILI, D. Analysis of Signals of DILI, 5. Overall Assessment of a Drug's Potential to Cause DILI [Page 16, Line 688]

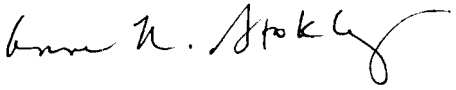
The guidance states: "Will some form of monitoring, by symptoms or serum testing, be needed? Usually, this would be considered only if there was evidence of severe liver injury or the potential for it." Please specify in the final guidance the circumstances where monitoring is needed.

IV. Clinical Evaluation of DILI, D. Analysis of Signals of DILI, 5. Overall Assessment of a Drug's Potential to Cause DILI [Page 16, Line 690]

The guidance states: "effectiveness of monitoring in the NDA database should be discussed." Please clarify in the final guidance what is meant by "effectiveness of monitoring" and how this can be assessed.

Again, we thank you for the opportunity to provide comments. Please contact me at (919) 483-6405 if you require clarification or have any questions about this submission.

Sincerely,



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