Boehringer Ingelheim

Division of Dockets Management (HFA-305)
Food and Drug Administration
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Boehringer Ingelheim
Pharmaceuticals Inc.

December 19, 2007

Docket No. 2007D-0396 Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation

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Dear Sir or Madam,

Boehringer Ingelheim Pharmaceuticals, Inc. is submitting comments on the **Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation,** as per the notice published in the Federal Register on 25-Oct-2007 (Vol. 72, No 206). For your convenience, the comments are attached to this letter.

We wish to thank FDA for the opportunity to comment on the **Draft Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation.**

Sincerely,

Pamela S. Snode for CDC

Christopher D. Corsico, MD, MPH
Vice President, Drug Regulatory Affairs

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General comments:

- Substantial improvement compared to the original Concept paper presented in January 2007.
- Some redundancy still present regarding DILI history and signals. The document could be further "tightened"
- Guidance should include recommendations for pediatric studies
- Guidance does not discuss the impact, if any, for compounds with positive preclinical liver signals.

Specific comments by line reference:

Line 171 (section III Signals of DILI and Hy's law): examples of "other reasons" should specifically include Gilbert's polymorphism for elevations in total bilirubin with an adequate explanation. Gilbert's is only mentioned briefly for the first time in line 243.

Line 175 (section III Signals of DILI and Hy's law): some context should be provided regarding the size of the clinical trial database and the observation of a single Hy's Law case, especially within megatrials.

Line 205 (section III Signals of DILI and Hy's law): How is an "excess" of AT >3xULN defined? Line 210 indicates that there are no good data available to better define this excess (e.g. 2-fold, 3-fold) but what data support even 2-fold? Are sponsors requested to conduct trials of sufficient size to demonstrate that the two-fold or three-fold excess are statistically significant? Given the low rates expected in controlled studies a statistical proof could require very large cohorts for some therapeutic areas where typically much cohort studies are required to demonstrate adequate safety and tolerability.

Line 215 (section III Signals of DILI and Hy's law): Similarly, how is a "smaller number of subjects" defined, e.g., 1 subject in a cohort of 1000?

Line 243 (section III Signals of DILI): There is limited discussion on Gilberts (perhaps only known to hepatologists) and no discussion regarding the importance of distinguishing unconjugated from conjugated bilirubin.

Line 269 (section IV-A(1) Patients with Liver Disease): The Guidance should specify that patients who have baseline liver test abnormalities or liver disease clinical history, if included in a Phase 3 trial, be analyzed as part of, and separated, from the remaining patients.

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Line 291 (section IV-A(2) Clinical Evaluations- Detection of DILI): There is justifiably a lot of emphasis on AT and TB as markers for serious DILI, but limited discussion as to the urgency to ask interview the patient adequately asking questions regarding clinical symptoms DILI and the urgency to intervene (discontinue experiemental drug, hospitalize, expert consultation, etc) when symptoms consistent with severe DILI are observed or elicited.

Line 421 (section IV-A(6) Evaluating Data for Alternate Causes): should recommend confirmation with the trial participant that the correct dosage and dose regimen was being adhered. The use of OTC compounds and herbal supplements should be mentioned as part of "concomitant treatment".

Lines 468-493 (section IV-A(9) Research Opportunities): The Guidance details almost 1 page on the "Critical Path Initiative" that, although important, is outside the purpose of this Guidance. Given the effort required to update guidance documents coupled with the length of time it will be for meaningful data to be generated from this research effort, the content of these lines will have very limited value to the reader.

Line 494 (section IV-B Case Report Forms): it is essential to clearly distinguish asymptomatic from symptomatic "hepatic events" on the CRFs, i.e., the Guidance should recommend differentiation in capturing "liver-related clinical adverse events" versus "liver related laboratory adverse events" on the CRFs. Since the Guidance provides for detailed analyses for signal detection within the laboratory data, what is the value or objective of capturing purely liver-related laboratory abnormalities as adverse events if there are no associated clinical symptoms? With the exception of Hy's cases, we propose that the Guidance clearly states that liver related laboratory abnormalities in the absence of symptoms should not *a priori* be considered an AE.

Line 505 (section IV-B Case Report Forms): change "drugs" to "compounds" - this should cover all other concomitant agents being taken, whether prescribed drugs, OTC, herbal supplements, etc.

Line 533 (section IV-C(1) Frequency and magnitude of Liver AT): need to define "excess" in context of Phase 2 or Phase 3 trials, and whether an excess should be statistically significant given the small sample sizes in Phase 2 trials and even in some Phase 3 trials in certain indications.

Line 575 (section IV-D Analysis of Signals of DILI): does this imply that these DILI assessments need to be done for all NDAs even in the absence of any signals from preclinical, Phase 1 or Phase 2 data?

Line 601 (section IV-D(2) Assessment of Liver-Related Adverse Events): Again, we strongly recommend not to describe these purely laboratory analyses as "Assessment of Liver-Related Adverse Events". The greatest confusion with such analyses in Phase 2-4 trials is the lack of standardized nomenclature and the frequent characterization of purel AT elevations > 5x or 10x ULN as "hepatitis" adverse events even in the complete absence of any clinical symptoms. The Guidance should devote a section to liver event nomenclature for reporting purposes. We do recommend that additional sub-analyses should be done for all grades of liver related laboratory abnormalities that are associated temporally with any clinical symptoms that are consistent with severe DILI, e.g. fever, nausea, abdominal pain, etc).