Pfizer

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December 20, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1060
Rockville, MD 0852

Dear Dockets Management:

Re: **Draft Guidance for Industry, Drug-Induced Liver Injury: Premarketing
Clinical Evaluation** [Docket 2007D-0396, 72 *Federal Register*,
60681-60682, October 25, 2007]

Pfizer submits these attached comments to the Draft Guidance for Industry:
Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 72 *Federal
Register,* 60681-60682, October 25, 2007.

Pfizer appreciates the opportunity to provide comments on this Draft Guidance
and would invite direct dialog with the Agency if you would consider the
opportunity valuable.

Sincerely.

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General Comments

Pfizer welcomes the opportunity to comment on the Food and Drug Administration's (FDA) "Draft Guidance for Industry: Drug-induced Liver injury: Premarketing Clinical Evaluation" (Fed.Reg. 72, no.206, 25 October, 2007). This document articulates the Agency's current thinking in clear terms and the authors are to be congratulated for producing such a concise, well written document. Drug-induced Liver Injury (DILI) is a major issue in drug development and accounts for a significant number of drug development program delays and discontinuations. We view regulatory guidance on DILI as an important mechanism for aligning sponsor-regulator assessment of, response to and management of liver toxicity in clinical trials.

Specifically, we welcome the establishment of criteria for evaluating DILI in clinical trials using Hy's Law and other assessments as familiar and well validated criteria. We also welcome 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 guidance recognizes that some understanding of the type and severity of DILI is fundamental to any subsequent informed risk-benefit based decision.

Pfizer would like to take the opportunity of the comment period for this draft guidance to provide commentary, feedback and input on a few key concepts (1-8 below) for the DILI Guidance and to provide an additional detailed list of comments and suggested alternatives.

Key Concepts and Proposed Revisions

1. *Detecting and Managing DILI on a background of Preexisting Disease or Concomitant Drug Therapy:*

The existing draft guidance sections identify preexisting disease (lines 267-277, 378-426) 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 Pfizer agrees with the concept of including patients with preexisting liver disease in clinical trials, the draft guidance does not provide clear guidance on the circumstances under which this can be done safely and appropriately, nor does it provide clear guidance on how DILI might be detected in the presence of non-drug induced liver impairment. Similarly, the guidance does not provide clarity 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.

It is our perspective and experience that Hy's Law may not apply directly in subjects with pre-existing liver disease or those receiving concomitant therapy, 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 (Section 6) dealing with Evaluating Data for Alternate Causes contain specific language noting this limitation of Hy's Law. We also propose that additional guidance be added to the document to describe "best practices" for inclusion of patients with preexisting AT elevations in clinical trials.

2. Sensitivity and Specificity vs. Positive Predictive value and Negative Predictive value:

Section III. "Signals of DILI and Hy's Law" 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. However, Pfizer believes that this discussion of test performance would be more complete and more informative for the reader if the performance of the assays and tests were also described in terms of test positive predictive value and test negative predictive value.

3. Repeat Testing Confirmation of Test Results:

Lines 301-316 ("Confirmation") describe a pragmatic approach for both confirming test results that are >3xULN and for monitoring the temporal direction and magnitude of test value changes. The approach is clearly described and appropriate for use as standard practice. This said, the provision for use of "local laboratory" data for follow up in outpatient studies etc. introduces a source of variance that is potentially problematic to the overall interpretation of laboratory data. Pfizer proposes that the guidance be modified to include a suggested method to compute change from baseline and correction factor if necessary (as part of the decision rule) when the repeat tests are done at a local laboratory rather than at the laboratory processing the original baseline sample.

4. Close Observation of potential DILI Cases:

The definition of Close Observation provided in the guidance (lines 318-339) is clearly worded, however, Pfizer considers the definition provided to be too specific and prescriptive. Taken literally, it is also possible that adherence to the provided definition of Close Observation could conflict with or interfere with medical Standard of Care. We propose that the Guidance be revised such that line 320 reads simply "Close Observation Endpoints and Assessments May Include (but are not limited to):" With this revision we would consider the bullet list of assessments and considerations provided (lines 322-332) to be reasonable and appropriate.

5. Timing of Reporting of Potential Hy's Law Cases to FDA:

Clear expectations for the reporting of potential Hy's Law cases to FDA are presented in lines 514 to 517 of the guidance. Pfizer considers the wording of this section to be overly simplistic and potentially incompatible with the time required to adequately assess the

cases in question. For example, a case that meets the Hy's Law definition as presented in the guidance could in fact be a consequence of underlying disease or therapy, and time is required for case assessment and follow up to make such a determination. It is also important to note that satisfaction of Hy's Law criteria is contingent upon being unable to establish an alternative explanation for the case.

Based on these concerns, Pfizer proposes that the guidance line 514 be revised to read: "Once it has been determined for any potential case that liver function test changes are of the magnitude described by Hy's Law and there is no other likely explanation for abnormal liver function, the case would meet criteria for Hy's Law and should be reported promptly to the FDA as a serious, unexpected adverse event."

This revision would be more consistent with the Agency's stated intended meaning of the term "should" (lines 35-39) and would clarify for sponsors that not all potential Hy's Law cases are required to follow serious unexpected adverse event reporting timelines.

6. 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 (lines 330-331), without any context or discussion of its use and limitations. Pfizer proposes that additional language be added to the guidance document in Section 3 and/or 4 to describe INR and its diagnostic purpose, appropriate use and limitations.

7. Case Report Forms:

The draft guidance provides very specific reference to Case Report Forms and what information should be recorded in the CRF for cases in which liver injury is found (lines 494-512). Pfizer considers the wording provided to be far too specific and prescriptive, and we are concerned that the existing text does not recognize inter-sponsor differences in CRF design and Safety Data Management. We propose 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..."

8. Binding of a drug or its metabolites to liver proteins:

The draft guidance states (lines 585-586) that in vitro assessment of drug or metabolite protein binding potential is possible, but the guidance does not provide any perspective on the value or limitations of such data. We note that there is a large body of evidence linking reactive metabolite formation (bioactivation) with certain types of drug induced liver injury. With a few exceptions (e.g., acyl glucuronides and some iminium ions), most reactive metabolites are unstable and not amenable towards isolation. Thus, assessment of drug bioactivation potential as it may relate to DILI should be primarily focused on the

characterization of downstream, stable products of reactive metabolites (e.g. mercapturic acid conjugates) and not on stable, non-reactive metabolites.

While *in vitro* methods to detect and quantify metabolism-dependent covalent adduct formation between reactive metabolites and macromolecules have been retrospectively used for many years to help explain mechanisms of DILI for specific xenobiotics, such methods have not been robustly tested for their fidelity in distinguishing prospectively hepatotoxic drugs from non-hepatotoxic drugs. Furthermore, to date, there has been no relationship derived between a measured amount of covalent binding generated *in vitro* and extent of hepatotoxicity. We acknowledge that a position paper on this topic has been published (Evans, et al., 2004) and includes a proposed cutoff value for *in vitro* covalent binding as being cause for concern for DILI. Likewise, other investigators have compared *in vitro* covalent binding across several hepatotoxic drugs (Masubuchi, et al., 2007). However there is no evidence to support this approach as being predictive of DILI because *in vitro* covalent binding approaches have not been systematically tested with non-hepatotoxic drugs. In our research laboratories, we have undertaken a large study to measure *in vitro* human liver microsomal covalent binding for eighteen drugs (including hepatotoxic and non-hepatotoxic drugs). Our results indicate that 77% of the drugs tested demonstrated *in vitro* covalent binding to microsomal protein <u>with no distinction between hepatotoxic and non-hepatotoxic drugs with regard to rate of covalent binding</u> (These results are presently unpublished and a manuscript describing this study is in preparation. We offer to share these findings with the FDA at request). It is noteworthy to point out that the drug with the highest rate of *in vitro* covalent binding in our study was the selective serotonin reuptake inhibitor paroxetine (Zhao et al., 2007) which has an extremely low incidence of DILI reported (Azaz-Livshitz, et al., 2002). Therefore it is our perspective that while *in vitro* covalent binding studies may be of value in retrospective testing of hypotheses regarding the cause of DILI, such studies are not predictive of the ability of a drug candidate to cause DILI.

Based on this understanding, Pfizer proposes that lines 585-586 be deleted, or replaced with the following: " *In vitro* covalent binding methods are also available that can be used to help explain observations of DILI in a retrospective fashion but these assays are not considered valid as prospective tools for the forward prediction of the potential of a given drug to cause liver injury. "

9. Analysis of Signals of DILI:

While section "D" lines 573-690 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). For a more complete assessment of DILI, we propose that the guidance specifically include knowledge of the drug target, mechanism, and primary and secondary pharmacology as well as any and all relevant evidence from preclinical toxicology studies.

Additional Detailed/Specific Minor Comments:

Line 125: remove "(AT elevations)" as AT elevations and hepatocellular injury are not synonymous.

Line 82: the statement could be construed to equate mild AT changes with mild liver injury, similar to line 125 comment above. Propose replace "...mild liver injury..." with "..mild AT elevations..." for consistency and accuracy.

Line 90: Hepatocellular injury can occur in the absence of rise in serum AT values. Therefore we propose modifying line 90 to read "...Hepatocellular injury is often but not always indicated by rises in serum AT activities...".

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 keep test data units consistent and to avoid confusion, we propose removing the parenthetical "i.e., a bilirubin >2 mg/dl" from line 154 and consistently referring to TBL changes in Hy's Law (line 169 and elsewhere) as "...elevation of serum TBL to >2x ULN".

Line 373: "worsening of fatigue" suggests change over time, however, the appearance of fatigue at all (rather than worsening) in combination with the other symptoms listed is justification to stop treatment. Therefore, suggest removal of "..worsening of..", line 373.

Line 530: for consistency replace "...AT values $\geq$ 3x-..." with "...AT values >3x-...".

Line 590: for consistency replace "bilirubin" with "TBL"

Line 628: apparent typo error, replace "ALP <2xULN" with "ALP >2xULN)

References:

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Evans, D.C., Watt, A.P., Nicoll-Griffith, D.A., and Baillie, T.A. (2004) Drug-Protein Adducts: An Industry Perspective on Minimizing the Potential for Drug Bioactivation in Drug Discovery and Development. Chem. Res.Toxicol. 17: 3-16.

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Vitro and in Vivo Generation of Reactive Intermediates and in Vitro Glutathione Conjugate Formation in Rats and Humans. Chem. Res.Toxicol. 20: 455-464.

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