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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

RE: [Docket No. 2007D–0396]
Draft Guidance for Industry: Drug Induced Liver Injury: Premarketing Clinical Evaluation.

Merck & Co., Inc. is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing Merck drug and biological product candidates through developmental testing, clinical trials and licensure, Merck scientists have acquired extensive experience in evaluating products for liver toxicity; we have utilized that experience to author the comments below.

General Comments
We commend the Food and Drug Administration (the Agency or FDA) for its commitment to foster innovation while serving the public health needs of American citizens. We thank the Agency for the opportunity to comment on the draft guidance for industry "Drug Induced Liver Injury: Premarketing Clinical Evaluation" (October 25, 2007 [Docket No. 2007D–0396]). We applaud the Agency's stated goal to provide guidance to assist the pharmaceutical industry and other investigators conducting new drug development in assessing the potential for a drug to cause severe liver injury (i.e., fatal, or requiring liver transplantation).

We note that in many sections of the draft guidance document, the Agency presents selected anecdotal examples of severe drug-induced liver injury (DILI) and also acknowledges the limitations of, or in some instances, complete lack of data on which to base more definitive guidance. The draft guidance further acknowledges that to date no genetic, metabolic, or other characteristic has been found to predict severe DILI. Given that background, we believe this draft guidance document should equally acknowledge that, based on the current state of science, severe DILI may still be detected unexpectedly in the post-marketing period even with the most rigorous effort to detect it in the pre-marketing period. To that end, we also believe it would be helpful to know if the Agency plans to publish additional guidance on post-marketing evaluation for DILI.

Related to the issue of the limitations of the data, the draft guidance cites instructive anecdotes involving drug products for which one or more patients met Hy's Law during clinical development and these products were ultimately found to cause severe DILI. However, the draft guidance does not speak to how many of the vast number of marketed drugs that do not cause severe DILI also may have been associated with a case or cases. It is therefore unclear whether the Agency reviewed a large sampling of marketed drugs not associated with DILI to attempt to identify cases that met Hy's Law and found none or whether that type of effort may still be needed. Given that there are literally thousands of marketed drugs that do not produce severe DILI, it would be useful to know how many of those have been systematically examined to see the number of them that crossed the 1/3000 Hy's law incidence threshold cited in the draft guidance.

We also note that in many places, the draft guidance regards every elevation of aminotransferases as "liver injury." This represents an inherent assumption that all aminotransferase elevations are a result of hepatocellular injury and there is no other cause for elevated aminotransferase levels. As that does not reflect an accurate understanding of what can cause elevations in transaminases, we believe that, in many appropriate places throughout the document, it would be more accurate to use the term "aminotransferase elevations" in place of "hepatocellular injury."

Although cholestatic liver abnormalities are mentioned briefly in the Background section of the document, there is minimal specific information on these types of abnormalities in the draft guidance. More detailed information and guidance on cholestatic liver injury would be helpful. In addition, there is no mention anywhere in the draft guidance about subjects who may have underlying chronic hemolytic conditions (sickle cell, thalasemia, etc) who often have elevated baseline aminotransferases and bilirubin. With increasing globalization of clinical trials, many such patients may be encountered during clinical development and some of them may have been previously undiagnosed. Although it could be argued that such patients will likely be excluded following screening, there may be need to specifically conduct trials in that population, hence the need to acknowledge them in a guidance on assessment of liver toxicity.

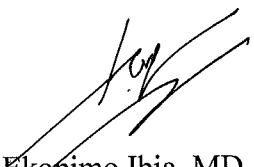
Specific Comments

We have identified areas in the draft guidance document that need additional clarification. As a guide, in the left column of the attached table we cite the line number of the draft guidance document where the subject text is located, the middle column presents a portion

of the text (in quotation marks or paraphrased) as appropriate as well as key comments with a rationale for our position, and the right column gives suggested language (in bold italicized font) for the proposed change (where applicable) with other recommendations and suggestions in regular font type. See attachment for more detail.

We appreciate the opportunity to share our comments with respect to the draft guidance document: Drug Induced Liver Injury: Premarketing Clinical Evaluation. Please do not hesitate to contact me, should you have any questions.

Sincerely,



Ekopimo Ibia, MD, MPH
Director
US Regulatory Policy

Attachment enclosed

Attachment

Specific Comments		
Line number	**Text, Comments and Rationale**	**Proposed Changes**
Draft Guidance for Industry **Drug Induced Liver Injury: Premarketing Clinical Evaluation**		
Lines 79-80	The draft guidance states that "Cases of severe DILI have rarely been seen in drug development programs of significantly hepatotoxic drugs." It is unclear if the phrase "significantly hepatotoxic drugs" refers to investigational or marketed products. Drugs showing significant hepatotoxic signals during pre-registration are not registered. There is also the issue of patient withdrawal from trials after regular clinic visit or laboratory screening reveals liver test abnormalities. We, therefore, interpret the statement to refer to marketed products.	We suggest this sentence be deleted. If it is retained, we recommend revising the sentence to read "***cases of severe DILI have rarely been seen during the development program of drugs subsequently found to be significantly hepatotoxic in the post-marketing period.***"
Lines 143-147 and Lines 183-189	The draft guidance considers elevated serum total bilirubin as "evidence of reduced overall liver *function.*" While we agree that serum bilirubin is the most sensitive index of impaired liver function, we note that the guidance is silent on fractionation of total bilirubin, a standard clinical laboratory practice to guide the differential diagnoses of liver impairment.	We recommend that the guidance clearly state that serum total bilirubin should be fractionated and clinical decisions be based both on the total and the conjugated fraction.
Lines 175-176 and Lines 191-194	The draft guidance considers one Hy's Law case in clinical trials as "ominous" and two as "highly predictive of a potential for severe DILI". As noted earlier, the draft guidance acknowledges the limited availability of concrete data and also that cases of severe DILI are generally unpredictable. Given the lack of adequate studies, the predictive value positive (PVP) and the predictive value negative (PVN) of the criteria the draft guidance regards as constituting Hy's Law remain uncertain. The guidance seems to recommend that finding one or two cases that meet the criteria for Hy's Law would immediately terminate the drug product development. While we agree that finding two cases that meet Hy's Law criteria will be most concerning, it is unclear what to do with a single case that meets such criteria, as the draft guidance does not seem to have taken	We recommend that in the event of a Hy's Law case during drug product development, the decision to continue or terminate the development program should be based on overall assessment of the potential benefit versus risk of the drug product. In addition, we suggest that the word "ominous" be deleted from the guidance or replaced with the word "***concerning***" or "***worrisome.***"

	into consideration the overall benefit versus risk of such a drug product.	
Lines 179-181	In citing a case of Hy's Law in the tasosartan clinical trial database, the draft guidance states that the "manufacturer was asked to do a large-scale safety study before the drug could be approved." The draft guidance adds that the "study was never conducted." The implication here is that the sponsor refused to do the trial. This seems unnecessary in a guidance document as there might have been a number of reasons why the sponsor could not do the trial.	We recommend the section be deleted or revised to read "***…tasosartan, an angiotensin II blocking agent, showed a single case of Hy's Law. No large-scale safety study was performed to examine any definite association.***"
Lines 196-200	Based on past experience, including three examples, the draft guidance states that …"there is a set of laboratory signals that have the ability to predict a potential for severe DILI with reasonable sensitivity and specificity in a database of several thousand subjects." The draft guidance seems to imply that drug development programs will always need a pre-market database of that size to evaluate the potential for severe DILI. Further, the draft guidance uses a database of 3000 as illustrative examples in some sections of the document. We believe the size of the database should be tailored to the specific development program with appropriate consideration of the benefit versus risk of the compound in development as well as the proposed dose and duration of treatment. We also suggest that the guidance give illustrative examples based on different sizes of the clinical database to avoid the unintended impression that a pre-market database of 3000 patients is what the Agency expects.	We request clarification if the draft guidance is recommending a pre-marketing clinical database of about 3000 patients for evaluation of the potential for a drug product in development to cause severe DILI, and whether this applies to all drug products or only to those in which there is a basis for concern regarding DILI. We recommend the size of the pre-marketing clinical database be tailored to the specific development program, including a consideration of preclinical and/or clinical signals of the potential for hepatic injury.
Lines 234-235	The draft guidance states "we are not aware of false positive Hy's Law findings." This implies that all cases (and even one case) of Hy's Law are associated with severe DILI and does not give any explanation of how rigorously this has been assessed by FDA.	We consider the statement "we are not aware of false positive Hy's Law" too vague and uninformative of the completeness of investigation for false positives. Therefore, we

		recommend the sentence be deleted or that it be revised and/or clarified to reflect the rigor of FDA's assessment.
Lines 267-277	The draft guidance recommends inclusion of subjects with liver impairment in at least phase 3 clinical studies if they are likely to be treated with the drug if marketed. The draft guidance states that there is no well-established reason to exclude such patients from trials, "except perhaps to avoid confusion between the previous disease and an effect of the test drug." We believe that, given the current state of science, exclusion of patients with underlying liver disease in order to improve assessment of safety findings is a reasonable and industry best practice approach. Besides confounding any potential liver abnormality findings, patients with baseline liver abnormality would most likely require additional measures to adequately protect them. We agree that patients with baseline liver abnormality should be studied if they will be treated with the product in development. However, we believe the current approach to conduct pharmacokinetic study in that population is sufficient. Even with the stepwise approach suggested in the draft guidance, enrolling patients with baseline liver impairment is unlikely to significantly contribute to a better understanding of the product in the total study population as the number of patients enrolled with impaired baseline liver abnormality will be relatively small and such patients are likely to have heterogeneous etiology of their underlying liver impairment. Additionally, fluctuations in serum liver enzyme assays are likely to be variable, depending on the underlying liver impairment, target disease, and properties of the investigational agent. Moreover, many of such patients will have significant additional co-morbidities and non-drug related adverse events that would make data interpretation extremely difficult, if not impossible.	Given the heterogeneity of patients with existing liver abnormalities, the relatively small patient population with such abnormalities, the likelihood for significant co-morbidities, and the challenge of interpreting worsening liver status in such patients, we recommend that the current practice of conducting only pharmacokinetic studies in liver impaired patients be maintained. Alternatively, enrolling patients with underlying liver abnormalities should be considered on a case by case basis, focusing on drugs that may be very prevalently used in such a population and that such studies are done with early and frequent Agency input. We believe that approach best protects such vulnerable patients.
Lines 281-282 and Lines 494-512	The draft guidance recommends monitoring liver function tests in normal subjects in early phase trials "at least for a few months." We note that the draft guidance does not specify if the proposed measures for evaluation and follow up are recommended to apply to all stages of drug development and for all drug development programs or for phase 3 only, and if specific plans for hepatotoxicity monitoring should be incorporated into all protocols. It is not clear exactly when should signals be looked for and how the finding of	Given the resource implications in the recommended period for monitoring liver function tests and the additional data to be collected in the case report forms, we request that the Agency provide further guidance

	potential signals should impact subsequent decisions on the program. It is also unclear what rationale should be used in determining the frequency of monitoring (preclinical findings, what is known about the compound or class of compound, patient population under study, duration of therapy, etc). In addition, the draft guidance lists information that should be collected in case report forms for cases in which liver injury is found (including control subjects with such injury). It is unclear if the term "liver injury" refers to elevated or abnormal levels of aminotransferases or it means more significant liver impairments. Given the rarity of severe DILI or even of Hy's Law cases in pre-market clinical studies as acknowledged by the draft guidance, it would be unlikely that phase 3 trial case report forms would have all the information at the outset of the study. It would assist in study planning, if the Agency provided a clearer guidance on when the case report forms should begin to capture the information stipulated in the draft guidance.	on the timing of the intense liver test evaluations implicit in the draft guidance document. We also request further guidance on how findings in early stage of development could inform the decision on subsequent stages of development.
Lines 456-492	The section on Research Opportunities seems misplaced.	We recommend that this section be moved to the end of the document.
Lines 514-515	The draft guidance regards a case of Hy's Law as a serious unexpected adverse event that should be "promptly" reported to the FDA. Although the word "promptly" leaves room to multiple interpretations by different sponsors and investigators, this recommendation in the draft guidance seems unnecessary as we believe a case of Hy's Law should be treated no different from any other significant adverse event.	We recommend that a case of Hy's Law be reported as any other significant adverse event.
Lines 600-603	The cutoff levels in the draft guidance are somewhat different from the levels used by the DILI Network of hepatology researchers. For both their retrospective and prospective studies, the Network defines "documented clinically significant" DILI as: • Jaundice or serum bilirubin > 2.5 mg/dL and any elevation in ALT, AST, or ALP • No jaundice and serum bilirubin < 2.5 mg/dL, but elevations in ALT or AST (> 5 x ULN) or ALP > 2 x ULN), or	Given the expertise of investigators in the DILI Network and the fact that their input is vital to a guidance like the current draft guidance on DILI, the expectation would be that the cutoff points in the guidance would be identical to those of the Network. Merck

	• In persons with known pre-existing liver disease, elevations in ALT or AST > 5 x baseline or elevation in ALP > 2 x baseline. Other investigators in the Network have used different cutoff levels for their studies. Granted the different levels by the Network investigators may be designed to enroll as many cases as possible, these are different from (albeit sometimes more conservative than) those proposed in the guidance (lines 600-607), we assume that the investigators are likely guided by a scientific rationale (probably from literature review) for their chosen cutoff levels.	encourages the use of a unified definition. One possible advantage of a cutoff point consistent with the DILI network is that data generated based on the DILI guidance could allow independent confirmation of findings from the Network studies.
Line 601	This bullet point in the draft guidance introduces a cutoff level for serum bilirubin of > 1.5 x ULN when analyzing pooled controlled data. Other sections of the draft guidance recommend a cutoff level of > 2 x ULN increase for bilirubin levels. There is no rationale given for the apparent inconsistency.	Keeping all the earlier comments in mind, we recommend that the guidance provide a consistent cutoff point for serum bilirubin.