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Because health matters

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December 18, 2007

Via fax and UPS

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

Re: Docket No. 2007D-0396

Draft Guidance for Industry on "Drug-induced liver injury: premarketing clinical evaluation"

Dear Sir/Madam:

Sanofi-aventis U.S. Inc, a member of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled **"Drug-induced liver injury: premarketing clinical evaluation".**

This draft guidance describes the sensitivity and specificity of various indicators of hepatotoxic potential, as well as the observations needed to evaluate those indicators, including detection, confirmation, and monitoring of liver test abnormalities, close evaluation and exclusion of other causes, and careful supportive care and follow-up to normality or return to baseline status.

In general, this draft guidance provides a good summary and is to be applauded.

GENERAL COMMENTS

Since the concept paper of January 2007, this guidance has been awaited due to several implications in the definitions and analysis of hepatotoxicity markers. This guidance is very welcome. It is well documented and clearly supported by the community of hepatologists. However, a few definitions would need to be refined in order to clarify the data interpretation, be in line with the current knowledge and facilitate the application of the guidance.

In addition, we suggest the revision of this guideline 2 or 3 years after its implementation in order to validate the proposed recommendations for predicting drug hepatotoxicity.

2007D-0396

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SPECIFIC COMMENTS:

Page Number, Line	Text	Comment
Page 1, Line 21	...***severe*** liver injury (i.e. fatal or requiring liver transplantation).	Is this definition of "severe" applies all along this guidance? - If yes, it is suggested to delete the brackets. In other terms this definition would be "irreversible liver failure". - If no, this definition should be as accurate as possible, e.g., what about a liver injury requiring a hospitalisation? Is a "clinical" jaundice would be sufficient to define the severity? The International consensus meeting of experts in Hepatology [1] defined the severity in three stages once the liver injury has been ascertained: (1) the jaundice or bilirubinemia over 5mg/dl, (2) the decrease of Prothrombin factor or better of factor V below 50% of normal and (3) hepatic encephalopathy (any grade). (1) Benichou C, 1990, Criteria of drug-induced liver disorders. Report of an International Consensus Meeting, Journal of Hepatology, 11: 272-6.
Page 2, Line 54	...hepatobiliary obstruction...	Is this term used to mean "biliary tract obstruction" or "cholestasis"? For the former it would be preferable to refer to the biliary **tract**. For the latter "cholestasis" should be defined as the decrease or the discontinuation of bile secretion function of the liver.
Page 2, Line 55	...but in general this condition is reversible after administration of the offending drug has stopped.	It is recognised that this is also true for the hepatocellular injury but may take longer for cholestatic liver injuries. In addition to the symptoms of cholestasis that include jaundice and (sometimes severe) pruritus, the main but rare risks of cholestatic liver injuries are the protracted evolution and hepatic fibrosis.
Page 2, Line 61	These injuries resemble almost all known liver diseases and there are no pathognomonic findings, even upon liver biopsy, that make diagnosis of DILI certain.	It is suggested to add: "In addition there is no sign or symptom specific to a liver injury except jaundice accompanied with dark urine and decolored stools which might be late in the development of the injury."
Page 2, Line 68	...such as chronic hepatitis C or nonalcoholic steatohepatitis (NASH), that may or may not have been recognized before exposure to the experimental drug.	But these conditions do not rule out possible drug hepatotoxicity and careful evaluation should be done to distinguish between an underlying liver disease or an acute liver injury and sometimes, both of them.
Page 2, Line 72-73	...are toxic to anyone receiving a large enough dose...	It is suggested to replace by (additions in bold) : "...are **usually** toxic **in several animal species and to most humans** receiving a large enough dose"...

Page 3, Line 99	The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals,...	It is suggested to replace by (addition in bold): "...**Most** drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals...". It should be emphasized that this statement does not apply to drugs that caused severe DILI during clinical development but were stopped thereafter.
Page 4, Line 145	...manifested by increased serum total bilirubin ...	Increased serum total bilirubin is not specific enough in this context since hemolysis would produce the same laboratory abnormality. Indeed serum total bilirubin includes unconjugated (indirect) and conjugated (direct) bilirubin making impossible to distinguish between (mild, moderate) hemolysis and liver injury . It would therefore be preferable to specify that the serum conjugated bilirubin, being a specific marker of altered liver function (except very rare inherited diseases involving an enzyme deficiency), should be measured in conjunction with ATs.
Page 5, Lines 179-180	Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. The manufacturer was asked to do a large-scale safety study before the drug could be approved. The study was never conducted.	This information does not help the reader to understand what to do: either this sentence should explain why the study was never conducted or should be removed. Does this example mean that a large-scale safety study has to be proposed as soon as one Hy's Law case is identified?
Page 5 Lines 211-212	...to suggest an increased risk of DILI."	It is suggested to add "severe": "...to suggest an increased risk of **severe** DILI."
Page 6, Lines 222-224	One or more cases of elevated bilirubin to >2xULN in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP in gall bladder or bile duct disease, malignancy), with no other explanation ...	In this guidance for the definition of hepatocellular injury it is proposed to take into consideration the alkaline phosphatase serum activity until 2 ULN. This limit would be very high as compared to ALT elevation above 3ULN. Indeed the range of ALT elevation is approximately 50-100 times that of ALP. That is the reason why it is suggested to use the criteria defined by the International Consensus Meeting of Experts (1) where late Hyman Zimmerman was an active participant and used by Björnsson et al (2) quoted several times in this guidance. Indeed the consensus was to measure the ratio ALT/ALP, each term expressed in ULN. When the ratio is above 5 the type of the liver injury is hepatocellular , below 2 it is cholestatic and in between, mixed. (1) Benichou C, 1990, Criteria of drug-induced liver disorders. Report of an International Consensus Meeting, Journal of Hepatology, 11:272-6. (2) Björnsson, E and R Olsson, 2005, Outcome and Prognostic Markers in Severe Drug-Induced Liver Disease, Hepatology, 42(2):481-9.
Page 6, Lines 238-239	...depends on the population exposed for a long enough time and on the rate...	It is suggested to add " **on the stringency of stopping rules"** as follows: "... depends on the population exposed for a long enough time, **on the stringency of stopping rules** and on the rate..."

Page 6, Lines 241-243	The implications of these three findings may be different in patients with existing liver disease such as fatty liver disease, NASH, or chronic hepatitis C or B, with bilirubin metabolism abnormalities (Gilbert's syndrome), ..	In order to ensure a proper interpretation of the Hy's Law it would be necessary to develop this paragraph on the limitations. In addition to a possible Gilbert's syndrome, increase in unconjugated bilirubin due to other causes must be ruled out. Then in case of increase in serum total bilirubin it should be recommended to measure the **serum conjugated bilirubin.** Regarding the definition of hepatocellular injury, see comments above, page 6 lines 222-224.
Page 6, Lines 243-244	...and in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir (Zhang and Chando et al. 2005).	It is suggested not to restrict this recommendation to drugs that inhibit bilirubin glucuronidation but more generally to all drugs that impair bilirubin transport (which includes uptake, glucuronidation and excretion).
Page 7, Line 283	It is uncertain whether early symptoms (...)	Since there is no sign and symptom specific to the liver injury it is suggested to insert: ..."early and **unspecific** symptoms (...)".
Page 8, Line 330	Obtaining additional tests to evaluate liver function, as appropriate (e.g., International Normalized Ratio (INR)).	As INR involves several clotting factors, all of them being vitamin K-dependent except Factor V(proaccelerin), this test would not be specific enough to determine the severity of the liver injury. It might be more appropriate to measure Factor V in plasma. This test can be performed in almost all laboratories and particularly in a central laboratory in the context of a clinical trial. The result of factor V assay is expressed as a percentage of normal and the limit of the clinical relevance is 50%. The smaller this percentage, the greater the severity of the liver injury. Needless to remind here that this measurement is one of the main criteria for the decision of liver transplantation.
Page 9, Lines 370-374	Criteria for drug discontinuation	The 4 proposed criteria are altogether difficult to implement in practice. Would it be possible to adopt one criterion consistent with the threshold used for assessing AT elevations, eg: ALT >3ULN (Page 5, lines 202-212).
Page 9, Line 402	...e.g., antinuclear antibodies...	It might be useful to emphasize that autoantibodies can be triggered in case of immunologically-mediated DILI.
Page 10, Line 404-407	Biliary tract disorders	It would be important to mention gallstone migration in the biliary tract as a possible cause of marked ALT elevation.
Page 10, Line 419	...or alpha-1-antitrypsin deficiency.	It is suggested to add the following sentence: "**However ALT is usually increased at baseline in these conditions**"
Page 10, Line 434	"...that liver injury was related to an underlying liver disease."	It is suggested to add the following phrase (in bold): "...that liver injury was related to an underlying liver disease **or to another drug taken by the patient and not yet identified**"

Page 11, Lines 451-454	If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge.	This guidance on rechallenge would be difficult to implement and it is likely that EC/IRB would not authorize such a procedure knowing the high risk of acute liver failure especially when we do not know whether an immunologic mechanism is involved in this adverse effect.
Page 11, Lines 468-476	Experimental models	For the sake of clarity it is suggested to distinguish models that are developed with an objective of early identification of DILI potential from those which help determine which patients would be at risk
Page 11, Line 489	...class-related hepatotoxic agents...	Clarification is needed for "class-related hepatotoxic agents". Does this refer to the chemical structure or pharmacological class ?
Page 12, Lines 514-515	Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to the FDA promptly.	Is this criterion (Hy's law) becoming a new one for – regulatory expedited reporting within 15 days?
Page 13, Lines 579-586	Assessment of Drug Metabolism	The section is vague and gives no guidance. Most non-hepatotoxic drugs are also oxidatively metabolized by the CYP450 system, and lead to some level of covalent binding. No quantitative threshold for covalent binding has been established to distinguish hepatotoxic from non-hepatotoxic drugs. This section should be removed from the guidance, and is more appropriate in a discussion of non-clinical approaches to evaluating hepatotoxicity.
Page 14, Line 603	Elevations of AT(>3 xULN) accompanied by elevated bilirubin(>1.5 xULN, > 2 xULN)	These 2 values for total bilirubin for one threshold for ALT are confusing. What would be the added value of having total bilirubin>1.5ULN? Wouldn't it be simpler to set one value for total bilirubin >2ULN
Page 14, Line 605	...and time-to-event analyses should be performed.	Time-to-event analyses are requested again in the next paragraph. It should be left at the sponsor's initiative to provide time to event analyses for the parameters with sufficient amount of patients. It is then suggested to delete the following sentence: " and time-to-event analyses should be performed."
Page 14, Line 611	Time-to-event analyses for elevated rates of significant individual events (e.g., elevated AT, bilirubin) should be provided.	It should be added that Kaplan-Meier plots are probably the most appropriate graphical representation of these data.

Page 15, Line 673	Were there any cases of probably drug-induced serious or severe DILI?	What is here the difference between "severe" and "serious"? Would "serious" be defined according to the regulatory definition? In that case, in order to avoid any confusion or misunderstandings, a clear definition of both terms should be provided in the guidance (see comments page1, line 21).
Page 17, Line 612	…, risk factors,…	It is suggested to specify risk factors known to be related to liver injury, e.g. gender, obesity, age, history of viral illness, history of liver disease, alcohol use, acetylator status. These 2 references may be relevant: (1) Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis 2002; 22: 145-55. (2) Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an overview. Expert Opin. Drug Saf. (2007) **6**(6):673-684. In modeling for probability of liver injury, the parameter of interest would be risk factor by treatment interaction.

On behalf of sanofi-aventis U.S. LLC, we appreciate the opportunity to comment on the *proposed Draft Guidance for Industry on drug-induced liver injury: premarketing clinical evaluation* and we hope that you will take our comments under consideration.

Sincerely,

Mark Moyer
Vice President US
Regulatory Development