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8 November, 2007

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

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

Dear Sir/Madam,

I am writing to comment on the above draft Guidance for Industry on drug-induced liver injury that was recently posted on the FDA website.

I am a clinical immunologist who is predominantly an HIV clinician researcher, with some experience in researching the safety of antiretroviral therapy. My comment may not, of course, apply to many other drug classes.

1. Lactic acidosis is a well-recognised complication of HIV nucleoside analogue reverse transcriptase inhibitors. They can cause mild through fatal steatohepatitis. Even with severe hepatitis, serum transaminases are often only modestly elevated and are rarely associated with elevations of bilirubin. I feel that this and other likely exceptions to Hy's Law should be acknowledged in the final Guidance along with suggestions as to how assessment might be different. In particular, measurement of plasma lactate is an essential component of diagnosing this condition.

2. The draft Guidance lists a considerable number of alternative causes that should be considered when evaluating patients with acute elevations in transaminases. A common cause that I could not find in the document is the recent introduction of other licensed drugs known to be associated with hepatotoxicity. Perhaps I missed this. In the HIV setting this would include a large number of drugs such as anti-fungals and anti-tuberculous drugs.

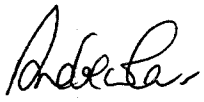
3. Improvements in immunological function with antiretroviral therapy can lead to flares of underlying untreated infectious diseases, commonly referred to as Immune Reconstitution Inflammatory Syndrome (IRIS). IRIS can include

hepatitis. This possibility may well apply to withdrawal of therapeutic immune suppression such as in transplantation.

4. Withdrawal of hepatitis B therapy can also lead to flares of chronic active hepatitis B infection. This might occur if a hepatitis B drug was ceased when enrolling in a clinical trial.

Thank you for the opportunity to comment on the Draft Guidance.

Yours sincerely,



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