PAULS

AFTERNOON SESSION, 26 MARCH 2008

DR. SENIOR: Gentlemen, ladies, please be seated. We're coming into the home stretch. The afternoon program includes two major items: an open public discussion and the three moderators' attempt to pull together and summarize the sense of the meeting. Now we can't take a vote. That's forbidden because this is not an advisory committee. This is simply an open conference, an open public conference, where we seek to hear as many opinions as possible.

Before I go any further, I'd like to get a round of applause for the superb work that Lana Pauls has done and that Diane Freeman has done in helping run this meeting. (Applause)

Diane is our registrar from the AASLD.

UNIDENTIFIED SPEAKER: The microphone's not working.

DR. SENIOR: Diane Freeman is our registrar from AASLD. Say hello. (Applause) Diane tells me that there were 226 registrants, about 65 percent from industry, about 25 percent from government and about 10 percent from academia, which is about as expected for a meeting that's really focused around discussing a guidance. So I think it's been a very successful meeting, and we've gotten great input. (Applause.)

MS. PAULS: A couple of housekeeping announcements before we start: The first one is if Peter Hoffmann and Rolf

Rosencrantz can please see Diane Freeman at the registration desk, we'd appreciate it.

A couple of other things: I had mentioned yesterday that there was a docket open for this meeting, and that we will be accepting comments from now to June 30th. There are some pieces of paper out by the registration desk that have the docket number, but just for those of you who are interested now, it is FDA-2008D-0128. So if you want to jot that down, we're still accepting comments on the Guidance document as a result of this meeting. And it's also on the website, and there will be a link to it.

The last item I have is for this afternoon. We had designed this meeting to have an open public time from 1:30 to 2:30, and in the docket for the announcement of this meeting, people were to contact me. I have only two contacts so far. So if anybody wants to make any kind of a public statement, please come let me know.

Dr. SENIOR: Now just to say what's going to happen beyond this, we are going to be gathering in all of the comments and posting everything on our website, on the main FDA open public website. Jjust enter in “livertox” in the search box and you'll get to it. We're going to put everything there.

The docket that Lana referred to, that number which you can't remember, is posted there and so further comments can be submitted to that docket until the end of June. Over the

summer our writing committee is going to try to gather all that information together, distill it, boil it down into a revised Guidance document, which will incorporate all of your good thoughts, and then we will submit that to the Agency for its clearance. Now clearance takes what? Six months? It took from April to October this time for the draft. So we probably won't get it out of the Agency until after the year 2009 has begun. If we submit it say in September, it may be March 2009 before it comes out because all of the Agency officials have to read it and add a few commas and maybe change a word or two. Then it will then be posted and it will be available for final comments before it goes into effect.

Now I want to emphasize that what we're writing is not a regulation. It is not something industry must do. It is something industry should consider that we hope it will do, we hope it will think about. It's a set of suggestions or recommendations. We hope that they'll be reasonable and that you will consider them and have some good substantial reason if you don't want to do it that way and let us know.

So with that, I want to thank Andrew Bartholomaeus who came all the way from Australia from their regulatory agency, called the Therapeutic Goods Administration of Australia. It's their equivalent to the FDA, but as Andrew said, it's about 1/15th the size in numbers of people.

I do want to mention an NIH-sponsored workshop on

standardization of nomenclature about drug-induced liver injury and causality assessment. I think it will be a very valuable exercise, and an important program. It's going to be held in December at the Lister Hill Center. Leonard, do you want to go to a microphone and say anything about that or do you just want to shout?

DR. SEEFF: This is an unexpected presentation. So I don't have any slides. Actually before I describe the meeting, let me just make a couple of comments about the DILI Network study. As many of you here know, the DILIN study has been in progress for about five years. The first year focused on developing the protocol and various forms which are routine for NIH network studies, and since then, we've been collecting cases. Lest you think we only have 250 cases, as was discussed earlier by Don Rockey, that's 250 that have been adjudicated. We actually have a little over 400 prospective cases and about 50 retrospective cases. And we also have published an RFA, under the guidance of Jose Serrano, the project officer, to expand the study, and all the applications will be reviewed shortly; we hope to expand the network to at least eight or maybe more centers so we can collect more cases.

So to the meeting. A problem that was actually mentioned by Arthur Holden is the concern about standardization of the nomenclature and causality assessment of DILI. So we have arranged for a meeting which is to be held at the end of

this year, December 1st and 2nd, 2008 at the Lister Hill Auditorium, at the National Library of Medicine. It will in fact be a discussion that will include an international group of investigators. We have people coming from the UK, from France, from Spain, people coming from Sweden, people coming from the Far East, from Japan, from Singapore and so on, but none from Australia. I wish we did. We aim to get together to talk about developing a common language so that we can agree on what we're all doing in regard to DILI. In particular, we want to review the issues around causality assessment, which is a really big problem. We tend to believe now that the use of an expert panel is the best way of doing it. Although it appears to be the best approach for the moment, I think that that's not the answer because we can't always have three experts to assess every single case in clinical practice, as we are doing in the DILIN study. Ultimately we shall need to improve the RUCAM system, making it more user-friendly, and that’s one of items that we will try to work on.

So if anyone might be interested, I do have some pamphlets about the meeting. The website has just opened and if anyone wants to know what the website is. . . . .

DR. SENIOR: I can tell them.

DR. SEEFF: Okay. You have it.

DR. SENIOR: Go to www.niddk.nih.gov/fund/other/diliworkshop2008. U

UNIDENTIFIED SPEAKER: Too fast.

DR. SENIOR: I think if you go to the regular NIH site, you can find your way there, and search for diliworkshop.

DR. SEEFF: If you go to the NIDDK website, it will tell you where to go for anyone who might be interested.

Oh, one other thing that we're doing. We're working with the National Library of Medicine to develop a central livertox database. This is going to be a spectacular project. I'm really absolutely amazed at what has already been accomplished and the database will hopefully be launched at the time of the meeting. The person at the National Library of Medicine who's working on the project will be presenting the information that has been developed thus far. We're aiming to review virtually all currently used drugs, whether or not they have caused liver disease, and will provide a description of the liver injury, where relevant, reviewing references dating back to far in the past. So I think that this will be a very, very useful and helpful resource for people who are interested in the area of DILI. Thank you, John.

DR. PEARS: Thank you, Leonard. We will be working, all of us, to actively in the next few weeks to gather all the information together and to post it at our FDA liver tox website. We hope to have there not only the slides and abstracts and bio-sketches, but also the actual comments made by the presenters and the discussion and also the references,

not only the citation, but whenever copyright will allow it, access linkage directly to the paper in this pdf form. So you'll be able to really read the papers that are behind the citations.

So with that, I turn the meeting over to Lana, who is going to run the open public session.

MS. PAULS: Good afternoon everybody. I think John made this my easiest part of the last two days because even though I'm to run this open public meeting part, there were only two people that asked to speak. So this may be really, really simple and really, really fast. If anybody else is interested in getting up to make a comment, feel free.

The first person is Marianne Keisu from AstraZeneca. You can just use the microphone in the back.

MS. KEISU: There's just one question that I would like to ask, and it's in reference to the guideline we have been discussing. We have been discussing now a lot about Hy's Rule, Law, whatever we call it, and the difficulty in actually deciding what is a real case or a potential case of Hy's Rule.

Looking at the Guidance document and trying to see how we as a pharmaceutical company would be able to adhere to the suggestion that these cases should be treated as serious adverse events, which I very much agree to if they are real. what I would like to ask is how does the FDA envisage when does the clock start for expedited reporting if we get this case of

a combination of ALT and bilirubin elevation which is a signal of a potential serious case? Now coming from that signal where you can really see the time point, the time point where we have some reasonable possibility to think that this is a real case of Hy's rule is kind of flexible, as information is usually coming into the company over a period of time, allowing the interpretation of the clock start date to vary. So I just was wondering whether we can get some more clarification and discussion around it to be able to apply this. Thank you.

MS. PAULS: Okay. So if I understand the question correctly, it's a little bit difficult to diagnose exactly when the event occurs --

MS. KEISU: Yes.

MS. PAULS: -- and you want to know when the 15-day adverse event clock begins.

MS. KEISU: Yes, because this is the only way you can translate something into the processes we are working with I think, if I ask 10 people to look at the same complicated case where information has been coming in at multiple time points , probably we will get 10 answers, and I guess none of them need to be wrong. It's just to see how we can do the right thing.

MS. PAULS: The first two people I'd like to address that are John Senior and Mark Avigan, please.

DR. SENIOR: What Marianne is suggesting is a very important issue and one that has been a thorn in the side of

the DILI group, if I'm correct in that: knowing when did the reaction begin, when was the true onset? What we get most often is when it was found, when it was discovered, and when it's discovered or detected may be weeks after the reaction actually started. So it makes it difficult to know how to apply that little formula of the multiples of the ALT elevation over the multiples of the alkaline phosphatase elevation to know whether it was initially cholestatic or hepatocellular injury. If you don't get the beginning, you don't know.

And so what DILIN has done is to use the time of detection, whenever that occurred, as the onset, but that's not the real onset. It's just when it happened to be discovered, which depends on patient reporting or the doctor's suspicion, or whatever it depends on. Paul, you may want to comment on that issue.

DR. WATKINS: Yes, I think the question is a regulatory one, which is if you define Hy's Law case as excluding all other possibilities.

MS. PAULS: We can't make a regulatory decision if we don't know when it happens. And you can't report it until you learn of it.

MS. PAULS: Use the microphone.

DR. AVIGAN: Can I take a stab at it? We will have to work on this a little bit. It would seem to me that once you identify the event, that the clock would start from when

the serum bilirubin is 2.0 or higher. Typically, with serum transaminase elevations, there will be hepatocellular injury. Serum ALT elevations may be trivial and self-limited or alternatively will often precede serum bilirubin elevations. It makes sense that once you get to a serum bilirubin level of 2.0 or greater, that would initiate the clock for reporting, if it's going to be reported as a 15-day event.

UNIDENTIFIED SPEAKER: Right, then the question --

MS. PAULS: Can I ask you to please go to a microphone if you're going to respond to him.

DR. COMER: I was going to ask the same question. Maybe I can get the clarification necessary. I think the question is: do we report based upon ALT and bilirubin elevation or do we confirm that it's actually a real case and that the alkaline phosphatase is not elevated and that there's no other probable cause? For example, pancreatic or liver cancer, or something like that. Do we need a complete case before we report, or are you interested in all possible cases that happen to have ALT and bilirubin regardless of other extenuating circumstances?

DR. AVIGAN: So I understand the question. I think we will get back to you with a firm answer, but I do think that within a clinical trial dataset, you're not going to get that many cases that simultaneously are marked with jaundice and elevations of transaminases due to DILI. Most likely we'll ask

for all cases and you will have then the opportunity to come back with a follow up report that gives us the necessary information to enable differential diagnosis and the exclusion of non-drug causes of liver injury. This can take some time, depending on the clinical scenario. As a gastroenterologist, I know that there are times when the ERCP or imaging study results and interpretation may become available at later time, so the final diagnostic and clinical outcome set of answers may come actually quite late. It may be difficult to wait for all follow-up data before reporting the event, and I think a better way to handle it would be to submit an initial report and then follow up with a subsequent report which would give us the follow up differential diagnosis and the most complete answer.

MS. PAULS: Dr. Bloom, a comment?

DR. BLOOM: Mark, you may want to also add to that clarification on the non-concurrent requirement, that is to say I've been asked that if you get a greater than 2 bilirubin and then 2 months later you get the enzyme elevation. Regardless of that particular hypothetical situation, it sounds like there needs to be some clarity around the fact that they don't have to be concurrent and the timeframe that needs to be considered.

DR. SENIOR: We're going to have to work on this to define the onset. Is the onset when the patient first begins to notice symptoms? Maybe. Is it the first elevation of transaminase? Maybe. Is it when they start to raise their

bilirubin or INR? Maybe. But like Mark, I think we would like to have an initial report as soon as you find a problem and then have a subsequent report when you fill in the details which may take sometime. It may be a long time before you establish the causality. Sometimes you don't know the patient has cancer of the pancreas. It may take some time to find out, and if you don't -- and as Mark said, you often get rise in enzymes before, sometimes weeks before the bilirubin goes up. It depends on the process. It depends on the process going on in the liver, which is related to the mechanism of injury that is not the same for every drug or every patient.

DR. AVIGAN: We will try to address that question, the answer with transaminase or the bilirubin, because there can be a delay in the rise in bilirubin and obviously there will be some kind of cutoff, but it can be variable according to the tempo of the injury.

DR. HUNT: Chris Hunt from GSK. Just stopping by to clarify, we do know that increasingly and certainly just talking about the HIV drugs, et cetera, that increasingly compounds can cause inhibition of transporters and combined with or without Gilbert's syndrome. We can see if the ultimate interest is ALT greater than three times, bilirubin greater than two times, you would potentially get false negative reports in patients with indirect bilirubin elevations and I'm just wondering if you want to clarify if the direct bilirubin

is greater than 35 percent or whatever the FDA believes is appropriate, that those events are not in need of reporting, that you're really interested in primarily direct bilirubin elevations, just for consideration.

MS. PAULS: I'm seeing Mark shake his head. So I think the answer to that question is yes.

DR. HUNT: Okay.

DR. ALVAREZ: Daniel Alvarez, Wyeth Pharmaceuticals. Good example, and I want to give you another one. So to be sure that in the guidelines we said that we clarify more than one issue, this guideline probably will not apply in cases of hemolysis, in case of Gilbert's, or drugs that inhibit UGTA1. We had a trial in which patients on baseline would have a drug for treatment of hepatitis C, who had ALT between three and five times ULN. So when we get results a few days later, many patients met Hy's Law criteria, because the total bilirubin was increased, mostly indirect. So having followed the guidelines, we reported 50 percent of our patients, 60 percent, 70 percent of our patients. So we did clarification and I understand that there're no data to define total bilirubin versus conjugated bilirubin. I think we have to make, for certain classic examples like UGTA1 inhibitors and drugs that cause hemolysis, a best estimate about the right bilirubin. Hepatitis C and HIV that are very important in development. We have to maybe make our best estimate at this point.

MS. PAULS: Okay. The other person that we have who requested a time -- Gail, did you do both of your questions already?

DR. COMER: No, I had one question that was sort of a corollary of Daniel's. I think the Guidance needs a little bit more information and guidelines for patients with liver disease that are in clinical trials, in terms of how to handle DILI in those patients. That was really it.

MS. PAULS: Okay. We will take that into consideration. Thank you.

Is there anybody else here that would either like to make a public statement or a comment, have a question on the Guidance before we move into a wrap up? Yes, please.

DR. OSTER: This is Manfred Oster, Sanofi-Aventis. I think the Guidance needs more clarity on the definition of Hy's Law in case of elevated alkaline phosphatase. According to the definition right now, there would be no Hy's Law cases above two times the upper limit of normal of alkaline phosphatase. I think we have to agree on what the definition of hepatocellular injury above that level is, and if there are any cases that would need to be reported and considered to be Hy's Law cases above that level.

MS. PAULS: Thank you.

DR. SENIOR: I think we hear what you're saying, and we'll have to work on clarifying it and we shall try to do so.

Now there was one other comment that came in. Herb Bonkovsky submitted a couple of reprints or papers, and I wandered, Herb, if you wanted to say something about what you sent just before the meeting.

DR. BONKOVSKY: I had suggested that a couple of recently published papers be discussed, and if there had been time included in the syllabus material, but it was too late. One of them has already been discussed. It was the paper that Naga spent a little bit of time talking about in another discussion, that was published just this week in the Archives of Internal Medicine. The first author is Brent Tetri from St. Louis University, and it's about the lab variations in ALT and what is behind that, and I think that was reasonably well summarized, but the full reference for those of you that might want to look at it is Volume 168, page 663, Archives of Internal Medicine, March 24, 2008. And again, the main point is that the main source of variability is actually the so-called reference range which is extraordinarily poorly defined in patients who really weren't evaluated very well. Some labs don't use any reference range. They just use historical reference ranges and the like. This whole issue of what should we consider as a normal ALT or an abnormal one, continues to be somewhat contentious, I guess one could say. I myself think that Naga's suggestion that we begin to think of the ALT kind of the way we think about glucose levels and make it outcome

oriented. That is, we now have a number of bits of information that indicate if your ALT is elevated, regardless of cause, there is adverse effect on mortality and long term outlook and things like that. It seems to me that a normal woman who is not obese and not on drugs X, Y and Z, and so on, by and large would not have an ALT above 20, and a normal man, who is not obese, et cetera, would not have an ALT above 30. So giving a little bit of room for leeway, we could say for men, it shouldn't be above 40, for women above 30. So I think that whole issue of what is going to be considered an elevated ALT is at least going to need to be addressed in the guidance document.

The second paper has just been published electronically. It's a review entitled "The Current State of Serum Biomarkers of Hepatotoxicity." The first author is Dr. Ozer from the Merck Research Laboratories. Others include Department of Pharmacology at BU, BioTrend and Drug Safety at Pfizer. It's available as an e-publication right now in the journal Toxicology. And it's sort of a general review on ALT and other proposed biomarkers for hepatotoxicity.

DR. SENIOR: Thank you, Herb. I think that this issue is an important one, and may be something that NIH would consider defining this, a standardization issue, about what is normal range of our most-used detector, the ALT measurement, the activity in serum. There's a lot of controversy on this,

and I think we need to have some clarification. It's no longer tolerable for a laboratory director just to have all the technicians stick out their arms and assume they’re normal, but that's the way it used to be done. That may include people who are obese, people who have undiagnosed liver disease, maybe chronic hepatitis C that may or may not be known, and so forth. But I think this is an issue that requires clarification and maybe the NIH will consider that in December.

MS. PAULS: Okay. We have one more. Jay.

DR. BARTH: Jay Barth from Merck. My question, and I don't know if you’ve the answer now, relates to applicability, or if there are differences in the application, of the Guidance to pediatric clinical trials, and if there are differences. I don't know if that would be addressed at some point in the future.

DR. SENIOR: Good point.

DR. BARTH: Thank you.

DR. HOFFMANN: If we have some time, may I ask a short question? Is this a no?

DR. WATKINS: Go ahead.

DR. HOFFMANN: It was mentioned -- Peter Hoffmann, Novartis. It was mentioned yesterday that the biologicals will be covered by this guideline, too. Is this assumption correct?

DR. WATKINS: Sorry, I didn't hear that question.

DR. HOFFMANN: It was discussed yesterday that

biological agents may be covered by this guideline, too. Is this assumption correct?

DR. WATKINS: That was my opinion; I just said it. There's no distinction, and I don't think anyone's presented any reason why there should be a distinction in the clinical aspect --

DR. HOFFMANN: Right.

DR. WATKINS: -- of assessing safety. I mean preclinically obviously there's no reactive metabolite, those sorts of things but clinically I'm unaware of any data why they should be handled any differently.

DR. HOFFMANN: Thank you.