Discussion IIB

DR. SELIGMAN: Let me ask Dr. Barth and Dr. Goldkind to come on up and join us. We have an additional 20 minutes for comments, discussion. I know that you've already had a chance to ask Dr. Goldkind questions. Dr. Barth has raised many provocative and interesting issues with his questions before us. So please.

DR. STONE: Hi. Marc Stone, FDA. This may seem kind of a strange question coming from the FDA to Dr. Barth, but I consider it more of a devil's advocacy for the purpose of discussion. You pointed out what a big problem DILI is for industry, in terms of drug development, and basically to the business model of producing effective drugs. That sort of suggests that if companies could find a better way to deal with DILI, individual companies, they may have a competitive advantage. But what you were saying in your talk was, for one thing, that having different companies doing it causes them to underestimate or overestimate the risk which with the Guidance, unless the Guidance is so unquestionably brilliant, and with all due respect to John Senior, all that is going to result in is that everyone is going to be either underestimating or overestimating the risks. And it seems like the principal advantage in adhering to a guideline rather than going independently is to avoid the risk that somebody's going to do it better than you. And that is, you know, kind of a

socialistic point of view.

DR. BARTH: That's an interesting perspective. I certainly hadn't thought of it that way. I certainly wouldn't question the brilliance of the Guidance. I think the pharmaceutical industry is looking for the best way to deal with the issues of DILI, and there probably isn't one right way or one only right way to deal with the various aspects of it. I think the Guidance proposes a very good approach to address these issues. There may be some areas in which one could find variations on the ways outlined in the Guidance, to do things a little differently, but overall if the industry as a whole adopts an approach that's uniform, that's considered to be very effective in detecting signals and analyzing data, then I think it will benefit industry as a whole and benefit the public as a whole to be able to develop drugs appropriately and terminate the development of drugs when that's appropriate as well. And that's really how I was looking at it, not from any way in which a competitive advantage could be gained through applying or not applying the guidance.

DR. READ: I have a short question. I'm Holly Read from Abbott Laboratories. During your discussions, all of you, I was curious to know what role the data monitoring board might play in discussing some of these issues? If they're being used more often, in what situations to do you decide that you need one?

DR. BARTH: I'll start with that. I think there

is widespread use of the monitoring boards, data monitoring safety committees and so on. Generally they're used when there is a particular concern that's known prospectively before the start of a trial, and that adjudication and assessment of causality will be helpful during the course of the trial. This is in order to protect the safety of the subjects and identify a problem during the course of the trial before all the patients are enrolled in the trial and get exposed to the drug. So I think it could be applied based on the rules, the rules for example that are in the Guidance, when there are anticipated concerns about liver toxicity. A data monitoring committee could be established, and the rules under which that committee would operate would be based on a lot of the strategy that's already in the Guidance.

DR. GOLDKIND: I think that's a good suggestion. The FDA, as you probably know, has a guidance out on data monitoring committees and how they might be used. It's actually quite extensive and quite well done. And although our regulations don't require the use of data monitoring committee in any regard except one area, and that's in the setting of emergency research where it's a highly visible and controversial setting where you have an exception from informed consent, we certainly do recommend them in many other venues.

DR. SELIGMAN: One of the considerations in the draft Guidance related to challenge, you talked about, has

the drug has shown important benefit? I guess the question I had is in the context of clinical trials where the question is still being asked, does the drug indeed have a benefit? How relevant do you think that question is in the context of making rechallenge decisions in the context of clinical development of a product?

DR. GOLDKIND: The way I was thinking about that scenario is that you're looking at this particular clinical trial within a larger context, and that's the context of the disease itself. What else is known about the other alternative therapies, their benefits and their toxicities? Clearly there's a lot that's not known about that particular drug but there might be some information about it in another disease or another population and there's certainly a larger context to the development plan so that that's how I was thinking about it.

DR. WATKINS: Yes. Hi. Paul Watkins, University of North Carolina. One of the comments I think may be a misperception. The Guidance doesn't say that if you see a clear Hy's Law case, that there's no reason to go any further, or even two Hy's Law cases. And if I think if Bob Temple were here, and I guess he's not, I don't think he would say that's the take-home message. But obviously there is an issue and there are a couple of reasons why that can occur.

First of all, a drug capable of causing irreversible liver injury can still be a useful drug, a la

isoniazid. The other thing is, there is a condition called idiopathic acute liver failure that Will Lee knows very well, occurs somewhere between 1 in 1,000,000 and 1 in 500,000 adults per year. If they happen to be in a clinical trial and that happens, that's obviously, you know, a death not more than a Hy's Law case.

Furthermore, in many cases, they're not as clear cut as the placebo arm or getting statins in men that are otherwise healthy. So if there's any kind of surgery involved or a serious illness, there's a condition, benign post-cholestasis. As somebody who does a lot of this, you'll see cases of somebody who will develop -- it will be a Hy's Law case, but the biopsy suggests it might be autoimmune hepatitis. Well, is that de novo autoimmune hepatitis or did the drug initiate autoimmune hepatitis? Well, you'd think, if you stop the drug, then the person should get better. But was one famous case with Ketek (telithromycin) occurred two weeks after he stopped the drug, developed jaundice, and had a biopsy. Experts on both sides argued back and forth, but a year later, his enzymes were still abnormal. You know, was that a Hy's Law case even in retrospect, now that we think the drug might have a problem. So there's plenty of gray area in the real world as you approach these cases. I think if Bob were here, he would say, he would agree that, this is a signal of great concern but it would not be a reason to stop the drug. It's not like a positive AMES test or something where you just

stop a drug in development, but if anyone else has comments, please make them.

DR. CHALASANI: Naga Chalasani from Indiana University. My question is not necessarily related to this session, but is in follow-up to Paul's comments about the monitoring, especially post-monitoring. It seems like the widespread opinion, at least now, that monitoring is not effective, whether it is because not done by physicians or whether what's being sought is such a rare even that it's not cost effective. I just wonder though if there is any arguement for more active monitoring? Right now it is pretty passive, you know, it's in the package insert that says do it, don't do it. In case of statins, we know that only about 30 percent get done. That's one point.

The other one is there anything like risk management in terms of warfarin, or the goal is to actually have a foolproof compound that actually has, you know, 1 in 1,000,000, risk of DILI? I think when you have a compound, you're going to have events. I wonder if we're just completely forgetting about whether we are heading towards not accepting any risk? I'm just not so sure.

And also about the risk management, rather than just passive recommendation to the clinicians, you know, should the patients be getting a urine dipstick, you know, looking for jaundice or some more, you know, patients in power rather than depending on blood draw.

DR. WATKINS: Naga told me to stand by the

microphone. So I did. Of course, there is some risk management. Isoniazid is an example where public health departments give one month's supply and the patient cannot get another month's supply until they're seen by a public health nurse, and they then say they feel fine. Then they get their next month's supply. So that would be, you know, one form of sort of risk management.

The problem comes when you start scheduling visits for monitoring that are more frequent than the patient would normally be seen by the physician. Then what usually happens is the marketing group in the company comes in and says this drug is no longer viable. You can't have special visits for monitoring.

There have been discussions of dipsticks, blood dipsticks for ALT which is technically feasible but in the discussions that I've been in, it turns out the companies that are in a position to develop them would lose money on the more standard way of doing liver chemistry. So it's an economic decision not to pursue it.

DR. OSTER: This is Manfred Oster from Sanofi-Aventis. I have a question regarding the extrapolation of risk from the cases of Hy's Law as they are defined in the current draft Guidance document. In the current version of the Guidance, I think there is an attempt to translate the clinical observations that Hyman Zimmerman made into cases that are defined by laboratory thresholds. My question refers to the extrapolation of risk for severe liver

damage, leading to transplantation or death, these 10 percent. Is there consensus among the experts that the cases as defined in the Guidance have the same predictive value as the clinical cases described by Hyman Zimmerman?

DR. WATKINS: Yes, I can take a crack at that. I mean to say that obviously what Hy Zimmerman was talking about is somebody who shows up yellow, jaundiced, in front of the physician. Actually at the time, it was a remarkable hypothesis, because if somebody's jaundiced for other reasons, like viral hepatitis, they don't have anywhere near a 10 percent mortality.

So what he was talking about were people that were much sicker, but the argument is in a clinical trial, you're catching these people much earlier and you're stopping the drug. So the data that’re used to say that the 10 to 1 extrapolation is correct from a clinical trial as the Rezulin, where there were two cases of jaundice in 2000 in the clinical trials, and so that's 1 to 1,000 and then 1 to 10,000 was the extrapolation in the real world, which you may argue about but is somewhere in the right ballpark or may be in the right ballpark. But that's an assumption, you know, obviously.

DR. BATKIEWICZ: Hi, I'm Leah Batkiewicz from New York. Given all the discussion we've had on Hy's Law for Phase III trials, the patient population size that we've seen before for these larger disease indications of 2 to 3,000 seem to be suitably adequate for going forward post-

marketing. I'm wondering what both industry and Agency think for more orphan indications, maybe genetic diseases and whatnot, what size patient population you might need for a Phase III program?

DR. SELIGMAN: Good question. Do we have someone from the FDA who wants to address the question related to orphan indications? It's not specifically addressed in the values, is it, John?

DR. SENIOR: I'm not sure.

DR. SELIGMAN: Yes, the question has to do with orphan products that were tested in a much smaller database and has a whole series or set of special criteria for moving those products to market. To what degree, I guess, does the Guidance document apply to those particular products?

DR. SENIOR: Regardless of the product, we're still struggling with numbers. If you have a very low incidence event like serious hepatotoxicity, you need large numbers of patients to find it. If you don't have the numbers, you can't find it. It doesn't happen. So we can't get away from what I call the tyranny of the numbers. The numbers are what they are. The incidence rate is what it is. If you don't have enough people exposed to see the cases, you won't see the cases. It doesn't mean they won't occur when millions of people are exposed later. So we're stuck with it.

DR. BARTH: Perhaps, too, the issue with an

orphan drug is that the population you have available to study is going to be small anyway, and you just won't have the numbers. And the nature of the condition may be that there are not alternative therapies, in which case the benefit may still outweigh the small chance of an event in a very small number with the condition, which is more of an issue than would be for a mainstream drug.

DR. ALVAREZ: Daniel Alvarez from Wyeth Pharmaceuticals. I just want to follow up in the comments and remarks John that made and Jay answered very clearly. If every company tries to develop its own guidance and tries to understand in every way and predict and make decisions individually, I think the advantages probably will be very miniscule. The advantage we'd have would be short-lived, and I think companies realize that you cannot do drug development, where you can be good at developing drugs, testing the drugs appropriately, and post-marketing. I think it is a very complicated issue between money and resources, not just for any individual company. And I think we realize, for example, that the Predictive Safety Testing Consortium is a way to find biomarkers for liver disease that are being used now in preclinical development. So I think it's not undoable that companies can try to engage themselves and with FDA trying to actually get this Guidance tested prospectively and trying to actually improve our success of bringing new drugs to development. So I think this is a very good start. We realize today

that we have a lot of great expert opinions, and very, very few data. So we are undertaking a lot of guidance with a good start based on no minimum data. Some things we are very far away from where we're supposed to be, so the only why I think is that we have to continue to start this kind of collaborative efforts.

DR. SELIGMAN: Thank you very much. One final comment please.

DR. PILLEMER: Yeah, Stan Pillemer from MacroGenics. I'd just like to follow up on the question about extrapolation from the data on which the Guidance is based. Well, it's emerged from the clinical rule. The drugs are for the most part chronically administered, although I guess there are antibiotics that could be administered more short term. They are small molecules and so I wonder what thought has gone into how this pertains to biologics and particularly, for example, monoclonal antibodies which may have specific targets but may not enter cells and may not act by some of the standard mechanisms that the small molecules do in creating toxicity.

DR. SELIGMAN: Anyone wish to comment on the question related to larger molecules in the applicability of this Guidance?

DR. WATKINS: I think the preclinical ways to screen for hepatotoxicity obviously are very different but I don't know there's any evidence that the clinical

evaluation with biologics would be any different. And, actually, the mechanisms that are now being proposed for at least the fulminant liver injuries, the people that don't adapt involve the innate immune system, the acquired immune system. So tinkering with that, whether it's a small molecule or biologic, really may not make any difference but the Guidance obviously doesn't recognize any difference. At least right now, I'm unaware of any rationale why a Hy's Law case should be considered any different in the two categories.

DR. SELIGMAN: Well, with that, thank you. It's been a long day. There's a reception following this and what time are we convening in the morning?

MS. PAULS: The reception is right up here on the mezzanine. We will reconvene at 8:00. For those of you who want a more substantial dinner, the cafeteria is open downstairs until 7:15 tonight. Okay.

(Whereupon, at 6:00 p.m., the meeting concluded.)