DISCUSSION IIIB

DR. PEARS: Perfect. Mark, Jack, Arthur: do you want to come and join me up here with the other speakers? While everybody's gathering, to use again a chairman's prerogative, just to try to summarize what I think I've heard, there're several assumptions being made, both in the Guidance document and the presentation this morning, that don't necessarily match. That might be a place to start our conversation as to whether they need to match. That is, the current way we use biomarkers we measure, that at the moment that aren't good enough for anything? We need better biomarkers in order to make decisions for patients and in follow up for drug development and the use of drugs in the public health scenario. The biomarkers need to help us to make decisions or otherwise they're not worth having. And the biomarkers have to be believed enough for those decisions to be made.

Those things aren't really explicit in the Guidance document. Perhaps they need to be. Certainly based on my own personal views, we need to do something, because doing something is better than nothing. At least if we start doing something, then the issues are going to get flushed out and then we can start addressing some of these issues more openly.

The ideas that I would like a bit more discussion

about are that a lot of what's been talked about is driven by new technology platforms. It's all thinking about tissue samples that we might collect and examine in different ways in the future. That adds an extra layer of complexity, because we've got the validitation of the assay platforms to understand. AstraZeneca actually collects and has been collecting an awful lot of stuff for years now, and one of the things that certainly we have got an interest in is looking at different ways of interpreting information we already collect. So, for example, poor old gamma-glutamyl transferase gets dismissed by everybody as being useless, but is that based on real true factors or is that based on prejudice because we don't really know? Are there other ways of looking at it and can you combine it, for example, with changes in INR? Can you use baseline body weight and age? Are there other ways of integrating what you've collected? So I'd like to have some sort of discussion about that.

And the other assumption that's kind of being made both in the Guidance document and in the presentations today is that beyond hypothesis generation, it's unlikely that any one stakeholder in this is actually going to solve the problem of new biomarkers, either for susceptibility or for distinguishing adaptors from tolerators.

So that's my thinking. I welcome any comments on that, any comments from the audience, any thoughts on the presentations you've heard. I'll remind you to identify

yourself for the record please.

DR. PIERCE: Ross Pierce, FDA/CBER. I think it was mentioned that one of the problems with identifying predicting biomarkers is a problem of power. If you're looking for biomarkers with any one particular agent, and you're only dealing with an incidence of Hy's Law cases or of DILI that's 1 in 1,000, or 1 in 10,000, it seems to me that if you have lost say 90 percent of your liver function before you start to see an INR, before you start to see a rise in bilirubin, it would be really useful if perhaps NIDDK can put out an RFP to encourage development of a new type of biochemical test that would give a linear response with the mass of functional hepatocytes. Instead of the tools that we have now that really show when you have fallen off the cliff, but would show when you're at a state of teetering on the cliff. I think that you then would have individuals identified in whom you could do these investigations into other sorts of genetic and metabolic problems. I don't know if it's more profitable because it may well be that people who run into the most trouble, have maybe four or five or six different things going on that in combination have some kind of multiplicative effect. Maybe if the people with 20 or 30 percent knockout of their liver function, which right now we're not identifying other than if they have a rise in ALT, which doesn't give us enough of a predictive value. Maybe if we see the dose had a cluster of 2 or 3 of these biomarkers and set us on the way of

getting to the bottom of this, it would help.

DR. PEARS: Thank you. Thoughts, comments.

DR. BLOOM: Yes, there are so many challenges in monitoring functional liver mass. We do not have the tools to do that effectively, as you imply, beyond application of Hy's Law with all it’s limitations.

I think, though, some of the ideas that John Senior introduced, including standardizing routine markers to optimize signal detection, are getting us closer. We're arguably also making progress in developing new biomarkers and validating them in patients under well controlled conditions using some of the molecular tools and analytical platforms I discussed.

From my perspective, the issue is not whether we're able to measure hepatotoxic effects; increasingly we are able to do that. The bigger issue is what may be the relevant patient populations and are they accessible? We can't develop a surrogate for a patient population without patients to study and the materials (including relevant, annotated biological specimens) and tools to achieve that. I'm afraid I keep coming back to that but I find that we're often talking cross purposes around this issue.

DR. AVIGAN: Given that these are rare events, we have to collect all of these specimens. You really have to have a systematic collection process and a consistent phenotyping process where you comprehensively document DILI cases but also systematically collect the specimens of

interest.

Now the biomarkers, as I said, are in two categories, the ones that indicate DILI susceptibility prior to drug exposure, and then the injury markers after drug exposure that predict outcomes. What is still unknown is whether all different liver injury events induced by different drugs all have the same linkages to a subset of genomic biomarkers. We don't know think that will be the case. Also, there is an evolving two-hit mechanistic hypothesis, early injury followed by loss of adaptation, but at this time it is merely a hypothesis. It's not proven and, in fact, one of the problems that we should bear in mind is that there's not a lot of literature about individual patients in the real world who have developed serious liver injuries at different times from different drugs. If you're postulating that certain individuals have an adaptation defect, then you would predict that you could find individuals who developed multiple DILI events. And I've scoured the literature for that, unsuccessfully. If anybody's made such an observation, I think that would be immensely important to know about.

DR. PEARS: Any more comments or questions for the record?

DR. KENNA: I'm Gerry Kenna from AstraZeneca. Thanks very much to all the speakers this morning for some excellent presentations and some very nice science.

A few personal perspectives: I feel that one of

the difficulties you're running into in this area is we're getting very complicated, and we know that science is very difficult, and we understand it incompletely. And while we understand the science incompletely, and we have imperfect models, it seems that attempts to find better biomarkers that address multiple issues could really be confounded by the difficulty of trying to invent the science as we're trying to monitor effects.

In this session, we haven't heard, for example, how mechanisms and mechanistic studies have a link to the basis of susceptibility. And my feeling is that the really strong insights with respect to susceptibility markers are coming from exactly those sorts of investigations. The Newcastle Group looked at UGT and at MRP2 and at CYP2C8 as potential genetic markers of susceptibility to DILI caused by diclofenac, because of previous investigations of mechanisms of toxicity. So we were coupling up mechanisms to hypothesis driven marker investigations. I think we need to be thinking of how to drive that forward as an integrated group, bringing together pharmaceutical companies and the best academics and bodies like NIH with close links to regulatory agencies because that's the only way we will make progress in such a challenging area.

I think with SAEC, the opportunities will come in from that avenue as well, a great example of the value you can get from integration. We've got the Predictive Safety Testing Consortium bringing people together as well. If we

don't pursue mechanisms, I think we're missing a trick.

One other comment is that I didn't hear anybody really talk today about the distinction between biomarkers that may just select safe drugs as compared to biomarkers that will enable us to manage the drug and the patient and as a preclinical person. My belief is we need to be doing both and to be really clear about how we're using biomarkers for those purposes.

I was very impressed by the nice science that was presented this morning talking about in vitro approaches and in silico approaches. To me the value of that is going to be selecting better drugs. When we've got the first drug from a new therapeutic class coming up and causing DILI, I think we used the term about the canary in the mine. Isn't that an indicator of how it’s important to attempt to select a better drug if DILI is identified in a new class of drugs, more than worrying about managing the patient with a potential problem?

DR. BLOOM: I don't think anybody would argue against that understanding mechanisms can lead to better candidate biomarkers, but what you say is aspirational. Further, for reasons I discussed, it will be impossible to do that without access to the susceptible patients at issue in a clinical trial setting. You alluded to some novel in vitro assays and models being applied to established putative DILI agents to explore mechanisms. These have been largely agents associated with a higher incidence of DILI,

whether it's isoniazid, acetaminophen or what have you, to make the associations, be they a mechanism or a drug interaction. The caveat here is whether mechanisms and risk factors associated with other more common hepatotoxicity are relevant to the hepatotoxic agent that affects 1 in 10,000 patients exposed. And I take your point, Mark, about adaptation, which may be more likely to be in common among these populations. My bias is that adaptation is probably far less critical as a risk factor, although I have no data to support that view. I think the DILI Network is more likely to identify that (i.e., the ability to adapt to an hepatotoxic insult) than other individual susceptibilities which I think are inevitably candidate specific, but I'd be interested in hearing your thoughts on that.

DR. AVIGAN: Well, I think that this gets to the heart of what specimens you want to collect. There are two strategies. One is to collect samples from all patients on all drugs, or as soon as you have somebody in trouble, on them along with matched controls. It could defeat you if they have different mechanisms than you've found in those with the effect. So you have to strategize in advance between those two possibilities. And I think from a scientific perspective your best bet would be to try to focus parameters about what you're collecting, just like you were doing a bench experiment and you do that as you would, try to minimize the number of extraneous variables, one being different drugs. And I've been talking about

this with John Senior and others, the idea of picking a tried and true drug like INH that John mentioned. Since it's such a broadly used drug across the world in so many clinics, and the incidence of serious liver injuries is sufficiently high that you could potentially use that as a model where you don't have to worry about diversity of mechanisms across different drugs. From a scientific kind of design approach, I think that is a better bet. You run a risk of missing a mechanism by mixing up different drugs, and I think this is one of the challenges that the DILI Network is going to face once they decide how to actually apportion their samples for analysis, since they've plugged in multiple drugs.

DR. KENNA: Can I come back once more--

DR. PEARS: Sure.

DR. KENNA: -- to the mechanistic thing. The reason I believe that this is doable in real time is because we have much better tools nowadays. So, for example, the in vitro human hepatocyte tools enable us to look at relevant mechanisms like mitochondrial dysfunction, BSEP interactions. We can do that in real time while clinical trial samples are being obtained, and we're doing that within our company. I know that all the companies have the capability and they're doing similar things. So I think with a bit more creativity, we can do it in our preclinical and clinical studies to a greater extent than what is being done at the moment most times.

DR. BLOOM: Again, the sophistication isn't directly proportional to the relevance of these biomarker applications. You can look at that in a highly sophisticated manner, and I was so impressed with the assay system the MIT group developed that I presented-- it almost defies credibility. It's a remarkable tool, but if you're not looking at the relevant population, such as that rarified group of patients that is susceptible to this idiosyncratic effect, it is not going to get us there -- that's really the issue.

DR. PEARS: Paul.

DR. WATKINS: Paul Watkins, Chapel Hill. To get back to the Guidance, is it going to encourage companies to explore new biomarkers or is it going to have the opposite effect? Now that the liver chemistries have been clearly defined, could clinical development people convince management to pay for alpha GST or serial methionine breath tests to see if that does predict who's going to go on to develop Hy's Law.

So I guess maybe that's a question for people here. Once the final Guidance comes out, clearly defines what the FDA's interested in looking at, will that actually reduce the likelihood that new research will be done in the biomarker area?

DR. PEARS: Let me give a personal opinion on that which is from one pharmaceutical company and doesn't necessarily reflect the company's opinion. I believe that

there is a growing awareness of the need to do this amongst the higher echelons of one pharmaceutical company that I can speak about. I think that one thing this group ought to seriously consider is independent engagement with pharmaceutical organizations. In some ways, we can't appreciate a choir with people that hear us preaching from PhRMA, and I think there's a higher level in organizations that ought to be engaged in discussion, a few of these here to address some of these issues, to make sure that we can help us overcome some of the issues around that disconnect.

DR. PEARS: Bob.

DR. TEMPLE: There is a non-specific paragraph in the Guidance that emphasizes the need to learn more, but of course it’s hard to be very specific about how to do that. So it strongly encourages investigators to try and figure out what makes people susceptible to toxicity, but it can't say too much more than that.

DR. BLOOM: I think that this is so important to the pharmaceutical industry, far more than most suspect. There are few things more costly — be it a withdrawal of a drug from the market, a phase III failure, or a negative image. We are highly, highly motivated to try to figure out a way to manage this risk more effectively. But as with NIH grant support, you're going to have to have a compelling proposal that gets us from point A to point B, and I think that's the challenge -- whether it's a particular breath test, as has been mentioned, or another novel marker that

can make early detection possible, or a genetic marker that is predictive of susceptibility, speaking for myself we would be VERY receptive to proposals that explore candidate markers with this potential.

As regards tissue sample banking, most of us now are banking from every clinical trial patient from whom we can have a specimen that is adequately annotated, which generally is almost all registration-phase studies. Prior to our policy of banking from all registration phase studies, we went through a situation where literally all of our late phase portfolio showed a potential genetic linkage to an efficacy outcome or a safety issue. In every case we would have paid a lot of money for specimens that could allow us to pursue those linkages. Most PhRMA sponsors now realize the difference between disease-associated genetic markers and pharmacogenomics. The former is studied by many academic investigators using various sources of specimens. The latter can only be explored in patients treated with the specific candidate drug. You can't go and just buy these samples, and well-controlled clinical trials is a once-in-a-lifetime chance to access specimens to explore this. That's a little advertisement for banking.

DR. TAUB: I wanted to just comment. Becky Taub from VIA. I just wanted to comment on that because I think there're two classes of biomarkers we're talking about here, one referring to just recognizing liver disease in DILI, which would be general for all drugs, and that's

where I think it's more likely that you will get that from academia I would say. However, I think what the drug companies are doing a lot of is looking for is a second kind of drug specific biomarker, and a few examples were provided, most in the metabolic pathways. In other words, how is a drug metabolized and who are at risk because they have altered metabolism?

So you might, with that type of biomarker, where I think you don't have to be able to identify the 1 in 10,000, if somehow you could just say 90 percent of these people taking the drug don't have this bad biomarker. So they're okay. And the 1 in 10,000 is going to be in a 10 percent population that are higher risk than you've identified a higher risk population.

And you can then choose to either treat or not treat those patients, and I think with the few examples we have so far, like the UGTA1, that's exactly the type of decision that's being made. And, you know, do those at risk people need more monitoring, et cetera. So I don't think it's as gloomy as having to identify 1 in 10,000.

DR. SENIOR: In response to comments by Becky and by Paul, Paul is suggesting that we don't want to suppress investigation of a new biomarker such as alpha-GST data and so forth. Probably more difficult is the problem of the tyranny of the numbers that I mentioned. We're not looking for a more sensitive marker; we're looking for a more specific marker of liver injury. I'm not sure that these

additional enzyme measurements will be more specific. So I think we have to keep specificity foremost in mind when we're looking for relatively rare liver events.

With regard to what Becky was saying, I don't think we should be looking so much for the different drug effects as the different patient responses to those drugs. It's the patient that is getting the drug who responds differently than others that we need to focus on. Am I okay on that, Becky?

DR. TAUB: Well, I think that is one way to look at it. I'm just trying to say, where have there been successes so far in recognizing patients at risk? What it looks like so far is is related to how they metabolize the drug, not so much with DILI but with other types of adverse drug reactions.

Now moving forward, maybe there will be other types of things that we can identify such as what you're suggesting.

DR. AVIGAN: Carbamazepine is a good example. If you have the HLA marker that I mentioned, and you happen to be Han Chinese and you live in Taiwan, then if you take carbamazepine, your chance or risk of getting skin reaction is about 4 to 6 percent, something like that. That's enough of a risk to legitimize avoidance of use of the drug in that subset of people. The key thing is that the test result has a very good negative predictive value, that is if you don't have that marker, you are home free. Part of

the problem here is that in some other cases with biomarkers, we may not have such pure discrimination between risk groups.

DR. PEARS: Yes. Thanks for waiting.

DR. LONG: Yes. Banking biological materials and clinical trial development is a wonderful thing to do. It gives you a lot of options if something goes wrong, whether it's the bone marrow, liver, kidney or whatever, but my question is about genetic testing. In our experience, we have a lot of trouble with IRBs and ECs, trying to bank samples if we don't exclude genetic testing on those samples, particularly abroad but sometimes here in the U.S. How do people get around that problem?

DR. PEARS: Identify yourself for the record.

DR. LONG: Oh, sorry. My name is Walker Long, AtheroGenics.

DR. BLOOM: One way to get around that is having a totally annonymized tissue bank, which we've developed at Lilly. Obviously, we have to obtain consent from patients. The patient must understand that they cannot “de-consent”, in terms of having their sample identified once it is de-identified. That has brought us through IRBs and provided us the right to operate in countries that allow no other sponsor to bank.

DR. PEARS: AstraZeneca has the same approach.

DR. BLOOM: Dr. Temple asked if we published our anonymized banking process. I'm pretty sure we have,

perhaps not in formal publication, but there have been three in-depth reviews by Ethics Committees world-wide, as well as FDA's IPRG (Interdisciplinary Pharmacogenomics Review Group), who are recommending this as a prototype. I think there may be one other totally anonymized bank right now.

DR. TEMPLE: This is a general problem. t has to be solved. It gets in the way of everything we want to do.

DR. PEARS: Thank you. We have time for two last questions. Please identify yourself.

DR. SISTARE: Frank Sistare from Merck. I want to come to something that John Senior just said and I want to make sure we all agree on that. John says we're looking for rare events, and our biomarkers really need to be able to pick up rare events. I think back to the presentation we had yesterday from FDA of a nice graphic description of the four panels, with ALT on the x-axis and Bili on the Y-axis. You had the four panels, and we had a significant number of patients that had sizeable ALT increases, approximately 6 percent. And we talked about tacrine, where 25 percent of patients had sizable ALT increases, and then we had one drug, Drug X which had a significant migration into that top panel. Then we had Drug C and we had two other examples of drugs yesterday where again a sizeable migration into that bottom right panel, increases in ALT (they call it Temple's Corollary in the right lower quadrant), but they did not get up into the Hy's Law right

upper quadrant where bilirubin was also elevated.

So is it a plausible hypothesis -- I want to come back to something Jack presented today -- that in the serum of those patients with Drug C and the other two drug examples, versus Drug X, that there's something different as compared to the patients with Drug X. Is there something different in the signal that appears in the serum there that we have not though to measure yet?

Now it may be, as John points out, not a more sensitive test. In fact, it may be somewhat less sensitive maybe more specific, that is very different biochemically, Is there a signal there that we should be looking for? Maybe it's alpha GST. Maybe it's GLDH. I think I heard Mark kind of dismiss those and say they're probably not going to help us here. But maybe they are. Do we have data that definitively says that we can rule out some of these other biomarkers that we have available to us.

DR. BLOOM: Again we might be able to make associations in those particular populations that may have absolutely nothing to do with DILI patients. I think that that kind of mechanistic work is and should be going on. But, again, the issue is whether that is the relevant patient population, as Becky mentioned. If we have 10 percent of those that qualify for Hy's Law that are truly susceptible (as we have heard), look at the few relevant patients we have to study! And if susceptibility factors (translated to markers) are not candidate specific, you can

see that we have very few patients to study.

DR. SISTARE: Well, I'm going to remove it from the rare Hy's Law cases and again just bring it back to the fact that there are significant numbers, 10 percent, 20 percent, 6 percent, whatever, patients in whom some drugs cause these ALT increases and the same relatively frequent events as with other drugs. So there seems to be something about the drug, not necessarily the patient but there's something unique about those two categories of drugs, some progress upward to a severe form of injury, some do not. And can we use samples from those 10 percent of patients that seem to be responding to some sort of "liver injury event", at least as defined by an ALT increase? We think it's liver injury but is there something different fundamentally about the biochemical signals that are generated there? I think we're just not looking at all the right molecules yet. Mark, I don't know if you want to comment on that?

DR. PEARS: Let me just comment. Probably one of the drug examples was one that we don't necessarily accept as a drug-related liver injury. There may be some question that we're not really looking at a drug-induced liver injury, and that's, that's why we need a test to separate out the noise from the real stuff. We just don't know how common that is because we haven't got a chance to do it.

DR. TEMPLE: I'm not sure if this is what Frank was asking but one of the big questions is whether you can

distinguish the people who will get a little transaminase bounce from their isoniazid from people who will get severe injury. That is critical because it's a drug you have to use. Your best shot at that is examining everything you can in the people who have these different kinds of responses. My understanding is that's part of the project that was being described yesterday.

DR. AVIGAN: Again, there are two questions that are being asked related to different questions that can be addressed by different biomarkers. One is - does the drug have a potential in a large population to cause a problem, and can you detect with the biomarker that there's a risk for that drug to be a hepatotoxin in drug development or after marketing? Separately, of those patients who develop DILI, will they develop clinically serious liver injury? That was the point I was trying to make -- that for different biomarkers the discrimination levels may be different. There may be something there but I think you have to actually explore that question by actually doing the test.

UNIDENTIFIED SPEAKER: Yes. I think it's a two step process.

DR. TEMPLE: And if you identify the people who do get into trouble, you could think about and then you might understand the mechanisms better so you can do something about it with another drug or you could screen them. I mean there're many things you could do if you

could identify those people.

DR. PEARS: Okay. Thank you very much.

DR. BONKOVSKY: Bonkovsky from Charlotte. First as a comment, I mean if you really think about it, surely the kinds of DILI that we're talking about, this so-called idiosyncrasy is going to turn out to be a matter of an interaction between a susceptible host and a given agent and, you know, that's always going to be the case. So there're going to be some host factors probably dependent on immune responses and things like that, but if you never take the drug, you'll never have the reaction. So I don't think we'll ever be able to get away entirely from that, and one of the striking things that we've observed in DILIN is how frequent people give a history of having some sort of allergy, not necessarily a drug allergy, although often a previous drug allergy or some sort of sensitivity. So I think there clearly is, you know, there're some people that are just more susceptible. And this is not just people that have out and out clear immunological reactions like, you know, high fevers and arthritis and things like that. It's broader than that.

But my question has to do with these large databases and doing these genome scans. Now you're going to find certain polymorphisms or variations that put people at higher risk of maybe drug-induced injury but maybe other diseases as well. How are you going to deal with that? I mean these people have said, well, we'll never find out the

results but suppose that you do something that has real implications for that patient or for that patient's family? What do you think is the moral and ethical obligation to inform those patients and families that they may be at risk for drug-induced liver injury but maybe other disease as well?

DR. BLOOM: I don't see the ethical problem just because it's genetic. Measuring Factor V Leiden does not pose an ethical problem in determining we have patients at risk in certain circumstances of bleeding. If, in fact, we're able to make an association, and if we're, in fact, able to determine that it is clinically relevant, I don't think, in the context of privacy issues, it is as problematic as many assume. As a practical matter, we can now de-identify individuals from the protein pattern in peripheral blood samples -- not just through genetic analyses. So the privacy concern is all encompassing, but I really don't see that as a limiting factor here.

DR. AVIGAN: I agree with Jack, and the reason is that you wouldn't have done the test. The alternatives are not to do any test, or to keep it anonymized. In that sense, the alternative of not testing does not enable better patient management. It would lead to a continuing guessing game surrounding DILI. In the end, I think we need to fast forward within maybe our own lifetimes. Truthfully, these genomic markers could be in your medical chart shortly after birth, I mean SNP profiles, et cetera.

As more research is conducted, potentially we may be in the position to know how to cross-index your genomic profile with whatever your risk for DILI would be.

To some extent, the argument is somewhat based upon where we are. My own view is that there is not an ethical problem here.

DR. BONKOVSKY: Well, I just don't agree with you. I think there is an ethical problem but I guess that's what makes a horse race.

DR. BLOOM: I'd be interested in when you can access studies, such as in breast cancer patients, and you're able to identify a profile of 12 SNPs, that together to define the significant risks of breast cancer as we're seeing them now trickle down to clinical practice, how's that different?

DR. BONKOVSKY: Well, you let the patients know.

UNIDENTIFIED SPEAKER: Well, of course.

DR. BLOOM: Well, I don't think that's unethical. I don't think we're contesting that at all.

DR. BONKOVSKY: Well, I thought you were saying that you never tell the patients what the results of your findings are.

DR. BLOOM: Oh, when you're using an anonymized bank-- Okay. So let's say we, five years later, find an association of something that may or may not have had to do with a specific patient. In most cases, it's no longer relevant to the way that patient is managed. Now there is

some pushback in saying the patient deserves intellectual property related to the discovery, and we are saying, sorry, there's no way to get that. But there are some arguments about that. The anonymization allows you to go forward and we can talk about it offline.

DR. PEARS: We're going to have the discussion.

DR. WATKINS: Well, I was just going to say that the DILIN Network maintains the identity link, and works very hard to do that sending, you know, holiday cards and things but it does create all kinds of dilemmas that you just don't have if you anonymize everything. IRBs are not concerned, you've solved your ethical dilemma.

DR. PEARS: Okay. Well, I guess one session out of two isn't bad finishing on time. Thanks very much to Mark and Jack and to Arthur. They were great, great presentations, great discussion. Thanks to you for all your input.

Lunch is outside. I guess you've already figured that out. We're going to be back here at 1:45. We got a stay for good behavior.

(Whereupon, a luncheon recess was taken.)