DISCUSSION IIIA

DR. PEARS: Could I ask the speakers to come and join me up in the front please? I'm just wondering how we could get a microphone to you if you have comments to make. I'm not a hepatologist. I have a job in developing drugs. So I've been to be involved in lots of this stuff before. I'm going to ask dumb questions just based on the draft Guidance because there're some assumptions in there, some things in there I don't understand, some things I think we need to just discuss a bit further and clarify.

And in the process of that discussion, what I'd like you all in the audience to do is to join in, chip in. I had some conversations with people yesterday and heard some presentations where somebody had specific questions or specific issues you want to ask. This is your chance to do it. If you don't take it, and we put out ideas the cross in your perspective, then that's your issue.

We're going to switch microphones so that you all have a microphone to play with. And I would just remind you that when you come to ask questions or give your comments, just identify who you are and your affiliation.

So my first question is about the draft Guidance document and the session presentations. The Guidance talks about patients with abnormal baseline tests and a history of liver disease. The title of the presentation was about stable liver disease. Are they the same thing? Is one

term going to be better than another? And if they're different, which is the right one to use? And can we define either or both of those terms in something which is a bit clearer or do we need to define either of those terms in a better way? So that's my first question

DR. LEE: What's the first one?

DR. PEARS: The first, the thing that's written in the Guidance document is about patients who are excluded because of baseline liver test abnormalities or a history of liver disease. That's what the Guidance document says. The title of the session this morning is about stable liver disease. This is a dumb question: is that the same thing?

DR. REGEV: I'm guessing, I think this was the original meaning. Stable liver disease includes those patients that are not in any acute or sub-acute phase of their diseases. And those are the ones that I mentioned in the first few minutes of my talk. I think we all agree that a patient with acute viral hepatitis is unstable. You don't know where he's going. He could be rapidly improving or he could be going into acute liver failure. I don't think anybody would want to discuss enrollment of these patients in a clinical trial. The same with patients that are in a stage of decompensating chronic liver disease. I think those are also unstable. They develop complications every other day. You wouldn't want to discuss enrollment of such patients. The ones we're discussing are the ones that seem to be stable clinically, have no variations in

their clinical status. Unfortunately many of those, as I mentioned, may have fluctuations in their lab results, which are built into their stable state, and that is something that you can't avoid, but those are considered stable patients.

DR. TEMPLE: I think the point was well made that if you have one or two of those people and they “bounce,” you're not going to know what to do. So you have to plan for this, and have enough people so that the occasional flares will happen in both the control group and the other group. I mean we have found over the years that lots of times a patient with an underlying disease will seem to bounce, and you only distinguish that from drug injury by following them up for a few months. Then you may find that they bounce on weekends and t other times, you may have an alternative explanation. So I think it's perfectly true, that one or two people with a disease can confuse you and wrongly kill a good drug.

That doesn't mean though that if you planned ahead of time, you couldn't have people with relatively stable disease with enough of them to allow you to compare across treatments.

Some of the reports you described actually suggested that there is interaction and if that's the case, you might want to know that. In treating HIV disease, you know, you probably need to know whether you should avoid the drug with someone who has a concomitant viral hepatitis

as well. But as I've said, you really have to plan it and think about it.

DR. LEE: Yes, I think what I'm saying is that we can usually predict or identify these cases either by history or through serologic testing. I'm going to possibly consider stopping the drug but in many instances you can go right through that. If that's what's happening, and they have hepatitis C, then it's probably a slow or very benign episode.

DR. PEARS: Okay. Let's take some questions. There's one, two, three, four.

DR. GELPERIN: Kate Gelperin, FDA. I just want to raise a point for clarification. Dr. Lee had mentioned that he had thought that case of fatal hepatic coagulopathy I presented yesterday was the one that had been lost to follow up. No, for the one I presented yesterday we had full information. There was an additional case in the clinical program of fatal hepatic coagulopathy who was lost to follow up when he went to visit his son in a different state, but that was not the case I presented yesterday.

DR. PEARS: Thank you. Yes.

DR. COMER: Hi. Gail Comer, Wyeth. As a hepatologist and a drug developer, I don't think that Phase III clinical trials, i.e., pivotal trials for approval, are really the place to include patients with underlying liver disease. However, I do recognize the need to get this important information and I would propose that we do a

better job in Phase I. If it's a disease for diabetes, that we should look at the effect on PK early on, to find out in NASH or fatty liver, or HIV, and we find out what's going to happen in patients in Phase I with hepatitis C and B. And then if it's really an important population, I suggest we handle it the way we do in HIV; that we do a co-infection study. This would be a smaller study looking at safety in a very careful and considered way. This is preferable to muddying the pivotal trial with these cases where we don't have enough patients to really figure out what the problem is and these patients will just make everything more difficult.

DR. PEARS: Can I just come straight back on that and ask if you're using your diabetes example, are you assuming that you would have excluded nonalcoholic fatty liver disease at trial entry?

DR. COMER: Yes, if you know that that's what they are, but prior to going into Phase III, I propose that you would have PK data in fatty liver and NASH to find out whether you need a dose adjustment. Perhaps you already know that you have an interaction, and that these patients should be excluded, or you at least have some inkling of what you're dealing with before embarking in a Phase III clinical trial where you put your drug in jeopardy.

DR. PEARS: Bob.

DR. TEMPLE: Well, you can definitely get the PK. That's in some sense the easy part, and needs to be done

for dose selection, but that's not the part everybody's worried about. What everybody's worried about is whether there's an interaction between pre-existing liver damage and drug hepatotoxicity.

But I think your point is correct. You don't want to just waltz into including people with liver disease without thinking about it. Whether you want a separate study or stratified group in your bigger study, I don't think matters that much but it’s important to think about it. A lot of people who are diabetic have some degree of underlying liver disease. Well, you almost certainly don’t want to exclude everybody with diabetes. But you might want to stratify and watch closely and be aware that a bounce in the diabetic population isn't quite definitive, and that you have to look at the control group.

DR. COMER: I think you make a good point. I think though that it's very difficult to handle a lot of these liver cases. I think that Will points out that a lot of the companies really don't know how to handle some of these cases. They're not really worked up fully beforehand to know what you're dealing with. And that if you had them in a separate study, you would be able to do more close monitoring. You would be able to do a better work up and I think it would be a lot easier. Granted, you're going to get some of these. If you do a diabetes study, you're going to get some of these patients anyway. They're going to have normal liver function. You're not even going to

know that they've got underlying liver disease. So you're going to get some of them anyway but if you had a group that had definite NASH, and controlled it more carefully, I think you'd get more information. You would have a much more closely monitored group because you're not going to want to do such close monitoring that you would want in a liver patient, in the general population in 1,000 patients.

DR. PEARS: Thanks. Next question please.

MS. ESGUERRA: Hi. Maritess Esguerra with Amgen. I know that a lot of the speakers and a number of participants here have actually touched on the importance of knowing the patients that you're enrolling in clinical trials. I was actually wondering, from the FDA's perspective, and other sponsors as well as investigators, about whether we should require hepatitis screening for all patients in all clinical trials, you know, regardless of the phase of development?

DR. PEARS: Okay. Thanks.

DR. LEE: Let me take a crack at that. I think you first want to look at your patient population. Who are the candidates for this? Do they have renal failure? Are they substance abusers? I mean obviously if you have a depressed group and you're looking at an antidepressant, I would look at all the viral markers. I think that's probably the easiest example. If you're looking at people already on immunosuppressants or people with Crohn's disease, they've all been transfused. So you probably

ought to look for hepatitis C in that group as well. I think you can look at your baseline population.

The other point that I probably didn't make, but I sort of thought of as we've been sitting here, is if you have a renal failure drug, your site investigators usually are nephrologists. What do they do when they see somebody yellow? They generally admit them to the hospital but they may still not have the algorithm right there in their head. If you're looking at an antidepressant, who are the site investigators? I presume they're all psychiatrists.

Do they have the hepatology mindset when it comes to assessing a case? I think we've had cases that I've reviewed where somebody came in with massive hepatic necrosis and the first test that was done was an ERCP. That doesn't make any sense. And also again that there're too little data in the cases that are identified, but if you don't identify them in the pre-approval process, you're never going to figure it out post-approval because there isn't much surveillance behind it.

DR. PEARS: All right.

DR. REGEV: I agree completely and I think this is something that's probably not done routinely. I think the criteria for screening a patient on enrollment for liver diseases should be like in the average primary care physician's clinic, and there are very clear guidelines as to what are the risk factors that should lead you to evaluating a patient for hepatitis B or C. This should be

done prior to enrollment because of the questions that are raised later on during the study.

For example, as we mentioned, a patient who has a history of IV drug use should not enter a clinical trial without having a screening test for hepatitis C or B.

Currently, that's not routinely done, and therefore we are surprised somewhere down the line when the patient develops abnormal liver tests during the study. Since we didn't know about the underlying liver disease, we didn’t monitor these patients as closely as we should. So I think we should adopt the guidelines that clinical medicine has recommended, and we should screen some of those patients for underlying liver diseases based on their history, physical findings and symptoms.

DR. TEMPLE: I don't think the Guidance addresses that very much yet. Would that be true, John?

DR. SENIOR: We're going to have to take that into consideration.

DR. TEMPLE: Yes, I think we need to put that on the list of things to look at.

DR. PEARS: Thank you very much. Yes.

DR. VIERLING: I am Dr. John Vierling with Baylor College of Medicine in Houston. I would echo the need to address in the guidelines the fact that after marketing, a number of patients with pre-existing liver diseases will be exposed to the drug. Based on the categories of the drugs and their indications, the prevalence of potential users of

the drug who have pre-existing liver diseases could be estimated. Regardless, many people with liver diseases in America will be at risk of being exposed.

Equally important, if one has not purposefully included during Phase III trials populations with high prevalences of chronic liver diseases, then one has not only missed the opportunity to scrutinize the potential for DILI in important subgroups but has also missed identifying many people with chronic liver diseases that do not know they have it. Some 70 to 80 percent of Americans with chronic hepatitis C have never been diagnosed, and a substantial proportion of patients with hepatitis B also remain undiagnosed. Within the Asian-American community living in the coastal regions of America, one can find up to 10% or more of individuals infected with hepatitis B, which you emphasized may be a potential risk factor for DILI.

So I do think we have to grapple intelligently with what the appropriate inclusion/exclusion criteria are needed in clinical trials in order to decide whether or not to include populations that may have higher prevalences of liver abnormalities but will ultimately be the users of these drugs after FDA approval. However, Dr. Temple's point is also well taken. If you include these patients, I would think that you would want to be prooactive in determining how many patients in any category should be enrolled so that you have an estimate of the probability that they

would be equally included in treatment and control groups. To just be willy-nilly and say that a person with a normal range ALT without a known or admitted risk factor is normal runs the risk of not identifying viremic patients with chronic hepatitis C during enrollment of a trial. So the question becomes what are the optimal inclusion and exclusion criteria to address the goals the Guidance wishes to achieve? It would seem to me that we must be much more explicit in our criteria regarding purposeful inclusion of patients with liver diseases.

DR. PEARS: Okay. Arie.

DR. REGEV: I completely agree. As I mentioned in my talk, if we ignore the prevalence of the various entities and make a sweeping recommendation to enroll all liver diseases, then we may end up enrolling patients that are impossible to randomize. As we mentioned before, in an average population in the United States, although there are almost two percent with chronic HVC, we are likely to enroll very few HCV patients in an average clinical trial because most of them don't even know about their disease, and we currently don't screen for HCV on enrollment. Those HCV patients that do know about their disease, many of them will be told by the physicians not to get involved in a clinical trial.

So for some liver diseases, and many of them I think are included in this category, it will be impossible to randomize and will be impossible to really extract very

substantial information. I think in these cases, the risk of destroying a study and discontinuing a drug for no good reason is higher than the opportunity to get information. How much information can you get from a 1,000-patient study with 2 patients or 1 patient with HCV enrolled in the study?

On the other hand, I think entities like fatty liver disease, which is much more common in the populations that we actually treat, we can sometime have 100 patients with fatty liver disease, and it would make much more sense, since we can randomize them and monitor them closely and get some information out of it.

DR. PEARS: Please.

DR. TAUB: Becky Taub from VIA. I just wanted to get back to the statement that individuals with underlying liver disease are not more susceptible to drug-induced liver injury. In reality, there's a lot of preclinical and as you saw, some clinical data that suggests that whether or not the incidence is increased, certainly the severity may be increased, and you provide some examples where the incidence has actually increased, and with some very important drugs like the anti-TB drugs.

So in reality, where are we with that statement? Is that statement correct, that the most common liver disease is now fatty liver disease? You see that those individuals don't do well with liver transplant, are more susceptible to methotrexate-induced fibrosis, et cetera.

I would just like to hear the counter argument on what data indicate that people with underlying liver disease are not more susceptible to drug-induced liver injury?

DR. PEARS: Thanks. You've been reading my notes. That was my next point. Thank you very much. Will.

DR. LEE: I would like to make one point about fatty liver disease, or high BMI patients. In the report of the acute liver failure study that we published in Clinical Gastroenterology last year, we did not show any increase in the number of people with fatty liver, compared to the rest of the population, across the board in ALF. They do worse post-transplant because they're overweight and they have complications post-transplant. We cannot see that their outcomes pre-transplant, all other things being equal, were any different nor were there more high BMI patients than we would expect in the normal population.

I want to get back to Arie's point, too. I think the point I've been trying to make is that we're not seeing in many of our study populations a random sample where you would have two out of 100, whatever it is, 2 percent with hepatitis C. We're seeing in a depressed population, that you're going to have a lot of hepatitis C, former IV drug use and present IV drug use, and so forth, and that's why the odds are higher post-marketing.

DR. PEARS: Thanks. I think that's an important question.

DR. TEMPLE: Obviously I haven't had a chance to

read all of Dr. Regev's papers that he referred to, but most of them weren't controlled trials. And so we don't really know whether the apparent higher rate was just because investigators were paying more attention to those people because they had preexisting liver disease.

But I guess the observation I'd make is that when you try to think of drugs that have gone down because of Hy's Law cases, I don't think you'll find any mistakes. I think the drugs were all hepatotoxic, as discovered in other countries where they were proved to be (dilevalol, ximelagatran), or as discovered by the accumulated data here. So I think we are generally able to sort through the problem of concomitant illness that was really the underlying disease. We're very conscious of that, of course, you know. The question always is: was it the person's disease or did the drug do it? So I'm not sure how much of a problem that has been historically.

DR. TAUB: Just one question. Obviously everyone wants to be able to identify those individuals who are at higher risk. So I think it is an important question to know whether people with underlying liver disease are at higher risk. I would agree that you need a more dedicated study with higher numbers of patients in order to know the answer, but I was just asking the question as to what are the studies that refute the ones that were cited today? And I still haven't heard the answer to that.

DR. TEMPLE: The problem is that those studies

don't show it. They raise the possibility, but they don't prove it. But what you really need is to have people with or without liver disease included in the trial and getting both drug and placebo and show that, yes, there's nothing in the group that doesn't have liver disease and there's a whopping something in the group that did. I don't know of any study that has ever shown that, but maybe there is if you look better.

DR. REGEV: I was threatened here. I was under a threat (laughter), but my view on this question is that there are a few specific drugs that we can say that do show increased toxicity with certain underlying liver diseases. One example that has a significant amount of data in the literature is the anti-HIV drugs and HCV. I think we've accumulated enough evidence to support this specific claim that some HAART drugs are more hepatotoxic in patients with underlying hepatitis C, probably HIV as well. I think the same thing can be said about anti-TB drugs. The studies are not great, but they're accumulating, and I think we can say that with some anti-TB drugs, there's some increased percentage of drug-induced liver injury when a patient has a background of hepatitis C and B.

Now remember, these are just two groups of drugs. There are thousands of other drugs about which we have no information. We cannot make this statement about other drugs, and we probably will never be able to make this statement because hepatotoxicity is so rare to begin with

that you cannot really look at the data. So I don't think that you can completely change the claim that underlying liver diseases do not predispose to DILI. I think you can probably say that we have a few examples where underlying liver disease does predispose to DILI, and those are the ones that I mentioned.

DR. PEARS: Okay. Thanks. Next question please.

DR. MAYNE: Yes, this has been a great discussion. Obviously --

DR. PEARS: Identify yourself please.

DR. MAYNE: Jim Mayne, Pfizer. Great discussion, and it’s very important to the stakeholders in the room on this topic. I just wanted to try and bring it back around to the question of what does this mean for a regulatory guidance document? And how does this excellent discussion get captured in the context of a guidance?

It seems like there's broad agreement that we do want to study patients with liver disease and we want to study them in an informed manner. But the question then becomes when and how do you study those patients? There also seems to be agreement that studying those patients, particularly with specific liver diseases that are at low incidence is very difficult to do in routine trials.

So spinning it back to guidance language, is there any greater insight now on how we might capture this discussion? Is this something that we can capture in granular detail in the form of a guidance on how and when

to study such patients, or as I think Arie has highlighted for us, is this a situation where, as so often is the case, we really need to let the old dictum of know your treatment population and study your treatment population, carry the day and make it a function of the program and the target population of interest?

DR. PEARS: Thanks. I'd ask the people who are helping finalize the Guidance to perhaps comment on that. John Senior.

DR. SENIOR: I want to hear what the people have to say. We're very interested in all these comments, and as Bob has already pointed out, we will be paying attention to them in the writing of the final Guidance.

DR. PEARS: Will.

DR. LEE: I would just say, recognize up front the patients who are likely to be treated with the drug. Including these maybe higher risk populations may be a risk pre-approval, but it's going to be an even bigger risk post-approval. So make the arrangement with the FDA that we are maybe even going to target so many hepatitis C patients in the study. Although I take Arie's point with certain drugs, it's not across the board for sure. For most other drugs, we don't see any interaction with hepatitis C.

DR. MAYNE: I think this --

DR. LEE: In HIV, it may be due to their improved constitution, which has to do with the fact that the immune system is getting better. Their HIV is actually

getting better and then they have a little flare with the disease, but it's complicated on the HIV side.

DR. PEARS: Please continue.

DR. MAYNE: Yes. It was something like hepatitis C. I think there is opportunity to target the population and study them directly, if there were enough of them (e.g. hepatitis C patients), you could run that trial. It's the other disease states that are at smaller incidence that I think that are the quandary, and it begs for real world type trials. I think Bob made that comment, but practical experience tells us real world trials are best run in the real world, which argues that that's a post-marketing type of activity.

DR. PEARS: Thanks. Jack.

DR. BLOOM: Jack Bloom, Eli Lilly. I don't think there's any question, from what we've heard today, that there are insurmountable logistical obstacles in establishing the risk-benefit ratio that's needed prior to marketing, and I think hepatotoxicity defines that challenge more than others. I don't think it's reasonable to say “we should just figure out how to do it”. It's interesting how the views appear to segregate: when we hear from the regulators and academicians, they are for more inclusion of patients with the underlying diseases at issue. Our industry colleagues more sensitive to the challenges this presents.

What I haven't heard discussed is maybe the need

to change the pivotal trial paradigm. We've heard suggestions about partnering to get candidate drugs out to the market (i.e., relevant patient populations) sooner, in a more controlled and regulated environment, partnering with the key stakeholders: care providers, regulators, payers, patient advocacy groups, etc. For example, (and I probably shouldn't be saying this) we've been occasionally embarrassed to realize that Kaiser Permanente and other payers sometimes know more about what was happening with our drugs like Cymbalta (duloxetine) in the marketplace than we do. They have access to information relating to efficacy, health economics and sometimes risk benefit (beyond serious AEs) etc sooner than we do. We need to be more intelligent as to how we can get out to the relevant populations sooner and, with the right controls in place, really be able to answer these questions sooner.

DR. PEARS: Thanks, Jack. Any comments on that?

DR. TEMPLE: To interpret the current environment as one that encourages putting drugs on the market sooner, with the later discovery of their toxicity, that amazes me. I can't believe that that's what industry wants or considers possible.

I think they need to learn how to do a better job, perhaps more efficiently in Phase III so they can have adequate exposure and not be too surprised so often. These surprises are very unwelcome and are playing badly. I don't think you want that.

With that said, there's no reason to think that trial efficiencies aren't possible, that large simple trials beginning in Phase III and continuing to Phase IV aren't possible. They've been done from time to time. Their cost can be controlled perhaps by including other countries. But seriously decreasing the safety database prior to approval, that just doesn't seem very likely to happen anytime soon.

DR. BLOOM: You're quite right that this would not work in the current paradigm. But it has already been suggested by our academic and regulatory colleagues that we conduct additional studies (postmarketing) that are more regulated. Dr. Lee, you had suggested that as an alternative. You're right that it would be irresponsible to suggest we should simply get out on the market sooner with all the landmines that we know are there. That's not what I'm suggesting at all. I'm suggesting we need to think about how to get to the relevant population sooner, partnering with the parties that are able to both resource and manage that. The current return on investment algorithm for PhRMA to acquire all the information required to adequately define the risk:benefit value proposition arguably is not there, and so we need to figure out how to be smarter to achieve that. This issue is larger than DILI risk management, but it's probable that DILI, as a rare serious idiosyncratic event, will continue to be discovered principally in the post-marketing setting. Perhaps it would

be discovered in a more timely fashion if the databases we This is distinctly different than the issue of small increases in incidence of heart attacks (as seen with Vioxx), which we are unlikely to discover through a payor database like Kaiser's. You discover them by a different kind of trial with novel collaborations. This is beyond the scope of this conference, but there's a lot of interest in that kind of drug effect today. The idea that we're going to have a serviceable database for that kind of AE detection derived from the relatively small, controlled pivotal trials we conduct today is a fantasy.

DR. PEARS: Okay. Two more questions.

DR. PIERCE: Ross Pierce, FDA. We've heard consistently that when there's a liver signal in a clinical trial, that often the quality of follow-up data and the work up is less than state of the art. I think what would help that situation would be if we saw in maybe all multidose protocols, an appendix that actually gave an example algorithm of how to work up a patient that has a signal. And maybe the algorithm would be different depending on, you know, whether the person had a known liver abnormality at the baseline, but it would really get into the nitty-gritty of, you know, doing PCR for hepatitis C and not just serology. When do you do, you know, once you've done an ultrasound, things of this nature, and I think if it was in the form of a flow diagram, that would make it easiest for the investigators to actually follow

that. So maybe that would be appropriate for the FDA Guidance document which right now has a rather general discussion on how to do this work up. Maybe an example flow diagram, if we were to do that, I think it would be very helpful for us to have more input from this group.

The other comment was that in the question of doing targeted trials versus stratifying in larger trials for inclusion of patients with certain categories of preexisting liver disease, I don't think in the stratified design, there would be anything that would preclude more intensive prospective planned follow up and testing for the particular stratifying subgroups.

DR. PEARS: Thank you very much. Yes.

DR. HUNT: Hi. I'm Chris Hunt from GSK. I just wanted to comment on the question that was raised earlier about how people are using hepatitis B and C screening. One of the ways that we're doing it at GSK is actually screening and excluding healthy volunteers in Phase I and then patients entering Phase II, if they're hepatitis B or C-positive. So therefore, we'll have a good understanding of the Phase II population what the constituents are, and these are global trials. So, Arie, I really enjoyed all your numbers because that's actually a realistic part of the equation of, you know, how are we going to be actually assessing these patients in Phase III, but in our global populations, we certainly have a lot more hep B, but your point about they're actually going to be sort of anecdotal

experience in some of these smaller Phase III but by screening and including them in Phase III, will get some information and we'll also understand, depending on the patient population, whether we'll actually need to do a dedicated substudy or perhaps we can include a case control study, or stratified in Phase III. So I guess there's multiple ways to address the issue, but I think we're all in agreement. Some information before marketing is certainly helpful for the patient safety angle. Thanks.

DR. PEARS: Thank you very much. Last comment.

DR. BONKOVSKY: Herb Bonkovsky from Charlotte, North Carolina. First I'd like to strongly support the comment just made by the fellow whose name I didn't quite catch about the need for a protocol. I brought this up yesterday. How do you approach someone who develops evidence of liver injury? I think that really should be a part of the Guideline.

Second, I just want to make the comment that in my experience, our IRBs are asking more and more questions about why are you saying you're going to exclude patients with this, that and the other thing, particularly HIV which, of course, is a very strong political lobby and things like that. So that needs to at least be taken into account. I suspect that the pharmaceutical companies are well aware of that. I don't know if others have had that as an issue.

The final comment I want to make is that we've

heard a lot about Hy's quote regarding whether preexisting liver disease increases the risk of hepatotoxicity. I just want to say that the absence of evidence is not the same as evidence of absence of an effect. I think Arie has shown very nicely a number of recent papers that I think quite clearly show that at least for certain drugs and certain combinations of disease, in fact there is an increased risk. We don't know how extensive it is.

As a practicing hepatologist, I always tell my patients to be very cautious in taking drugs and herbal remedies and only if there's a good indication. But we as liver doctors everyday use drugs in these patients that if you used only the official package insert as a guide, you'd probably not use them. Nevertheless, we do use them because we think, in a particular patient, the benefits outweigh the risks.

I do think that, for patients with underlying liver diseases, such as chronic viral hepatitis, NASH, alcoholic liver disease, and others, there probably are increased risks of development of DILI from at least some, if not most drugs and herbal remedies. So it becomes a matter of trying to balance the hope for a benefit versus what might be some increase in risk, and of following such patients more closely than perhaps the patients without preexisting liver disease.

DR. PEARS: Thank you very much. Any response to that?

DR. TEMPLE: The previous speaker was Dr. Pierce just to get it on the record.

DR. WATKINS: To state the obvious, if really there is no increased risk of hepatotoxicity and the incidence is the same, and the only concern is that if someone with preexisting liver disease has less reserve and it's really a severity of injury issue, you get both of those things, both the incidence and severity from trials with people who don't have liver disease. So there would be no reason to study those people. It has to be a concern that they actually are more susceptible if you're going to do a trial to see, with liver disease as an end point. If the issue is altered pharmacokinetics, then you can do a dedicated PK study.

So I think what Bob was saying is just there's enough doubt to get this by an IRB, but obviously the concern is whether they really are more susceptible or you wouldn't need to do the study.

DR. PEARS: Thanks, Paul. Okay. Thank you very much. What happens now is that there's a coffee break. We're finished about on time. You may think that's by chance but I think it's because you've got a superb moderator (laughter). The moderators are always right in these circumstances. You all will have another chance to make comments, because one of the great things about being a moderator of this meeting is that we have to bring back a summary of discussion this afternoon to present to you,

about what we think we heard this morning. So you'll have another chance to have a go at it. So I'm going to try and synthesize all that conversation. Now we have a half-hour break. We're due back here at 10:30 for another great discussion. Thanks to you and thanks to all the speakers. Thanks very much. (Applause.)

(Whereupon, a short recess was taken.)