K:GOLDKIND (discussion)

DR. SELIGMAN: We have a moment to take questions or comments to Dr. Goldkind. Yes.

DR. TAUB: You mentioned that with once a month monitoring with troglitazone for example, you didn't capture the acute hepatic failure cases. I'd like to ask if there is any evidence that with more frequent monitoring, particularly for a drug that may manifest toxicity within the first six weeks to two months, that you actually can pick up the cases that would be severe? So is there any evidence that supports that? For a drug it would be very valuable.

DR. GOLDKIND: So I'll answer the part of that question that related to my talk, and then maybe, John, if you want to respond more fully, you can.

The point that I was trying to make in my talk was just the fact that we frequently think of certain activities as reducing risk to subjects that are enrolled. We think of using animal data to help us inform risk. We think of more frequent monitoring as possibly a way of capturing something early on, withdrawing that subject from the trial or making whatever interventions are necessary, and so I was just simply trying to say with that particular example, that I think from my review of the literature and you all are certainly much more familiar than I am with hepatotoxicity specifically, that may not necessarily give us the kind of reassurance that we want. So that's the

point that I was trying to make there.

John, do you want to add to that?

DR. SENIOR: I don't have any other comment, unless Becky Taub, who is walking back up, does. I don’t have anything further to say on that issue, but I would ask about one point that you mentioned where you said --

UNIDENTIFIED SPEAKERS: We can't hear you.

DR. SENIOR: Is that microphone working?

DR. GOLDKIND: No.

DR. SENIOR: Is it working or not? Well, I'll just shout.

DR. GOLDKIND: Here, you can use my microphone.

DR. SENIOR: You said that trials should be kept as short as possible to minimize the risk to the subject. I wonder about that because an inadequate rechallenge --

DR. GOLDKIND: Right.

DR. SENIOR: -- is worthless, and it would give you a false sense of security and a wrong answer and put the patient at more risk. I think that the rechallenge has to be adequate in dose and duration. A lot of drugs don't cause immediate reaction. It takes a while before it happens.

DR. GOLDKIND: Right.

DR. SENIOR: So you've got to allow for that and not just give the drug for one or two days because it's short, and then conclude it's safe.

DR. GOLDKIND: Right.

DR. SENIOR: It may not be safe.

DR. GOLDKIND: What I said was that I think that you should try and keep the duration as short as you can while still trying to generate the scientifically valid information you need. So in other words, that's a qualified, that means that how long you rechallenge for is exactly what you're saying, based upon the information you have to date, what would be --

UNIDENTIFIED SPEAKER: We can't hear anything.

DR. GOLDKIND: You lost me?

DR. SENIOR: The purpose of rechallenge is that you can then go ahead and give the drug safely for a long time.

DR. GOLDKIND: Right.

DR. SENIOR: So you've got to be really sure you can do that safely.

DR. GOLDKIND: Right. Can you hear me now?

UNIDENTIFIED SPEAKERS: No.

DR. GOLDKIND: Can you hear me? Let me see if I can hold this. Is it better now?

UNIDENTIFIED SPEAKER: Yes.

DR. GOLDKIND: Okay. John and I are saying the same thing but with different words. What I had said in my talk was that I think that you should try and be cognizant of keeping the rechallenge for duration as short as possible but that's based upon what would be scientifically valid, what information do you have that drug product to date. So -- yes.

DR. WATKINS: Well, just to get back to Becky's

question about does monitoring work, it's obviously a key question because a decision on whether to continue to develop a drug that clearly has a liver issue, you know, the company may agree that they're going to accept monitoring but obviously it doesn't work. That's a problem.

And there have been opportunities where this could have been tested like with Rezulin, at the time it was clear they had a signal, there could have been a randomized prospective study for a large study, but no one had the guts to do that I think for medical/legal reasons. But with Rezulin, there was some evidence that monitoring worked and, Will Lee, you may need to validate this, but the Acute Liver Failure Study picked up, I think, two acute liver failure cases from Rezulin early on and then when monitoring was put in place, I think it was monthly monitoring, they then didn't see anymore cases. Am I correct on that, Will?

DR. LEE: More.

DR. WATKINS: Oh. Which way?

DR. LEE: Four in the first year.

DR. WATKINS: They saw four acute liver cases in the first year and then when monitoring went into place, and actually the liver injury came uncharacteristically four to seven months after start of treatment, and actually the prescription data suggested, although there was some falloff, the actual number of individuals that remained in that susceptible window, didn't change very much subsequently at

least for a period of time. So the fact that it went from four in the first year to zero suggests that there was some efficacy of monitoring. Whether it was just physician awareness or whether it was actually the ALT value, it's not so clear. But I mean it's a very fundamental question, and if other people have data on it, please step up to the microphone.

DR. GOLDKIND: Jack.

DR. UETRECHT: Jack Uetrecht, University of Toronto. One thing that I find interesting is that the hematologist, if there's a problem with agranulocytosis or some other sort of bone marrow toxicity, like clozapine, they monitor every week, and it works. But for some reason, hepatologists can't conceive of doing it that frequently, and I think you're fooling yourself with once a month. You either do it frequently or don't do it at all, because once a month is just too infrequent. If you're talking about increasing patient safety, not talking about picking up a signal during drug development when you initially may have no reason to believe that the drug is going to cause liver toxicity to begin with, but I think you either do it frequently or don't bother to do it at all, and I don't think in most cases people are willing to do it once a week. But they do it with schizophrenic patients who are not the most compliant.

DR. HANIG: I want to congratulate you on a great presentation. An awful lot of the examples that you gave though sound a lot like very, very good medical judgment. Of course, you are a physician. The practice of medicine is an extremely,

or is supposed to be an extremely, ethical profession. So what I'm really going to ask you is: are there any instances that you can think of where the ethical call would be different from the most educated and ethical medical call? Where, if any, is there a difference between the two philosophies and points of view?

DR. GOLDKIND: Well, I am a firm believer as I said before in good ethics being informed by good science and good medicine. So I find it very hard to tease those apart as you're suggesting, and provide you an example of one, you know, sort of ethics existing alone. However, I would say that for a physician-researcher who is enrolling patients in a clinical trial, as well as for a principal investigator who does not have a primary role in patient care, there still has to be the understanding that the first and foremost obligation is to the enrolled subject, not to sort of the generation of generalizable knowledge or public health, but most importantly to the well-being of that enrolled subject or patient. So I would say that I think is important, although it's very significant that we try to get the information that we need, that we make educated decisions about the balance of the minimization of risk for the enrolled subjects and the accumulation of knowledge that will be to the benefit of public health. Still when we're facing the subject in that clinical trial, and it has to be our barometer what's in the best interest of that person.

DR. HANIG: Thanks a lot. That works for me.

DR. GOLDKIND: Can I just make one more comment about

informed consent, which came up earlier this morning. I'll just make a quick comment about that. So I think that how you handle informed consent depends on what you knew when you were writing the informed consent document prospectively at the outset of the trial. If you knew there were certain risks, or there might be certain risks and a requirement for a more intensive monitoring scheme, then that could be built in or it should be built into the informed consent document. However, that's sort of learned. As the trial is going on, there are new research-related risks that are discovered. Then you want to go back and rediscuss those risks with the subjects who are enrolled, where the risks that are pertinent to them. That would be my understanding of that situation. Thank you.