**INTRODUCTIONS**

DR. WOODCOCK: Thank you very much, Lana, and good morning. I would like to thank John Senior in particular, who is still struggling with the computer system here, and the organizers for inviting me and for putting on this meeting.

I consider this sort of a landmark, given first of all the venue. This is a great venue we have, very near to our new White Oak location where much of the Center for Drugs has now moved, and also because we have such huge attendance at this meeting. I think that's a very significant change from kind of small beginnings. We're going to really get some movement on this problem.

Today and tomorrow I think you're going to be talking about findings of liver injury during clinical trials. It's a subset of a problem that we are encountering during drug development. We're into findings that may signal potential injury, can disrupt and often stop development programs of otherwise promising agents because we don't know what these signals mean.

Over the last several years, this series of meetings has been struggling with thinking about ways to better understand and predict drug-induced liver injury. It's a problem that has been a matter of academic inquiry for a long time, but we still don't have the answers.

Under the critical path initiative, over the last three or four years, FDA has been urging all the members of academia, industry and Government, to come together and try to develop new ways of addressing many of these problems. While we have new science that has been developed, everything from genomics to proteomics to new types of pharmacoepidemiology, it's clear that most of these are not going to be able to be applied strictly in a single development program or within a single company or single academic area. They are going to require population-based investigations that need more firepower put behind them, than any single entity can muster.

So we need consortia and we need to come together in new ways to address and solve these problems; the good news is that we now have the scientific tools, or we're developing the scientific tools, that we can use to apply to these problems and actually develop solutions.

So over the next couple of days as you talk about what to do in a clinical trial when you encounter a signal, I think you're seeing -- it's always been a problem and now we need to view that also as an opportunity because when you see a signal in a clinical trial -- now we may have the opportunity to actually study this.

And I said this many times, and I'm sorry, John, if I'm being repetitive but, you know, our approach to drug-induced toxicity in general over the past 20 years in my mind, has been,

I call it sort of botanical, in that we observe things and we characterize them and we write them down in lists. Okay. And then if the drug happens to get out on the market or wherever, then we have a nice list of all the side effects and the frequencies and then we have a descriptive list.

Now should be the time where we get beyond description and into mechanism and hopefully into action, prevention, characterization, intervention. Are there things we can do to identify people at risk? Are there things we can do when an event starts to evolve to abort that or prevent that and are there better ways to treat something when it has actually happened, is unfolding? And, the answers to these questions can only come about if we actually do studies in the relevant populations.

This, of course, raises all kinds of issues. It raises ethical issues. It raises scientific issues. It raises the issues of how we're going to collaborate in order to get the appropriate resources applied to that single patient, wherever that patient might have been identified, in a clinical trial or elsewise, to get the proper studies done. And I hope those are the kind of questions that you will address today and tomorrow and we will be coming up with some sort of answers.

I'm very optimistic. I think just the size of this meeting, the number of people here and the quality of the agenda reflects the fact that we're taking this problem seriously

across all the sectors and that we have proposals to discuss amongst all the participants of ways to deal with this.

So I hope that you do make progress in this meeting. Given that you have John leading, I'm sure you will make progress and that we can come out of here with a set of proposals or understandings that over the next year can move us forward in this area in studying drug-induced liver injury when it occurs in clinical trials, of having ways to better generalize that and bring it to actual knowledge rather than just observational findings, and ultimately I think to understand some of the root causes of drug-induced liver injury and ways we can prevent this in the future.

Thanks very much for coming, and good luck in the next couple of days and, John, thank you again. (Applause.)

DR. SENIOR: Thanks, Janet. Janet was alluding to putting our organizations and our efforts and our money together, and I will be proposing in my talk, which is the second one today, such a study, a big study. It's going to be very important. It's going to cost a lot of money but it's going to, I hope, do just what you said. We'll see.

Now right now I am not John Senior. I am speaking for Dr. Alan Goldhammer because Alan, who is the representative of PhRMA, the Pharmaceutical Research and Manufacturers of America (can we put Alan's slide up?). He was called away without much notice to California, and he's out there right now. PhRMA is a

big outfit; it's got a lot of member companies, a lot of big, big powerful companies.

He sent this message yesterday: "John, I'm sorry I cannot attend this year's workshop. PhRMA is celebrating its 50th anniversary and I must attend a business meeting associated with that. This is the first workshop I have missed since the initial one at the Westfield Conference Center in 2001. It is gratifying to see all the progress that has been made in this area, and I look forward to the outcome of this year's meeting. There remains more to be done to move forward."

And with that in mind, I'll say the purpose of this meeting is not to present a series of lectures at you. It is meant to include some thought provoking presentations to elicit discussion from you. So the main purpose of the conference is to get your discussion. The lectures are just the bait.

So I will now introduce John Vierling, Past President of the American Association for the Study of Liver Diseases (AASLD), who will give you greetings from another of our sponsors.

DR. VIERLING: Thank you very much, John, and good morning, ladies and gentlemen.

On behalf of the AASLD, I want to tell you what a pleasure it is for us to cosponsor this important workshop along with FDA's Center for Drug Evaluation and Research and the Pharmaceutical Research and Manufacturers of America.

We have been endeavoring to do this in the AASLD as a part of our mission which is to advocate and advance the science and practice of hepatology, liver transplantation and hepatobiliary surgery, with about 3400 members internationally to date.

I'm going to emphasize a couple of points because time is precious. The first is that the AASLD does seek increasing partnerships with the federal agencies: NIH, FDA, CD; and with industry. We do so in order to achieve the goals that have already been elaborated of the mutuality of our mission and to put together our resources, including financial resources, to achieve them. This enhances our mission for professional education. It also allows us a better fine tuning of our public policy advocacy, both for budgets of federal agencies, for research funding, and for the accomplishment of our goals.

We have added to this, fundraising in the last year, and many of you will hear more about this. I'm pleased to say that that fundraising effort is now supporting grants at the cusp of funding in NIH that might not otherwise be funded without bridge funds from our organization. We're very dedicated to this type of endeavor and to this particular topic.

And the last thing I would mention is that when we look for signals of liver injury, we have few and we're going to be discussing that in detail, including novel biomarkers of injury. You should be aware that for the last two years, the

AASLD has embarked upon a campaign of awareness to the public under the banner of “What's My ALT?”, with a twofold question: One: what is alanine aminotransferase? And for the individual asking the question to their physician, Two: what is my level, and should I have any other concern or diagnostic testing?

So without further comments, again thank you for the opportunity to cosponsor, and we're looking forward to a very successful workshop.

DR. SENIOR: Thank you, John.

(Applause.)