The Symposium convened in Solidarity Hall of the Kirkland Center of the National Labor College, located at 10000 New Hampshire Avenue, Silver Spring, Maryland, at 8:00 a.m., John Senior and Lana Pauls, Co-Chairs, presiding.
CO-CHAIR SENIOR: Welcome. I’m John Senior. I’m acquainted with many of you, maybe not most, but we have 205 people who have registered, which is a very good turnout.

We encourage all of you to think about what's being said and to be ready to leap up with penetrating questions. This is an open, public meeting, not private or closed. It is open not only to this audience, but to the world, which we do by posting what is shown and said on the internet. We don't edit it, except to correct spelling and punctuation, make little corrections.

Business and government speakers usually have all their presentations pre-cleared by their organizations, but some academic people are concerned that this posting on the internet might be considered pre-publication and impair their chance of getting papers accepted. We have taken that question to the New England Journal of Medicine, to its editor Jeffrey Drazen, and he said: no, this is not pre-publication; it is scientific discourse. It is not edited, not reviewed, not approved. It is just scientists talking together with each other. So, it's okay; don't worry. What you say and show and post is not going to impair your chance of publication, at least in the New England Journal.

(laughter.)

Now I can't speak for all editors of all journals, but I think the principle is probably sound. Now, with that said, I would like to introduce Lana, who has some really key tidbits of information for you.

CO-CHAIR PAULS: Thank you, John.

For those of you who don't me, I am Lana Pauls. I head up the Quality Management and Strategic Planning in the
Office of Surveillance and Epidemiology. But, for purposes of today, I'm the Co-Chair of the Hepatotoxicity Special Interest Group at FDA. This is our 10th Annual Meeting, and I am excited to see all these people here. John, I'm sorry to correct you, but we have 210, not 205 registered.

CO-CHAIR SENIOR: Okay.

CO-CHAIR PAULS: We went from 160 people to 210 people in one week. So, we are very excited about the incredible turnout here today. I want to go on record by thanking John because he came up with a fabulous program in terms of the science and medicine, and coupling those together.

I have a couple of logistical issues: First, the women's room is right behind me. The men's room is over on the far side of the hallway, right past the steps as you are coming up.

The other thing is, as you know, the cost of coming to this conference is probably pretty low as compared to the majority of conferences you go to. We are asking $225 for government, academia, and $450 from industry. That being said, one of the ways that we defray our cost is for those people who are staying at the National Labor College here on campus, we have used your meal tickets to help defray the cost of the food on the buffet lines for everybody here. So, those of you who were expecting to go to dinner for free tonight, we invite you to happy hour, which we will have from 6:00 to 8:00 tonight with heavy hors d'oeuvres. If you still want to go to the cafeteria, which closes at 7:15, you are going to have to pay for that, if you are staying here on campus. That is the deal that was worked out. We appreciate those people that are helping us defray the cost.
If you need anything logistically or any-otherwise, please come and see me or one of the team that you may have met at the registration desk. We will be here for the next couple of days. I will be facilitating and moderating a session tomorrow afternoon.

And on another matter, in terms of what John said about the slides, one of the things that we did this year that is a little bit different from before is that we opened a new ocket for this particular public meeting. I don't think the Federal Register notice is actually published yet because it went through the system quite late, but we shall post the number and invite your written comments.

Approximately a week after the meeting, I am guessing maybe April 6th or so, we will have all of the slides posted to the docket. The docket is very easy for anybody in the world to access. You go into regulations.gov. and type in the docket number, to see the slides.

In addition, as has been done in years past, we are preparing an official transcript. As John said, we are not going to be editing it. We will clarify, make sure the names are spelled correctly, and that sort of thing. The contract is to have the transcript in my hands within 14 days. So, we will probably have the transcript posted within about three weeks.

And again, here is my contact information. If you have any questions whatsoever, feel free to contact me directly.

Now, I am going to go ahead and welcome Dr. Doug Throckmorton who is is the Deputy Center Director from the Center for Drug Evaluation and Research at the FDA. Either he and/or the Center Director typically makes some
opening remarks.

Dr. Throckmorton?

DR. THROCKMORTON: Thank you, Lana. Thank you, John, very much.

I want to talk very briefly about what you all have accomplished over the last, I guess, 10 years now, John. I didn’t know before that this conference had been going on for 10 years.

To prepare, I first asked John Senior what he wanted me to talk about. So, John said, put your scientist hat on, not your administrator hat. I said, okay. So, no FTEs, no money, and I don't know what; no hall passes. I have to talk about science, and that is, of course, a pleasure.

But the second thing I did, then, was I went on the web at the FDA “liver toxicity” site and I started revisiting the kinds of programs that you all have had, the kinds of things that the FDA has done around the topic of drug-induced liver injury.

And if I leave one message to you, I hope that you too should step back sometime and do that yourselves, to celebrate where you have come in that last decade. What you have done is tremendously important, both for the Center and for the FDA and for the American public. You have moved a field really in very dramatic fashion. As I watch other fields in other areas of drug safety, those sorts of issues typically take a very long time to make material progress, because people need to get together; they need to come to a common definition, a common mind.

You all have made tremendous progress.

I hope that you find a time to celebrate that and think about the accomplishments you have made. I would
also like to say I am very proud that the FDA has been able to play a role in this through the Critical Path Initiative, through some of the work that we have been able to support, that you all have done in partnership. I think, again, tremendous progress has been made.

The third thing that I am going to leave you with is that I hope you recognize you are far from done. Despite that progress, just this last year we have been reminded again of the real importance of drug-induced or, let's call it, ingredient-induced liver injury, and that the public is watching us and really expecting us to make continued progress in this.

So, go back a decade. John Senior and I were both medical reviewers in various divisions, and we were watching products show liver injury, then either stopped them late in development before approval or shortly after post-marketing. Controversy arises; people have to decide what to do.

You can all remember troglitazone and the challenges that we faced there. I don't know how many of you remember tasosartan, which was the fifth or sixth sartan, an anti-hypertensive, effective anti-hypertensive drug product that didn't go forward because there were concerns about liver toxicity, a product that otherwise would have been on the market.

Those sorts of things were happening then. They are continuing to happen now. But we as an Agency said, we really need to understand drug-induced liver injury better than we do. John Senior, obviously, took a great interest in that, as did others in the GI Division and other places.

In the very first critical path document in 2004, we highlighted the need to understand the issues around
hepatotoxicity of drugs better than we did. Among the "urgently-needed" tools we needed were new techniques to assess drug liver toxicity. In addition, early foci included proteomic and toxicogenomic tools and the need for better in silico technologies to predict things like liver injury. So, very early on in the critical path, the FDA recognized this was a particular area of focus, that we needed to be doing better at that than we were able to do at present, and that it was impeding efficient medical product development.

The result, well, you are the result. Many of you are helping, partnering with us to make those differences.

Arthur Holden's work with the Serious Adverse Events Consortium is one of the things that I would highlight that the FDA has been able to partner with you all to make a difference, to move the field, understand better the science around drug-induced liver injury, make a difference, make a better, more efficient medical products development.

The second thing that we have done, obviously, is the guidance. John and I remember working on the concept paper, explaining that concept papers were useful, that it was useful to move a product from a concept paper to a draft guidance, to now a final guidance, a final guidance that you all published in July last year.

So, again, a relatively rapid pace for the development of a guidance, reflecting the important work that you all have been doing. As I looked at the programs since 2004, it also was interesting to see the change in the kinds of things that have been worked on in the various yearly meetings. We began with the important work around genomics, the ongoing work that Arthur Holden
and his group and others are working on, the work around understanding the metabolism of the products and their contribution.

Now, as I look at what you all are talking about these next two days, I see a tremendous broadening, a movement into areas that have not, at least to me, were not being looked at two and three and four years ago, things like the inflammosome, which I didn't even know existed until I looked at the program for today, and whether that contributes to drug-induced liver injury.

We really need to have a new focus on informatics and understanding, a common taxonomy around drug injury, before we are going to be able to move this field along. We need a focused effort to try to build an integrated liver toxicity knowledge database, to really understand all of the available data. There was an initial effort seven or eight years ago within the Center to collect all of the examples of liver injury.

And, John, it may have been you, I don't even remember. A group of people went around and interviewed all of the medical officers that remembered having a drug that had caused liver injury and tried to make an integrated database. Obviously, that was a very important effort. What we need is a more systematic effort, a way to make that kind of thing, put it together, and then share it, to the extent that you possibly can, make that kind of information available to the public. That is the kind of thing I am seeing now that I don't see in the work that was going on two and three and four years ago.

And then, obviously, the ongoing, continued collaborative efforts, the work between private and public partnerships that I speak commonly about, and how
important and powerful I think that is. I see a lot of that going on. Again, I salute you for your ability to set those things up.

Then, the last interesting item that I saw, looking at the programs, and maybe a new area, maybe not, was the effort to try to figure out why one person has liver injury and not another. It is an ongoing -- you commented on it in various places for some time. Why is it that one individual has a drug-induced liver challenge out of 200 or 100.000 individuals? What is it about that idiosyncrasy? And there is that word "idiosyncrasy" in one of the programs today. I am really looking forward to hearing what you all come up with there.

It is terribly important because, at the end of the day, what we want to be able to do is predict who that individual is. We want to be able to develop the tools to mitigate the risk of liver injury, the way we have been able to develop the tools to mitigate the injuries due to abacavir, the HIV product that we were able to find a genomics test for that could predict in some sense who was likely to get into trouble. You want that in the field of drug-induced liver injury.

Finally, I guess I will just remind you this all matters. So, we spent last year, parts of last year, working with Hydroxycut, not a drug, but a substance or an ingredient, probably an unapproved drug, in a dietary supplement that resulted in, well, we know of 20-some-odd cases of severe liver injury. We anticipate that there were many others that were not reported to us.

It just reminds us that the things that we take as drugs have consequences, can, in fact, cause severe liver injury; that we need to understand better. It also reminds us that the public is paying attention. Liver
injury, something people sort of understand is a very bad thing. So, when it happens, the press pays attention; everybody pays attention. It is something that we live with and have to respond to. It is also something we need to understand scientifically better than we are at present.

We also have continued failures in drug development due to hepatotoxicity, failures late in development. Think of ximelagatran. That was a failure of the system. That was inefficient medical product development. That is something I think we all have an obligation to try to change. To have a product with that kind of a signal not found until late in the development of it means that large numbers of people have been exposed, large amounts of resources have been expended, for a product that ultimately may not be able to come to market.

We would like to be able to find a way to keep that on the market, find that test to predict who is going to get that toxicity. But, absent that, we would like to be able to find that signal of injury earlier in development, so that we don't have those resources and inefficient medical product development that so many people write about, that I know we all want to change.

What's needed, then, are predictive biomarkers. We need better understanding of what predicts exactly who's going to get into trouble, what products are going to cause liver injury. And again, I know you all are working very hard on that in terms of various predictive platforms and the like. And I, again, applaud that effort. I really think it is terribly important in terms of medical product development.

So, I am going to end just where I started by saying I hope you are able to sit back, go on the web,
celebrate where you are now versus where we were even five years ago. Tremendous accomplishments, tremendous movement, both in terms of digging deeper into subjects, as well as finding new areas to explore and understand better.

But, remember, the challenge continues. We have had high-publicity failures late in development, and products in the public eye that are causing drug-induced liver injury just this last year. So, your work is not done. Thank you so much for inviting me to talk, and congratulations. Really, marvelous work you all are doing. Thank you very much.

(Applause.)

CO-CHAIR PAULS: Okay. As you know, this conference is co-sponsored by FDA, AASLD, and PhRMA. Alan Goldhammer from PhRMA has a few opening remarks also.

DR. GOLDHAMMER: Thank you, Lana. It is really a pleasure that we have been able to sponsor this for the last 10 years and actually take part, I guess 9 years ago, when we had that first initial large meeting on this topic in 2001.

I just want to take a couple of minutes to tell you about an exciting project that we started just about five years ago at PhRMA. That was to think about how we could use observational medical outcomes data to do both risk and benefit assessments.

We spent about two years working with industry experts trying to create an idea of how one would do this. Then, we brought in not only FDA but academic experts to give some peer review to a project that we thought we could fund and get off the ground and make a
contribution to drug safety.

The project did secure funding and actually got off the ground a little over a year ago. It is called the Observational Medical Outcomes Partnership. It is housed at the Foundation for the National Institutes of Health and involves FDA, academia, and PhRMA. There is an independent Executive Board that Dr. Woodcock chairs.

I just want to relate to you some of the scientific findings that have come out, particularly in the hepatotoxicity area. I think that while these are preliminary, I told John that you probably could have a speaker on this topic at next year's meeting who could give you some, I think, pretty exciting results.

Although this is an experiment, it is not designed to be anything but that, but as you well know, FDA is moving forward with a larger project called the Sentinel Network that will involve a variety of nodes that will collect information throughout the country to look at drug safety.

That said, even though this is a small project, we have 120 million covered patient lives right now that we are looking at. And we are looking at a variety of health outcomes of interest and a variety of drug adverse events and drug benefits related to those health outcomes of interest.

One of those is hepatotoxicity. What we have done is to take, starting off with the very broad definition of abdominal pain, and then querying the databases and refining that definition, incorporating a variety of other things related to Hy's Law.

You can see a large number of queries that come back to you with abdominal pain, but as you start adding things in, you start narrowing things down until you
finally can get to individual patient case report forms or clearance forms that are directly linked to a hepatotoxic event.

The goal, however, is not just that, to identify the health outcomes of interest, but then to go back and link those particular drugs that have been taken by those patients.

The end result is we hope to be able to inform the Sentinel Network of new methods and tools that can do real-time drug surveillance, so that you can then pluck these cases out and make a contribution there.

As I said, this is a project that is ongoing. It is due to be completed later on this year. All of the results are going to be published. There is a website. I don't have slides, but I will get the web link to Lana, so that it can go up on the site here.

I would like to thank you all for participating. We certainly look forward, again, to next year.

(Applause.)

CO-CHAIR PAULS: Lastly, for our opening remarks, we have Paul Watkins. He is the current Co-Chair of the Hepatotoxicity Special Interest Group at AASLD.

DR. WATKINS: The American Association for the Study of Liver Disease is the largest professional organization in the world of people interested in the liver and liver diseases and has been supporting this, and I think clearly recognizes that this field is at its most exciting stage in history.

The incredible amount of new information and insight that is pouring in really indicates it’s a unique time in the history of this field. In recognition of
that, the AASLD established a special interest group, which is what they do in an area that has got sufficient momentum and excitement to justify a special emphasis within the organization.

I think the field is where it is today in no small part because of John Senior and these meetings that he holds every year. It is a labor of love, an enormous effort for John to do this. Every year he turns out a tremendous program, for which you don't need any other evidence than the enormous turnout that he gets for these meetings.

Then, Lana, with a very small staff, handles all the accommodations and all the practical details.

So, I am going to leave just by asking everybody for a round of applause for Lana and John.

(Applause.)