Thank you, John. I have the distinction of starting off this session. Really, I am only going to be talking for about five or six minutes, just to set the stage so you can be aware and think of some of the other speakers in this session. I am one of the only non-clinicians here that will be speaking today, but I am doing this from an aspect of being here for the last 15 years and listening to a group of you very intently over the last 15 years and learning a lot.

So, with that, I was charged with looking at this from a very different perspective, literally talking about whether it is the drug, the chemical, the hepatotoxic agent, and/or the person. As I said, the theme of this session is really all about understanding one another. I am going to present some basic concepts. And then, John is going to focus on what we have to do to get it right. And then, Dr. Alice Chen is going to focus on some more clear definitions and terms which we have been struggling with for numerous years.

About 10 years ago, I was involved in one of the subcommittees on nomenclature, and we still never finished that. So, that is another issue that we have on a regular basis.

Drs. Carter and Hicks will focus on the true causes and various disorders
associated with this. And then, Dr. Temple will close out the session talking about some labeling concerns that we have.
Here's my standard FDA disclaimer. I want to start out with some known facts about DILI. And I am speaking to people that know this very, very well.
We all know that DILI is a major concern in medical practice and public health. We also know it is one of the leading causes of acute liver failure in the world. We do also know it is a major cause for drug failure in clinical trials. If you look a little bit further down here, up until 1997, it was actually the leading cause for withdrawal of an FDA-approved drug – 8 WDs; 4 for liver failure*.

• Incidence:
  – 14-19/100,000 in general population**
  – 30-35/100,000 using EMR data*** – under-reported?

* http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm

We all know that DILI is a major concern in medical practice and in public health. We also know it is one of the leading causes of acute liver failure in the world. We do also know it is a major cause for drug failure in clinical trials. If you look a little bit further down here, up until 1997, it was actually the leading cause for withdrawal of any drug from the market. That year of 1997, FDA approved eight drugs later withdrawn, four of which were for liver failure.

We also know it is a very rare problem. So, it is very hard to find in clinical trials. Anytime we see an incidence of it or a detection of it, we really are concerned about it.

And lastly, we all know that, associated with the adverse events, they are severely, severely underreported. So, we really don’t know the actual incidence. Liver failure is associated with not just prescription drugs, but it is also associated with other agents, including over-the-counter medicines.
Dr. Lee was not able to be here this year. So, I felt compelled to show his data because this slide gets shown at every single conference. This slide shows data through 2014. As you can see, 974 cases were associated with acetaminophen.
Here is the list of drugs that, again, were approved in 1997, four of which came off of the market that year.

<table>
<thead>
<tr>
<th>Established Name Proprietary Name / Sponsor</th>
<th>Intended Use Toxicity</th>
<th>Approval Date</th>
<th>WD Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troglitazone Rezulin / ParkeDavis</td>
<td>Diabetes Fatal liver failure</td>
<td>01/29/97</td>
<td>05/01/02</td>
</tr>
<tr>
<td>Bromfenac Duract / Wyeth</td>
<td>Analgesic Fatal liver failure</td>
<td>07/15/97</td>
<td>07/03/03</td>
</tr>
<tr>
<td>Trovafoxacin Trovan / Pfizer</td>
<td>Antibiotic Liver Failure</td>
<td>12/18/97</td>
<td>03/09/05</td>
</tr>
<tr>
<td>Alatrofoxacin Trovan IV / Pfizer</td>
<td>Antibiotic Liver failure</td>
<td>12/19/97</td>
<td>03/09/05</td>
</tr>
</tbody>
</table>
So, moving to the fundamental questions associated with DILI, is it the drug that is toxic or is it specifically a susceptible person? Well, actually, it is usually a little bit of both, and sometimes it is very, very difficult to discern the difference there.
So, even though there may be a safe dose for most people, it is not necessarily safe for all. I know for a fact that, when I speak on behalf of the FDA, quite frequently, people that are unfamiliar with the way that we do business often think that just because a drug is approved that it is has kind of, sort of, got a Good Housekeeping Seal of Approval and it is safe for everybody. But, as clinicians and other healthcare providers, we know that that is not necessarily the case.

A couple of the other facts associated with DILI: As I indicated, the same drug might be quite safe for most people, but it is toxic for a number of them. And it is associated with different severity, consequences, what the time course is. And when I say "serious," this can lead to a minor disability, an inability to work, hospitalization, liver failure, or in the worst case even death.

We also know that the liver has an amazing capacity to recover from injury. The fact that you can have it two-thirds resected and it can regrow, even if some of the hepatocytes are killed or removed, and it is very, very adaptable.
So, one of the problems associated with this is the identification of what is going on are very challenging. We have to look at the dose and the properties of the drugs that impact the initial cellular damage. We have to look at the host factors that drive susceptibility as well as repair. Idiosyncrasy of the host is responsible for many of the cases of DILI after marketing.*

Of course, this conference wouldn’t be this conference if we didn’t mention Dr. Zimmerman on a number of occasions. John, of course, just mentioned Hy’s Law that goes back at least 25 years. Dr. Zimmerman had a lot of different ideas, one of which he talked about was that liver injury is also associated with, again, not just drugs, but other substances, including plants and animals. So, you can think of things like, other things that cause these injuries. And he always talked about these along a spectrum of toxicity.
So, there are also risks in humans that are likely to be determined by multiple factors, including the drug properties, the patient attributes, and the various DILI mechanisms. Nobody ever said that this was easy, and that is probably why we convened this workshop every year for the last 15 years.
Some of the different drug properties related to DILI include threshold dose, lipophilicity, reactive metabolites, oxidative stress, and mitochondrial liability. I am not going to go into those any further because this is going to be the primary focus of Dr. Chen's talk tomorrow afternoon. So, be looking for that.
We also know that predicting serious liver injury has its challenges. We know that biomarkers are not necessarily specific enough. We also know that negative rechallenge can be unconvincing, especially for rare events. We know that positive rechallenges is powerful but dangerous. And lastly, we know that it is very difficult to determine causality.
Again, over the last 15 years, I have been listening to all of you and I have been learning a lot. I have always wondered myself what makes the certain people respond better to the same dose and regimen of the same drug than do others? What makes certain people susceptible to serious adverse effects, when most people aren’t?

As I Have Listened, I Ask, and You Should Continue to Ask…

- What makes certain people respond better to the same dose and regimen of the same drug than do others?
- What makes certain people susceptible to serious adverse effects, when most people aren’t?
So, all I am asking now, at the end of this talk, is that you listen carefully to the speakers who follow me. They are going to be addressing a lot of the topics that I highlighted in this opening session. Thank you.