DR. SELIGMAN: What I'm going to attempt to do in the next five minutes is provide a synthesis of a number of very rich presentations as well as a very engaging discussion from yesterday afternoon. As you know, there's always a danger in summarizing things, and I do so with a bit of trepidation. But this is my synthesis of the question that John Senior has posed to us yesterday and this afternoon which is, “When should rechallenge be done or not done?” Let's have the next slide.

Draft Guidance

- "Generally, rechallenge of subjects with significant (>5xULN) AT elevations should not be attempted." If subjects rechallenged,
  - Follow closely
  - Demonstrated important benefit from drug
  - Other options not available
  - Substantial data do not show potential for severe injury
- "Patient should be made of aware of potential risk and consent to rechallenge."

In the Guidance document, the whole issue of rechallenge is covered in 15 lines. The first 10 lines cover some of the issues related to rechallenge and the remaining 5 lines are summarized in the slide above which basically says that in general, rechallenge of subjects with a significant (greater than 5 times the upper limit of normal) AT elevations should not be attempted. If subjects are rechallenged, they should be followed closely; there should be a demonstrated important benefit from the drug; there should be no other options available; there should be substantial data that do not show the potential for severe injury; and patients should be made clearly aware of this potential risk when being rechallenged and should consent to such rechallenge. So that's the wording in the current draft Guidance. Next slide.

Themes

- Sharpening definitions
- Criteria for re-challenge
- Defining injury
- Science of DILI
- Ethical equipoise
- International consistency
- Expectations for clinical trials

I identified seven themes that came out of the discussions yesterday. The first relates to the sharpening of definitions; the second relates to criteria for rechallenge; the third defining injury; the fourth spans many of the discussions we've had over the last two days related to science of drug-induced liver injury. An issue related to what I call ethical equipoise which I'll discuss further. And then some issues that aren't specific necessarily to rechallenge but are significant as related to this whole field in general such as international consistency and what can you expect from clinical trials. Let's have the next slide.

Sharpening Definitions

- *Continuing challenge*
  - continued use with raised enzymes
  - "hope of establishing adaptation rather than liver injury"
- *Deliberate re-challenge*
  - re administration "intent to re induce liver injury" to assess causality
- *Inadvertent challenge*
  - unknowing reuse
  - shouldn't be an issue in clinical trials
  - happens too often in post market – better records systems/communication

We heard in Dr. Seeff's presentation a proposal for considering three ways of looking at challenge. He talked about "continuing" challenge, basically the use of the drug product with raised enzymes, with the hope of establishing adaptation rather than liver injury.

A second category that he as "deliberate rechallenge" which is what most of us generally think about when we think about a "rechallenge, which is the readministration with the intent to not re-induce liver injury, but to try to settle one way or the other whether the initial elevations were drug related or to assess "causality.

And the third category related to "inadvertent" challenge. We heard in the presentation from Dr. Papay from GSK a summary of very interesting, valuable and detailed work that they have done related to post-marketing studies that involve a large number of what we would call "inadvertent" challenges, where the reuse was unknowing, not known. I think we would all agree that generally inadvertent challenge is not an issue or shouldn't be an issue in clinical trials, that it probably does happen too often in the post-marketing environment and that it is, as she pointed out yesterday, really a matter of better clinical management, record keeping and communication. Sharpening definitions would be a valuable ongoing discussion, and I imagine it will probably come up again when the NIDDK hosts its meeting in December. Next slide.

Sharpening Definitions (2)

- *Current draft guidance can be viewed as providing criteria for "continuing challenge"*
  - Confirmation
  - Close observation (retesting guidance for elevated AT <3xULN)
  - Stopping rules
  - Evaluation of alternative causes
- Follow-up to resolution
  - irrespective of whether study subject continues on test drug or not
- Presence of jaundice as an exclusion criteria for consideration of re-challenge

In thinking about this question of the criteria for continuing challenge, it is in many ways, the current Guidance document. By proposing stopping rules, and on the reverse side of the coin, of course, by proposing rules upon which one should continue or allow individuals to continue to be treated in the context of the clinical trial, the Guidance is essentially defining the criteria in that context for what I would call "continuing" challenge. It talks about issues related to confirmation, close observation, the stopping rules that were previously discussed, the careful and thoughtful evaluation of alternative causes, as well as the importance of emphasizing follow-up to resolution irrespective of whether the study subject continues on the test drug or not, to insure that there is a complete understanding of where the patient ends up and what the ultimate diagnosis of any hepatic abnormalities observed in the context of the trial.

As was mentioned yesterday, one consideration that I think would be valuable addition to the current definition in the Guidance, is to indicate that the presence of jaundice as well should be an exclusion criteria for consideration of rechallenge in addition to the AT elevations. Next slide.

Criteria for Re-challenge

- When to initiate re-challenge after discontinuation
  - how long to wait
  - at what dose
  - how long to treat
  - replication of circumstances
  - what constitutes a positive challenge (symptoms vs. biochemical abnormalities)
  - what is the meaning of negative re-challenge?

The other question that came up had to do with the criteria for rechallenge and when to initiate rechallenge after discontinuation, and a number of questions were posed related to how long one should wait. At what does should one rechallenge? If indeed one does so, how long you would treat once an individual is again reexposed to the drug product, whether one needs to replicate all of the circumstances that existed at the time of the initial observe abnormalities and, of course, the tricky questions related to what constitutes a positive rechallenge, whether it's the replication of symptoms, biochemical abnormalities, one or the other and/or both. Of course, a good question is, what is the true meaning of a negative rechallenge? Next slide.

Science of DILI

- Mechanisms of injury
  - adaptation (innate vs. adaptive immune system, not independent),
  - role autoimmune memory
  - metabolic vs. immune idiosyncrasy
  - one mechanism not likely to explain all DILI.
- Biomarkers
  - predict toxicity
  - assess the nature of toxicity
  - guide whether re-challenge is safe or even appropriate
  - mechanisms of adaptation
- Development of applicable animal models

Clearly, there's a lot that needs to be done related to the science of drug-induced liver injury. We've spent two full days talking about all sorts of issues related to the mechanisms of injury, biomarkers, development of applicable animal models. Dr. Uetrecht gave an outstanding presentation that laid out for all of us the issues related to adaptation, the role of the innate versus adaptive immune system and the fact that the two may not be independent phenomenon, the role of autoimmune memory, and issues related to metabolic versus immune idiosyncrasy, et cetera. And, of course, as we've heard today, the need to develop biomarkers to predict toxicity, assess the nature of toxicity and to provide a solid basis for guiding us as to whether rechallenge both safely and appropriately. Next slide.

Defining the injury

- Value in making decisions about *continuing challenge* in a trial
- Utility in post-market studies
- Guidance regarding circumstances when re-challenge could be considered and “safely” done
  - acute injury, hepatocellular injury vs. cholestatic
  - metablolic vs. immune-mediated, features of both

The next issue relates to what I call defining the injury, and particularly in terms of the value of making decisions about continuing a challenge in a clinical trial. There was a lot of discussion looking forward to the next meeting of this group when we hopefully challenge the utility of the use of rechallenge in post-marketing studies. Clearly, there's a lot of interest around the Guidance regarding circumstances when rechallenge could be considered and safely done. I think the field would certainly benefit not only amongst those with tremendous expertise in the area of hepatology, and I'm certainly not one of them, but clearly there needs to be clear definitions around what we mean and clear definitions that are widely understood and widely communicated regarding hepatocellular injury, cholestatic injury, mixed injury, et cetera, as well as a clear understanding of the role and value of distinguishing between metabolic versus immune-mediated injury and the features of both. Next slide.

Ethical equipoise

- Critical importance of robust science
  - minimize risks for enrolled subjects
  - reliable data upon which to make public health decisions
- “Known important benefit” to treatment that justifies the risk of re-challenge
  - limited applicability to trials
- More likely a consideration in postmarket clinical decisions and studies
  - uniquely beneficial
  - absence of alternative therapies

The presentation on ethics was a very valuable one. It talked about the critical importance of robust science, the clear need to minimize risks for enrolled subjects clearly weighed against the need for reliable data upon which to make public health decisions. There was the discussion about the importance of having a known important benefit to treatment that would justify the risk of rechallenge, and the fact that such a known important benefit may have limited applicability when making such decisions in the context of a clinical trial. It's clearly more likely consideration in the post-marketing environment where physicians and patients are making decisions about whether to reinstitute a therapy particularly in the context where that therapy is uniquely beneficial and there are no other alternative therapies. Next slide.

International Consistency

- Global enterprise - trials going on in every continent
- Reliance on internationally agreed upon approaches
- Value of meetings of this nature and guidance on best practices in premarket clinical evaluation

We heard a presentation from Dr. Bartholomaeus from Australia about something that I think we all recognize very well. This is indeed a global enterprise and the discussions that we've been having here these last couple of days clearly apply globally with trials are going on I guess on every continent, except maybe Antarctica. Maybe there are trials in the Antarctica. There's a tremendous value of such meetings as well as guidance on best practices that would be applicable not only to the United States market but in global development as well. And next slide please.

Expectations of Clinical Trials

- Practical
- Justified – scientific and ethical basis
- Post-marketing vigilance/studies – how to do it
- Phase III studies – continuing on into Phase IV

There was a lot of good discussion about the expectations of clinical trials, and whether it's practical or even justified on a scientific or even ethical basis to even consider rechallenge in the context of a clinical trial. A lot of those discussions, of course, came out of the discussion this morning related to whether one should, for example, enroll individuals with preexisting or underlying liver disease. And clearly if one were to consider that, indeed, a lot of the cases of drug-induced liver injury are likely to be observed with wider use of the product in populations with different kinds of co-morbidities and wider use of concomitant medications, and that the greatest value in terms of understanding and what information could be gained out of rechallenge, might indeed be in the post-marketing environment, it raises a whole host of issues about both surveillance studies, how to do them, how to take information that's learned in the context of clinical trials in Phase III and continuing them on into Phase IV where the product is more widely available. Next slide, John.

Final Words

- Re-challenge has challenges
  - practical, ethical, scientific
- Need ways to evaluate/study those at greatest risk/experience harm
- Need better assessment tools and methods
  - diagnostic
  - study at-risk populations

So clearly rechallenge has many challenges that are both practical, ethical as well as scientific. We clearly continue and need ways to evaluate and study those who are at greatest risk or experienced harm in the context of clinical trials and beyond. It may be that in the context of this discussion, and in the context of this Guidance, which is focused essentially on the evaluation during clinical trial development, that the question of rechallenge may be the challenge for consideration on how we continue to develop the product once it's moved out of the narrow and rarified environment of the clinical trial and into wider use. Clearly we need better assessment tools and methods both in terms of diagnosis as well as to be able to study at-risk populations.

So that's my attempt at synthesis and I'm looking forward to your questions and discussion.