Moderator’s overview
Sessions IIIA and B

John Pears

DR. PEARS: Thank you, audience. I'm impressed by your tenacity in staying around and still contributing to an ongoing discussion. It reflects I guess the interest and importance that we all feel about this set of draft guidelines.

I have three development slides. The first one is just a title slide. I'm just going to summarize the discussions that we had this morning. I thought ours were the best presentations and the best discussions, but I'm biased.

I was disappointed that I couldn't write down the words Dr. Hunt very eloquently and succinctly used to describe, the summary of the discussion that we had about including patients in clinical trials this morning.

And I think there was general agreement that we all agree with the Guidance document. I'm assuming that everything in the guidelines is okay unless you have specifically addressed it yourself [in the discussion]. So I'm just trying to reflect the areas where there might be still some thought.

Including more patients with stable liver disease in trials - I

- General agreement that we could do more to understand the interaction between the drug and patients with liver disease who may take the drug when marketed
- Still some doubt about the evidence to prove that baseline liver disease is not associated with increased incidence of DILI
  - Studies not been done
- We already do include some patients as we do not exclude routinely beyond a history/clinical evidence of acute liver disease/NASH

I think we generally agreed that we could do more to include in a clinical trial population more patients' with underlying liver disease. That's not to say that it's straightforward and it's easy and can be done without thought and just generally randomize or include lots of patients with liver disease. You have to give some consideration, as Dr. Barth was just saying, if you have a particular disease population with a very high prevalence of underlying liver disease, it might be easier to show an effect, while if you have a very low prevalence, it would be much harder.

There were some other areas of contention about the statement in the Guidance on whether having baseline liver disease is not associated with an increased incidence of drug-induced liver injury. I think that not everybody was convinced by the evidence that supports that statement, and there may be some room to do some prospective studies to support that, if the studies can be done, or by alternative ways of gathering material information to do that.

I believe the comment was already made that we do actually already include patients with underlying liver disease, but we probably don't know that they have it. As I said earlier, there are still significant issues that we need to address before going ahead and putting more patients with underlying liver disease into Phase III clinical trials. We need to know from the early clinical studies whether there is a potential issue for DILI in man. We need to think about what patients have been studied and what the benefit-risk balance might be in that population. We need to understand the pharmacokinetics of the drug in humans and to know what the routes of metabolism and excretion are ,and how that would be affected in patients with liver disease.

Including more patients with stable liver disease in trials - II

- There are significant issues to be considered before doing this:
  - Is there a liver signal?
  - Which patients are being studied
  - Phase III studies or specifically designed studies in parallel
  - DMPK
  - Stratified randomisation?
  - Sub-group sizes and analysis?
  - More frequent/detailed follow-up of such subjects
  - More use of expert “DSMB” to assess causality
- Suggested other additions to the draft guidance:
  - Better establish baselines and inclusion/exclusion for “stable liver disease” e.g. hepatitis testing
  - More detailed suggested standard follow-up (flow diagram in the guidance?)

We need to think about how we're going to get meaningful data from treating those patients. If it's a common disease being studied, as Dr. Barth indicated, then that may be very easy to do. If there are very few patients in the patient population with liver disease to whom the drug will be prescribed, it's actually going to be quite difficult to get a meaningful number of patients to say whether the signal is the same or different in patients with underlying liver disease.

We might think of other ways of doing this rather than stratified randomization, thinking about sizes of subgroups. Do we want to do specific trials in patients with disease of interest where we specifically select for having liver disease? So there're all sorts of things that we could address as things to consider, rather than for the FDA to prescribe to us as what can be done.

And once we have those people in trials, because there may be more specific issues, we may want to have a different monitoring scheme, more frequent or more detailed monitoring of those patients. And certainly we support Dr Lee’s suggestion that you probably want to have a DSMB active, to be using external experts to make sure the trials are designed properly to assess the causality, in trying to distinguish drug from underlying disease effects in these populations.

Some other suggestions were made in addition to the draft guidelines. One was about establishing baselines and trying to think about what points to consider for inclusion and exclusion criteria in defining stable liver disease. What would be the recommendations for testing for viral hepatitis or perhaps testing for nonalcoholic fatty liver disease or other common liver diseases in the baseline population? Collecting more adequate baseline data than what the pharmaceutical industry currently does in general related to underlying liver disease could be important to understanding the situation.

Novel biomarkers/research opportunity

- General acceptance of the current draft guidance
- Recognition of significant issues in getting this done
  - Ownership
  - Science
  - Designing the experiments
  - Logistics of sample collection, signal generation and hypothesis testing
- Some support (not universal) for
  - mechanism based biomarkers
  - biomarkers with linear response of loss of hepatocyte mass

There was also a suggestion about having a more detailed standard protocol, to even have a flow diagram, about what testing should be done when and by whom, which can be put in the Guidance and perhaps taken forward.

So those were my comments about the patients with underlying liver disease, dealing with some things that we need to think about before just going ahead and inclusing them into routine phase III clinical trials

We then had presentations, conversation and discussion about the opportunity for new research on biomarkers. I think, in general, that the draft Guidance was accepted. The conversation beyond that was really beyond the scope of the Guidance. It was around designing a standard which is about having the ability to actually make it happen, and how we're going to get around to some of the issues that are there in terms of setting up and making this thing happen. For example: who's going to own it, who's going to say we're going to drive this, we're going to make it happen, i.e. what the fundamentals are. We understand the science enough to be able to identify the need for biomarkers and to construct platforms around them, and to design the experiments in a way that will give us meaningful data with qualified biomarkers. Then there's some logistical stuff about come collection, signal generation and hypothesis from these data. That last bullet about working together in consortia is what Arthur Holden was talking about.

And there was some discussion about universal support for mechanism-based biomarkers and issues around biomarkers with linear response through loss of hepatocyte mass. And those were the things that I took away from the discussion this morning. Please be gentle with me. I only had lunchtime to prepare the slides. My follow moderators had the luxury of an overnight period to prepare (laughter). So I'm sure you'll be kind to me. So I'll be glad to take any questions, thoughts, comments. If you're going to throw something, give me a chance to hide behind Dr. Senior please. (Laughter.)