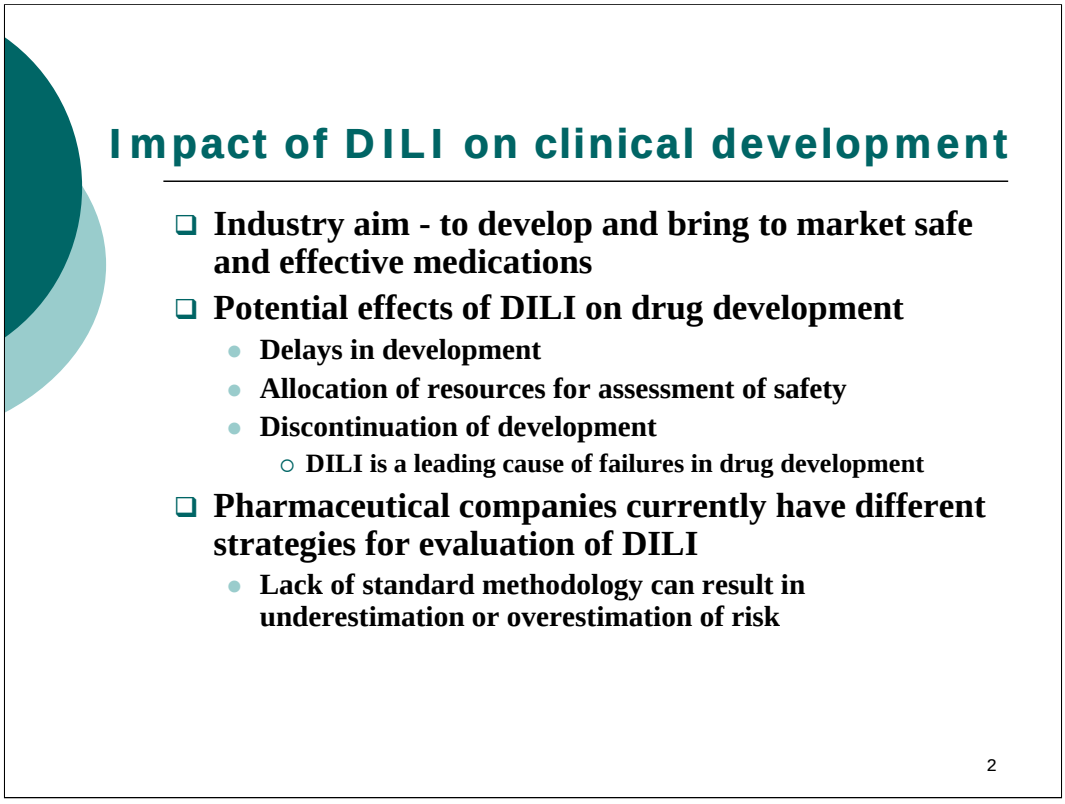

DR. SELIGMAN: Our next presenter is Jay Barth from Merck Research Laboratories, to provide us with an industry perspective. Jay.

DR. BARTH: Thank you. Hi, everyone. Thank you, Dr. Senior, for giving me the opportunity to speak here but I'll start by giving you a disclaimer. Despite the lofty title of industry perspectives, I won't pretend to represent all of industry or even my own company, but share some of my own thoughts from the perspective of industry and myself. My background is pediatric gastroenterology and hepatology, a physician in that area before joining the pharmaceutical industry. So I come to this issue both from the perspective of a clinician who has treated patients but also having been in the industry for a number of years. The considerations that we have in conducting clinical trials, and that's the perspective from which I'm coming, and taking Dr. Senior's point of trying to elicit comments and not just share thoughts with everyone, I have structured this in terms of some of the key points that I think should be highlighted in this draft Guidance that I thought merit further discussion and clarification and hopefully will lead to some discussion on the part of everyone here. I'm sure there are a number of people from industry who would like to share their thoughts on these issues as well. So please feel free to do that when we get to the discussion section.

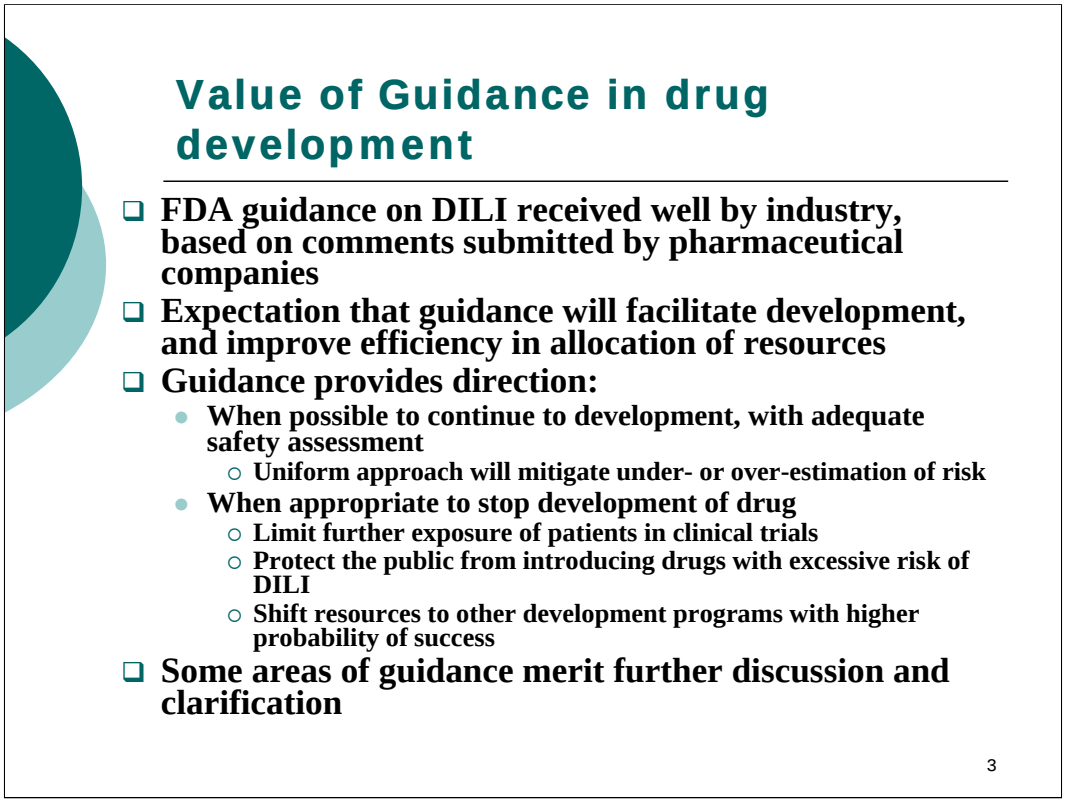



With a little background, the impact of DILI on clinical development clearly is profound. The aim of the pharmaceutical industry is to develop and bring to market safe and effective medications, but the issue DILI can certainly arise in a number of ways during drug development. One of them, of course, is delaying the development of drugs which will withhold treatments that would prove to be effective from getting to the public.

In terms of the allocation of resources, which is reality of the pharmaceutical industry and any industry, that there is a limited number of resources that can be given to different drugs that are in the pipeline, and where should those be allocated and if there's a way to distinguish those that have a safety issue associated with them, that not put additional resources towards those drugs but shift them towards drugs that have a better chance of success.

And, of course, the ultimate impact of DILI on drug development is discontinuing development of that drug and DILI, in fact, as you well know is the leading cause of the failure of drugs during development. So in a number of ways, DILI does impact on what we do in the pharmaceutical industry.

And currently, that is in the absence of a guidance or before there was a draft Guidance, pharmaceutical companies would basically pursue their own strategies and methods of dealing with DILI, and there is no uniformity in the way that this is done. And the lack of standardization in the way DILI is assessed and dealt with can result either in the overestimation or underestimation of risk of the drug, how safety signals are identified, analyzed and so on and this lack of uniformity can have effects that either curtail the development of promising drugs or allow development of drugs that really should not go further. And that is the context in which this Guidance comes.

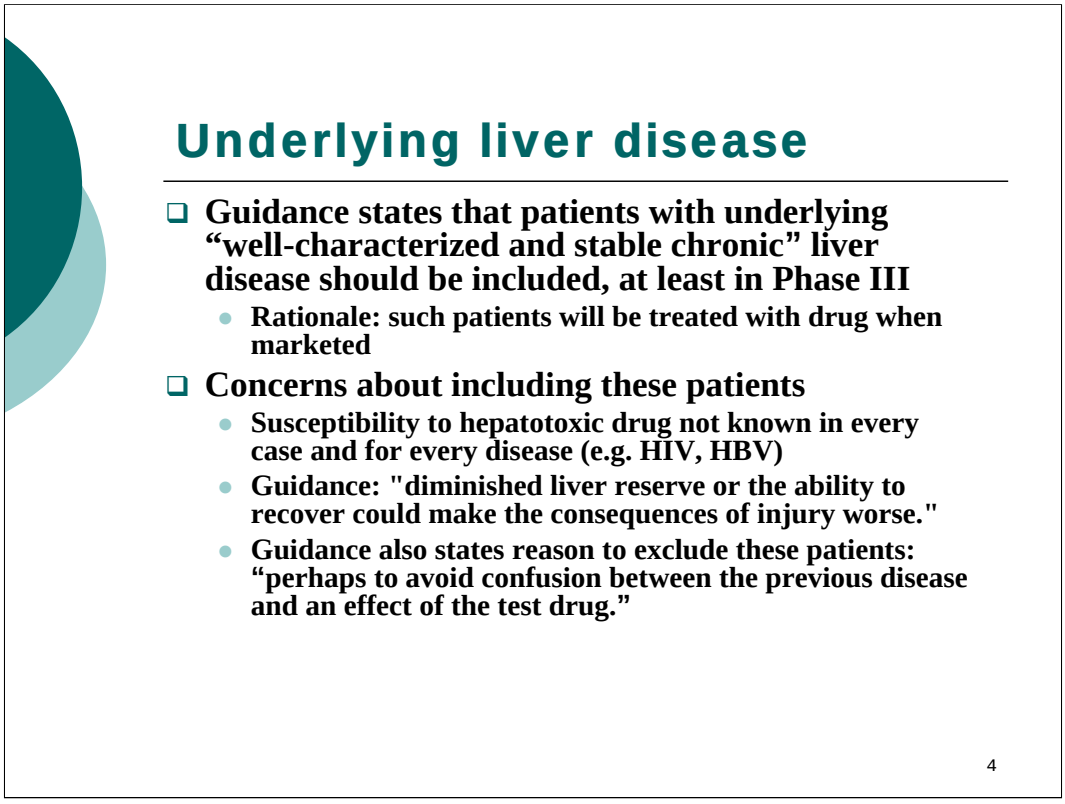



So the value of that this Guidance brings to the pharmaceutical industry is quite substantial. The comments that were posted when the draft Guidance was sent out from the pharmaceutical industry and from PhRMA, the organization, really reflect the fact that the pharmaceutical industry welcomes this Guidance, that it's going to be a help to drug development.

And the expectation is that this Guidance by laying out a path and a strategy for dealing with the issues of DILI, will facilitate development, making things more efficient in the way that we develop drugs.

And this is done through a number of ways. The Guidance provides direction about when it is possible to continue development with adequate safety monitoring, and by instituting a more uniform approach to the assessment of DILI, that will hopefully mitigate either the underestimation or overestimation of risk that may be occurring right now.

It will also help guide industry, we hope, when it is appropriate to stop develop of the drug which is often a difficult thing to do. Once a lot of investment has already occurred, both financial and emotional and otherwise, that the people working on the drug have towards the drug in development, sometimes becomes difficult to terminate development but if there are objective criteria that can be applied, in this case through the assessment of risk of DILI, that will help limit the exposure of further patients and clinical trials if the drug development is terminated. It will protect the public, of course, from introducing drugs that have an increased risk of a severe DILI, and as I mentioned before, by terminating development in a drug that has this increased safety risk, in terms of liver toxicity, it will allow resources to be shifted for its other more promising drugs that, again those will ultimately benefit the public.




But as I mentioned when I started, there are some areas of the Guidance that I do think bear some further discussion and clarification that will help those of us in industry be able to proceed in a more clear manner in some of the areas that are addressed by the Guidance. And to highlight some of them, I'll start with the issue of underlying liver disease which has already been touched on in some of the talks, and I think we'll get back to during this meeting. The Guidance states that patients with underlying well-characterized and stable chronic liver disease should be included at least in Phase III trials with a logical rationale that such patients will be treated with the drug when it is marketed, and certainly those of us in the pharmaceutical industry can agree with that fact, that these drugs will be used by the general public among whom there will be patients with underlying liver disease.

Nevertheless, there are concerns about including these patients in clinical trials. One is that even though it seems to be generally accepted that there isn't an increased risk or increased incidence of DILI in patients who have underlying liver disease, that may not be true in every case, for every patient, for every disease, HIV and HBV, that may be examples in which the underlying liver disease may be exposed to a higher risk or a higher degree of DILI if it does develop. And another issue of concern would be, and I think Dr. Senior mentioned before, even if the incidence of DILI is not increased by the presence of underlying liver disease, the response, if it does occur, may be more severe in patients who have a chronic liver disease based on the diminished liver's ability to recover from the injury due to the drug.

And the Guidance itself states one reason that these patients may not be included or a reason to exclude these patients is that it may confuse, create confusion between the previous disease, the underlying disease and the effect of the test drug. If a person who has a chronic liver disease does develop some further abnormalities during the course of a clinical trial, attributing it to the underlying disease versus the drug, it becomes more difficult. DILI is a diagnosis of exclusion and anymore complicating factors during the course of the clinical trial, that would make it even harder to make the diagnosis of DILI, will make the database harder to interpret and the results of the study harder to interpret and could interfere with the further development of the drug

## Underlying liver disease

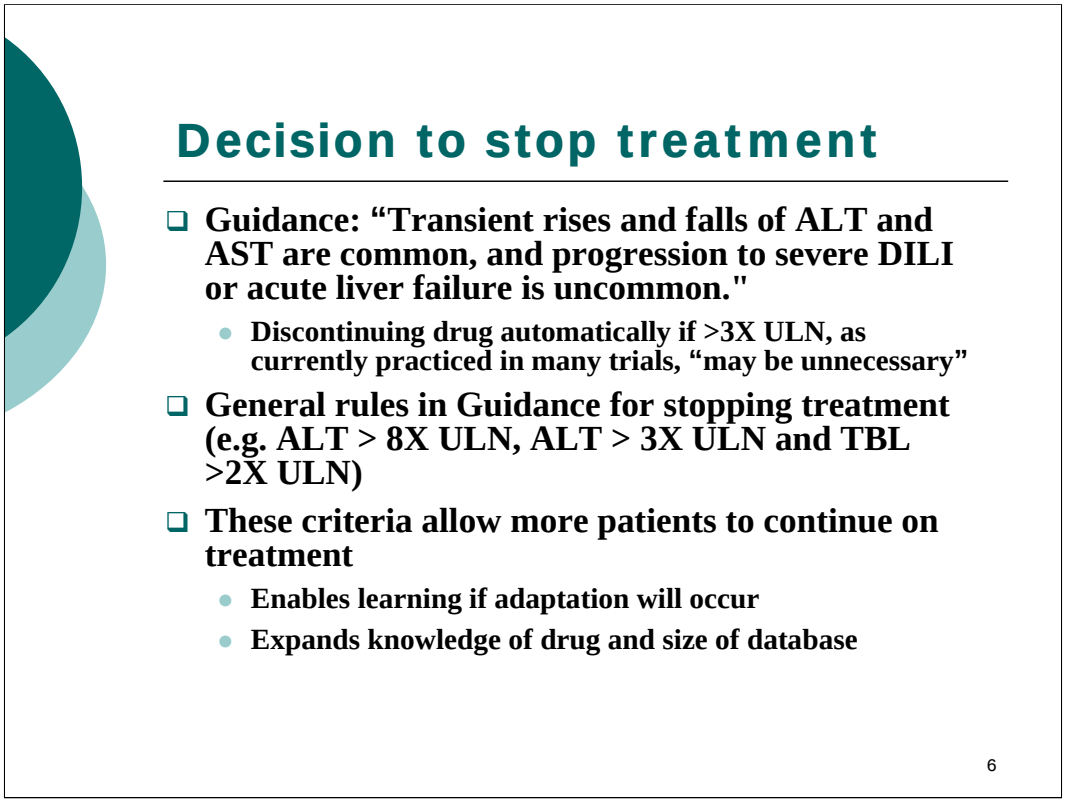
**Questions:**

- **Which patients/diseases should be included or excluded from clinical trials?**
- **What is benefit/risk of including these patients?**
- **If these patients are included, how to distinguish DILI from underlying disease?**

5

And what is the benefit and risk of including these patients? The risk, of course, to these individual patients, the benefit to the public by testing the drug in patients with liver disease, but then if you think about it, if you allow inclusion of some or more of these patients with underlying liver disease, the numbers of these patients within any given clinical trial will likely be rather small, not even constituting likely a subgroup large enough to analyze by itself. So will we really get meaningful data that they can interpret from a trial in the general population if there are only a few subjects who have underlying liver disease included?

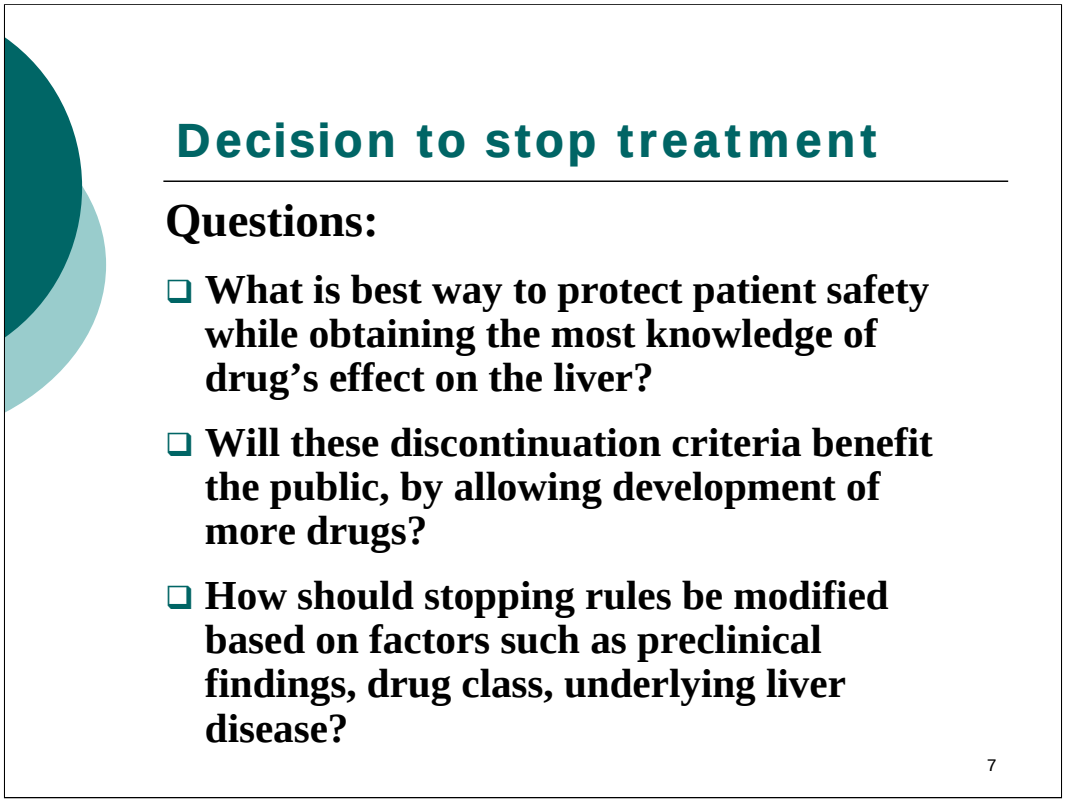
Even if these patients are included, ultimately on a case-by-case basis of assessing causality, will we be able to know with any definitiveness, is the drug or is it the underlying liver disease?




Another point that the Guidance does address is the decision to stop treatment in the individual patient in the trial. As cited in the Guidance, the transient rises and falls of ALT and AST are common, progression to severe DILI or acute liver failure is uncommon. And therefore, discontinuing the drug automatically if it reaches a threshold such as greater than three times the upper limit of normal, which is currently practiced in many clinical trials, maybe be unnecessary, and it's interesting, when I saw this, my reaction this is certainly an area where it seems less restrictive than what is already being done or has been done over time in the pharmaceutical industry where out of a sense of caution and to protect the safety of the individual patients, the treatment would be terminated if it reached even a threshold of three times or perhaps greater than two times upper limit of normal. So this is an area where the Guidance would allow patients to continue in trials even with higher elevations.

The Guidance does go into a lot of specifics about what the stopping rules would be such as greater than eight times the upper limit. That's been discussed already or a combination of greater than three times the upper limit for ALT and elevation of total bilirubin.

And, as I mentioned, these criteria would allow more patients to continue on treatment than currently practiced probably in many trials and enable us to learn if adaptation will occur and will expand knowledge of the drug in patients who have these elevations of transaminases and also increase the size of the database by allowing more patients to continue on treatment.




But here we get to the balance that we feel in the industry as well between protecting individual patient safety by comparing that with the knowledge we would obtain in general, the drug's effect on the liver, as it affects the general population, and we deal with that all the time, how to balance the risk and, of course, any clinical development involves risks and that's acknowledged by industry and the investigators and is shared, of course, with patients through informed consent but in each case, it's something that we think about, balancing these two sometimes conflicting interests.

And will these discontinuation criteria really benefit the public by allowing more drugs to continue in development by allowing more patients to remain in the clinical trials?

And then more specifically and on a more technical level, how should the stopping rules be modified by other factors that exist in some patients or with the drug, either preclinical findings, the drug class, underlying liver disease, things that would make us consider having different stopping rules, perhaps more restrictive stopping rules than what's outlined in the Guidance.

## Decision to rechallenge

- **Guidance states: "Whether or not to rechallenge a subject who showed mild DILI is a difficult question."**
  - **Consider if the subject "has shown important benefit from the drug and other options are not available" or if "substantial accumulated data…do not show potential for severe injury"**
- **Cases in which rechallenge warranted are limited, but not specifically defined**

8

The decision to rechallenge I think has been addressed pretty extensively already in the previous session. So I won't dwell on this at all. I think what has been acknowledged is that rechallenging, there may be some cases where it's warranted, but it's not specifically defined in the Guidance. And from the discussion before, it certainly sounded, and I'll add Merck to that list of cases where clinical trials is not the setting where rechallenging would occur as a rule.

## Decision to rechallenge

**Questions:**

- **What is the appropriate balance between individual risk vs. confirming that drug is associated with DILI?**
- **Will rechallenge achieve the aim of confirming DILI, or if liver tests remain normal, could this be explained as adaptation?**

9

And again, it gets to the balance of the risk to the individual patient versus confirming that the drug is associated with bili, and even with rechallenging, can you actually do that because there will be some unknowns. Is it a negative rechallenge or is it adaptation that's going on? But I won't spend more time on rechallenging since that's been discussed previously.

## Confirmation of liver test abnormalities

- **Guidance states: "In general, an increase of serum AT to >3X ULN should be followed by repeat testing within 48-72 hours"**
- **Retesting lower values, < 3X ULN, not generally necessary**
  - **Elevations <3X ULN are "common and non-specific"**
- **Retesting plan in guidance is thorough and detailed**

10

Another area that's dealt with in the Guidance is confirmation of liver test abnormalities or retesting when there are abnormalities. In general, the Guidance states an increase of transaminases greater than three times upper limit of normal should be followed by repeat testing shortly thereafter, and outlined pretty specifically in the Guidance are the follow up testing that should be done on an individual patient basis.

Retesting, if the ALT is below three times upper limit of normal is not generally necessary because they're considered common, non-specific.

## Confirmation of liver test abnormalities

**Questions:**

- **If criterion for retesting is >3X ULN, are there circumstances in which retesting should be conducted at lower elevations?**
- **How prescriptive should clinical trial protocols be with regard to retesting, or should investigators have some discretion in this area?**

11

But this raises the question for somebody who is involved with designing and conducting these clinical trials, if the criteria for retesting stated in the Guidance is, once it reaches the threshold of greater than three times upper limit of normal, are there circumstances and what are those circumstances in which retesting should be conducted even if they are lower elevations?

And one of the other issues that this gets into is the responsibility of the investigators versus the sponsor because should any of the discretion be left to the investigators in terms of the types of retesting, doing more than what's prescribed in the protocol versus how much should be prescribed in the protocol by the sponsor of these trials.

## Premarketing signals of DILI

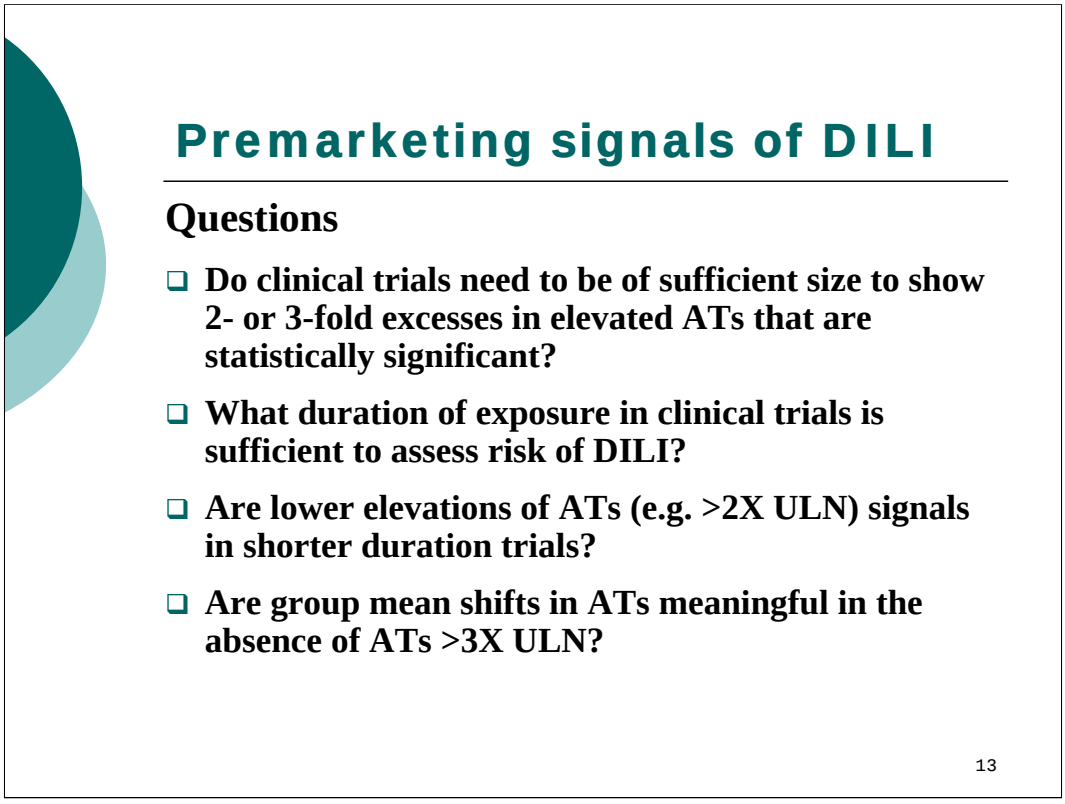
- **Guidance cites an "excess of AT elevations to >3X ULN compared to a control group" as an indication of potential for severe DILI**
  - **"Excess" not defined; "2-fold, 3-fold" is suggested**
  - **Duration of exposure required in clinical trials not defined**

12

Of course, the goal of the testing is to identify signals in the premarketing phase, during the clinical trial phase of DILI, and the first level of a signal that would be identified as has been already noted here several times is an excess of transaminase elevations to greater than three times upper limit of normal compared to a control group.

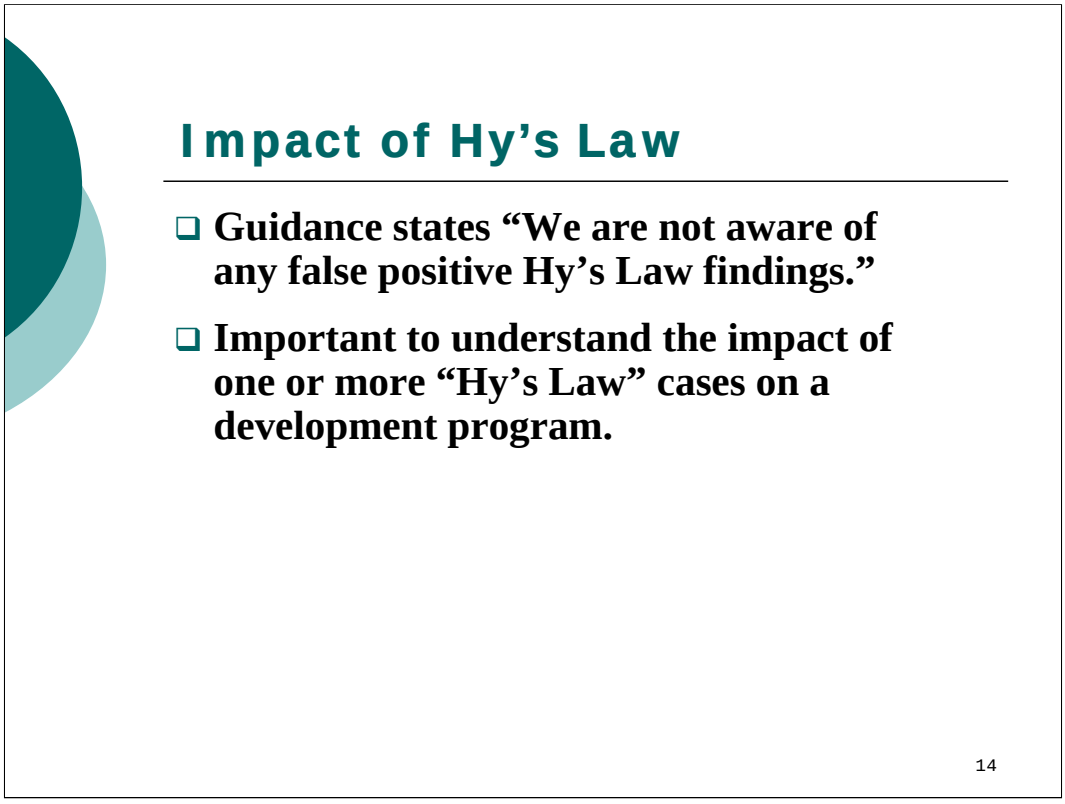
The word excess is not defined specifically in the Guidance. Twofold or threefold are suggested as possible definitions of what this excess should be but I think it would be important to know as we in the industry are analyzing data, don't want to miss a signal, but don't want to find a signal when there isn't one there, to know, are we going to be looking for twofold elevations compared to control or threefold? There is a difference there. What are the circumstances where it would be one versus the other or a different definition of what excess is.

And the duration of exposure in clinical trials that's needed in order to pick up the signal is also not defined as specifically in the Guidance although it is touched on.

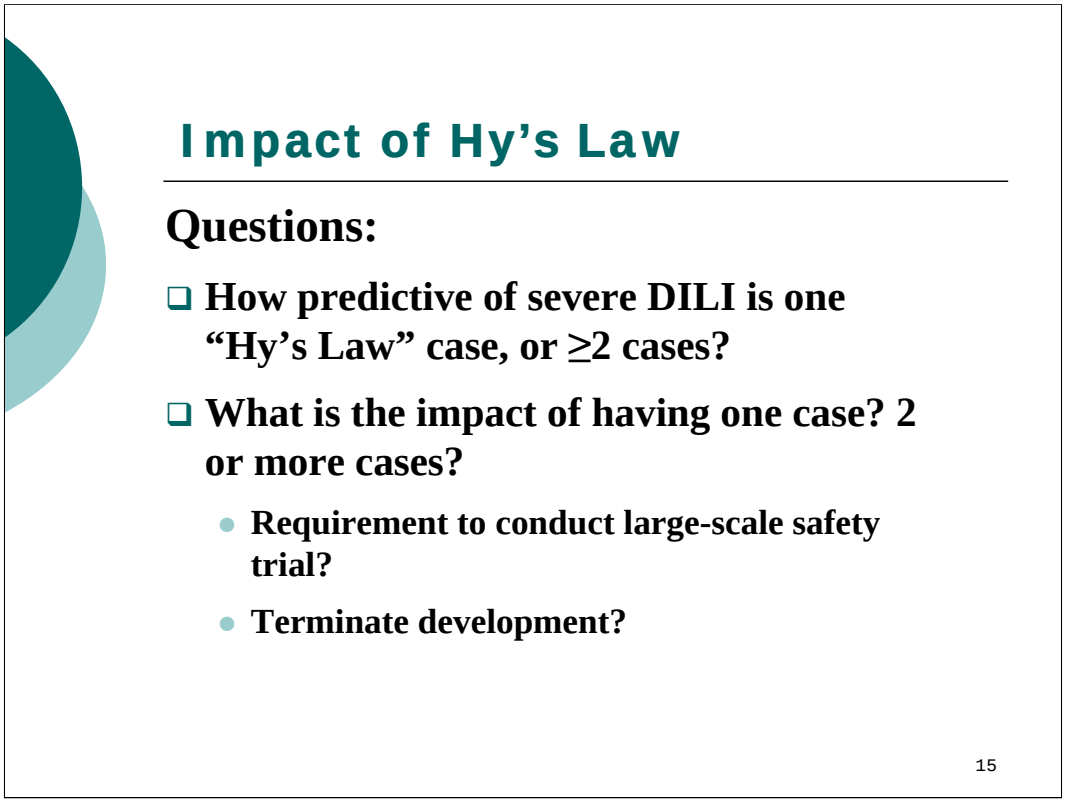



And the questions that this raises are, do the clinical trials need to be of sufficient size, in excess of two or threefold elevations in transaminases need to be statistically significant? Is it a criteria that would be applied to individual trials or to a database as a whole which would have a lot larger number of subjects?

And then in terms of the duration, what is the minimum duration of exposure in clinical trials that would be sufficient to assess the risk of DILI? Because clearly, with longer duration trials, you'll have enough exposure in order to see elevations three times, eight times and so on, but in shorter term treatments, within shorter clinical trials, may not have the opportunity for the transaminases to rise that high. Are there signals that we should be looking for in these short term treatment trials that are lower than the threshold for the longer term treatment trials? Perhaps greater than two times upper limit of normal or perhaps differences in the group means compared to control in transaminases, if the number of subjects in the trials, the shorter duration trials, and I'm thinking more of the Phase I trials, where you don't have the opportunity to necessarily look for the patients who have elevations greater than three times, are there other ways to look for signals in these smaller, short term, earlier base trials?




Now Hy's Law, I won't go into what the definition of it should be. That's been discussed today and probably will continue to be more during this meeting, but clearly from industry perspective, it is important to recognize cases of Hy's Law and to understand what the impact of one or more cases are on a development program, not just when an NDA is ready for submission or under review, but during development, how should industry think about cases of Hy's Law that occur during the course of development?




And it does get to the question of how predictive is one case or two or perhaps more cases and what is the impact on the development program as it's proceeding forward of seeing one case or seeing a second case? Will that lead to a requirement to conduct large scale safety trial or trials in order to assess it further, or should threatened drug be terminated at that point already? And I think that's an area certainly in terms of planning and knowing what resources should be devoted to a drug, that it will be helpful for industry to understand further what the impact is as we are going through the course of development.

## Size of database

- **Guidance states that "absence of Hy's Law cases in an NDA or BLA database may allow an estimate of an upper limit of the rate for severe DILI, using the Rule of 3"**
  - **Refers to database of 3,000 subjects, which gives 95% confidence of DILI rate ≤ 1/1,000, which suggests rate of severe DILI ≤ 1/10,000**

16

Size of the database, not to go into the specifics here, but the number of patients that are cited in the Guidance, in a typical NDA database is 3,000 which based on the Rule of 3 would rule out with some confidence an incidence of greater than 1 in 10,000 of severe DILI. And this question arises, an example of typical size of database or is this saying that this is a sufficient size and this number, 1 in 10,000, is appropriate to rule out? If this is an acceptable size database, are there other factors that could influence it that may require us to collect a larger size database for submission, either the class of the drug, mechanism of action, preclinical data, things that would raise concern even if you don't see any signals of severe DILI.

## Size of database

**Questions:**

- **What is an acceptable size database, and what factors involved in this decision?**
  - **Drug class, mechanism of action, preclinical data, early clinical data.**
- **What incidence of severe DILI in the post-marketing general population should be ruled out in the clinical trial population?**

17

And then ultimately, what is the incidence of severe DILI in the post-marketing general population that should be ruled out during clinical trials? Is that target 1 in 10,000 or should it be higher perhaps, lower, or does it depend on the drug class, other factors and so on? And these are the things in a planning and development program that, of course, are important for us to understand.

## Preclinical assessment of risk of DILI

- **Guidance is focused on clinical development, Phases I – III.**
- **Guidance: "The drugs that have caused severe DILI have not shown clear hepatotoxicity in animals"**
  - **Preclinical studies are not necessarily predictive of risk in humans; "false positives" and "false negatives" occur**
- **Industry would benefit from FDA guidance on preclinical liver safety assessment**

18

Preclinical assessment of DILI, I won't spend a lot of time on, since it's not strictly within the scope of the Guidance except to say that it is touched on in the Guidance, drugs -- mentioning of drugs that have caused severe DILI and not shown clear hepatotoxicity in animals. And, preclinical studies don't necessarily predict the risk in humans. There are false positives, false negatives in terms of the animal data, predicting human data. And ultimately, the industry would benefit from guidance relating to preclinical liver safety assessment.

## Preclinical assessment of risk of DILI

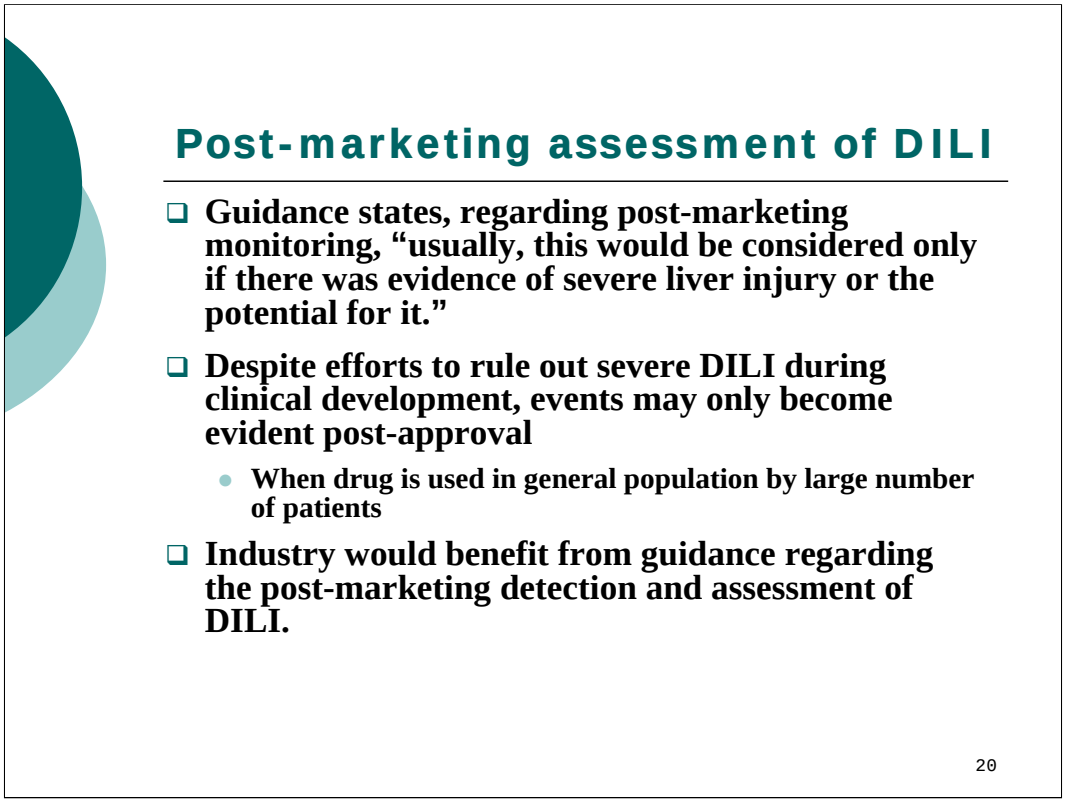
### Questions:

- **How much impact should preclinical findings have on the extent of monitoring in clinical trials?**
- **How important are preclinical findings in overall assessment of risk of DILI?**

19

And the questions, or some of the questions that I would want to see answered in that is what is the impact on preclinical findings on the extent of monitoring in clinical trials?

And ultimately, how important are the preclinical findings in the overall assessment of risk of DILI?  Once you have clinical data, how important are the preclinical, how important are the preclinical findings in retrospect?




The post-marketing period is also not strictly within the scope of the Guidance but it is mentioned as it relates to monitoring, and that I think was brought up in the last question and answer period, which is when post-marketing monitoring should be done. Usually, according to the Guidance, it should be considered when there's evidence of severe injury or potential for it.

And, despite all efforts and the best efforts to exclude severe DILI during clinical development, the events may only occur or become evident in the post-approval period, when the drug is out in the general population taken by a large number of patients with comorbidities, concomitant medications and so on, and guidance that would help industry understand the post-marketing detection and assessment of DILI would certainly be helpful.

## Post-marketing assessment of DILI

**Questions:**

- **What impact is the Guidance expected to have on the post-marketing incidence of severe DILI?**
- **When is post-approval monitoring warranted and what is its expected effect?**
- **If potential for severe DILI is not demonstrated during clinical development, how can it best be detected post-marketing?**

21

Some of the questions I've raised for that are what is the impact of the current Guidance expected to have on the post-marketing incidence of severe DILI? Clearly, it is to reduce it but is it to eliminate it or to what extent is it expected to reduce DILI, severe DILI? When is post-marketing approval warranted? And if the potential for severe DILI is not demonstrated during clinical development, how is the best way we in industry working with the FDA can achieve a plan to detect it in the post-marketing period?

## Research opportunities

- **Industry eager to participate in research in DILI**
  - **Improve prediction and detection of DILI**
  - **Identify and exclude individuals susceptible to DILI, and allow development of drugs that will benefit those not susceptible**
- **Critical path initiative – FDA, industry, academia working to understand the "biochemical and genetic bases of DILI."**
  - **Consortia aimed at developing biomarkers and identifying genetic variants associated with DILI**

22

And lastly, certainly research opportunities are of great interest to the pharmaceutical industry to improve prediction, detection of DILI, to identify and exclude individuals who are susceptible to DILI, and allow development of drugs that will benefit the general population who are not susceptible. And, critical path initiative which is familiar to everyone here, is working towards that.

## Research opportunities

**Question:**

- **What are the most effective ways that industry can collaborate in research to understand DILI?**
- **How best to protect DILI-susceptible patients while allowing the general population to benefit from new treatments?**

23

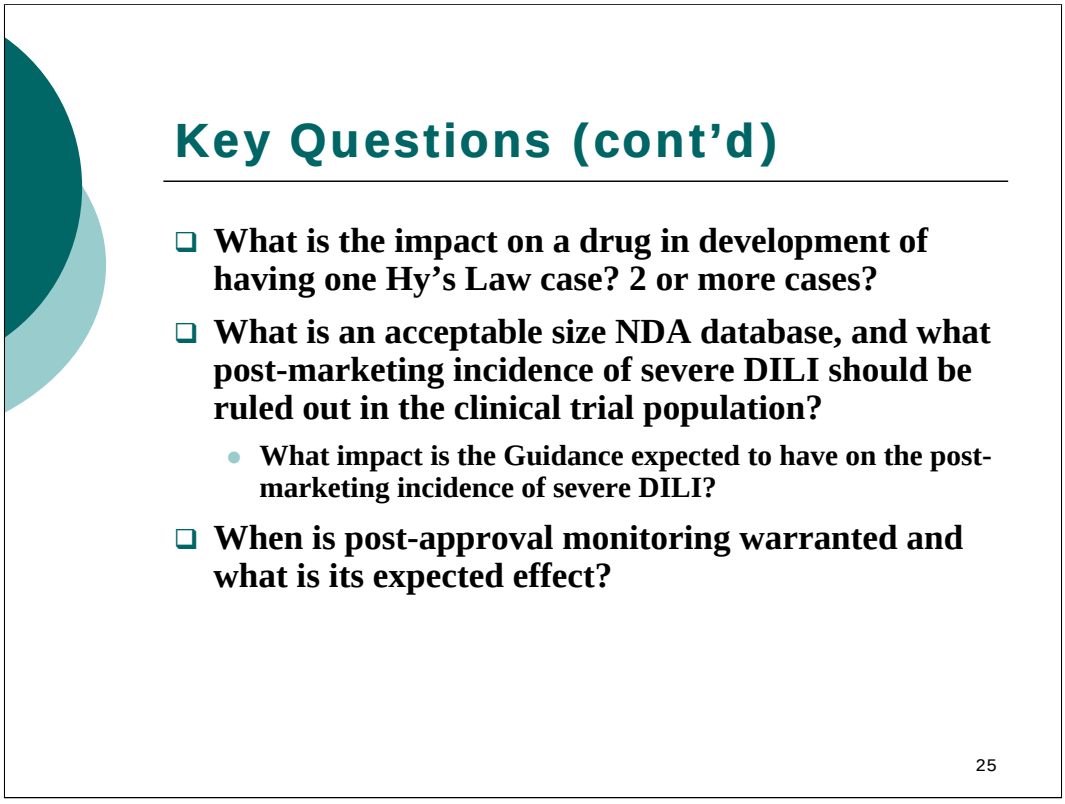
And we deal with the questions of how industry can most effectively collaborate in this research to understand DILI and how to protect those who are susceptible to DILI while allowing the general population to benefit from new treatments if they are not susceptible.

## Key Questions

- **What is benefit/risk of including patients with underlying liver disease in clinical trials?**
- **How should individual patient safety, in stopping treatment or rechallenging, be balanced with allowing drug development to proceed?**
- **What duration of exposure in clinical trials is sufficient to assess risk of DILI, and are lower elevations of ATs (e.g. >2X ULN) signals in shorter duration trials?**

24

Key questions – shown without comment.




Key questions – shown without comment.

Thank you, and hopefully there will be good discussion in the time remaining.

(Applause.)