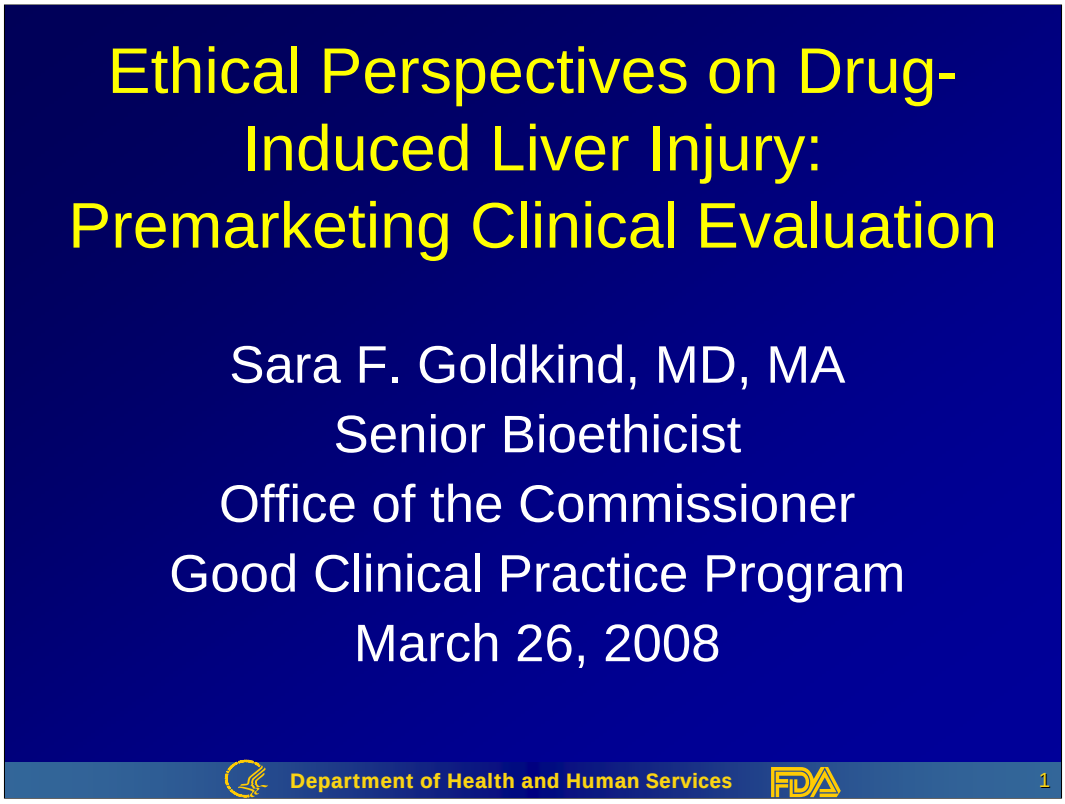
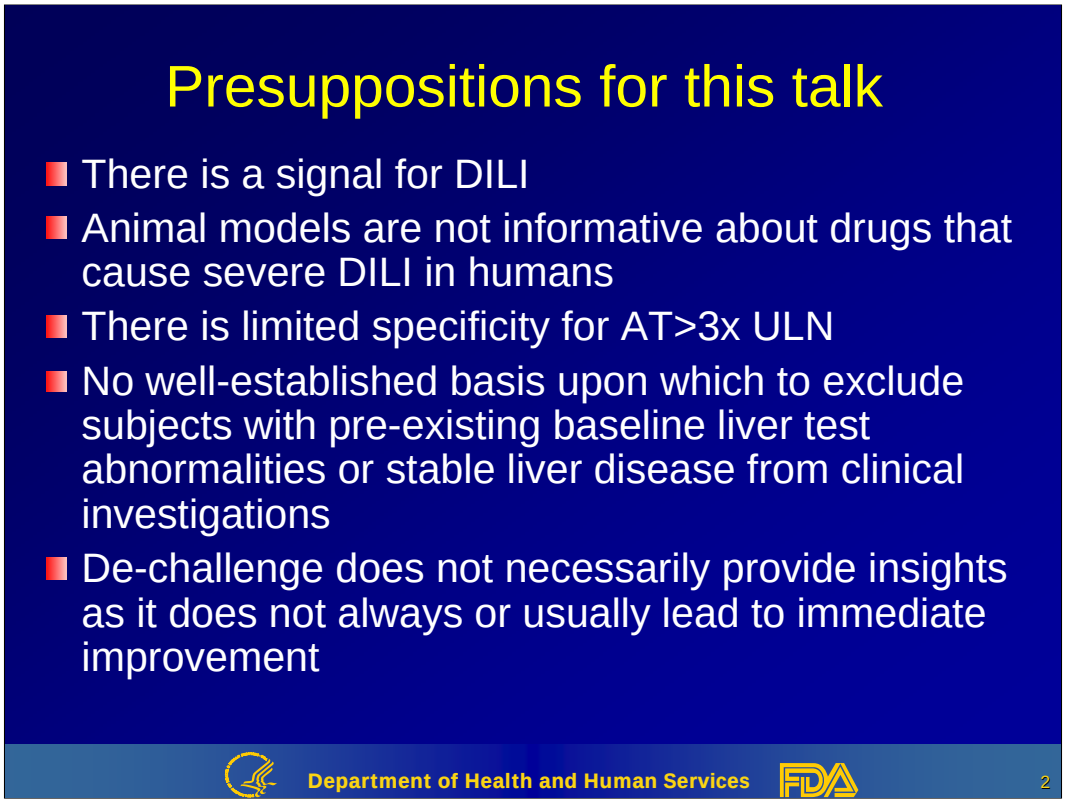


DR. GOLDKIND: Good afternoon. Can you all hear me? Okay. Well, I'm not going to stand in the way of wine and cheese. So I'm going to try and be brief, and I'm the Senior Bioethicist at the FDA in the Office of the Commissioner and my background is internal medicine. And Mark Seigler, who is a clinical ethicist at the University of Chicago said that the role of a good ethicist is to put himself or herself out of business, largely I think through teaching.

I would like to make the bold statement that I think that many of the ethical issues related to the topic that we've been discussing today could be mitigated or resolved by more data and evidence-based information. And with that in mind, I would compliment John Senior for really doing a lot to provide evidence and to help put me out of my job.



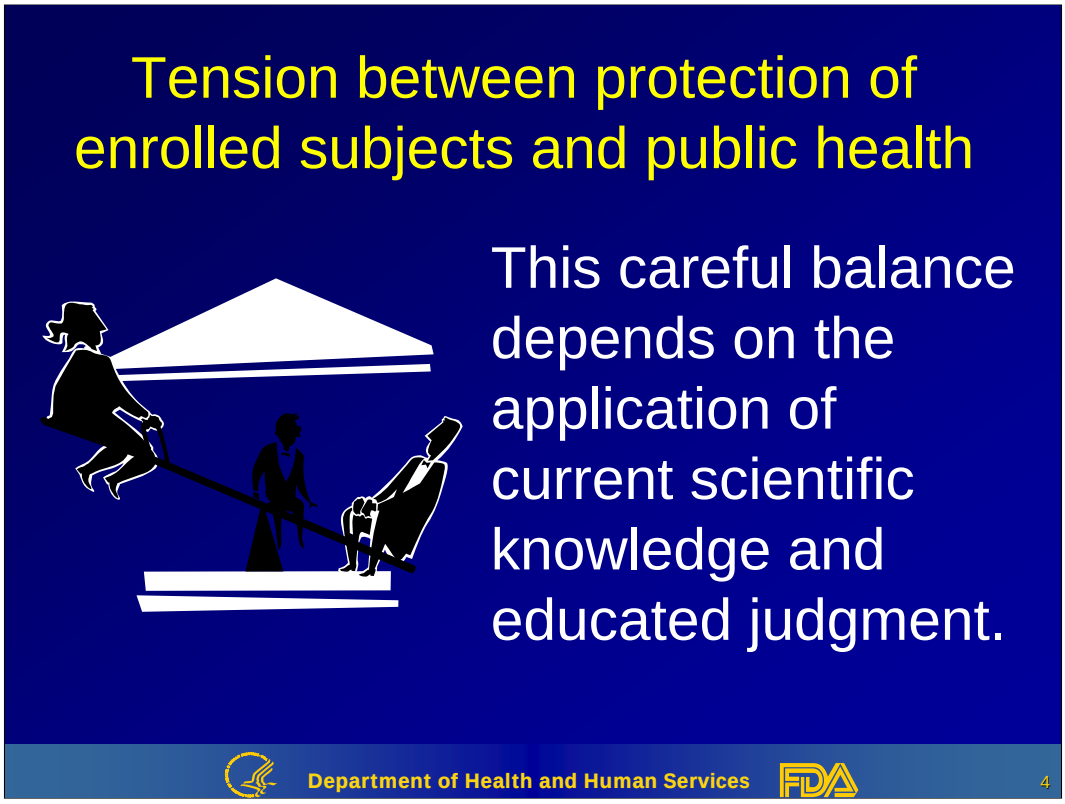
So what I thought I would do is just briefly present an ethical framework in which you can think about some of the issues that we've talked about today that are all very familiar to you. And I list a series of presuppositions for this talk, and the first is, of course, that there is a signal for drug-induced liver disease. That's what I'm going to be discussing in my remarks.

And then some of the other presuppositions that I'm making is that you can't through some of the more classic mechanisms that we think about minimize risk. So animal models are non-informative about drugs that cause severe DILI in humans. There's a limited amount of specificity for aminotransferase above three times the upper limit of normal. So you can't necessarily exclude reliably folks with that level of aminotransferase elevation.

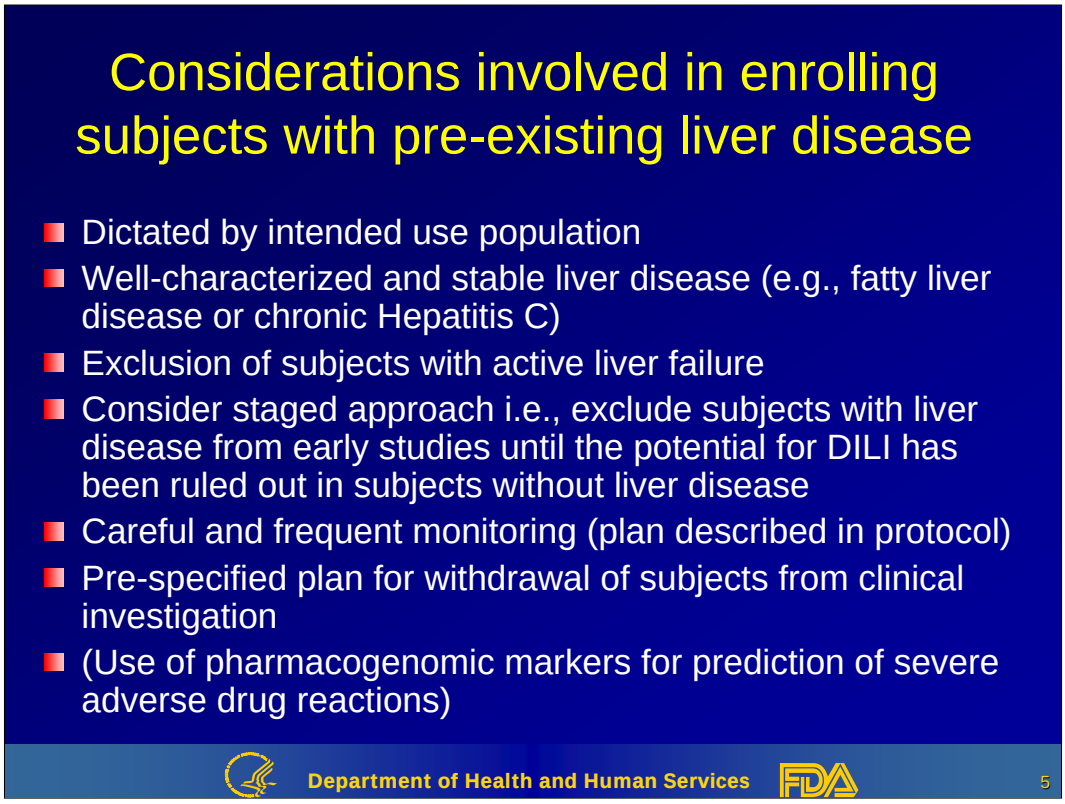
And then there's no well-established basis upon which to exclude subjects with preexisting baseline liver test abnormalities or stable liver disease from clinical investigations. So, in other words, there's the sense that you can't definitely minimize risk by saying that that population who has preexisting liver disease should not be included in the clinical trials.

And then dechallenge does not necessarily provide insights as it does not always or usually lead to immediate improvement. So another mechanism for gaining information that might be ethically acceptable is to remove the drug that's causing the liver injury to begin with but again that may not necessarily provide us the information that we need.

So I would maintain that there are two ethical goals that are in balance in this situation. The first is the minimization of research related risks for the enrolled individual subjects. That's very clear. And then secondly, the other goal that's very clear is that we want to establish reliable data upon which to make regulatory decisions that result in well-informed approval for public use and public health.



So I'm going to present that I think that there are two tensions, ethical tensions in this arena. The first is the tension between the protection of enrolled subjects and public health. And that depends on the careful balance on the application of current scientific knowledge and educated judgment, and we'll go through that in more detail.

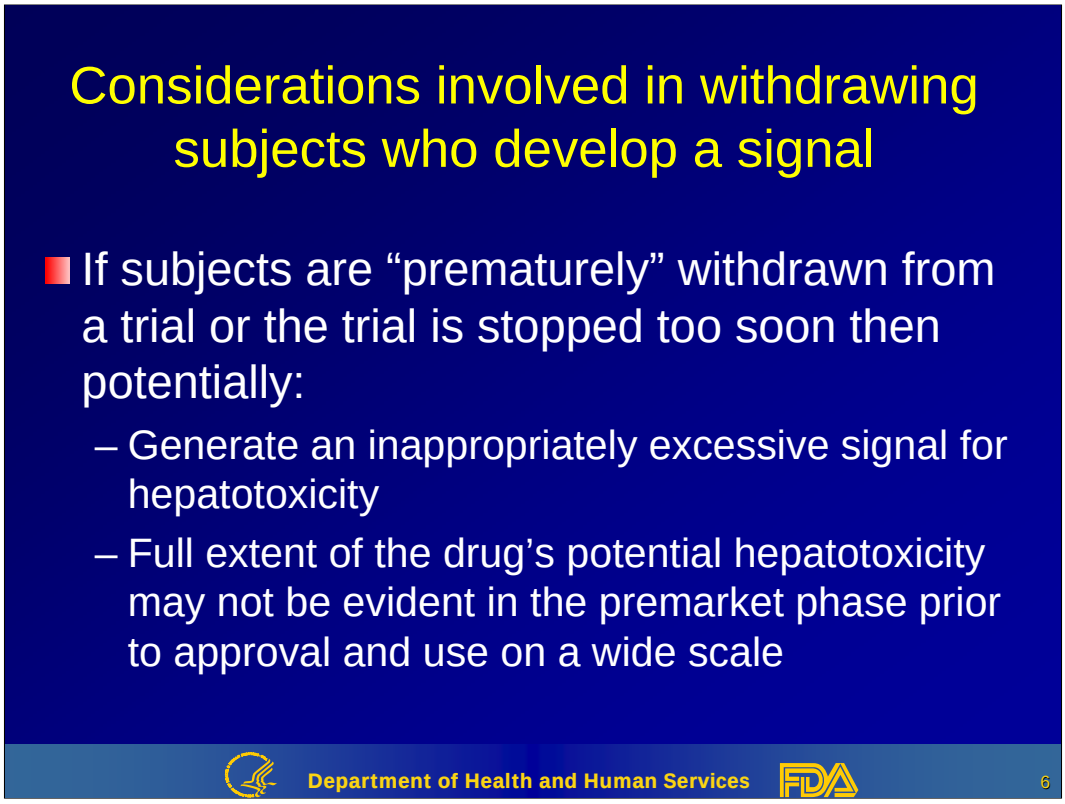


So what are some of the considerations involved in enrolling subjects with preexisting liver disease? And this is again with the idea of can we minimize risk to that population? Should we exclude that population or should they be enrolled in the clinical trials?

And one of the considerations that we have to think about is that what will the intended use population be and will it, as a general matter, include subjects -- will it include people who have preexisting liver disease? So you would like, if at all possible, to mimic that intended use population in a controlled setting.

Is their disease well characterized and stable? So, for example, ight it be fatty liver disease or chronic stable Hepatitis C. You wouldn't necessarily want to include subjects who have acute liver injury or liver disease that is not stable, and include them in a clinical trial. As I said, you'd want to exclude subjects with acute liver failure, and you'd want to consider whether you can get the information you need in a reliable scientifically sound manner in a staged approach. So could you exclude subjects with liver disease from early studies until the potential for DILI has been better characterized or ruled out in subjects without liver disease?

And then could there be careful and frequent monitoring and that would be described in the protocol, and we'll talk a little bit more about this in my talk, but we've also mentioned that at times, monitoring can be quite helpful but it also has its limitations. So that's not a fail safe mechanism for excluding subjects once they start to deteriorate or stopping the tria for certain subjects and terminating those subjects.

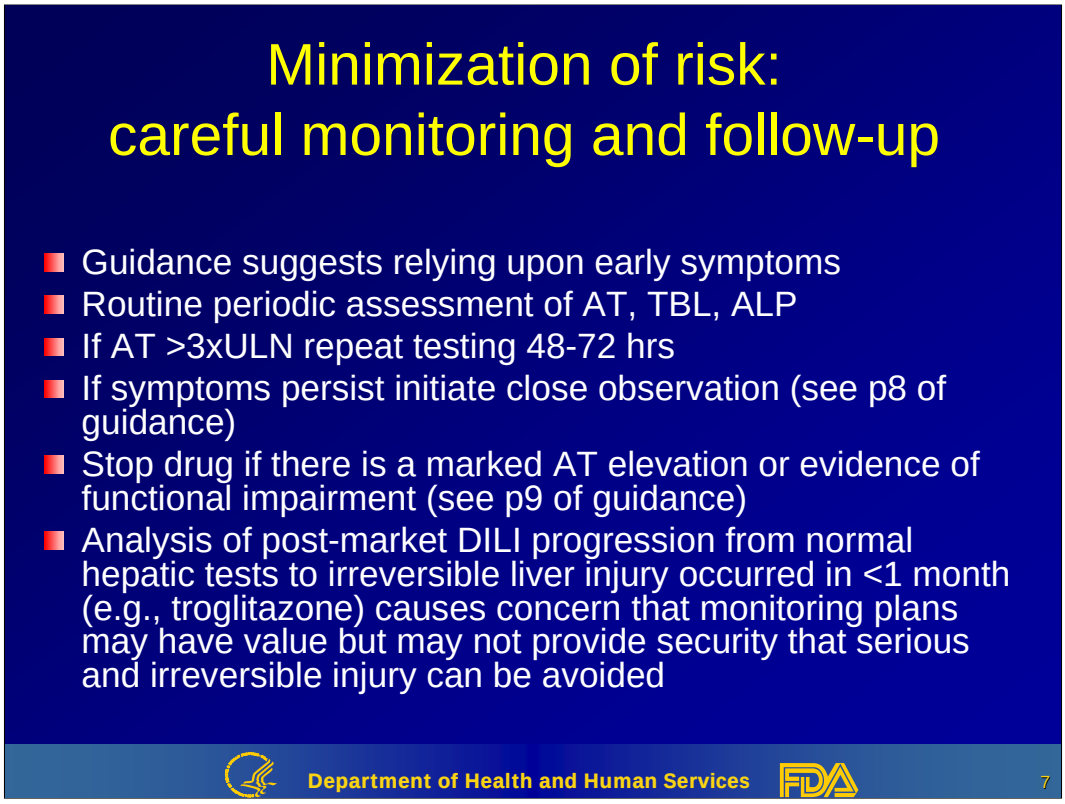


And then is there a prespecified plan for withdrawal of subjects from the clinical investigation based on either monitoring or symptomatic deterioration or elevation in aminotransferases and total bilirubin, et cetera?

And then what's in development but not part of this talk is whether or not you can use pharmacogenomic markers for prediction of severe adverse drug reactions. That might be something in the future that we can discuss. o another arena where I think ethical issues come up and the tension that I mentioned before arises, is what are the considerations involved in withdrawing subjects who develop a signal, a concerning signal? And this goes to the balance of making sure again that we minimize the risks to the enrolled subjects but not-if possible-at the expense of generating information that can be useful.

So if the trial is stopped too soon or subjects are prematurely withdrawn, there's the potential of generating an inappropriately excessive signal for hepatotoxicity. We've discussed a lot today about how variable the aminotransferase levels can be and that there can be a certain amount of adaptation, that you could withdraw subject as the aminotransferases have peaked or if they were on the way down but you missed that point if you removed them prematurely.

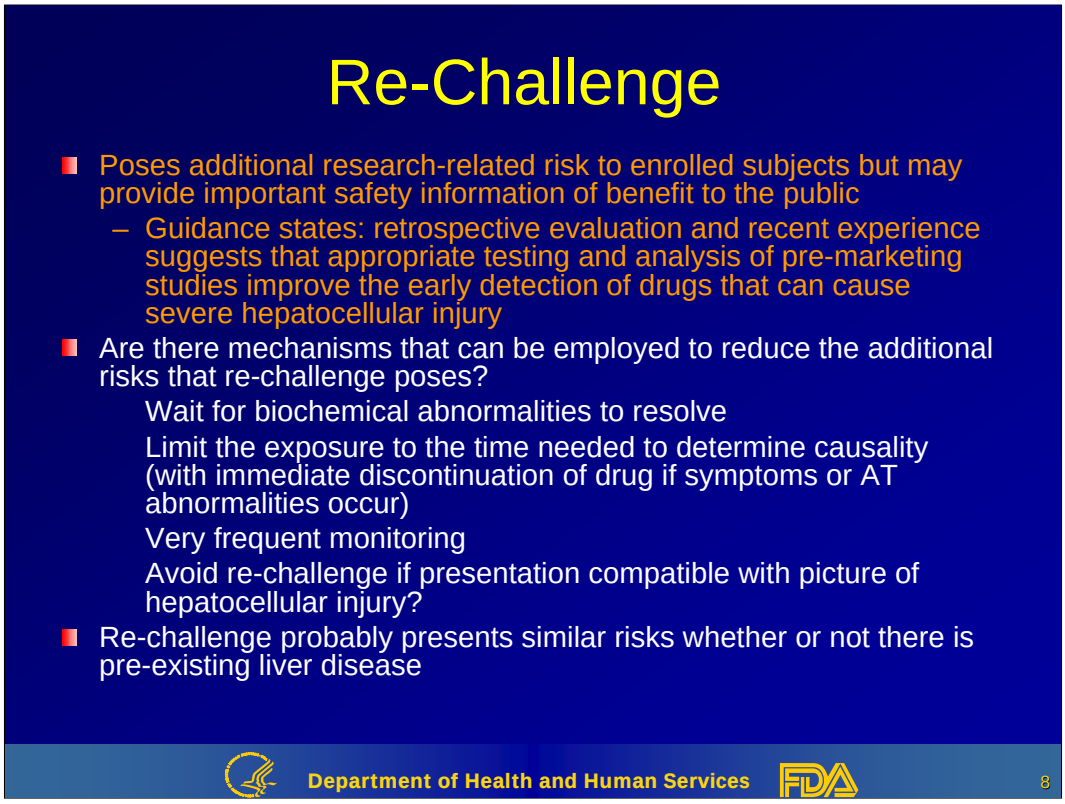
And then the full extent of the drug's potential hepatotoxicity may not be evident in the premarket phase prior to approval and use on a wide scale. So you just may not generate enough information about that drug to make the appropriate decisions before putting it out on the market.



So what are some mechanisms additionally to minimize the risk of enrolled subjects? Well, careful monitoring and follow up and the Guidance provides us with a fair bit of information and suggestions on that, and again everything that's in my presentation is really up for discussion as has been the course during the day.

The Guidance suggests that there should be a reliance upon early symptoms. That's been clear throughout the day, and that's embodied in the Guidance and that there should be routine periodic assessment o aminotransferases, total bilirubin and alkaline phosphatase. And if the aminotransferases go above three times the upper limit of normal, there should be an increase in the repetition of those tests within 48 to 72 hours. If the symptoms persist, there should be initiation of close observation and the Guidance goes into great detail as to what close observation means.

Now the Guidance also suggests that there be a discontinuation of the drug if there's a marked aminotransferase elevation or evidence of functional impairment. Even though this is a Guidance looking at premarket evaluation and testing, we can learn from some experiences that we've had in post-market drug-induced liver progression. As John Senior described for Isoniazid, we also have the example of Troglitazone, and in that arena, once there was an identification that the drug caused concerning liver changes, there were monitoring plans put in place but there was not necessarily security in those monitoring plans because of the rapidity of the liver deterioration.



Another arena that we've talked about is rechallenge, and I think this is another setting in which we get into the ethical tension between minimization of risk to the enrolled subjects and trying to ascertain as much information as possible about the drug under study.

Rechallenge poses additional research related risks obviously to the enrolled subjects but may provide important safety information of benefit to the public and the Guidance states that retrospective evaluation and recent experiences suggest that appropriate testing and analysis of premarketing studies improve the early detection of drugs that can cause severe hepatocellular injury. So clearly there's motivation to try and get as much information as possible in the premarket setting but how can we then try and minimize risks to the enrolled subjects and still get that information?

So one possibility that's been described earlier is waiting for biochemical abnormalities to resolve prior to the rechallenge, limiting the exposure to the time needed to determine the causality. So, trying to keep the rechallenge period as short as possible while still trying to get the information that's needed. Doing very frequent monitoring and avoiding rechallenge if the presentation is compatible with the picture of the hepatocellular injury, and that's left as a question because that has been discussed earlier, hepatocellular versus cholestatic presentation.

Re-Challenge (cont'd.)

- Guidance recommends that subjects who develop AT >5xULN should not be re-challenged unless there are mitigating circumstances
  - Enrolled subjects have shown an important benefit from the drug
  - Proposed benefits offer unique advantages
  - Potentially life-threatening conditions involved with no good alternatives

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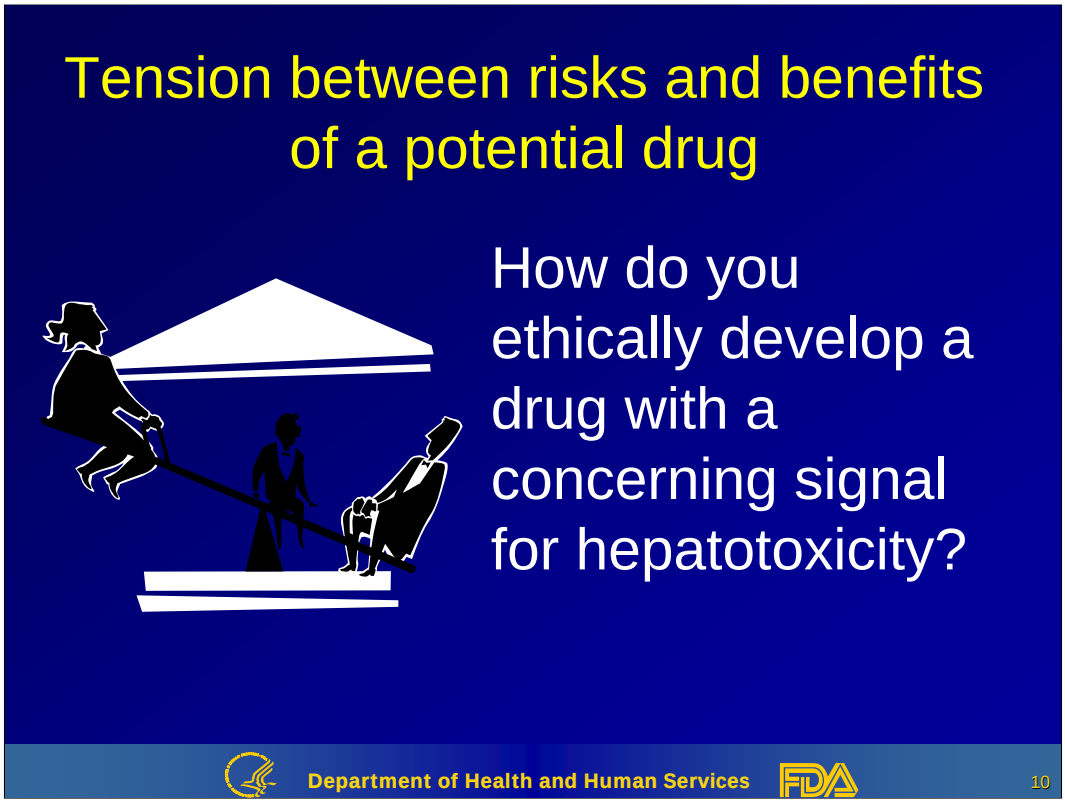
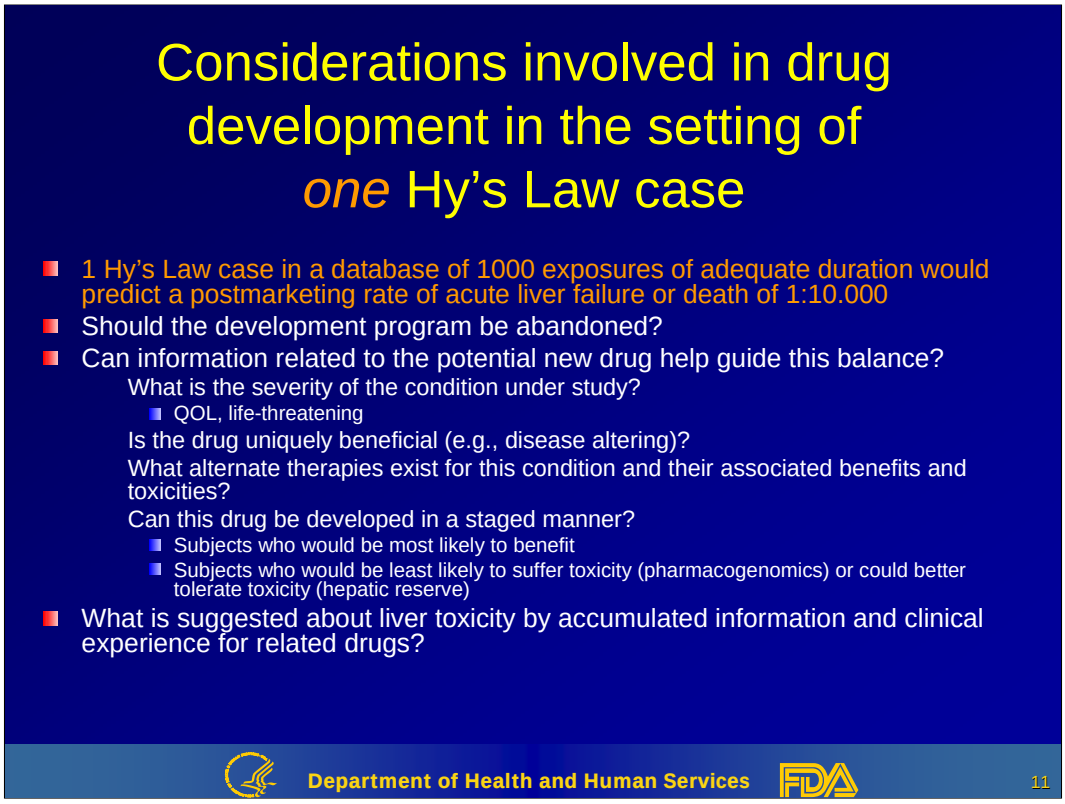
Rechallenge probably presents similar risks whether or not there's preexisting liver disease. So this is another point in terms of if you have subjects who are in the clinical trials who have preexisting liver disease, and they develop additional Hy's Law, or aminotransferase elevations that you think warrant a rechallenge, are you going to go through that with them or are you going to decide that there is not enough perhaps liver reserve to warrant the dangers of the rechallenge? Clearly there are other considerations involved in that as well.

The Guidance recommends that subjects who develop aminotransferase levels greater than five times the upper limits of normal, should not be rechallenged unless there are mitigating circumstances. So some of the mitigating circumstances have been touched upon earlier and those are enrolled subjects have shown an important benefit from the drug, the proposed benefits offer unique advantages and there's a potentially life-threatening condition involved with no other good alternatives. So these are very high positives on balance. There are high positive reasons for the rechallenge.

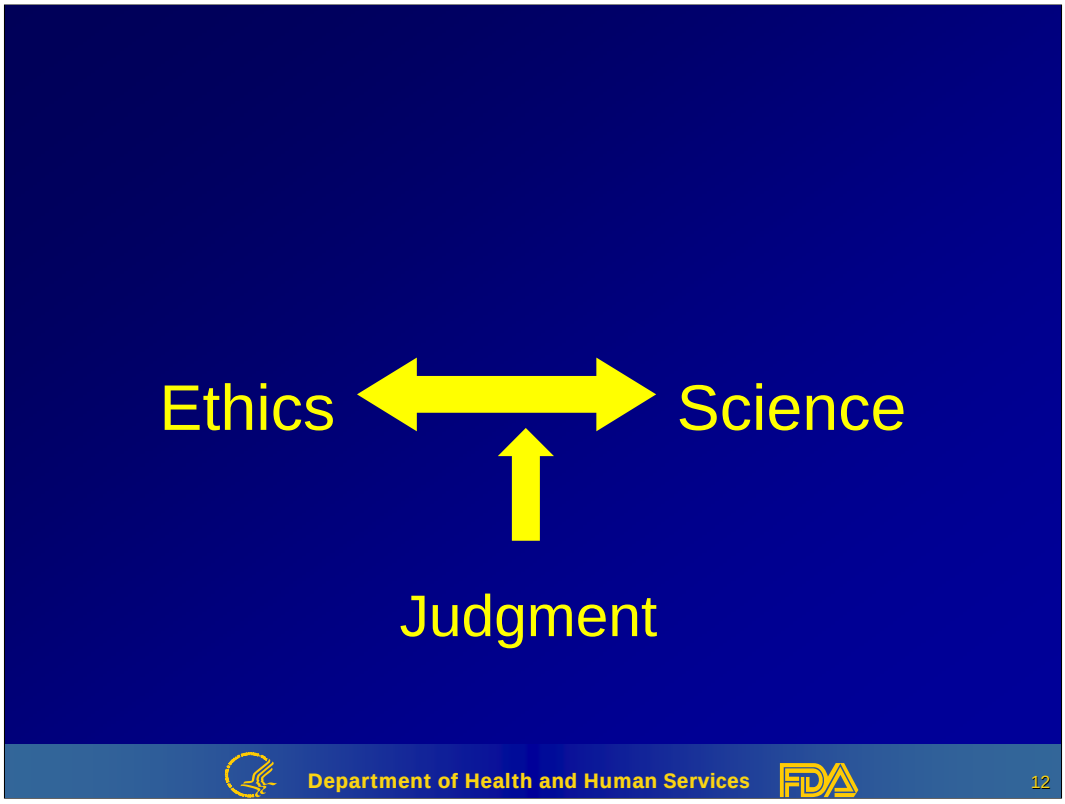


Now I would say that there's another arena in which there's tension and that is a tension between the risks and benefits of a potential drug. So now if we take away the direct comparison of the enrolled subjects to public health, what do we do in a scenario where we have a drug that has a concerning signal for hepatotoxicity? And, I didn't put Hy's Law up there or aminotransferases greater than eight. I just left it very broad, a concerning signal for hepatotoxicity. Should the drug be canned altogether or not?



Some of the considerations that I think that we can discuss are whether or not there's some unique benefit to this particular drug development program. And I decided to sort of push the case and say, well, in the face of one Hy's Law case, would the drug development continue? And published literature shows that 1 Hy's Law case in a database of 1,000 exposures of adequate duration would predict a post-marketing rate of acute liver failure or death of 1 in 10,000.

So with that in mind, should the drug development program be abandoned, and so the questions that I think arise as we try and think about this from an ethical perspective is can information related to the potential new drug help guide this balance? What is the severity of the condition under study? Is it a quality of life indication or is it an indication related to life threatening disease? Is the drug uniquely beneficial? Is it disease altering? What alternative therapies exist for this condition? And what are their associated toxicities and benefits? And can this drug be developed in a staged manner? Can you use subjects who would be most likely to benefit or subjects who would be least likely to suffer the toxicities of liver disease? And what is suggested about liver toxicity in the accumulated information for related drugs?



In this arena, I always say that good ethics are informed by good science. I think that's particularly true here although as we've talked about causality assessments and review of databases and many other situations, I think there's a tremendous component as well of clinical judgment that's involved, and so that I think is the concluding paradigm for my talk. Thank you.

(Applause.)