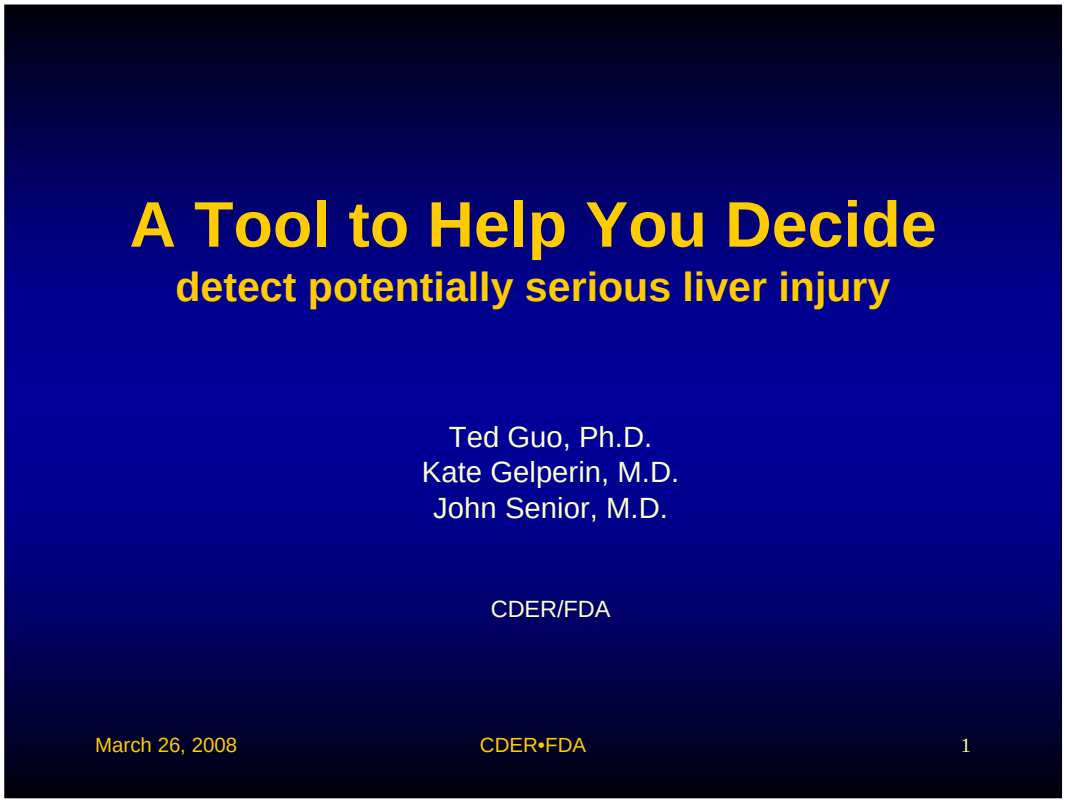
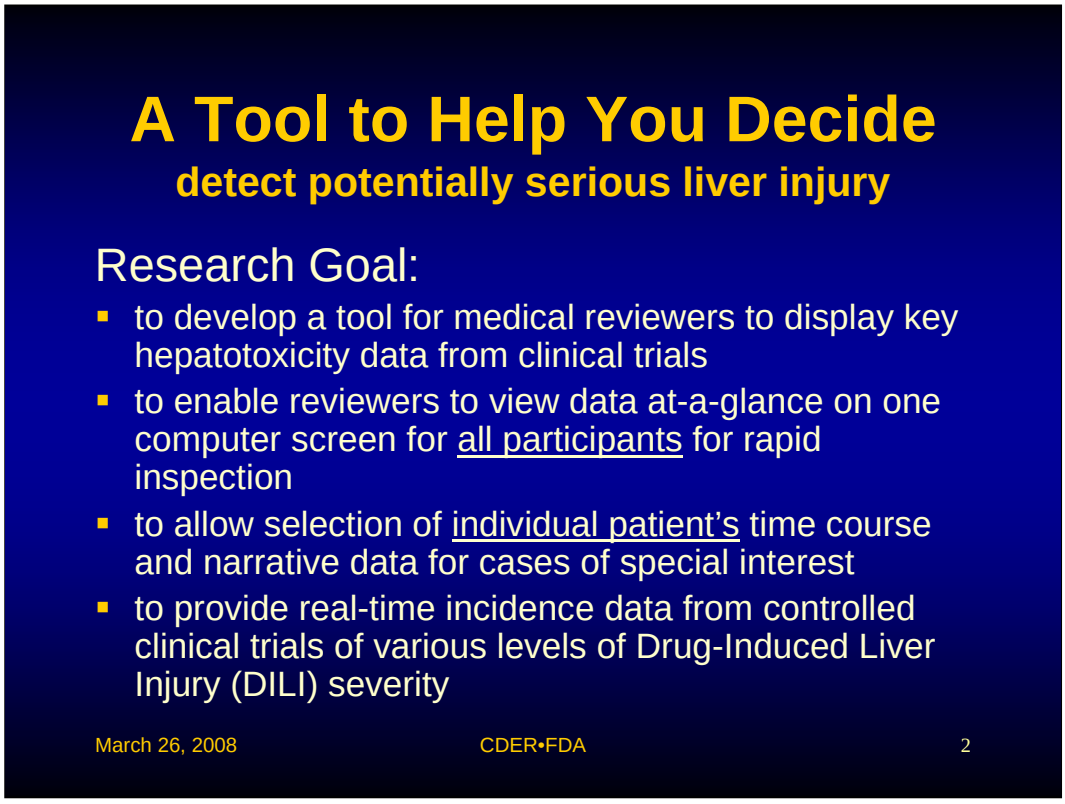


DR. WATKINS: Well, continuing on our theme, we're now going to talk about tools to help decide when to stop treatment, and the first speaker is actually going to be a duo. It's Kate Gelperin who is a medical officer in the Office of Surveillance and Epidemiology, and she's going to share her time with Ted Guo who is a statistician in the Office of Biostatistics. They're going to talk to us on a simple tool for finding important cases in a clinical trial. Kate.

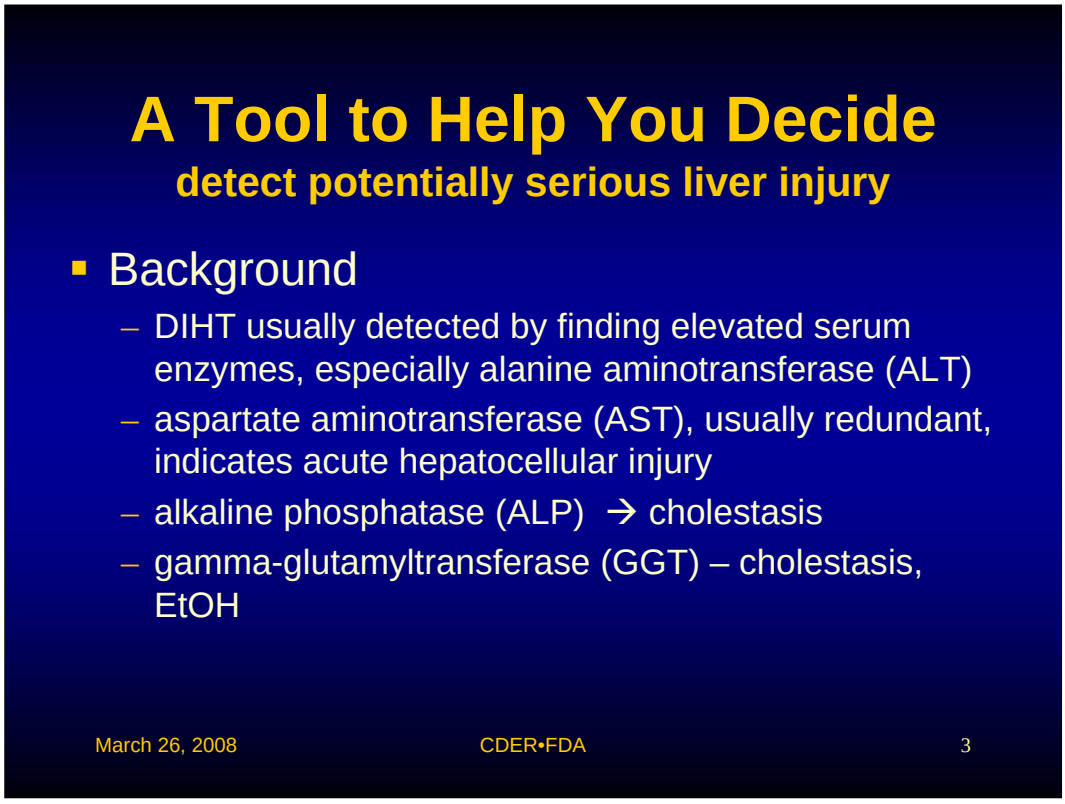
DR. GELPERIN: Thanks, Paul. Good morning. In the next 20 minutes or so, Ted Guo and I are going to tell you about some work we've been doing at FDA to develop a graphic tool to simplify the review of lab data from large clinical trials and help to identify participants with possibly serious hepatotoxicity.

Ted is a statistician in the Office of Biostatistics and as Paul mentioned, I'm a medical officer in the Division of Epidemiology in the Office of Surveillance and Epidemiology.

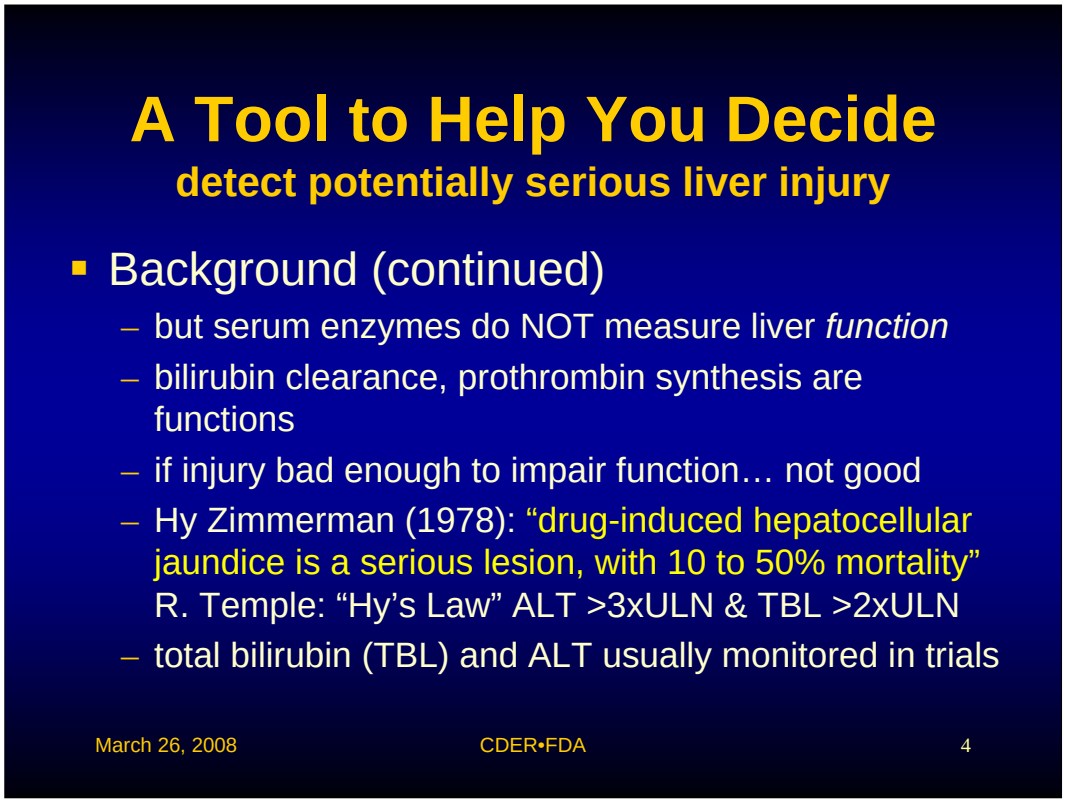
The ideas and direction for this work came from John Senior, who is our host here today.



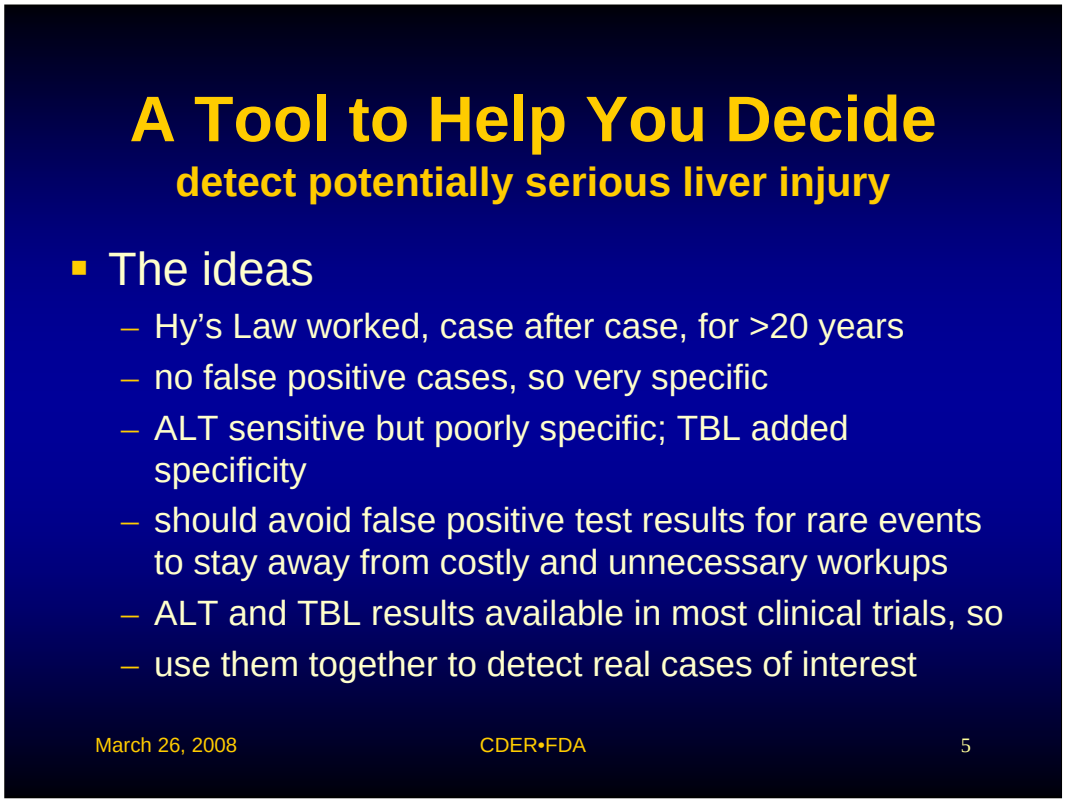
Our goal has been to develop a user-friendly tool for medical reviewers that enables them to view relevant lab data from an entire clinical trial at a glance, as well as to view individual patient data by clicking on the graphic display.



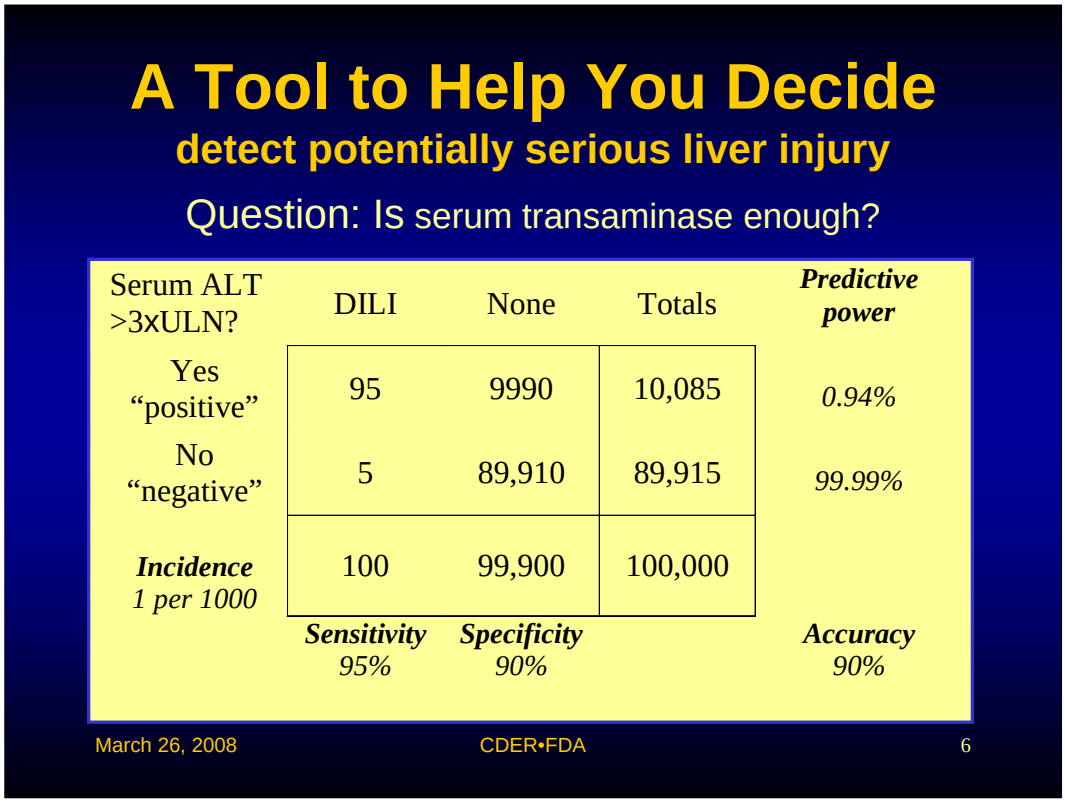
Serum enzymes, such as some of the ones listed here, are usually measured periodically in clinical trials to detect potential hepatotoxicity. However, serum enzymes are not indicative of liver function, as you've heard earlier this morning. Impaired clearance of bilirubin or impairment of prothrombin synthesis are signs of impaired liver function. More than 30 years ago, Dr. Hyman Zimmerman observed that drug-induced hepatocellular injury with jaundice is a grave illness, with an estimated mortality rate of 10 to 50 percent.



So this combination of ALT greater than three times the upper limit of normal (3xULN) and total bilirubin (TBL) 2xULN, which Dr. Robert Temple of the FDA dubbed "Hy's Law" findings, has proved over the years to add greatly increased specificity to ALT testing in clinical trials.



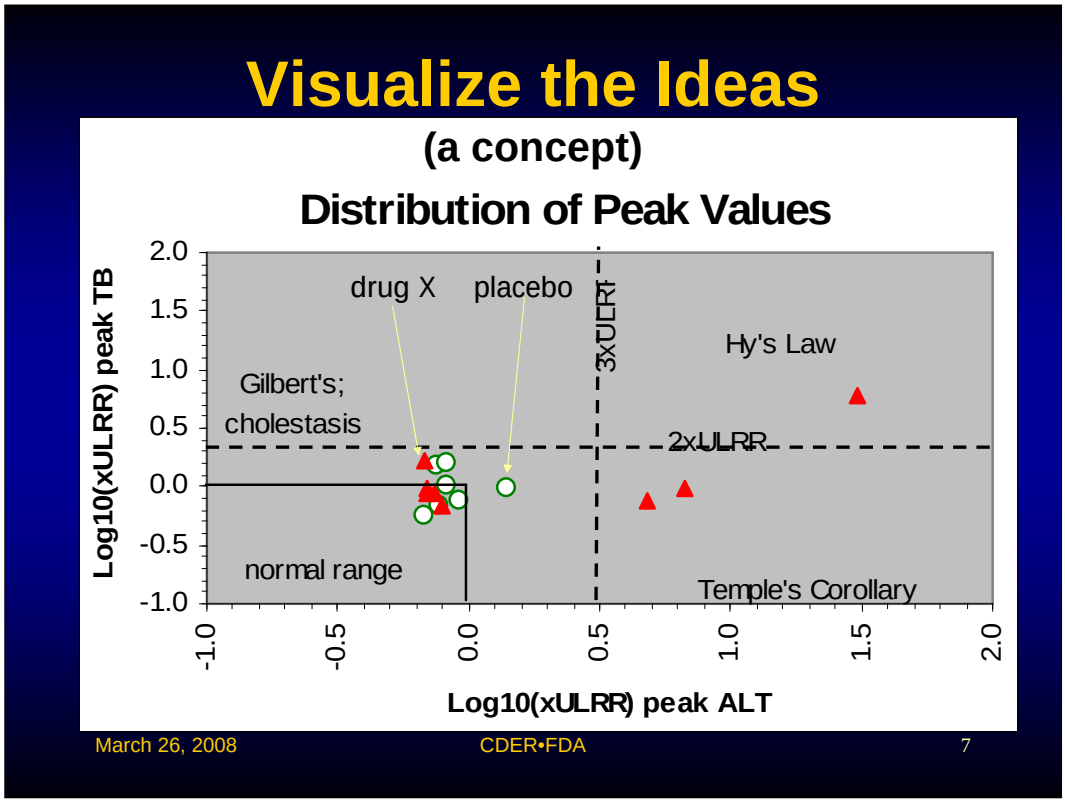
Hy's observation has been repeatedly confirmed in our experience at FDA over the past 25 years. Confirmed concurrent or sequential elevations of ALT and total bilirubin invariably point to serious liver injury. So false positives are highly unlikely.



This slide depicts a hypothetical situation, perhaps like the isoniazid situation that John was just talking about, where the true incidence of serious hepatotoxicity for drug X is 1 per 1,000 treated patients. If serum ALT >3xULN is used as a cutoff indicator in 100,000 people to look for serious drug-induced liver injury (DILI), these numbers would be illustrative of the anticipated number of test results: 95 had true-positive results, and 5 false-negative results, in the 100 patients with DILI. The sensitivity of the test measure is therefore 95%, quite a good and sensitive test. However, even if the specificity were as good as 90%, test results would be negative in 98,910 of the 99,900 who did not have DILI, but falsely positive in 9990 of them. Therefore, positive test result would be correct in 95 and wrong in 9,990 of those tested, a very poor predictive value of a positive test result in this population of less than 1%.

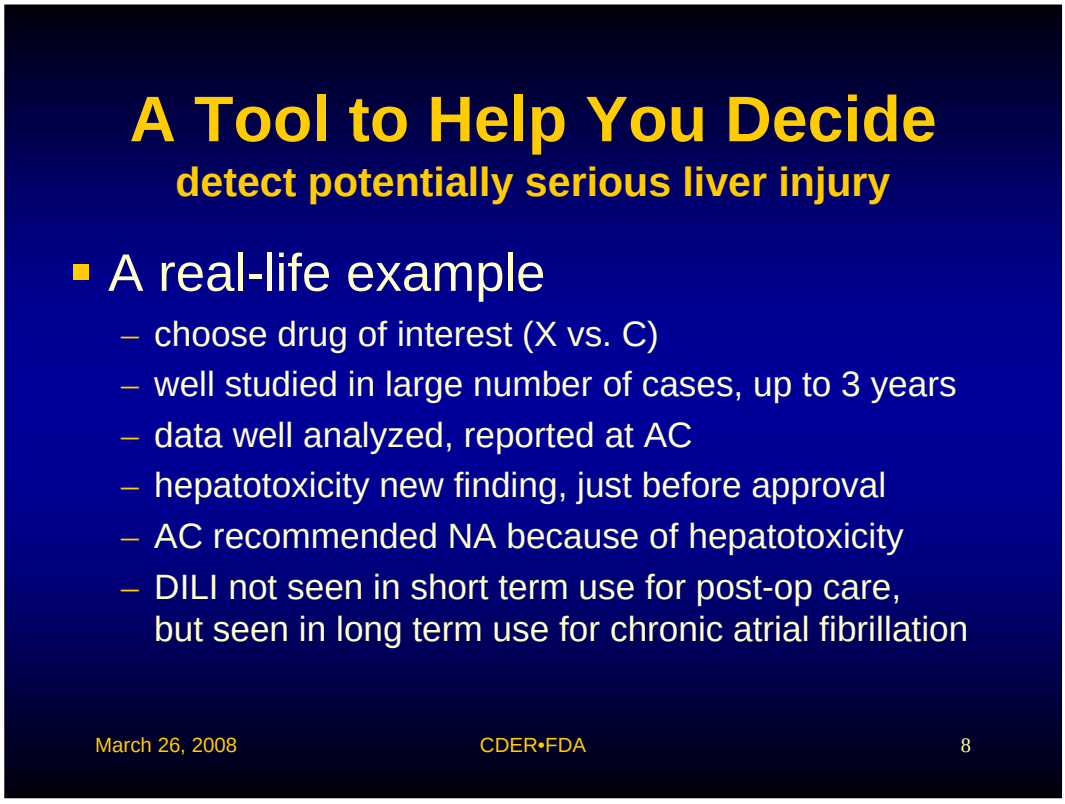
To restate this example, with large numbers of false positives and only a few true positives, because of the low incidence of DILI in the population tested, a positive serum transaminase screening test is by itself poor at confirming serious drug-induced liver injury. On the other hand, it will pick up 95 percent of all cases of interest, so it is fairly sensitive, just not specific enough.

A negative result is good at reassuring that a patient does not have serious drug-induced liver injury. The negative predictive value is almost 100 percent and correctly identifies 90 percent of those who do not have serious drug-induced liver injury. The positive predictive value, as you heard earlier from Bob Tipping, is not intrinsic to the test. It depends also on the incidence or prevalence of the problem being sought in the population tested.

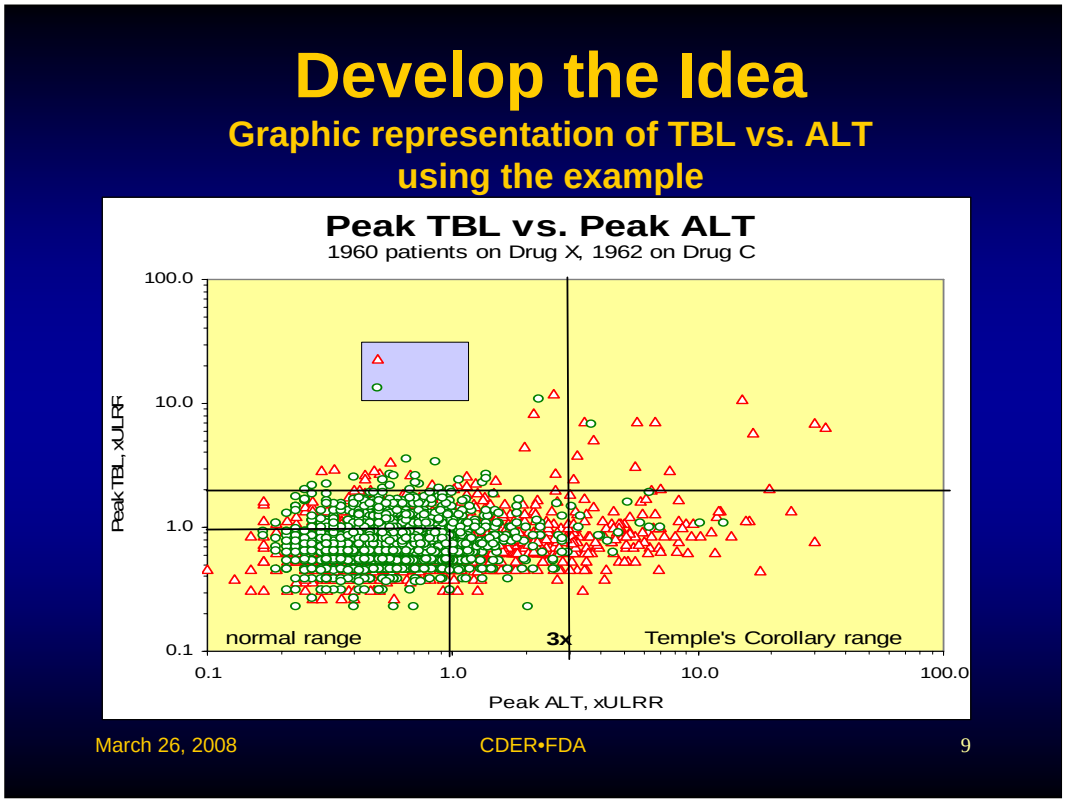


This slide shows the graphic concept of plotting both the peak ALT and TBL observed in a series of measurements in a lot of people, with acknowledgement to Dr. Senior for the idea of displaying them graphically. A single data point for each subject from a clinical trial depicts that individual's peak serum ALT on the X axis, and the peak TBL on the Y axis, both shown on a logarithm to base 10 scale of the multiple of the upper limit of normal or the reference range.

Presentation of data on a logarithmic scale can be helpful when the range of values for one variable (ALT) is so much greater than for the other (TBL), since the logarithmic scale reduces the data to more visually comparable ranges. Subjects randomized to drug X are shown with red triangles here and those randomized to control drug C are shown as green circles. Values within or near the reference range are found in the left lower quadrant. The reference range is depicted within the lines indicating 1xULN. Subjects with elevated TBL in the absence of ALT elevations, such as patients with Gilbert's normal variant are shown in the left upper quadrant. Subjects with increased ALT but no increase in total bilirubin are found in the right lower quadrant, and so-called Hy's Law cases with ALT >3xULN and TBL >2xULN in the upper right quadrant. On can assess results in a large number of study subjects with a single glance.in a large number pf study subjects with a single glance.

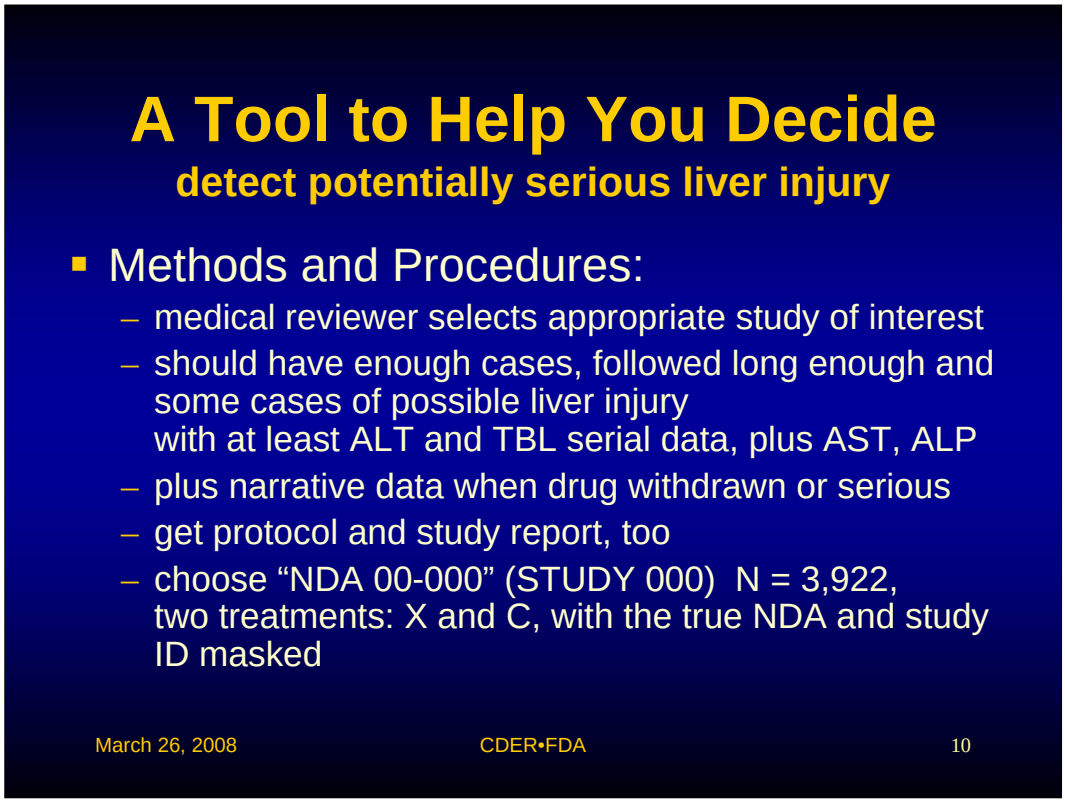


To take John's concept to the next level, we identified a large study of a drug with a serious liver injury signal that had previously been discussed at an Advisory Committee a few years ago for a drug not approved because of the hepatotoxicity issues.



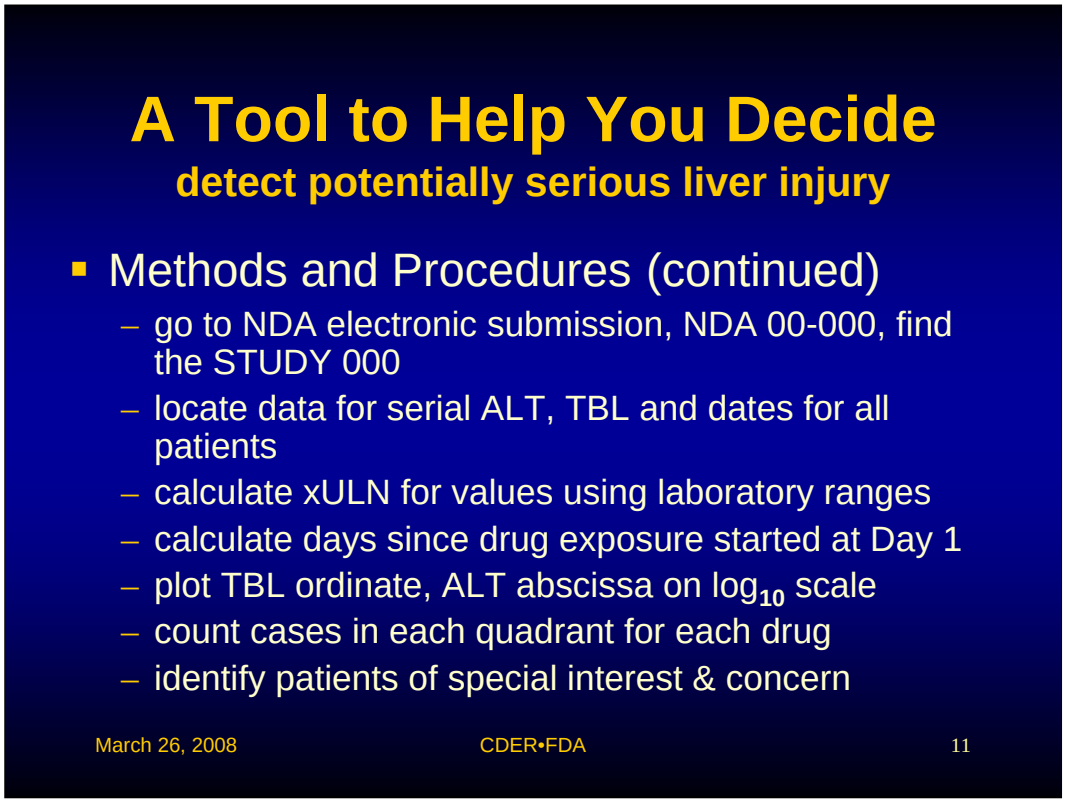
This slide shows data from that study displayed graphically in Excel, showing peak TBL and peak ALT values for 1,960 subjects randomized to experimental drug X and 1,962 subjects randomized to control drug C. You can see at a glance, that there were quite a few data points with ALT >3xULN, about 7 times more for drug X than drug C, and 14 times as many for drug X than drug C in the right upper quadrant. The next step was to evaluate whether the abnormalities were drug-induced or diseased induced, which required much more information, including the narratives and close examination of the time course of changes for individual patients.

Ted will tell you now about how we use this case study to develop the graphic tool we've come to call eDISH, the Evaluation of Drug-Induced Serious Hepatotoxicity.

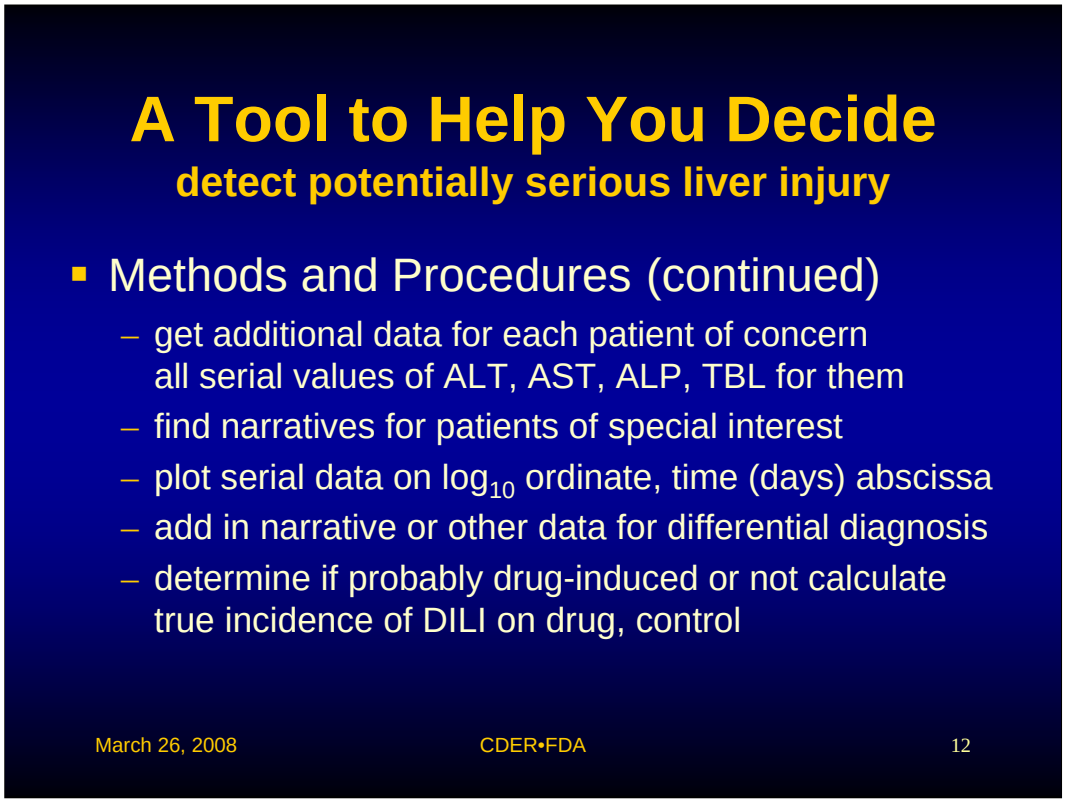


DR. GUO: Now let's move from the concept to the process and that eventually leads to the review tool. The first step is for the medical reviewer to find a suitable study. So what qualifies for a good study? It should be large enough, which means it should have a lot of data and include a lot of patients, the patients should be followed long enough, and there should be cases of possible liver injury. This means that information about the ALT, AST, ALP, and TBL must be available.

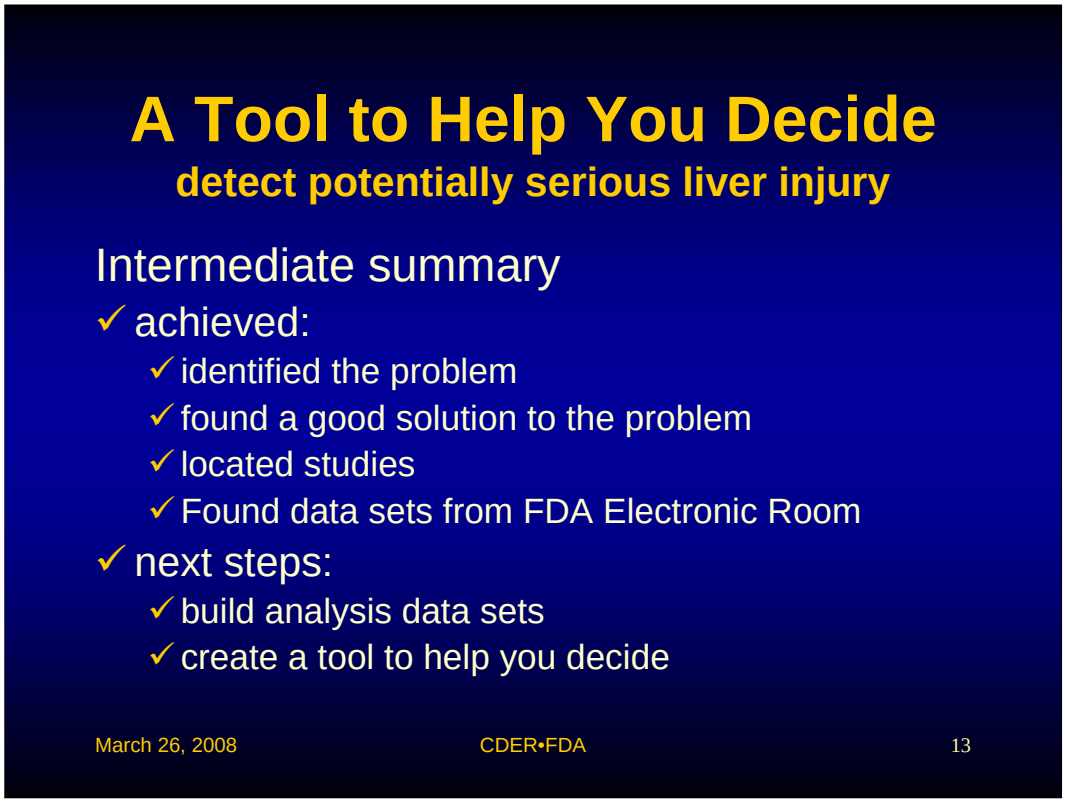
We also need to get the patient narratives, and the study report including the protocol, to understand exactly what and how data were collected, as we do in NDA reviews. Here we find a real life study, but the actual NDA number is replaced with zeros for confidentiality. It includes more than 3900 patients randomized into two groups, either to investigational drug X, or to control drug C.



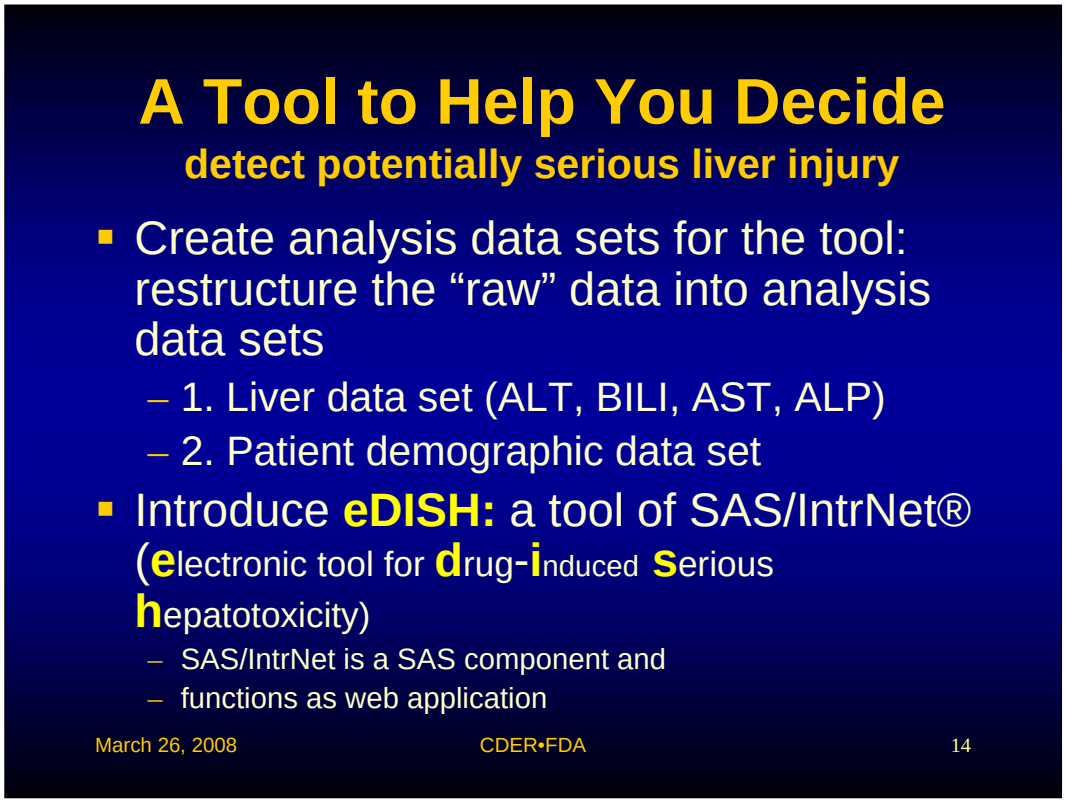
Dr. Senior pioneered this work and he himself did a lot of the calculations. To continue, we searched FDA's electronic document room, found the study report and protocol, and also located the data sets that include ALT and TBL. We calculated xULN for ALT and TBL, using laboratory normal ranges and we also calculated time-related variables. Even though some variables were provided by the sponsor, we still do our own calculations for verification. We then plot the peak TBL versus peak ALT using SAS programs.



As we press on, we feel we need more information about certain of the patients, especially those in the right upper quadrant of the x-y plot. So we went into the database again and got ALP and AST values and all values of all liver variables over the full course of observation of the person. Their narratives contained additional information to aid in the differential diagnosis of whether the problem was likely to be drug-related or not.



Now as a brief summary of what we have achieved, we identified the problem of finding the DILI needles in the study population haystack, and we have a pretty good idea how to investigate further the patients of special interest.

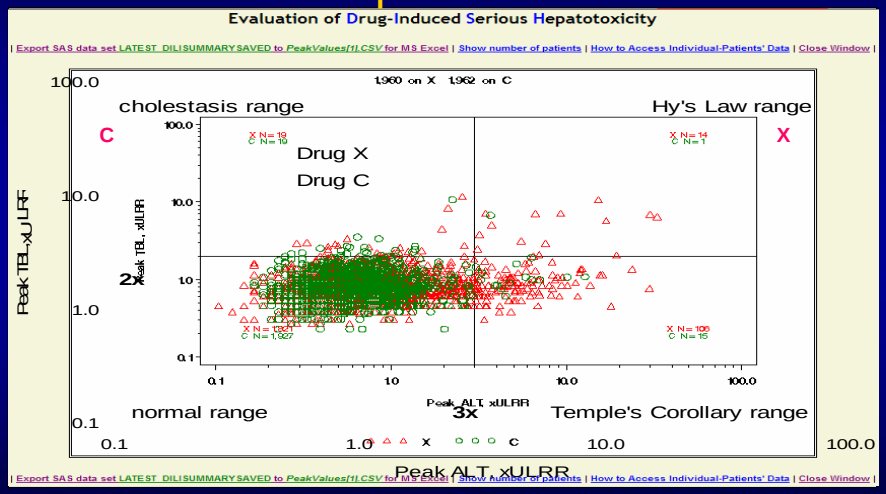


The next step we need to review our data analysis sets and we also need to finally create a review tool. Now we know the original data sets cannot always be directly used because we pull data from different sources and that they are submitted in different formats. We cannot use them without restructuring and reformatting and merging data together. And finally we decided to have two analysis data sets. One is called liver data, includes TBL, AST, ALT, and ALP values.

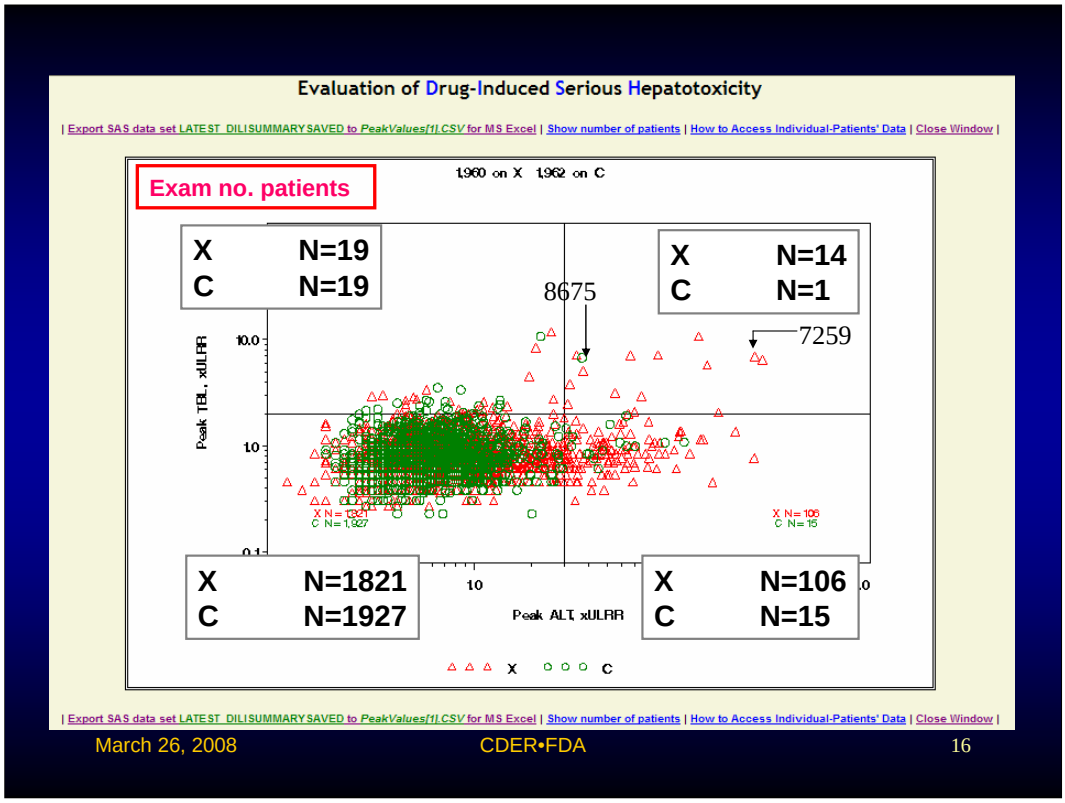
For each patient there are multiple lines in the database representing multiple observations over time. The other data analysis set includes patient characteristics. Each patient has one line including everything we need to know about that patient, not changing with time over the course of the study. We combine those two data sets, which should be well organized, well structured, and well formatted. We aim to standardize these data sets for different studies, using CDISC (Clinical Data Interchange Standards Consortium) methods and definitions.

Now we gave our tool a name. It's called eDISH, which stands for **e**lectronic tool for **D**rug-**I**nduced **S**erious **H**epatotoxicity. We need to have another tool to build into this tool. The tool we have chosen is a SAS component called SAS/IntrNet. It is a programming tool allowing us to view the web-based classification, which should be user-friendly and easily accessible, and also can be deployed over the FDA's intranet.

Graphic Representation of TBL vs ALT
A snapshot of eDISH

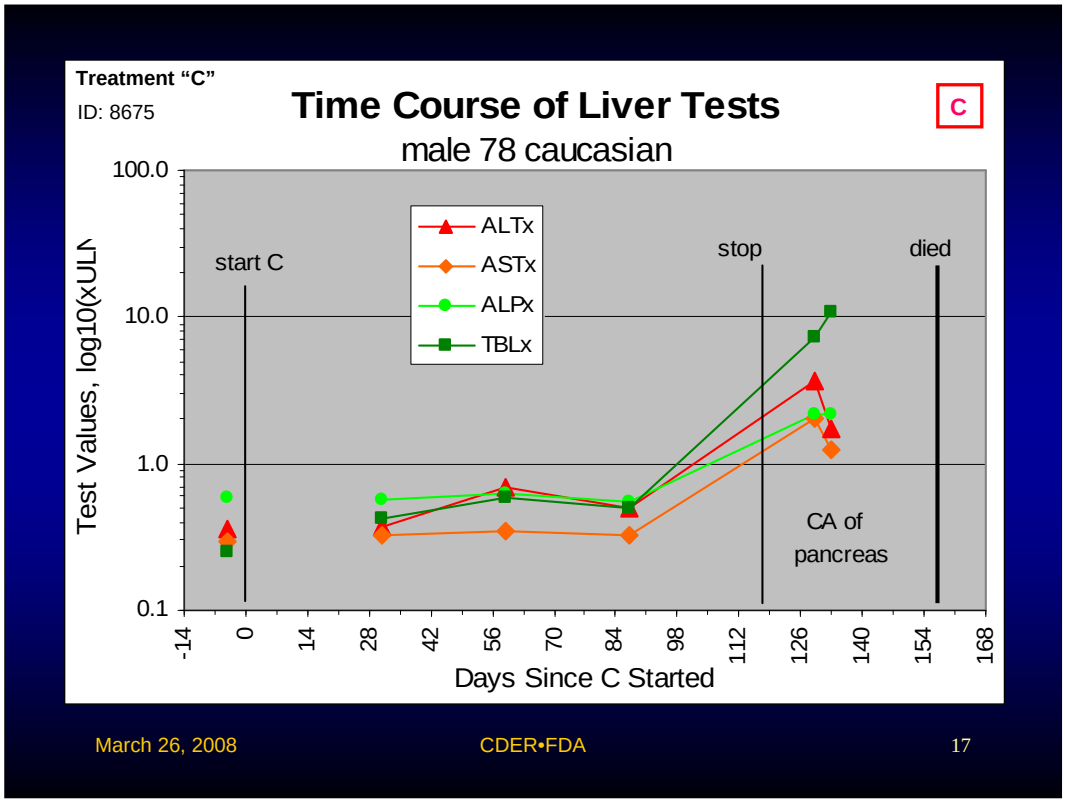


This is the look of one of the results of this tool. Compare the Excel graph with how it appears using eDISH. Now Kate is going to continue to explain what those points mean.

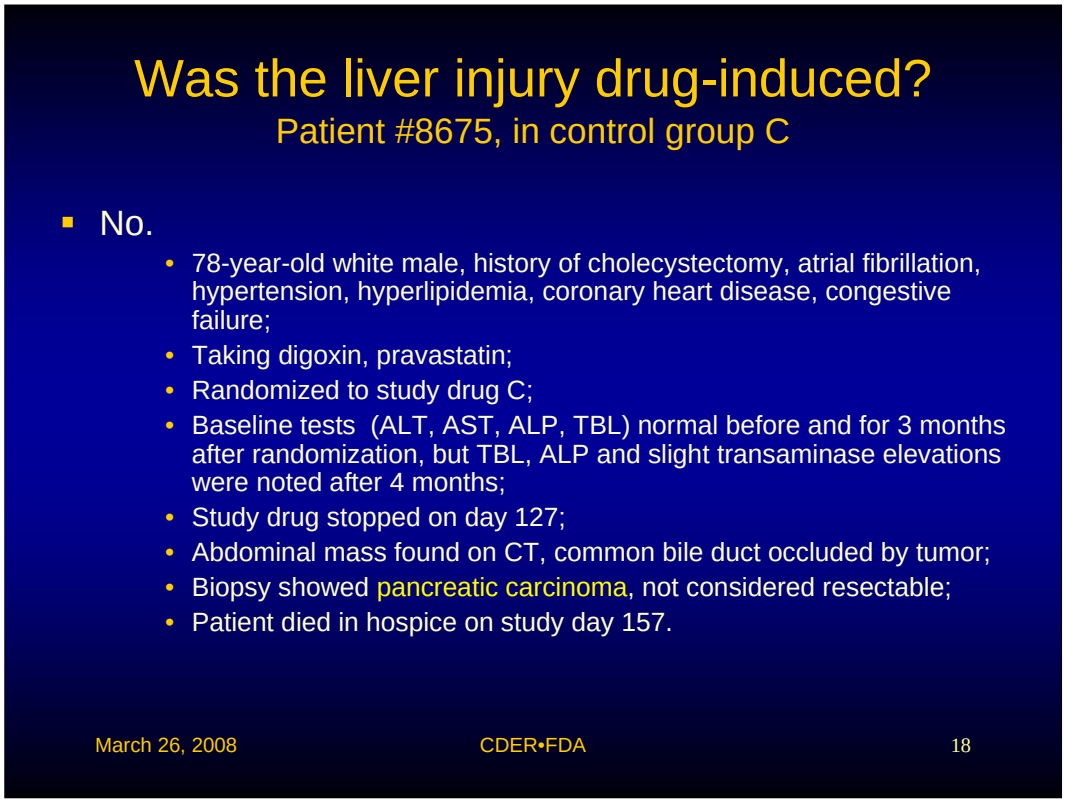


DR. GELPERIN: Thanks, Ted. So as you see, the eDISH graphic looks similar to the Excel graph you saw earlier, but. it has some additional capabilities. You can investigate individual subjects of interest by clicking on their symbol to see all of that individual's lab data over time and even their narrative if it's available in a text format.

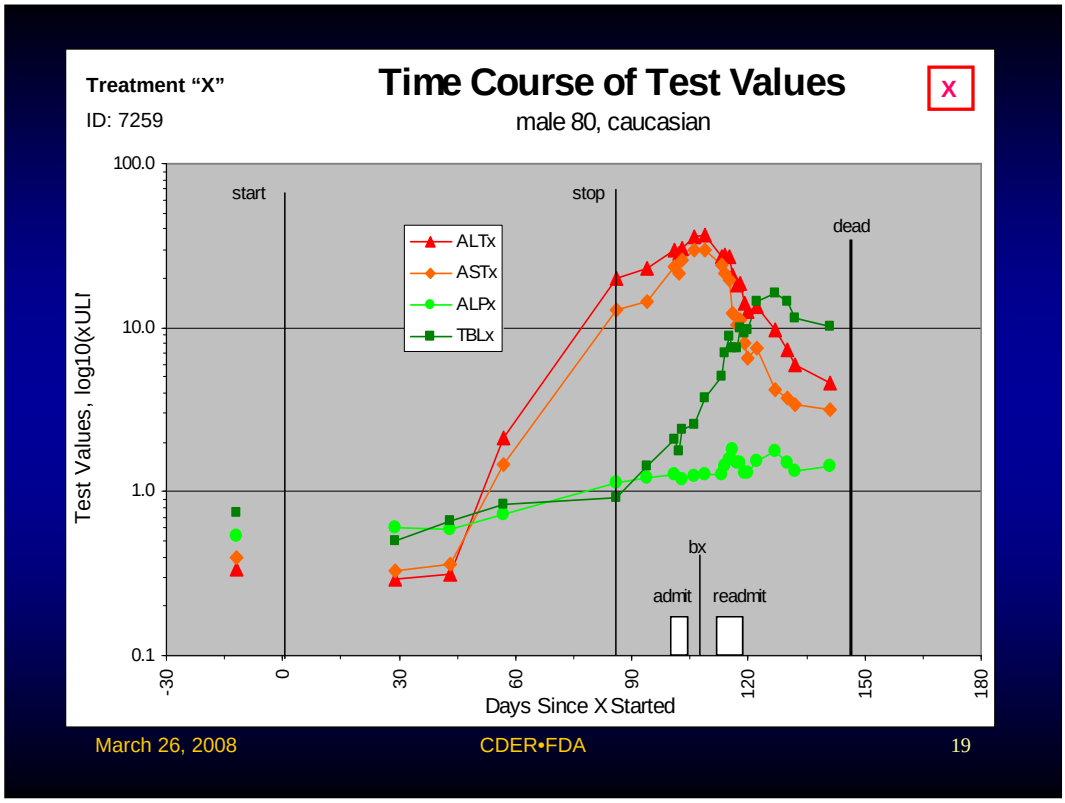
In this graph, as I said a few minutes ago, subjects randomized to control group C are indicated in green circles and subjects randomized to experimental drug X are indicated with red triangles. We can use use the computer program to count the relative proportions of subjects from each treatment group in each quadrant, and could set the cut-points at various levels if we wish.



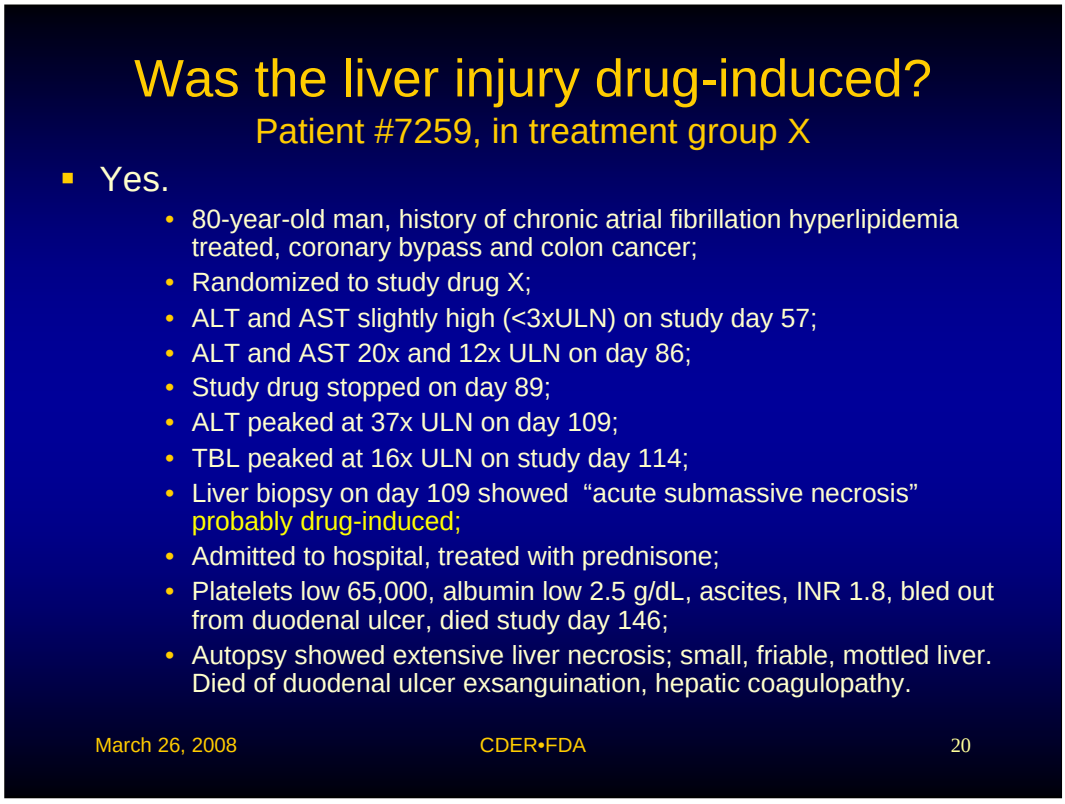
So within eDISH, the reviewer can click on an individual study subject to review that person's individual data. Let's choose subject 8675 on control drug and subject 7259 on the experimental drug. So here's the control subject, a graphic display of the serum ALT, AST, ALP and TBL results obtained during the course of the study for the 78-year-old male, who is randomized to control drug C, the lab tests were normal at baseline and for the first 3 months of study. However, slight transaminase elevations were noted after four months, and study drug was stopped on day 127.



The clinical information disclosed that the patient died of disease, pancreatic cancer metastatic to the liver, not drug-induced liver injury.

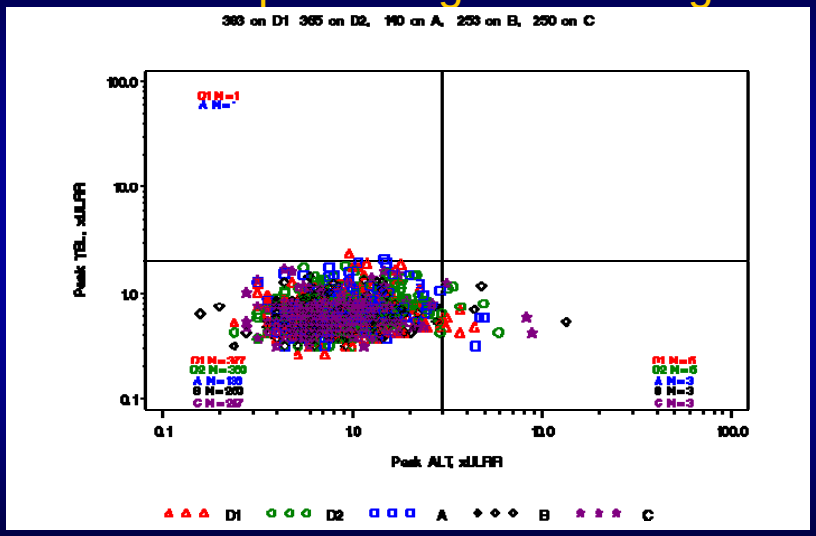


Now let's look at a subject who was randomized to experimental drug X, an 80-year-old male who developed a rise in ALT after 56 days on study drug. His ALT and AST were slightly high initially, less than 3xULN on study day 57, but by study day 86, the ALT was 20xULN, and study drug was stopped on day 89. The ALT peaked at 37 times the upper limit of normal on day 109 and the TBL peaked at 16xULN on day 114. A liver biopsy was done on day 109 which showed acute submassive necrosis and was considered to be probably drug-induced because no other explanation could be found. This patient was admitted to hospital and treated with prednisone. However, his condition progressed; his platelets decreased to 65,000 and his albumin decreased to 2.5. He developed ascites, his INR rose to 1.8 and he bled to death from a duodenal ulcer on study day 146.



Autopsy showed extensive liver necrosis, a small friable, mottled liver. Death was due to duodenal ulcer with hepatic coagulopathy secondary to acute drug-induced liver failure and exsanguination.

Graphic Representation of TBL vs. ALT an example of negative findings



Data from Brown WV et al. Am Heart J. 2002;144:1036-43.

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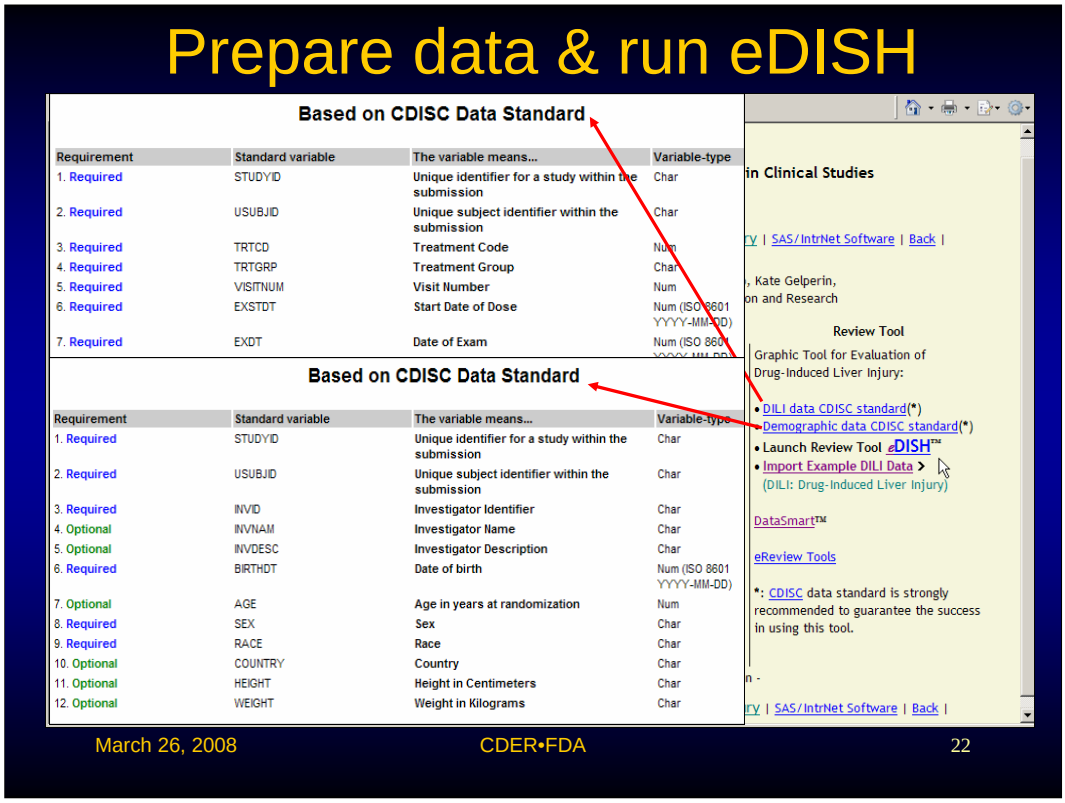
For an interesting contrast, I'd like to show a work in progress in which we've identified clinical laboratory results for three fairly large, long term studies with various statin treatment regimens. Overall in these data, about one to two percent of subjects have peak ALTs >3xULN. You see the data points here, and interestingly, there were no cases of isolated bilirubin elevation possibly because patients with Gilbert's normal variant were perhaps excluded from entering these studies at baseline. And of greater interest, there were no cases whatsoever that would quality as Hy's Law cases.

One caveat I would mention is that if subjects are dropped from the clinical trial due to ALT elevation, all of the subsequent lab tests must be captured from the follow up at local labs or in the hospital and entered into the database if this tool is to be of value. So that's something to keep in mind, which may be unlikely to be an issue in this example, but in general, the case report forms need to be designed in such a way that the relevant lab data and TBL and ALT are completely captured to follow up any transaminase elevation cases to resolution, not just recorded on protocol-specified visits.

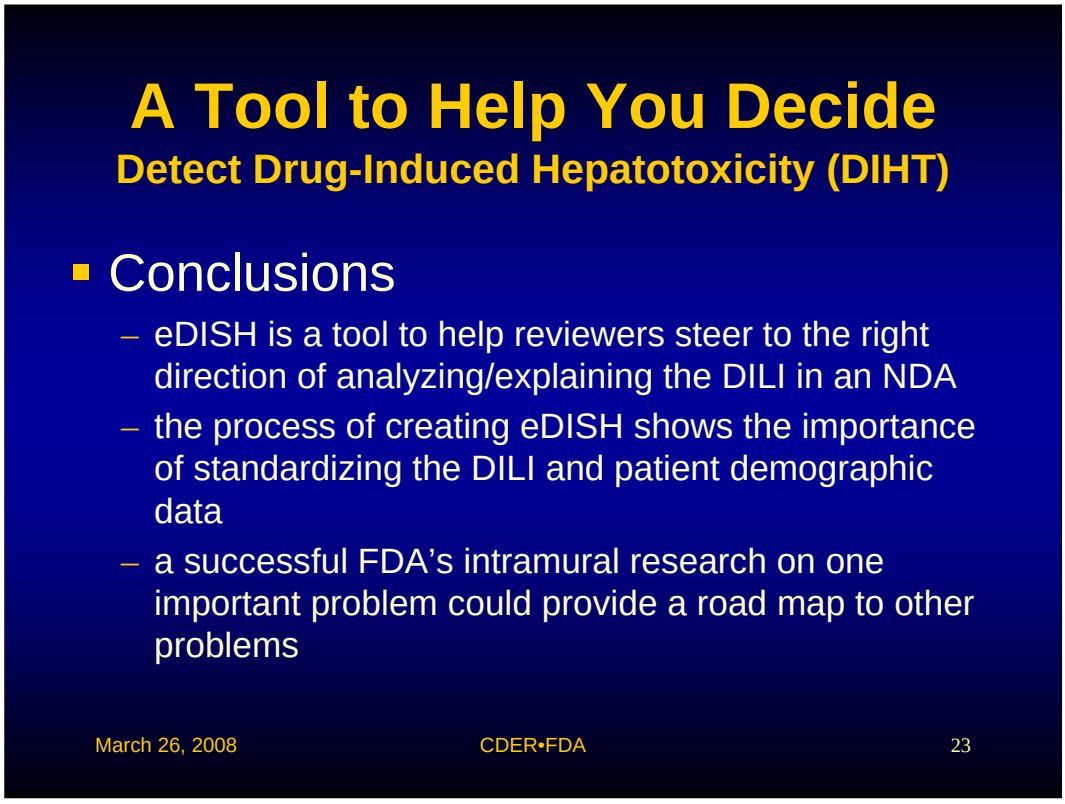
So I'm going to turn it back to Ted to finish up.



DR. GUO: Now here's how to prepare the data and how to run eDISH. This is the home page, a snapshot of the home page of eDISH, and there are links that are for the interest of the user if they want to know more about our research, our presentations and publications, they can go into and look at and get more information about the background of our work.

And on the right, there are links that takes you to the data specification. For example, on the liver data and for user and us, we strongly recommend the data be prepared in accordance with the CDISC standards. We have some specific requirements, and they all require standardization of variable names and we hope the data format in a particular way so that it is -- and will run. And this is our specification for demographic data. For example, like Patient H, since we already have required date of birth, so we don't need to have -- it's not necessary to have age for example. If we have good data in hand, then we can run eDISH.

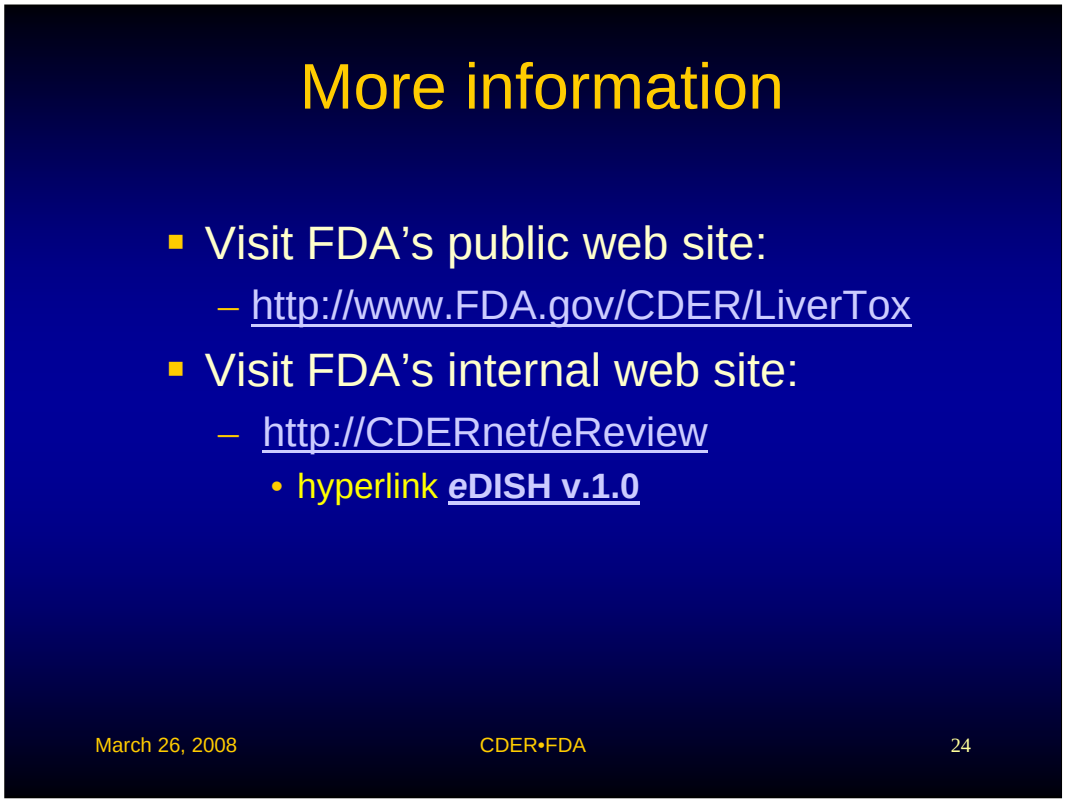
If you click the links on the eDISH, and it will take you to the next screen and the instructions there will tell you what to do next.



Now some concluding remarks, about eDISH as a tool to help reviewers to steer in the right direction in analyzing and explaining drug-induced liver injury in a NDA.

The second point is the process of creating this tool shows that it's very important to standardize the liver data and the patient demographic data.

So lastly, the experience that we gain from doing this project will give us a roadmap for solving a different problem in a different area.



For more information about DILI and related issues, please visit the LiverTox website, which is open to the public

Additional information about eDISH or other review tools can be found on CDER's eReview web site.

This is the end of our presentation. Thank you very much for the attention.