Ted Guo, PhD
Statistical Reviewer
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research, FDA

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The Story of eDISH
(evaluation of Drug-Induced Serious Hepatotoxicity)

John Senior and Ted Guo
For DILI Conference XV
18 March 2015
A historical account of eDISH

• Met John Senior by chance – 2002, then to -09
  – RSR (Regulatory Science Review) enhancement program to aid reviewers at CDER
• He had an interesting idea and I was willing to get outside of the “box”
  – What is DILI? Can a biopsy determine DILI?
  – He taught me about differential diagnosis
  – We used powers of computers to search data, and of humans to recognize patterns at a glance
The Concept

- How can we see all subjects in the study?
- And see all the data for a selected subject?

Distribution of Peak Values

- Log10(xULRR) peak ALT
- Log10(xULRR) peak TB

- Normal range
- Drug X, placebo
- Gilbert's; cholestasis
- Hy's Law
- Temple's Corollary
- 2xULRR
- 3xULRR
The Concept (Con’t)

• We wanted to see all the liver test data for a single selected subject over the time of study
Visualization of a Concept – Step 1

• More than 3900 subjects on one graph
• Drug X showed 7 times as many ALT elevations >3x ULN, and 14 times as many in RUQ with both ALT >3xULN and TBL >2xULN
• Inspection showed that many were probably drug-induced; no other explanation
• Drug X was not approved – and later it was found that certain people were especially susceptible to X-induced liver injury
Time Course of Liver Tests- Step 2

• When ALT rise (hepatocellular injury) precedes the rise in serum bilirubin (liver dysfunction), then it is likely that the injury caused the dysfunction; it may take a few days for bilirubin to accumulate in the circulation.

• If bilirubin rise or fluctuating elevation precedes the ALT rise, look for some other cause, such as Gilbert’s syndrome of genetically impaired conjugation with glucuronide, and not DILI.

• Look at whether the AST rises more than ALT - ?muscle injury to heart of skeletal; is the ALP elevated, possible biliary obstruction.
Get a clinical narrative - Step 3

• The critical piece of the diagnostic puzzle:
  • What is or should be in a narrative?
  • Who should write it?
  • What should the narrative include?

• Not just a data dump from case reports
• Not by IT personnel, but by a physician
• Not a product of an automation process
• Protocols can’t anticipate all AEs that occur
A growing database

• eDISH data from clinical trials in a uniform format and maintained in one place
eDISH2 : Enhancement of eDISH

• More features, for research exploration
• More data to augment basic liver tests
• Clearer eDISH-data specifications, especially for the narratives
• The goal is to

get it right, make the best possible diagnosis of what's causing the problem
More Data

- Viral-load data and other chemical enzyme data shown in the same graph
- Viral-load-data request as part of the eDISH Data Requirements
Get a clinical narrative - Step 3

- Dr. Senior will comment briefly about narratives
Get a clinical narrative - Step 3.1

- eDISH is meant to be a clinical, medical diagnostic tool, not a statistical exercise of counting numbers;
- protocols cannot anticipate all possible adverse effects of a drug, especially if rare, so extra information is needed;
- physicians uniquely worry about causality, because they have responsibility to treat or prevent problems;
- ideally, narratives should be written by MD investigator at the site who can determine what extra information is needed to establish the probable cause of the problem;
- narratives should not be made by summarizing case records
Get a clinical narrative - Step 3.2

• Hy’s Law is NOT just elevated ALT and TBL, but requires a determination of probable cause; there is no such thing as “Hy’s Law chemistries”

• Hy Zimmerman said “drug-induced hepatocellular jaundice is a serious lesion”, with considerable mortality. The first requirement is that the drug caused the liver injury, and not something else. The second is that hepatocytes are injured and not biliary obstruction. Third, jaundice results because of the first two, indicating that enough hepatocytic injury has occurred that remaining cells cannot clear plasma bilirubin.

• How many times do we need to repeat this?
Get a clinical narrative - Step 3.3

• Preparing narratives should not be an afterthought when clinical data are being summarized for NDA submission;
• DILI can be rapid and serious, even fatal, and not done in retrospect. The investigator at the site may have to act quickly and make the right decisions;
• There are many possible causes for elevations in ALT or AST, bilirubin, alkaline phosphatase. They are not simple biomarkers, but indications for close observation and very active diagnostic inquiry;
• Very high ALT levels do not measure severity of liver injury, but indicate the urgency to investigate!
Get a clinical narrative - Step 3.4

- Clinical trials are not just data gathering exercises to get information to support approvals of new drugs, but are real world tests of drug effects, both good and bad in real people who may vary in how they respond;
- It is difficult to specify all the details needed for writing a good narrative. Go to medical school first, then practice a while, and you may begin to know what’s needed;
- The purpose of eDISH is to assist reviewers to scan over all the subjects, learn which ones may need special attention and further investigation to understand the cause of their test abnormalities and clinical findings.