

Spotting DILI (Drug-Induced Liver Injury) for FDA Submissions

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Drug-induced liver injury

What is DILI?

- ✓ DILI = liver injury caused by a hepatotoxic drug
- ✓ Severe DILI = death or transplant required

Drug-induced liver injury

Why is DILI important?

„DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (...), continuing to the present (...).“ [1]

Drug-induced liver injury

Spotting DILI (1)

- ✓ No specific findings
- ✓ Seek alternative causes of liver injury

Drug-induced liver injury

Spotting DILI (2)

- ✓ Severe DILI is rarely seen even for significantly hepatotoxic drugs
- ✓ Hepatotoxic drugs caused severe DILI in ≤ 1 per 10000 patients

Which drugs are likely to cause severe DILI?

Hy's Law

Major indicators of a potential for severe DILI

- ✓ Excess of ALT/AST elevations $> 3 \times \text{ULN}$
- ✓ Marked elevations of ALT/AST to $5 \times$, $10 \times$ or $20 \times \text{ULN}$ in modest numbers
- ✓ One or more cases of Hy's Law

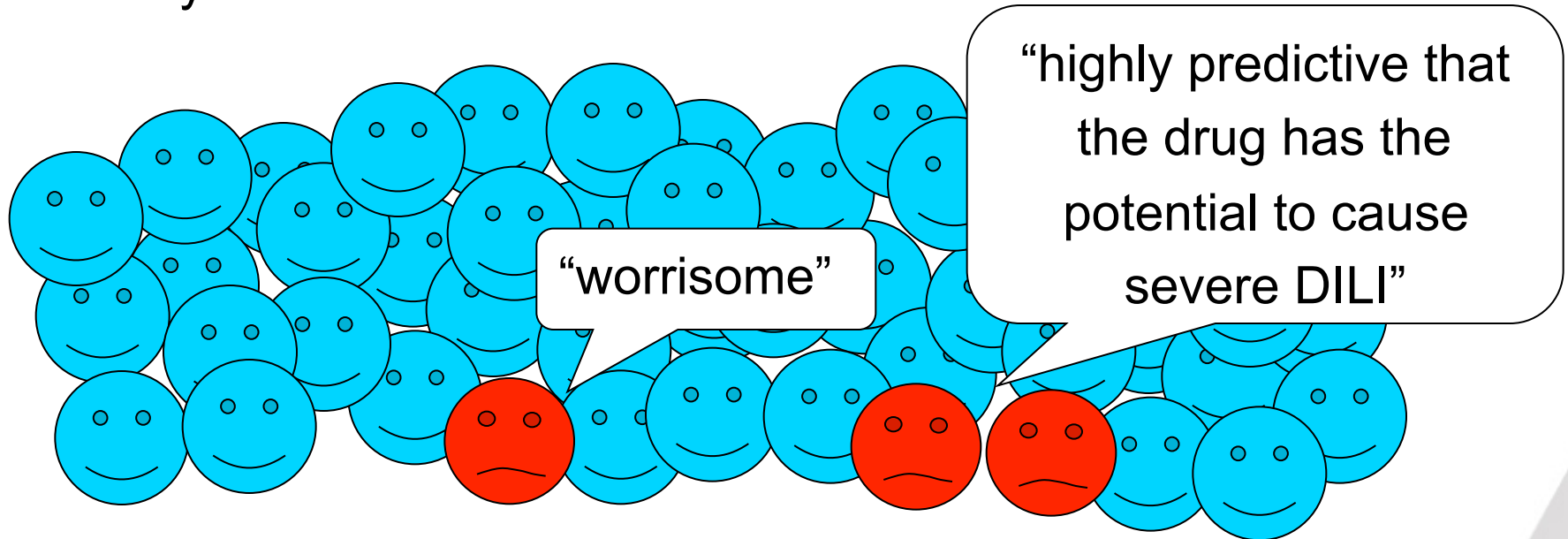
Hy's Law

Definition of Hy's Law

- ✓ ALT/AST elevations $\geq 3 \times \text{ULN}$ more frequent than control
- ✓ TBL elevations $> 2 \times \text{ULN}$
- ✓ No alternative cause for ALT/AST/TBL elevations

Hy's Law

Hy's Law and the submission database



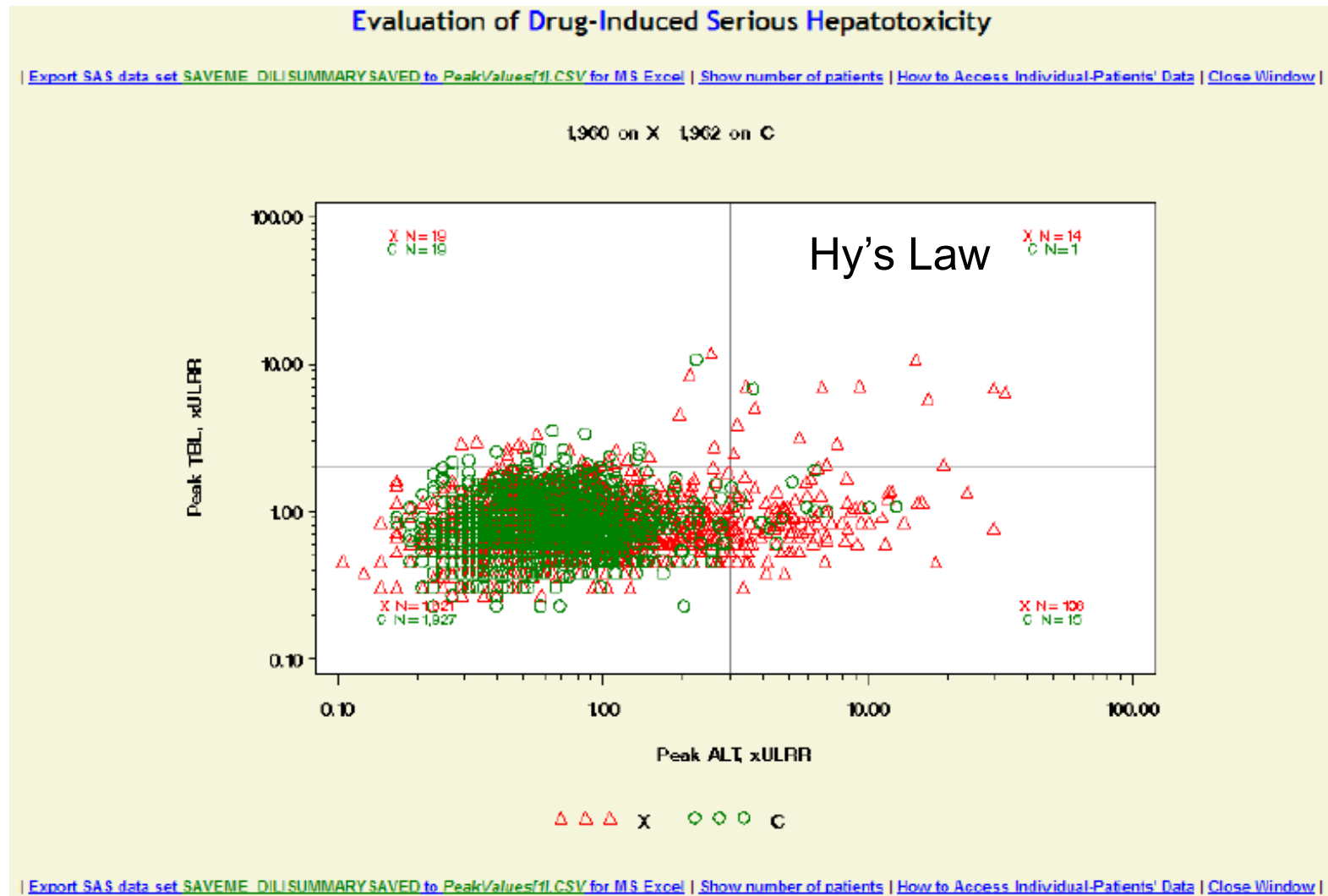
- ✓ Two or more Hy's Law cases: drug causes severe DILI
- ✓ Severe DILI at a rate $\geq 10\%$ of Hy's Law cases

eDISH – A tool for DILI evaluation

Overview

- ✓ eDISH = Evaluation of Drug-Induced Serious Hepatotoxicity
- ✓ Created using SAS/Intrnet
- ✓ Runs on CDISC data standard
- ✓ Goal:
 1. Summarize subjects' lab data
 2. Identify cases of interest
 3. Drill-down to individuals' lab data over time

eDISH – A tool for DILI evaluation



Source of picture: [1], page 13

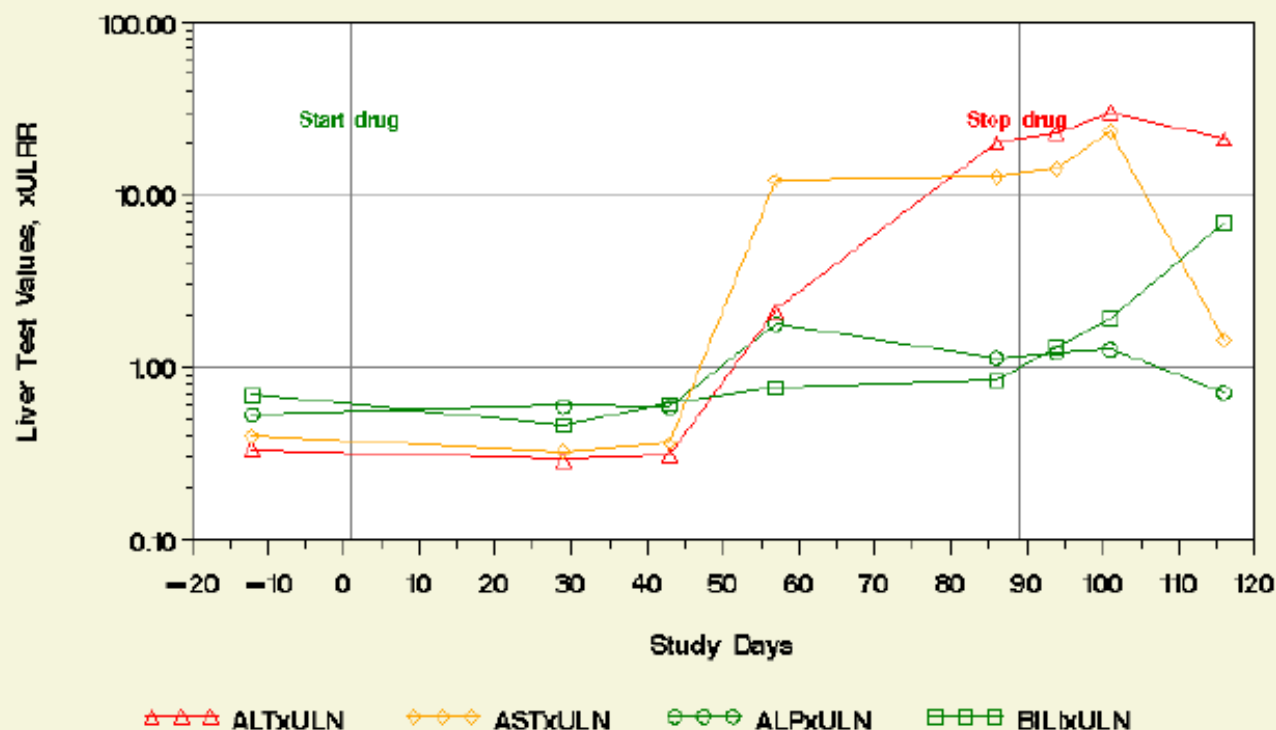
eDISH – A tool for DILI evaluation

[Option 1 \(default\): Free scales to show all data](#) | [Option 2: Apply pre-specified scales](#) | [Option 3: Show graph with data table](#) | [Option 4: Show original patient records](#) | [Close Window](#)

Go to Narrative of Patient: [7259](#)

Unique Study Identifier	Investigator Identifier	Unique Subject Identifier	Treatment Group	Start Date of Dose	End Date of Dose	Sex	Race	Height in Centimeters	Weight in Kilograms	Body Mass Index	Age
SH-TPA-0005	620	7259	X	05/11/01	09/07/01	Male	Caucasian	170.18	65.32	22.55	80

Time Course of Liver Tests
Patient #7259



Source of picture: [1], page 14

DILI in an FDA submission

Overview

- ✓ No CDISC submission
- ✓ DILI analysis as part of safety
- ✓ Deliverables:
 - eDISH peak ALT/AST - peak TBL plot
 - Listing showing Lab-values over time
 - Patient narratives

[Click for example document](#)

References

- (1) Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

- (2) How a SAS/IntrNet tool was created at the FDA for the detection of potential drug-induced liver injury using data with CDISC standard (Ted Guo, John Senior, Kate Gelperin, U.S. FDA, Silver Spring, MD)

<http://www.lexjansen.com/wuss/2009/cdi/CDI-Guo.pdf>

Thank you for your attention!