Assessing and Managing DILI Risk in Trials: A Consultant's Perspective

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Potential Conflicts

- Abivax, Abbvie, Accorda, Actelion, Agios, Akebia, Allergan, Almirall, Alnylam, Amgen, Astellas, Axovant, Belhus, Biocryst, Biogen, Biohaven, BMS, Cytier, Debiopharm, Diaichi-Sankyo, ERX, Ferring, Frazier, Gilead, GW, Hoffman LaRoche, HRA, Indalo, Intercept, F2G, Janssen, KBP Biosciences, Novartis, Palladia, Pfizer, PTC , Receptos, Seattle Genetics, Sojournix, Spark Therapeutics, Strongbridge, Sumitomo Dianippon, TB Alliance.
- Chair, SAB – DILI-sim Initiative
- Equivalent to equity in DILIsym Services, Inc.

Advisory Committee meeting in the early 1990's

"Company hired hepatologists never think the study drug was responsible"…..

FDA Staff Member

Recent communication from FDA to Sponsor (Feb 2019)

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Dear Dr. xxxxxxxxx

We are reviewing your application for NDA xxxxxxxxxxxxxx and have the following recommendation and information request.

The Agency recommends that you convene a hepatic advisory committee (HAC) with one or more individuals who have recognized clinical expertise in the assessment of DILI risk to…determine the severity and causality of each case of liver injury in the development program of xxxxxxxxxxxxxxxxx

Thoughts on the New Guidance

1). Define “signatures of DILI”

2). Encourage mechanistic research

3). Encourage novel use of DILI biomarkers and eDISH

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DILI typically has drug-specific “signatures”

- **1). Hepatocellular, cholestatic, mixed (R-value)**
- **2). Latency “window”**
- **3). Rate of progression, rate of resolution.**
- **4). Extra-hepatic manifestations (e.g. hypersensitivity signs)**

“Drugs causing DILI generally have “signatures”, but sometimes the signature is illegible…”

Willis Maddrey

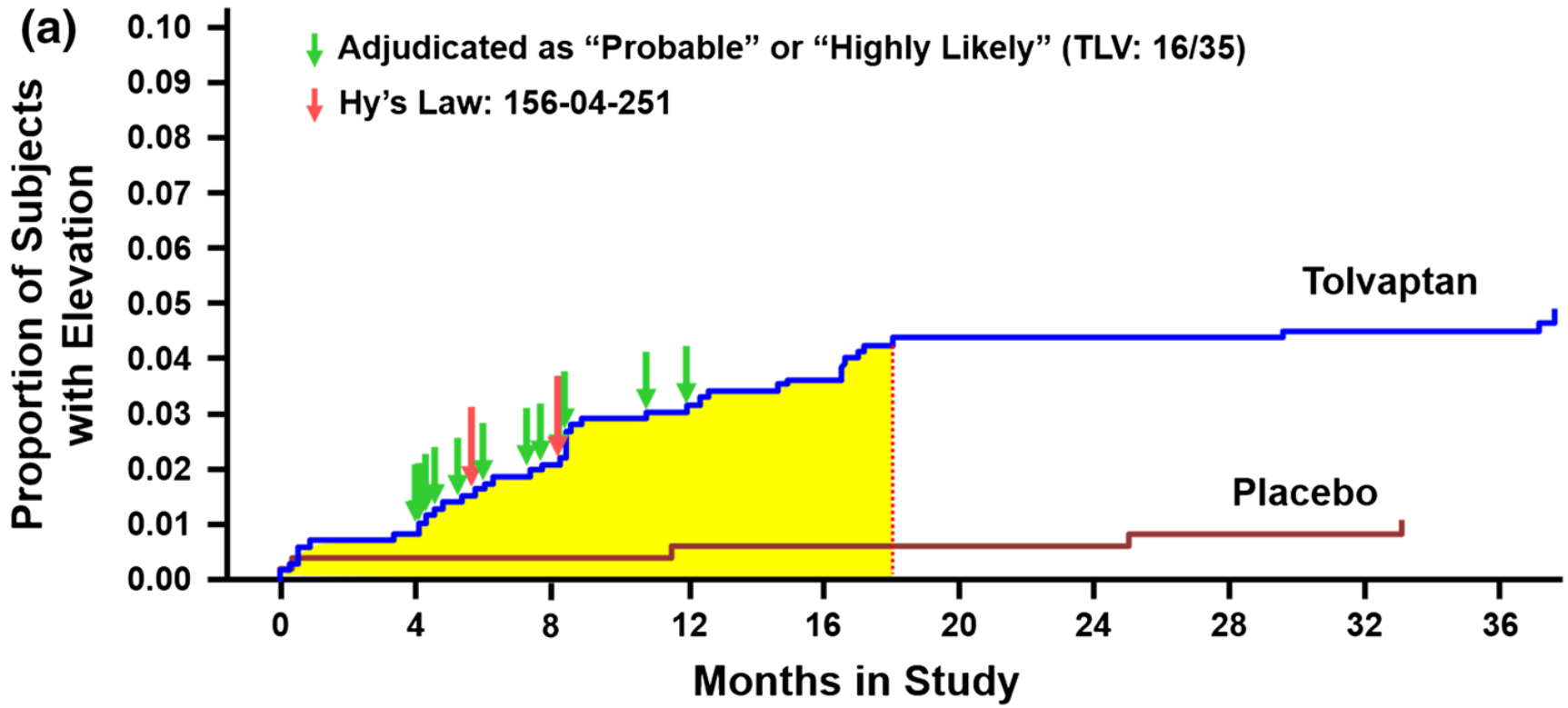
Drug Saf (2015) 38:1103–1113
DOI 10.1007/s40264-015-0327-3

ORIGINAL RESEARCH ARTICLE

Clinical Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic Kidney Disease: Analysis of Clinical Trials Database

Paul B. Watkins[1] · James H. Lewis[2] · Neil Kaplowitz[3] · David H. Alpers[4] · Jaime D. Blais[5] · Dan M. Smotzer[5] · Holly Krasa[5] · John Ouyang[5] · Vicente E. Torres[6] · Frank S. Czerwiec[5] · Christopher A. Zimmer[5]

K-M type analysis to define DILI “signature”



Days in Study	0	100	200	300	400	500	600	700	800	900	1000	1100
Tolvaptan N=	961	884	836	812	796	774	765	751	740	734	726	268
Placebo N=	483	476	468	459	452	445	442	433	425	422	415	147

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E. Analysis of Signals of DILI

Based on the FDA's experience, the following analyses related to liver injury potential should be carried out and included in an NDA or BLA, or included in an investigational new drug application when DILI is suspected and being evaluated.

1. Assessment of Drug Metabolism

The metabolism of a drug can markedly affect the safety profile of the drug. A drug may be metabolized to a hepatotoxic metabolite (e.g., acetaminophen, halothane, isoniazid). Most hepatotoxic drugs have been oxidatively metabolized by the CYP450 system.

2009 guidance

DILI consortial efforts where industry leader has been laid off

- Predictive Safety Testing Consortium
- MIP-DILI (IMI Initiative)
- Transbioline (IMI Initiative)

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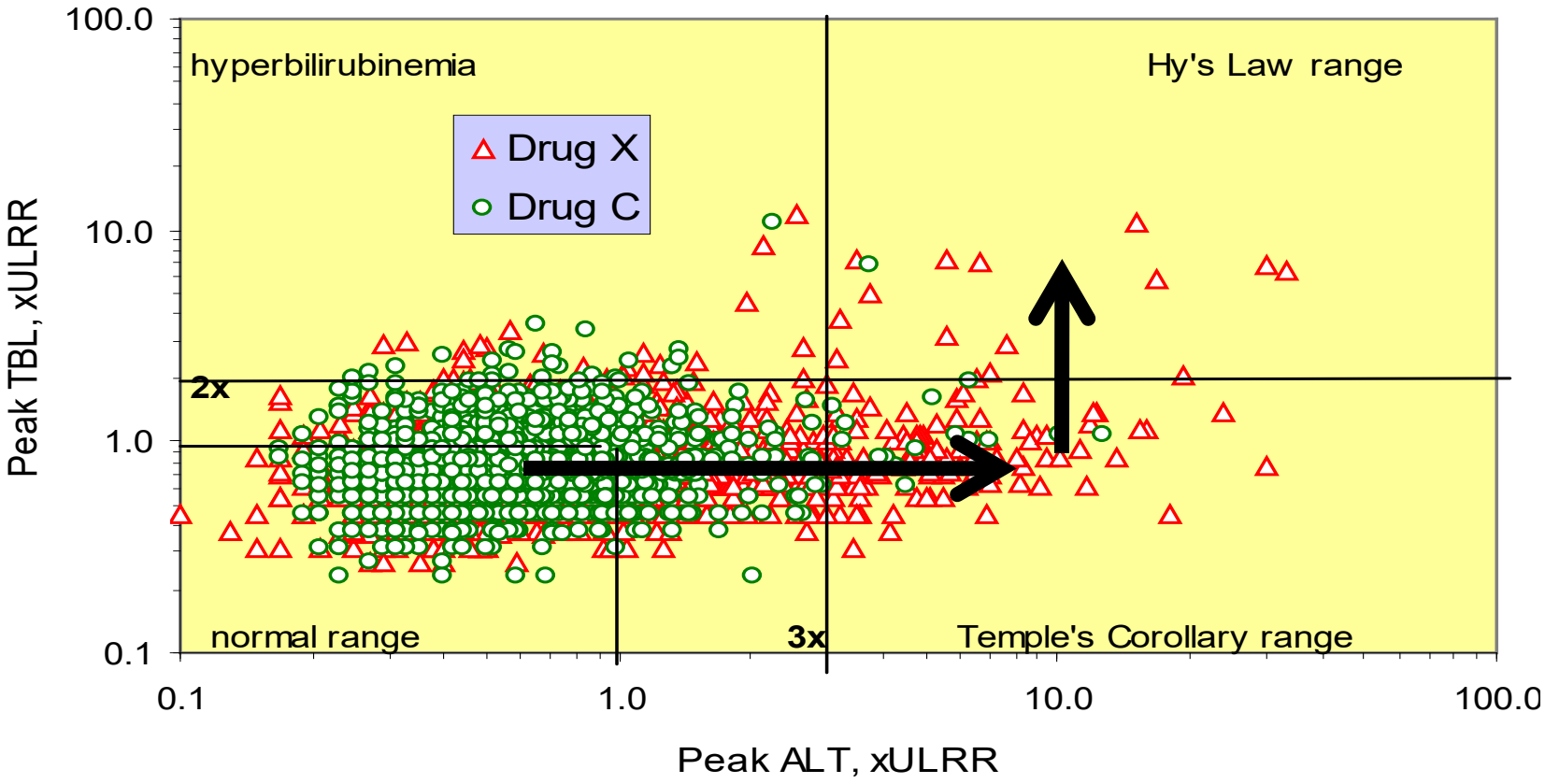
eDISH format for display of clinical trial liver safety data



Slide provided by John Senior, MD

Two problems with treat to liver dysfunction

1). **Size of trials**: to exclude liver failure in 30,000 treated patients need to exclude a Hy's Law Case in 1:3,000. Rule of three requires a study of 9,000 patients.

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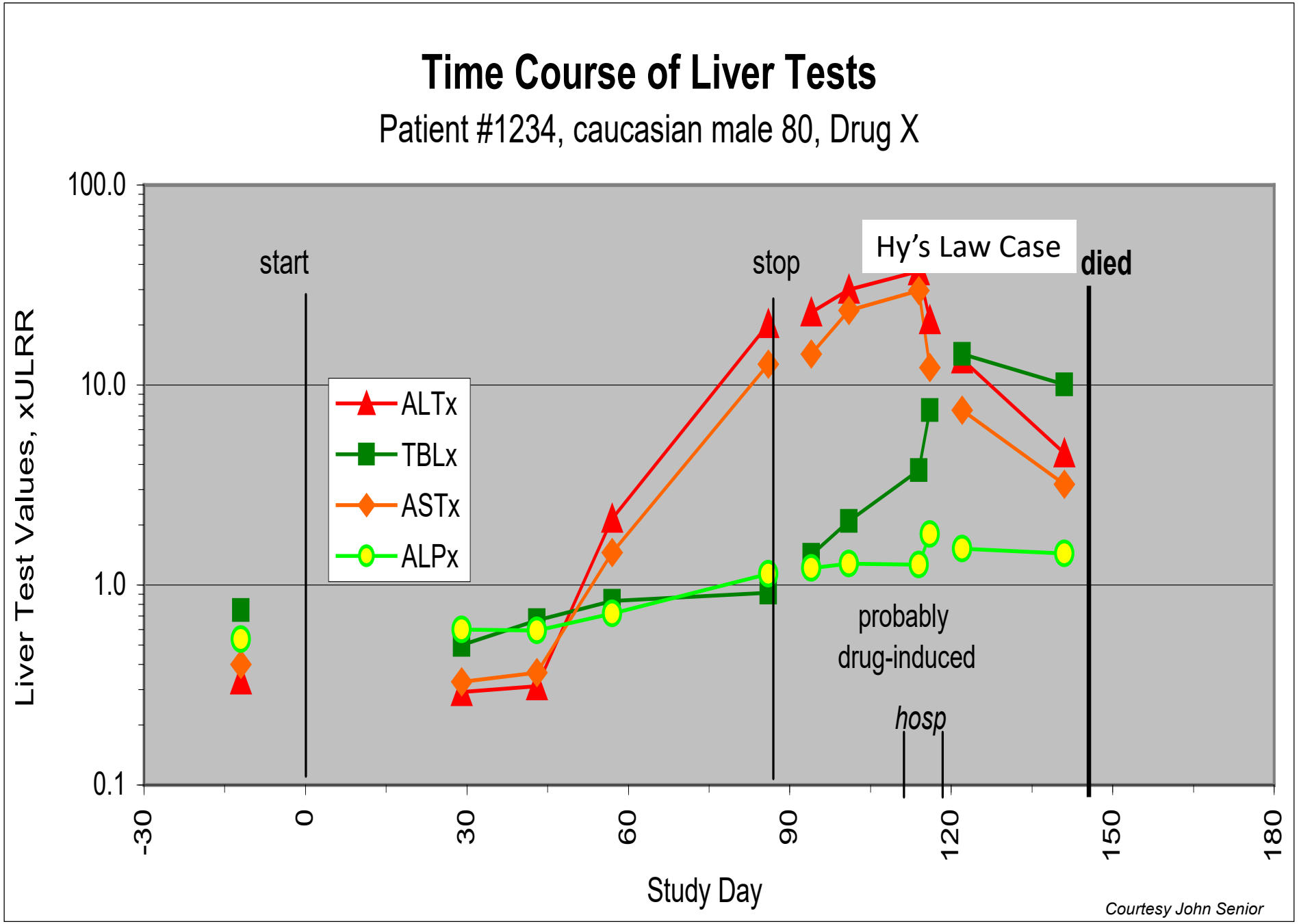
Two problems with treat to liver dysfunction

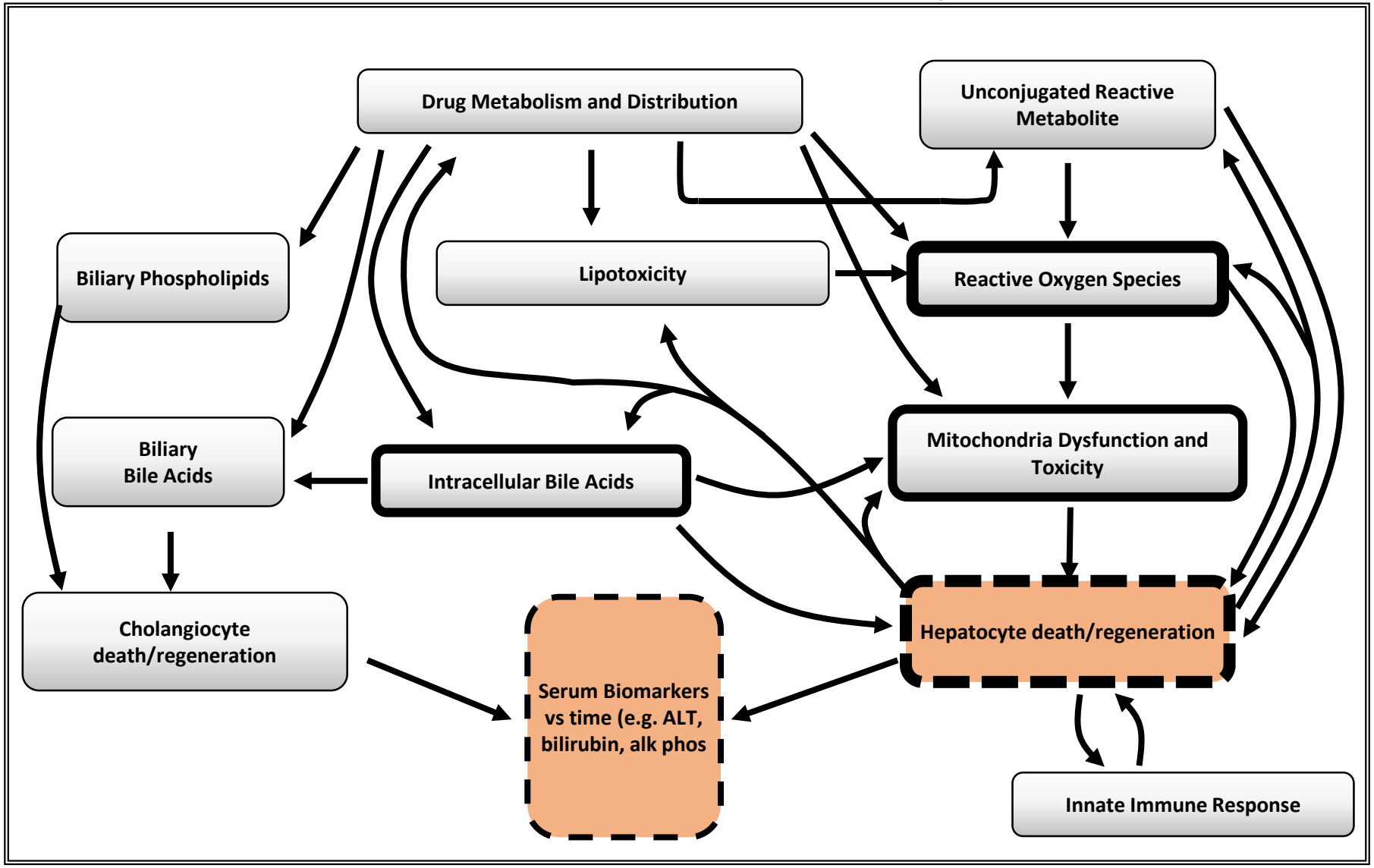
1). **Size of trials**: to exclude liver failure in 30,000 treated patients need to exclude a Hy's Law Case in 1:3,000. Rule of three requires a study of 9,000 patients.

2). Puts clinical trial subjects at risk of liver failure.

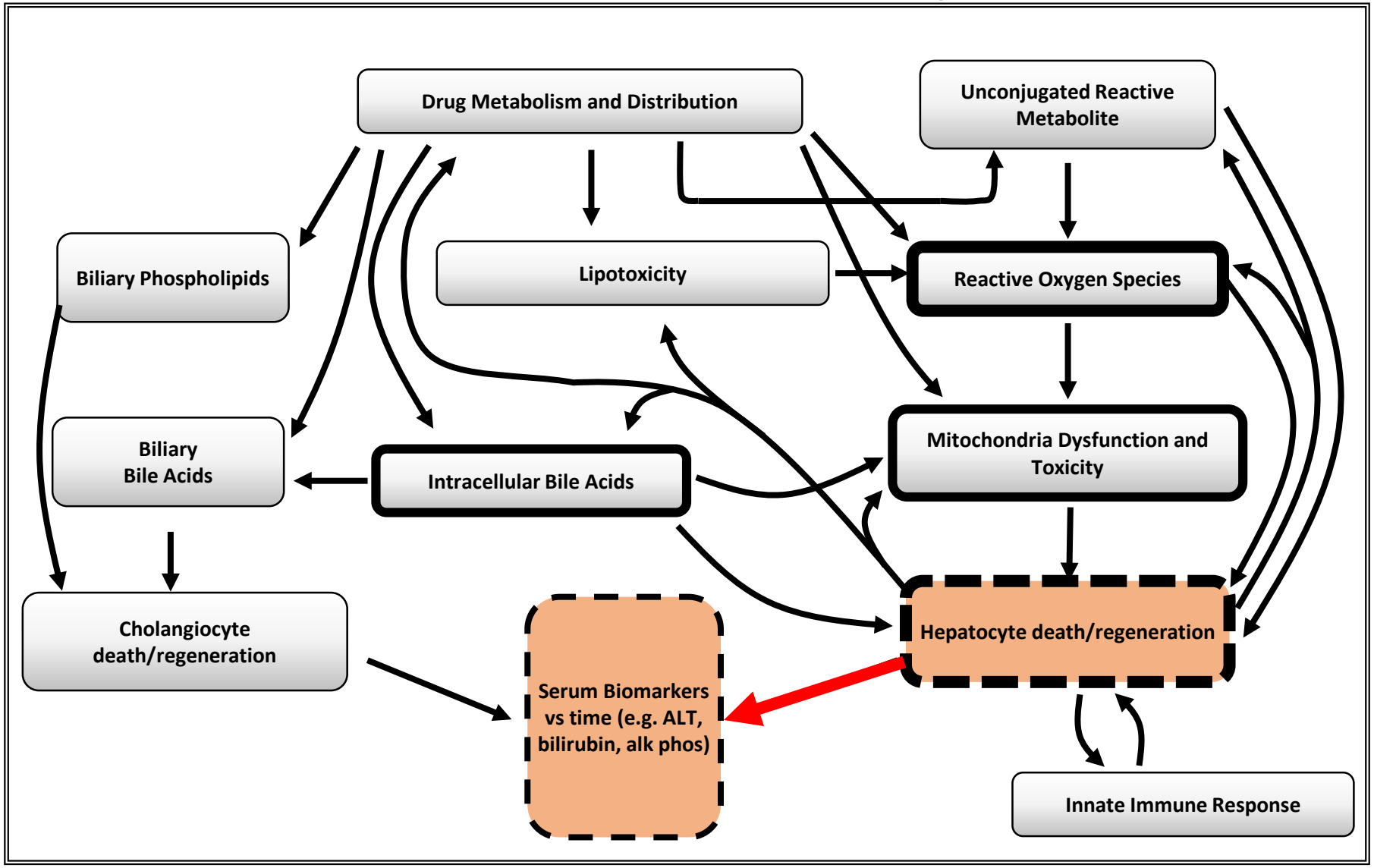

Time Course of Liver Tests
Patient #1234, caucasian male 80, Drug X
Liver Test Values, xULRR
100.0
10.0
1.0
0.1
start
stop
Hy's Law Case
died
ALTx
TBLx
ASTx
ALPx
probably
drug-induced
hosp
-30
0
30
60
90
120
150
180
Study Day
Courtesy John Senior

DILI-sim Initiative – A Public-Private Partnership

Submodels in DILIsym

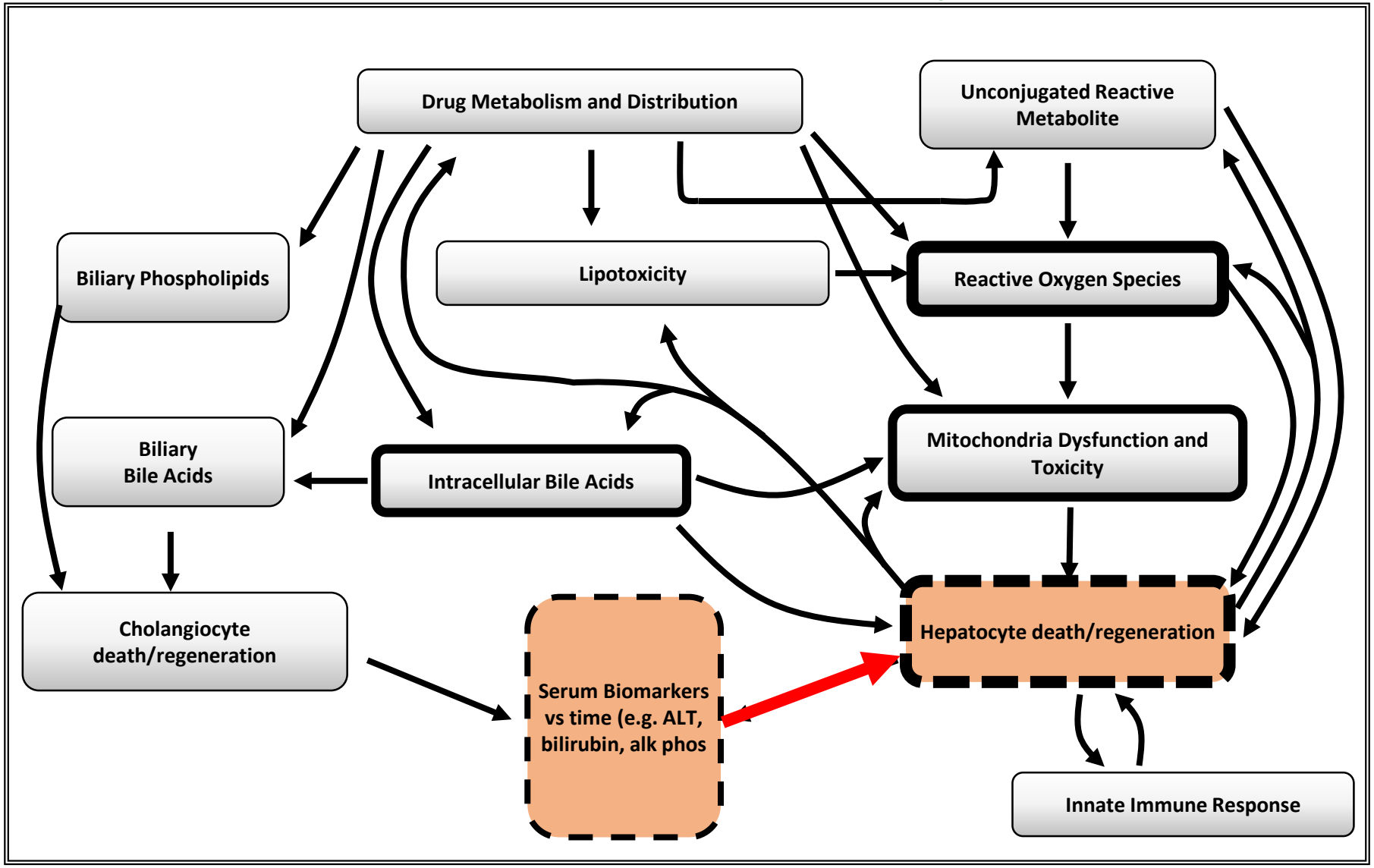


DILI-sim Initiative – A Public-Private Partnership
Submodels in DILIsym

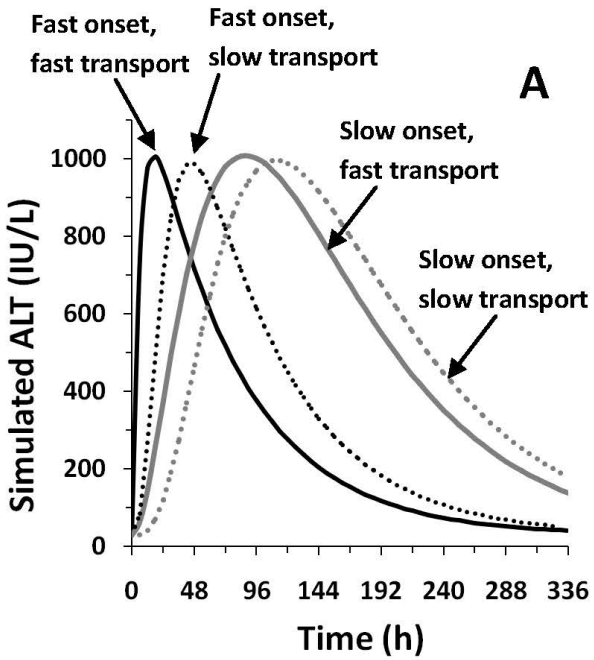


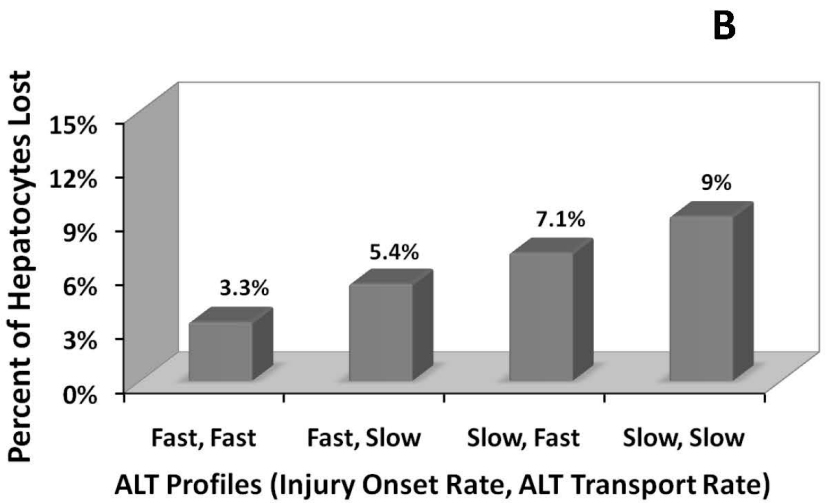
DILI-sim Initiative – A Public-Private Partnership

Submodels in DILIsym



The Kinetics of Serum ALT Profiles are Critical for Assessment of Extent of Injury





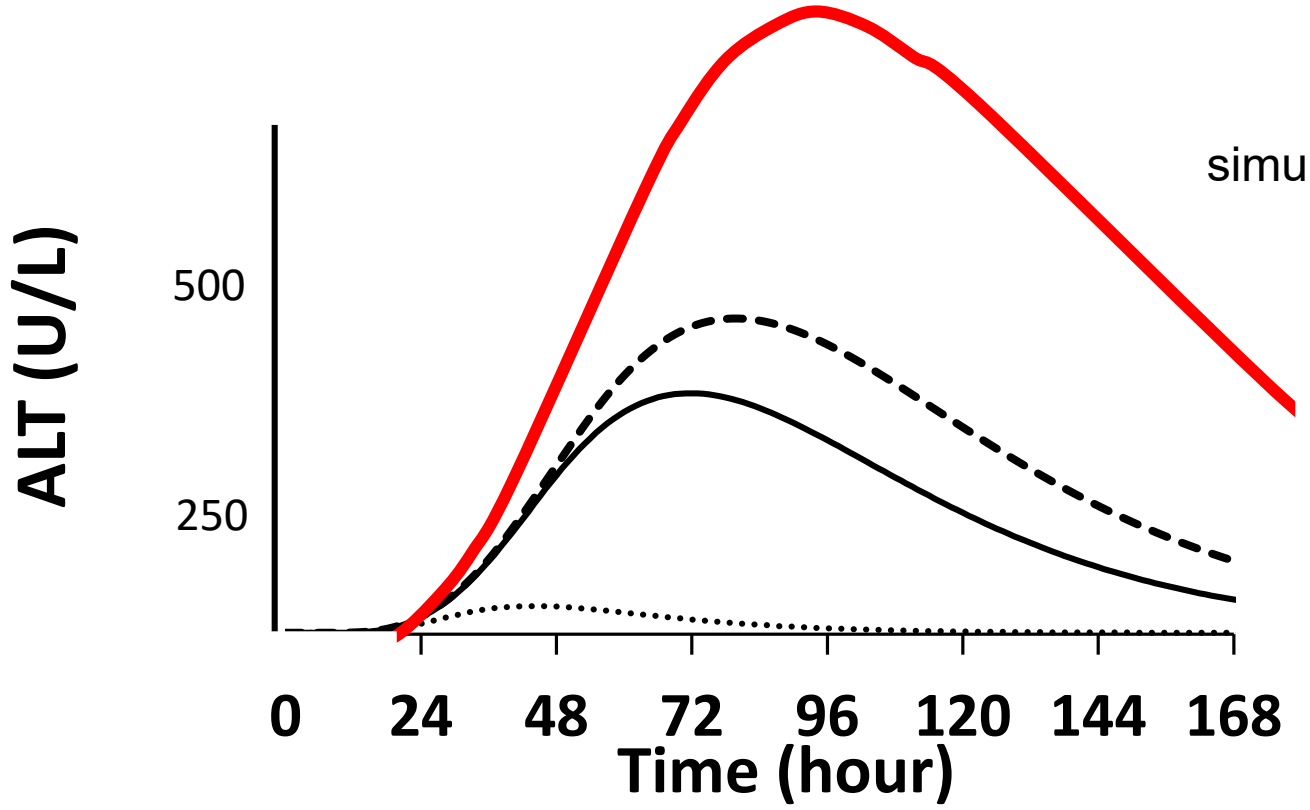
<u>Conclusion:</u> Interpretation of peak serum ALT values varies depending on kinetics

CPT Pharmacometrics Syst Pharmacol. 2014 Feb;3(e98).

Simulation Results

Cimaglermin Alfa (biologic)

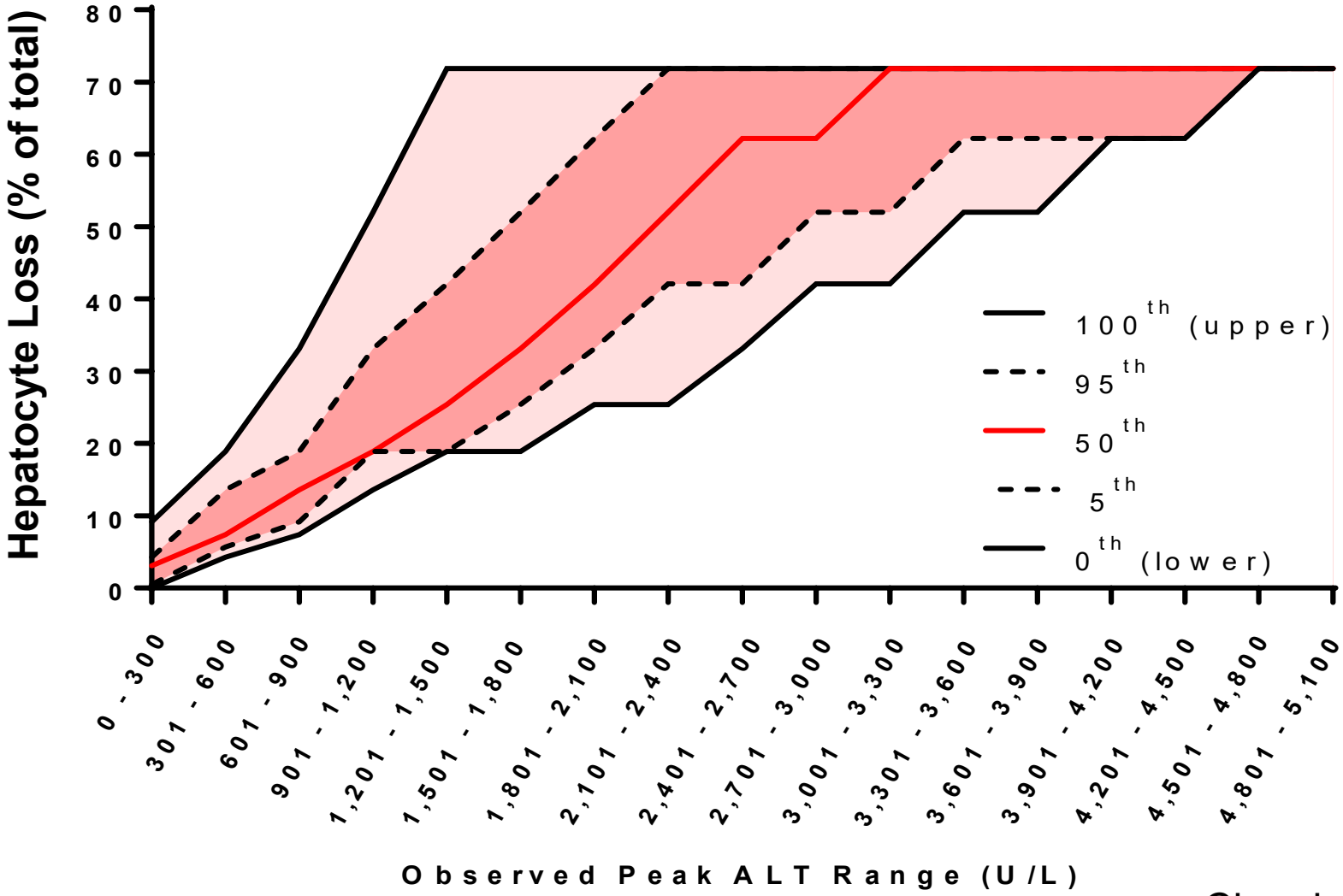
- Serum aminotransferase elevations were observed and had similar time course in all affected subjects



Approach for Introducing Population Variability into % Hepatocyte Loss Simulations

Components Varied to Construct Population Sample
Hepatocellular ALT content
ALT $t_{1/2}$
Hepatocyte proliferation rate

% Hepatocyte Loss vs Variation in Peak Serum ALT for Drug X



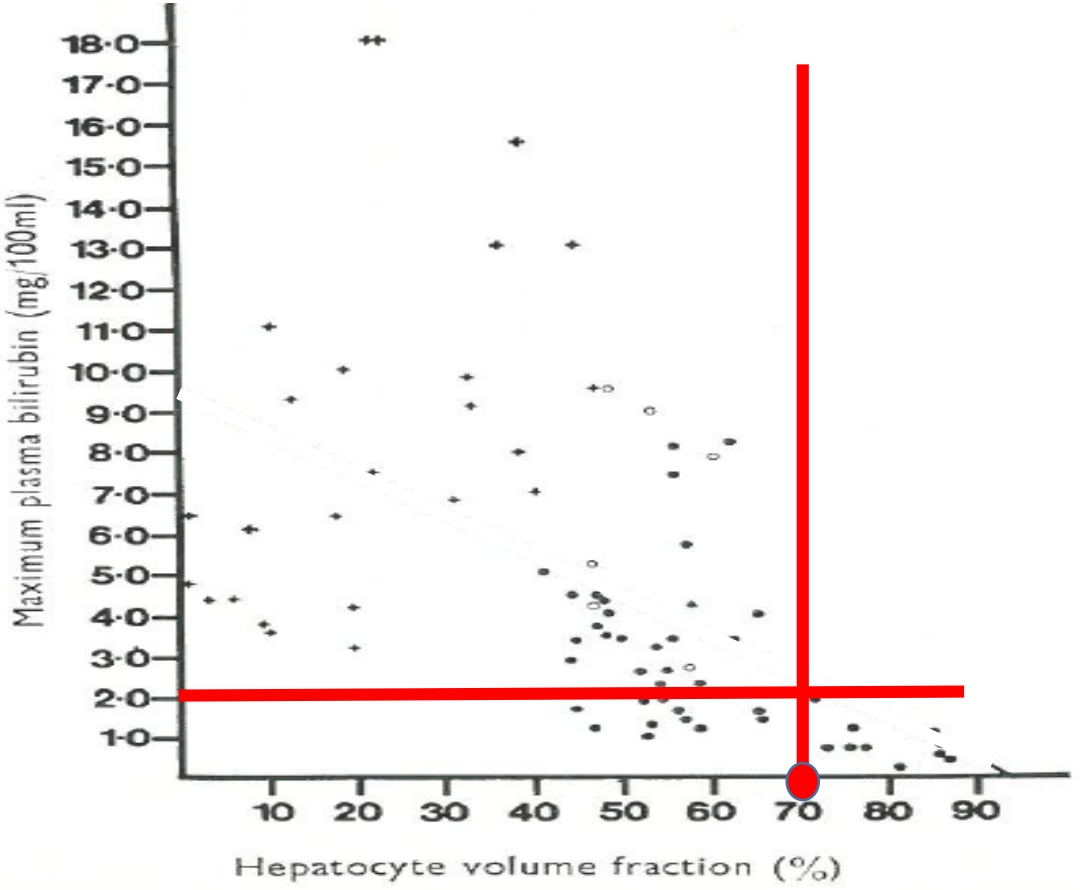
Church and Watkins -Exp Biol Med 2018 Feb;243(3):300-307

Simulation Results

But… What % Hepatocyte Death would Result in a Rise in Serum Bilirubin?

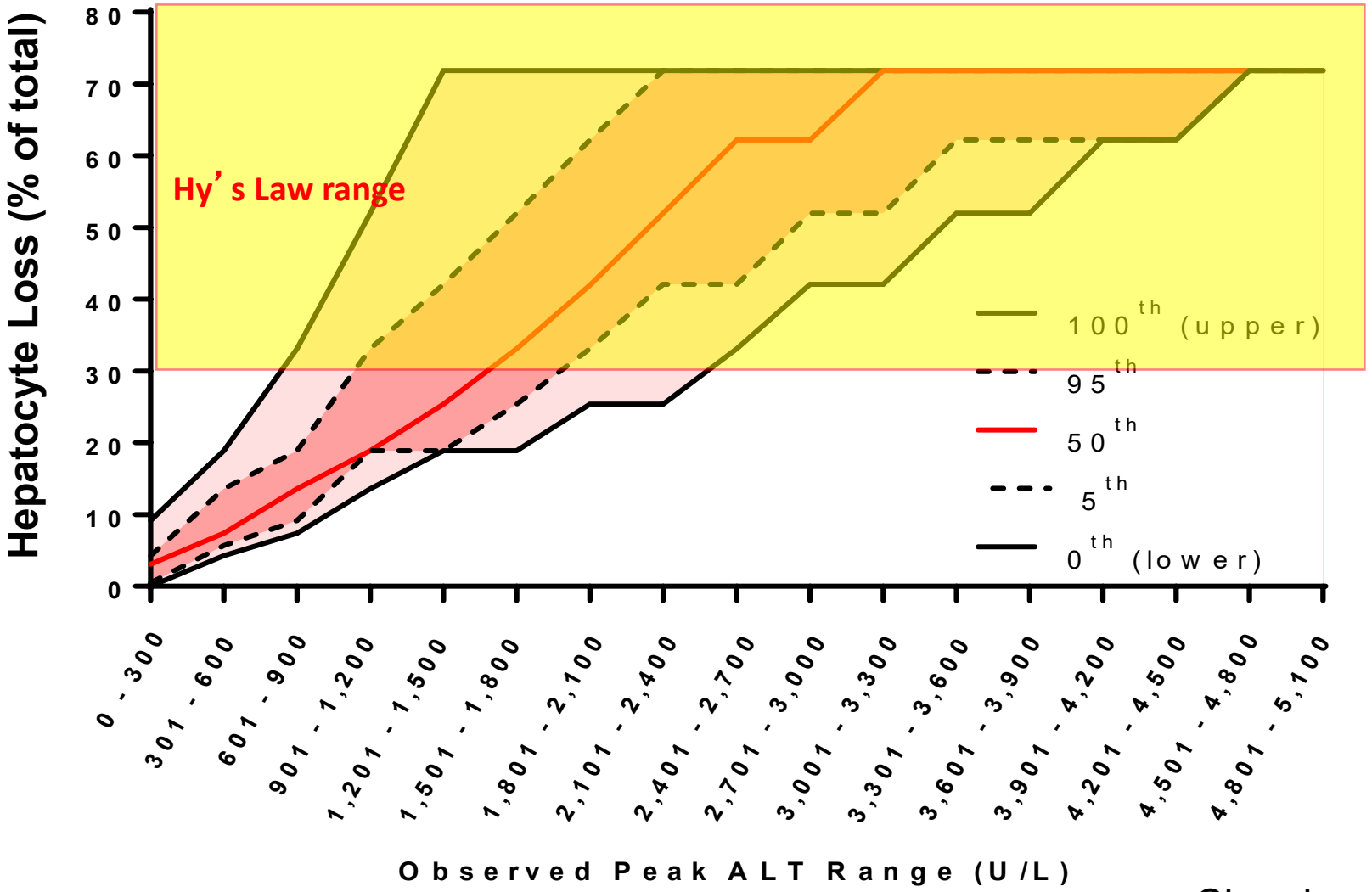
Also, can't hepatocytes be "sick" but not die and therefore not be accounted for in the modeling?

Viable Hepatocyte Fraction vs Peak Serum Bilirubin in People with APAP Overdose Who Underwent Liver Biopsy



Portmann, 1975

% Hepatocyte Loss vs Variation in Peak Serum ALT for Drug X



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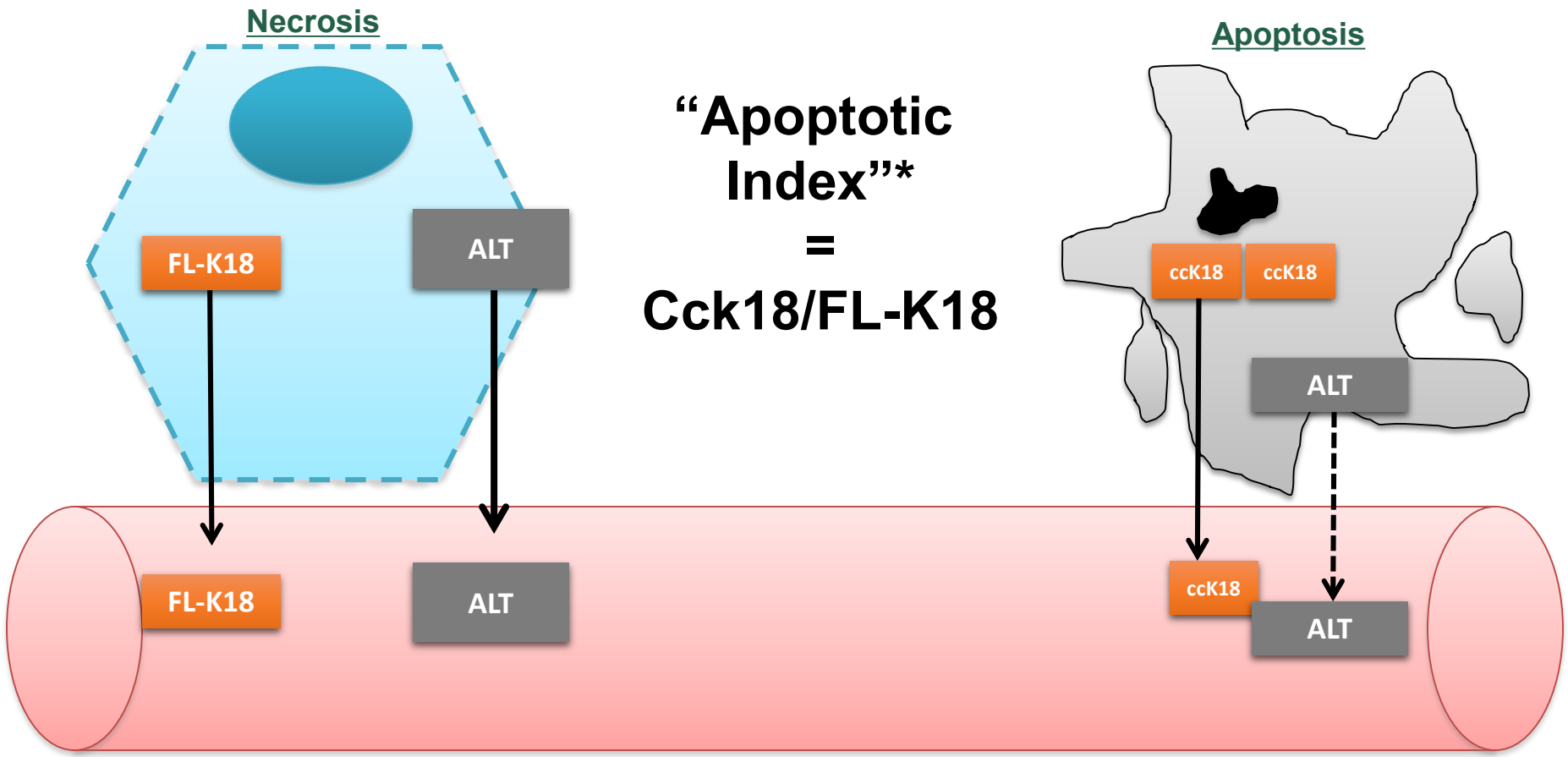
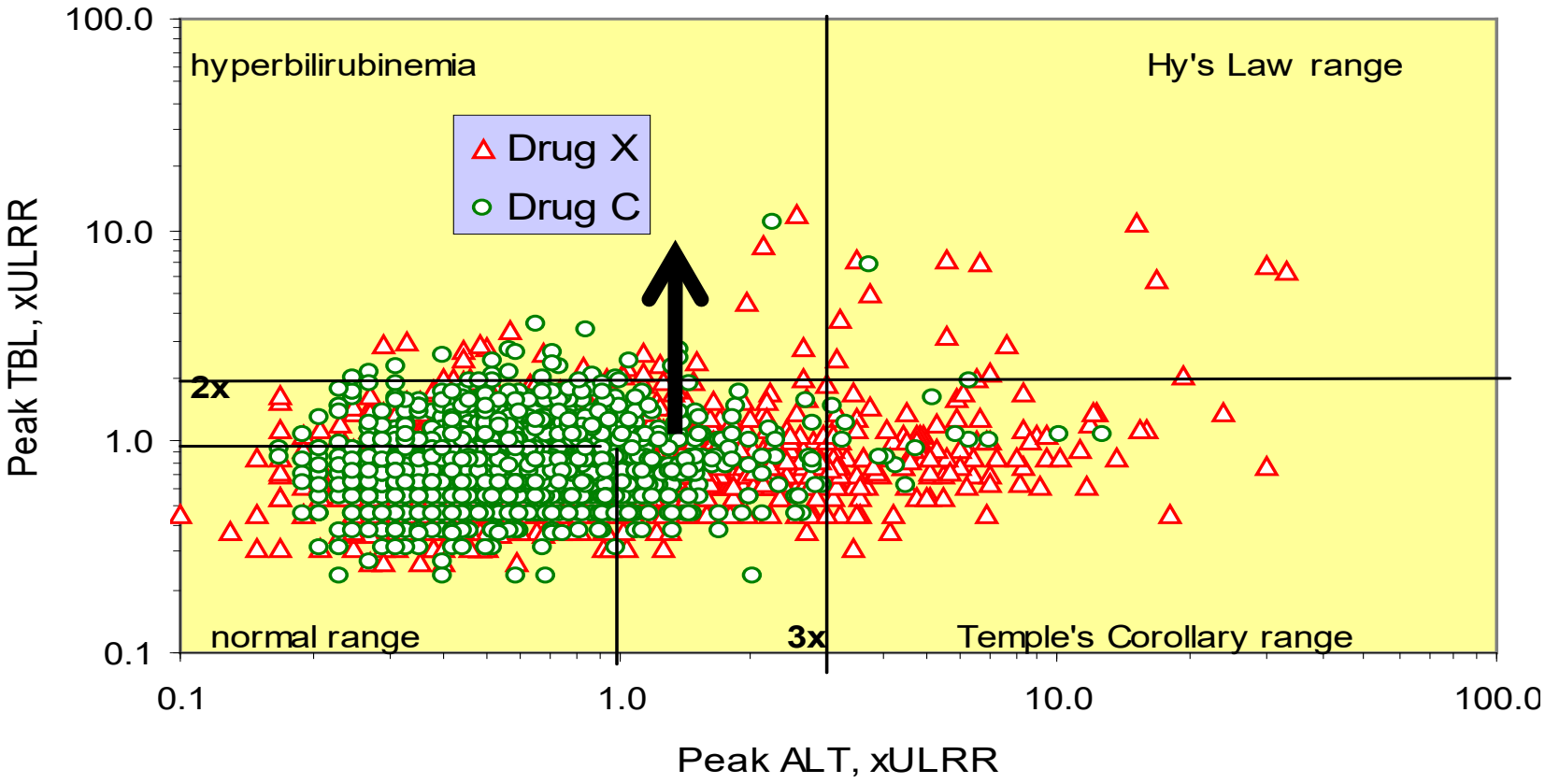
Simulation Results

Biomarkers of Apoptosis and Necrosis



*Liver Int. 2015 Apr 16. doi: 10.1111/liv.12850.

eDISH format for display of clinical trial liver safety data



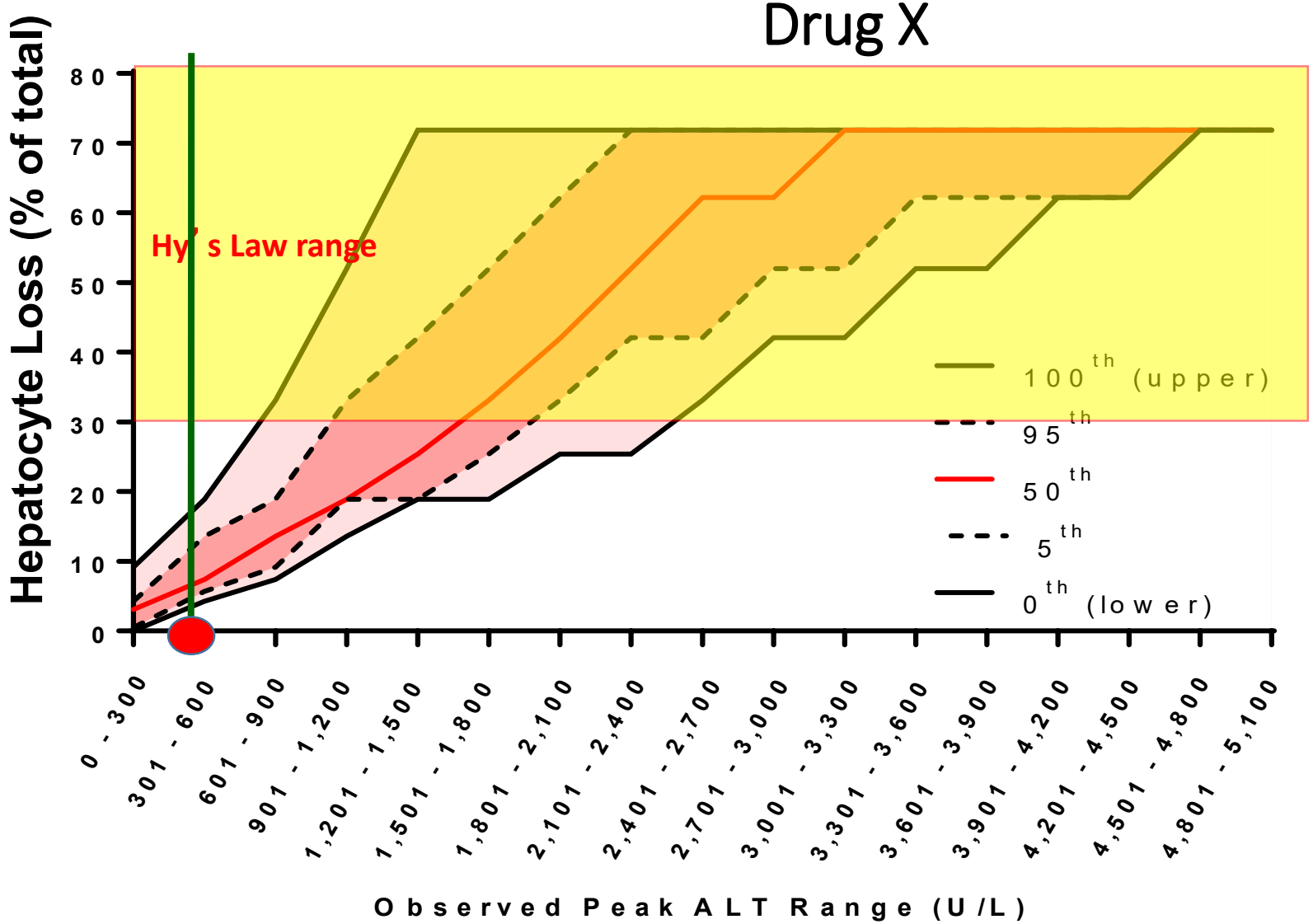
Slide provided by John Senior, MD

Refining Liver Safety Risk Assessment: Application of Mechanistic Modeling and Serum Biomarkers to Cimaglermin Alfa (GGF2) Clinical Trials

DM Longo[1], GT Generaux[1], BA Howell[1], SQ Siler[1], DJ Antoine[2], D Button[3], A Caggiano[3], A Eisen[3], J Iaci[3], R Stanulis[3], T Parry[3], M Mosedale[4,5] and PB Watkins[4,5]

Clin Pharmacol Ther. 2017 Dec;102(6):961-969

% Hepatocyte Loss vs Variation in Peak Serum ALT for Drug X



Church and Watkins -Exp Biol Med 2018 Feb;243(3):300-307

Simulation Results

Innovation in eDISH is proceeding

The FDA Liver Toxicity Work Group (LTWG) and the Office of Computational Science meeting May 9 “to introduce the DIA-ASA liver toxicity and clinical workup tool”.

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