

# **Drug-Induced Liver Injury (DILI)**

CLINICAL INVESTIGATOR TRAINING COURSE  
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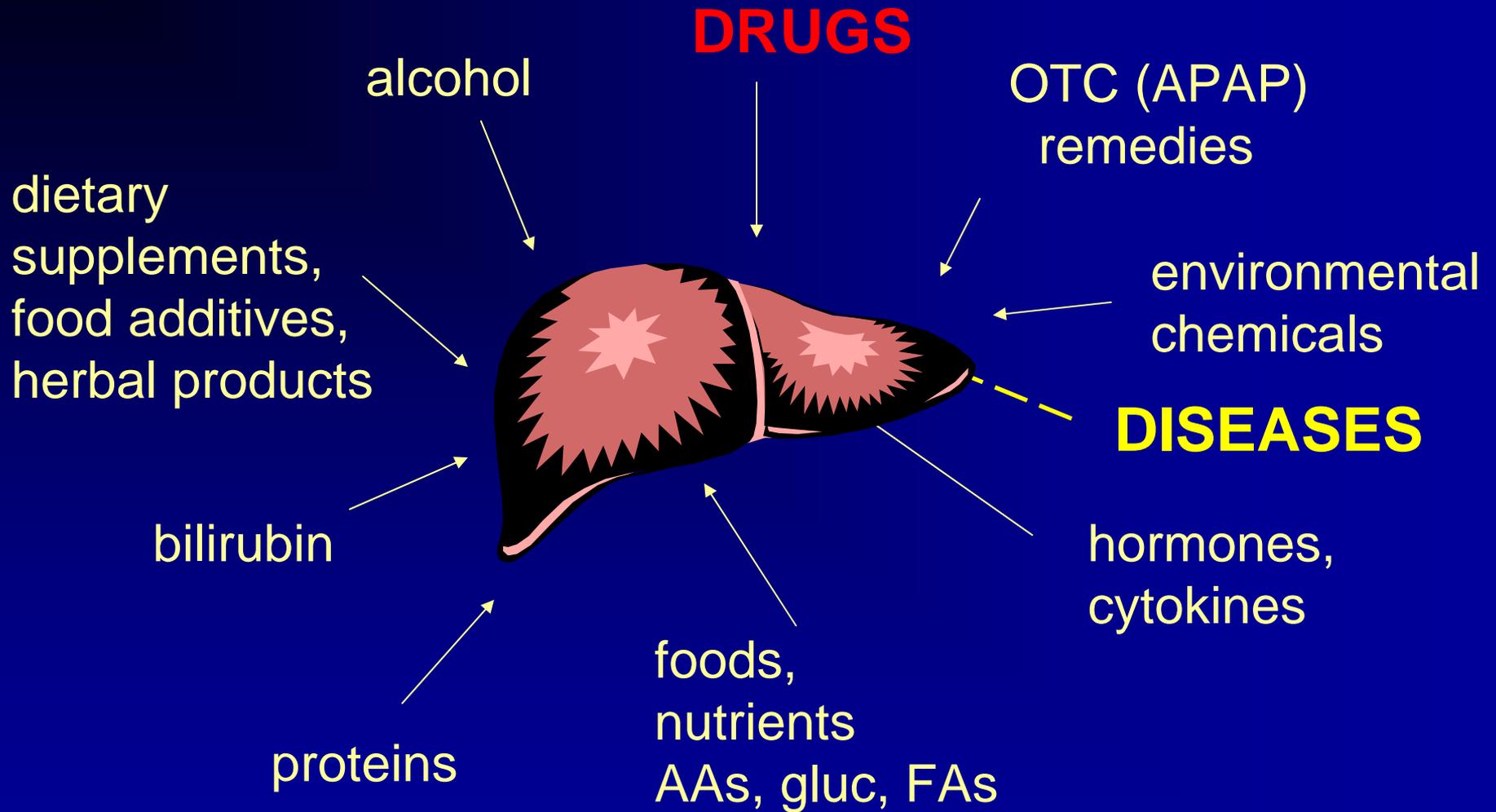
Office of Surveillance & Epidemiology  
Center for Drug Evaluation and Research  
Food and Drug Administration

# ***Why Should We Care about DILI?***

1. Drugs used for therapeutic intent may cause serious or fatal liver injury in some patients – *unpredictable, scary*
2. Although rare, DILI may result in disapproval of a new drug or its removal from the market – *very costly*
3. It is a troublesome problem for drug development, regulatory agencies, and patient care – *difficult problem*
4. It's not necessarily a dangerous drug, but may be an especially susceptible patient or subject

# *What Does the Liver Do?*

- The liver serves as the body's chemical engineering and control center, regulating the metabolism of internal compounds and coping with compounds coming in from the environment, such as DRUGS
- It has an astounding ability to:
  - adapt, change itself
  - alter activities of its enzymes and transporters
  - regenerate rapidly if cells are killed or removed

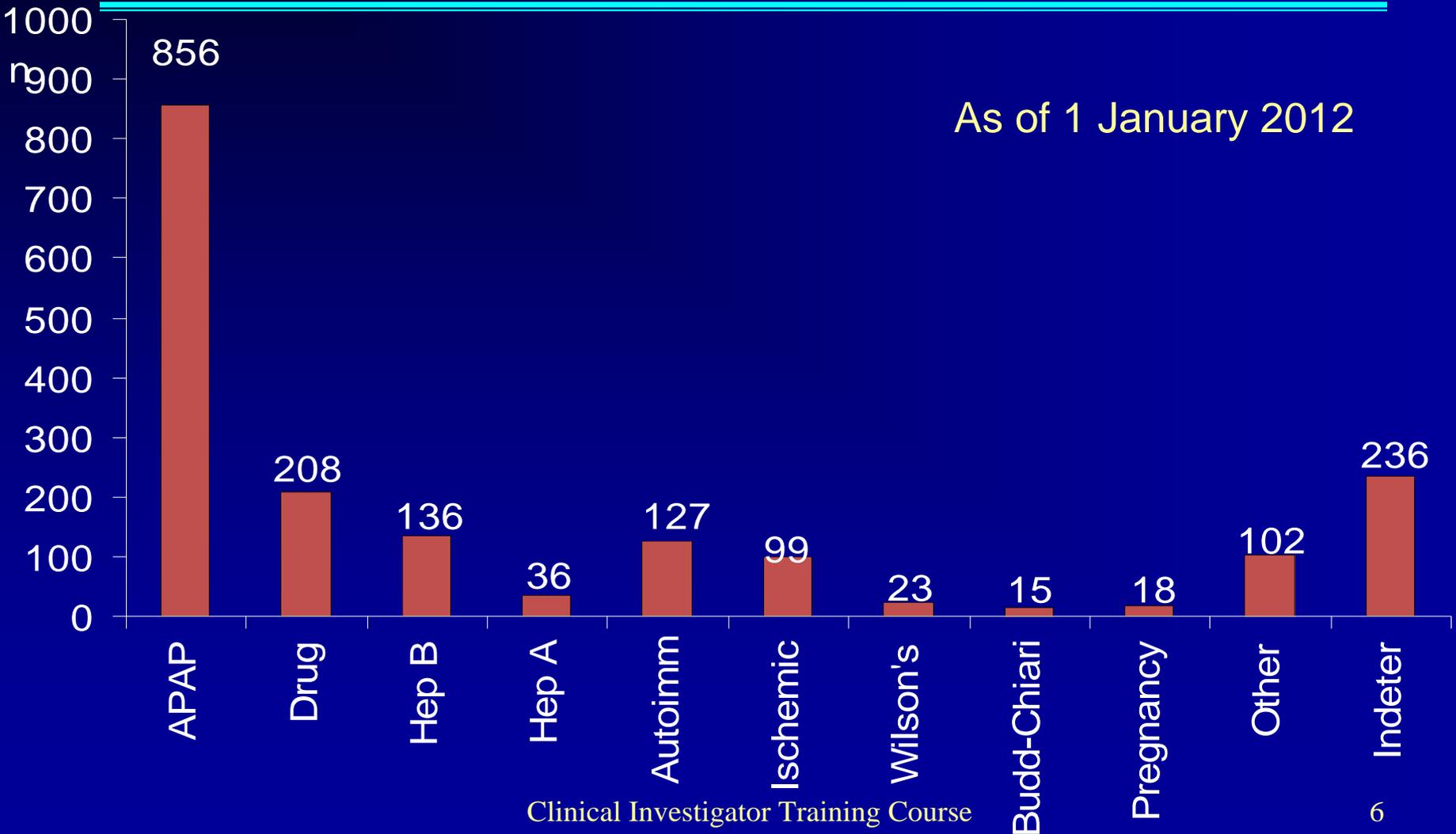


*Approved drugs are the most common  
cause of **acute liver failure** in the  
United States  
--- by far*

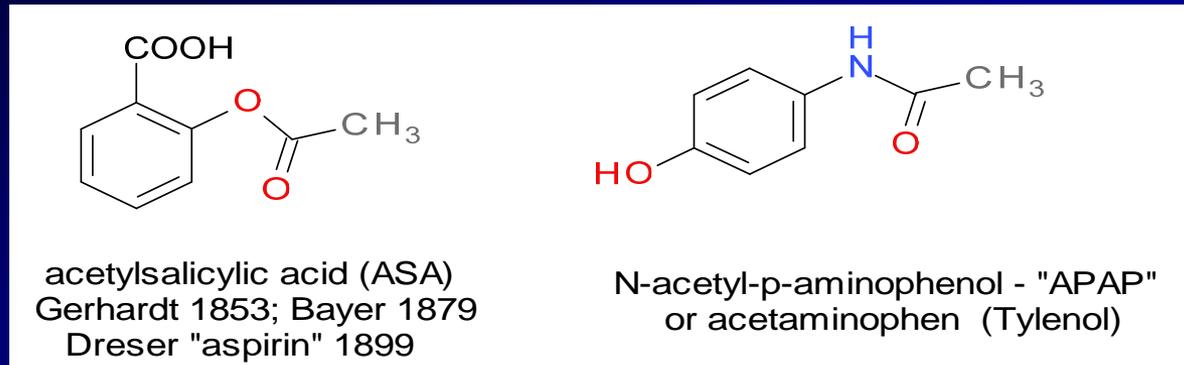
# Etiology of ALF in the USA

Adult Registry (N=1,896) – courtesy W. Lee, M.D.

As of 1 January 2012



# Why So Much Trouble with Acetaminophen? (a.k.a. "APAP" = *N*-acetyl-*p*-aminophenol {Lee}, *paracetamol* {England}, *TYLENOL* {trade})?



Because of its very successful McNeil-J&J marketing in the U.S. following the 1986 scare about the use of aspirin in children with "flu" symptoms causing Reye's syndrome, sold widely as the "safe" aspirin  
(sold as *Tylenol*, *Panadol*, *Datril*, *Tempra*, *Anacin3*, and many others)

*--- but the diagnosis of **cause** is difficult to make, requiring medical differential diagnosis to exclude other possible cause than the drug, so “indeterminate” as a cause is second to acetaminophen overdose because not enough information is gathered for diagnosis*

## ***What is an “Hepatotoxic Drug”?***

*... an oxymoron: if the substance is truly and consistently hepatotoxic , it is not or should not be a drug*

*Admittedly some drugs are more likely to cause liver injury than are other drugs ---*

*but also some patients are more susceptible to the same drug and dose than are most people.*

*Drugs are not intended to cause harm.*

# Drugs that Cause DILI

*Rates of mild transient liver injury & ALF*

## *Incidence*

*ALT > 3X ULN*

*ALF*

**Isoniazid**

**~ 10%**

**< 0.1%**

**Troglitazone**

**~ 2%**

**< 0.05%**

**Ximelegatran**

**~ 8%**

**< 0.05%**

# Regulatory Actions due to DILI

## *Marketed Drugs: 1995-2009*

### Withdrawals

bromfenac

troglitazone

pemoline

ximelegatran\*non-US

lumaricoxib\*non-US

### Special Use

trovofloxacin

felbamate

tolcapone

### Warnings

acetaminophen

nefazodone

pyrazinamide/rifampin

valproic acid

atomoxetine

saquinavir

bosentan

erlotinib

(kava)

leflunomide

nevirapine

terbinafine

zifirlukast

interferon 1b/1a

infliximab

telithromycin

natalizumab

(lipokinetix)

# Idiosyncratic DILI: Some Inciting Drugs

**Hepatocellular injury, immunoallergic:** phenytoin, sulfonamides, allopurinol, halothane, diclofenac, quinolones, telithromycin,

**Hepatocellular injury, metabolic:** INH, troglitazone, ximelagatran, bromfenac

**Cholestatic:** estrogens, 17a androgens, chlorpromazine, clavulanic acid, piroxicam

**Bile duct injury:** carbamazepine, chlorpromazine, chlorpropamide, cyproheptadine, thiabendazole, haloperidol

**Microvescicular steatosis:** valproate, tetracycline, didanosine

**Phospholipidosis & pseudoalcoholic hepatitis:** amiodarone, perhexiline maleate

**Chronic autoimmune-like hepatitis:** dantrolene, methyldopa, nifurantoin, oxyphenisatin, propylthiouracil, tienilic acid

# What Do We Need to Know about DILI?

1. *How clinically severe is it?*
2. *How probable is it that it was caused by the drug implicated?*

*Severity CANNOT be assessed by the level of serum enzyme elevation; it may indicate the rate of hepatocellular injury but does not measure the ability of the liver to function and support life. The only true function tests often done are serum bilirubin and plasma prothrombin time.*

*Causality is another matter – very difficult*

# Serum Enzymes are NOT Liver *Function* Tests !

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It is NOT a true function of the liver to regulate levels of enzyme activity in the plasma. Elevated levels may reflect injury to liver cells if injured, but **function** must be measured by other tests.

The only tests commonly done that measure a true function of the liver are:

    bilirubin concentration, BILI

    prothrombin time, or its INR derivative

***\*Don't call serum enzymes "LFTs", just say LTs.\****



# Likelihood That the Liver Problem was Caused by DILI

NCI/ FDA			DILIN
1	5 to 25%	“unlikely”	5
2	>25 to 50%	“possible”	4
3	>50 to 75%	“probable”	3
4	>75 to 95%	“very likely”	2
5	>95%:	“certain, definite”	1

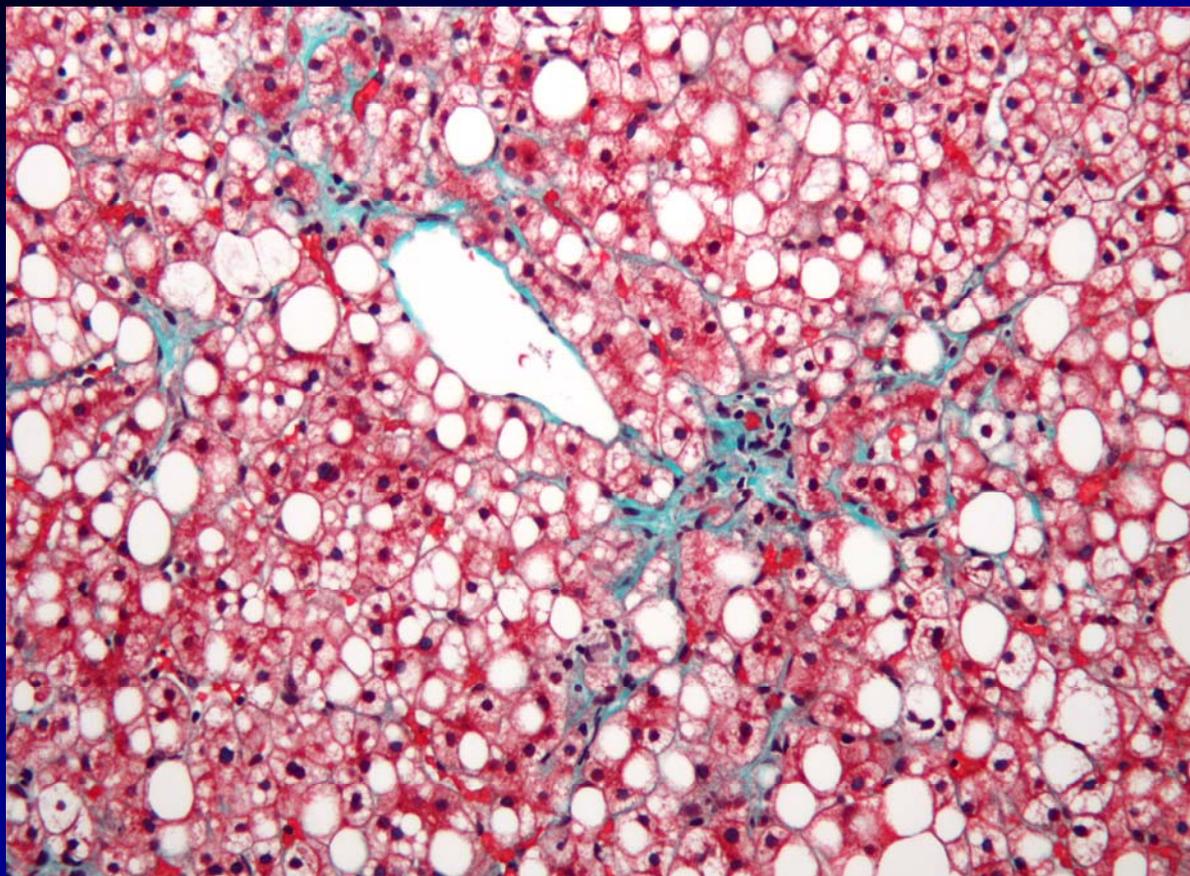
**Conversion: (6 - FDA/NCI) = DILIN**

# Clinical Importance (SEV-LIK score) for Individual Cases

DILI <u>L</u> ikelihood	<u>S</u> everity of Liver Dysfunction					
	5 fatal or transplan t	4 acute liver failure	3 serious:	2 “Hy’s case”	1 enzyme rises only	0 none detectable
5: definite >95% likely	25	20	15	10	5	0
4: very likely >75 to 95% likely	20	16	12	8	4	0
3: probable >50 to 75% likely	15	12	9	6	3	0
2: possible >25 to 50% likely	10	8	6	4	2	0
1: unlikely 5 to 25% likely*	5	4	3	2	1	0
0: certainly not <5% likely**	0	0	0	0	0	0

\*... and some other cause very likely ;

\*\*... and another cause almost certain, definite



**Hy Zimmerman**  
1916 - 1999



# What is “Hy’s Law”?

- Hyman Zimmerman said, repeatedly:  
“drug-induced hepatocellular jaundice is a serious lesion, with mortality from 10 to 50%” ... *he did not say it was a law and didn’t want it named for him*
- Bob Temple articulated in 1999 a modified form of this observation for use in controlled clinical trials and as a screening threshold and dubbed it “Hy’s Law.”
  - {ALT or AST >3x upper limit of normal **AND** TBL > 2xULN}
  - Not primarily cholestatic; not caused by disease but by drug

***It was catchy and now seems impossible to change***

# What “Hy’s Law” is NOT!

- Not just abnormal serum chemistries: ALT>3xULN & TBL >2xULN --- but they signal the need to look closer
- Should not be initially cholestatic: ALT<sub>x</sub> / ALP<sub>x</sub> <2
- Must not be probably caused by other than drug --- find out
- Requires clinical adjudication (differential diagnosis) to determine probable cause of liver test abnormalities
- Often misunderstood by sponsors and their staffs, even by their consultants
- Important to find the probable cause of liver dysfunction

# Identifying a DILI Signal: *Clinical Trial Studies*

*Finding liver injury associated with exposure to a drug may indicate a higher risk to others exposed to the same drug –*

*(note: “associated with” or “related to” does not prove “caused by”)*

1 – Look for imbalance of liver injuries (enzyme rises) in randomized trials: more frequent and severe in those on drug, as suggestive indicators

2 - Hy’s case:  $ALT > 3 \times ULN \rightarrow bilirubin > 2 \times ULN$ , not cholestatic and probably caused by drug: If present, predicts that serious idiosyncratic DILI cases may be more likely in post-marketing treatment population

# FDA Experience

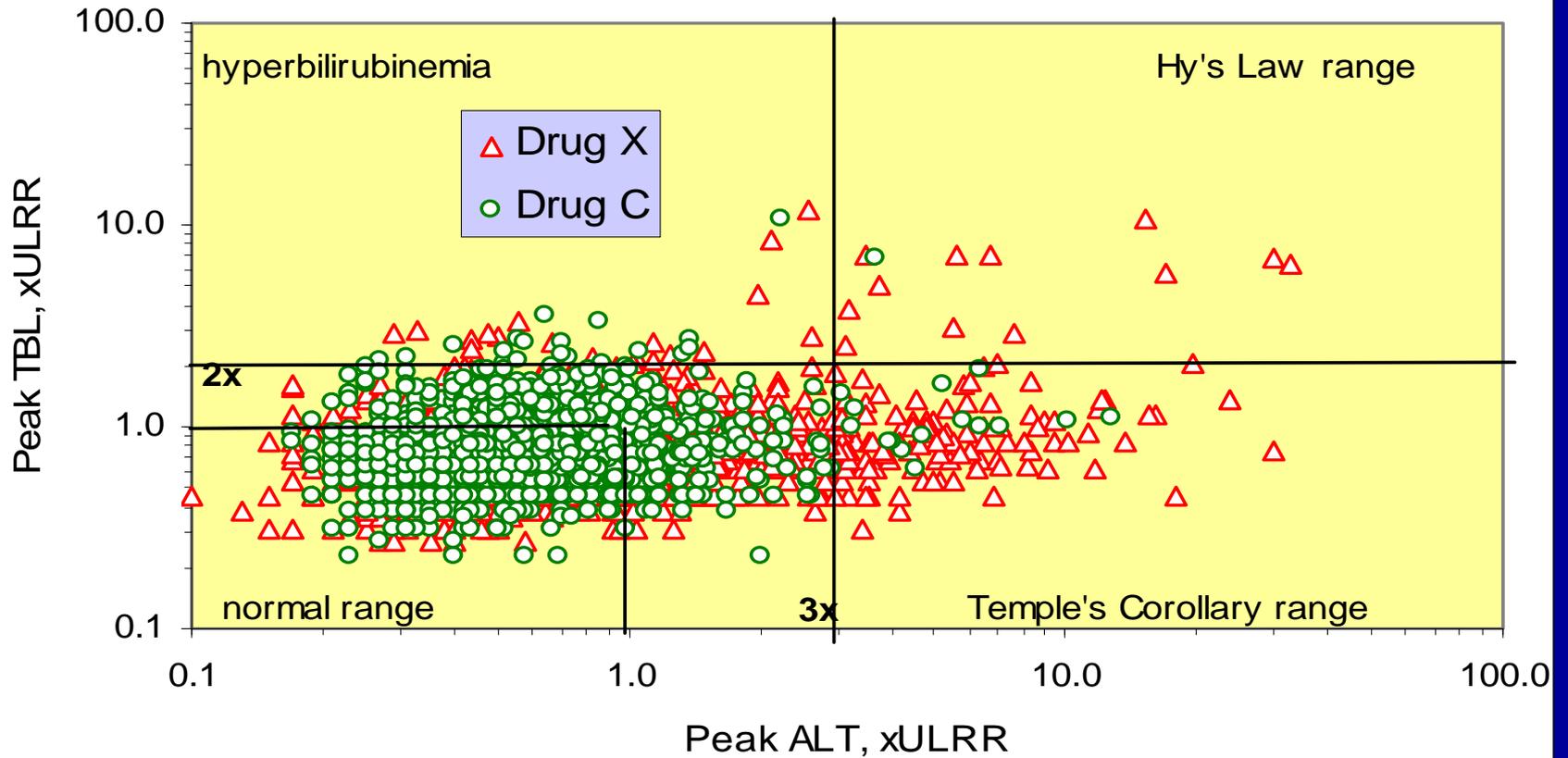
- Limitations of clinical trials
  - Subjects treated in a monitored setting
  - Have the disease being tested, nothing else
  - Selected participants, exclusion criteria
  - Limited numbers, limited time
- After product approval . . .
  - Often used off label, without monitoring, in patients different from those studied in the clinical trial, only voluntary reporting, burden on FDA to prove danger, huge numbers exposed
- But still the largest by far database of experience in the world!

*The FDA Reviewers' Helper --- **eDISH**  
--- an analytical tool, software program*

*(**e**valuation of **D**rug-**I**nduced **S**erious **H**epatotoxicity)*

*... to find quickly the “needles in the haystack” (rare subjects of special interest), out of large controlled clinical studies ... the few patients or subjects who need to be looked at more closely to determine if the case is clinically serious (disabling, hospitalized) or worse, AND probably caused by the drug*

# “eDISH”



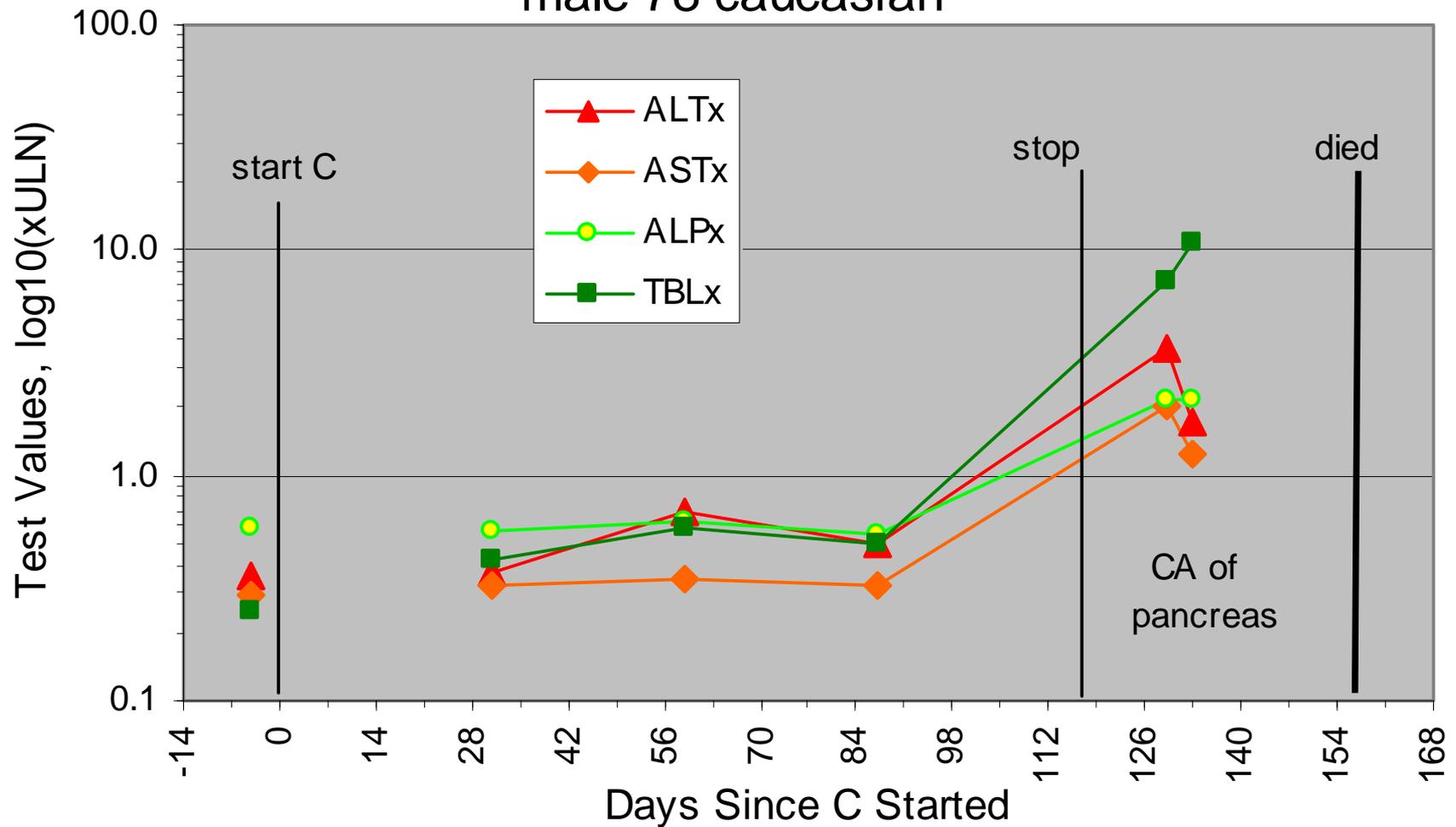
Treatment "C"

ID: 8675

# Time Course of Liver Tests

C

male 78 caucasian



Subject #:8675, treatment: C, 78 yrs, white

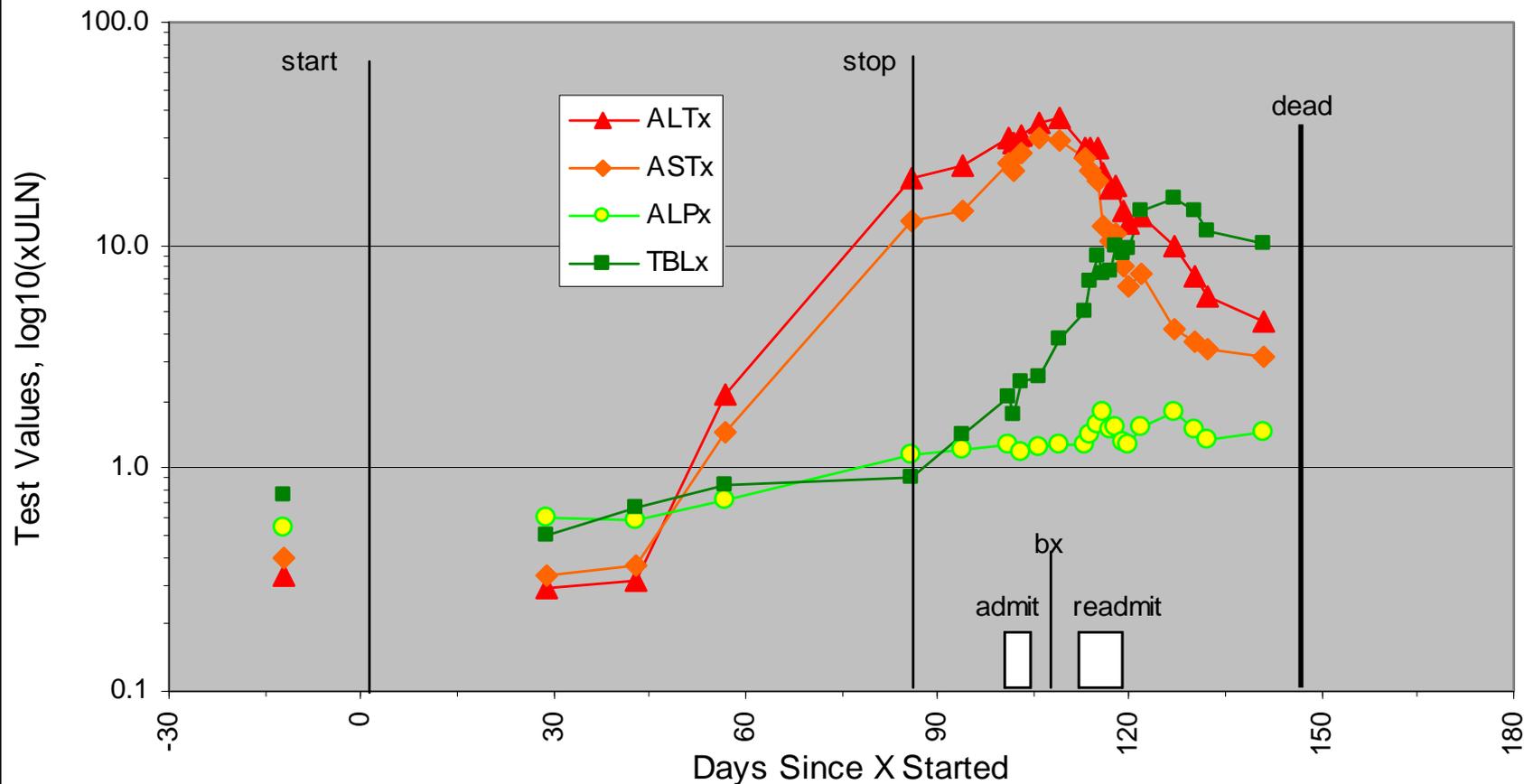
## Narrative:

78-year-old white male, history of cholecystectomy, atrial fibrillation, hypertension, hyperlipidemia, coronary heart disease, congestive failure. Taking digoxin, pravastatin. Started Coumadin 13 Nov 2001, all tests (ALT, AST, ALP, TBL) normal before and for 3 months, but TBL, ALP and slight transaminase elevations noted March 2002. Stopped Coumadin 20 March. Abdominal mass found on CT, common bile duct occluded by tumor; bx = **pancreatic carcinoma**, not considered resectable. Patient died in hospice on 19 April 2002.  
*.... this was not a Hy's case, not caused by the drug.*

ID: 7259

# Time Course of Test Values

male 80, caucasian



# eDISH

*In addition to the x-y log-log plot of peak ALT and TBL values for each person in the study, you then also need*

The time course of all liver tests (ALT, AST, ALP, TBL) for patients or subjects of interest, and

- The clinical narrative, for clues to probable cause and severity of the liver dysfunction; differential diagnosis and should be written by a physician
- Try to determine the probable cause! Treat the cause if possible; if drug-induced, stop the drug.

# Randomized Clinical Trials

- *Benefits*
  - Finding one or more true  $H_0$ 's case alerts to possible serious DILI in larger future exposure population post-marketing
- *Limitations*
  - Selected population sample for inclusion in study
  - Insufficient powering for rare serious DILI events
  - Short duration of treatment may limit risk of seeing DILI
  - Isolated ALT increases not predictive of serious DILI

# ***DILI Risk***

## ***Questions with Regulatory Impact***

- Does a drug cause clinically significant DILI in the target treatment population?
- What is the clinical signature of injury associated with the drug?
- What ranges of dose & duration of exposure are associated with increased risk?
- What are the critical patient susceptibility factors?
- What incidences of mild & severe liver injury can be predicted in a large treatment population?

# ***When Should We Ask These Questions?***

**At all phases of the drug's life cycle!**

- Preclinical, before human exposure
- Clinical trials, leading to approval
- Post-marketing, after approval

# People Are All Different in Their Responses to Drugs

- No detected injury ('tolerators') - does not preclude micro-adaptive changes in liver cells
- Mild (transient & selective) injury ('adaptors') reflecting liver cell change followed by return to normal even if drug continued
- Clinically significant injury ('susceptibles') may be reversible when drug is withdrawn

# Pattern and Extent of DILI

## *Patient 'Susceptibility' Factors*

- Pre-existing conditions or diseases
- Age & Gender
- Nutritional status
- Alcohol (chronic vs acute)
- Concomitant drugs
- Genetic variants
- Multiple DILI phenotypes

# Pattern and Extent of DILI

## *Patient 'Susceptibility' Factors*

There are no “idiosyncratic drugs,” only idiosyncratic recipients (whether people or animals)!

***(idio = one's self + syn = together + crasy = mixing;***

*A person's unique particular mixing together of inherited traits and life experiences that may make his/her responses different than that of most others*

# Assessment of DILI Risk

***--- ask and find out:***

1. How many? population frequency
2. How much? severity of liver dysfunction
3. How soon? rapidity of onset, progression
4. How likely? probability of drug causation

# CIOMS Diagnostic Scale (*RUCAM*)

## *Roussel-Uclaf Causality Assessment Method\**

<u><i>Individual Criteria</i></u>	<u><i>Range of Scores</i></u>
Time from start of Rx until event	+1 to +2
Time from stop of Rx until event	0 to +1
Course after stop of Rx	-2 to +3
Age	0 to +1
Alcohol/Pregnancy	0 to +1
Concomitant Rx	-3 to 0
Non drug-related causes	-3 to +2
Previous drug information	0 to +2
Dechallenge/Rechallenge	-2 to +3

### *Causality Assessment: Total Scores*

If 8-10: highly probable; 6 or 7, probable; 3-5, possible; 1 or 2, unlikely.

\*Danan & Benichou, J. Clin. Epidemiol.; 1993

# The NIH DILI Network\* (DILIN)



\*Sponsored by NIDDK  
<http://dilin.dcri.duke.edu>

# Registries

## Geographically/academically defined site-specific networks of inpatient/outpatient referral systems

- DILIN (US DILI); RRHSS (Spain DILI), SADRAC (Sweden DILI)
- ALFSG (US ALF network)
- UNOS (US liver transplant network)
- Vigibase (Europe)

### • **Benefits**

- Registries for serious outcomes both in US & Europe
- Structured clinical assessment of all patients referred for evaluation
- Useful sampling of 'what's out there'

### • **Limitations**

- Severe under-reporting
- Poor content quality of reports

# DILI Guidance (July 2009)

## Evaluation & Management Steps in Clinical Trials

- characterization of baseline liver conditions/diseases
- efficient detection of acute liver injury (early symptoms, systematic serum lab tests); confirmation with repeat testing
- observation & workup of patients with liver injury
- guideline study *stop rules*
  - ALT/AST > 8x ULN or ALT/AST remains > 5x ULN over 2 wks
  - ALT/AST > 3x ULN & T Bili > 2x ULN or INR > 1.5
  - ALT/AST > 3x ULN with symptoms (e.g. fatigue, N&V, RUQ pain, fever, rash) or eosinophilia
  - *rechallenge* generally should be avoided with ALT/AST > 5X ULN unless no other good therapeutic options, informed consent encouraged

# Drug Life-Cycle Data Streams

## *DILI Risk Assessment* – Needs Improvement

- Randomized clinical trials – best data; too small/short
- AERS reports – usually inadequate data given
- Published case reports – spotty quality
- DILI in registries – often aimed at cost control
- Observational cohort studies – limited value
- Case-control studies – need confirmation

# Summary

- Individual idiosyncratic susceptibility factors determine if subjects or patients exposed to a new drug will be '*tolerators*', '*adaptors*' or '*susceptibles*'
- In pre-approval clinical studies, milder injury may be important especially if function disturbed
- Post-market DILI risk assessment is more difficult to evaluate for severity and cause, mainly because of poor information, as well as under-reporting
- Predictive biomarkers of DILI that identify *susceptible patients* are needed but do not yet exist

# DILI Best Practices

- We all know there's a problem,  
– *but what should we do about it?*
- but haven't been able to make ourselves well understood.  
– *we have found the enemy -- it's us*
- We need to embrace the problem;  
– *in fact, kiss it – keep it simple, stupid.*

# Concern for Possible DILI

- “Hy’s law” was derived from Dr. Hyman J. Zimmerman’s repeated clinical observation that **drug-induced hepatocellular jaundice** is a serious lesion, with substantial mortality
  - It recognizes that hepatocellular (not biliary) injury sufficiently extensive to cause jaundice (whole liver dysfunction, reduced ability to clear plasma bilirubin) is an ominous indicator IF caused by a drug
- Definition of Hy’s law:
  - It CANNOT be defined just by serum chemistry values of ALT and BILI, but requires clinical investigation as to the possible causes, such as viral hepatitis, liver diseases drugs or chemicals, that must be ruled out before concluding it was drug-induced
  - The term “biochemical Hy’s Law” is wrong and should not be used. It is better to say “alert indicators” for probable drug causation of serious dysfunction (requires more clinical information for medical diagnosis of the most likely cause), in cases showing both {ALT >3xULN & BILI >2xULN}, conservatively low threshold values

# How should liver test elevations be handled?

- Sponsors of studies should make sure that their investigators know what to do, and report cases immediately
- They should confirm abnormalities promptly, in local laboratory as needed
- If confirmed, interrupt drug administration and follow ALT, AST, ALP, BILI serially and closely
- Serum enzyme activities do not measure liver functions; BILI and INR do
- Investigate clinically for probable or most likely cause
- Rule out as more likely causes: acute viral hepatitis; autoimmune/alcoholic hepatitis; other liver diseases; other drugs/chemicals, dietary supplements
- Liver biopsy, scans are rarely diagnostic; no pathognomonic test for DILI
- Request consultative help if needed to diagnose most likely cause
- Follow subject's course until resolution; record and report findings

# Questions about DILI?

- E-mail: [iana.pauls@fda.hhs.gov](mailto:iana.pauls@fda.hhs.gov)  
[john.senior@fda.hhs.gov](mailto:john.senior@fda.hhs.gov)
- <http://www.FDA.gov> enter “liver toxicity”
- *March 20-21, 2013 Annual Meeting, co-sponsored by FDA/PhRMA, C-Path and AASLD*