Sweet and Sour DILI Keynotes

John R. Senior, M.D.

Office of Pharmacovigilance & Epidemiology
Office of Surveillance & Epidemiology
Center for Drug Evaluation & Research
Food and Drug Administration
We have had the sweet smell of success a few times . .

1) Reaching FDA/CDER/OND reviewers 1999 ---

2) Secondarily reaching industry sponsors of NDAs;

3) Participation by industry in annual DILI meetings;

4) Reducing approvals of drugs causing serious DILI;

5) Development of eDISH, based on Hy’s Law.
...but also the sour taste of misunderstanding of what we tried to make clear and have failed to do:

1) Misunderstanding of Hy’s Law as simple elevations of serum ALT and total bilirubin concentration with no probable likelihood of causation by drug;

2) Misunderstanding eDISH first step (x-y, log-log plot, right upper quadrant) as diagnostic of Hy’s Law, as in JReview.
Will say a few words about each of the sweet and sour items in hope of generating discussion, understanding and even consensus of at least this audience in presentations and debates that follow.

One aim is to consider revision of the 2009 DILI Guidance to say it better, more clearly.

Another to write eDISH2 as free public software program that everybody will use to analyze their own confidential data.

... nobody said it was easy; it isn’t.
The first DILI conference was for CDER reviewers and attracted 325 to the April 1999 meeting at Shady Grove campus (University of Maryland)… and a rerun by Bob Temple and me for 75 more in November.

Industry then asked to be and was included in 2001, annually since 2003.

NDA quality improved so withdrawals for DILI of approved drugs stopped.

Everybody won: patients not harmed; review time was shortened, reviewers got better quality reviews including data on liver safety of new drugs.
How to clear up the misunderstandings?.

They seemed to begin by word-of-mouth transmission from reviewers who were at the 1999 first meeting to others who weren’t, and to non-medical people without experience in the process or need for differential diagnosis.

Hy Zimmerman was a gastroenterologist, hepatologist, and finally specialized in drug-induced liver disease. He saw thousand of patients with various forms of DILI, and alone wrote two editions of his classic text, cited almost 4000 papers, read them all, had copies of them all. He said and wrote “drug-induced hepatocellular jaundice is a serious lesion, with 10-50% mortality.”
We need to think about the larger issues of drug safety to find better ways to assure it both to the patients who take the drugs and to their prescribing physicians. Because of the rarity of serious drug hepatotoxicity it is not reasonable to expect that large enough trials be done for long enough to provide safety compared to the efficacy findings.

Reliance on voluntary reporting of adverse events after approval and marketing of a new drug is a failed concept. In the real world, doctors just don’t report, and the required reports forwarded by industry lack sufficient information to draw any valid conclusions about causality, incidence, etc.