Biosketch

Dr. Robert Temple was recently appointed Deputy Center Director for Clinical Science of FDA’s Center for Drug Evaluation and Research and is also Acting Director of the Office of Drug Evaluation I (ODE-I). He has served in this capacity since the office's establishment in 1995. Dr. Temple received his medical degree from the New York University School of Medicine in 1967. In 1972 he joined CDER as a review Medical Officer in the Division of Metabolic and Endocrine Drug Products. He later moved into the position of Director of the Division of Cardio-Renal Drug Products. In his current position, Dr. Temple oversees ODE-1 which is responsible for the regulation of cardio-renal, neuropharmacologic, and psychopharmacologic drug products. Dr. Temple has a long-standing interest in the design and conduct of clinical trials and has written extensively on this subject, especially on choice of control group in clinical trials, evaluation of active control trials, trials to evaluate dose-response, and trials using “enrichment” designs.

Abstract 2017 II-7: Need for Consideration of Issues for Guidance Revision

FDA’s liver injury guidance describes how to detect and anticipate potential for serious hepatocellular injury and has helped us avoid major toxins (ximelagatran, tasosartan, dilevalol, lumiracoxib) and could perhaps have also avoided bromfenac and troglitazone. All of these drugs met “Hy’s Law” criteria: increased rates of aminotransferase elevation probably covered by the drug and a few cases of elevated bilirubin. Thus, a “pure” hepatocellular injury large enough to raise bilirubin indicates substantial liver injury (maybe more than half the liver damaged).

But as guidance makes clear, Hy’s Law is not met if there is evidence of obstruction (elevated AP) because elevated bilirubin no longer reflects massive liver necrosis. The guidance is therefore not very helpful in detecting potential massive injury when there is either drug-induced obstruction or concomitant liver injury with an obstructive component. How to assess potential for major injury in these settings needs further evaluation.

**Aprile: ask Bob to consider this slight revision,**

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But as guidance makes clear, Hy’s Law is not met **confounded** if there is evidence of obstruction (elevated AP) because elevated bilirubin no longer reflects massive liver necrosis. The guidance is therefore not very helpful in detecting potential massive injury when there is either drug-induced obstruction or concomitant liver injury with an obstructive component. How to assess potential for major injury in these settings needs further evaluation.


--- as the Guidance states:

“Briefly, Hy’s Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.”