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## **Biosketch**

Dr. Poonam Mishra is the Deputy Director for Safety in the Division of Antiviral Products at the Food and Drug Administration (Center for Drug Evaluation and Research). Dr. Mishra joined FDA in 2008 as a Medical Officer in the Division of Antiviral Products where she has been involved in the review of direct-acting antiviral agents for the treatment of chronic hepatitis C. Prior to joining FDA, Dr. Mishra completed her fellowship training in General and Transplant Hepatology at the University of Chicago Medical Center. Dr. Mishra received her Master of Public Health degree from Johns Hopkins Bloomberg School of Public Health.

## **Abstract: Recognizing, Assessing and Managing Acute DILI in HCVD – FDA Challenges**

Diagnosis of drug-induced liver injury (DILI) remains a major diagnostic challenge in the absence of specific diagnostic biomarkers. Moreover, the clinical presentation is heterogeneous and can mimic any form of hepatobiliary disease, from non-specific changes in liver enzymes to fatal hepatic necrosis.

Traditionally, Hy's Law [defined as ALT > 3x ULN and TB > 2x ULN without initial findings of cholestasis (ALP < 2xULN) and no evidence of another cause] is used by FDA to identify drugs potentially capable of causing severe liver injury. Application of Hy's law in the trial population of chronic hepatitis C (CHC) patients with pre-existing liver disease is challenging as these patients often have elevated liver enzymes at baseline. Further, patients with advanced liver disease such as decompensated cirrhosis may have elevated bilirubin values at baseline.

Hence, which criteria should be used for identification and evaluation of DILI in clinical trials of drugs used to treat CHC remain a regulatory challenge. Change in laboratory values relative to "ULN" is not helpful in patients with elevated liver enzymes at baseline. Moreover, the "ULN" values do not reflect the changes in a given patient relative to their pre-exposure status. If we use a patient's own baseline values, how do we define a "baseline value"? How many time-points should we look at?

Treatment of CHC with DAAs results in a decline in viral load which usually is associated with declines or normalization of liver enzymes. Should we use postbaseline on-treatment nadir value as a comparator to identify any abnormal trends in liver enzymes? Any elevations after the nadir values are reached on treatment may potentially indicate a drug-associated effect once a viral breakthrough has been ruled out.

We need to have pre-specified criteria prior to initiation of trials. These criteria will differ based on the stage of the disease such as patients with compensated liver disease compared to those with decompensated liver disease or those who are liver transplant recipients. Discerning drug toxicity from natural progression of liver disease in settings of pre-existing advanced liver disease remains a challenge for clinical practitioners and regulators.