Biosketch:

Rajanikanth (Raj) Madabushi, Ph.D., is a Team Lead for Guidance and Policy Team in the Office of Clinical Pharmacology, Center for Drug Evaluation and Research, FDA, Silver Springs, MD. Dr. Madabushi received his Ph.D. degree in Pharmaceutical Sciences from Birla Institute of Technology and Sciences (BITS), Pilani, India. Following his Ph.D., he did a post-doctoral fellowship with Prof. Hartmut Derendorf at University of Florida, Gainesville. He joined the Pharmacometrics Group at FDA in 2005. As a pharmacometrics reviewer, he was predominantly involved in the application of quantitative clinical pharmacology approaches for regulatory decision making and addressing various drug development issues in the areas of Cardio-Renal, Hematology and Endocrinology drug products. In 2009, he became the Team Leader in the Division of Clinical Pharmacology I, specifically focusing the area of Cardiovascular, Renal and Hematology products. In 2016, Dr. Madabushi became the Team Lead for the newly formed Guidance and Policy Team in the Immediate Office of the Office of Clinical Pharmacology. Since then, he has been involved in the drug development, regulation, research and policy from a clinical pharmacology perspective.

Abstract I-2: DILI: Clinical pharmacology considerations for risk assessment

Drug induced liver injury (DILI) is one of the leading causes for drug withdrawal from the market. Though uncommon, DILI is the leading cause of acute liver failure and a major reason for liver transplantation. It is generally hard to predict DILI due to its
idiosyncratic nature. However, following oral administration, the liver represents the major target organ in the metabolism and detoxification of drugs and toxins and plays a crucial role in determining the toxicity of drugs. Drugs whose metabolism is predominantly (> 50%) hepatic are more frequently associated with adverse hepatic events compared to drugs that do not undergo significant hepatic metabolism. The CYP450 enzymes and the enzymes involved in Phase II reactions are functionally important in the formation of reactive metabolites that may be involved in the pathogenesis of DILI. Further, the role of hepatic transporter proteins in DILI cannot be understated. The inhibition of these transporters by drugs or their metabolites can lead to intracellular accumulation of harmful cholephilic compounds and subsequent cholestatic liver injury. The genetic variation in the metabolizing enzymes and transporter proteins could further explain susceptibility of some individuals to DILI. The characterization of the relationship between exposure and markers of liver injury such as ALT especially in the latter stages of drug development could be very valuable towards understanding of the risk for DILI. The emergence of physiological based pharmacokinetic modeling, presents opportunities for better characterization of exposure in the liver cells and inform the risk assessment. A few illustrative examples will be discussed to highlight the various clinical pharmacology considerations. While prediction of DILI remains challenging, clinical pharmacology assessments represent one of the key tools towards a more informed benefit-risk assessment.

200 words