Predicting hepatotoxic potential of new drug candidates in patients using DILIsym

Brett A. HOWELL
The Hamner-University of North Carolina Institute for Drug Safety Sciences, USA

A mechanistic, multi-scale, mathematical model is being developed through the DILI-sim Initiative to assist in the safety characterization of compounds in clinical development. The model is made available in the form of DILIsym® software. The primary goals for DILIsym® include understanding how in vitro toxicity assay results translate to in vivo scenarios, the relevance of pre-clinical results for humans, and how biomarker results translate to patient safety. The primary mechanistic areas of focus within the model include reactive oxygen/nitrogen species, mitochondrial dysfunction, steatosis (lipotoxicity), innate immunity, and bile acid homeostasis and disruption. Case studies will be presented demonstrating how drug metabolism and disposition intersect with hepatotoxicity, and how utilizing mechanistic modeling approaches incorporating this information allows for a better understanding of safety risks. Key areas of focus will include clinical trial optimization, novel biomarkers and their relevance in the clinical trial setting, and the use of modeling and simulation methods to provide context for biomarker signatures that are difficult to interpret.