The Southern California Drug Metabolism Discussion Group presents:

Leveraging ADME Data In Metabolites In Safety Testing (MIST)

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Considerable attention has been recently focused on the potential role of human drug metabolites in drug safety, and how to provide a risk assessment for these molecules using preclinical safety models. However, an analysis of drugs withdrawn from the market over the past 20+ years due to unacceptable safety issues suggests that the instances of the "toxic metabolite" as culprit are exaggerated. Even in those instances when it was likely that a metabolite was involved in toxicity, it was the case that the metabolite was generated in abundance in animal species used in safety evaluations of the parent drug. Data from standard definitive ADME studies that utilize radiolabelled drugs can be leveraged to establish the types of metabolite exposures seen in humans and animals. However, the manner in which these data are gathered lead scientists to make assignments regarding which metabolites are "major" based on the percentage that the metabolite comprises of total circulating drug-related material or percentage of dose in excreta. This thinking regarding metabolites as "percentages of the whole" has formed the basis of proposed decision criteria regarding the importance of metabolites in both a PhRMA white paper on the topic as well as draft guidance from the US FDA (*Toxicol. Appl. Pharmacol.* 182: 188, 2002 and http://www.fda.gov/cder/guidance/6366dft.htm). However, it is imperative that such percentage-based data be converted to absolute quantities/concentrations prior to making decisions regarding whether a metabolite needs to undergo additional safety evaluation. This would ensure that metabolites across drugs of varying doses and across species that received varying doses of an individual drug are compared appropriately and is consistent with the well-accepted notion that "The dose makes the poison" (Paracelsus). These concepts will be discussed and a proposal put forth as to how to handle the issue of drug Metabolites in Safety Testing (MIST).

Wednesday, April 18, 2007

5:00 p.m. Registration and Buffet Dinner

7:00 p.m. Presentation Begins

Salk Institute, Frederic de Hoffmann Auditorium

10010 North Torrey Pines Road

Price $15 Advance Registration, $15 At the Door (includes buffet dinner and soft drinks / beer / wine)

The SCDMDG was established in 2003 as a forum for Southern California scientists working in drug metabolism in both academic and industrial settings to meet and discuss issues and share information for the public good.

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