

ADME Special Interest Group  
SBS St. Louis, MO  
April, 2008

The ADME SIG changed facilitators for Pauline Gee to Charles Crespi and session format from one focused on break out sessions around a specific topic to seminar-based facilitated discussion around an ADME topic of interest. There were about 30 in attendance for the session.

This year, Dr. Larry Wienkers of Amgen, Seattle, WA, gave a presentation entitled “P450 DDI assays in drug discovery, exploring experimental factors which influence data relevance and robustness.” In this presentation, Dr. Wienkers provided a background as to why the primary concern for DDI is inhibition of cytochrome P450 and the FDA guidance in the area and how this should influence design and execution of P450 inhibition assays. Other parameters which affect assay results were discussed. These included, properties of an appropriate P450 probe substrate, choice of solvent for delivery of the potential inhibitor, choice of enzyme source (cDNA-expressed or liver microsomes) and the impact of the P450’s electron transport partners, the effects of buffer components, experimental design for measuring  $IC_{50}$  and  $K_i$  with the hazards of quantitative extrapolations from sparse data sets and “atypical” effects such as heterotropic activation.

Dr. Wienkers then moved on to discuss how to use these data to support lead optimization and the appropriateness of specific “go”/“no go” cut off values and performing SAR to reduce inhibition potency. Dr. Wienkers closed with a reminder that while we typically think of enzymes as being efficient and selective, the drug metabolizing P450s are exactly the opposite, inefficient and non-selective. (Mammals compensate for the inefficiency of the enzyme by expressing them at high levels.) The inefficient and non-selective nature of these enzymes provides a context to unmask the atypical enzyme kinetic observations which are too typical with P450s.

Throughout Dr. Wienkers presentation, there were frequent pauses for questions and discussion from the audience. Specific experiences were shared from both a large pharma and a biotech perspective.

The ADME SIG closed with a discussion of topics for our session next year. Three topics were elevated: methods for measurement of irreversible P450 inhibition (an area of increasing regulatory concern), methods and approaches for measuring P450 induction in a high throughput environment (also an area of increasing regulatory concern), and stem cells as models in ADME/Tox. Input of these and other topics are most welcome. Please contact the ADME SIG facilitator, Charles L. Crespi, BD Biosciences, [Charles.Crespi@BD.com](mailto:Charles.Crespi@BD.com).