Evaluation of ADMET Drug Properties in Drug Discovery and Development

Course Scope and Description

The course will describe scientific concepts and practice of ADME and toxicology studies in drug development, including preclinical in vitro and in vivo studies, clinical studies, IND and NDA submissions, and analytical chemistry. The content of this course will assist pharmaceutical, biotechnology, and CRO researchers and managers in understanding the requirements for a well-designed and successful drug development program, conducted in accordance with current best practices and in compliance with regulatory guidelines. Various disciplines including safety, toxicology, in vitro / in vivo metabolism, drug delivery, bioanalysis, animal and human pharmacokinetics, protein binding, mass balance, tissue distribution, metabolite isolation and identification, and toxicokinetic support, will be discussed. Study designs and possible interpretations of results and representative case studies will be presented. The generation of study protocols, study reports and data summaries for the purpose of submission to regulatory authorities will be delineated.

This course is specifically designed for personnel in the pharmaceutical and biotechnology industries and contract research organizations (CROs) who need to understand the state-of-the art for the evaluation ADME-tox drug properties: Absorption, distribution, drug metabolism (DM), elimination, pharmacokinetics/toxicokinetics (PK/TK) and toxicology during the discovery, lead-optimization, IND- and NDA-enabling drug development processes.

Participants should have some knowledge of these processes and desire to learn more about how ADME, bioanalysis, PK/TK, and DM studies are designed, conducted, and interpreted in order to characterize the fate of a drug candidate. Nonclinical and clinical scientists, project managers, and study team leaders at pharmaceutical companies and related industries will gain a detailed understanding of the types of safety/toxicology, ADME, bioanalysis, PK/TK, and DM research studies required to support submissions to regulatory authorities.

Evaluation of ADMET Drug Properties in Drug Development

Session I: ADMET Scientific Concepts (Albert P. Li)

1. Overview: ADMET and drug development
2. Principles of drug absorption
3. Principles of drug metabolism and distribution
4. Principles of toxicology

Session II: In Vitro Evaluation of ADMET Drug Properties (Albert P. Li)

1. Overview: Why in vitro?
2. Intestinal absorption
3. Metabolic stability
4. Drug-drug interactions
5. Drug Toxicity
6. Class exercises

Session III: In Vivo PK/PD/TK Studies (Souzan Yanni)

1. Overview: In Vivo PK/PD/TK and drug development
2. Regulatory guidelines for preclinical PK/PD/TK studies.
3. Experimental design for preclinical and clinical PK/PD/TK studies
4. Technologies and approaches to select animal model and to predict mechanism of drug disposition
5. Integration of non-clinical and preclinical data to aid design of clinical studies
6. Case studies: Assessment of the mechanism of drug disposition and safety based on preclinical and clinical data

Session IV: Clinical Studies (Souzan Yanni)

1. Overview: Objectives of Phase I, II, III and IV clinical studies
2. Clinical study design, enrollment, sites and documentation
3. Clinical safety studies: Adverse events vs. adverse drug reactions
4. Clinical PK, pharmacology, drug-drug interaction studies
5. Studies in special populations
6. Statistical analysis and documentation
7. Examples of success and failure in clinical drug development

Session V: Regulatory Submission (Souzan Yanni)

1. Overview: IND and NDA submissions
2. FDA guidelines on IND and NDA submissions
3. Studies required for IND and NDA submissions for oncology, HIV, cardiovascular indications
4. Timelines and requirements
5. On-label vs. off-label drug use
6. Class exercises

Session VI: Bioanalytical Chemistry (David Kwok)

1. Overview: Bioanalytical Assay Method Development and Validation
2. Review of current bioanalytical regulatory guidance (US FDA and EMEA)
3. Bioanalytical assay development in support of in vitro and in vivo studies (LC/MS/MS, GC/MS and ELISA)
4. Case studies on LC/MS/MS assay pitfalls and "silent errors"
5. Future prospects: Dried-blood spot assay supporting preclinical and clinical programs

Session VII: Plasma Protein Binding Assay

1. Overview: Pharmacokinetic fundamentals and applications:
2. Determination of plasma free fraction, plasma/blood fraction, and protein-drug conjugate binding affinity
3. A review of methodologies - ultrafiltration and equilibrium dialysis using unlabeled drug or ^{14}C-labeled drug
4. LC/MS/MS or liquid scintillation counting assays of serum/plasma ultrafiltrate or dialysate
5. Validation of ultrafiltration and equilibrium dialysis assays

Session VIII: Metabolite Profile Studies

1. Overview: Principles and approaches for metabolite structure elucidation and identification
2. Metabolite profile study design with unlabeled and 14C-labeled drugs
3. Metabolite profile data - strategy to address MIST guidance 2008
4. Assays to provide evidence on reactivity metabolites - GSH-trapping and covalent binding, reversibility in covalent binding

Session IX: Mass Balance Evaluation

1. Overview: Why mass balance?
2. Mass balance excretion study objective and design with labeled and unlabeled drugs
3. Design of drug and metabolite mass balance study in preclinical species - whole body autoradiography (QWBA), combustion assay, and liquid scintillation assay
4. Mechanistic study on bile excretion and hepatic first-pass metabolism

Session X: Class Discussion: ADMET and Drug Development

End of Course

For more information contact:

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