DMPK: Experimentation & Data Interpretation

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Prerequisite: Entry-level scientists with hands on experience in LC/MS as well as advanced students who wish to learn more about mass spectrometry applications in drug metabolism, pharmacokinetics (DMPK) and bioanalysis. The course is a unique opportunity for scientists already in the pharma, biotech, and other industries to broaden or enhance their expertise and knowledge. Due to the highly interactive format, managers and project leaders also may benefit from discussions on decision making, analytical technology, and emerging applications in DMPK and related topics.

Course materials: Electronic copies of PowerPoint presentations and a reference book (M. Lee and M. Zhu. Mass Spectrometry in Basic Short course: DMPK: Experimentation & Data Interpretation Drug Metabolism and Disposition: Principles and Applications. John Wiley & Sons) will be provided.

Course Overview

Mass spectrometry has become the dominant analytical tool throughout the DMPK and bioanalytical research areas in drug discovery and development continuum. This short course will provide thesis on mass spectrometry in DMPK and bioanalysis in support of drug discovery, development and regulatory registration. The course will use case studies to focus on the "why" and "how" knowledge base with regard to the use of mass spectrometry to analyze small molecule drugs, biologics, and new drug modalities such as antibody-drug conjugates (ADCs) and oligonucleotides .

Contents will include an introduction to the concepts / principles of DMPK, an overview of drug discovery / development processes, and common practices in DMPK studies. Current mass spectrometry technologies applied in ADME (Absorption, Distribution, Metabolism and Excretion) screening in lead optimization, drug quantification in PK studies, drug metabolite identification in animals and humans, as well as GLP bioanalysis quantification in clinical and toxicology studies will be discussed along with updated industry practices for experimental design, data interpretation, and data reporting. Case studies to solve common DMPK and bioanalytical issues will be given to reinforce concepts and analysis techniques learned in class.

MAJOR TOPICS COVERED IN THIS COURSE

• **Basic DMPK concepts applied in pharmaceutical research**: This portion will include basic principles of drug metabolism and pharmacokinetics, introduction of PK concepts and parameters common metabolic reactions, metabolizing enzymes, drug-interaction and ADME processes.

• **Role of DMPK in drug discovery and development**: This portion will provide an overview of various types of drug metabolism and bioanalytical studies throughout the lifetime of a drug candidate.

• **In vitro ADME screening with high-throughput LC/MS.** This portion will cover the rationale and conduct of early in vitro ADME screening to optimize drug-like properties for lead optimization. Commonly used software, automation and high-throughput LC/MS technologies to facilitate these ADME screening workflows will be discussed.

• **Drug metabolite profiling and identification (MetID)**: This portion will cover concepts, technologies and practices of MetID using LC-HRMS. Common LC-HRMS based data acquisition and data mining techniques for MetID and typical MetID experiments in drug discovery and development will be discussed in detailed.

MAJOR TOPICS COVERED IN THIS COURSE

• **In vitro evaluation of drug-drug interaction (DDI) potentials:** this portion will cover the principals and in vitro methodologies to assess DDI potentials including CYP inhibition and induction, metabolizing enzyme phenotyping, transporter substrate analysis and inhibition.

• **Quantitative analysis of drug candidates and their metabolites in vitro and in vivo by LC/MS:** This portion will cover science, technique, regulation and compliance of bioanalysis, sample preparation, and LC/MS/MS technologies for quantification in preclinical and clinical studies. Quantification of protein and conjugate drugs by LC/MS also will be discussed. Focus will be placed on LC and MS technology and technique.

• **Application of LC/MS technologies in conducting special drug metabolism and ADME studies.** This position will cover radiolabeled ADME studies in support drug development, including concept, assay, analytical method and case studies. In addition, strategy and method for studying ADME of ADCs and untargeted metabolite profiling of oligonucleosides and peptides will be discussed.

• **Applications of LC/MS in analysis of biologics and biomarkers**: This portion will cover recent applications of LC/MS in quantification of protein therapeutics and biomarkers as well as study of biotransformation / disposition of antibody-drug conjugates for characterization of ADME / PK of biologics and PK/PD of small molecule drugs.

Preliminary course schedule

Day One (9:00 – 4:30 with lunch 12:00 to 1:00 and coffee breaks 10:15 to 10:45 and 2:30 to 3:00)

1 - Introduction (20 min)
1.1. DMPK Experimentation and Data Interpretation– Course overview (10 min)
1.2. DMPK Experimentation and Data Interpretation – Feedback on what students want to learn (10 min)

2 - DMPK in drug discovery/development (1 hr 30 min)
2.1 Basic pharmacokinetics and applications (30 min) (NW)
2.2 Basics of drug metabolism reaction, enzymes and experimental models (30 min) (MZ)
2.3 Basics of drug-drug interaction studies (30 min) (WS)

3 - Fundamentals of the use of LC/MS technology for DMPK (2 hr)
3.1 Overview of drug metabolism in drug discovery and development (30 min) (MZ)
3.2 High-throughput MS techniques for DMPK/bioanalysis (30 min) (WS)
3.3 Practices and technology of bioanalysis (30 min) (NW)
3.4 Drug metabolite profiling and identification (MetID) using LC-HRMS technologies (30 min) (MZ)

4 – Workflows / problem solving in DMPK to move drug candidates forward (1 hr 20 min)
4.1 In vitro ADME screening with LC/MS and automation (40 min) (WS)
4.2 Common MetID experiments in drug discovery and development (40 min) (MZ)

Preliminary course schedule

Day two (9:00 – 4:30 with lunch 12:00 to 1:00 and coffee breaks 10:15 to 10:45 and 2:30 to 3:00)

4 – Workflows / problem solving in DMPK to move drug candidates forward – continued (2 hr)
4.3 Regulated bioanalysis for toxicology and clinical studies (30 min) (NW)
4.4 Concept and practice of free fraction and protein binding measurement by LC/MS (30 min) (WS)
4.5 Radiolabeled ADME study in animals and human: concept, method and case study (30 min) (MZ)
4.6 In vitro methods to assess drug-drug interaction potentials (30 min) (WS)

5 - New Applications in PK, PD, and metabolism (2 hr 30 min)
5.1 LC/MS in biomarker analysis (30 min) (NW)
5.2 Analytical methods and strategy for studying ADME of ADCs (40 min) (MZ)
5.3 Acoustic ejection MS for DMPK applications (30 min) (WS)
5.4 Roles and LC-HRMS approaches of profiling oligonucleotide metabolites (40 min) (MZ)
5.5 LC-MS bioanalysis of biologics and new drug modalities (30 min) (NW)

6- Concluding remarks, last questions, and feedback (30 min)
The time devoted to each of the course topics will be customized to meet the stated needs of the students enrolled. A preliminary course schedule is given above.