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 discovery & development. The course is a unique opportunity for scientists already in the pharmaceutical, 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 Drug Metabolism and Disposition: Basic Principles and Applications. John Wiley & Sons, May, 2011) will be provided.

Course Overview

- Mass spectrometry has become the dominant tool throughout the drug discovery / development continuum. This short course will provide a thesis on mass spectrometry in drug metabolism, pharmacokinetics (DMPK), and pharmacodynamics (biomarker) in support of R&D and the registration process. The course will use case studies to focus on the "why" and "how" knowledge base with regard to the use of mass spectrometry to measure small molecule drugs, biologics, and their conjugates in the discovery and development phases. Contents will include an introduction to the concepts / principles of DMPK, an overview of drug discovery / development processes, regulatory submission requirements, and common practices in DMPK studies. Current mass spectrometry technologies applied in ADME 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. Practice sessions will be given to reinforce data analysis techniques learned in class.

MAJOR TOPICS COVERED IN THIS COURSE

- **Basic DMPK concepts applied in pharmaceutical research:** This portion will include principles of pharmacokinetics, introduction of First in Human Clearance and Volume of Distribution prediction, common metabolic reactions and metabolites and metabolizing enzymes and associated drug-drug interactions.
- **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 life time of a drug candidate.
- **ADME screening and characterization in lead optimization and clinical candidate selection:** This portion will cover LC/MS assays for in metabolic stability, CYP inhibition, induction and reaction phenotyping as well as in vitro absorption assays and transporter DDI studies. Balanced focus will be given on analysis techniques, workflows, and decision making.

MAJOR TOPICS COVERED IN THIS COURSE

- **Drug metabolite profiling and identification in drug discovery and development:** This portion will cover basic concepts of drug metabolite identification (Met ID) including LC/MS workflow and mass spectral interpretation. Typical Met ID experiments will be discussed in detailed such as metabolic soft-spot identification and reactive metabolite screening in drug discovery, and metabolite identification in humans in drug development. Focus will be given on applications of a variety of MS techniques to metabolite detection and characterization, including high-resolution MS and Q-trap instruments

MAJOR TOPICS COVERED IN THIS COURSE

- **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.
- **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 Course overview – importance of an interactive atmosphere (5 min) (ML)
- 1.2 Feedback on what students want to learn (15 min) (ML)
- **2. Basic concepts of drug metabolism and pharmacokinetics** (1 hr 10 min)
- 2.1 Overview of drug ADME process (20 min) (ML)
- 2.2 Basic pharmacokinetics and applications (25 min) (NW)
- 2.3 Basics of drug metabolism and experimental models (25 min) (MZ)
- **3. DMPK in drug discovery** (2 hr 20 min)
- 3.1 Overview of DMPK in drug discovery (15 min) (ML)
- 3.2 Overview of DMPK in drug development (15 min) (MZ)
- 3.3 In vitro assays, common practices and LC/MS approaches (45 min) (MH)
- 3.4 Metabolite identification strategy and mass spectral interpretation (25 min) (ML)
- 3.5 Common LC/MS techniques for metabolite identification (40 min) (MZ)
- 3.6 Animal PK studies; common practices and LC/MS approaches (30 min) (NW)
- **4. Workflows / problem solving in DMPK to move drug candidates forward** (1 hr 30 min)
- 4.1 Assessing causes of low bioavailibility using in vitro assays: how and what to do (50 min) (MH)
- 4.2 Practices and problem-solving in LC/MS bioanalysis (40 min) (NW)

✓ 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.

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** (40 min)
- 4.3 Use of LC/MS in addressing metabolite-related issues in drug discovery (40 min) (MZ)
- **5. New Applications in PK, PD, and metabolism** (2 hr 45 min)
- 5.1 Overview of new research areas in the pharmaceutical / biomedical sciences (30 min) (ML)
- 5.2. LC/MS Protein quantification with application in PK and biomarker analysis (45 min) (NW)
- 5.3. Introduction to targeted metabolomics and its application in small molecule central nervous system biomarkers (45 min) (MH)
- 5.4. Introduction to antibody-drug conjugates and its LC/MS analysis (45 min) (MZ)
- 6- Hot topics in new technology (1 hr 55 min)
- 6.1. Application of micro-flow and nano flow LC/MS for quantitation (20 min) (ML)
- 6.2. HRMS-based non-targeted analysis of xenobiotics: application to herbal medicines and beyond. (20 min) (MZ)
- 6.3. Bioanalytical considerations for biological and drug conjugates (20 min) (NW)
- 6.4. On-line SPE to automate sample clean up for drugs and biomarkers (20 min) (MH)
- 6.5. Hot topics at ASMS meeting (35 min) (a guided open discussion: ALL)
- **6. Concluding remarks, last questions, and feedback** (10 min)
- 6.1 Feedback: thorough course & instructor evaluation is crucial! (5 min) (MH)
- 6.2 Last course questions and a welcome to ongoing dialogue (5 min) (all)

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