TWO-DAY COURSE

02 Clinical Diagnostics: Translational Mass Spectrometry; LC-MS/MS Assay Development and Validation for Use in Clinical Diagnostic Testing

Instructors

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This course will cover aspects of mass spectrometric analysis as applied to clinical diagnostics. Rather than approach the use of diagnostic mass spectrometry from the ground-up, the course will focus on those components which are singular to the clinical diagnostics industry. Attendees will be provided with details and practical examples of laboratory operations in an environment which is regulated by the FDA Office of In Vitro Diagnostics (FDA-IVD), College of American Pathologists (CAP) and the Clinical Laboratory Improvement Act (CLIA).

The various phases of utilizing mass spectrometry in the clinical diagnostics setting will be discussed with emphasis on the components of development (innovating a new test), validation of a laboratory-developed test (LDT), implementation of new assays and operationally analyzing samples. Particular care will be taken to address the regulatory aspects of clinical diagnostics under the most up-to-date guidance with consideration given to those guidance documents which are in draft.

Following completion of this course, attendees will have been provided the detailed information required to translate discovery assays into a clinical measurement in support of diagnostic interpretation. As part of this short course, the instructors will provide attendees with practical, detailed examples and references for the following subsections as they pertain to clinical diagnostics analysis:

Method Development/Innovation

- **Calibration materials:** Sources, Analytical grade versus reference materials, Hierarchy of matrices for calibration materials, external proficiency programs
- **Multi-transition monitoring:** Explanation, acceptance criteria and solutions to single transition analysis
- **Enzyme kinetics (Proteins):** Peptide versus protein level control for calibration and internal standardization.
- **Pre-validation experimentation:** Precision/accuracy, specificity, selectivity, correlation, linearity, carry-over

Assay Validation

- **Additional stability experiments**: Shipping considerations, calibration materials longitudinally measured,
- **Using statistics in the diagnostics environment:** Deming regression, Passing-Bablock, McNemars Test, Reference interval generation
- **Specificity:** Transition ratio monitoring
- **Selectivity:** Matrix considerations, tube type comparison, Lipemia, icteria and hemolysis, concomitant medicines,
- **Ion suppression** (CAP Guidance CHM 18825 and CHM 18900)
- **Internal standard response cutoff** (CAP Guidance CHM 18850)
- **Documentation of validation of LDT's** (CAP Guidance COM 40200)
- **Assays that cannot feasibly meet CAP criteria**: Unstable molecules and hydrolysis controls for every analyte in drug of abuse testing

Implementation

- **Before the test launches:** Test procedures, training, training records, documentation

- **Laboratory Information Management Systems/Interfaces:** Data flow considerations
- **Mass spectrometry and electronic medical records:** How-to-guide and expectations

Operations

- **HIPAA:** In the mass spectrometry laboratory
- **Dealing with change**: Verification of materials, controls, calibration (EP Evaluator Protocols), column chromatographic characteristics (CAP Guidance CHM 16770), QC Lots, Standard Lots, New Guidance
- **Before each analysis:** System suitability tests (CAP Guidance CHM 16950)
- **Ensuring accuracy:** Proficiency samples (sampling policy, retention of samples, re-analysis)
- **Maintaining control**: Understanding quality control schemes for quantitative and qualitative analysis
- **Throughput:** Analyte and chromatographic multiplexing, automation
- **No proficiency program:** Assays for which proficiency testing samples are not available (CAP Guidance COM 01500)

Prerequisites: Attendees are expected to have a fundamental understanding of liquid chromatographic and mass spectrometric techniques (i.e. through attendance in previous ASMS short courses). Further, attendees that have practical experience validating and performing sample analysis in compliance with FDA bioanalytical guidance (May 2001) or previous experience with the requirements of clinical diagnostic testing will benefit from a foundation that will enable understanding of the different principles described within this course.