Liquid Chromatography–Mass Spectrometry Education for Clinical Laboratory Scientists

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KEYWORDS

• Liquid-chromatography–tandem mass spectrometry • Training • Competency

KEY POINTS

- Quantitative liquid chromatography–tandem mass spectrometry (LC-MS/MS) as used in diagnostic laboratories is highly complex and requires a theoretic knowledge base and hands-on expertise by bench technologists, managers, and directors to insure acceptable quality and productivity.
- Training for quantitative LC-MS/MS is not included or is covered only briefly in programs for clinical laboratory scientists and may or may not be addressed in clinical chemistry fellowship and pathology residency training programs. As a consequence, training for this subspecialty takes place primarily on the job, within the diagnostic laboratories performing the testing.
- This article stratifies and lists the competencies required for bench personnel, research and development scientists who develop and validate methods, laboratory managers, and directors as an aid toward designing training curricula and assessing trainees and staff.

INTRODUCTION AND BACKGROUND

The world of quantitative diagnostic mass spectrometry (MS) is evolving toward automation and greater ease of use. For diagnostic laboratories, that means migration from manual procedures in esoteric testing sections of the laboratory to automated,

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high-throughput core laboratory sections. The holy grail of diagnostic MS automation is regulatory-compliant quantitative assays (eg, Food and Drug Administration approved or Conformité Européene [CE] mark) on a fully automated liquid chromatography (LC)–tandem mass spectrometry (MS/MS) instrument. Such a system would have ease of use similar to automated clinical chemistry analyzers—random-access workflow, minimal down-time, 24/7 service and support, and validated and ready-to-use reagents and calibrators supplied by the vendor. These systems would not require specialized end-user skills for operation and would have sampling and software that permit integration to track systems along with ASTM/HL7 interfaces to laboratory information systems.

A parallel goal is that no trade-off will have been made between ease of use and the impressive sensitivity, selectivity, and precision that are possible with LC-MS/MS. At this time, at least 1 vendor has made significant progress toward these goals and is poised to ship quantitative LC-MS/MS instruments designed for operation in highly automated diagnostic core laboratories.

To clarify terms, this article uses *diagnostic laboratory* to define settings in which the sole purpose of laboratory testing is to report results to the medical record for patient care in a regulated environment. Because MS is widely used in clinical research and clinical trials as well as diagnostic laboratories, *clinical MS* is defined as the much broader and less regulated practice encompassing all those activities, of which *diagnostic laboratory MS* is a smaller subset.

Why has quantitative LC-MS/MS remained, until now, a specialized practice, widely used in commercial diagnostic reference laboratories but not feasible in many hospital laboratories? Primary barriers for hospital laboratories are the expertise required to develop and validate procedures[1,2] and the challenging finances associated with large capital expenses for initial instrument purchases. In stark contrast, use of qualitative MS in the diagnostic microbiology laboratory has been rapidly adopted by most hospitals, transforming routine practice. The value proposition of matrix-assisted laser desorption/ionization (MALDI)-time of flight (TOF) in the microbiology laboratory is well justified based on reduced time to identification and decrease in reagent costs.[3,4] Because qualitative MALDI-TOF MS for diagnostic microbiology is becoming the norm, the technique is being integrated into training programs at all levels. The other rapidly developing field in diagnostic MS is imaging. The differences between training for imaging MS versus for quantitative LC-MS/MS are profound. Avoiding detail to address the 2 subspecialties in 1 article does both a disservice. Therefore, this article selectively addresses training for quantitative diagnostic LC-MS/MS, only 1 of the areas in which MS has become important in laboratory medicine.

If automated LC-MS/MS is widely implemented in core laboratories, then basic LC and MS/MS theory will become a standard feature in training curricula, as for spectrophotometry and electrophoresis. Will the need for personnel in diagnostic laboratories with specialized hands-on LC-MS/MS training disappear? An analogy can be made to typesetting—once a highly skilled, multifunctional profession that was made obsolete by revolutions in printing technology.[5] The premise of this article is that routine production with quantitative laboratory developed tests (LDTs) using stand-alone, open LC-MS/MS instruments will remain financially viable for some time in diagnostic laboratories. Therefore, the extensive training needed for such practice is described in detail.

Diagnostic laboratories that perform quantitative LC-MS/MS testing now have tremendous variance in their extent of automation, throughput, and test workload. The authors believe more useful descriptors than these to distinguish between current versus new MS testing paradigms are the site of assay development/validation and whether the LC-MS/MS system is open or closed. Open instruments can be used

with assays from any source whereas closed systems are restricted to regulatory approved assays sold only by the instrument vendor. The traditional model of in-house test development/validation by the laboratory performing the assay on open LC-MS/MS systems are called LDT-open MS. The emerging system of regulatory-approved assays sold by in vitro diagnostic (IVD) companies for dedicated, closed systems are called IVD-closed MS. Laboratories performing Food and Drug Administration cleared or CE mark assays on open LC-MS/MS systems are considered in the LDT-open MS group.

This article describes training for LDT-open MS practice in sections defined first by function and secondarily by academic degree, licensure, and job title. Scientists with a bachelor of science degree and postbaccalaureate on-the-job training as well as physician-scientist laboratory directors with doctoral training in MS are successfully engaged in method development, validation, and troubleshooting for LDT-open MS laboratories. Because training and experience are so diverse in this field, desired competencies are focused on rather than academic qualifications and licensure.

TRAINING FOR BENCH PERSONNEL

Few training programs for diagnostic laboratory bench personnel in the United States include quantitative LC-MS/MS in their curriculum. An encouraging development is diagnostic MS coursework offered in a few academic clinical laboratory scientist (CLS) training programs, for example, Michigan State University and Virginia Commonwealth University. Short courses in quantitative diagnostic LDT-open MS are available online,[6] at scientific meetings,[7,8] and with a hands-on component[9] but are not included in the staff training budget of most diagnostic laboratories.

As a consequence, LDT-open MS diagnostic laboratories in North America expect to train all levels of personnel onsite. Although certification versus licensure has important distinctions, for the purposes of this article the terms are used interchangeably to indicate that a structured system for diagnostic laboratory personnel qualification has been defined by a regulatory body.

The bench tasks in an LDT-open MS laboratory are stratified by increasing skills and training:

1. Reagent and calibrator preparation
2. Sample preparation
3. Instrument operation (order of B and C may be reversed based on the level of automation)
4. Data analysis/review/reporting functions

Competencies recommended for these tasks are (assume appropriate active verbs as used in learning objections, such as *demonstrate*, *describe*, and *display*, precede all these listed functions) as follows.

Reagent Preparation

1. Correct use, cleaning, and storage of laboratory glassware for LC-MS/MS trace analysis
2. Competency with volumetric glassware, pH meters, analytical balances, positive displacement, air displacement and volumetric pipets
3. Best practices for handling of source materials (primary solvent containers, blank biological matrices, primary analytical standards [certified reference materials]) to avoid contamination from the environment or from improper containers

[e.g. phthalate plasticizers] or cross-contamination from mg/mL to pg/mL or analyte-free solutions
4. Measurement principles for solvents and water to achieve highly consistent solvent:water ratios of mobile phases and autosampler wash solutions
5. Laboratory safety (strong acids, bases, volatile organic solvents, and fire/explosion risk)
6. Lot, source material, and purity tracking, labeling for chemicals, solvents, and prepared reagent lots

Calibrator and Internal Standard Preparation

Consistent preparation of internal standards is important for the long-term stability of any quantitative LC-MS/MS assay and is more demanding of good laboratory technique than is simpler reagent preparation. In addition to the skills listed for reagent preparation, training and documented competency in the precise gravimetric and volumetric measurement of nonaqueous standard solutions (eg, stable isotope–labeled methanol stock solutions) is necessary.

The authors recommend a proficiency test of all new hires for pipetting and weighing performance. Competency testing should include gravimetrically assessed precision and accuracy with air displacement, positive displacement, and glass volumetric pipets for aqueous and nonaqueous liquids and gravimetric competency with National Institute of Standards and Technology–certified standard weights using an analytical balance.

Accurate calibrator preparation to within a $\pm$ 5% or 10% tolerance using certified primary stock solutions and validated blank biological matrices is a task that demands excellent laboratory technique. An alternative is custom calibrator preparation by a vendor, which can be surprisingly expensive. Calibrator preparation requires all the competencies listed for reagent and internal standard preparation as well as appropriate handling of expensive stock standards in volatile solvents and preventing cross-contamination from milligram per milliliter concentration stock standards to nanogram per milliliter or picogram per milliliter calibrator pools, laboratory consumables and pipets.

Sample Preparation

Manual sample preparation may persist in LDT-open MS laboratories as long as automated liquid handler (ALH) prices remain prohibitively high and batches of less than 100 samples are financially viable. Competencies for manual sample preparation include

1. Pipetting proficiency with air and positive displacement pipets with aqueous and nonaqueous solutions
2. Temperature and thermal equilibration effects on pipetting precision and accuracy
3. Best practices for avoiding cross-contamination between samples, reagents, internal standards, labware, and pipets
4. Calculations for and performing dilutions
5. Best practices for maintaining sample identification integrity with multiple transfers during extraction
6. Mitigation for nonspecific binding of measurands to surfaces (containers, caps, and so forth)
7. Plasticizer contamination from consumables (tubes, caps, parafilm sealant, and so forth)
8. Handling for alternate specimen types, such as oral fluid, meconium, and hair and tissue samples, for example, umbilical cord

9. Safe handling and disposal of acids, bases, organic solvents, body fluids, and tissues of human origin

Competency with extraction options other than dilution and protein precipitation may include but is not limited to

1. Solid-phase extraction media
2. Supported liquid extraction media
3. Liquid-liquid extraction
4. Protein precipitation filtration media
5. Phospholipid removal media
6. Tecan Immobilized Coating Extraction (Tecan Schweiz AG, Mannedorf, Switzerland)-coated AC Extraction Plate
7. Trypsin digestion for protein analyses
8. Glucuronide hydrolysis of urine samples
9. Stable Isotope Standards and Capture by Anti-Peptide Antibodies workflows for protein and peptide measurands

Use of ALH for LC-MS/MS sample preparation can deliver major advances in productivity. ALH programming is complex, however, and requires instrument-specific software training. Proficiency at programming ALH may have less relation to level of formal education and be more closely associated with a talent for process improvement, compulsive attention to detail, tolerance of excessive iteration for optimizing liquid handling steps, and basic programming capabilities. Recommended competencies for programmers/key operators of ALH include

1. Software version control, backup, and documentation best practices
2. Liquid handling basic principles for aqueous and nonaqueous fluids
3. Basic robotics programming—principles covered in vendor training courses, for example
4. Best practices for ALH script or program validation and documentation
5. Completion of an ALH vendor's training course or comparable in-house training with assessment

In contrast, operators of ALH for production who do not program and use only validated pipetting/extraction methods may not require extensive training. Safety training to prevent injury from or damage to robotic arms or pipetting channels is a priority.

The most useful competencies may be for recovery from human error, such as

1. Misplaced labware
2. Misplaced carriers
3. Misplaced reagents and samples
4. Selecting the wrong script
5. Software-hardware communication errors
6. Shortages of tips, plates, reagents

Liquid Chromatography–Tandem Mass Spectrometry Instrument Operation, Maintenance, and Troubleshooting

Daily LC-MS/MS maintenance and routine batch submission for LDT-open MS systems is done in some laboratories by unlicensed personnel, with limited LC-MS/MS training. This can work well as long as there are no problems. Review of LC-MS/MS system suitability test (SST) results, MS/MS component cleaning and replacement, LC plumbing, and troubleshooting, however, requires not only hands-on experience but also knowledge of LC and MS/MS theory.

One approach is to stratify instrument operators on the premise that an 80:20 rule applies. This assumes that 80% of batches are problem-free so routine operators need less expertise. With good procedures in place for recognition and referral of problems, the 20% of problematic runs can be referred to a subset of troubleshooting personnel with higher-level LC-MS/MS competency. In smaller laboratories, the expertise needed for complex troubleshooting overlaps with that for method development; hence, the same person may fulfill both job functions.

Basic operator competencies:

1. Daily check, replacing of instrument fluids, liquid waste disposal
2. Daily check, recording of instrument parameters—gas pressures and supplies, vacuum pressures
3. Daily check of thresholds for replacing chromatography consumables
4. Basic computer maintenance
5. Manual install of computer operating system updates, antivirus updates (if not scheduled)
6. Remove/clean/reinstall atmospheric pressure source components (eg, curtain plate, cone, or skimmer)
7. Run SST

Troubleshooting competencies—the LC is the source of most problems. This list, therefore, emphasizes LC skills[10] and the terms, *recognize*, *solve*, and *develop*, are the active verbs that should precede many of these learning objectives:

1. Stationary/mobile-phase differences between reverse-phase and hydrophilic interaction liquid chromatography
2. Effects on LC back pressures of column architecture, mobile-phase composition, flow rate, temperature:
   a. LC stationary-phase particle size
   b. LC column dimensions
3. Problems caused by excess LC extracolumn dead volume
4. Problems caused by aged LC components
5. Rules for composition of injection matrix
6. Sources of column overload (volume overload, mismatch of injection solvent and mobile-phase conditions, and mass overload)
7. LC pressure traces to find leaks, overpressure, and aged LC pump check valves
8. SST, maintenance calendar annotation, and postcolumn infusion to distinguish between human error, sample preparation, and LC or MS/MS instrument failure
9. Isolate LC segments with overpressure or obscure leaks.
10. Change LC pump check valves, plunger seals, and plungers; dispel air from the LC pump head.
11. Change autosampler needle, needle seal/seat, sample loops, and syringes, and dispel airlocks.
12. Problems of no baseline/no peaks/shifted retention times/abnormal baseline/abnormal peak shape
13. Perform MS/MS detector voltage optimization test
14. Change MS/MS source components
15. Problems with failing vacuum systems
16. Ballast and change oil for foreline (roughing) vacuum pumps.
17. Investigate need for MS/MS interface cleaning.
18. Vent and pump down the MS/MS.
19. Exchange used for cleaned/new MS/MS interface components (ion guides).

20. Perform mass resolution and calibration, evaluate reports.
21. Use of qualitative data review to compare and contrast shifts and trends in signal-to-noise ratio, peak shape, and retention time

Quantitative Liquid Chromatography–Tandem Mass Spectrometry Data Review and Reporting

The availability of sophisticated automation software for data review (eg, Indigo ASCENT [BioAutomation, Carmel, Indiana], MultiQuant [SCIEX, Framingham, MA], and Skyline [MacCoss Lab Software, University of Washington, Seattle, WA]) with options for "review by exception" has changed expectations for this component of the LDT-open MS workflow.[11–14] Competencies necessary for manual data review are listed, with the expectation that similar expertise is required for review by exception but with large improvements in throughput due to the limited number of chromatograms that require review when auto-verification rules are applied. The learning objective terms preceding many of these items should be *recognize deviation*, *find the source of the problem*, and *apply corrective action for*.

1. Abnormal peak shape, detector saturation, unacceptably low signal-to-noise ratio, dwell time errors
2. Peak shape degradation for 1 versus all samples in a batch
3. Trends/shifts in LC-MS/MS metadata, for example, ion ratios, internal standard peak areas
4. Retention time (Rt), relative retention time flagging, variance, trends, shifts, and acceptable versus unacceptable deviations
5. Blank sample acceptance criteria and review for carryover from high to low concentration samples
6. Drug and hormone metabolite abnormalities
7. Review of calibration curve parameter and acceptance criteria
8. Quality control (QC) failures
9. Referral criteria for secondary review, sample rejection, reinjection, repeat extraction, dilution, and customized report comments
10. Maintenance of batch records

TRAINING FOR METHOD VALIDATION AND DEVELOPMENT

The authors are not aware of any academic training specific for diagnostic quantitative LC-MS/MS method development and validation. Clinical chemistry fellowships and short courses (American Society for Mass Spectrometry (ASMS) and Mass Spectrometry: Applications to the Clinical Laboratory (MSACL)) are the best training resources to the authors' knowledge.[7,8] The most effective training for this highly complex task is exposure in a diagnostic laboratory to a mentor with experience and expertise in both LDT-open MS and laboratory medicine.

The skills and experience needed to implement robust methods for production are not well characterized. What do we mean by *robust* and *production*? Production is defined as daily reporting of results from validated LDT-open MS quantitative assays in a regulated diagnostic laboratory. Robust is less easy to characterize. Differences of note between less regulated research MS assays and the performance of and practice necessary for production assays that can be described as robust include

1. Reliability (low rate of batch failures) and better precision (eg, CVs <10%)
2. Less than or equal to 15% between sample variance in matrix effect after correction for internal standard response

3. Faster turnaround times with low exception rates
4. Extensive validation (eg, Clinical & Laboratory Standards Institute (CLSI) C62-A document and other CLSI guidance)
5. Routine tracking of SST results and MS/MS metadata with validated action limits
6. Routine tracking of reagent, solvent, chemical, internal standard, calibrator, and consumable lots with lot to lot validation testing
7. QC schema, action limits, and review consistent with regulatory requirements
8. As available, uninterrupted chain of traceability to standard reference materials
9. Testing can be performed by CLS level personnel

The following competencies are proposed for robust method development/validation personnel:

1. All skills listed previously for materials preparation, sample preparation, instrument operation, troubleshooting, and data review
2. Writing development and validation plans
3. Developing an MS/MS method
   a. Selecting, optimizing MRMs, dwell times, and grouping/timing of Multiple Reaction monitoring precursor/product ion pairs for optimal points/peak
   b. Optimizing source parameters
      i. Using design of experiments for source optimization
   c. Characterizing ionization based on mobile-phase composition, positive/negative mode
4. Screening and selecting LC columns, guard columns, inline filters, and mobile phases
   a. High-throughput screening of stationary phases, column dimensions, and particle types with automation
5. Minimizing LC dead volume
6. Developing an LC gradient, screening gradients
   a. High-throughput screening of solvents/gradients with automation—see also "4".
   b. 2-D LC
   c. High-temperature LC
   d. Online solid phase extraction
   e. LC multiplexing
7. Defining boundaries for injection solution solvent, pH composition, and injection volume
8. Evaluating analyte chemistry and desired lower limit of quantitation to select sample preparation options
9. Knowledge of common sample preparation methods for LDT-open MS, options to concentrate analytes while depleting matrix
10. Quantifying extraction precision, recovery, and matrix effect
    a. Optimizing extraction, LC, and MS/MS to minimize matrix effect variance
    b. Screening for nonspecific binding, solubility problems
11. Use of postcolumn infusion to optimize LC gradients and sample preparation and reduce between-sample variance in matrix effect
12. Use of single-source native matrix samples early in development
13. Defining the analytical measurement range, validating precision at the lower limit of quantitation
14. Designing calibration strategies and materials
15. Selection of QC materials and concentrations

16. Concepts of method robustness, process optimization, minimizing liquid transfers, and optimizing extraction containers
17. Prevalidation studies
18. Fit for purpose validation of methods and compliance with regulatory guidance
19. Writing validation reports
20. Writing Standard operating procedure (SOPs), training production personnel
21. Transitioning methods to production

TRAINING TO MANAGE PRODUCTION AND QUALITY

Supervisors and managers with diagnostic laboratory but no MS experience may find it challenging to adapt to oversight of LDT-open MS laboratories. The advantage of LC-MS/MS technology is that many more options exist to assess and control quality than with less complex measurement techniques. Every result from an LC-MS/MS system has a wealth of instrument metadata that can be used to evaluate the acceptability of the analysis. Although less accessible, in diagnostic laboratories there should also be noninstrument information documented for each result (lot and source material validation, QC and sample preparation history, analyst competency, batch records, instrument SST, and service records). The difficulty is that most open source data management and automation solutions for creating, storing, queries of, and useful presentation for LDT-open MS big data were developed for proteomics research and only recently have been applied in diagnostic laboratories.[14–17] The authors know of no formal training for, but believe that managers should become familiar with and may want to implement, the solutions and best practices recommended:

1. Centralized (secure server) storage of all LC-MS/MS raw data with automated backup
2. Automated tracking of SST results with exception flagging, notification, and remote review capability
3. Software to mine archived LC-MS/MS metadata for between batch, short-term, and longer-term monitoring to forecast instrument/batch failure and track metrics to improve method robustness
4. Database storage, tracking, and queries for information NOT stored in laboratory information or QC software systems, such as
   a. Lots in use for chromatography consumables
   b. Lots in use and certificates of analysis for primary standards
   c. Lots in use for water, chemicals, solvents and prepared reagents, calibrators, and lot-to-lot validations
   d. Instrument maintenance and service records
   e. Batch records
   f. LC- MS/MS, ALH method edits, version control, and SOP document control
   g. Autoverification rules validation and version control

TRAINING FOR INSTRUMENT SELECTION, TEST MENU, AND CLINICAL OVERSIGHT BY LABORATORY DIRECTORS

Formal training for directors of LDT-open MS laboratories takes place in some but not all clinical postdoctoral fellowship and laboratory physician (clinical pathology and medical biochemistry) residency programs. The degree to which doctoral scientists and physicians engage in learning the technical and informatics competencies described in this article for LDT-open MS varies with the training program and the trainee. Board certification examinations are increasingly likely to include questions

about LC and MS/MS theory and practice. The authors recommend the following competencies specifically for training directors of LDT-open MS laboratory sections. They also may be useful for generalist laboratory directors who should be aware of the challenges to using MS technology in the diagnostic laboratory and need to assess the qualifications of candidates to direct LDT-open MS laboratory sections.

1. Basics of quadrupole and hybrid MS/MS theory and function
2. Differences between triple quadrupole, time of flight, and (Orbitrap mass analyzer, Waltham, MA) for quantitation
3. Compromises between ideal function and routine performance of LDT-open MS and IVD-closed MS production instruments in diagnostic laboratories
4. Basics of LC theory, practice, optimization, and limitations when used with MS/MS for quantitation
5. Compare and contrast sample preparation methods for quality, cost, and productivity (less sample cleanup may translate to more instrument down time)
6. Basic principles of LDT-open MS method development, validation, implementation, and quality management in production as appropriate for job function
7. Selection of and implementing training, assessing initial competency, and continuing performance for personnel who will perform LDT-open MS bench testing, method development and validation, quality management, and production oversight
8. Leadership, collaboration, or delegation to implement evolving informatics solutions for LDT-open MS automation and quality management
9. Strategies for increasing LC-MS/MS throughput and selectivity (LC multiplexing, MS/MS multiplexing, and developing technologies [eg, ion mobility])
10. Writing return on investment and request for proposal/tender documents for instrument purchase
11. Communicating the value of MS testing to clinicians and recruiting clinician support for MS instrument purchase
12. Selecting team members for instrument purchase due diligence
13. Ranking vendors and quotations, negotiating for instrument purchase, service contracts, and training and application support
14. Engagement with clinicians, laboratory, finance, and regulatory administrators to assess LDT-open MS versus IVD-closed MS testing demand, laboratory budgets, test reimbursement, and constructing and modifying LDT-open MS test menus

SUMMARY

A menu of competencies is proposed in some detail for personnel working in LDT-open MS diagnostic laboratories. The goal is that online training resources, short courses, and clinical chemistry postdoctoral fellowship and residency training programs can use and further develop these guidelines to the benefit of their trainees.

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