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Liquid Chromatography–Mass Spectrometry Education for Clinical Laboratory Scientists

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Authors

Stone, Judith A

Fitzgerald, Robert L

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LCMS Education for Clinical Laboratory Scientists

author names and degrees

Judith A Stone, MT(ASCP), Ph.D.
Robert L. Fitzgerald, Ph.D.

author Affiliations

Stone:
Sr. Technical Specialist, Toxicology/Mass Spectrometry Laboratory, University of California, San Diego Health Center for Advanced Laboratory Medicine, San Diego, CA, U.S.A.

Fitzgerald:
Professor, Department of Pathology, Director- Toxicology/Mass Spectrometry Laboratory, University of California, San Diego, CA, U.S.A.

author Contact information

Both authors - University of California San Diego Health System, CALM Suite 150, Rm. 1314, 10300 Campus Point Drive, San Diego, CA 92121.
jastone@ucsd.edu
rfitzgerald@ucsd.edu

Corresponding Author

Stone:
University of California San Diego Health System, CALM Suite 150, 10300 Campus Point Drive, San Diego, CA 92121.
jastone@ucsd.edu

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Key Points

- Quantitative liquid-chromatography-tandem mass spectrometry (LC-MS/MS) as used in diagnostic laboratories is highly complex and requires a theoretical 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 sub-specialty takes place primarily on the job, within the diagnostic laboratories performing the testing.
- This chapter stratifies and lists the competencies required for bench personnel, R&D scientists who develop and validate methods, laboratory managers and directors as an aid towards designing training curricula and assessing trainees and staff.

Synopsis

This chapter describes the need for, stratifies the complexity of, and proposes detailed lists of training competencies for diagnostic laboratory personnel using quantitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) for patient care. Although quantitative LC-MS/MS is evolving towards greater automation with less need for technical expertise, gaps remain in resources for training and assessment.

1. Introduction and Background

The world of quantitative diagnostic mass spectrometry (MS) is evolving towards automation and greater ease of use. For diagnostic laboratories, that means migration from manual procedures in esoteric testing sections of the laboratory to automated, high throughput core laboratory sections. The holy grail of diagnostic MS automation would be regulatory compliant quantitative assays (e.g. FDA approved or CE mark) on a fully automated liquid chromatography-tandem mass spectrometer (LC-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, 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 permits integration to track systems along with ASTM/HL7 interfaces to laboratory information systems (LIS).

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 one vendor has made significant progress towards these goals and is poised to ship quantitative LC-MS/MS instruments designed for operation in highly automated diagnostic core laboratories.

To clarify our terms, we are using “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, we define “clinical MS” 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 MALDI-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 mass spectrometry is imaging. The differences between training for imaging MS versus quantitative LC-MS/MS are profound. Avoiding detail in order to address the two sub-specialties in

one chapter would do both a disservice. Therefore, this chapter selectively addresses training for quantitative diagnostic LC-MS/MS, only one of the areas in which mass spectrometry 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 could be made to typesetting – once a highly skilled, multifunctional profession that was made obsolete by revolutions in printing technology (5). The premise of this chapter 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 - we describe in detail the extensive training needed for such practice.

Diagnostic laboratories that perform quantitative LC-MS/MS testing now have tremendous variance in their extent of automation, throughput and test workload. We think 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 we will call “LDT-open MS”. The emerging system of regulatory-approved assays sold by in-vitro diagnostic (IVD) companies for dedicated, closed systems we call “IVD-closed MS”. We consider laboratories performing FDA cleared or CE mark assays on open LC-MS/MS systems to be in the LDT-open MS group.

This chapter describes training for LDT-open MS practice in chapter sections defined first by function and only secondarily by academic degree, licensure and job title. Scientists with a BSc degree and post baccalaureate on-the-job training as well as physician-scientist laboratory directors with doctoral training in mass spectrometry are successfully engaged in method development, validation and troubleshooting for LDT-open MS laboratories. As training and experience are so diverse in this field, we focus on desired competencies rather than academic qualifications and licensure.

2. 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 e.g. Michigan

State University and Virginia Commonwealth University. Short courses in quantitative diagnostic LDT-open mass spectrometry 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 chapter 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 here by increasing skills and training:

A. reagent and calibrator preparation
B. sample preparation
C. instrument operation (order of B & C may be reversed based on the level of automation)
D. data analysis/review/reporting functions.

Competencies recommended for the tasks above are:
(assume appropriate active verbs as used in learning objections, such as "demonstrate, describe, display" would precede all of these listed functions)

A1. Reagent preparation

a. correct use, cleaning and storage of laboratory glassware for LC-MS/MS trace analysis
b. competency with volumetric glassware, pH meters, analytical balances, positive displacement, air displacement and volumetric pipets
c. Handling of primary solvent containers and prepared solutions to avoid contamination with plasticizers, environmental contaminants, biological matrices, primary analytical standards
d. Measurement principles for solvents and water to achieve highly consistent solvent:water ratios of mobile phases and autosampler wash solutions
e. Laboratory safety (strong acids, bases, volatile organic solvents, fire/explosion risk)
f. Lot, source material, and purity tracking, labeling for chemicals, solvents, prepared reagent lots

A2. 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 non-aqueous standard solutions (e.g. stable isotope labeled methanol stock solutions) is necessary.

We 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 non-aqueous liquids and gravimetric competency with NIST certified standard weights using an analytical balance.

Accurate calibrator preparation to within a +/- 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 of 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 mg/mL concentration stock standards to ng or pg/mL calibrator pools, laboratory consumables and pipets.

B. 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 <100 samples are financially viable. Competencies for manual sample preparation include:

a. pipetting proficiency with air and positive displacement pipets with aqueous and non-aqueous solutions.
b. temperature and thermal equilibration effects on pipetting precision and accuracy
c. best practices for avoiding cross-contamination between samples, reagents, internal standards, labware and pipets
d. calculations for and performing dilutions
e. best practices for maintaining sample identification integrity with multiple transfers during extraction
f. mitigation for non-specific binding of measurands to surfaces (containers, caps, etc.)
g. plasticizer contamination from consumables (tubes, caps, parafilm sealant, etc.)
h. handling for alternate specimen types such as oral fluid, meconium, hair and tissue samples e.g. umbilical cord
i. 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:

a. solid phase extraction media

b. supported liquid extraction media
c. liquid-liquid extraction
d. protein precipitation filtration media
e. phospholipid removal media
f. TICE® coated AC extraction plate
g. trypsin digestion for protein analyses
h. glucuronide hydrolysis of urine samples
i. SISCAPA workflows for protein and peptide measurands

Use of ALH for LC-MS/MS sample preparation can deliver major advances in productivity. However, ALH programming is complex and requires instrument specific software training. Proficiency at programming ALH may have less relation to one's 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 relatively basic programming capabilities. Recommended competencies for programmers/key operators of ALH include:

a. software version control, backup and documentation best practices
b. liquid handling basic principles for aqueous and non-aqueous fluids
c. basic robotics programming – principles covered in vendor training courses for example
d. best practices for ALH script or program validation and documentation
e. 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:

a. misplaced labware
b. misplaced carriers
c. misplaced reagents and samples
d. selecting the wrong script
e. software-hardware communication errors
f. shortages of tips, plates, reagents

C. LC-MS/MS instrument operation, maintenance and troubleshooting (10)
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 so long as there are no problems. However, review of LC-MS/MS system suitability test (SST) results, MSMS component cleaning and replacement, LC plumbing and troubleshooting 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 will apply. 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:

a. daily check, replacing of instrument fluids, liquid waste disposal
b. daily check, recording of instrument parameters - gas pressures and supplies, vacuum pressures
c. daily check of thresholds for replacing chromatography consumables
d. basic computer maintenance
e. manual install of computer operating system updates, anti-virus updates (if not scheduled)
f. remove/clean/re-install atmospheric pressure source components (e.g. curtain plate, cone, or skimmer)
g. run SST

Troubleshooting competencies:
The LC is the source of most problems. This list therefore emphasizes LC skills (10) and the terms “Recognize, solve, develop” are the active verbs that should precede many of these learning objectives

a. stationary/mobile phase differences between reverse phase and HILIC chromatography
b. effects on LC back pressures of column architecture, mobile phase composition, flow rate, temperature:
    i. LC stationary phase particle size
    ii. LC column dimensions
c. problems caused by excess LC extra-column dead volume
d. problems caused by aged LC components
e. rules for composition of injection matrix
f. sources of column overload (volume overload, mis-match of injection solvent and mobile phase conditions, mass overload)
g. LC pressure traces to find leaks, over pressure, and aged LC pump check valves
h. SST, maintenance calendar annotation, and post-column infusion to distinguish between human error, sample preparation, LC or MS/MS instrument failure
i. Isolate LC segments with over-pressure or obscure leaks
j. change LC pump check valves, plunger seals, plungers, dispel air from the LC pump head.

k. change autosampler needle, needle seal/seat, sample loops, syringes and dispel airlocks
l. problems of no baseline/no peaks/shifted Rts/abnormal baseline/abnormal peak shape
m. perform MS/MS detector voltage optimization test
n. change MS/MS source components
o. problems with failing vacuum systems
p. ballast and change oil for foreline (roughing) vacuum pumps
q. investigate need for MS/MS interface cleaning
r. vent and pump down the MS/MS
s. exchange used for cleaned/new MSMS interface components (ion guides)
t. perform mass resolution and calibration, evaluate reports
u. use of qualitative data review to compare and contrast shifts and trends in signal to noise (S:N), peak shape and Rt

D. Quantitative LC-MS/MS data review and reporting

The availability of sophisticated automation software for data review (e.g. Indigo BioAutomation ASCENT, SCIEX MultiQuant, MacCoss Lab Software Skyline) with options for "review by exception" has changed expectations for this component of the LDT-open MS workflow (11-14). We list competencies necessary for manual data review, 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"

a. abnormal peak shape, detector saturation, unacceptably low S:N, dwell time errors
b. peak shape degradation for one versus all samples in a batch
c. trends/shifts in LC-MS/MS metadata, e.g ion ratios, internal standard peak areas
d. retention time (Rt), relative retention time (RRt) flagging, variance, trends, shifts, acceptable versus unacceptable deviations
e. blank acceptance criteria, review for carryover from high to low concentration samples
f. drug and hormone metabolite abnormalities
g. review of calibration curve parameter and acceptance criteria
h. QC failures
i. referral criteria for secondary review, sample rejection, re-injection, repeat extraction, dilution, and customized report comments
j. maintenance of batch records

3. Training for method validation and development

We are not aware of any academic training specific for diagnostic quantitative LC-MS/MS method development and validation. Clinical

chemistry fellowships and short courses (ASMS, MSACL) are the best training resources to our 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 we define 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 includes:

a. reliability (low rate of batch failures) and better precision (e.g. CVs <10%)
b. ≤15% between sample variance in matrix effect after correction for internal standard response
c. faster turn-around times with low exception rates
d. extensive validation (e.g. CLSI C62-A document and other CLSI guidance)
e. routine tracking of SST results and MS/MS metadata with validated action limits
f. routine tracking of reagent, solvent, chemical, internal standard, calibrator, consumable lots with lot to lot validation testing
g. quality control schema, action limits and review consistent with regulatory requirements
h. as available, uninterrupted chain of traceability to standard reference materials
i. testing can be performed by CLS level personnel

We propose the following competencies for robust method development/validation personnel (*functions in italics may be less universally applied*):

a. all skills listed previously for materials preparation, sample preparation, instrument operation, troubleshooting and data review
b. writing development and validation plans
c. developing an MS/MS method
    i. Selecting, optimizing MRMs, dwell times, grouping/timing of MRMs for optimal points/peak
    ii. optimizing source parameters
        - *Using design of experiments for source optimization*
    iii. Characterizing ionization based on mobile phase composition, positive/negative mode
d. screening and selecting LC columns, guard columns, inline filters, mobile phases
    i. *High throughput screening of stationary phases, column dimensions, particle types with automation*

e. minimizing LC dead volume
f. developing an LC gradient, screening gradients
    i. *High throughput screening of solvents/gradients with automation – see also d.*
    ii. *Two-dimensional LC*
    iii. High temperature LC
    iv. Online SPE extraction
    v. LC multiplexing
g. defining boundaries for injection solution solvent, pH composition and injection volume
h. evaluating analyte chemistry and desired lower limit of quantitation to select sample preparation options
i. knowledge of common sample preparation methods for LDT-open MS, options to concentrate analytes while depleting matrix
j. quantifying extraction precision, recovery, and matrix effect
    i. optimizing extraction, LC and MS/MS to minimize matrix effect variance
    ii. screening for non-specific binding, solubility problems
k. use of post-column infusion to optimize LC gradients and sample preparation, reduce between-sample variance in matrix effect
l. use of single source native matrix samples early in development
m. defining the AMR, validating precision at the lower limit of quantitation
n. designing calibration strategies and materials
o. selection of QC materials and concentrations
p. concepts of method robustness, process optimization, minimizing liquid transfers, optimizing extraction containers
q. pre-validation studies
r. fit for purpose validation of methods, compliance with regulatory guidance
s. writing validation reports
t. writing SOPs, training production personnel
u. transitioning methods to production

4. 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 non-instrument 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). We 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 below:

a. centralized (secure server) storage of all LC-MS/MS raw data with automated backup
b. automated tracking of SST results with exception flagging, notification and remote review capability
c. software to mine archived LC-MS/MS metadata for between batch, short and longer term monitoring in order to forecast instrument/batch failure and track metrics to improve method robustness
d. database storage, tracking and queries for information NOT stored in laboratory information or quality control software systems such as
    i. lots in use for chromatography consumables
    ii. lots in use and certificates of analysis for primary standards
    iii. lots in use for water, chemicals, solvents and prepared reagents, calibrators, lot to lot validations
    iv. instrument maintenance and service records
    v. batch records
    vi. LC-MSMS, ALH method edits, version control, SOP document control
    vii. Auto-verification rules validation and version control

5. 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 post-doctoral fellowship and laboratory physician (clinical pathology, medical biochemistry) residency programs. The degree to which doctoral scientists and physicians engage in learning the technical and informatics competencies described here for LDT-open MS varies with the training program and the trainee. Board certification exams are increasingly likely to include questions about LC and MS/MS theory and practice. We recommend the following competencies specifically for training directors of LDT-open MS laboratory sections. They may also 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.

a. basics of quadrupole and hybrid tandem mass spectrometer theory and function
a. differences between triple quadrupole, time of flight, Orbitrap MS for quantitation
b. compromises between ideal function and routine performance of LDT-open MS and IVD-closed MS production instruments in diagnostic laboratories
c. basics of LC theory, practice, optimization, and limitations when used with MS/MS for quantitation

d. compare and contrast sample preparation methods for quality, cost and productivity (less sample cleanup may translate to more instrument down time)
e. basic principles of LDT-open MS method development, validation, implementation and quality management in production as appropriate for job function
f. selection of, 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
g. leadership, collaboration or delegation to implement evolving informatics solutions for LDT-open MS automation and quality management
h. strategies for increasing LC-MS/MS throughput and selectivity (LC multiplexing, MS/MS multiplexing, developing technologies e.g. ion mobility)
i. writing return on investment (ROI) and request for proposal/tender (RFP) documents for instrument purchase
j. communicating the value of MS testing to clinicians, recruiting clinician support for MS instrument purchase
k. selecting team members for instrument purchase due diligence
l. ranking vendors and quotations, negotiating for instrument purchase, service contracts, training and application support
m. engagement with clinicians, laboratory, finance and regulatory administrators to assess LDT-open MS versus IVD-closed MS testing demand, laboratory budgets, test reimbursement, constructing and modifying LDT-open MS test menus

6. Conclusions

We have proposed a menu of competencies in some detail for personnel working in LDT-open MS diagnostic laboratories. Our goal is that online training resources, short courses, and CLS, post-doctoral fellowship and residency training programs can use and further develop these guidelines to the benefit of their trainees.

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