Teaching Method Validation in the Clinical Laboratory Science Curriculum

TARA C MOON, VICKY A LEGRYS

With the Clinical Laboratory Improvement Amendment's (CLIA) final rule, the ability of the Clinical Laboratory Scientist (CLS) to perform method validation has become increasingly important. Knowledge of the statistical methods and procedures used in method validation is imperative for clinical laboratory scientists. However, incorporating these concepts in a CLS curriculum can be challenging, especially at a time of limited resources. This paper provides an outline of one approach to addressing these topics in lecture courses and integrating them in the student laboratory and the clinical practicum for direct application.

ABBREVIATIONS: ASCLS = American Society for Clinical Laboratory Science; CLIA = Clinical Laboratory Improvement Amendment; CLS = Clinical Laboratory Science; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; NAACLS = National Accrediting Agency for Clinical Laboratory Science.

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***Tara C Moon MS CLS(NCA)** is **assistant professor**, Division of Clinical Laboratory Science, The University of North Carolina at Chapel Hill, Chapel Hill NC.*

***Vicky A LeGrys DA CLS(NCA)** is **professor**, Division of Clinical Laboratory Science, The University of North Carolina at Chapel Hill, Chapel Hill NC.*

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***Address for Correspondence:** Tara C Moon MS CLS(NCA), Suite 4100 Bondurant Hall, Campus Box 7145, Division of Clinical Laboratory Science, The University of North Carolina at Chapel Hill, Chapel Hill NC 27599-7145. (919) 843-4353, (919) 966-5200 (fax). tmoon@med.unc.edu.*

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Central to the role of any clinical laboratory scientist is the desire to report accurate patient results. Method validation is an imperative part of that process. There are many occasions when practitioners use the concepts of method validation such as establishing new methods, implementing commercial tests, or performing periodic assessments of established methods. The American Society for Clinical Laboratory Science (ASCLS) includes these skills in its definition of the CLS profession and scope of practice.[1] Additionally, method validation is a requirement of laboratory regulations which state that performance of new methods be verified prior to reporting patient test results and periodic assessment of accuracy and precision must occur.[2]

Despite the attention that quality in the laboratory has received as of late and the new regulations and policies that have resulted, it remains an area that can be improved. Many method validation procedures are still carried out inappropriately or are interpreted incorrectly.[3] In the past, when the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has inspected laboratories, the most frequently cited deficiency involved quality control problems.[4] Reasons for these deficiencies in spite of improved regulations and awareness are unknown. It is clear, however, that correcting problems with laboratory methods is difficult and requires higher cognitive processes of analysis coupled with a strong command of the method evaluation process. Giving CLS students a more solid foundation in this area could prove to diminish these inadequacies in future laboratories.

In addition to ASCLS, the National Accrediting Agency for Clinical Laboratory Science (NAACLS) also includes method validation in their description of the profession.[5] To many, these skills seem abstract and are often more difficult to

integrate in a CLS curriculum. Educators are very comfortable teaching technical practices, but the situations and analytical processes that are required for method evaluation can be more difficult to simulate in an educational setting. Barriers to teaching method validation in the CLS curriculum can include limited time, reagents, and automation.

Due to the dynamic nature of the field, faculty struggle when choosing the amount of content to include in CLS educational programs. It can be easy to dismiss an emphasis on method validation in a CLS curriculum for entry-level positions because it is often viewed as a skill that is only needed by the experienced CLS. However, in Beck and Doig's 2005 survey of managers, practitioners, and educators, respondents indicated that they expected a CLS to be competent in the procedures of method validation at entry-level.[6] About half of those surveyed stated that they expected the CLS to be able to assess and evaluate methods, adopt new methods, and perform method evaluation studies with no additional education.[6] Practitioners expect that these skills are acquired in educational programs and are not learned on the job or with additional training.

Clearly, technology in the laboratory is changing every day. With some assays, it is becoming easier to operate the instrument that performs the assay on a routine basis. However, the cognitive skills that are required to perform the quality control, validate the assay, and ensure that the test results are valid are much greater. Additionally, expansions in the area of molecular diagnostics have required more complex method validation for those assays that are developed in-house. It is easy to imagine that the role of the CLS in method validation will only increase in the future. No matter what the technology is, how it evolves, or what level of practitioner is performing the testing, method validation will always be an integral part of the clinical laboratory and an essential skill for students to obtain in their educational programs.

The following is a review of how one educational program has incorporated the concepts of method validation into the CLS curriculum. This overview focuses on the course materials and methods that are used to teach the concepts of method validation and prepare CLS students for entry-level responsibilities. Instruction for these methods comes intermittently throughout the two year curriculum using a variety of instructional techniques. Didactic lectures are used to present information in the students' first semester, while laboratory exercises are used for active learning and simulation in the second semester. The method validation course work culminates with the clinical practicum in which the students investigate data and problems from actual laboratory scenarios. Other statistical and research design methods, such as odds ratios, type I and type II errors, and analysis of variance, are not included in this discussion as they are covered in a separate research course that is offered during the fall semester of the second year of the CLS curriculum.

RESOURCES FOR METHOD VALIDATION INFORMATION

There are a variety of Internet resources available for both the student and instructor on the topic of method validation. The Centers for Medicare and Medicaid Services has an overview of the Clinical Laboratory Improvement Amendment (CLIA) at http://www.cms.hhs.gov/CLIA and the specific requirements for method validation for nonwaived and modified tests from Subpart K can be found at http://www.cms.hhs.gov/CLIA/downloads/apcsubk1.pdf (Table 1). Other governmental websites with information about CLIA include the Centers for Disease Control (www.phppo.cdc.gov/clia/default.aspx) and the Food and Drug Administration (www.fda.gov/cdrh/CLIA/index.html). The College of American Pathologists Laboratory Accreditation Program Inspection Checklist for Chemistry, available from http://www.cap.org/apps/docs/laboratory_accreditation/checklists/chemistry_and_toxicology_april2006.pdf, contains

Table 1. CLIA requirements for method validation[2]

Test type	Required verifications of manufacturer's performance
New, unmodified, nonwaived tests	Accuracy Precision Reportable range Reference ranges
Test system that has been modified or developed in-house	Accuracy Precision Analytic sensitivity Analytic specificity to include interfering substances Reportable range Reference intervals

items and commentary defining and describing the practice and appropriate documentation for method validation. The Clinical Laboratory Standards Institute (CLSI) Evaluation Protocol documents (EP series) contain useful procedures for implementing method validation studies and analyzing the results (www.clsi.org).

Dr. James Westgard's website (www.westgard.com) contains an extensive set of lessons on method validation that are very useful for students. Each lesson contains the purpose of the given experiment, factors to consider, examples of data calculations, criteria for acceptance, and selected references. In addition, the website contains data calculation tools that can be used by the student in assignments to generate standard deviation, linear plots, and reportable range. Other commercially available sources of method validation software include EP Evaluator (http://www.dgrhoads.com) and Analyze It (http://www.analyse-it.com/products/clinical/overview.htm). Some of these products can be purchased for limited use for student assignments.

IMPLEMENTATION IN THE CLS CURRICULUM

Didactic lectures

Because the lecture method is effective in disseminating a large amount of information, we initially present the information concerning method validation in the students' first semester Laboratory Mathematics and Quality Assurance course. The topics covered in the lectures are listed in Table 2 and begin with a description of the importance of method validation. They move from the simplest assays (precision studies) to the more complex (interference and lower limit of detection), ending with a conclusion reviewing all the parts of method validation and summarizing the key points. The lectures are supplemented with problem sets, requiring the student to calculate parameters such as imprecision, linearity, and bias, and to apply appropriate criteria to evaluate the results for acceptability. Students are evaluated on the material based on their answers to the problem sets and scores on several quizzes.

A limitation of the lecture format is that the student is not involved in the generation of data and the ideas and application can seem abstract, especially if the material is presented to the student early in their curriculum before they have had the opportunity to become familiar with clinical assays. The instructor may need to provide additional clinical details and ensure that the student has later opportunities in the curriculum to apply the concepts presented in the lecture to actual practice of method evaluation.

Some students struggle with the calculations and theory associated with method validation, often due to differences in their backgrounds and abilities in mathematics and basic statistics. To help the students master the material, tutoring sessions are available from a second year student in the late afternoons, twice a week. The student tutor prepares and evaluates additional problems in method validation, working closely with the instructor to monitor performance. The tutoring sessions have been very beneficial as they allow the student additional opportunities to integrate the information and master the material.

Laboratory course

The application of method validation procedures is implemented in the second semester of the program's first year in the clinical chemistry laboratory. It is included in the chemistry laboratory for several reasons: 1) there is little automation in the student laboratory, 2) manual methods are used primarily in the first year laboratory courses, and 3) many of the reagent kits on which we have long depended have been discontinued. The inability to obtain certain reagent kits left some vacant time in the chemistry laboratory schedule which was not available in any other course. The reagent kits that are available are simple to use and require very little applica-

Table 2. Topics for method validation (MV) lectures

Unit	Topics
1	Purpose of MV
2	CLIA requirements for MV
3	Types of analytical errors • Determining total allowable error
4	Precision studies
5	Linearity/analytic measurement range
6	Method comparison studies • Bias plots • Comparison plots
7	Verifying/establishing reference intervals
8	Comparing analytical sensitivity and specificity to clinical sensitivity and specificity
9	Recovery studies
10	Interference studies
11	Detection limits
12	Drawing conclusions: Is the method acceptable? • Appropriate criteria • Factors influencing decision making

tion of chemistry theory. However, by adding the method validation concepts to the procedures, students can become proficient at some basic skills as well as incorporate a more complex cognitive level to the laboratory exercise.

Method validation is performed by comparing the two manual methods, glucose oxidase and glucose hexokinase. Glucose was chosen because it is inexpensive, it is a very common analyte, and the manual methods for glucose determination are not time consuming. These factors allow more ground to be covered in the student laboratory.

The method validation studies span four sessions of the clinical chemistry laboratory course. Students begin by performing the procedure to develop technical competency and then move on to the specific method validation procedures listed in Table 3. In the interest of time, students are divided into two groups for the laboratory exercises. Half of the class performs the glucose oxidase procedure and the other half performs the glucose hexokinase procedure. At the end of each laboratory session, the groups share their data and have time to compare the results of the two methods. While allowing students to share data compromises error reduction, it also allows for exposure to more experiments and overall, a more robust laboratory experience. With explanation, the students are able to understand this tactic and it does not detract from their understanding of the principles. In addition to the laboratory exercises, two assignments are given: a data analysis exercise and a method evaluation paper.

Because learning the concepts and mathematical operations is imperative to the students' understanding of the procedures, calculations and graphs are done by hand in the student laboratory. However, the potential for human error in the manual calculations and hand-drawn graphs is contrasted with the benefits of using a computer when the students use statistical software for the data analysis assignment and method evaluation paper. In addition to their printed results and graphs, students also submit a written interpretation of the statistical results. To make interpretations, students are

Table 3. Laboratory schedule and activities

Laboratory exercises		Goals
Session	**Topic**	
1	Perform glucose assays with controls and unknowns.	Develop competency with procedure.
2	Analytic measurement range and precision	Assess the useful analytical range of a method and verify the reportable range from the manufacturer. Define acceptable limits for glucose. Estimate imprecision.
3	Method comparison	Estimate inaccuracy, systematic error.
4	Recovery study	Determine proportional error.
Additional assignments		**Goals**
Session	**Topic**	
2	Data analysis exercise	Evaluate raw data using computer software.
5	Method evaluation paper	Using all the concepts of method validation, prepare a written evaluation of two methods and a recommendation for the use of one of the methods in the clinical laboratory. Describe the effects of the implementation of a new method on clinical practice.

required to research CLIA guidelines and use online resources to determine acceptable limits. They are asked to make decisions regarding their data and its acceptability in the clinical laboratory, as well as relate this information to the clinical setting and explain what this means for patient results.

The overall goal for the method evaluation paper is for the student to take all of the concepts and methods that have been performed over the previous laboratory sessions, provide an interpretation of the entire picture, and give a recommendation for the use of one of the methods. Prior to this, the students' analyses have included one procedure at a time. For the method evaluation paper, they are given additional data and some summary statistics to analyze. This data complements the data that they collected in their laboratory exercises. They are asked to address specific questions regarding t-test statistics, the linear regression line, and correlation coefficient. In this final assignment, a complete analysis of all of the studies and a summary is expected. The students are required to integrate the concepts from their lecture course and the application of those concepts in the laboratory, then apply them to make a decision regarding the clinical utility of a new method.

Writing the method evaluation paper is where the students struggle the most. They are able to analyze individual pieces of information during each laboratory exercise, but they have trouble putting those pieces together to give a complete analysis. They are hesitant to recommend one method over the other as they are still trying to develop some confidence in their skills and become nervous about making an incorrect decision. Another area they struggle with is relating these studies to the clinical situation. They understand what error is present and they can explain it, but they have some difficulty applying that knowledge to patient values, understanding how it may influence an interpretation of a value, and what implications adopting a new method may have for clinicians and their patients. These issues are often resolved during the clinical practicum when students perform additional method evaluations and are able to consult with practitioners about real laboratory cases.

Clinical practicum

Method validation occurs in all areas of the clinical laboratory and is well suited to some degree of student involvement. Depending on the design and scheduling of clinical rotations in the CLS curriculum, students may be able to perform the validation assays with supervision. Some curricula are designed to allow students to complete specialized rotations and projects in method validation. Other programs may not have the time to allow students to actually perform the assays, however, in these situations, students can use the data generated by others and apply their own data analysis and interpretation using commercially available evaluation software. Often it is not until students are involved in the performance of "real lab" method validation do they begin to understand the principles and appreciate the importance of error detection as it relates to patient care.

SUMMARY

By including method validation as an integral part of the CLS curriculum, we emphasize quality and give students the background they need to feel competent in applying this knowledge on the job. The approach described in this review has lessened issues of student difficulties with calculations and their struggles to integrate the many concepts of method validation. This was accomplished primarily by the addition of activities such as organized student tutoring, student preparation of a written synopsis with an interpretation of results, and the use of real cases in the clinical practicum.

CLS students need to have a solid background in method validation, because performing method validation in a real world setting can be tedious and time consuming, especially if it is done incorrectly. We try to give our students the necessary skills for this process when they face it in the real world, recognizing that most College of American Pathologists (CAP) checklists ask for a plan in place for validating methods, without indicating *how* to validate methods. Teaching CLS students to perform these procedures properly is important to save time, money, and resources when they are functioning in a clinical setting in their future roles.

Instilling in students an appreciation for quality and quality standards and regulations throughout the CLS program is imperative. The studies of method validation provide a unique opportunity to discuss quality from a slightly different perspective. In addition, expertise in method validation is a skill that is very specific to CLS practice. While another healthcare professional may be able to perform a point-of-care test, he or she will not be able to perform the method validation for that instrument. Some of the procedures that are included in our scope of practice can overlap with other healthcare professionals, but method validation does not. This is something that only the CLS is educated to do and we should continue to strive for excellence in this arena.

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REFERENCES

1. American Society for Clinical Laboratory Science. 2001 Scope of practice, position paper. Available from http://www.ascls.org/position/scope_of_practice.asp. Accessed 2007 Jun 7.
2. US Department of Health and Human Services. 2003 Laboratory requirements relating to quality systems and certain personnel qualification. Final Rule. Federal Registry 2003. CLIA subpart K, analytical systems, section 493.1253. Available from http://www.phppo.cdc.gov/clia/regs/subpart_k.aspx#493.1253. Accessed 2007 Jun 7.
3. Westgard JO. Points of care in using statistics in method comparison studies. Clin Chem 1998 Nov;44(11):2240-2.
4. Belanger AC. The joint commission and CLIA: A 5-year retrospective. MLO: Medical Laboratory Observer 1998 Feb;30(2):46-8.
5. National Accrediting Agency for Clinical Laboratory Science. Standards of accredited educational programs for the clinical laboratory scientist/medical technologist. Available from http://www.naacls.org/PDFviewer.asp?mainUrl=/docs/standards_cls-mt.pdf. Accessed 2007 Jun 7.
6. Beck SJ, Doig K. CLS competencies expected at entry-level and beyond. Clin Lab Sci 2002 Fall;15(4):220-8.