CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

EP19

A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures

This report uses the "measurement procedure lifecycle" framework to aid users of CLSI evaluation protocols documents during establishment and implementation of measurement procedures developed by both commercial manufacturers and clinical laboratories, ie, for laboratory-developed tests.

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A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures

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Abstract

Clinical and Laboratory Standards Institute document EP19—*A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures* is a reference guide for the use of CLSI documents in method evaluations. It is intended to be especially accessible and useful to those who are new to CLSI documents. To this end, EP19 introduces and explains helpful statistical concepts that are used in CLSI documents, especially as they may be helpful in measurement procedure establishment and implementation. The document also introduces the measurement procedure lifecycle concept to illustrate the utility of all CLSI documents, as well as helpful guidelines from other sources, which are used for method evaluations. EP19 defines all measurement procedure developers as manufacturers, regardless of whether they are commercial entities or noncommercial laboratories that develop their own measurement procedures. It clarifies many terms, including method "establishment" by manufacturers, which includes "development" and "validation," and "implementation" by end users, which includes "verification."

Checklists are provided to help users document steps in the establishment and implementation stages of the measurement procedure lifecycle. EP19 was vetted with the various CLSI document development committees to ensure completeness and accuracy of the described documents. Recognizing that CLSI documents are continuously created, CLSI will update content through the Measurement Procedure Lifecycle schematic (see Figure 1), which will be available on the CLSI Method Evaluation Community (http://community.clsi.org/me/).

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Contents

Foreword

This revision of EP19 is redesigned and expanded in order to increase its utility as a reference guide for the use of CLSI documents in method evaluations, especially for relatively unknowledgeable or new users. EP19 is not an evaluation protocol (EP) in the traditional sense. Rather, it is a report that references existing CLSI method evaluation documents, organized around the measurement procedure lifecycle concept.

The document development committee followed a consensus process that was as inclusive as possible. After adopting the measurement procedure lifecycle model, the committee agreed upon the evaluations for consideration at each stage of the lifecycle, and searched CLSI documents for helpful guidance. During this period of investigation, the committee attempted to become familiar with all CLSI documents applicable during the measurement procedure lifecycle. In addition, the committee agreed to reference the American Society for Microbiology Cumitech documents that are helpful for certain microbiology procedures.[1] The draft was also circulated to all relevant consensus committees in order to identify documents that the document development committee may have missed. Cases are noted for which certain kinds of evaluations are often performed, but for which there are currently no CLSI documents. Despite these efforts, it is important to note that CLSI documents are created and revised on a regular basis. Therefore, it is expected that EP19 will need to be updated regularly to be accurate and maximally useful.

When describing the relevant documents, the document development committee was careful not to insert guidance that disagrees with any current CLSI documents, or to give advice that supplements existing CLSI documents. Although this report can be used by measurement procedure manufacturers from any country around the world, it is likely to be most helpful to users in the United States. From the outset, the committee was aware that the US Food and Drug Administration is working toward an approach to regulate certain laboratory-developed tests. Although EP19 is intended to help users identify appropriate CLSI documents, it cannot suffice alone to inform either commercial or laboratory-based manufacturers to address every aspect of establishment of a new measurement procedure. In many cases, a measurement procedure may require special evaluations for which there are no available CLSI resources. The committee believes that it is appropriate to treat all entities that create new measurement procedures as manufacturers. This label includes commercial manufacturers and all laboratories that create new measurement procedures or modify commercially available measurement procedures in a significant way that might modify performance.

To facilitate the use of CLSI documents used for establishment and implementation stages of the measurement procedure lifecycle, EP19 includes checklists to use for permanently documenting decisions made based upon relevant CLSI documents. The checklists provide a convenient starting point for users, who may customize the data they desire to track based upon their individual needs (see Appendix B).

Overview of Changes

The second edition of EP19 replaces EP19-R. The document's original intent to provide a useful, high-level guide has not changed. Significant changes from the prior version include:

- Expansion beyond CLSI EP documents to include the full range of CLSI documents that pertain to method evaluations, including specialties such as microbiology

- Adoption of the measurement procedure lifecycle concept to facilitate the use of EP19 and other CLSI documents

- Clarification and consistent use of terms that correspond to stages of the measurement procedure life cycle, including validation and verification

- Treatment of all measurement procedure developers as “manufacturers”
- Introduction to helpful statistical concepts that are used in CLSI documents, especially as they may be helpful in establishing and implementing measurement procedures (see Appendix A)
- Introduction of the concept of risk management as a criterion for deciding how much testing is needed for evaluations

Key Words

Establishment, evaluation, implementation, measurement procedure, validation, verification

A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures

Chapter 1: Introduction

This chapter includes:

- Document scope and applicable exclusions
- Background information pertinent to the document content
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the document
- Abbreviations and acronyms used in the document

1.1 Scope

EP19 is organized around the measurement procedure lifecycle paradigm (see Tables 1 and 2), which follows the concept that all measurement procedures undergo an initial establishment phase performed by manufacturers, followed by implementation in laboratories. The document follows the measurement procedure lifecycle and is logically organized in a step-by-step manner. The steps describe the considerations and requirements for measurement procedure evaluations including planning and the selection of appropriate CLSI documents and other related documents for validation, verification, and other evaluations. EP19 is designed to organize the evaluation process for the use of CLSI documents.

EP19 defines and explains the many kinds of evaluations that may be performed during the development of a measurement procedure, its initial trial for acceptable suitability by end users, and ongoing demonstration of acceptable performance. EP19 assembles the existing CLSI resources, especially evaluation protocol (EP) documents, and presents them in a logical manner. It is written to facilitate users' identification of the specific kinds of evaluations they may wish to perform. To aid in the understanding of CLSI standards and guidelines used for measurement procedure evaluations, this report includes definitions of several relevant statistical terms and descriptions of specific statistical tools.

Because CLSI documents are updated regularly, they are considered an authoritative source for how evaluations should be performed. EP19 is only intended to provide general guidance on which specific CLSI documents may be used for evaluations and considerations for how users might most effectively use them, depending upon their needs. Users of EP19 will need to refer to the relevant CLSI documents for sufficient details to perform the evaluations correctly. Some measurement procedures, eg, those that produce an index result (ie, discreet categories, eg, positive, negative, specific mutation result) will involve special evaluations for which, currently, there are no CLSI documents.

1.1.1 Intended User

EP19 is intended for use by clinical laboratory professionals, manufacturers, and governmental agencies. The term "manufacturers" includes both commercial manufacturers and clinical and other laboratories that

conduct research and measurement procedure development. Clinical laboratories that modify commercial measurement procedures, eg, by changing the reagent, sample volumes, or sample types; adding analyte-specific reagents (ASRs); changing to sample types that are not mentioned in the product labeling; as well as many other potential modifications, are essentially creating a new measurement procedure. In this case, the laboratory needs to establish acceptable performance through analytical validation and clinical validation, and then reverify performance as part of implementation.

It is important to clarify the need for laboratories to assume the responsibility for establishment of performance, regardless of whether they have a recognized research and development facility, or are clinical laboratories that incorporate presumably minor modifications to a measurement procedure or measuring system. According to EP19, both laboratories that create new measurement procedures and those that make relatively minor changes to commercial measurement procedures are considered manufacturers.

EP19 was written to be especially useful for laboratorians who are just beginning to use CLSI documents, including those who work in laboratories that may have been modifying commercial measurement procedures without performing any subsequent evaluations. These laboratories may have been using CLSI documents to a limited extent or not at all. The EP19 high-level roadmap is expected to be a helpful resource in these settings.

1.2 Background

Organizing the existing CLSI standards and guidelines into the EP19 framework requires articulation of a new concept, the measurement procedure lifecycle (see Tables 1 and 2), which categorizes evaluations into two major functions, or **stages:** establishment and implementation. Establishment, which is conducted by the manufacturer regardless of whether it is a commercial manufacturer or a clinical laboratory, consists of orderly **steps:** feasibility, design, development, and validation. In addition, before the measurement procedure system is launched, there may be additional field demonstration of acceptable performance in a small number of clinical laboratories. After the measurement procedure system is cleared or approved by regulatory authorities and is deemed ready for market, it is launched by the manufacturer. Thereafter, the end user conducts implementation evaluations to support several stages, including preliminary evaluations, verification, measurement procedure launch, and measurement procedure maintenance.

In the United States, for laboratory-developed tests (LDTs), the US Food and Drug Administration (FDA) previously exercised enforcement discretion. Therefore, FDA did not enforce applicable regulatory requirements on clinical laboratories (found in 21 CFR Part 820[2]), such as obtaining clearance or approval before transitioning into implementation, if the LDT is used by the same laboratory that developed and manufactured the measurement procedure. However, FDA recently released draft guidance documents indicating that it intends to regulate certain LDTs, especially those with higher risk to the patient. It is anticipated that a European Union Directive may also address LDTs,[3] but at this time the issue of how LDTs used in-house would be regulated has not been clarified. The document development committee felt strongly that there is a need to provide guidance for laboratories that are essentially manufacturing their own measurement procedures. Regardless of regulatory authority decisions or actions, laboratories in the United States must comply with quality system requirements under the Clinical Laboratory Improvement Amendments of 1988 (CLIA)[12] to establish performance of a *de novo* or modified FDA-cleared or -approved measurement procedure. EP19 is expected to be useful for establishing each LDT's performance characteristics.

EP19 emphasizes the need to make judgments on acceptable risk. In general, risks that manufacturers may consider include patient risks due to incorrect or delayed measurement procedure results or risks related to the collection of a patient specimen, as applicable to the intended use of the measurement procedure results. Other risks involve possibilities of inaccurate analytical performance, including incorrect measurement procedure results. Of course, the two kinds of errors are linked because when risks of inaccurate testing increase, the risk to the patient also increases. For nearly every evaluation, the relevant stage in the

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system (QMS) approach in the development of standards and guidelines, which facilitates project management; defines a document structure using a template; and provides a process to identify needed documents. The QMS approach applies a core set of "quality system essentials" (QSEs), basic to any organization, to all operations in any health care service's path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The QSEs are as follows:

Organization	Personnel	Process Management	Nonconforming Event Management
Customer Focus	Purchasing and Inventory	Documents and Records	Assessments
Facilities and Safety	Equipment	Information Management	Continual Improvement

EP19 addresses the QSEs indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on page 60.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
					X	X	X	AUTO 03 AUTO07		X	
						AUTO08 AUTO10 C24 C56 EP05 EP06 EP07 EP09 EP10 EP12 EP14 EP15 EP17 EP18 EP21 EP23 EP24 EP25 EP26 EP27 EP28 EP31 GP27 GP29 M07 M11 M22 M23 M27 M28 M40 MM03 MM17				EP10 EP18 GP27 GP29	EP18 GP27
		M29					M07				
QMS01	QMS01	QMS01	QMS01	QMS01	QMS01 QMS13	QMS01	QMS01 QMS02	QMS01	QMS01	QMS01	QMS01

Related CLSI Reference Materials*

AUTO03 **Laboratory Automation: Communications With Automated Clinical Laboratory Systems, Instruments, Devices, and Information Systems. 2nd ed., 2009.** This document provides standards to facilitate accurate and timely electronic exchange of data and information between the automated laboratory elements.

AUTO07 **Laboratory Automation: Data Content for Specimen Identification. 1st ed., 2004.** This document provides specifications for the content of linear bar codes on specimen container tubes in the clinical laboratory and for use on laboratory automation systems.

AUTO08 **Managing and Validating Laboratory Information Systems. 1st ed., 2006.** This document provides guidance for developing a protocol for validation of the laboratory information system (LIS) as well as protocols for assessing the dependability of the LIS when storing, retrieving, and transmitting data.

AUTO10 **Autoverification of Clinical Laboratory Test Results. 1st ed., 2006.** This document provides a general framework that will allow each laboratory to easily design, implement, validate, and customize rules for autoverification (automated verification) based on the needs of its own patient population.

AUTO13 **Laboratory Instruments and Data Management Systems: Design of Software User Interfaces and End-User Software Systems Validation, Operation, and Monitoring. 2nd ed., 2003.** This document identifies important factors that designers and laboratory managers should consider when developing new software-driven systems and selecting software user interfaces. Also included are simple rules to help prepare validation protocols for assessing the functionality and dependability of software.

C24 **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions. 3rd ed., 2006.** This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.

C56 **Hemolysis, Icterus, and Lipemia/Turbidity Indices as Indicators of Interference in Clinical Laboratory Analysis. 1st ed., 2012.** This document provides background information on mechanisms of hemolysis, icterus, lipemia/turbidity (HIL) interference; intended usefulness of HIL indices; establishment of HIL alert indices; availability of automated HIL detection systems; and interpretation, strengths, limitations, and verification of HIL indices in the clinical laboratory.

EP05 **Evaluation of Precision Performance of Quantitative Measurement Procedures. 3rd ed., 2014.** This document provides guidance for evaluating the precision performance of quantitative measurement procedures. It is intended for manufacturers of quantitative measurement procedures and for laboratories that develop or modify such procedures.

EP06 **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach. 1st ed., 2003.** This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.

EP07 **Interference Testing in Clinical Chemistry. 2nd ed., 2005.** This document provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interfering substances on clinical chemistry test results.

EP09 **Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed., 2013.** This document addresses the design of measurement procedure comparison experiments using patient samples and subsequent data analysis techniques used to determine the bias between two *in vitro* diagnostic measurement procedures.

EP10 **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures. 3rd ed., 2006.** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

Related CLSI Reference Materials (Continued)

EP12 **User Protocol for Evaluation of Qualitative Test Performance. 2nd ed., 2008.** This document provides a consistent approach for protocol design and data analysis when evaluating qualitative diagnostic tests. Guidance is provided for both precision and method-comparison studies.

EP14 **Evaluation of Commutability of Processed Samples. 3rd ed., 2014.** This document provides guidance for evaluating the commutability of processed samples by determining if they behave differently than unprocessed patient samples when two quantitative measurement procedures are compared.

EP15 **User Verification of Precision and Estimation of Bias. 3rd ed., 2014.** This document describes the estimation of imprecision and of bias for clinical laboratory quantitative measurement procedures using a protocol that can be completed within as few as five days.

EP17 **Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures. 2nd ed., 2012.** This document provides guidance for evaluation and documentation of the detection capability of clinical laboratory measurement procedures ie, limit of blank, detection, and quantitation), for verification of manufacturers' detection capability claims, and for the proper use and interpretation of different detection capability estimates.

EP18 **Risk Management Techniques to Identify and Control Laboratory Error Sources. 2nd ed., 2009.** This guideline describes risk management techniques that will aid in identifying, understanding, and managing sources of failure potential failure modes) and help to ensure correct results. Although intended primarily for *in vitro* diagnostics, this document will also serve as a reference for clinical laboratory managers and supervisors who wish to learn about risk management techniques and processes.

EP21 **Estimation of Total Analytical Error for Clinical Laboratory Methods. 1st ed., 2003.** This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method which can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay's total analytical error by using quality control samples.

EP23™ **Laboratory Quality Control Based on Risk Management. 1st ed., 2011.** This document provides guidance based on risk management for laboratories to develop quality control plans tailored to the particular combination of measuring system, laboratory setting, and clinical application of the test.

EP24 **Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves. 2nd ed., 2011.** This document provides a protocol for evaluating the accuracy of a test to discriminate between two subclasses of subjects when there is some clinically relevant reason to separate them. In addition to the use of receiver operating characteristic curves and the comparison of two curves, the document emphasizes the importance of defining the question, selecting the sample group, and determining the "true" clinical state.

EP25 **Evaluation of Stability of *In Vitro* Diagnostic Reagents. 1st ed., 2009.** This document provides guidance for establishing shelf-life and in-use stability claims for *in vitro* diagnostic reagents such as reagent kits, calibrators, and control products.

EP26 **User Evaluation of Between-Reagent Lot Variation. 1st ed., 2013.** This document provides guidance for laboratories on the evaluation of a new reagent lot, including a protocol using patient samples to detect significant changes from the current lot.

EP27 **How to Construct and Interpret an Error Grid for Quantitative Diagnostics Assays. 1st ed., 2012.** This guideline describes what an error grid is, why it is useful, and how to construct one and interpret the information. Guidance is provided for manufacturers and for the clinical laboratory.

EP28 **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory. 3rd ed., 2010.** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests.

EP30 **Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine. 1st ed., 2010.** This document provides information to help material manufacturers in the production and characterization of commutable reference materials, as well as to assist assay manufacturers and laboratorians in the appropriate use of these materials for calibration and trueness assessment of *in vitro* diagnostic medical devices.

Related CLSI Reference Materials (Continued)

EP31 **Verification of Comparability of Patient Results Within One Health Care System, Interim Revision. 1st ed., 2012.** This document provides guidance on how to verify comparability of quantitative laboratory results for individual patients within a health care system.

GP27 **Using Proficiency Testing to Improve the Clinical Laboratory. 2nd ed., 2007.** This guideline provides assistance to laboratories in using proficiency testing as a quality improvement tool.

GP29 **Assessment of Laboratory Tests When Proficiency Testing Is Not Available. 2nd ed., 2008.** This document offers methods to assess test performance when proficiency testing PT) is not available; these methods include examples with statistical analyses. This document is intended for use by laboratory managers and testing personnel in traditional clinical laboratories as well as in point-of-care and bedside testing environments.

M07 **Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 10th ed., 2014.** This document addresses reference methods for the determination of minimal inhibitory concentrations of aerobic bacteria by broth macrodilution, broth microdilution, and agar dilution.

M11 **Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria. 8th ed., 2012.** This standard provides reference methods for the determination of minimal inhibitory concentrations of anaerobic bacteria by agar dilution and broth microdilution.

M22 **Quality Control for Commercially Prepared Microbiological Culture Media. 3rd ed., 2004.** This document contains quality assurance procedures for manufacturers and users of prepared, ready-to-use microbiological culture media.

M23 **Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters. 3rd ed., 2008.** This document addresses the required and recommended data needed for the selection of appropriate interpretive criteria and quality control ranges for antimicrobial agents.

M27 **Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 3rd ed., 2008.** This document addresses the selection and preparation of antifungal agents; implementation and interpretation of test procedures; and quality control requirements for susceptibility testing of yeasts that cause invasive fungal infections.

M28 **Procedures for the Recovery and Identification of Parasites From the Intestinal Tract. 2nd ed., 2005.** This guideline addresses the collection, processing, and examination of intestinal tract specimens for the identification of parasites.

M29 **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

M40 **Quality Control of Microbiological Transport Systems. 2nd ed., 2014.** This document provides criteria to assist manufacturers and end users of transport devices in providing and selecting dependable products for the transport of microbiological clinical specimens.

M50 **Quality Control for Commercial Microbial Identification Systems. 1st ed., 2008.** This document provides guidance for quality control of commercial systems for microbial identification from culture, including information that pertains to manufacturers, distributors, and laboratory users. The intent is to ensure optimal performance of a microbial identification system in an efficient streamlined) manner.

M100S **Performance Standards for Antimicrobial Susceptibility Testing. 25th ed., 2015.** This document provides updated tables for the Clinical and Laboratory Standards Institute antimicrobial susceptibility testing standards M02-A12, M07-A9, and M11-A8.

Related CLSI Reference Materials (Continued)

MM03 **Molecular Diagnostic Methods for Infectious Diseases. 2nd ed., 2006.** This guideline addresses topics relating to clinical applications, amplified and nonamplified nucleic acid methods, selection and qualification of nucleic acid sequences, establishment and evaluation of test performance characteristics, inhibitors, and interfering substances, controlling false-positive reactions, reporting and interpretation of results, quality assurance, regulatory issues, and recommendations for manufacturers and clinical laboratories.

MM17 **Verification and Validation of Multiplex Nucleic Acid Assays. 1st ed., 2008.** This guideline provides recommendations for analytic verification and validation of multiplex assays, as well as a review of different types of biologic and synthetic reference materials.

QMS01 **Quality Management System: A Model for Laboratory Services. 4th ed., 2011.** This document provides a model for medical laboratories that will assist with implementation and maintenance of an effective quality management system.

QMS02 **Quality Management System: Development and Management of Laboratory Documents. 6th ed., 2013.** This document provides guidance on the processes needed for document management, including creating, controlling, changing, and retiring a laboratory's policy, process, procedure, and form documents in both paper and electronic environments.

QMS13 **Quality Management System: Equipment. 1st ed., 2011.** This guideline provides recommendations for establishing equipment management processes from selection through decommission of equipment used in the provision of laboratory services.

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