CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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EP17-A2

Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition

This document provides guidance for evaluation and documentation of the detection capability of clinical laboratory measurement procedures (ie, limits of blank, detection, and quantitation), for verification of manufacturers' detection capability claims, and for the proper use and interpretation of different detection capability estimates.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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For further information on committee participation or to submit comments, contact CLSI.

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Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition

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Abstract

Clinical and Laboratory Standards Institute document EP17-A2—*Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition* provides guidance for evaluating the detection capability of clinical laboratory measurement procedures (ie, limits of blank, detection, and quantitation), for verification of manufacturers' detection capability claims, and for the proper use and interpretation of different detection capability estimates. EP17 is intended for use by manufacturers of *in vitro* diagnostic tests, regulatory bodies, and clinical laboratories.

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1 Scope

This document provides guidelines for the evaluation and verification of detection capability claims of clinical laboratory measurement procedures (ie, limit of blank [LoB], limit of detection [LoD], and limit of quantitation [LoQ]), as well as for their proper use, documentation, and interpretation. This guidance is suitable both for commercial products as well as laboratory-developed tests. It is particularly important for measurement procedures for which the associated measurand's medical decision level is low (ie, approaching zero).

The intended users of this guideline are manufacturers of *in vitro* diagnostic (IVD) reagents, regulatory bodies, and clinical laboratory personnel.

2 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all known infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. The Centers for Disease Control and Prevention address this topic in published guidelines that focus on the daily operations of diagnostic medicine in human and animal medicine while encouraging a culture of safety in the laboratory.[6] For specific precautions for preventing the laboratory transmission of all known infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious diseases, refer to CLSI document M29.[7]

3 Terminology

3.1 A Note on Terminology

As a global leader in standardization, CLSI is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, International Organization for Standardization (ISO), and European Committee for Standardization (CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI's consensus process for development and revision of standards and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

Because of the widespread application of the LoD and LoQ concepts, a variety of terms are in common usage. This document does not attempt to explain or reconcile all of these terms. Terms particular to this document are defined in Section 3.2. However, there are two common terms that have nonstandard usage in the clinical laboratory. To prevent confusion, these terms are discussed in Sections 3.1.1 and 3.1.2.

3.1.1 Nonstandard Use of "Critical Value"

The term "critical value" is defined in ISO 11843-1[1] as the highest result that can reasonably be expected from a blank sample (ie, a sample with concentration at or near zero) for a given error probability α. However, the term is widely used in clinical laboratories for test results that indicate an important medical condition (also sometimes referred to as "alarm value"). In this document, the ISO term is replaced by "LoB."

3.1.2 Nonstandard Use of "Sensitivity"

The term "sensitivity" and its variants "analytical sensitivity" and "functional sensitivity" are not promoted in this document, because of the existence of several conflicting common uses of these terms across multiple technical disciplines. LoD is the preferred term for the detection capability attribute previously associated with analytical sensitivity (ie, signaling presence of a measurand in a sample) because of its more precise definition and common use. Similarly, LoQ is the preferred term for the detection capability attribute previously associated with functional sensitivity (ie, denoting quantitative detection of a measurand in a sample with known measurement accuracy).

3.2 Definitions

accepted reference value – a value that serves as an agreed-upon reference for comparison, and that is derived as a) a theoretical or established value, based on scientific principles; b) an assigned or certified value, based on experimental work of some national or international organization; c) a consensus or certified value, based on collaborative experimental work under the auspices of a scientific or engineering group; and d) when a), b), and c) are not available, the expectation of the (measurable) quantity, ie, the mean of a specified population of measurements (ISO 3534-1).[8]

accuracy – closeness of agreement between a test result and the accepted reference value; **NOTE:** The term "accuracy," when applied to a set of test results, involves a combination of random components and a common systematic error or bias component (ISO 3534-1)[8]; see **trueness.**

analytical sensitivity – quotient of the change in a measurement indication and the corresponding change in a value of the quantity being measured (modified from JCGM 200:2012)[9]; **NOTE 1:** VIM uses the term "sensitivity of a measuring system" (JCGM 200:2012)[9]; **NOTE 2:** The analytical sensitivity of a measuring system is the slope of the calibration curve; **NOTE 3:** Analytical sensitivity should not be used to mean detection limit or quantitation limit, and should not be confused with diagnostic sensitivity (modified from ISO 18113-1).[10]

bias – difference between the expectation of the test results and an accepted reference value (ISO 3534-1)[8]; **NOTE:** Bias is a measure of **trueness.**

blank – sample that does not contain the analyte of interest, or has a concentration at least an order of magnitude less than the lowest level of interest.

censored data – the situation in which measurement results are simply reported as greater than or less than an imposed threshold rather than expressed in quantitative units; **NOTE:** For example, a result is known to be less than a stated limit but the actual result value is not available.

functional sensitivity – the measurand concentration at which precision of a measurement procedure, under stated experimental conditions, meets a stated performance requirement; **NOTE 1:** It is typically determined from a precision profile; **NOTE 2:** The term "limit of quantitation" with stated requirement for accuracy is recommended.

The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The quality management system 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

EP17-A2 addresses the QSE 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 the following page.

Organization	Customer Focus	Facilities and Safety	Personnel	Purchasing and Inventory	Equipment	Process Management	Documents and Records	Information Management	Nonconforming Event Management	Assessments	Continual Improvement
		M29				X C51 EP05 EP06 EP07 EP12 EP14 EP15 MM03				MM03	EP07

Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

EP17-A2 does not address any of the clinical laboratory path of workflow processes indicated in the grid below. For a description of the document listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

Preexamination				**Examination**			**Postexamination**	
Examination ordering	Sample collection	Sample transport	Sample receipt/processing	Examination	Results review and follow-up	Interpretation	Results reporting and archiving	Sample management
	MM03	MM03	MM03	MM03	MM03		MM03	

Related CLSI Reference Materials*

C51-A **Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline (2012).** This guideline describes a practical approach to assist clinical laboratories in developing and calculating useful estimates of measurement uncertainty, and illustrates their application in maintaining and improving the quality of measured values used in patient care. A CLSI-IFCC joint project.

EP05-A2 **Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (2004).** This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers' precision performance claims and determining when such comparisons are valid; as well as manufacturers' guidelines for establishing claims.

EP06-A **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (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-A2 **Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition (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.

EP12-A2 **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition (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-A2 **Evaluation of Matrix Effects; Approved Guideline—Second Edition (2005).** This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two measurement procedures are compared.

EP15-A2 **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2006).** This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods utilizing a protocol designed to be completed within five working days or less.

M29-A3 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** 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.

MM03-A2 **Molecular Diagnostic Methods for Infectious Diseases; Approved Guideline—Second Edition (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.

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

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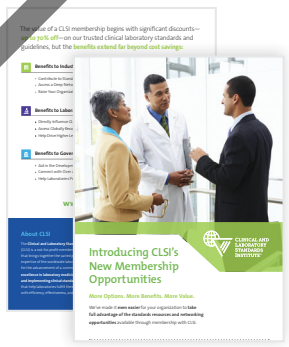
Fundamentals for implementing a quality management system in the clinical laboratory.



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