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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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Clinical and Laboratory Standards Institute  
950 West Valley Road, Suite 2500  
Wayne, PA 19087 USA  
P: 610.688.0100  
F: 610.688.0700  
[www.clsi.org](http://www.clsi.org)  
[standard@clsi.org](mailto:standard@clsi.org)

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

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James F. Pierson-Perry  
Jeffrey E. Vaks, PhD  
A. Paul Durham, MA  
Christian Fischer, MD  
Cornelius Gutenbrunner, PhD  
David Hillyard, MD  
Marina V. Kondratovich, PhD  
Paula Ladwig  
Robert A. Middleberg, PhD, DABFT, DABCC

### 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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## Committee Membership

### Consensus Committee on Evaluation Protocols

**James F. Pierson-Perry**  
**Chairholder**

**Siemens Healthcare Diagnostics**  
**Newark, Delaware, USA**

Rex Astles, PhD, FACB, DABCC  
Centers for Disease Control and  
Prevention  
Atlanta, Georgia, USA

Jonathan Guy Middle, PhD  
University Hospital Birmingham  
NHS Trust  
Birmingham, United Kingdom

**Mitchell G. Scott, PhD**  
**Vice-Chairholder**

**Barnes-Jewish Hospital**  
**Washington University School of**  
**Medicine**  
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Jeffrey R. Budd, PhD  
Beckman Coulter  
Chaska, Minnesota, USA

James H. Nichols, PhD, DABCC,  
FACB  
Baystate Medical Center  
Springfield, Massachusetts, USA

Karl De Vore  
Bio-Rad Laboratories, Inc.  
Irvine, California, USA

Gene Pennello, PhD  
FDA Center for Devices and  
Radiological Health  
Silver Spring, Maryland, USA

### Document Development Committee on Detection Capability for Clinical Laboratory Measurements Procedures

**James F. Pierson-Perry**  
**Chairholder**

**Siemens Healthcare Diagnostics**  
**Newark, Delaware, USA**

Marina V. Kondratovich, PhD  
FDA Center for Devices and  
Radiological Health  
Silver Spring, Maryland, USA

Luann Ochs, MS  
*Senior Vice President – Operations*

**Jeffrey E. Vaks, PhD**  
**Vice-Chairholder**

**Roche Molecular Diagnostics**  
**Pleasanton, California, USA**

Paula Ladwig  
Mayo Clinic  
Rochester, Minnesota, USA

Ron S. Quicho  
*Staff Liaison*

Patrice E. Polgar  
*Project Manager*

Christian Fischer, MD  
Abbott GmbH & Co. KG  
Wiesbaden-Delkenheim, Germany

Robert A. Middleberg, PhD,  
DABFT, DABCC  
National Medical Services, Inc.  
Willow Grove, Pennsylvania, USA

Megan P. Larrisey, MA  
*Editor*

Ryan J. Torres  
*Assistant Editor*

David Hillyard, MD  
University of Utah  
ARUP Laboratories  
Salt Lake City, Utah, USA

#### **Staff**

Clinical and Laboratory Standards  
Institute  
Wayne, Pennsylvania, USA

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A. Paul Durham, MA  
Culver City, California, USA

Cornelius Gutenbrunner, PhD  
Siemens Healthcare Diagnostics Products GmbH  
Marburg, Germany



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## Foreword

Detection capability is a fundamental performance characteristic of clinical laboratory measurement procedures, most often serving to denote the low-end boundary of a measurement procedure's measuring interval. However, understanding and evaluating detection capability may often be confusing because of the different types of estimates, experimental protocols, and nomenclature used in manufacturers' product claims, as well as within scientific literature throughout the past several decades.

The use of multiple detection capability estimates arises from a need to reflect increasing quantitative certainty within the low-end region of the measuring interval. This ranges from an upper boundary on blank sample measurements (the limit of blank or LoB), through "yes/no" detection of measurand presence (the limit of detection or LoD), up to the minimal measurand amount that can be quantitated reliably with respect to defined accuracy goals (the limit of quantitation or LoQ). Depending on the particular measurement procedure and its application, one, two, or all three of these estimates may be necessary to adequately characterize performance in the low-end region of the measuring interval.

The LoB and LoD are objective statistical constructs that are calculated solely on the basis of the inherent measurement procedure precision and bias. In contrast, the LoQ reflects performance of the measurement procedure vs a preestablished accuracy goal. This is a more subjective value, because the LoQ for a given measurement procedure may vary among different users or applications depending on what are used as the relevant accuracy goals.

The LoD and LoQ are critical when detection of extremely small amounts of a measurand is necessary to define disease states, screen for presence of disease, identify significant exposure, or reveal the presence or absence of substances such as toxins, pollutants, carcinogens, contaminants, infectious agents, and drugs. Knowledge of these estimates also is important for laboratory measurement procedures that measure circulating levels of tumor markers, hormones, infectious disease agents, therapeutic drugs, and other biomarkers for which low results separate subjects into different disease or exposure categories. Even for measurement procedures that report results in qualitative or semiquantitative units, as long as the measurand is a quantity value the developer can use knowledge of the measurement procedure's detection capability to ensure that the measurement procedure design goals were achieved.

Since its original publication in 2004, EP17 has been widely used by manufacturers of *in vitro* diagnostic products to establish product performance claims and by clinical laboratory personnel to verify the claims, and is recognized internationally by regulatory bodies. The present revision builds on the original document by expanding the evaluation protocols to include molecular measurement procedures and providing a more parametric estimate of LoD, as well as by addressing issues of clarity, protocol experimental design requirements, and data analyses. The document title was changed to reflect a broader focus on detection capability as a whole, rather than confining the document to the scope implied by the previous title, *Protocols for Determination of Limits of Detection and Limits of Quantitation*.

Content of this guideline is aligned with International Organization for Standardization document 11843, *Parts 1–5: Capability of detection*.<sup>1-5</sup>

## Key Words

Analytical sensitivity, functional sensitivity, limit of blank, limit of detection, limit of quantitation, nonparametric statistics, precision profile, probit



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

### **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.<sup>6</sup> 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.<sup>7</sup>

### **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.