CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition

This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

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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Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition

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Abstract

Clinical and Laboratory Standards Institute document EP10-A3-AMD—*Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition* is intended to facilitate a limited, preliminary evaluation of the performance of a measurement procedure or device. Using the experimental design and data analysis procedure described, determination of whether a device has problems that require further evaluation or referral to the manufacturer can be done with a minimum expenditure of time and material. Included in Appendixes A and B are sample data sheets that should facilitate the analysis of the data. Appendix C contains a more sophisticated, powerful, statistical method for determining the possible causes of imprecision.

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Foreword

Before using a new measurement procedure or instrument for *in vitro* diagnostic use, the laboratory must make a preliminary decision about its acceptability. This initial performance check is neither a rigorous characterization of long-term performance nor an evaluation of the many factors that can affect results produced by the device. Rather, this experiment is a quick check to rule out major problems and a starting point for accumulating data and experience that will enable the user to make a final decision. The primary purpose of this document is to help detect performance problems that would warrant immediate correction, referral to the manufacturer, or expanded investigation before a new device is placed into service.

This document may also now be used by manufacturers to either establish the magnitude of factors that can affect performance or verify that such magnitude is acceptable.

Additional revisions since the last edition of EP10 (2002) include:

- a figure to illustrate which error sources the EP10 protocol can detect with respect to all error sources and other EP documents (see page viii);
- suggested sample sizes, so now the document is useful for manufacturers;
- instructions for the multiple regression calculations;
- revised references; and
- revised definitions.

Key Words

Carry-over, comparison of methods, drift, evaluation protocol, experimental design, linearity, multiple regression, outlier, precision

Note that the trade name Microsoft® Excel is included in Section 16 of this document. It is Clinical and Laboratory Standards Institute's policy to avoid using a trade name unless the product identified is the only one available, or it serves solely as an illustrative example of the procedure, practice, or material described. In this case, the working group and consensus committee believe the trade name is an important descriptive adjunct to the document. In such cases, it is acceptable to use the product's trade name, as long as the words, "or the equivalent" are added to the references. It should be understood that information on this product in this standard also applies to any equivalent products. Please include in your comments any information that relates to this aspect of EP10.

Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition

1 Scope

Before starting a complete evaluation of a new measurement procedure, kit, or instrument for *in vitro* diagnostic use, it is often necessary to make a preliminary decision about its acceptability. This initial performance check is neither a rigorous investigation into the procedure's long-term performance, nor an evaluation of the many factors that can affect results produced by the device. The primary purpose of this document is to help detect problems that are severe enough to warrant immediate correction, referral to the manufacturer, or expanded investigation. Accreditation bodies may have requirements for verification or validation that exceed the procedures in this document (see CLSI document EP15[1]).

Manufacturers can also benefit by performing this protocol either as assays are developed or when they are validated. By performing more than five runs, manufacturers can detect trends in the effects estimated by EP10 or document their absence.

2 Introduction

This document describes a procedure for the preliminary evaluation of linearity, proportional and constant bias, linear drift, sample carry-over, and precision of a clinical laboratory measurement procedure. Preliminary evaluations should be performed before new procedures are used to test patients' samples and when any modifications of procedures are made. This guideline is based on a protocol and procedure developed for continuous flow analyzers.[2] The rationale for recommending a protocol based on so old a system is explained in Section 13.1. The experiment is intended primarily for evaluating automated instruments but may be appropriate for kits, manual procedures, or other *in vitro* diagnostic devices. By repeating a sequence of only ten samples, performance characteristics may be evaluated by plotting the data and performing some simple calculations. Using a statistical technique called multiple linear regression analysis, further information about the factors influencing accuracy (such as sample carry-over linear drift, and nonlinearity) can be obtained. Instructions are given for simple data analysis, in case a computer is not available.

The experiment is intended to provide preliminary estimates of those performance characteristics that may be used to determine the ultimate acceptability of the device. The results should be used only to determine whether the device has grossly unacceptable performance.

The following sections outline the materials and procedures to be used. Many variations on this basic experiment are possible (such as extending the number of days or eliminating the priming samples when appropriate). Variations should be dictated by the complexities of the device, the particular characteristics of the measurement procedure, and the resources available to the user.

3 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 infectious agents and thus are more comprehensive than universal precautions which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the U.S. Centers for Disease Control and Prevention (Garner JS, Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. *Infect Control Hosp Epidemiol*. 1996;17(1):53-80). For

specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to the most current edition of CLSI document M29—*Protection of Laboratory Workers From Occupationally Acquired Infections*.

4 Terminology

4.1 A Note on Terminology

CLSI, as a global leader in standardization, is 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, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all obstacles to harmonization. In light of this, CLSI recognizes that harmonization of terms facilitates the global application of standards and is an area of immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

Specifically, in EP10, the following terms have been changed to be consistent with accepted international usage (where appropriate): *accuracy* has been changed to *trueness; analyte* has been changed to *measurand*; *analytical method* has been changed to *measurement procedure; total error* has been changed to *error (of measurement);* and *precision* has been changed to *imprecision* (if expressed quantitatively).

4.2 Definitions

acceptability – based on individual criteria that set the minimum operational characteristics for a particular measurement procedure.

accepted reference value – a value that serves as an agreed upon reference for comparison, and which 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, i.e., the mean of a specified population of measurements.[3] (ISO 3534-1)

accuracy (of measurement) – closeness of the agreement between the result of a measurement and a true value of the measurand (VIM93)[4]; **NOTE 1:** In practice, an accepted reference value is substituted for the true value (ISO 3534-2)[5]; **NOTE 2:** Accuracy refers to a combination of trueness and precision (ISO 3534-2).[5]

adjusted variance – a statistical manipulation that adjusts the measured variance by subtracting components from other sources of variance; **NOTE 1:** For example, between-run variance is adjusted by subtracting the contribution from within-run variance; **NOTE 2:** Appendix C of this document describes a measurement procedure for determining adjusted variance.

analyte – component represented in the name of a measurable quantity[6] (ISO 17511); **NOTE:** Formerly in this document, analyte was used to describe both a single component (analyte) as well as the analyte in its specific matrix (**measurand**).

assigned value – value attributed to a particular quantity and accepted, sometimes by convention, as having an uncertainty appropriate for a given purpose (VIM93).[4]

The Quality 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 approach is based on the model presented in the most current edition of CLSI/NCCLS document HS1—*A Quality Management System Model for Health Care.* The quality management system approach applies a core set of "quality system essentials" (QSEs), basic to any organization, to all operations in any healthcare service's path of workflow (i.e., 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 quality system essentials (QSEs) are:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessments—External and Internal	Facilities & Safety

EP10-A3-AMD addresses the quality system essentials (QSEs) indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI/NCCLS Publications section on the following page.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
	EP18	EP18			X EP5 EP6 EP7 EP9 EP12 EP14 EP15 EP17 EP18 EP19 EP21 GP10 X5		EP18	X EP18	EP7 EP18		

Adapted from CLSI/NCCLS document HS1—*A Quality Management System Model for Health Care*.

Evaluation Protocols Documents, Descriptions, and Key Words

EP5-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.

Evaluation protocol, experimental design, medical devices, outlier, precision, quality control

EP6-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.

Allowable difference, allowable error, linearity, matrix effects, measurement error, total error, uncertainty

EP7-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.

Evaluation, hazard analysis, interference, interferent, matrix effects, performance claims, risk management, specificity, validation, verification

EP9-A2 Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (2002). This document addresses procedures for determining the bias between two clinical methods, and the design of a method comparison experiment using split patient samples and data analysis.

Bias, evaluation protocol, experimental design, linear regression, method comparison, quality control, residuals

EP12-A User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline (2002). This document contains a protocol to optimize the experimental design for the evaluation of qualitative tests; to better measure performance; and to provide a structured data analysis.

Analytical goals, qualitative test, semiquantitative test

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.

Analytical interference, bias, matrix, matrix effect, physicochemical interference

EP15-A2 User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2005). 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.

Bias, precision, repeatability, trueness, verification of performance

EP17-A Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004). This document provides guidance for determining the lower limit of detection of clinical laboratory methods, for verifying claimed limits, and for the proper use and interpretation of the limits.

Limit of blank, limit of detection, limit of quantitation, nonparametric statistics

EP18-A Quality Management for Unit-Use Testing; Approved Guideline (2002). This guideline recommends a quality management system for unit-use devices that will aid in the identification, understanding, and management of sources of error (potential failure modes) and help to ensure correct results. It is targeted for those involved in the supervision of laboratory-testing quality management, and it addresses issues related to specimen collection through reporting of test results.

Quality assurance, quality control, quality management, quality system, unit-use system

Evaluation Protocols Documents, Descriptions, and Key Words (Continued)

EP19-R A Framework for NCCLS Evaluation Protocols; A Report (2002). This document describes the different types of performance studies that are conducted to evaluate clinical assays.

Demonstration, evaluation protocol, validation, verification

EP21-A Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline (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.

Error, error of measurement, measurement error, total analytical error, total analytical error interval

GP10-A Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristics (ROC) Plots; Approved Guideline (1995). This document provides a protocol for evaluating the accuracy of a test to discriminate between two subclasses of subjects where there is some clinically relevant reason to separate them. In addition to the use of ROC plots, the importance of defining the question, selecting the sample group, and determining the "true" clinical state are emphasized.

Clinical accuracy, false-negative fraction, false-positive fraction, medical decision analysis, performance evaluation, receiver operating characteristic (ROC) plot, sensitivity, specificity, true-negative fraction, true-positive fraction

Other Related Publication

X5-R Metrological Traceability and Its Implementation; A Report (2006). This document provides guidance to manufacturers for establishing and reporting metrological traceability.

Calibrator, certified reference material, commutability, metrological traceability, reference measurement procedure, uncertainty of measurement, validation, value assignment

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