CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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EP05-A3

Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition

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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.

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

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Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition

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Abstract

Clinical and Laboratory Standards Institute document EP05-A3—*Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition* provides guidance for evaluating the precision of *in vitro* diagnostic quantitative measurement experimental designs and includes recommendations for establishing precision performance. Included are guidelines for duration, experimental designs, materials, data analysis, summarization, and interpretation—techniques adaptable for a wide spectrum of measurands and system complexity. These guidelines are intended for manufacturers or developers of clinical laboratory measurement procedures, and for users who wish to determine their own performance characteristics. A balance is created in the document between complexity of design and analysis, and simplicity of operation.

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Foreword

Current clinical laboratory literature contains numerous examples of product evaluations. For characterizing basic precision types, many of these examples use the basic concepts, designs, and analyses discussed in this guideline. In special cases, more complex and customized experimental designs have been used for both published studies and regulatory purposes. However, there remains a strong need in the clinical laboratory community for the basic rationales and approaches described in this document for assessing the precision performance characteristics of quantitative measurement procedures.

The great diversity of *in vitro* diagnostic devices currently available makes it impossible to recommend a single experimental design for all measurement procedures and associated devices. Nevertheless, requirements for materials, procedures, data analysis, and interpretation must be adaptable for the widest possible variety of measurands and instruments. In developing the standardized protocols in this document, many recommendations for duration, inclusion of QC procedures, and methods of determining the relevant sources of variation were carefully considered. The resulting protocols represent a balance between complexity of design and data analysis, and simplicity of implementation and efficiency. This document was written to provide general guidance consistent with other international consensus standards.

KEY WORDS

Analysis of variance

Evaluation protocol

Experimental design

Imprecision

Outliers

Precision

Precision profile

Quality control

Repeatability

Reproducibility

Variance components

Within-laboratory precision

Overview of Changes

The third edition narrows the scope of EP05 by limiting its discussion of single-site experimental designs to procedures suitable for establishing or validating precision performance characteristics. Accordingly, EP05 is now addressed primarily to manufacturers and developers. Recommendations for end-user laboratories for verifying repeatability and within-laboratory precision claims can be found in CLSI document EP15[1]. The precision verification protocol in that guideline has been tailored for compatibility with EP05's single-site study designs.

The single-site protocol familiar from previous editions of EP05—calling for measurements on 20 days, with two runs per day and two replicates per run for a given sample, reagent lot, etc.—is retained in this third edition as a standardized experiment for use by manufacturers and developers in evaluating the repeatability and within-laboratory (within-device) precision of a measurement procedure (or "assay").

No matter how these performance characteristics are established, it is important that the assessments be verifiable, and that they characterize precision over a substantial period of time and across most of the assay's stated measuring interval. The single-site experimental designs described in EP05 meet these requirements (see Chapter 3). It is expected that the original "20×2×2" design will continue to serve well for the great majority of quantitative assays used in clinical laboratories. However, extensive guidance was added on how to optimize this design for a given assay in light of its sources of variation and their relative magnitudes and interrelationships (see Chapter 2).

Moreover, in recognition of the wide diversity of quantitative devices in use today, which differ in character and complexity, variants of the 20×2×2 design are also discussed. Appendix C is devoted to advanced models—multifactor designs—for use when a two-factor design lacks the ability to do justice to the major sources of

NOTE:

The **original 20×2×2 protocol** is expected to continue to serve well for most assays.

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NOTE:

New to EP05 is an ancillary multisite protocol for estimating **reproducibility.**

NOTE:

EP05 now includes a **tutorial** on precision concepts for the nonstatistician.

IMPORTANT NOTE:

The user should have access to software for variance component analysis, such as **CLSI's StatisPro.**

variation affecting an assay's within-laboratory precision. Depending on the assay, some of these models should also prove useful to manufacturers for the insights they can yield both during assay development and optimization and after the assay enters routine production.

New to EP05 is a second standardized experiment: a multisite protocol calling, minimally, for repeated measurements at three sites on five days. Both 3 (sites) × 5 (days) × 5 (replicates per day) and 3 (sites) × 5 (days) × 2 (runs per day) × 3 (replicates per run) implementations are described (see Chapter 4). This ancillary protocol addresses site-to-site variability and estimates of reproducibility. It has been tailored for suitability in the context of validating a new assay, when such a study may be required due to the assay's character and/or to regulatory demands.

To help foster understanding of basic concepts, the new edition includes an extensive tutorial for the nonstatistician (see Section 1.5). Numerical examples illustrating a single-site 20 × 2 × 2 study and a complete multisite 3 × 5 × 5 study are presented in the appendixes.

Due to the complex nature of the calculations in this guideline, it is recommended that the user have access to a computer and statistical software, such as StatisPro™ method evaluation software from CLSI.

Consistency With International Standards

EP05 is largely consistent with recommendations in the ISO 5725 series of standards, particularly ISO 5725-3.[2] EP05's single-site study incorporates the basic concepts in ISO 5725-2.[3] Whereas the ISO 5725 perspective places primary emphasis on interlaboratory sources of variation, EP05 has focused on within-laboratory sources of variation accumulating over time. However, EP05's newly introduced multisite study addresses site-to-site sources of variation and estimates of reproducibility.

Furthermore, while the ISO 5725 series requires characterizing both repeatability and reproducibility across the entire measuring interval, this is encouraged (but not required) in EP05.

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Chapter 1

Introduction

This chapter includes:

- Document scope and limitations
- Standard precautions information, as applicable
- Terminology: definitions, abbreviations, and symbols
- Introduction to basic concepts: a tutorial on precision and precision evaluation studies

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Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition

1 Introduction

1.1 Scope

This document provides guidance for studies intended to establish the within-site precision performance characteristics of quantitative measurement procedures used in clinical laboratories, and also for studies addressing site-to-site variability. Multiple experimental protocols are described, along with considerations on how to select and optimize the protocol(s) best suited for a specific measurement procedure (or "assay") and its intended use.

1.1.1 Intended Users

Intended users of this document are:

- Developers of a new measurement procedure who wish to establish its precision characteristics, be it a manufacturer that wants to distribute the product to multiple laboratories, or a clinical laboratory developing it for their own use
- End users who modify an existing assay and therefore need to reassess its precision performance
- Users who want to understand how precision performance estimates are established and/or want to perform rigorous precision assessments of their own
- Manufacturers in need of advanced methods (see Appendix C) for obtaining deeper insights into the precision characteristics of a quantitative measurement procedure during assay development, optimization, and routine manufacture

It is assumed that readers of this document have some familiarity with statistical data analysis, including basic analysis of variance (ANOVA), or access to statistical support resources. Section 1.5 provides a brief introduction to several of the basic concepts involved; while CLSI document EP15[1] includes a detailed discussion of one-way ANOVA.

NOTE:

For guidance on **verifying precision claims,** consult CLSI document EP15.[1]

1.1.2 Limitations on Use

Those wishing only to verify a manufacturer's claims for the precision of a quantitative clinical measurement procedure should follow the guidance in CLSI document EP15.[1]

The protocols in this document may not be applicable to some quantitative measurement procedures for which appropriate test materials do not exist. In particular, the standardized single-site and multisite procedures are not directly applicable to measurement procedures involving samples with **inadequate stability** (eg, RBC count or blood gas determinations)

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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

EP05-A3 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
						X					
						C24					
						C56					
						EP10					
						EP12					
						EP15					
						EP17					
						EP25					
						EP29					
		M29									

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Related CLSI Reference Materials*

C24-A3 **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition (2006).** This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.

C56-A **Hemolysis, Icterus, and Lipemia/Turbidity Indices as Indicators of Interference in Clinical Laboratory Analysis; Approved Guideline (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.

EP10-A3-AMD **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2014).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

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.

EP15-A3 **User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition (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-A2 **Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition (2012).** 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.

EP25-A **Evaluation of Stability of *In Vitro* Diagnostic Reagents; Approved Guideline (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.

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* 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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Related CLSI Reference Materials (Continued)

EP29-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.

M29-A4 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Fourth Edition (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.

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