

EP15-A3

User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition

SAMPLE

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.

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

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User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition

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Abstract

Clinical and Laboratory Standards Institute document EP15-A3—*User Verification of Precision and Estimation of Bias; Approved Guideline—Third Edition* describes the verification of precision claims and estimation of relative bias for quantitative methods performed within the laboratory. Included are guidelines for duration, experimental designs, materials, data analysis summarization, and interpretation—techniques adaptable for the widest possible range of analytes and device complexity. A balance is created in the document between the complexity of design and formulae, and the simplicity of operation. The protocol is designed to be completed within five working days based on a uniform experimental design yielding estimates of imprecision and bias.

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Foreword

Before a laboratory can introduce a new measurement procedure for reporting results of patient testing, it must evaluate the procedure's analytical performance. Typically, laboratories specify the performance required of the procedure and then verify that the procedure's performance meets the specification. Performance requirements may be defined by regulatory requirements and/or medical usefulness requirements.

In this edition of EP15, the user is **verifying** the manufacturer's claim for precision, and **estimating** bias, because there is unlikely to be a bias claim to verify. The document development committee felt that it was necessary to keep precision and trueness together in one document because the document demonstrates how to measure both in the same experiment.

Most manufacturers follow CLSI document EP05¹ to establish precision claims, and these claims are relatively easily verifiable using the approach prescribed in EP15. The committee chose to keep the number of days in the experiment at five, and to increase the number of replicates per day to five, in order to obtain more reliable estimates of repeatability and within-laboratory imprecision. The most complicated calculations were replaced by tables to make calculations easier and to reduce the opportunities for mathematical errors.

This document is primarily intended for use when an established measurement procedure is initially set up in the laboratory. It may also be used to verify performance after corrective action following a failed proficiency testing event.

 **NOTE:**

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™² method evaluation software from CLSI.

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KEY WORDS**Bias****Imprecision****Repeatability****Trueness****Verification of performance****Within-laboratory imprecision**

Overview of Changes

In this revision of EP15, the experiment to demonstrate trueness using materials with known concentrations was expanded to five days, with encouragement to work with the same sample materials used in the precision verification experiment. The intention of the document development committee was for the user to perform a single experiment to verify precision and trueness simultaneously. This experiment is designed to produce reliable estimates of bias between the mean measurand concentration observed by use of the candidate measurement procedure and the assigned measurand concentration of the material. The degree to which the observed bias is a measurement of trueness depends on the quality of the measurement procedure used to assign the measurand concentrations of the material. As with the precision experiment, complicated calculations were replaced by tables wherever possible.

Similar to previous editions of the document, the document development committee had two principal goals during the development of EP15. One goal was to develop a testing protocol that is suitable for use in the large clinical laboratory, yet simple enough to be applicable in the point-of-care or physician's office laboratory. The second goal was to develop a protocol that is sufficiently rigorous to provide statistically valid conclusions for verification studies. The bias is assessed by a recovery experiment. Instead of manual worksheets, calculations may be readily performed with CLSI's StatisPro² software or generic spreadsheet software (see recommendation below).

The committee feels that it is important to provide the interested user with an explanation of the statistical procedures that are used in the document. If the user has access to software specifically designed to perform the calculations described in the document, such as StatisPro,² a detailed understanding of the statistics is not necessary. Flow charts are included to provide the user with the necessary overview of the experiment and data processing. In any case, the user must follow the protocol described as closely as possible in order to obtain reliable results.

 **NOTE:**

Instead of manual worksheets, calculations may be readily performed with **CLSI's StatisPro² software** or generic spreadsheet software.

 **IMPORTANT NOTE:**

In any case, the user must follow the protocol described **as closely as possible** in order to obtain reliable results.

Chapter 1

Introduction

This chapter includes:

- ▶ Document scope and applicable exclusions
- ▶ Background information pertinent to the document content
- ▶ Standard Precautions information, as applicable
- ▶ Terms and definitions used in the document
- ▶ “Note on Terminology” that highlights particular use and/or variation in use of terms and/or definitions, where applicable
- ▶ Abbreviations and acronyms used in the document



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IMPORTANT NOTE:

This document is **not** intended to establish or validate the precision performance of a measurement procedure.



NOTE:

Because this document's scope is limited to verification of precision and estimation of bias,

other more rigorous CLSI protocols (eg, see CLSI documents EP06,³ EP17,⁴ and EP28⁵) are employed to validate the measurement procedure's performance against the user's needs. **CLSI documents EP05¹ and EP09⁶ were developed to assist manufacturers in establishing the performance of a diagnostic device for precision and trueness, respectively.** (Also, see CLSI documents EP06,³ EP17,⁴ EP28,⁵ and EP10.⁷) CLSI document EP10⁷ is intended for the rapid preliminary evaluation of precision, bias, sample carryover, drift, and nonlinearity.

1 Introduction

1.1 Scope

This guideline was developed as a protocol for simultaneously verifying a manufacturer's claims for precision of a measurement procedure and the trueness of the measurement procedure relative to the assigned values of materials with known concentrations.

The precision verification section of the guideline was developed for situations in which the performance of the procedure has been previously established and documented by experimental protocols with larger scope and duration. It has relatively weak power to reject precision claims with statistical confidence, and should only be used to verify that the procedure is operating in accordance with the manufacturer's claims. This document is **not** intended to establish or validate the precision performance of a measurement procedure.

The bias estimation section of the guideline relies on 25 or more measurements by the candidate procedure, made over five or more days, to estimate the measurand concentrations of materials with known concentrations. These estimated measurand concentrations are compared to the assigned measurand concentrations of the materials to estimate bias. The observed bias is a measure of trueness if a high-quality measurement procedure was used to assign the concentrations of the materials.

Because this document's scope is limited to verification of precision and estimation of bias, other more rigorous CLSI protocols (eg, see CLSI documents EP06,³ EP17,⁴ and EP28⁵) are employed to validate the measurement procedure's performance against the user's needs. CLSI documents EP05¹ and EP09⁶ were developed to assist manufacturers in establishing the performance of a diagnostic device for precision and trueness, respectively. (Also, see CLSI documents EP06,³ EP17,⁴ EP28,⁵ and EP10.⁷) CLSI document EP10⁷ is intended for the rapid preliminary evaluation of precision, bias, sample carryover, drift, and nonlinearity.

One may also note that the EP15 protocol has an implicit assumption: Namely, that if the estimated precision and bias are acceptable, then the overall error (eg, total analytical error) of the measurement procedure is acceptable. This implied model can lead to an underestimation of the total analytical error⁸ in cases in which other effects are important. Besides conducting more extensive evaluations mentioned above, one could also consider performing the protocol within CLSI document EP21.⁹ This protocol is a direct estimation of total analytical error, and does not rely on a model.

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

EP15-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					
						EP05					
						EP06					
						EP09					
						EP10				EP10	
						EP14					
						EP17					
						EP21					
						EP28					
		M29									
			QMS03								

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.
- EP05-A3** **Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition (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-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.
- EP09-A3** **Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition (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-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.
- EP14-A3** **Evaluation of Commutability of Processed Samples; Approved Guideline—Third Edition (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.
- 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.
- 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.

* 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)

- EP28-A3c** **Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition (2010).** This document contains guidelines for determining reference values and reference intervals for quantitative clinical laboratory tests.
- 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.
- QMS03-A3** **Training and Competence Assessment; Approved Guideline—Third Edition (2009).** This document provides background information and recommended processes for the development of training and competence assessment programs that meet quality and regulatory objectives.
- StatisPro** **StatisPro™ (2013).** This feature-rich, easy-to-use method evaluation software can be used for establishing or verifying performance characteristics of a laboratory test method. This robust statistical tool can report on precision, linearity, bias (related to trueness), comparability, reference intervals, limits of detection, and limits of quantitation based on the most up-to-date CLSI guidelines.

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