CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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EP15-A2

User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition

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.

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

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User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition

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Abstract

Clinical and Laboratory Standards Institute document EP15-A2—*User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition* describes the demonstration of method precision and trueness for quantitative methods performed within the laboratory. Included are guidelines for the duration, procedures, materials, data summaries, and interpretation techniques that are 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. Definitions are provided for repeatability, within-laboratory precision, and other terms and concepts used in the document.

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The Area Committee on Evaluation Protocols would also like to recognize the original Clinical and Laboratory Standards Institute (CLSI) Subcommittee on User Demonstration of Performance who developed the first approved-level edition of this guideline.

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Summary of Editorial Corrections in This Edition

Section 8.6 (3)

- The equation for the verification value was corrected by adding a square root sign in the denominator.

Section 9.1 (9)

- The t-values used in calculations of the verification limits for bias were changed to two-sided t-values. Appendixes D, E, and F were revised accordingly.

Section 9.2.2

- This section was revised to clarify the calculation of the standard error of the assigned value of the reference material.

Section 9.2.4 (4)

- The calculation of the verification interval for bias was corrected to account for the number of replicates tested and to use two-sided t-values.

Appendix B, Step 5, Verification of Within-Laboratory Precision Claim

- The calculation of the effective degrees of freedom, T, was corrected. The final result was unchanged, but there was a transcription error in an intermediate step.

Appendixes D and E, Step 3, Calculation of verification limits for bias in reportable units and percent bias

- The calculation of the verification limits was corrected to use two-sided t-values.

Appendix F

- The figures were revised to demonstrate the power curves of the bias test using two-sided t-values.

Appendixes G and H, Step 2, Calculation of standard error of the mean

- This section was previously named “Calculation of standard deviation.” It was corrected to account for the number of replicates and renamed.

Appendixes G and H, Step 3, Calculation of verification interval for bias

- The calculation of the verification interval was corrected to account for the number of replicates tested and to use two-sided t-values.

Foreword

Before a laboratory can introduce a new method for reporting results of patient testing, several steps are required. First, the laboratory must specify the required performance for the method. Performance specifications may be defined by regulatory requirements and/or medical usefulness requirements. Second, the laboratory must select a method whose manufacturer's claims meet the required performance specifications. Finally, the laboratory must perform experiments to verify that the manufacturer's claimed imprecision and bias are achieved by the laboratory. If these steps are successful, the method is introduced into routine use for patient testing.

The focus of this guideline is verification of performance claims, for precision and trueness of a measurement procedure, that were previously validated by the manufacturer. This guideline is intended as a companion document to CLSI/NCCLS documents EP5—*Evaluation of Precision Performance of Quantitative Measurement Methods* and EP9—*Method Comparison and Bias Estimation Using Patient Samples*. EP5 and EP9 focus on the establishment and verification of performance claims. This document assumes that the manufacturer developed and validated performance claims using the protocols in EP5 and EP9. EP15 is intended to verify that a laboratory's performance is consistent with these claims.

The subcommittee had two principal goals during the development of EP15. One was to develop a testing protocol that is simple enough to be applicable in laboratories with a wide variety of sophistication and resources, from the point-of-care or physician's office laboratory to the large clinical laboratory. The second was to develop a protocol that is sufficiently rigorous to provide statistically valid conclusions for verification studies. To meet these two needs, the subcommittee developed a five-day testing protocol and simplified worksheets for all data gathering, statistical calculations, and tests of observed precision and trueness. A computer spreadsheet is provided to simplify and standardize the statistical calculations and tests of observed precision and trueness.

The first edition of EP15 used by clinical laboratories was judged by some to be difficult to understand for users who are not comfortable with statistics. EP15-A2 has removed the three-day protocol since it was determined that most methods did not qualify to use it. This protocol has fewer replicates than in EP15-A, and the spreadsheet should simplify calculations. Several terms have been changed to facilitate international harmonization (see below).

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

A Note on Terminology

Clinical and Laboratory Standards Institute (CLSI) recognizes that harmonization of terms facilitates the global application of standards, and as a matter of organizational policy, is firmly committed to employing terms that are generally used internationally. This initiative includes a mechanism to resolve ISO/CEN/CLSI differences in nomenclature.

However, CLSI is also aware 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. Therefore, implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

The term *precision* is a measure of "closeness of agreement between independent test/measurement results obtained under stipulated conditions."[1] The terms in this document are consistent with uses

defined in the ISO 3534 and ISO 5725 series of standards. In these models, *repeatability* and *reproducibility* are considered to be the extreme measures of precision, with repeatability being the smallest measure (same operator, measurement procedure, equipment, time, and laboratory) and reproducibility being the largest (different operator, equipment, and laboratory). All other measures of precision are "intermediate measures" and must be explicitly described. Therefore, in this document, *within-run precision* has been replaced by *repeatability*. Reproducibility is not estimated since the EP15-A2 protocol does not require multiple laboratories. All other measures of precision from EP15-A have been retained, although the term *total precision* was eliminated because it is not clearly defined. In this document, *total precision* has been replaced by *within-laboratory precision*. Other harmonization changes include changing *specimen* to *sample* and *reportable range* to *measuring interval*.

Key Words

Bias, precision, repeatability, trueness, verification of performance

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1 Scope

This guideline was developed for situations where the performance of the method was previously established and documented by experimental protocols with larger scope and duration. The experimental and statistical protocols of this guideline have relatively weak power to reject claims with statistical confidence, and should only be used to verify that the method is operating in accordance with the manufacturer's claims. This document is *not* intended to establish or validate the analytical performance of a method.

Since this document's scope is limited to verification of precision and trueness, other more rigorous CLSI/NCCLS protocols (e.g., EP6—*Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*; EP17—*Protocols for Determination of Limits of Detection and Limits of Quantitation*; and C28—*How to Define and Determine Reference Intervals in the Clinical Laboratory*) are employed to validate the method's performance against the user's needs. CLSI/NCCLS documents EP5—*Evaluation of Precision Performance of Quantitative Measurement Methods* and EP9—*Method Comparison and Bias Estimation Using Patient Samples* were developed to assist manufacturers in validating the performance of a diagnostic device for precision and trueness, respectively. CLSI/NCCLS document EP10—*Preliminary Evaluation of Quantitative Clinical Laboratory Methods* is intended for the rapid preliminary evaluation of precision, bias, sample carryover, drift, and nonlinearity. However, it is fairly complex since it is based on a multifactor design and is limited in the amount of data generated. EP10 should only be used as a preliminary evaluation of analytical performance.

One may also note that the EP15 protocol has an implicit assumption: namely, that if the estimated precision and trueness are acceptable, then the overall error (e.g., total analytical error) of the method is acceptable. This implied model can lead to an underestimation of the total analytical error[2] in cases where other effects are important. Besides conducting more extensive evaluations mentioned above, one could also consider performing the CLSI/NCCLS protocol EP21—*Estimation of Total Analytical Error for Clinical Laboratory Methods*. This protocol is a direct estimation of total analytical error and does not rely on a model.

2 Introduction

This guideline was written to assist the laboratory in verifying an established measurement procedure. It presumes that the procedure was checked by the manufacturer and is functioning properly. This guideline provides a minimum implementation protocol to verify that a particular example of a measurement procedure is operating in accordance with the manufacturer's claims. The laboratory must test the procedure against these targets for the protocols in this guideline to be applicable.

This guideline can also be used as a protocol to demonstrate acceptable performance when corrective actions are taken after failing proficiency testing (external quality assessment).

The specific characteristics addressed in this document are repeatability, within-laboratory precision, and trueness (as estimated by measures of bias) relative to an accepted standard. Upon successful completion of the protocols recommended in this guideline, the laboratory will have verified that the method is operating in accordance with the manufacturer's claims for precision and trueness.