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User Demonstration of Performance for Precision and Accuracy; Approved Guideline

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Abstract

NCCLS document EP15-A—*User Demonstration of Performance for Precision and Accuracy; Approved Guideline* describes the demonstration of method precision and accuracy for analyte determinations 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 or less. Definitions are provided for "within-run" and "total" precision.

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Foreword

Before a clinical laboratory method can be used for testing patient samples, its analytical performance must be evaluated to demonstrate that the method provides the medically required precision and accuracy. The scope of method evaluation varies according to what organization is performing the evaluation and what is already known about the analytical performance of the method. In order of decreasing amounts of effort, the scopes of evaluation are:

- Evaluation — a measurement of the analytical performance characteristics of a new method by means of laboratory experiments.
- Validation — a) action (or process) of proving that a procedure, process, system, equipment, or method used works as expected and achieves the intended result; or b) confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.
- Verification — confirmation by examination of objective evidence that specified requirements have been fulfilled.
- Demonstration — assessing whether a laboratory can follow the manufacturer's instructions and obtain expected results.

The focus of this guideline is a demonstration of analytical precision and accuracy of an analytical method by a laboratory. This guideline is intended to be a companion document to NCCLS document EP5 — *Evaluation of Precision Performance of Clinical Chemistry Devices* and NCCLS document EP9 — *Method Comparison and Bias Estimation Using Patient Samples.* EP5 and EP9 are intended for validating and verifying performance claims. EP15 is intended for demonstrating (rather than "proving") that a laboratory's performance is consistent with these claims.

This guideline has been developed to guide the user through minimum studies necessary to demonstrate that the user can obtain precision and accuracy performance consistent with the manufacturer's claims and, if proficiency testing materials are used, consistent with the test system's peer group as well. It is assumed that the method's performance has previously been evaluated by the manufacturer, using protocols designed to validate and verify performance. It is also assumed that the method being evaluated has been thoroughly evaluated previously in other settings, and that the method and user are inherently capable of the performance claimed by the manufacturer. The experimental and statistical protocols have relatively weak power to reject claims with statistical confidence and therefore should only be used to demonstrate that the method, as performed by the laboratory, is operating in accordance with the manufacturer's claims. This guideline is very limited in scope and is appropriate only for demonstration studies.

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 demonstration studies. To meet these two needs, the subcommittee developed three- and five-day testing protocols and simplified worksheets for all data gathering, statistical calculations, and tests of observed precision and accuracy.

This document is primarily intended for use when an established method is being initially set up in the laboratory. It provides protocols for demonstrating precision and accuracy. Protocols for validating the manufacturer's suggested reference ranges are included in the most current edition of NCCLS document C28 — *How to Define and Determine Reference Intervals in the Clinical Laboratory*.

There is another NCCLS guideline requiring minimal effort to assess analytical performance: EP10 — *Preliminary Evaluation of Quantitative Clinical Laboratory Methods*. While fairly complex, since it is

based on a multifactor design, it is fairly limited in the amount of data generated. As its title states, EP10 is only appropriate as a preliminary study. EP10 is intended for use in rapid preliminary evaluations of precision, bias, sample carryover, drift, and nonlinearity.

Key Words

Accuracy, demonstration of performance, precision

A Note on Terminology

NCCLS 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/NCCLS differences in nomenclature.

However, NCCLS 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 NCCLS, 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.

Of particular note in EP15-A are several terms whereby NCCLS intends to eliminate confusion, over time, through its commitment to harmonization. These terms and their ISO counterparts include: *Accuracy* vs. *Trueness*; *Analyte* vs. *Quantity; Analytical method* vs. *Measurement procedure; Total precision* vs. *Reproducibility; Within-run precision* vs. *Repeatability; Reportable range* vs. *Measuring range; and Total error* vs. *Error of measurement.* The users of EP15-A should understand that the fundamental meanings of the terms are identical, and to facilitate understanding, the terms are defined along with their ISO counterpart in the guideline's Definitions section.

All terms and definitions will be reviewed for consistency with international use, and revised appropriately during the next scheduled revision of this document.

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1 Introduction

This guideline has been written to assist the laboratory in bringing an established method (or device or analytical system) on line. It presumes that the method has been checked by the manufacturer and is known to be functioning properly. This guideline provides a minimum implementation protocol necessary to demonstrate that a particular example of a method is operating in accordance with the manufacturer's claims. The laboratory must test the method against these targets for the protocols in this guideline to be applicable.

The guideline is also intended to provide a procedure with which a laboratory can demonstrate acceptable performance as a follow-up to corrective actions taken after a failed proficiency-testing event.

The specific characteristics addressed in this document are precision (within-run and total) and accuracy relative to an accepted standard. Upon successful completion of the protocols recommended in this guideline, the laboratory will have demonstrated that the system is operating in accordance with the manufacturer's claims for precision and accuracy.

This document leads the user through the process of determining the match between the laboratory's actual performance and the expected performance of the method. If the laboratory's performance is not consistent with the expected level of performance, remedial actions will probably be required.

Underlying this protocol is an assumption that the user can operate the method properly and obtain the performance claimed by the manufacturer.

1.1 Scope

Prior to selecting a method for an analyte and evaluating that method's analytical performance, the laboratory must establish minimum performance specifications for the method based on the laboratory's clinical and proficiency testing needs. Lists of medically based analytical performance standards are given in the references.[1-4] Some regulatory and accrediting programs[a] (e.g., CLIA, CAP) specify minimum performance standards, most frequently for proficiency testing. If regulatory performance standards apply, these define the minimum performance the method must achieve. These standards are expressed in terms of total allowable difference (total error) from a reported group mean value or true value of the concentration of the analyte. Precision and accuracy goals in terms of allowable standard deviation and bias must be derived from allowable total error. Discussions of the relationship between allowable error and allowable standard deviation and bias are included in some of the publications listed in the references.[1-4]

For the performance characteristics evaluated in this document, the following performance goal formats are recommended in order to conform to the evaluation result formats:

Precision. Precision goals should be stated as the maximum allowable SD and/or CV at each analyte concentration to be tested.

[a] For example, in the U.S., CLIA and CAP.

Accuracy. Accuracy goals should be stated as maximum allowable bias at each analyte concentration to be tested. Maximum allowable bias may be expressed as either an absolute concentration or as a percentage of the concentration.

Total Error. Total error goals should be stated as the maximum permissible difference between an individual specimen's result and the target value for that specimen. The target value may be determined by:

(a) the method's peer group in proficiency testing

(b) an assigned reference method in proficiency testing

(c) a comparative method in a comparison of patient samples experiment

(d) the manufacturer of a reference material

Ideally the laboratory can select a method whose manufacturer's claims for precision and accuracy are within the limits of the performance standards specified by the laboratory. Other factors in this selection include application characteristics such as cost of operation, sample size, turnaround time, etc.

The approach taken in this protocol is to demonstrate that observed performance is consistent with the manufacturer's claims. When multiple analytes are tested on a single analytical system, it may not be possible to select a single system, which has acceptable claimed performance for every analyte. Although the performance characteristics of most products fall within manufacturers' claims, when a product's claimed performance does not meet performance goals, this protocol is not appropriate for demonstrating performance. Other, more rigorous NCCLS protocols should be employed to validate the methods performance against the user's needs.

This document provides experimental protocols and data analysis procedures designed to enable a user laboratory to demonstrate that it has obtained analytical performance comparable to that established by the manufacturer of an *in vitro* diagnostic device. Generally this guideline will be employed when a new device is being evaluated prior to its application for routine testing in the user's laboratory.

As this guideline is very limited in scope, it is not intended for validation or verification of the analytical performance of a diagnostic device. Other NCCLS guidelines have been developed for that purpose. This guideline has been developed for use in situations in which the performance of the device has been previously established and documented by experimental protocols of much larger scope and duration. Most often such documentation has been provided by the manufacturer and is part of the product labeling. The present guideline is to be employed by the user laboratory to demonstrate that it has obtained performance consistent with that documented by the manufacturer.

Accreditation and regulatory agencies require laboratories to establish performance specifications for each analytical method, and to verify or demonstrate that the method's analytic performance meets these specifications. This guideline specifically deals with demonstrating analytic precision and accuracy.

More complete evaluations of precision and accuracy (as would be required to validate or verify the performance of a newly developed method), as well as guidelines for developing or validating reference ranges and for evaluating sensitivity and specificity are given in related NCCLS publications listed at the end of this document.

Related NCCLS Publications*

C24-A2 **Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition (1999).** This guideline provides definitions of analytical intervals; plans for quality control procedures; and guidance for quality control applications.

C28-A2 **How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline (2000).** This document provides guidance for determining reference values and reference intervals for quantitative clinical laboratory tests.

EP5-A **Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (1999).** This document offers guidelines for designing an experiment to evaluate the precision performance of clinical chemistry devices; recommendations on comparing the resulting precision estimates with manufacturer's precision performance claims and determining when such comparisons are valid; and manufacturer's guidelines for establishing claims.

EP6-P2 **Evaluation of the Linearity of Quantitative Analytical Methods; Proposed Guideline–Second Edition (2001).** 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.

EP7-P **Interference Testing in Clinical Chemistry; Proposed Guideline (1986).** This document provides background information and procedures for characterizing the effects of interfering substances on test results.

EP9-A **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (1995).** This document addresses procedures for determining the bias between two clinical methods or devices and design of a method comparison experiment using split patient samples and data analysis.

EP10-A **Preliminary Evaluation of Quantitative Clinical Laboratory Methods; Approved Guideline (1998).** This guideline addresses experimental design and data analysis for preliminary evaluation of the performance of an analytical method or device.

GP10-A **Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Approved Guideline (1995).** This document describes the design of a study to evaluate clinical accuracy of laboratory tests; procedures for preparing ROC curves; glossary of terms; and information on computer software programs.

NRSCL8-A **Terminology and Definitions for Use in NCCLS Documents; Approved Standard (1998).** This document provides standard definitions for use in NCCLS standards and guidelines, and for submitting candidate reference methods and materials to the National Reference System for the Clinical Laboratory (NRSCL).

* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.

