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Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline

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.

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

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For additional information on committee participation or to submit comments, contact CLSI.

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Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline

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Abstract

Clinical and Laboratory Standards Institute document EP29-A—*Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline* describes the principles of estimating measurement uncertainty and provides guidance to clinical laboratories and *in vitro* diagnostic device manufacturers on the specific issues to be considered for implementation of the concept in laboratory medicine. This document illustrates the assessment of measurement uncertainty with both bottom-up and top-down approaches. The bottom-up approach suggests that all possible sources of uncertainty are identified and quantified in an uncertainty budget. A combined uncertainty is calculated using statistical propagation rules. The top-down approach directly estimates the measurement uncertainty results produced by a measuring system. Methods to estimate the imprecision and bias are presented theoretically and in worked examples.

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Foreword

When measurements are repeated, some variation of the results will be observed due to random variation of the measurement conditions. The differences will be noticeable if the sensitivity and resolution of the measuring system is sufficient. Therefore, for measurement results to be useful, such result variability (uncertainty) needs to be quantified so that those performing measurements and those receiving results have an objective estimate of the quality (reliability) of the results produced. Quantification of the variability of measurement results also allows a result to be meaningfully compared with the results of other similar measurements that may have been made at different times using the same measurement system. The concept of measurement uncertainty provides a theoretical and practical framework for objectively estimating the reliability of results produced by any given measurement system.

Knowledge of the sources of uncertainty and their relative magnitude may also provide opportunities for modifying a measurement system to improve the quality of results. Uncertainty estimates at various analyte concentrations also contribute to determining uncertainty profiles, which can be important in defining the measuring interval of measurement systems to ensure that the quality of results issued meets clinical requirements.

This document describes the principles of estimating measurement uncertainty and gives guidance on the specific issues to be considered for implementation of the concept in laboratory medicine. The concept of measurement uncertainty and its use in measuring quantities in laboratory medicine is provided for clinical laboratories and *in vitro* diagnostic device manufacturers.

Key Words

Bias, bottom-up, measurement uncertainty, precision, top-down, trueness

Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline

1 Scope

This guideline explains the concept, estimation, and application of measurement uncertainty in the field of clinical laboratory medicine. The recommendations provided are consistent with the *Guide to the expression of uncertainty in measurement* (GUM)[1] and with the International Organization for Standardization (ISO) standards concerned with laboratory accreditation.[2,3]

This guideline briefly discusses, but does not fully address, the following nonmeasurement sources of uncertainty of a measurement result:

- Biological variation of the measurand
- Pre- and postmeasurement processes

The guideline discusses the definition of what is intended to be measured, lists sources of measurement uncertainty, describes the generation of statistical estimates of uncertainties and their combination, and discusses the use of uncertainty estimates. The guideline applies only to quantitative measurements. In measurement procedures that are reported in qualitative terms based on a quantitative measurement, the uncertainty at the threshold(s) for a qualitative interpretation should be considered when making the qualitative assessment.

This guideline is intended for clinical laboratories and *in vitro* diagnostic (IVD) device manufacturers.

2 Introduction

Regardless of method, repeated measurements produce different results due to inherent variations within a sufficiently sensitive measurement procedure. Some knowledge of the result variability expected from a given measurement system is required if results are to be meaningfully compared with previous results from the same patient or important clinical decision limits. In addition, evaluation and elimination of bias in a measuring system relative to the relevant reference material or reference procedure is essential if results from different laboratories using the same or different measuring systems are to be compared for the same patient.

Characterization of the variability of repeated measurement results and identification of the factors that contributed to that variability can provide useful insights into the reliability of results and potential means for improvement. Existing quality control (QC) and method verification data can be used to define the performance characteristics of routine measuring systems. This document provides guidance on how measurement uncertainty can be estimated and used in the field of laboratory medicine. The principles for expression of measurement uncertainty provided in this document illustrate how the components of measurement uncertainty can be combined to help estimate the performance characteristics that can be reliably achieved by the measuring system.

The objectives of this document are to:

- Familiarize the reader with the concept of measurement uncertainty.

- Describe the processes of implementing the concept of measurement uncertainty in laboratory medicine.

- Describe practical approaches to developing relevant and useful estimates of measurement uncertainty.

- Discuss uses of the measurement uncertainty information obtained.

3 Terminology

3.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly 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 European Committee for Standardization (CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI's consensus process for development and revision of standards and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

A hierarchy of terminology was agreed upon, involving ISO (www.iso.org), CEN (www.cen.eu), CLSI (www.clsi.org), and the Bureau International des Poids et Mesures (BIPM) (www.bipm.org).

Essentially, new documents are obliged to adhere to the *International Vocabulary of Metrology – Basic and General Concepts and Associated Terms* (VIM),[4] whenever an ambiguity in the interpretation or understanding of terms occurs. The VIM deals with general metrology and terminology that should be useful for most disciplines that measure quantities.

The understanding of a few terms has changed during the last decade as the concepts have developed. Particularly, *trueness* (measurement trueness) is defined as expressing the closeness of agreement between the average of an infinite number of replicate measurements and a reference value; and *precision* (measurement precision) is defined as closeness of agreement between indications or measured quantity values obtained by repeated measurements of the same sample and quantity under specified conditions. Consequently, *accuracy* (measurement accuracy) is the closeness of agreement between a measured value and a true quantity value of a measurand. Thus, this concept comprises both trueness and precision, and applies to a single result. *Measuring interval* has replaced *reportable range* when referring to "a set of values of a measurand for which the error of a measuring instrument (test) is intended to lie within specified limits." An *interval* [*a*;*b*] is delineated by two limits *a* and *b* ($b > a$), whereas a *range* (r[*a*;*b*]) is expressed as the difference between *b* and *a* ($b - a$). Thus, the range of the interval [*a*;*b*] is the difference ($b - a$) that is denoted by r[*a*;*b*].

The term *measurand* is used when referring to the quantity intended to be measured instead of *analyte* (component represented in the name of a measurable quantity); the term *measurement procedure* replaces *analytical method* for a set of operations, used in the performance of particular measurements according to a given method.

Verification focuses on whether specifications of a measurement procedure can be achieved, whereas *validation* verifies that the procedure is fit for purpose. Both concepts can describe procedures of varying complexity. This document specifically deals with verification.

In this document, the terms *preanalytical, analytical,* and *postanalytical* appear parenthetically after the terms *preexamination, examination,* and *postexamination* where appropriate. Furthermore, in order to align the usage of terminology in this document with that of ISO and CLSI document GP02,[5] the term *standard operating procedure (SOP)* has been replaced with the term *procedures/instructions.*

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

EP29-A 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 EP07 EP09 EP10 EP15 EP21	GP02	GP02		EP10	EP07

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-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.

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.

EP07-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.

EP09-A2-IR **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (Interim Revision) (2010).** 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.

EP10-A3 **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2006).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

EP15-A2 **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2006).** 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.

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 that 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.

GP02-A5 **Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition (2006).** This document provides guidance on development, review, approval, management, and use of policy, process, and procedure documents in the medical laboratory community.

* 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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