

Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Proposed Guideline

PLEASE



This proposed document is published for wide and thorough review in the new, accelerated Clinical and Laboratory Standards Institute (CLSI) consensus-review process. The document will undergo concurrent consensus review, Board review, and delegate voting (ie, candidate for advancement) for 60 days.

Please send your comments on scope, approach, and technical and editorial content to CLSI.

Comment period ends

24 November 2008

The subcommittee responsible for this document will assess all comments received by the end of the comment period. Based on this assessment, a new version of the document will be issued. Readers are encouraged to send their comments to Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; Fax: +610.688.0700, or to the following e-mail address: customerservice@clsi.org.



COMMENT

This document provides information to help material manufacturers in the production and characterization of commutable reference materials as well as assist assay manufacturers, proficiency testing providers, and laboratorians in the appropriate use of these materials for calibration and trueness assessment of *in vitro* diagnostic medical devices.

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



Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Proposed Guideline

Hubert Vesper, PhD
Hendrik Emons, PhD
Matthew Gnezda, PhD
Chandra P. Jain
W. Gregory Miller, PhD
Robert Rej, PhD
Jill Tate, MSc
Linda Thienpont, PhD
Gerhard Schumann, PhD
Jeffrey E. Vaks, PhD

Abstract

Reference materials are an important requisite for ensuring reliable laboratory measurements and thus appropriate patient care. To ensure that a reference material is suitable for its intended purpose, its characteristics need to be assessed in a defined manner, taking all relevant aspects into consideration. This document provides information to help material manufacturers in the production and characterization of commutable reference materials as well as assist assay manufacturers, proficiency testing providers, and laboratorians in the appropriate use of these materials for calibration and trueness assessment of *in vitro* diagnostic medical devices. Guidance on qualification requirements of reference materials related to the definition of the measurand, the intended use of the material, and other material specifications is provided. Information on study designs, data evaluation, and uncertainty assessment is included that is supplemental to existing guidance documents about the assessment of homogeneity, stability, and property values. This document provides a revised definition of the term 'commutability' and provides guidance on how to perform commutability evaluation.

Clinical and Laboratory Standards Institute (CLSI). *Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Proposed Guideline*. CLSI document C53-P (ISBN 1-56238-678-6). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2008.

The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI/NCCLS documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org. If your organization is not a member and would like to become one, and to request a copy of the catalog, contact us at: Telephone: 610.688.0100; Fax: 610.688.0700; E-Mail: customerservice@cls.org; Website: www.clsi.org



Contents

Abstract.....	i
Committee Membership.....	iii
Foreword.....	vii
1 Scope.....	1
2 Introduction.....	1
3 Standard Precautions.....	4
4 Terminology.....	4
4.1 A Note on Terminology.....	4
4.2 Definitions.....	5
4.3 Abbreviations/Acronyms.....	7
5 Qualification Requirements.....	7
5.1 Definition of the Measurand.....	7
5.2 Intended Use.....	8
5.3 Material Specifications.....	8
6 Characterization of Homogeneity, Stability, and Property Value.....	9
6.1 Characterization of Homogeneity.....	9
6.2 Characterization of Stability.....	11
6.3 Establishing Traceability.....	13
7 Characterization of Commutability of Reference Materials.....	19
7.1 General Considerations Regarding Samples and Measurement Procedures Used for Commutability Validation.....	19
7.2 Logistical Considerations of a Commutability Validation.....	21
7.3 Procedures for Commutability Validation and Assessing Numeric Relationships.....	22
7.4 Selection of a Procedure to Validate Commutability.....	31
7.5 Criteria for Acceptance of the Equivalence of the Mathematical Relationship for Native Clinical Samples and Candidate Reference Materials.....	32
7.6 Reporting Commutability Information.....	32
8 Considerations for Reference Materials Intended for Immediate Use and/or Limited Available Quantities.....	33
References.....	35
Appendix A. Examples of Value Transfer Procedures.....	37
Appendix B. Hypothetical Data Set Used for Examples of Procedures for Assessment of Commutability.....	38
Appendix C. Description of Mathematical Model Used for Evaluating Commutability of Reference Materials Using Deming Regression.....	39
Appendix D. Procedure for Establishing Commutability of a Reference Material With Native Clinical Specimens for a Pair of Measurement Methods With Deming Regression.....	44

Contents (Continued)

The Quality Management System Approach46

Related CLSI Reference Materials47

Foreword

Appropriate patient care and effective public health activities critically depend on reliable laboratory measurements. Reliability in this context comprises ensuring accurate measurements over time across laboratories and measurement procedures. This is accomplished by evaluating and controlling the trueness and precision of measurement results and procedures. Trueness is of particular importance, because it affects the comparability of results across laboratories and measurement procedures, which is crucial for the creation and implementation of clinical guidelines and public health efforts. The definition of trueness as formulated by the International Organization for Standardization (ISO)¹ implies that a true value of a measurand is established. This can be accomplished by appropriately characterizing a reference material. Therefore, reference materials are an important component of a reference system for ensuring reliable laboratory measurements.

A variety of ISO documents provide guidance to characterize and to assign property values to reference materials. Characteristics that are important for reference materials include stability, homogeneity, and commutability (ISO Guide 34,² ISO Guide 35,³ ISO 15195,⁴ ISO 15194,⁵ and ISO 17511⁶). Some of these documents are intended for a broad scientific audience dealing with a wide range of different types of measurements, and therefore do not provide the level of detail needed for applications in laboratory medicine.

The issue of commutability is of special importance in laboratory medicine, where measuring systems are optimized to perform measurements directly in native patient samples without any prior isolation or purification of the analyte. Therefore, the assessment of trueness of the clinical measurement result needs to be ensured for measurements performed in native patient samples, and the materials used to assess trueness need to reflect the specific properties and characteristics of a native patient sample. However, the amounts of patient-derived specimen matrices such as serum, plasma, or urine from a single patient are normally not sufficient to create reference materials. Therefore, specimens are pooled and otherwise altered, making them different from the usual native specimen matrices. Consequently, reference materials used in laboratory medicine need to be assessed to show whether these alterations affect the measurement results in a manner that prevents the use of the reference materials for assessment of trueness and assignment of values to calibrators when establishing metrological traceability.

This document provides information to assist reference material manufacturers in the production and characterization of materials, and to assist users of these materials, such as test system manufacturers, external quality assessment or proficiency testing providers, and laboratorians, to assess the applicability of a material for a specific measurement procedure or clinical application.

Invitation for Participation in the Consensus Process

An important aspect of the development of this and all CLSI documents should be emphasized, and that is the consensus process. Within the context and operation of CLSI, the term “consensus” means more than agreement. In the context of document development, “consensus” is a process by which CLSI, its members, and interested parties (1) have the opportunity to review and to comment on any CLSI publication; and (2) are assured that their comments will be given serious, competent consideration. Any CLSI document will evolve as will technology affecting laboratory or health care procedures, methods, and protocols; and therefore, is expected to undergo cycles of evaluation and modification.

The Area Committee on Clinical Chemistry and Toxicology has attempted to engage the broadest possible worldwide representation in committee deliberations. Consequently, it is reasonable to expect that issues remain unresolved at the time of publication at the proposed level. The review and comment process is the mechanism for resolving such issues.

The CLSI voluntary consensus process is dependent upon the expertise of worldwide reviewers whose comments add value to the effort. At the end of a 60-day comment period, each subcommittee is obligated

to review all comments and to respond in writing to all which are substantive. Where appropriate, modifications will be made to the document, and all comments along with the subcommittee's responses will be included as an appendix to the document when it is published at the next consensus level.

Key Words

Commutability, homogeneity assessment, material qualification, reference material, stability assessment

Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Proposed Guideline

1 Scope

This guideline provides recommendations for the characterization, assessment of commutability, and assignment of analyte concentration or activity values to reference materials that are used for calibration and trueness assessment of *in vitro* diagnostic medical devices. This includes materials such as:

- certified reference materials (CRM);
- materials without a formal certificate, but with the characteristics of a CRM and attached information sufficient for use in instrument calibration or trueness control (eg, external quality assessment [EQA] or proficiency testing [PT] materials used to assess trueness).

This guideline is not intended to be applied for materials used to assess consistency of peer groups in EQA/PT or interlaboratory quality control programs, control materials used for routine (field) methods, manufacturer's product-specific calibrators, or noncommutable secondary reference materials.

The document integrates existing standards and guidelines with new recommendations. References to existing documents addressing certain aspects of material characterization and assignment of values are provided, and new recommendations for assessment of commutability and value transfer procedures are described.

This document provides information to assist reference material manufacturers in the production and characterization of materials, and to assist users of these materials, such as test system manufacturers, external quality assessment or proficiency testing providers, and laboratorians, to assess the applicability of a material for a specific measurement procedure or clinical application.

2 Introduction

The definition of the term 'reference material' from the Council Committee on Reference Materials of the International Organization for Standardization (ISO REMCO) states that a reference material (RM) is a "material, sufficiently homogeneous and stable with reference to specified properties, which has been established to be fit for its intended use in measurement or in examination of nominal properties. **NOTE 1:** Examination of a nominal property provides a nominal property value and associated uncertainty. This uncertainty is not a measurement uncertainty. **NOTE 2:** Reference materials with or without assigned quantity values can be used for measurement precision control whereas only reference materials with assigned quantity values can be used for calibration or measurement trueness control."³

This CLSI guideline considers only reference materials that are commutable with native clinical samples and are to be used for method calibration, to provide metrological traceability of a measurement result, or as a trueness control. Consequently, the following two subgroups of RMs are covered.

Certified reference material (CRM)³ is defined as "reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures. **EXAMPLE:** Human serum with assigned quantity value for the concentration of cholesterol and associated measurement uncertainty stated in an accompanying certificate, used as a calibrator or measurement trueness control material." Metrologically

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 approach is based on the model presented in the most current edition of CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*. 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:

- | | | | |
|--|--|---|--|
| Documents & Records
Organization
Personnel | Equipment
Purchasing & Inventory
Process Control | Information Management
Occurrence Management
Assessments—External &
Internal | Process Improvement
Customer Service
Facilities & Safety |
|--|--|---|--|

C53-P addresses the QSEs 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.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessments—External & Internal	Process Improvement	Customer Service	Facilities & Safety
					X C37 EP05 EP06 EP07 EP14 M29 X05				EP07		M29

Adapted from CLSI/NCCLS document HS01—*A Quality Management System Model for Health Care*.

Related CLSI Reference Materials*

- C37-A** **Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline (1999).** This guideline details procedures for the manufacture and evaluation of human serum pools for cholesterol measurement.
- 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.
- EP14-A2** **Evaluation of Matrix Effects; Approved Guideline—Second Edition (2005).** This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two measurement procedures are compared.
- M29-A3** **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** 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.
- X05-R** **Metrological Traceability and Its Implementation; A Report (2006).** This document provides guidance to manufacturers for establishing and reporting metrological traceability.

* Proposed-level documents are being advanced through the Clinical and Laboratory Standards Institute consensus process; therefore, readers should refer to the most current editions.