CLINICAL AND LABORATORY STANDARDS INSTITUTE®

May 2010

EP30-A

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

This document provides information to help material manufacturers in the production and characterization of commutable reference materials, as well as to assist assay manufacturers 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.

Clinical and Laboratory Standards Institute

Setting the standard for quality in medical laboratory testing around the world.

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

Consensus Process

Consensus—the substantial agreement by materially affected, competent, and interested parties—is core to the development of all CLSI documents. It does not always connote unanimous agreement, but does mean that the participants in the development of a consensus document have considered and resolved all relevant objections and accept the resulting agreement.

Commenting on Documents

CLSI documents undergo periodic evaluation and modification to keep pace with advancements in technologies, procedures, methods, and protocols affecting the laboratory or health care.

CLSI's consensus process depends on experts who volunteer to serve as contributing authors and/or as participants in the reviewing and commenting process. At the end of each comment period, the committee that developed the document is obligated to review all comments, respond in writing to all substantive comments, and revise the draft document as appropriate.

Comments on published CLSI documents are equally essential, and may be submitted by anyone, at any time, on any document. All comments are managed according to the consensus process by a committee of experts.

Appeals Process

When it is believed that an objection has not been adequately considered and responded to, the process for appeals, documented in the CLSI Standards Development Policies and Processes, is followed.

All comments and responses submitted on draft and published documents are retained on file at CLSI and are available upon request.

Get Involved—Volunteer!

Do you use CLSI documents in your workplace? Do you see room for improvement? Would you like to get involved in the revision process? Or maybe you see a need to develop a new document for an emerging technology? CLSI wants to hear from you. We are always looking for volunteers. By donating your time and talents to improve the standards that affect your own work, you will play an active role in improving public health across the globe.

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

Clinical and Laboratory Standards Institute
950 West Valley Road, Suite 2500
Wayne, PA 19087 USA
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@clsi.org

EP30-A
Vol. 30 No. 12
ISBN 1-56238-726-X
Formerly C53-A
ISSN 0273-3099
Vol. 30 No. 12

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

Volume 30 Number 12

Hubert Vesper, PhD
Hendrik Emons, PhD
Matthew Gnezda, PhD
Chandra P. Jain
W. Gregory Miller, PhD
Robert Rej, PhD
Gerhard Schumann, PhD
Jill Tate, MSc
Linda Thienpont, 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 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; Approved Guideline*. CLSI document EP30-A (ISBN 1-56238-726-X). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2010.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

ifcc International Federation of Clinical Chemistry and Laboratory Medicine

Suggested Citation

CLSI. *Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline*. CLSI document EP30-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.

Previous Edition:
September 2008

Reaffirmed:
April 2016

ISBN 1-56238-726-X
ISSN 0273-3099

Contents

Contents (Continued)

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

1 Scope

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

- Certified reference materials (CRMs)
- 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 to materials used to assess consistency of peer groups based on target values determined from participant results in EQA/PT or interlaboratory quality control programs, control materials used for routine (field) methods, manufacturer's product-specific calibrators, or noncommutable secondary RMs.

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 RM manufacturers in the production and characterization of materials, and to assist users of these materials, such as test system manufacturers, EQA or PT 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 ISO (ISO REMCO) states that an 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:** RMs with or without assigned quantity values can be used for measurement precision control whereas only RMs with assigned quantity values can be used for calibration or measurement trueness control."[3]

This CLSI guideline considers only RMs 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.

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 valid procedures for the production

and certification of RMs are given in, among others, ISO Guides 34[2] and 35.[3] ISO Guide 31[7] gives guidance on the contents of certificates.

The other RM subgroup[8] to be considered here consists of the materials used for direct calibration or other value transfer operations, or as trueness controls. They are often called 'analytical standard,' 'calibration standard,' and so on. But this misperception originates only from a mixing of classification systems. Basically, calibration materials have to be sufficiently homogeneous and stable as to ensure that the assigned property value and its uncertainty are valid for any calibration sample used according to the given specifications. Therefore, they fall under the RM definition given earlier. The term *calibrant* or *calibrator* may be appropriate for this RM subgroup. The necessary additional features of a calibrant in comparison to the general RM characteristics are a stated property value with an uncertainty useful for calibration and metrological traceability of the property value. It appears to be acceptable that no formal "certificate," which provides the comprehensive information specified in ISO Guide 31 for CRM certificates,[7] is available for many calibrants.

From the point of view of material composition, a distinction can be made between 'pure substance' RMs and matrix RMs. The former ones are either pure compounds or mixtures thereof (possibly, also in a solvent), whereas matrix RMs for laboratory medicine are typically blood, plasma, serum, urine, or other samples that have been processed to an RM. The process of creating RMs may include, but is not limited to, pooling of specimens from different donors; applying procedures such as filtering, freezing, or lyophilizing; and chemical treatments such as adding analytes, preservatives, or antimicrobial agents. Any of these procedures may change the characteristics of the RM in a manner that affects the results obtained with a measurement procedure, causing results to be different compared with an authentic clinical sample with the same nominal properties.

The goal of laboratory medicine is that results for patients' samples will be comparable, meaning they result in the same clinical interpretation independent of the measurement procedure or laboratory that performed the measurement.[9] This can be accomplished by establishing metrological traceability for each measurement result. The objective of a chosen metrologically traceable calibration is to transfer the degree of trueness of an RM value to values obtained by a procedure that is routinely used. Routine measurement procedures of acceptable analytical selectivity, which include a calibration step traceable to the same higher order RM or reference measurement procedure, should produce numerical values for clinical samples that are comparable across various analytical methods used in clinical laboratories. However, this concept requires an RM to have interassay properties comparable to the properties demonstrated by authentic clinical samples when measured by more than one analytical method. This property is referred to as commutability.[10,11] Fasce et al[12] first introduced the term *commutability* in 1973 to identify the properties of calibrators and quality control preparations that had measurement results equivalent to those for authentic patient samples. This term was used by the authors at that time, because it connoted the idea of equivalent, or convertible, results.[11]

The concept of commutability was originated and first applied to enzyme activity measurements approximately 30 years ago to emphasize that the materials for both internal and external quality control programs must exhibit properties comparable with those of clinical specimens. It implies that the relationship between any two analytical procedures for patient specimens would also apply to a commutable RM. Following this original definition, commutability refers to the ability of an RM to show interassay properties comparable with those demonstrated by authentic clinical specimens. Although the concept of commutability was originally applied to enzyme activity measurements, the term *commutability* has been accepted and broadly applied to all quantitative measurements. Different definitions for the term *commutability* or *commutable material* have been used, such as

- Ability of a material to yield the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations of the relationships obtained when the same procedures are applied to other relevant

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 CLSI 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 as follows:

Documents and Records	Equipment	Information Management	Process Improvement
Organization	Purchasing and Inventory	Occurrence Management	Customer Service
Personnel	Process Control	Assessment—External and Internal	Facilities and Safety

EP30-A 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 and Records	Organization	Personnel	Equipment	Purchasing and Inventory	Process Control	Information Management	Occurrence Management	Assessment—External and Internal	Process Improvement	Customer Service	Facilities and Safety
					X C37 EP05 EP06 EP07 EP14 X05				EP07		M29

Adapted from CLSI 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.

* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Explore the Latest Offerings From CLSI!

As we continue to set the global standard for quality in laboratory testing, we are adding products and programs to bring even more value to our members and customers.

By becoming a CLSI member, your laboratory will join 1,600+ other influential organizations all working together to further CLSI's efforts to improve health care outcomes. You can play an active role in raising global laboratory testing standards—in your laboratory, and around the world.

Find out which membership option is best for you at **www.clsi.org/membership.**

Find what your laboratory needs to succeed! CLSI U provides convenient, cost-effective continuing education and training resources to help you advance your professional development. We have a variety of easy-to-use, online educational resources that make *e*Learning stress-free and convenient for you and your staff.

See our current educational offerings at **www.clsi.org/education.**

When laboratory testing quality is critical, standards are needed and there is no time to waste. eCLIPSE™ Ultimate Access, our cloud-based online portal of the complete library of CLSI standards, makes it easy to quickly find the CLSI resources you need.

Learn more and purchase eCLIPSE at **clsi.org/eCLIPSE.**

For more information, visit www.clsi.org today.

CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®

950 West Valley Road, Suite 2500, Wayne, PA 19087 USA

P: 610.688.0100 **Toll Free (US):** 877.447.1888 **F:** 610.688.0700

E: customerservice@clsi.org **www.clsi.org**

ISBN 1-56238-726-X