

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

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24 November 2008

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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.



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Advancing Quality in Health Care Testing

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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.

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Committee Membership

Area Committee on Clinical Chemistry and Toxicology

David A. Armbruster, PhD,
DABCC, FACB
Chairholder
Abbott Diagnostics
Abbott Park, Illinois

Christopher M. Lehman, MD
Vice-Chairholder
Univ. of Utah Health Sciences
Center
Salt Lake City, Utah

John Rex Astles, PhD, FACB
Centers for Disease Control and
Prevention
Atlanta, Georgia

David M. Bunk, PhD
National Institute of Standards and
Technology
Gaithersburg, Maryland

David G. Grenache, PhD,
MT(ASCP), DABCC, FACB
University of Utah, ARUP
Laboratories
Salt Lake City, Utah

Steven C. Kazmierczak, PhD,
DABCC, FACB
Department of Pathology
Oregon Health and Science
University
Portland, Oregon

Linda Thienpont, PhD
University of Ghent
Ghent, Belgium

Jeffrey E. Vaks, PhD
Roche Molecular Diagnostics
Pleasanton, California

Hubert Vesper, PhD
Centers for Disease Control and
Prevention
Atlanta, Georgia

Jack Zakowski, PhD, FACB
Beckman Coulter, Inc.
Brea, California

Advisors

Mary F. Burritt, PhD
Mayo Clinic
Scottsdale, Arizona

Paul D'Orazio, PhD
Instrumentation Laboratory
Lexington, Massachusetts

Carl C. Garber, PhD, FACB
Quest Diagnostics, Incorporated
Lyndhurst, New Jersey

Uttam Garg, PhD, DABCC
Children's Mercy Hospitals and
Clinics
Kansas City, Missouri

Neil Greenberg, PhD
Ortho-Clinical Diagnostics, Inc.
Rochester, New York

Harvey W. Kaufman, MD
Quest Diagnostics, Incorporated
Lyndhurst, New Jersey

W. Gregory Miller, PhD
Virginia Commonwealth University
Richmond, Virginia

Gary L. Myers, PhD
Centers for Disease Control and
Prevention
Atlanta, Georgia

David Sacks, MD
Brigham and Women's Hospital
and Harvard Medical School
Boston, Massachusetts

Bette Seamonds, PhD
Mercy Health Laboratory
Swarthmore, Pennsylvania

Dietmar Stöckl, PhD
University of Ghent
Ghent, Belgium

Thomas L. Williams, MD
Nebraska Methodist Hospital
Omaha, Nebraska

Subcommittee on Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine

Hubert Vesper, PhD
Chairholder
Centers for Disease Control and
Prevention
Atlanta, Georgia

Hendrik Emons, PhD
Institute for Reference Materials
and Measurements (IRMM)
Geel, Belgium

Matthew Gnezda, PhD
Roche Diagnostics Corporation
Indianapolis, Indiana

Chandra P. Jain
Beckman Coulter, Inc.
Brea, California

W. Gregory Miller, PhD
Virginia Commonwealth University
Richmond, Virginia

Robert Rej, PhD
New York State Dept. of Health
Albany, New York

Jillian Tate, MSc
Queensland Health Pathology
Service
Herston, Australia

Linda Thienpont, PhD
University of Ghent
Ghent, Belgium

Advisors

David M. Bunk, PhD
National Institute of Standards and
Technology
Gaithersburg, Maryland

Neil Greenberg, PhD
Ortho-Clinical Diagnostics, Inc.
Rochester, New York

Mary M. Kimberly, PhD
Centers for Disease Control and
Prevention
Atlanta, Georgia

Martin H. Kroll, MD
Dallas VA Medical Center
Dallas, Texas

Advisors (Continued)

Gary L. Myers, PhD
Centers for Disease Control and
Prevention
Atlanta, Georgia

John D. Nagle, PhD, BCLD
Maine Standards Company, LLC
Windham, Maine

Prof. Dr. Gerhard Schumann
Insitute of Clinical Chemistry
Hannover, Germany

Jeffrey E. Vaks, PhD
Roche Molecular Diagnostics
Pleasanton, California

A. Milford Ward, MA, MB, BChir,
MRCS
Sheffield, United Kingdom

Staff

Clinical and Laboratory Standards
Institute
Wayne, Pennsylvania

Lois M. Schmidt, DA
*Vice President, Standards
Development and Marketing*

Jane M. Oates, MT(ASCP)
Staff Liaison

Tracy A. Dooley, BS, MLT(ASCP)
Project Manager

Melissa A. Lewis
Editor

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Heinz G. Schimmel, PhD
Institute for Reference Materials and Measurements (IRMM)
Geel, Belgium

Dr. Zhiguo Wang
National Center for Clinical Laboratory
Beijing, People's Republic of China

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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