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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.

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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.

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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 true values of a measurand are established. This can be accomplished by appropriately characterized reference materials (RMs). Therefore, RMs 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 RMs. Characteristics that are important for RMs include stability, homogeneity, and commutability (ISO Guide 34,[2] ISO Guide 35,[3] ISO 15195,[4] ISO 15194,[5] and ISO 17511[6]). 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 RMs. Therefore, specimens are pooled and otherwise altered, making them different from the usual native specimen matrices. Consequently, RMs 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 RMs for assessment of trueness and assignment of values to calibrators when establishing metrological traceability.

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, external quality assessment (EQA) or proficiency testing (PT) providers, and laboratorians, to assess the applicability of a material for a specific measurement procedure or clinical application.

Key Words

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

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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