Why Commutability Matters

A fundamental goal of laboratory medicine is that results for patients’ samples will be comparable independent of the medical laboratory that produced the results. Routine measurement procedures of acceptable analytical specificity that have calibration traceable to the same higher-order reference material or reference measurement procedure should produce numerical values for clinical samples that are comparable irrespective of time, place, or laboratory generating the result.

The term “commutability” was first used to describe the ability of a reference or control material to have interassay properties comparable to the properties demonstrated by authentic clinical samples when measured by more than one analytical method (1–3). More recent metrologic documents expand the concept; they describe commutability as the equivalence of the mathematical relationships between the results of different measurement procedures for a reference material and for representative samples from healthy and diseased individuals (4, 5).

A reference material is typically used to establish or verify the traceability of a measurement procedure to a value assigned to the material that represents the best estimate of the correct, or true, value. Concentration or activity values are assigned to reference materials by higher-order measurement procedures, when possible, or alternatively by a consensus process when reference measurement procedures are not available. When a reference material is intended to be measured by a routine clinical method, commutability must be validated among all of the methods that will use the material, including the reference measurement procedure when appropriate. Ultimately, a reference material is used to ensure that the results for clinical samples assayed by routine measurement procedures have numerical values that are equivalent, irrespective of the clinical routine method used for the measurement.

When commutability of a reference material is not established, the results from routine methods cannot be legitimately compared with the assigned value to determine whether a bias exists in calibration, nor can the reference material be used as a calibrator. Observed biases are attributable either to the noncommutability of the reference material or to the differing specificities and calibration procedures of the methods examined. Without an assessment of the commutability of the material used in the method comparison, it is not possible to determine whether any observed biases are artifacts of the comparison, as a result of an inadequate material, or are genuine biases among the methods examined.

Noncommutability of a reference material can be caused by a matrix alteration or by a nonnative analyte. A matrix effect or a matrix bias can be caused by differences in sample matrix between the reference material and the native clinical samples. The sample matrix includes all components of a material system except the analyte itself (4). A matrix effect is defined as the influence of a property of the sample, independent of the presence of the analyte, on the measurement and thereby on the value of the measurable quantity (4). Nonnative forms of the analyte, such as enzymes of nonhuman origin, conjugates with nonphysiologic molecules (e.g., ditaurobilirubin), or protein complexes modified during isolation from human sources, can produce a different measurement signal than expected for native forms of the analyte. Biases attributable to matrix effects and nonnative analytes have been reported for many reference and control materials used in laboratory medicine (1–3, 6–9).

Lack of specificity is a potential limitation for any analytical procedure, but it is of particular importance for immunoassays, in which antibody specificities (e.g., for various epitopes of an analyte) can differ among measurement procedures (9, 10). Nonspecificity for the analyte found in native clinical samples is a method limitation distinct from noncommutability influences, but it can be a confounding factor when the commutability of a reference material is being validated among methods.

Calibration of measurement procedures with reference materials that are not commutable can cause poorer, rather than improved, agreement of results among methods for native clinical samples. Such a degradation in performance can occur when the observed bias is actually attributable to noncommutability of the material, rather than being a true calibration bias. Consequently, the traceability of the calibration to the reference system is not valid, and the net impact on results for native clinical samples cannot be predicted.

In the February issue of this journal, Bunk and Welch (11) reported the characterization of a new certified reference material for human cardiac troponin I. The report provided characterization of the subunit composition of the troponin complex used in the material and a mass value assignment for the troponin I component that is traceable to the Système International d’Unités (SI). The stated intended use of the reference material is for calibration of clinical cardiac troponin I assays. The commutability of this reference material with native clinical samples has not been validated but is underway (11). When commutability data are available, the reference material will be compliant with ISO 15194 (4). However, the reference material described in the report (NIST SRM 2921) has been made commercially available without the commutability validation data. Although this material has the potential to improve interlaboratory agreement of troponin I analyses, this potential can be realized only when the material’s commutability among clinical methods has been validated.

Historically, the importance of commutability for harmonization and standardization of results in laboratory medicine has been poorly appreciated. A review of the Joint Committee for Traceability in Laboratory Medicine list of approved reference materials shows that very few have been validated for commutability with native clini-
cal samples (12). Some reference materials on the list are pure substances or trueness controls that are intended for use with reference measurement procedures rather than with routine clinical methods. However, many reference materials on the list are either stated or implied to be intended for use with routine measurement procedures without adequate information on commutability being provided. International standards for description of reference materials (4) and for metrorologic traceability of values assigned to calibrators and control materials (5) call for commutable reference materials when the intended use is for routine clinical measurement procedures. The property of commutability is also an appropriate characteristic for external quality assessment (proficiency testing) materials. All clinical testing laboratories participate in such efforts, and use of commutable materials would obviate the need for peer groups or method-specific target values in many cases. True errors in analytical technique have been shown, in some instances, to be obscured by use of peer grading techniques (13, 14).

Providers of reference and trueness control materials that are intended for calibration of routine measurement procedures (or for assessment of calibration status) must include commutability validation as an essential requirement. Good laboratory practice requires that reference materials intended for measurement with routine procedures be provided with commutability information included in the certificate of analysis or product labeling.

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

References

W. Greg Miller1*
Gary L. Myers2
Robert Rej3

1 Department of Pathology
Virginia Commonwealth University
Richmond, VA

2 Division of Laboratory Sciences
National Center for Environmental Health
Centers for Disease Control and Prevention
Atlanta, GA

3 Wadsworth Center for Laboratories and Research
New York State Department of Health
and
School of Public Health
State University of New York at Albany
Albany, NY

* Address correspondence to this author at: PO Box 980286, Richmond, VA 23298-0286. Fax 804-828-0375; e-mail gmiller@vcu.edu.

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