



Harmonization: Its Time Has Come

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The importance of standardization of laboratory test results has a long history traceable to the first proficiency testing results in 1947 that demonstrated large discrepancies among results from 59 hospital laboratories (1). The AACC published a series of monographs in 1953–1972 titled *Standard Methods of Clinical Chemistry* that promoted a single measurement procedure (MP)² for a measurand. This effort ultimately failed because technology and commercial interests produced different MPs for the same measurand. A conference organized in 1977 by the Centers for Disease Control [now the Centers for Disease Control and Prevention (CDC)], the Food and Drug Administration (FDA), and the National Bureau of Standards (now NIST) spawned the National Reference System for the Clinical Laboratory that established the hierarchy of Certified Reference Materials (CRMs) and reference measurement procedures (RMPs) that are now accepted as higher-order references for standardization of measurand results (2). The IFCC and professional organizations in various countries began to publish RMPs for different measurands in the mid-1970s. About this time, professional organizations and metrology institutes introduced matrix-based CRMs as the basis for calibration traceability of medical laboratory MPs for measurands for which there were no RMPs.

In 1998, the European Union (EU) passed a regulation known as the EU Directive that for the first time required calibration traceability to higher-order references, when available, for medical laboratory MPs (3). This landmark legislation with an effective date of 2003, although only applicable to products sold in the EU, had a global influence to improve standardization of results for medical laboratory MPs. The International Organization for Standardization (ISO) responded to the EU Directive by publishing, in 2003, standard 17511 that specified requirements for calibration traceability to

higher-order references that included several levels of traceability depending on how complete a reference system existed for a measurand (4). ISO also published standards for CRMs, RMPs and reference laboratories that performed RMPs (5–7).

Cooperation among the International Bureau of Weights and Measures, the IFCC, and the International Laboratory Accreditation Cooperation established the Joint Committee for Traceability in Laboratory Medicine (JCTLM) in 2002. The JCTLM maintains a database of CRMs, RMPs, and reference laboratories that conform to the ISO requirements (8). Manufacturers of MPs use the JCTLM listed resources to ensure the calibration traceability hierarchies they use will be compliant with the EU Directive. An important attribute of a RMP and a CRM is that they can be reproduced at any time or location with the expectation of being suitable for use in a calibration traceability hierarchy.

The term standardization has traditionally been used when equivalent results, within medically meaningful limits, were achieved among different MPs by having calibration traceable to a RMP or CRM. However, the standardization principles described in ISO 17511 have 2 key limitations. One is that pure-substance CRMs and RMPs do not exist and are not likely to be developed because of technical limitations for hundreds of important but complex measurands in laboratory medicine. In the preceding situation, calibration can be traceable to a matrix-based CRM but these too are only available for a relatively small number of measurands. The second limitation is that many matrix-based CRMs have not been validated to be commutable with patient samples and in many cases are not commutable and thus are not suitable for use in an ISO 17511 compliant calibration traceability hierarchy (9). In fact, tracing calibration to a non-commutable CRM will cause differences in results for clinical samples among different MPs. For example, 5 commercially available MPs for parathyroid hormone had 1.4–4.2-fold differences in results for patient samples that caused errors in medical treatment decisions (10).

Harmonization is a generalization of the concept of standardization that means achieving equivalent results, within medically meaningful limits, among different MPs using a scientifically sound approach. Standardization as described above is a special case of achieving harmonization when a suitable CRM and/or RMP is avail-

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Received April 18, 2017; accepted April 25, 2017.

Previously published online at DOI: 10.1373/clinchem.2017.274860

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² Nonstandard abbreviations: MP, measurement procedure; FDA, Food and Drug Administration; CRM, Certified Reference Material; RMP, reference measurement procedure; EU, European Union; ISO, International Organization for Standardization; JCTLM, Joint Committee for Traceability in Laboratory Medicine.

able. An international forum was organized by AACC in 2010 to discuss challenges and recommend solutions for harmonization when no pure-substance CRM, RMP, or commutable matrix-based CRM was available for a measurand (11). One recommendation from the conference was to develop protocols for harmonization that provided consensus processes to achieve equivalent results when development of a RMP was not technically feasible in a reasonable time frame and commutable matrix-based CRMs were challenging to prepare.

In this issue of *Clinical Chemistry*, Thienpont et al. report phase IV of a carefully developed step-wise approach to harmonize thyroid stimulating hormone results from 14 commercial MPs (12). This report is the culmination of a series of reports that developed the science behind a protocol for harmonization. This report of a successful harmonization protocol is an important advance in laboratory medicine because it demonstrates an approach to achieve fit-for-purpose agreement among patient results measured by different MPs when a CRM or RMP is not available for calibration traceability. A harmonization protocol represents a practical solution for calibration traceability for a large number of measurands that would otherwise remain nonharmonized and thus potentially contribute to errors in medical decisions.

This harmonization protocol used panels of authentic individual serum samples that fill the role of harmonization reference materials. A key advantage of using panels of individual samples is that commutability issues do not influence their use as harmonization reference materials because they are the samples intended to be measured by the MPs. Although sample specific influences may exist in an individual sample, the effects can be identified and addressed by statistical approaches. The protocol included specifications for selection of individuals as sample donors for the phases that progressed from using normal thyroid function donors to assess MP performance, to using panels that included hypo- and hyperthyroid patients in the recalibration algorithms applied by each commercial producer of the MPs. The authors referred to this process as a step-up approach for harmonization because several qualification and proof-of-principle steps were fulfilled during the collaboration between the MP manufacturers and the IFCC Committee for Standardization of Thyroid Function Tests.

Among the technical challenges in this work was developing a robust statistical approach for value assignment of the panel of individual samples. Another challenge was developing an approach to sustain the harmonization over time since a limited volume of the panel of individual samples was available. The authors developed a separate panel of individual samples prepared to the same specifications that were value assigned in the same experiment with the phase IV panel. The continuation

panel serves the role to sustain the recalibration process in subsequent steps as well as to provide a link to the original recalibration panel for subsequent panels. The final key component of a harmonization protocol is surveillance of continued harmonization over time among results from the MPs. The report proposes to monitor harmonization over time using a patient sample results based feedback program from medical laboratories. Another approach to surveillance could be proficiency testing or external quality assessment with commutable samples (13).

The International Consortium for Harmonization of Clinical Laboratory Results recognized the importance of harmonization protocols as one of the levels of calibration traceability hierarchy to be recognized by ISO. A proposal was submitted and approved for development by ISO TC 212 (*Clinical Laboratory Testing and In-Vitro Diagnostic Test Systems*) in 2016 to develop a new standard ISO/NP 21151: *In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Requirements for international harmonization protocols intended to establish metrological traceability of values assigned to product (end user) calibrators and patient samples* (14). When this new standard is completed and published, harmonization protocols that conform to the standard can be listed by JCTLM to enable their use by manufacturers of MPs to achieve harmonized results among different MPs for the same measurand.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures or Potential Conflicts of Interest: Upon manuscript completion, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

Employment or Leadership: W.G. Miller, *Clinical Chemistry*, AACC, and CLSI.

Consultant or Advisory Role: None declared.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: None declared.

Expert Testimony: None declared.

Patents: None declared.

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