Commentary

Harmonisation of Measurement Procedures: how do we get it done?

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Abstract

Clinical laboratory measurement results must be comparable among different measurement procedures, different locations and different times in order to be used appropriately for identifying and managing disease conditions. Harmonisation in the broad sense is the overall process of achieving comparability of results among clinical laboratory measurement procedures that measure the same measurand. The term standardisation is used when comparable results among measurement procedures are based on calibration traceability to SI using a reference measurement procedure of the highest available order. When there is no higher order reference measurement procedure available, and it is unlikely that one can be developed, the term harmonisation refers to any process for achieving comparable results among measurement procedures for an individual measurand.

This review explains calibration traceability and focuses on the principles of harmonisation for those measurands for which a reference measurement procedure does not exist. We discuss the value of harmonisation, the importance of commutable reference materials, the barriers to harmonisation that exist today, and conclude with a discussion of a current global effort to improve the state of harmonisation.

Why Comparable Results from Different Measurement Procedures are Important

The goal of doing any laboratory test is to detect the presence or absence of disease in a patient, and to subsequently manage the disease to ensure the best patient outcome. The clinical community is increasingly recognising the value of basing clinical decisions on evidence-based medicine.[1] Unfortunately, physicians, including those developing clinical practice guidelines that include clinical laboratory measurements in diagnosis or treatment monitoring algorithms, may not be aware of the variability that exists in results obtained from different measurement procedures. This variability can lead to clinical misclassification or inappropriate treatment, thus jeopardising patient safety.[2,3] Binkley et al, for example, pointed out the difficulty for a clinician to reliably categorise individuals as having low or adequate Vitamin D concentrations due to the differences that exist among the various vitamin D measurement procedures available;[4] while Sturgeon et al, pointed out the difficulties clinicians may experience following current treatment guidelines for patients with chronic kidney disease due to the variability in parathyroid hormone results.[5]

How Can we Achieve Comparable Results Among Different Measurement Procedures?

More than 30 years ago, Tietz[6] described a model for a 'comprehensive, coherent measurement system' based on developing a reference measurement procedure (RMP) and a primary (pure substance) reference material (RM) for a measurand, with the goal of the system being to achieve comparability of results from different routine measurement procedures across laboratories. In the ensuing years, various national and international organisations have developed programs for accomplishing standardisation of measurands based on RMPs and RMs. The term standardisation is used when comparable results among measurement procedures are based on calibration traceability to SI using a RMP.

The calibration traceability principles used today are described in the International Organization for Standardization (ISO) standard 17511,[7] which describes five categories of traceability of a routine measurement procedure's product calibrator. Figure 1 shows a complete traceability chain. The ISO 17511 traceability categories differ according to whether or not a RMP is available; and the availability of primary

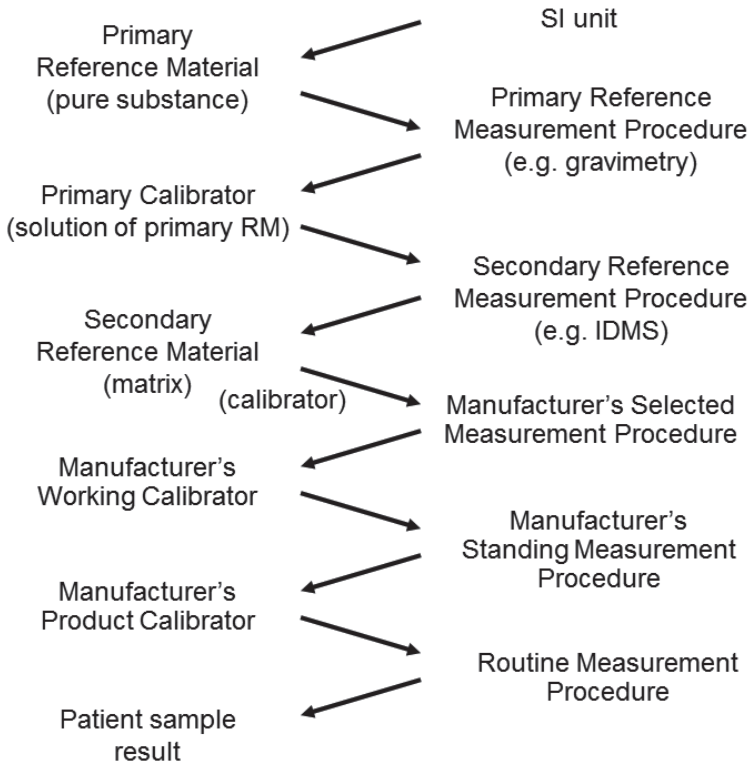

Figure 1. Calibration traceability chain.

(pure substance) RMs and secondary RMs. Secondary RMs are not pure substances, but rather the measurand exists in a matrix and its value is assigned using various value transfer processes. ISO 17511 refers to secondary RMs as international conventional calibrators. Note that the traceability for a routine measurement procedure's calibration may end at a manufacturer's working calibrator, at a secondary RM, at a secondary RMP or at a primary RM and RMP which provide traceability to the International System of Units (SI).

When a secondary RMP is available, or can realistically be developed, it provides the most desirable approach to standardise the various routine measurement procedures available to obtain numerically aligned results (that is, results that are equivalent for clinical use). For many important measurands, such as viruses, tumor markers and protein hormones, it has not been possible to develop either a RMP or a primary RM. In these situations, traceability of a product calibrator is to a secondary RM or to a manufacturer's internal working calibrator. The term harmonisation is used here to mean any process for achieving comparable results among measurement procedures for an individual measurand when no higher order RMP exists.

In 2008, Thienpont[8] challenged clinical laboratorians to 'have the courage to agree on pragmatic solutions' in those situations when development of a RMP is not likely going to be possible. Various national and international organisations have produced a number of secondary RMs intended for use as calibrators for routine measurement procedures when no RMP exists. In some cases a purified measurand has been added to a matrix and the nominal concentration of the measurand is stated. In most cases, the target values assigned to such secondary RMs are arbitrary. Nonetheless, an arbitrary value assignment is adequate to enable harmonisation as long as the secondary RM is suitable for use with all routine measurement procedures for which it is intended (that is, the secondary RM is commutable). Although some secondary RMs have contributed to improved comparability of results among different routine measurement procedures, many of the currently available secondary RMs are not commutable with native clinical samples and they have failed to accomplish the intended goal of achieving harmonised results.

Key Components for Traceability to a Secondary Reference Material

Important technical items that must be considered when establishing traceability of a product calibrator to a higher order reference system include the following:

- The measurand should be well-defined
- The measurement procedure should be specific for the measurand
- The calibrator should be commutable with the samples intended to be measured

These technical items are applicable to all steps in a traceability chain in a value assignment scheme whether the chain ends at a secondary RM or extends to a RMP and a primary RM.

The first point is that the measurand should be well-defined, meaning the chemical entity intended to be measured should be known, including the molecular form of interest in a given clinical situation. For example, human chorionic gonadotropin is known to have several isoforms and in different clinical settings, such as pregnancy or tumors, different molecular forms are expressed.[9] Consequently a given routine procedure may not be designed to measure all forms and perhaps a different procedure is needed for each of the clinically relevant measurands. Another example is troponin which is present as a molecular complex whose composition varies with time after cardiac tissue damage. Consequently, a different measurand will be measured depending on the circulating complex and the epitopes to which antibodies are directed.[10] Another example is brain natriuretic peptide (BNP). When measurements for BNP were first introduced, it was thought that there was only one form of BNP, an active hormone, in the circulation. It was subsequently discovered, however, that several different forms of BNP are present in the blood.[11] To the extent that a measurand is not well-defined, there will be ambiguity in what chemical entity is being measured and traceability may not be technically possible, or traceability may not lead to comparable results among routine measurement procedures because they are not measuring the same thing.

The second point that a measurement procedure should be specific for the measurand implies that, to the extent a procedure's result is influenced by molecules other than the measurand, or by other molecular forms of the measurand, traceability of the product calibrator may not ensure traceability of an individual patient's result. It is possible for a number of routine procedures, all purporting to measure the same measurand and having their calibrators traceable to a higher order reference system, to fail to have comparable results for patient samples due to lack of adequate specificity for the measurand. Depending on the measurement procedures' designs, inadequate specificity may cause a few patient sample results to differ or may cause a general increase in result variability for most samples.

The third critical technical component is the commutability of a RM used as a calibrator in any step in the traceability chain. Despite the description of commutability in the early 1970s and its importance in achieving comparability of results among different procedures, the concept is still poorly understood and appreciated.[12-14] Commutability is a property of a RM such that values measured for a RM and for the samples intended to be measured have the same relationship between two, or more, measurement procedures for the same measurand. It is important to note that commutability applies to a RM used as a calibrator at any step in a traceability chain including earlier steps where a manufacturer's working calibrator, rather than patient samples, may be the intended sample. For example, a manufacturer's working calibrator to be used with the manufacturer's standing measurement procedure may be value-assigned by a secondary RMP. In this case, it is the commutability of the calibrator of the secondary RMP with the manufacturer's working calibrator (the sample intended to be measured) that must be validated between the two measurement procedures used in that part of the traceability chain. In this review, we are focusing on a secondary RM intended to be used as a calibrator for a manufacturer's standing measurement procedure, which is typically the same as the routine procedure, as a calibrator for the routine measurement procedure itself, or to verify calibration traceability of a routine measurement procedure. Consequently the commutability of a secondary RM with native patient samples among the routine measurement procedures for which that RM is intended to be used is of particular importance.

Historically the importance of the commutability of secondary RMs has not been adequately appreciated and there are a number of secondary RMs available that have not been validated for commutability with native patient samples. Lack of commutability breaks the traceability chain and, even though routine measurement procedures claim traceability to such RMs, the results for patient samples may not be comparable among the procedures. Examples where routine measurement procedures have failed to achieve comparable results for patient samples despite claiming traceability to the same secondary RM include: C-peptide,[15] human chorionic gonadotropin,[9] cytomegalovirus,[16] follicle stimulating hormone,[17] prostate-specific antigen,[18,19] insulin,[20] thyroid stimulating hormone,[21] and Troponin I.[22]

One of the principal challenges facing laboratory medicine is to change our practice to require commutability validation for RMs intended for use with manufacturer's standing

procedures or routine clinical laboratory procedures. A recent guideline from the Clinical and Laboratory Standards Institute describes characterisation and qualification of commutable reference materials for laboratory medicine.[23]

These and other important barriers to achieving harmonisation that have been identified are listed below.[8,14]

- Inadequate definition of the measurand (heterogeneous analyte)
- Inadequate analytical specificity for the measurand
- Lack of commutable reference materials
- Materials are labeled as 'reference materials' that have not been validated to be commutable for the intended measurement procedures
- Lack of globally accepted protocols to use to achieve harmonisation when there is no reference measurement procedure
- Unwillingness of some in the profession to accept 'less than perfect' approaches for harmonisation
- Lack of agreement on clinically relevant analytical performance requirements
- Lack of a systematic process to identify and prioritise measurands
- Lack of an organised process to manage harmonisation activities in the clinical laboratory community (particularly when there is no reference measurement procedure)
- Inadequate funding to support harmonisation efforts
- Amount of time/effort required for harmonisation to be accomplished

How Can we Improve the Harmonisation of Routine Measurement Procedures?

A recent report from an international workshop proposed a roadmap for harmonisation of clinical laboratory measurement procedures.[14] The conference attendees suggested that an international program be created to organise prioritisation of measurands; to coordinate the activity of all interested parties to standardise, i.e. develop a RMP and a primary RM whenever technically possible, or to harmonise results from routine clinical laboratory measurement procedures; and to conduct harmonisation activities for specific high priority measurands when no other entity is addressing that measurand. A diagram of the proposed infrastructure is shown in Figure 2. The roadmap proposal was primarily directed to establishing both a global program to organise and coordinate

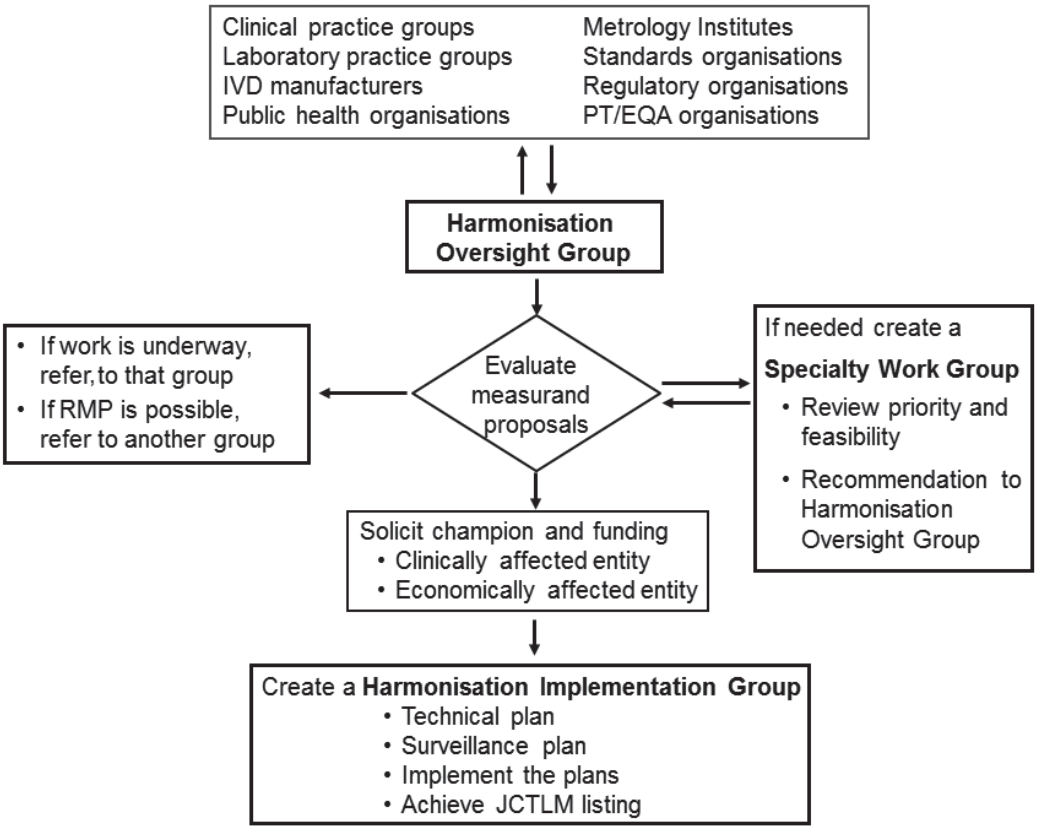

Figure 2. A suggested approach for the global management of harmonisation activities for a measurand. (modified with permission from Ref. 14).

harmonisation activities, and to specifically address technical procedures for harmonisation of measurands for which there was no RMP likely to be developed but a RM was feasible and of measurands for which there was no RM likely to be developed. A Harmonisation Oversight Group will manage the process by interacting with stakeholders to seek input on candidate measurands for standardisation or harmonisation, to form a Specialty Work Group to evaluate evidence for prioritisation and technical feasibility to achieve standardisation or harmonisation, and when a RMP can be developed to refer standardisation work to an organisation with expertise and procedures established for that work. If no RMP is likely to be developed, the Harmonisation Oversight Group will seek funding and establish a Harmonisation Implementation Group to develop a technical protocol and pursue the work needed to accomplish harmonisation.

The American Association for Clinical Chemistry has supported a steering committee and three task forces who are working to develop the organisational infrastructure and a set of potential harmonisation approaches for this initiative. The goal is to have a program to organise global standardisation and harmonisation operational by the end of 2012. An information web site has been established that will evolve into a communications portal for global harmonisation activities.[24] All clinical laboratorians are encouraged to become involved in the harmonisation initiative, and the improvements that are anticipated to result from it.

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