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Update on current concepts and meanings in laboratory medicine — Standardization, traceability and harmonization

Neil Greenberg *

Neil Greenberg Consulting Services, LLC, 40 Chipping Ridge, Fairport, NY 14450, USA

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ABSTRACT

An increasingly important quality objective in laboratory medicine is ensuring the equivalence of test results among different measurement procedures, different laboratories and health care systems, over time. In recent years, interest in sharing a single patient's clinical laboratory data, regardless of where the measurements are performed, has moved out of the domain of the scientific community and spilled over into the domain of regulators, lawmakers and the general population in many parts of the world. For all parties involved in the dialog, establishing and maintaining a clear understanding of the essential concepts that are vital to achieving global equivalence among clinical laboratory measurements have therefore become a priority. Concepts that are critical to this discussion include *standardization*, *traceability* and *harmonization*. This report provides an updated discussion and practical definitions for these terms and others that are linked to metrological principles.

1. Introduction

Increased analytical accuracy is a hallmark of improved quality in a laboratory measurement system, and is strongly associated with improved health care. Because multiple measurement methods and procedures may be available for a given measurand, harmonization of test results, especially in reference to internationally agreed measurement standards, creates the opportunity for sharing results among different health care systems as well as across geographic boundaries and time. In addition, clinical laboratory measurement harmonization is a critical issue to be addressed in successfully designing clinical trials intended to demonstrate the efficacy of new and improved therapeutic agents [1] and in translating clinical research into routine practice.

The benefits of improved performance and harmonization of reported values for different clinical laboratory measurement procedures for a given measurand are illustrated by quality enhancements in routine clinical laboratory serum cholesterol measurements realized over the thirty-year period from 1970 to 2000 [2,3], which coincided with a profound reduction in the mortality rates for coronary heart disease (CHD) in the US [4]. While many of the improvements achieved in diagnosis and treatment of CHD are attributable to a variety of factors not directly related to the clinical laboratory, the economic yield of the investment in harmonization of blood cholesterol measurements in the US alone is very conservatively estimated to be in the range of several hundred million to several billion US dollars annually [5].

The need for harmonization of clinical laboratory measurements has also been emphasized as an essential element of key legal constructs that regulate the delivery and commercialization of laboratory medicine products and services in many world markets. The regulatory focus on harmonization is exemplified by the EU IVD Directive [6], where it is an essential requirement that "…the traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order." Implementation of this EU regulatory requirement was further supported by the publication of an ISO standard concerning traceability of values assigned to calibrators, ISO 17511:2003 [7]. A similar regulatory expectation is defined in the U.S. Code of Federal Regulations 21CFR Part 809.10 (b)(12) [8], where it is stated that manufacturers of commercial IVD reagents must provide information to users regarding "…specific performance characteristics … accuracy, precision, specificity, and sensitivity."

As a result of the recent launch of the International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) measurement harmonization initiative under stewardship of the American Association for Clinical Chemistry (AACC) [9–11], discussion of the concept of harmonization among different measurement procedures for the same measurand has achieved increased visibility among the various stakeholders, such as routine and reference laboratories, IVD reagents,

Abbreviations: CHD, coronary heart disease; IVD, *in vitro* diagnostic medical device; EU IVD Directive, Directive 98/79/EC of the European Parliament; ISO, International Organization for Standardization; VIM, International Vocabulary of Metrology; GUM, Guide to Expression of Uncertainty in Measurement; BIPM, Bureau International des Poids et Mesures; JCTLM, Joint Committee for Traceability in Laboratory Medicine; WHO, World Health Organization; RMP, Reference Measurement Procedure; ICHCLR, International Consortium for Harmonization of Clinical Laboratory Results; NMI, National Metrology Institute.

* Tel.: +1 585 317 8791.
E-mail address: ngreenbe@frontier.com.

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systems and calibrator manufacturers, and accreditation and regulatory bodies.

In the broadest sense, harmonization of measurements refers to any process that enables the establishment of equivalence of reported values produced by different measurement procedures for the same *measurand*, i.e. the quantity intended to be measured [12]. In laboratory medicine, harmonization of results for a given measurand can be achieved by two main methods, where the selected method is predetermined based on availability of suitable reference measurement procedures and reference materials for the target measurand. Method 1, commonly referred to as standardization, is the conventional approach, and is dependent on application of a well-understood reference measurement procedure and commutable reference materials to establish the calibration for each available routine measurement procedure. The second method, Method 2, to be considered only when reference measurement procedures are not available, is based on application of a factor or other data manipulation strategy to manufacture arbitrary equivalence of otherwise disparate results generated by the various (non-standardized) routine measurement procedures.

The stated focus of the ICHCLR harmonization initiative is the achievement of *harmonization* of reported values among multiple routine measurement procedures for the same measurand when there are no reference measurement procedures (RMPs) available [9–11], and the development of practical solutions for the establishment of equivalence of reported values among different measurement procedures that are not traceable to SI. Realization of these initiatives will enable the practical implementation of common cutoff values and/or reference intervals, as well as retrospective application of *harmonized* clinical decision values to legacy clinical trials data that were used to establish the clinical sensitivity and specificity characteristics for many of these types of measurands. The complete rationale for the ICHCLR Harmonization Initiative has been described elsewhere [10,11].

Three key words in the current dialog regarding improving the equivalence of reported values among different clinical laboratory measurement procedures for the same measurand are therefore *standardization*, *traceability*, and *harmonization*. With the co-existing technical and legal contexts of these terms that are so central to defining the quality of laboratory measurements, the definitions of these and other related terms such as "higher order reference materials," are at times confused and misused among the diverse range of participants involved in the discussion.

2. What is *standardization*?

Standardization is probably the most widely used of these three key words, as it is a term that is well rooted in many technical and non-technical disciplines and languages worldwide. For purposes of this discussion, the most appropriate supporting definition is found in *the International Vocabulary of Metrology* (VIM) [12], which defines a *measurement standard* as the… "realization of the definition of a given quantity, with stated quantity value and associated measurement uncertainty, used as a reference."

The term *quantity* as used above describes a measurable property of a given substance or material, where the magnitude of the measured property can be described with a numerical value and a reference (i.e. a measurement unit.) Examples of the kinds of quantities that comprise the Système International (SI) "base units of measurement"[13] and which are particularly important in the field of laboratory medicine include mass (kilogram, kg), length (meter, m), amount of substance (moles, mol), time (second, s) and thermodynamic temperature (Kelvin, K). Note that these SI base units are also essential to the definition of other important measured SI quantities, called derived SI quantities [13], which are obtained from mathematical equations supported by various SI base unit quantities, e.g. volume (cubic meter, m^3), mass density (kilogram per cubic meter, kg/m^3), amount of substance concentration (mol/m^3).

The expression, "realization of the definition of a… quantity" concerns the establishment (by agreement) of either a physical *material* or a *highly reproducible physical phenomenon or constant*, which by definition and/or by agreement is the ultimate standard, i.e. it physically embodies the measurement unit, or a submultiple or multiple thereof. For example, the basic metric unit for mass, the kilogram, exemplifies a definition of a particular quantity for which the "realization" is based on a physical material. The prototype kilogram (a cylinder made of a platinum–iridium alloy) is maintained by the Bureau International des Poids et Mésures (BIPM) in Sèvres, France. To effect the global promulgation of the standard kilogram at the regional and national level in support of scientific and industrial applications of mass measurement, the prototype reference kilogram is used to make metal alloy copies that are maintained by various national metrology institutes (NMIs) worldwide.

Given the above definition of a measurement standard, *standardization* is a harmonization process in which the values assigned to hierarchically lower order standards (e.g. a value assigned to a commercial stainless steel reference mass of approximately 1 kg, intended for calibration of commercial field balances) are systematically determined either by a direct comparison to the highest order reference standard available (i.e., the prototype platinum–iridium alloy kilogram at the BIPM), or indirectly, by comparison with an intermediate (lower order) reference standard, such as a platinum–iridium "copy" prototype kilogram maintained at an NMI.

In the fields of analytical chemistry and laboratory medicine, for the practical implementation of a harmonization process that can be characterized as *standardization*, trueness is transferred by way of a systematic step-wise process from highest order available (traceable to SI) standards to successively lower-order routine/commercial calibrators. Such assigned-value transfer processes may include the use of various hierarchically intermediate-order reference standards as calibrators in multiple measurement stages, as long as the provider of such intermediate-order reference standards makes available adequate information concerning their assigned values and uncertainties, including a description of the applicable calibration hierarchy and higher order references (material standards and measurement procedures), with a cumulative accounting for uncertainties propagated from any higher order references. The accompanying information for any applied intermediate-order standards should also state what is known about the compatibility of such standards with the available measurement procedures, especially with respect to the performance of these reference materials in comparison to the types of samples usually intended to be measured (e.g. patient samples in the field of laboratory medicine) for the quantity of interest. Further comments on this point are given below in the discussion on *traceability*.

3. What is *traceability*?

The concept of calibration *traceability*, although certainly not a new one, has received increased emphasis in the field of laboratory medicine in recent years, primarily because of the very specific language in the essential requirements of the EU IVD Directive [6], declaring that "the traceability of values assigned to calibrators and/or control materials must be assured…" Although there are many kinds of *traceability* in a broad array of disciplines (e.g. document traceability, accounting traceability, design traceability, information source traceability, etc.), the type of *traceability* that is the focus of the essential requirements of the IVD Directive is *metrological traceability*. *Metrological traceability* is defined in the VIM, clause 2.41[12] as the "property of a measurement result whereby the result can be related to a reference (a standard) through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty."

The International Laboratory Accreditation Cooperation (ILAC) Policy on Traceability of Measurement Results [14] states that the essential elements of a *traceable* measurement include (1) an unbroken chain