Opinion Paper

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The roadmap for harmonization: status of the International Consortium for Harmonization of Clinical Laboratory Results

https://doi.org/10.1515/cclm-2017-0907
Received October 8, 2017; accepted November 20, 2017; previously published online April 19, 2018

Abstract: The International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) was established to fulfill recommendations identified by an international conference convened to review the available infrastructure and challenges in achieving harmonization of results among different measurement procedures. The specific objectives of the ICHCLR are to: prioritize measurands by medical importance, coordinate the work of different organizations, and stimulate development of technical and regulatory processes to achieve harmonization. Central to these objectives is the website "www.harmonization.net" developed by the ICHCLR as an information portal designed to provide a resource center for global activities to harmonize and standardize results from clinical laboratory measurement procedures. Priorities based on medical impact are provided for measurands for which harmonization is needed or work to implement harmonization is incomplete or inactive. By making information available regarding harmonization activities in progress or planned, coordination of work to harmonize laboratory measurement procedures will minimize duplication of effort and optimize the use of limited resources. A toolbox of technical procedures developed by ICHCLR to be considered when developing a process to achieve harmonization for a measurand is presented. The ICHCLR initiated a proposal to ISO Technical Committee 212 for a harmonization protocol as the basis for calibration traceability when there are no other higher order reference system components available. The ICHCLR offers a unique service to prioritize measurands in need of harmonization and to provide a centralized approach to organize global efforts to achieve harmonization of clinical laboratory test results.

Keywords: harmonization; standardization; traceability.

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Introduction

A conference sponsored by the American Association for Clinical Chemistry in 2010 reviewed the available infrastructure and challenges in achieving harmonization of results among different measurement procedures. The conference was attended by 90 people from 12 countries representing 60 professional organizations and *in vitro* diagnostic (IVD) manufacturers. At that time, there was a well-developed infrastructure for calibration traceability described in the International Organization for Standardization (ISO) standard 17511, *In vitro diagnostic medical devices – measurement of quantities in biological samples – metrological traceability of values assigned to calibrators and control materials* [1]. The infrastructure focused on developing certified reference materials and reference measurement procedures as higher order references for standardization or harmonization of results among different clinical laboratory measurement procedures. However, there were no certified reference materials or reference measurement procedures for a very large number of measurands measured by clinical laboratories. Furthermore, there were certified reference materials in use that were not commutable with human samples and thus when used for calibration traceability caused discrepant results among different measurement procedures [2–12].

The recommendations from the conference were reported in 2011 as a roadmap for harmonization of clinical laboratory measurement procedures [13]. The principal recommendation was to create an organization that would provide several unmet needs: (1) prioritize measurands that needed harmonization based on their importance in medical decisions and use in clinical practice guidelines; (2) provide an information portal to catalog

harmonization activities being conducted by different groups worldwide to promote coordination and minimize duplication of effort; (3) promote processes for harmonization; and (4) address in particular the situation when there is no suitable certified reference material or reference measurement procedure for a measurand.

The International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) was created and became operational in 2013 to fulfill the recommendations from the conference. The ICHCLR is governed by a Council made up of organizations with a commitment to harmonization and who make a substantial financial contribution to its administrative support. The Council appoints a Harmonization Oversight Group (HOG) to implement the activities of the ICHCLR. In addition, interested stakeholders can support the ICHCLR by joining the Stakeholder Member group. The website www.harmonization.net provides additional information on the ICHCLR as well as an information portal through which the ICHCLR fulfills its mission to provide a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results. This report reviews activities of the ICHCLR to advance harmonization of results.

The ICHCLR website and measurand information portal

The ICHCLR has addressed coordination of harmonization activities by developing a website as an information portal to provide a resource center for global activities to harmonize and standardize results from clinical laboratory measurement procedures. The ICHCLR website has been updated and moved to a new platform to provide better functionality for the end user. Now in its second version, the website provides a global portal for information on the status of standardization/harmonization for measurands and coordination of the activities of organizations working to harmonize a given measurand. The website is the only resource in the world that catalogs international organizations' activities in standardization/harmonization, prioritizes measurands requiring harmonization, and provides citations for important peer reviewed articles on standardization/harmonization and related topics.

The website provides information on the administrative structure and operation of the ICHCLR. The "Resources" tab contains the operating procedures for the ICHCLR, links to a number of important publications, minutes from meetings of the Council and HOG, Stakeholder Member update reports, and a toolbox of technical procedures to be considered when developing a process to achieve harmonization for a measurand (discussed later).

The central feature of the web site is the "Measurands" tab that provides information on the status of harmonization or standardization of measurands. Priorities based on medical impact are provided for measurands for which harmonization is needed or that have an incomplete or inactive implementation of a harmonization activity. A challenge in the prioritization process is the limited information from EQA programs that use commutable materials to assess the state of the art in agreement with results for measurands among different measurement procedures. Another key feature on the measurand table provides additional information regarding the harmonization status and medical impact which can be viewed by clicking on the measurand name. Information on reference materials, reference measurement procedures, and reference laboratory services listed by the Joint Committee for Traceability in Laboratory Medicine (JCTLM) are indicated in the resources column. Links to organizations actively addressing harmonization of particular measurands are also provided for additional information on those projects. The "Measurands" table is a continuous work in progress and is regularly updated as new measurands are reviewed and new information becomes available.

The information provided on www.harmonization.net is a unique resource for organizations conducting or considering conducting harmonization activities, international metrology institutes that develop reference measurement procedures and certified reference materials, proficiency testing providers developing surveys using commutable materials for assessment of harmonization status, IVD manufacturers and regulatory bodies around the world. The prioritized list of measurands will assist such organizations in determining where resources should be directed to improve clinical laboratory test results. The information on current global activities will minimize duplication of effort and lead to better communication and collaboration among organizations.

The toolbox of technical procedures

The "Resources" tab of the website includes a toolbox of technical procedures to be considered when developing a process to achieve harmonization for a measurand. The first step is to assess the feasibility for harmonization by considering properties related to the measurement procedures and to the harmonization tools that exist or need to be developed. Harmonization is feasible when measurement procedures measure the same molecular species,

have adequate selectivity for the measurand and use a suitable calibration model for the measuring interval of the procedure. In addition, tools to achieve harmonization must be available or be developed to support the activity. Tools include a fit-for-purpose reference material, that can be a panel of clinical samples, and a reference measurement procedure when technically feasible and cost effective to develop. A reference material used as a calibrator must be commutable with clinical samples for all measurement procedures for which it will be used, requires a process for value assignment and an estimate of its uncertainty, and properties of stability and sustainability over time. Other important considerations once it is agreed that harmonization is technically feasible, are assessment of the effort and cost to achieve harmonization, a commitment of the technical work group and IVD manufacturers to provide the resources to collaborate to accomplish the harmonization activity, and finally an assessment of sustained success of harmonization.

The toolbox includes two experimental designs. One is an integrated harmonization protocol that describes a single experiment to determine the feasibility of harmonization and to identify a technical approach based on reference system components that are available or can be developed. The second is a step-up design for harmonization that is intended to establish harmonization of measurements when there is not a reference measurement procedure nor a suitable commutable reference material. The step-up design is based on a series of patient sample comparisons that verify properties of measurement procedures and qualify the panel of patient samples to define a harmonization protocol.

The integrated approach was applied by the IFCC Working Group on Standardization of Carbohydrate-Deficient Transferrin [14]. The initial experimental design included 40 patient samples and four candidate reference materials measured by six commercial measurement procedures and a candidate reference measurement procedure. The results of the initial experiment concluded that the routine measurement procedures had characteristics that allowed harmonization, that some candidate reference materials did not have suitable commutability for use as calibrators but one batch of candidate reference materials based on frozen human serum pools was suitable. A subsequent stability assessment concluded that these candidate reference materials were stable for at least 3 years when stored at –70 °C [14]. Two follow-up pilot assessments demonstrated the success of harmonization of the commercial measurement procedure results when calibrated using the candidate reference materials with values assigned by the candidate reference measurement procedure [14]. The integrated approach from the toolbox was also applied to identify commutable reference materials suitable for calibration of hepcidin measurement procedures [15].

The step-up design was developed by the IFCC committee for standardization of thyroid function tests for thyroid stimulating hormone [16, 17]. In this approach, a series of comparisons of results for panels of individual patient samples including initially euthyroid, followed by hyper- and hypo-thyroid patients, among approximately 15 different commercial measurement procedures was performed (each of the steps did not include the same measurement procedures) [17]. The comparisons allowed determination of the feasibility for harmonization, qualification of measurement procedures for harmonization, development of harmonization algorithms to be applied to the calibration traceability hierarchies for each measurement procedure, and validation of the success of the recalibration procedures applied by each measurement procedure manufacturer. Successful results at each step allowed to step-up to the next comparison until a fully validated harmonization protocol was ready for implementation [17].

Development of an International Organization for Standardization (ISO) standard for a harmonization protocol

During development of the toolbox of technical procedures, the ICHCLR realized that an ISO standard for a harmonization protocol was needed to enable such a protocol to be listed by the JCTLM. JCTLM lists in its database higher order reference system components that conform to applicable ISO standards. The ICHCLR initiated submission of a preliminary work item proposal to ISO Technical Committee 212, Clinical Laboratory Testing and *In vitro* Diagnostic Test Systems, to develop a new standard for a harmonization protocol as the basis for calibration traceability. The project was approved in 2016 by ISO member countries and is now an active work item 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 human samples* [18]. When published, the new standard can be used by the JCTLM as the basis to list harmonization protocols as one of several

types of higher order reference system components for calibration traceability.

The European Union Directive 98/79 in 1998, effective 2003, was the first legal requirement that clinical laboratory measurement procedures have calibration traceable to higher order reference system components [19]. The replacement of the 1998 directive by the European Union Regulation 2017/746 in 2017, effective 2022, continues that requirement [20]. The EU directive stimulated development of the ISO standards for traceability [21], reference materials [9], reference measurement procedures [22] including procedures for catalytic activity [23] and reference laboratories [24]; as well as formation of the JCTLM as a body to determine that reference system components conform to the ISO standards [25]. Calibration traceability should be to the highest order reference system component available for a given measurand. Consequently, a reference measurement procedure and/or a certified reference material are preferred when available. A harmonization protocol provides a higher order reference system component that can be developed for the large number of measurands for which reference measurement procedures and/or suitable certified reference materials are not available [26].

ICHCLR's role in coordination of global harmonization activities

A report in the September 2017 issue of *Clinical Chemistry* [27] highlighted a situation where several research efforts to harmonize C-peptide were started independently of each other and the challenges subsequently encountered with implementing a reference measurement system for calibration traceability of C-peptide. These independent non-coordinated approaches to establishing standardization of C-peptide left manufacturers of measurement procedures without a clear direction regarding how to implement calibration traceability that would result in global standardization of C-peptide measurements.

The situation with c-peptide exemplified a challenge where lack of coordination of harmonization activities presented a major barrier that could have cost hundreds of man-hours and hundreds of thousands of research dollars to be inappropriately expended to achieve harmonization for a single measurand. A more coherent approach among researchers and organizations is required when developing reference measurement systems for metrological traceability in laboratory medicine [28].

One of the ICHCLR's important functions is to survey international organizations to provide information on their activities addressing harmonization of particular measurands. By making information available on its website regarding harmonization activities in progress or planned, coordination of work to harmonize laboratory measurement procedures will optimize the use of limited resources, avoid duplication of effort and ensure coordination of global harmonization of results for a measurand.

Regulatory issues impact implementation of a harmonization activity

As components of reference measurement systems are developed for specific measurands, the IVD industry is encouraged to change the calibration traceability of existing IVD devices to align with the accepted national or international consensus standards to improve the quality of clinical decisions based on laboratory test results. It is best laboratory practice to have calibration traceable to the highest order reference system components available for a measurand including an accepted reference measurement procedure, a fit-for-purpose commutable reference material, or a harmonization protocol when the preceding are not available to ensure harmonization among results from different IVD devices. The regulatory process associated with IVD device recalibration can be expensive, time consuming and a potential barrier to successful harmonization of a measurand. The ICHCLR works with the IVD industry and regulatory agencies in several countries and regions, for example the US Food and Drug Administration (FDA), regarding regulatory considerations faced when recalibrating IVD devices. The goal is to simplify the regulatory approval process for recalibration while maintaining the essential role to ensure patient safety.

A forum between the US FDA and IVD Industry was initiated and organized in 2013 by the ICHCLR in collaboration with AdvaMedDx (a division of the Advanced Medical Technology Association) and the American Association for Clinical Chemistry. The forum discussed regulatory considerations related to recalibration of measurement procedures to conform to international recommendations for harmonization or standardization. A summary report from the forum is available in the "Resources" tab on https://www.harmonization.net/media/1007/harmonization-forum-summary-comments.pdf. Several important conclusions were reached regarding implementing a recalibration

process to conform to an international program for harmonization of results. The purpose for recalibration is to achieve equivalent results among different IVD devices to enable safe and effective application of clinical practice guidelines. In many cases, fixed decision values are used for interpretation of laboratory results and harmonization of results from all IVD devices enables correct application of a guideline. Because all stakeholders share this goal for clinical effectiveness, the regulatory process for implementation should be as efficient as possible to enable harmonization to be implemented as expeditiously as possible.

Recalibration through traceability to a higher order reference system always affects the numeric values of results to achieve harmonization among different IVD devices. In this case, reference intervals and the measuring interval (lower and upper limits of quantitation, or limits of detection or blank as applicable) can be adjusted mathematically according to the magnitude of change in the numeric values of results. Other measurement procedure performance characteristics such as precision, selectivity for the measurand or influence of interfering substances are not altered by recalibration of IVD devices. Consequently, an abbreviated regulatory review process should be appropriate.

Summary and path forward

The ICHCLR was established to fulfill recommendations identified by an international conference convened to review the available infrastructure and challenges in achieving harmonization of results among different measurement procedures. The ICHCLR offers a unique service to prioritize measurands in need of harmonization and to provide a centralized approach to organize global efforts to achieve harmonization of clinical laboratory test results.

Looking to the future, the ICHCLR will continue to expand the list of prioritized measurands based on medical impact and work with regulatory bodies to simplify regulatory processes for harmonization of results from existing measurement procedures. To avoid duplication of effort and possible conflicting approaches, the ICHCLR will continue to develop its information portal to catalog activities of organizations developing reference systems and harmonization processes to promote collaboration and cooperation.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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