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Why is harmonization important for traceability in laboratory medicine?

This special report discusses the importance of harmonization of several related activities needed to achieve metrological traceability in laboratory medicine. When laboratory test results differ, the potential exists for misinterpretation of results possibly leading to wrong diagnosis or treatments and adverse patient outcomes. To successfully achieve harmonized test results requires calibration traceability to reference systems of higher-order that now includes a harmonization protocol. Related activities that also require harmonization include: global coordination of harmonization activities, developing reference system components for high priority measurands, addressing issues with non-commutable reference materials, and coordinating global regulatory approaches for approving harmonized measurement procedures. The report includes a discussion of current resources for harmonization.

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Importance of harmonization

Clinical laboratory tests are essential for providing high-quality patient care. Patients and healthcare professionals assume that clinical laboratory tests performed by different laboratories at different times on the same type of specimen are equivalent and can be reliably and consistently interpreted. When laboratory tests are not equivalent, the entire spectrum of patient care can be affected in profound ways. The difference in test results presents the potential for diagnostic and treatment errors resulting in adverse patient outcomes, and can also lead to unnecessary follow-up diagnostic procedures and treatments, adding unnecessary costs to patient care. In addition, many clinical decisions are based on clinical guidelines that are anchored to a specified laboratory test result for treatment decisions. If the test used in a guideline is not harmonized, clinical guidelines become compromised and results can mislead physicians and defeat the purpose of following the guideline. We use the terms harmonized and harmonization to mean equivalent results, within clinically meaningful limits, among different measurement procedures intended to measure the same measurand. Standardization is a closely related term that achieves harmonization by having metrological traceability of calibration to higher order reference materials and/or reference measurement procedures.

Resources for harmonization

Achieving harmonized test results is primarily a function of establishing a measurement procedure's calibration hierarchy traceable to a reference measurement system as described in the ISO17511:2020 requirements (1). Examples of harmonization successes that have contributed to significant improvements in identifying and managing individuals with chronic diseases are diabetes and heart disease (2,3). Efforts to develop reference system components for more measurands and health conditions were highlighted and discussed during the JCTLM's workshop in 2019: Accurate results for patient care. However, despite these successes and current efforts the number of laboratory tests for which reference systems are currently available is limited to a little over 100 measurands.

There are resources currently available to provide important information on available reference measurement system components that can be used to accomplish harmonization through metrological traceability of calibration according to ISO17511. The JCTLM maintains a database (www.bipm.org/jctlm/) of reference measurement procedures, reference materials, and reference measurement laboratories certified against appropriate ISO standards. Strict criteria are required for inclusion in the JCTLM database, including evidence of commutability of matrix-based reference materials and measurement uncertainty. IVD manufacturers use the JCTLM listed resources to ensure their measurement procedures meet calibration traceability requirements and provide harmonized test results. The JCTLM database also provides information to researchers on what reference system components have already been developed by various international organizations for specific measurands. However, the JCTLM database does not provide any information on what is currently under development or what is a priority need.

In 2010 the AACC convened an international leadership conference to address some of the issues that hamper calibration and traceability to accomplish harmonization in laboratory medicine. The output from this conference was a proposed roadmap that recommended a framework to

address unmet needs for harmonization of clinical laboratory measurement procedures (4). The key point in the roadmap was a recommendation to develop an infrastructure to coordinate harmonization activities worldwide. Lack of coordination of harmonization activities is a major barrier that can cost hundreds of man-hours and cause hundreds of thousands of research dollars to be inappropriately expended to achieve harmonization for a single measurand. Collaboration among researchers and organizations is important to remove potential bottlenecks and better stimulate development of a coherent solution to analytical problems faced in developing higher order reference systems for calibration hierarchies.

To fill this void, the International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) was formed to provide a resource center for information on global activities to harmonize clinical laboratory measurement procedures. The ICHCLR has three main functions: one is to prioritize on the basis of medical impact measurands for which harmonization is needed or for which implementation is incomplete. The second is to provide information on activities by international organizations that are actively addressing harmonization of particular measurands. By making available information on harmonization activities that are either in progress or are being planned, coordination of work will improve, thereby resulting in minimized duplication of effort and better use of limited resources. The third main function is to organize and promote collaboration among stakeholders to address issues that affect successful implementation of harmonization activities. For example, harmonizing global regulations to simplify adopting a new calibration hierarchy program can shorten the time to realize the clinical benefits.

The ICHCLR maintains a website at www.harmonization.net, which is designed to serve as an information portal on global harmonization activities. The website's "Measurands" tab lists measurands with a harmonization status, including priority for harmonization, justification for that priority, and links to organizations actively addressing harmonization. With the appropriate information provided by international organizations, the ICHCLR can serve as a clearing-house for harmonization activities worldwide and support better cooperation in developing reference measurement systems. Organizations are encouraged to contact the ICHCLR through its website and provide information on their activities to develop reference system components for harmonization.

A table in an eJIFCC editorial (5) lists more than 40 international clinical chemistry societies and other professional groups including External Quality Assurance Schemes (EQAS) that are working on harmonization projects. Not included in the list are the many national metrology institutes which are the source for most of the reference measurement procedures and reference materials listed in the JCTLM database. The listed harmonization activities are not limited to just the development of reference systems but include harmonization of all aspects of the total testing process. With so many stakeholders involved in harmonization, it is vital to establish mechanisms to inform and coordinate global harmonization activities. A goal of the ICHCLR is to fill this important need.

This concern for international collaboration was also the focus of a special mini-workshop session convened at the JCTLM Workshop: Accurate results for patient care. The aims of this mini-workshop, 'Working together towards standardization in laboratory medicine – co-ordination of international activities' were:

- To map out the key components of a roadmap describing how international and national organizations can work together most effectively in a coordinated way to promote comparability of results in laboratory medicine;
- To develop common proposals which would subsequently be subject to more open consultation and discussion.

A copy of the proceedings from the mini-workshop is available from the JCTLM Secretariat at jctlm@bipm.org.

Achieving harmonization

The JCTLM database lists approved reference measurement procedures, reference materials, and reference measurement services that the IVD industry, clinical laboratories and EQAS programs can use as the basis for calibration traceability and performance assessment following technical concepts described in ISO 17511. When no reference system components are available for a measurand, harmonization is still possible. The ICHCLR developed a toolbox of technical procedures to be followed when harmonizing a measurand when a reference measurement procedure or certified reference material does not exist. The toolbox includes two experimental approaches. One is an integrated protocol for harmonization that details 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 unique step-up approach 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 approach is based on a series of comparisons using patient samples that verify properties of measurement procedures and qualify the use of patient samples to define a harmonization protocol. The integrated approach was applied by the IFCC Working Group on Standardization of Carbohydrate-Deficient Transferrin (6) and also applied to identify commutable reference materials suitable for calibration of hepcidin measurement procedures (7). The step-up approach was used by the IFCC committee for standardization of thyroid function tests for harmonization of thyroid stimulating hormone (8,9). While the ICHCLR toolbox of technical procedures provides important guidance to develop a harmonization protocol for measurands where a reference measurement procedure is not available, the toolbox is not recognized as an international standard to achieve harmonization.

The ICHCLR realized that a new ISO standard was needed to provide requirements and guidance for developing and implementing a harmonization protocol as the basis for metrological traceability of calibration hierarchies. The ICHCLR initiated submission of a preliminary work item proposal through the US delegation to ISO TC 212, Clinical laboratory testing and in vitro diagnostic test systems, to develop a new standard for a harmonization protocol. ISO 21151 "In vitro diagnostic medical devices Requirements for international harmonization protocols intended to establish metrological traceability of values assigned to calibrators and human samples" (10) has been approved and is being published as an international standard in 2020 along with the revised ISO 17511 standard. The ISO 21151 standard will be an important new tool to achieve equivalent results among different measurement procedures when no certified reference material or reference measurement procedure is available, and will allow harmonization protocols certified against this standard to be listed in the JCTLM database.

Challenges to harmonization

There are many challenges to achieving harmonization of laboratory test results. The lack of available reference measurement procedures and reference materials for the majority of measurands has already been mentioned. When a need is recognized the technical and regulatory processes to achieve harmonization can take 10 or more years. In most projects, the technical processes can be complex and require substantial research to develop practical reference system components.

A major challenge to harmonization is the lack of commutability of reference materials. Many reference materials are not suitable for use in calibration hierarchies because they were not developed and validated to be commutable with all measurement procedures for which they were intended to be used (11, 12). The net effect is that when such non-commutable reference materials are used in calibration hierarchies, patient results are not equivalent when measured using different measurement procedures despite the apparent traceability to higher order reference systems. The IFCC Working Group on Commutability has published a series of reports concerning commutability (13-16).

Achieving regulatory approval following recalibration to harmonize measurement procedures can provide considerable challenges to IVD manufacturers. Regulatory agencies approve the performance characteristics of measurement procedures including their calibration traceability as safe and effective for use in medical decisions for diagnosis and management of diseases. During the JCTLM Workshop: Accurate results for patient care in December 2019, the participants commented that more than 100 countries have developed or are developing regulations for certifying IVD measurement procedures. At the present time, there is no concerted effort to coordinate common regulatory approaches for approving post-harmonization of measurement procedures on a global basis. It would be desirable to have convergence of international medical device regulations and incorporate a regulatory approval process for recalibration that is more straightforward and as simple as possible while maintaining the essential role to ensure patient safety. Regulatory simplification is reasonable since harmonization is undertaken to reduce medical errors caused by non-harmonized results.

Conclusion

The key stakeholders who will benefit from harmonization are the patients, the clinical laboratory community, diagnostic industry, clinicians, professional societies, information technology providers, consumer advocate groups, regulatory and governmental bodies. These stakeholders expect to receive the RIGHT result so that the RIGHT interpretation with the RIGHT decision as to what to do for the patient is provided. This expectation should be irrespective of the laboratory or the measurement procedure that produces the result and is achievable through harmonization.

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