

Harmonization of clinical laboratory test results

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EDITORIAL

Clinical laboratory testing is now a global activity with laboratories no longer working in isolation but as regional and national networks, and often at international levels. We now have all of the electronic gadgetry via internet technology at our fingertips to rapidly and accurately measure and report on laboratory testing but are our test results harmonized?

WHAT IS HARMONIZATION OF LABORATORY TESTING?

In the context of Laboratory Medicine, harmonization of laboratory testing refers to our ability to achieve the same result (within clinically acceptable limits) and the same interpretation irrespective of the measurement procedure used, the unit or reference interval applied, and when and/or where a measurement is made.

Laboratories may use different analytical methods that may not be harmonized, possibly with different units of reporting. We should not assume that the differing numbers can be directly compared especially if the transfer of results from the laboratory to the report recipient does not highlight differences in units of reporting or in assay methods in use. To

the contrary, the assumption made by patients, clinicians and other healthcare professionals is that clinical laboratory tests performed by different laboratories at different times on the same sample and specimen are comparable in their quality and interpretation.

WHY IS HARMONIZATION NEEDED IN LABORATORY MEDICINE?

When laboratory test results differ the potential exists for misinterpretation of results, wrong treatments and adverse patient outcomes. It is our responsibility as laboratory professionals to identify where gaps exist in laboratory testing and endeavour to harmonize these where possible, thereby minimising misinterpretation of test results.

WHO IS HARMONIZATION OF LABORATORY TESTING INTENDED FOR?

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. The clinical laboratory community includes all disciplines of Laboratory Medicine. As potential consumers of laboratory testing ourselves, we expect to receive not only the Right result on the Right patient at the Right time in the Right form, but also the Right test choice with the Right interpretation with the Right advice as to what to do next with the result. This should be irrespective of the laboratory that produced the result and is achievable through harmonization (1).

AN OVERVIEW OF HARMONIZATION

In this harmonization issue Mario Plebani, who has been a proponent of harmonization in Laboratory Medicine for over 20 years provides an overview of the current and future strategies

needed to achieve harmonization of clinical laboratory information (1, 2). He emphasises the importance of considering the complete harmonization picture to ensure the comparability of laboratory information in all aspects of the total testing process (TTP) including the request, the sample, the analysis and the report.

As discussed by Plebani and others in this issue, a systematic approach to harmonization is needed that requires the following:

1. Awareness by the Laboratory Medicine community that there is a need for harmonized processes not only for the analytical phase but across all steps of the TTP (3);
2. Awareness that harmonization processes are complex; hence a systematic and evidence-based approach that reflects best laboratory practice is needed;
3. An organizational plan or roadmap for the set-up and implementation of each harmonization activity is a pre-requisite and must identify and describe the problem in detail, identify relevant groups including external bodies when forming a working group, determine a funding source, gather technical information and data from various sources, consider the solutions, produce a discussion paper, seek feedback comments from the relevant stakeholders through discussion and revise recommendations, publish endorsed recommendations, promote and implement them, then monitor and survey their introduction (4-6);
4. Communication with main stakeholders, i.e. pathologists, scientists, clinical groups, regulatory bodies, IT developers, and consumer groups is central to the success of any harmonization project with a consensus outcome arrived at through cooperation and discussion (4,7,8).

What is the status of harmonization activities globally?

In Europe there is a recent initiative to promote harmonization activities among the 40 European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) member societies. The Working Group on the Harmonization of the Total Testing Process (WG-H), chaired by Ferruccio Ceriotti, was formed the aims being to survey national European harmonization initiatives, coordinate the dissemination

of promising harmonization initiatives among the EFLM member societies, and specifically to harmonize nomenclature, units and reference intervals where possible at a European level. As described by Ferruccio Ceriotti in this issue (9), based on the results of a survey questionnaire some activities promoting the dissemination of best practice in blood sampling, sample storage and transportation, in collaboration with WG on the Preanalytical Phase (WG-PRE), are already being promoted (10-13). See Table 1.

Table 1 Harmonization of the Total Testing Process (TTP) – global harmonization activities		
TTP phase	Harmonization activity	International and national stakeholders
Pre-analytical	1. Test requesting – demand management and reflex testing – harmonized test profiles	1. ACB Clinical Practice Section – National Minimum Retesting Interval Project (UK)
	2. Guidelines/position papers	2. CDC, CLSI, EFLM WG-CM, EFLM WG-G, EFLM WG-PRE, AACC
	3. Patient preparation and sample collection	3. EFLM WG-PRE, RCPAQAP KIMMS
	4. Sample handling and transport	4. EFLM WG-PRE
	5. Quality indicators	5. IOM, IFCC WG-LEPS, EFLM TF-PG
Analytical	1. Traceability – promoting use of traceable assays	1. BIPM, JCTLM, ILAC, EQAS
	2. Development of commutable secondary reference materials (RM)	2. NIST, IRMM, WHO, IFCC WG-Commutability
	3. Harmonization of measurement values for methods where no RM or reference measurement procedure	3. ICHCLR, IFCC
	4. Harmonization of Mass Spectrometry (MS) methodology	4. APFCB WP-MS Harmonization, AACB MS Harmonization SIG, CDC Hormone Standardization program, COST DSDnet –WG-3: Harmonization of Laboratory Assessment

Post-analytical	1. Standardization of reporting units	1. IFCC C-NPU, IUPAC, IFCC WG-HbA1c, Pathology Harmony (UK), RCPA PITUS (Australia)
	2. Standardization of reporting terminology	2. Pathology Harmony (UK), RCPA PITUS (Australia)
	3. Harmonization of calculated parameters	3. ACB Albumin-adjusted calcium, AACB WP-Calculations
	4. Common reference intervals (RIs) across multiple platforms for traceable analytes	4. IFCC C-RIDL, Nordic countries (NORIP), Pathology Harmony (UK), Turkey, Japan, Canada (CALIPER and CHMS), Australia & New Zealand (Common RIs project)
	5. Platform-specific RIs and decision limits for immunoassay analytes where there is method bias	5. AACB Harmonisation Committee (Australia & New Zealand), CALIPER & CHMS (Canada)
	6. Standardization of report formatting	6. RCPA PITUS (Australia)
	7. Critical laboratory results (CLR) – harmonized processes for management and communication of critical results; list of critical tests	7. EFLM, CLSI, AACB-RCPA WP-CLR (Australia)
	8. Interpretative commenting – harmonization of commenting for EQA	8. IFCC WG-Harmonisation of Interpretative Commenting for EQA
	9. Biological variation – harmonized approach to validation of quality of BV data for use with RCV interpretation (EFLM project)	9. EFLM WG-BV
	10. Surveillance of: – pre-analytical and post-analytical processes – common RIs – calculations – test profiles – interpretative commenting – report formatting	10. IFCC WG-LEPS, RCPAQAP KIMMS, EFLM TFG-Harmonisation of performance criteria for EQA program surveillance, RCPAQAP Liquid Serum Chemistry, calculations, RIs and test profiles program (Australia)
	11. Quality indicators	11. EFLM WG-POST, EFLM WG-PSEP

Post-post analytical	1. Promotion of clinical and laboratory relationships	1. IFCC Taskforces, AACC Strategic Clinical and Laboratory partnerships
	2. Lab Tests Online (LTO) – a global educational tool	2. LTO around the globe
	3. Patient focus	3. ACB, EFLM WG-PFLM

- AACB: Australasian Association of Clinical Biochemists;*
AACC: American Association for Clinical Chemistry and Laboratory Medicine;
ACB: Association for Clinical Biochemistry and Laboratory Medicine (UK);
APFCB: Asia-Pacific Federation for Clinical Biochemistry and Laboratory Medicine;
BIPM: Bureau International des Poids et Mesures;
CALIPER: Canadian Laboratory Initiative on Pediatric Reference Intervals;
CDC: Centers for Disease Control and Prevention;
CHMS: Canadian Health Measures Survey;
CLSI: Clinical and Laboratory Standards Institute;
C-NPU: Committee on Nomenclature: Properties and Units (IFCC and IUPAC);
C-RIDL: Committee on Reference Intervals and Decision Limits (IFCC);
COST-DSDnet: European Cooperation in Science and Technology initiative action BM1303, "A Systematic Elucidation on Differences of Sex Development";
DSDnet; Working group 3; <http://www.dsdnet.eu/wg-3.html>;
EFLM: European Federation of Clinical Chemistry and Laboratory Medicine;
EQAS: External Quality Assurance Scheme;
ICHCLR: International Consortium for Harmonization of Clinical Laboratory Results (AACC);
IFCC: International Federation of Clinical Chemistry and Laboratory Medicine;
ILAC: International Laboratory Accreditation Cooperation;
IOM: Institute of Medicine;
IRMM: Joint Research Centre Institute for Reference Materials and Measurements;
IUPAC: International Union of Pure and Applied Chemistry;
JCTLM: Joint Committee for Traceability in Laboratory Medicine;
KIMMS: Key Incident Monitoring and Management Systems (RCPAQAP);
LTO: Lab Tests Online;
NACB: National Academy of Clinical Biochemistry (AACC);
NIST: National Institute of Standards and Technology;
NORIP: Nordic Reference Interval Project;
PITUS: Pathology Information Terminology and Units Standardisation (RCPA);

RCPA: Royal College of Pathologists of Australasia;

RCPAQAP: Royal College of Pathologists of Australasia Quality Assurance Programs;

RM: reference material;

SIG: Special Interest Group;

TFG: Task and Finish Group (EFLM);

TF-PG: Task Force on Performance goals in Laboratory Medicine (EFLM);

WG-BV: Working Group on Biological Variation (EFLM);

WG-CM: Working Group on Cardiac Markers (EFLM);

WG-G: Working Group on Guidelines (EFLM);

WG-LEPS: Working Group on Laboratory Errors and Patient Safety (IFCC);

WG-PFLM: Working Group on Patient Focused Laboratory Medicine (EFLM);

WG-POST: Working Group on Postanalytical Phase (EFLM);

WG-PRE: Working Group on Preanalytical Phase (EFLM);

WG-PSEP: Working Group on Performance Specifications for the Extra-analytical Phases (EFLM);

WHO: World Health Organization.

In Table 1 many of the EFLM harmonization activities involving pre-analytical, post-analytical and post-post analytical activities are described. As noted by Ceriotti, a PubMed search for the words “harmonization” or “harmonisation” resulted in 972 items, with a sharp increase in the numbers of publications in the last 5 years. It is apparent that in many countries clinical chemistry societies and other professional groups including External Quality Assurance Schemes (EQAS) are working on harmonization projects (Table 1).

A pathway for global harmonization of assays

While the metrological concepts of standardization, calibration traceability to reference materials and measurements, and measurement uncertainty are described in the International Organization for Standardization (ISO) standards ISO 17511 (14) and 18153 (15) and assure the accuracy and equivalence of clinical laboratory results, harmonization is required to achieve uniform results among

different measurement procedures for the same laboratory test where there is no reference measurement procedure available. Gary Myers and Greg Miller describe how an international consortium for harmonization of clinical laboratory results (ICHCLR) has been formed to organize these global harmonization efforts (5, 16).

The role of the ICHCLR infrastructure is to address: 1) prioritizing measurands by medical importance, 2) coordinating the work of different organizations, 3) developing technical processes to achieve harmonization when there is no reference measurement procedure or no reference material and 4) promoting surveillance of the successes of harmonization. A key focus of the ICHCLR is cooperation with other organizations already actively working to improve harmonization of laboratory test results such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

The major advantages of harmonized test results include the use of common decision limits specified in clinical guidelines across all methods and uniform interpretation of results. An example of a current IFCC standardization project involving harmonization is that for thyroid function tests with the Committee on the Standardization of Thyroid Function Tests led by Linda Thienpont using a step-up harmonization approach. Other up-to-date information about measurands in need of harmonization is available online at: <http://www.harmonization.net>, together with a toolkit with information about harmonization protocols.

What is the role of the IVD industry in harmonization?

The In Vitro Diagnostics (IVD) industry is expected to provide traceability information indicating that their routine assays are traceable to reference materials and/or reference methods. However, traceability does not necessarily ensure comparability of patient test results. Rather, both harmonization and metrological traceability of assays are required to provide test results that are clinically equivalent between different manufacturers' analytical systems (5). In their paper on the role of the IVD industry in the harmonization of clinical laboratory test results, Dave Armbruster and James Donnelly describe here the six "pillars" that are needed to achieve traceability and harmonization (17). These are: 1) reference measurement procedures; 2) reference materials; 3) reference measurement laboratories; 4) universal reference intervals; 5) EQA programs using commutable samples with reference method target values to allow accuracy-based grading of manufacturers' assays; and 6) harmonized basic terminology and units.

As both authors state, the new challenge for the IVD industry is to work with the many

professional organizations and each other to attain harmonization, and still retain viable businesses. In their view industry support can be best achieved when harmonization initiatives are coordinated and prioritized. Major factors to be considered are:

1. Competing project priorities for companies;
2. Requirements by regulatory agencies for re-registration and associated additional costs and other manufacturing issues;
3. Need for cooperation between companies through contributing to the prioritization of projects, design of experiment, etc.;
4. Device manufacturer's typically register products with the US FDA using a predicate device to demonstrate product acceptance. In such cases proof of substantial equivalence is essential to demonstrate the assay is safe and effective. Ideally companies want to compare their assay with a traceable reference assay that is listed on the JCTLM website (Joint Committee for Traceability in Laboratory Medicine);
5. Does a harmonization effort add value to patient care? The cost of harmonization which includes physician education, patient safety and investment in product redevelopment needs to be assessed against the clinical benefit of harmonization.

How do we derive harmonized Reference Intervals?

In the post-analytical phase laboratory test results are compared to reference intervals (RIs) or decision limits depending on the analyte measured. However, where the same values are interpreted differently due to differences in RIs or decision limits this may lead to inappropriate over- or under-investigation or treatment of the patient. The use of harmonized or common RI across different platforms and/

or assays aims to give the same interpretation irrespective of the pathology provider or the method, provided the same unit and terminology are used. Harmonization of RIs occurs optimally for those analytes where there is sound calibration and traceability in place and evidence from between-method comparisons shows that bias would not prevent the use of a common RI.

Jill Tate, Gus Koerbin and Khosrow Adeli provide an opinion in this issue on how to derive harmonized reference intervals (18). A pre-determined checklist approach to acquiring the evidence for common RIs provides an objective means of developing and assessing the strength of the evidence. The selection of the RI will depend on various sources of information including local formal RI studies, published studies from the literature, laboratory surveys, manufacturer's product information, relevant guidelines, and mining of databases.

Several countries and regions including the Nordic countries, United Kingdom, Japan, Turkey, and Australasia are using common RIs that have been determined either by direct studies or by a consensus process. In Canada the Canadian Society of Clinical Chemists Taskforce is assessing the feasibility of establishing common reference values using data from the formal reference interval studies of CALIPER (Canadian Laboratory Initiative on Pediatric Reference Intervals) and CHMS (The Canadian Health Measures Survey) as the basis. Development of platform-specific common reference values for each of the major analytical systems may be a more practical approach especially for the majority of analytes that are not standardized against a primary reference method and are not traceable to a primary or secondary reference material.

The authors encourage laboratories to consider adopting reference intervals consistent with those

used by other laboratories in your region where it is possible and appropriate for your local population. Validation of reference intervals by local laboratories is central to the adoption of common RIs nationally as is validation of flagging rates to ensure the expected number of results outside the RI is acceptable.

How do we manage critical risk results?

Que Lam, Eva Ajzner, Craig Campbell and Andrew Young write in this issue about the current situation and existing practices for the management of critical risk results (19). They describe the need for more evidence from outcomes studies of critical risk results management to support laboratory practices and the need for harmonized terminology. New harmonized terminology has recently been proposed, e.g. "high-risk results", results requiring immediate medical attention and action, and "significant-risk results", results which signify a risk to patient well-being and require follow-up action within a clinically justified time limit (20). The authors discuss the recently released Clinical and Laboratory Standards Institute (CLSI) guideline CLSI GP47-Ed1 for the management of laboratory test results that indicate risk for patient safety (21), as well as presenting the Australasian recommendations. In order to promote best laboratory practice, Lam et al. recommend that laboratories consider risk assessment when compiling alert tables and involve laboratory users when setting up protocols. They state: "Harmonization in this area cannot simply be a matter of shared definitions and procedures, but must involve the determination and implementation of best practice. The challenge is to define best practice and to obtain the evidence required to support this".

CONCLUSIONS

It is obvious that harmonization does not happen overnight but is a long term consensus process that ideally is based on hard evidence that has been systematically compiled and has involved close interaction between the laboratory and the clinician to ensure successful implementation. It must be a shared responsibility of all stakeholders interested in patient care. Harmonization aims to add value to Laboratory Medicine measurements and their interpretation. Harmonized test results will ensure that clinical guidelines that call for the use of laboratory tests can be universally implemented. Harmonization still allows for innovation through discussion and the input of new ideas. It should extend beyond clinical chemistry across to all other pathology and Laboratory Medicine disciplines as the problems are not unique to chemistry.

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