Harmonization in Laboratory Medicine: A Paradigm Shift Beyond Clinical Chemistry

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Abstract: The goal of harmonizing laboratory information is to contribute to quality in patient care, ultimately improving upon patient outcomes and safety. The main focus of harmonization and standardization initiatives has been on analytical processes within the laboratory walls, clinical chemistry tests in particular. However, two major evidences obtained in recent years show that harmonization should be promoted not only in the analytical phase but also in all steps of the testing process, encompassing the entire field of laboratory medicine, including innovative areas (e.g. “omics”) rather than just conventional clinical chemistry tests. A large body of evidence demonstrates the vulnerability of the extra-analytical phases of the testing cycle. Because only “good biological samples” can assure good analytical quality, a closer interconnection between the different phases of the cycle is needed. In order to provide reliable and accurate laboratory information, harmonization activities should cover all steps of the cycle from the “pre-preanalytical” phase (right choice of test at right time for right patient) through the analytical steps (right results with right report) to the “post-post-analytical” steps (right and timely acknowledgment of laboratory information, right interpretation and utilization with any necessary advice as to what to do next with the information provided). In addition, modern clinical laboratories are performing a broad menu of hundreds of tests, covering both traditional and innovative subspecialties of the discipline. In addition, according to a centered viewpoint, harmonization initiatives should not be addressed exclusively to clinical chemistry tests but should also include all areas of laboratory medicine.

Keywords: extra-analytical phases; harmonization; laboratory information; patient outcomes; quality; standardization.

Introduction

Harmonization is fundamental to quality in laboratory medicine, its end point being to improve patient outcomes by providing accurate and actionable information [1]. Although the importance of standardization and harmonization of laboratory results has been evident for more than four decades, only recently adequate attention has been paid to the increasing need to address this issue. Clinical laboratories can no longer work in isolation, and greater efforts are being made to promote standardization and harmonization in view of the challenges incurred by globalization. Harmonization in laboratory medicine is, in fact, crucial to ensuring that data from different laboratories are comparable and that improvement is made to the accuracy and consistency of results and their interpretation, thus facilitating clinical decision making and assuring valuable patient care [2–4]. Although patients, clinicians and other healthcare operators tend to assume that clinical laboratory tests performed by different laboratories at different times on the same sample and specimen can be compared and results can be reliably and consistently interpreted, this is not necessarily the case. Not only are many laboratory test results highly variable, poorly standardized and harmonized, but also harmonization efforts are often limited to the analytical phase. In addition, although the focus of initial standardization and harmonization activities has been on improving clinical chemistry assays, a broader approach involving the entire field of laboratory medicine is now urgently needed. As shown in Figure 1, in the last few years, the main developments in the field branch in two directions. Harmonization should, in fact, (a) be promoted not onlyanalytical phase but in all steps of the testing process and
(b)
take
into
consideration not only conventional clinical chemistry tests but also the entire field of laboratory medicine, including innovative areas (e.g. “omics”).

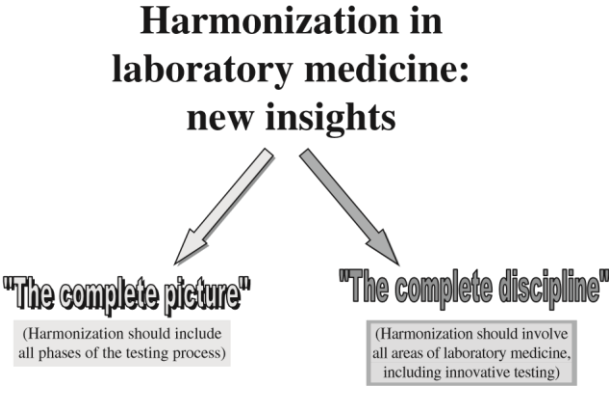

Figure 1: Harmonization in laboratory medicine as a complete picture for all disciplines.

Harmonization in laboratory medicine as a complete picture

The initial focus was on standardizing and harmonizing analytical processes and methods, but it has at last been acknowledged that harmonization must reach further, to include all steps of the total testing process (TTP) or, rather, the brain-to-brain loop [5, 6]. As recently stated by Miller [7], the history of the awareness of the importance of standardization can be traced back to the seminal paper by Belk and Sunderman [8] who, in 1947, demonstrated wide discrepancies between results of 59 US hospital laboratories. The findings made in their survey paved the way for the development of external quality assurance (EQA)/proficiency testing (PT) programs and prompted efforts to establish the hierarchy of certified reference materials (CRMs) and reference measurement procedures (RPMs) that could be accepted as high-order references for the standardization of measurand results [9, 10]. However, increasing consensus has been achieved on the need to focus on a global picture of harmonization, mainly in view of (a) the nature of errors in laboratory medicine [11]; (b) the evidence of large variations in terminology, units and reference intervals [12]; and (c) the risks for patient safety related to the above issues [1]. A body of evidence collected in recent years demonstrates the vulnerability of the extra-analytical phases, and the need to promote quality and harmonization in each and every step of the testing cycle [1–6]. The importance is now well recognized of the right terminology, units, report formats, reference intervals and decision limits, as well as appropriate tests and test profiles, requests and criteria for interpretation. Harmonization activities should cover all steps of the cycle from the "pre-pre-analytical" phase (right test choice at right time on right patient) through the analytical steps (right results with right report) to the "post-post-analytical" steps (right and timely acknowledgment of laboratory information, right interpretation and utilization with any necessary right advice as to "what to do next with the information") [1,3]. The right environment for harmonization programs is the understanding of the interdependence and interconnection between the different phases of the cycle: preanalytical quality is needed for accurate results, and essential information should be introduced in the postanalytical phase to facilitate interpretation and clinical decision making [13]. Only "good samples make good assays" and only "good reports make good laboratory information". This, in turn, calls for a global view of harmonization in laboratory medicine. In response to the new paradigm of quality and patient safety in laboratory medicine by the Clinical and Laboratory Standards Institute [14], I modified the definition of harmonization to include not only analytical results but also the ultimate laboratory information. According to this re-definition, harmonization is "the process of recognizing, understanding, and explaining differences in all phases of the TTP, while taking steps to achieve uniformity of the laboratory information, or at minimum, a means of identifying and spreading common policies and procedures, such as different groups can use the data obtained from different laboratories interchangeably" [5].

Harmonization in pre-pre- and preanalytical phases

To ensure the answer to a clinical question is reliable, and to obtain accurate laboratory results, "five rights" should be observed in the pre-pre-analytical phase: the right patient, the right time, the right test, the right sample collection/handling and the right sample transportation. Elsewhere, I reported on the evidence available in the literature on the problems of patient and sample identification, the issues of timing and re-testing intervals, the need for an appropriate management of test demand as well as variations in procedures for sample collection/handling and, finally, the overlooked question of adequate sample transportation [13]. Harmonization initiatives are needed to overcome the current state of the art and to promote better clinical practices [15]. Several programs are in progress for harmonizing the initial steps of the cycle, starting with the issue of demand management. The acceptance of the definition of "inappropriate test demand", apparently "a request that is made outside some form of agreed guidance" [16, 17], is a seminal achievement. The type of guidance given should range from international guidelines, allowing a higher degree of harmonization, to locally agreed behaviors between laboratory professionals, clinicians and other care operators. An interesting proposal has been to use evidence-based re-testing intervals, defined as the "minimum time before a test should be repeated based on the properties of the measurand and the clinical context in which it is used" [18]. As underlined in several surveys, patient/sample identification errors, which are still frequent, can have dramatic consequences [19]. The Joint Commission for Accreditation of Healthcare Organizations and the College of American Pathologists have identified accurate patient identification as a cardinal patient safety goal, and the Working Group for the Preanalytical Phase (WG-PRE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has issued recommendations for harmonizing patient identification and

tube labeling [20]. The use of harmonized standard operating procedures (SOP), assuring multiple identifiers, as well as automated systems for patient/sample identification and information technology facilities, should obviate the risks of patient misidentification and "wrong blood in tube", true nightmares for any clinical laboratory [21]. Major advancements have been achieved in standardizing patient preparation, sample collection and handling procedures, thanks also to the efforts of working groups, in particular, the WG-PRE of the EFLM [22–27]. Finally, further work to optimize and standardize sample transportation procedures [28, 29], and to harmonize criteria for evaluating the quality of biological samples and accepting/rejecting them has been largely promoted and reported, also by means of automated workstations and serum indexes [30, 31]. The importance of pre-pre-analytical (and preanalytical) variables in affecting the integrity of biospecimens has recently been stressed as a major concern in the pipeline of biomarker discovery, development and translational steps [32, 33]. The harmonization of preanalytical processes, is therefore a fundamental pre-requisite for reducing and controlling preanalytical biological and analytical variability and assuring quality in all fields of laboratory medicine, including "omics" and innovative tests [34].

Harmonization in post- and post-post-analytical phases

The evidence of significant variations in the units used for reporting laboratory results, which can lead to misinterpretation of laboratory data and endanger patient safety, has prompted initiatives aimed at the adoption of a single standardized set of units [5, 12]. Major efforts have been made to promote the harmonization of reference intervals, with should be traceable to reference measurement procedures, and the use of common intervals in huge geographical areas such as Australasia, Asia and Canada [15, 35]. Several initiatives have been successfully promoted to harmonize the management and notification of critical results [36, 37], as well as the practice of providing interpretative comments [38]. As a part of the model of quality indicators, harmonized indicators of timeliness have been proposed to improve this fundamental category of quality of laboratory testing [39, 40]. Other quality indicators have been designed for recording and monitoring data transcription errors, erroneous and/or delayed reports [41].

Harmonization in laboratory medicine: not only clinical chemistry

In an editorial published in the journal some years ago, we stated that we "were clinical chemists once and young. Now we are getting older and specialists in laboratory medicine", thus recognizing the terrific rate of recent advances and changes in laboratory testing, which has attained unprecedented levels [42]. In the last few decades, clinical needs and technological advancements have changed the landscape of laboratory medicine [43]. The consolidation of different specialties in clinical laboratories answers physicians' need to receive a unique laboratory report with results from clinical chemistry, hema tology, coagulation, molecular diagnostics and microbiological-virological tests. This, in turn, has been facilitated by technological improvements, automation and informatics. Now, a modern clinical laboratory is performing a broad menu of hundreds of tests, covering both traditional and innovative subspecialties of the discipline. A widely debated issue in the harmonization of measurements hinges on the evidence that standardization has been already achieved and seems to be promoted almost exclusively in the field of clinical chemistry and for a limited number of measurands. Efforts in standardizing laboratory tests began in the field of clinical chemistry, and specific requirements for calibration traceability to high order references (CRMs and RPMs) have been applied some clinical chemistry tests. However, in recent decades, awareness has been raised that the standardization principles, namely, those described in ISO 17511, have three major limitations. First, no pure-substance CRMs and RPMs are yet available, and they are unlikely to be forthcoming because of technical limitations for hundreds of important but complex measurands [7]. Moreover, not only is the number of measurands included in the list continuously updated, particularly for the development of new biomarkers, innovative techniques such as "omics", but the list also includes measurands of significant clinical value. Second, many matrix-based CRMs have not been validated as commutable with patient samples, and in many cases it has been clearly demonstrated that they are not commutable and therefore not suitable for use in an ISO 17511 compliant calibration traceability hierarchy [44]. A body of evidence demonstrates that tracing calibration to a non-commutable CRM causes differences in results for clinical samples among different measurement procedures, which, in turn, may translate in errors in diagnostic and therapeutic decisions. Third, the uncertainty goals based on medical relevance of the measurand cannot be always achieved with RPMs [45, 46]. In view of the above considerations, and the pressing need to

promote greater comparability in laboratory information, efforts are being made to achieve equivalent results even when it is not technically feasible to develop an RMP in a reasonable timeframe and the preparation of commutable matrix-based CRMs is challenging. Through harmonization, equivalent results can be achieved within medically meaningful limits, also when standardization is a "mission impossible", because it is applicable to laboratory fields other than clinical chemistry. In coagulation, one of the most successful and effective examples of harmonization is prothrombin PT expression, for which there is an international normalized ratio (INR). PT results in INR are corrected mathematically by raising the PT ratio to a power equal to the international sensitivity index (ISI). Substantial improvement in interlaboratory harmonization of INRreported values has been achieved by standardizing reagents/equipment, and by using a novel approach for the verification and harmonization of ISI and MNPT (mean normal PT) values [47]. The reduction of interlaboratory variation in INR reporting translates in the true clinical goal, which is to reduce INR value variability in patients receiving oral vitamin K antagonist anticoagulants, who might be tested at different sites and times, according to a truly patient-centered approach. Similar approaches have been used for harmonizing the results of other coagulation tests, including D-dimer [48]. In the field of autoimmunity, harmonization initiatives have been promoted as standardization still represents a challenging goal. In fact, autoantibodies are complex and structurally heterogeneous molecules due to posttranslational modification and are present in biological fluids in different types due to oligoclonality. This, in turn, precludes the definition of both pure substance CRMs and RPMs. However, the several initiatives underway in this diagnostic area include all the phases of the total testing process: in the preanalytical phase, appropriateness of test requests, harmonization of autoantibody terminology and adoption of uniform nomenclature for laboratory tests; in the analytical phase, harmonization of measurements and sharing of test profiles and diagnostic algorithms; and in the postanalytical phase, harmonization of data reporting and criteria for interpreting immunoserological results, especially harmonization of units, reference intervals, decision limits and definition and notification of critical values [49]. The diagnosis of celiac disease is a paradigmatic example of the importance of harmonization in this field. After the discovery of the clinical value of immunoglobulin A (IgA) anti-tissue transglutaminase (tTG) antibody assay, which is the test of choice for detecting the disease, it was suggested that a histological assessment might be omitted in symptomatic children who have anti-tTG IgA levels 10-fold the upper reference limit (URL), as shown in data from some primary studies [50, 51]. However, this is an arbitrary cutoff value, and a wide disparity of results and poor comparability, both between methods and between laboratories, has been reported [52]. Efforts to standardize and harmonize anti-tTG assays are therefore needed, particularly as the clinical goal, namely, the avoidance of an invasive examination, represents a major advantage for patients' safety and healthcare costs. For other immunoassays of hormones and proteins with different circulating molecular forms (e.g. thyroid stimulating hormone, insulin, parathyroid hormone [PTH] and troponin), harmonization protocols using panels of authentic individual serum samples and commutable control materials used in EQA schemes have allowed between methods agreement to be achieved. In addition to the utilization of commutable sera, this approach is based on the development of robust statistical approaches for value assignment of the panel of individual samples and or EQA materials [53–57]. Serological testing and virological testing are other areas of interest in standardization and harmonization initiatives. For example, the standardization of antibody and DNA measurements and harmonization of laboratory procedures are crucial to the success of cancer prevention strategies through screening methods as well as for development and implementation of vaccination against human papilloma virus (HPV). The WHO supported the preparation and initial analysis of a panel of candidate serological and DNA reference reagents aimed at facilitating interlaboratory comparisons and the detection of HPV worldwide. HPV-DNA standards will contribute to the field of HPV prevention, diagnosis and treatment. If made available throughout the world, they will allow for the reference calibration of HPV-DNA tests, thereby enabling manufacturers to further validate and develop HPV detection reagents and kits, which will enable reliable disease and vaccination monitoring worldwide [58]. In tuberculosis (TB), human immunodeficiency virus (HIV) and malaria, molecular analytical tools are yielding the initial hints regarding the mechanisms underlying protection against, or susceptibility to, clinical disease. It is therefore high time that standardization and harmonization of sample collection, storage and molecular analysis are used to ensure highest quality data from these precious samples. Efforts have been made to achieve the standardization of immunological and global platforms that will allow their effective use in a clinical setting, their use for biomarker discovery and validation and their use in generating data sets that can be compared across different platforms and across different preclinical settings and/or different clinical trials [59]. Antimicrobial susceptibility testing with phenotypic methods requires breakpoints, namely, a minimum inhibitory concentration (MIC) categorizing microorganisms into susceptible, intermediately susceptible and resistant to the relevant antimicrobial agent [60]. Historically, there have been

multiple guidelines for antimicrobial susceptibility testing, often with different MIC breakpoints dividing organisms into categories of susceptibility. Consequently, the same organism causing similar infections in different countries might be reported as susceptible or resistant, depending on the guidelines followed. The harmonization process calls for a comprehensive review of breakpoints, and includes the application of recent techniques, such as pharmacodynamic analysis, and current data, where available, on susceptibility distributions, resistance mechanisms and clinical outcome related to *in vitro* tests [61]. Molecular methods, used in a variety of ways, detect, quantify and sequence nucleic acid throughout many areas of laboratory medicine. These tests, in fact, are used to diagnose cancer, provide prognostic assessments, aid in treatment selection and monitor the effectiveness of therapy, also through the detection of minimal residual disease for a single patient. However, particularly in the field of nucleic acid testing for infectious diseases and clinical genetics, the proliferation of assay methods, the number of targets for molecular diagnostics and the absence of standard reference materials contribute to variability in test results among laboratories [62]. In particular, there is a lack of established and globally accepted reference materials to serve as primary standard for comparing performance characteristics and results performed in different laboratories and/or using different methods. In fact, it is increasingly important to harmonize quantitative assays assays, such as viral load measurements, and/or to establish the analytic sensitivity of qualitative assays. However, the availability of reference materials alone does not assure harmonization: reliable approaches for their implementation in test development and validation should be uniform according to guidelines, consensus documents, documentary standards and reference method publications [62]. In the last few years, the fast emergence and the great success of next-generation sequencing (NGS), allowing the fast generation of thousands to millions of base pairs of DNA sequence of an individual, herald a new era in molecular diagnostics. However, the new technologies bring challenges, both at the technical level and in terms of data management, as well as for the interpretation of results. Some guidelines issued appear valuable tools for the harmonization and quality assurance of NGS diagnostics, serving as yet another example of the need to consider the harmonization process a global picture, starting with the need to validate tests before introducing them into clinical practice, to include in the analysis only genes with a known relation between the aberrant genotype and the pathology and to report NGS results in clear and consistent manner [63]. In diagnostic areas based on the microscopic evaluation of tissue and cell morphology, interpretation is hampered by subjectivity, and its quality depends on the competence of professionals [64]. Repeated efforts should be made to effectively train laboratorians and pathologists, showing that interobserver variability can be decreased, but that reproducibility remains a challenge [65]. In turn, harmonization efforts should be reiterated, through both better accreditation and continuing education programs [66] and reference image databases developed with the input of experts in the field [67].

Conclusions

The landscape of laboratory medicine and clinical laboratories has dramatically changed in recent decades. The menu of laboratory tests has increased not only in terms of absolute numbers, but also, even more importantly, in terms of complexity and diagnostic areas. Now, most clinical laboratories perform not only traditional clinical chemistry tests, but also undertake coagulation, hematological, immunological, molecular and microbiological-virological examinations. It is widely recognized that effective patient care, patient safety and clinical research call for comparability of laboratory information independent of time, place and measurement procedure. Comparability is achieved by establishing metrological traceability, which assures that measurement procedures measure the same quantity and that the calibration of measurement procedure is traceable to a common reference system consisting of reference methods and materials [68]. Standardization ensures traceability to the International System of Units (SI), but it should be achieved only in the presence of both the following conditions: (a) the measurand is clearly defined and (b) the agreement of test results is attained by establishing traceability to a higher-order reference measurement procedure or pure substance reference material that can be defined by using the SI. Unfortunately, today the number of measurands that can be standardized is limited in relation to the hundreds of tests performed in laboratory medicine and mainly includes “clinical chemistry” tests. The other way of achieving result (and information) comparability is harmonization, which ensures traceability to a reference system agreed on by convention. For a multitude of measurands, SI and therefore standardization are not yet applicable, particularly when the components in the measurand are heterogeneous: complex molecules such as proteins, peptides, hormones, autoantibodies and many biomarkers create difficulties because they are often structurally heterogeneous due to posttranslational modifications (e.g. glycosylation, sialylation, sulfation, complexes and catabolic fragments). This complexity, in turn, can hinder our current understanding of whether one, several or all forms of a measurand are of clinical interest. Of the many

examples, human chorionic gonadotropin (HCG) [5], troponin [56] and PTH [69] represent paradigmatic and commonly requested laboratory measurands. In the last few years, the increased awareness of the lack of clearly defined measurands, reference methods and/or reference materials for many measurands of absolute clinical value has prompted further efforts to achieve harmonization, particularly as the final goal is to assure the comparability not only of analytical results but also of the ultimate laboratory information and not only in clinical chemistry but also in all fields of laboratory medicine. The paradox of comparability in laboratory medicine is that standardization of assays does not always lead to harmonization of information, and harmonization of test results does not always call for standardized reference methods [70]. Many initiatives are in progress, promoted by scientific and professional organizations, including the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), EFLM, the American Association of Clinical Chemistry (AACC) and the International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR). Of particular interest are the initiatives of the ICHCLR, designed to coordinate harmonization activities at an international level [71], but only a closer cooperation between these organizations, laboratory professionals, *in vitro* diagnostics (IVD) manufacturers, accreditation and regulatory bodies will allow us to achieve greater interchangeability and comparability of laboratory information. This – first and foremost – is a duty and an ethical mandate for laboratory professionals and their scientific organizations. These initiatives should have main drivers in common: (a) harmonization should be promoted in the total testing cycle ("global picture"), and (b) harmonization and standardization initiatives should involve not only the traditional area of clinical chemistry, but all fields of laboratory medicine.

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