

Editorial

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Standardization and harmonization in laboratory medicine: not only for clinical chemistry measurands

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Some articles published in this issue of the *Journal* offer the opportunity to discuss further the important subject of standardization and harmonization in clinical laboratories. Both terms standardization and harmonization are often used interchangeably, because their final endpoint is basically identical, i.e., providing laboratory results to stakeholders (i.e., clinicians and patients) that could be compared across different laboratories, over time [1]. Although the importance of standardizing and/or harmonizing laboratory test results has been clear for four decades or more, adequate focus has only recently been given to the increasing need of pursuing these goals. Clinical laboratories can no longer work in isolation, and a wide effort is being proffered to foster standardization and harmonization in view of the challenges imposed by globalization, the historical need to improve patient safety and effectiveness of laboratory services, as well as for avoiding to reiterate unpractical recommendations that patients should always refer to the same laboratory for receiving equivalent results [2]. Nonetheless, these two terms reflect in their essence to different concepts. Standardization should be used when test results are uniform across routine measurement procedures and traceable to a recognized standard reference material defined by the International System of Units (SI) through a high-order primary reference material and/or a reference measurement procedure. Harmonization, is instead aimed to make test results more comparable irrespective of the analytical procedure, mainly because neither a reference measurement procedure (RPM) or a primary reference material (RM) are available [3]. Notably, this

latter case involves the vast majority of the analytes measured in clinical laboratories, most of which represent an essential source of information for both clinical decision-making and patient care. It is hence increasingly clear that efforts should not only be made for developing further standardization initiatives, but also to assure comparability of laboratory results and information for those measurands for which no RMP neither RM were, are and will be available in the near future. In addition, standardization and harmonization initiatives should be promoted not only in the analytical phase, but throughout all other steps of the total testing process (TTP), thus improving quality and safety of laboratory information [4].

The first article published by Braga and Colleagues deals with definition and application of performance specifications for measurement uncertainty of 23 common laboratory tests [5]. Laboratories should, in fact, estimate and validate measurement uncertainty (MU) of the tests performed using analytical performance specifications (APS). The estimation of MU is a vital information in laboratory medicine, and is also an essential aspect for the accreditation of medical laboratories according to the ISO 15189:2012 standard [6]. The ISO Technical Specification 20914:2019 provides a guidance on how MU shall be estimated, using the so-called “top-down” approach which combines all sources of MU throughout the selected traceability chain [7]. In their work, the authors allocated 23 commonly ordered laboratory tests (i.e., measurands) to the models endorsed by the 2014 EFLM Strategic Conference, with the goal of precisely deriving APS for MU [8]: a) the outcome-based model (Model 1); b) the biological variation-based model (Model 2); and c) The Model 1 and 2 (a hybrid mode). The performance of commercial measuring systems used in their laboratory were then verified in order to establish whether the criteria could be fulfilled. Manufacturers were asked to provide metrological traceability information for identifying higher-order references (materials and/or procedures) used for assigning traceable values to their calibrators and obtaining a description of the applied calibration hierarchy. Therefore,

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this article could be seen as a very interesting and useful application of APS to define reliable MU in the context of metrological traceability for well-defined measurands. The second article authored by Dimech and colleagues address the problem of comparability in serology testing [9]. According to the authors, significant differences exist between the measurement of clinical chemistry analytes and serology of infectious diseases. In clinical chemistry, the measurand is typically an “inert chemical” (e.g., glucose, creatinine, sodium) with definite biochemical structure, molecular weight and almost invariable structure and composition over time. However, “when testing for antibodies, the test system is determining the binding of antibodies to a given antigen”. It is now universally recognized that patient samples with “low levels of antibodies but high affinity and avidity to a specific antigen, could have higher level of reactivity compared with a sample with high concentration of low-avidity antibodies” [9]. Therefore, the humoral response may considerably vary over time. Test systems for antibodies must account for this array of variables, highlighting the difference between infectious disease serology and testing for inert and highly stable analytes such as glucose or potassium, since measurands assayed with infectious disease serology are heterogenous and may also considerably vary using different test systems. In a previously published article, one of the authors of this paper concluded that “principles of standardization and control applied to clinical chemistry analytes cannot be used in infectious disease serology” [10]. The ongoing coronavirus disease 2019 (COVID-19) pandemic has magnified the differences in serology testing which are responsible for poor test results comparability, encompassing a large number of commercial available SARS-CoV-2 serological immunoassays which differ in terms of (a) antibody class detected (binding antibodies may include single immunoglobulins, their variable combinations, along with assays measuring “total” anti-SARS-Cov-2 antibodies); (b) target antigens (whole disrupted virus, aminoacid sequences of recombinant spike protein or its receptor binding domain, as well as of the nucleocapsid protein); (c) the continuously evolving structure of viral antigens, which may originate from one or more SARS-CoV-2 variants and/or sublineages; and (d) analytical procedure (e.g., later flow immunoassays, colorimetric microtiter enzyme immunoassays, fluorimetric or chemiluminescent immunoassays, plaque neutralization assays, and so forth).

Several efforts have been done made for improving comparability of anti-SARS-CoV-2 serological immunoassays, including development of the first, and more recently,

the second WHO International Standard for anti-SARS-CoV-2 immunoglobulin and Reference Panel for antibodies to SARS-CoV-2 variants of concern (<https://www.who.int/publications/m/item/who-bs-2022.2427>). These two standards have been basically developed for being use with SARS-CoV-2 neutralization assays which (especially the plaque reduction neutralization test; PRNT), are still considered the gold standard. This types of “functional” tests must always be used for evaluating the agreement with antibody binding assays, in that the closer is the agreement, the more clinically valuable is the information delivered by each specific immunoassay. Serology testing is not the unique area of laboratory medicine that is experiencing serious challenges in adopting metrological traceability criteria: functionally specific assays are used for measuring some hormones and other measurands which may be characterized by heterogenous biochemical structure, and/or are composed by mixtures of different substances and isoforms (e.g., human chorionic gonadotropin, growth hormone, adiponectin, and even troponin I). Standardization and harmonization initiatives, therefore, must be carried out not only considering virtually “inert” clinical chemistry analytes, but also other measurands and areas of laboratory medicine, thus targeting analytical aspects together with all the other essential steps of the TTP that lead to the final generation of an “analytically reliable and clinically usable” test result [11]. According to our personal perspective, in fact, the final goal is not the “level of standardization” that could be achieved, but the possibility to make laboratory test results more “comparable” (that is, harmonization). Same concerns exist also for quality control systems, which may probably need different and more comprehensive approaches [12]. The heterogeneity of laboratory medicine, in terms of both measurands and analytical sectors, would require “personalized” approaches. The International Federations of Clinical Chemistry and Laboratory Medicine (namely IFCC and EFLM), as well as other scientific bodies, shall thus acknowledge the evidence that “we are no more clinical chemistry, but laboratory medicine professionals”. The *Journal* is and will remain an open platform for offering the opportunity to discuss these challenging subjects, tolerating different and even opposite, if not heretical, opinions.

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