Mini Review

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Commutability of reference and control materials: an essential factor for assuring the quality of measurements in Laboratory Medicine

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Abstract: Traceability to a common reference ensures equivalence of results obtained by different assays. Traceability is achieved by an unbroken sequence of calibrations, using reference materials (RMs) that must be commutable. Using non-commutable RMs for calibration will introduce a bias in the calibrated method producing incorrect results for clinical samples (CS). Commutability was defined in 1973 as "the ability of an enzyme material to show inter-assay activity changes comparable to those of the same enzyme in human serum" and later extended as a characteristic of all RMs. However, the concept is still poorly understood and appreciated. Commutability assessment has been covered in CLSI guidelines and requires: (a) selection of 20 CS spanning the relevant concentration range; (b) analysis of both RM and CS with the pair of procedures; (c) data elaboration using regression analysis and calculation if RM fall within the 95% prediction interval defined by CS. This approach has been criticized and to improve it The International Federation of Clinical Chemistry and Laboratory Medicine established a working group that recently finalized recommendations. Commutability is also a requirement for the applicability of external quality assessment (EQA) results in the evaluation of the performance of participating laboratories in terms of standardization of their measurements. Unfortunately, EQA materials are usually not validated for commutability.

Keywords: commutability; standardization; uncertainty.

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Introduction

Traceability to a common reference (ideally up to the International System of Units [SI]) ensures a high quality and long-term equivalence of measurement results obtained by different measuring systems. The traceability of measurement results is achieved by an unbroken sequence of calibrations, each contributing to the uncertainty of results of clinical samples (CS) [1]. Reference materials (RMs) have been described as one of the six pillars of the "temple of laboratory standardization", together with other classical key elements of the reference measurement system (i.e. higher order reference procedures and reference laboratories performing them), the definition of traceable reference intervals and decision limits, the implementation of analytical quality control programs that meet metrological criteria, and the establishment of targets for uncertainty and error of measurement that are fit for purpose [2]. To ensure the sequence continuity, RMs intended for direct value assignment to manufacturer's calibrators must however be extensively investigated for commutability. Quoting Ian Young [3], "it is no longer be enough to ask whether a method is traceable; traceability must be to a [reference] material demonstrated to be commutable to have true value".

The commutability concept

Fasce et al. [4] first defined commutability in 1973 as "the ability of an enzyme material to show inter-assay activity changes comparable to those of the same enzyme in human serum". This definition was later extended as a characteristic of all RMs [5]. Despite that the first description of commutability happened more than 45 years ago, the concept is still poorly understood and appreciated. Sometimes, the term commutability is mistakenly applied to analytical methods or reagents instead of considering it a property of an RM. Some people still confuse

"commutability" with "comparability" of test results. The Tietz *Textbook of Clinical Chemistry* in its first three editions did not mention commutability at all; the book started to address the definition of commutability in the 4th (2006) edition and the concept became integral part of the "Quality control" chapter only in the last 6th (2018) edition. Accordingly, although the term has appeared in the title of scientific publications since the early 1980s, the numbers of publications remained in single figures each year until the current decade (Figure 1).

The International Vocabulary of Metrology (VIM) defines the commutability of an RM as the property demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in the material (employed as a calibrator), obtained according to two given measurement procedures, and the relation obtained among the measurement results for CS [6]. In more everyday language, the commutability of an RM (calibrator) is the ability of a material to show inter-assay properties comparable to those of human samples. As mentioned before, only commutable RMs can be used for direct value assignment to manufacturers' calibrators, ensuring the continuity of the metrological traceability chain, and for a trueness check of laboratory results. The use of non-commutable RMs for calibration will introduce a bias in the calibrated procedure, therefore producing incorrect results for CS [7]. It is important to distinguish the non-commutability of an RM from the non-selectivity of a procedure, leading to problems with CS also. In other words, the commutability assessment should not be intended to evaluate the selectivity of measurement procedures for the measurand; so that, the qualification of measurement procedures about their selectivity should be done independently and in advance.

Table 1 shows the main factors involved in non-commutability of RMs, derived from the sample matrix and from the analyte itself [8]. In general, to produce RMs of acceptable quality in terms of commutability (and traceability), some requirements should be fulfilled [9]. To avoid the matrix effects different from CS, RMs should be prepared in a human matrix. Materials produced in bovine or aqueous matrices have a very high probability to be non-commutable.

Table 1: Factors causing non-commutability of reference (calibrator) materials (modified from Ref. [8]).

Matrix	Analyte itself
Turbidity, pH	Enzymes/proteins of nonhuman origin
Abnormal viscosity	Isoenzyme pattern
Presence of endogenous interfering substances	Partially denaturated proteins
Use of procedures that result in physical changes, e.g. lyophilization	
Addition of preservatives, antimicrobial agents, stabilizers or other additives	

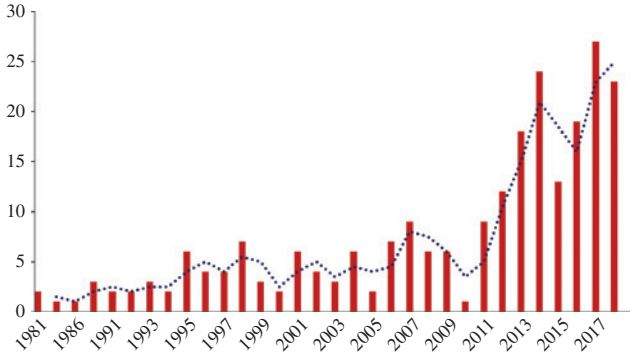

Figure 1: Number of hits retrieved from PubMed using the key word "Commutability" (www.ncbi.nlm.nih.gov/pubmed, Accessed January 2019).

Commutability of reference materials

Historically, for many RMs, commutability with laboratory measurement procedures was not recognized as an issue and was typically not assessed. Consequently, there are a number of RMs, particularly the oldest ones, that are non-commutable with CS for laboratory procedures. As an example, Infusino et al. [10] tested the commutability of two RMs listed in the Joint Committee for Traceability in Laboratory Medicine (JCTLM) database for two commercial lithium assays using different analytical principles (potentiometry vs. colorimetry). Results demonstrated that the National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 956c was non-commutable for the evaluated methods, whereas the BCR-304, provided by the Institute for Reference Material and Measurements (IRMM), showed a better behavior concerning commutability and should be preferred to align lithium assays to SI.

The same RM may be commutable for some measurands and non-commutable for others. To ensure continuity of the standardization of the serum proteins measurements, in 2008 the IRMM released the ERM-DA470k/The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), replacing the no longer available ERM-DA470 [11]. Both materials, first ERM-DA470 and then

ERM-DA470k/IFCC, have been adopted by in vitro diagnostics (IVD) manufacturers across the world to value-assign their commercial calibrators and allow standardization of serum protein measurements. Commutability of the ERM-DA470k/IFCC for serum albumin and, more recently, for immunoglobulin A (IgA) was checked and confirmed [12, 13]. However, in two independent studies the same material was found to be non-commutable for ceruloplasmin [14, 15]. Consequently, commercial methods tracing their calibration to the ERM-DA470k/IFCC produced discrepant results for ceruloplasmin in CS.

The results of a study performed by the IFCC Working Group on Standardization of Thyroid Function Tests elegantly showed as a non-commutable RM used as calibrator breaks the traceability chain [16]. The study evaluated 16 commercial assays measuring thyroid-stimulating hormone (TSH), all claiming to be traceable to the WHO International Standard 94/674, showing a 35% variability in results from 40 CS that could be attributed to the non-commutability of this RM. The use of a non-commutable RM for calibration traceability caused an incorrect value assignment to commercial calibrators and, consequently, wrong results for CS, with the risk of erroneous medical decisions. The top of the traceability chain is vital for transferring trueness, so that criteria to select RMs that should be on the top as common calibrator must be carefully fulfilled. Among those, commutability of RM with CS for all measurement procedures with which it will be used represents the priority.

Responsibility of commutability evaluation

Who should do commutability evaluation of RMs has also been long debated. In 2006, Miller et al. [17] finally suggested that providers of RMs must change practice by including the commutability validation for RMs intended for calibration of commercial measuring systems and provide commutability information in the certificate of analysis. More recently, the same authors became stronger in recommending that all providers should take responsibility to ensure that their RMs are commutable with representative CS, also extending this responsibility to providers of materials intended to be used to assess the agreement of results in external quality assessment (EQA) programs [18]. This responsibility is now laid down in ISO 15194 and ISO 17034 standards about RM requirements [19, 20].

Recent examples show that RM providers are now carefully dealing with commutability evaluation. When the NIST SRM 967 for standardizing serum creatinine measurements was released, an *ad-hoc* commutability experiment was conducted [21]. SRM 967 demonstrated commutability with native CS for most of the commercially available creatinine assays, whose names were listed in the National Kidney Disease Education Program (NKDEP) website. The use of SRM 967 was indeed effective in standardizing creatinine assays. On the other side of the Atlantic Ocean, the Joint Research Centre (JRC) of the European Commission (formerly known as IRMM) has performed a series of commutability studies for all the recently released RMs [22, 23].

How to assess commutability

Commutability has been covered in two Clinical and Laboratory Standards Institute (CLSI) guidelines [24, 25]. According to them, assessing commutability of RMs does not seem very complicated. Briefly, documents recommend selecting 20 native CS spanning the relevant concentration interval, analyzing both RM and CS with the pair of procedures (e.g. reference procedure and commercial assay), trying to minimize the random error by performing measurements in a single run and an adequate number of replicates, and elaborating data using regression analysis and checking if the RM fall within the 95% prediction interval (PI) defined by the CS (Figure 2). However, this approach has some limitations. The statistically defined PI size from the regression plot is determined by how well correlated CS results by the compared procedures are; more scatter in the relationship should more easily make an RM commutable. Furthermore, the PI approach is unable to apply different commutability criteria based on the RMs' intended use (e.g. calibrator or trueness control material). Characteristics of the selected set of CS should also be considered as they may influence the obtained results: healthy vs. diseased patients' source, use of native vs. pooled samples (individual samples should be preferred, but pooled samples may be needed to meet volume requirements), the presence of potential interfering substances, freeze-thaw artifacts. In general, the CLSI approach gives just a 'yes-no' assessment of commutability, which is dependent on: (a) the statistical methods used, (b) the assay variability and (c) the concentration range or representativeness of the CS, without providing an assessment of how effective the RM will be in controlling inter-assay differences.

In 2013, the IFCC established a Working Group on Commutability (WG-C) with the goal of improving the

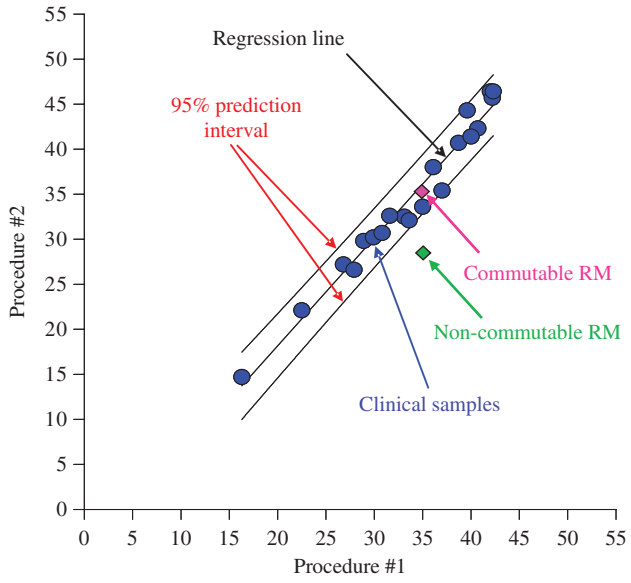

Figure 2: Schematic diagram showing the behaviour of a commutable (pink) and a non-commutable (green) reference material (RM) when assessed according to the Clinical and Laboratory Standards Institute guidelines [24, 25].
Note: Procedure #1 in x-axis should be reference measurement procedure when available.

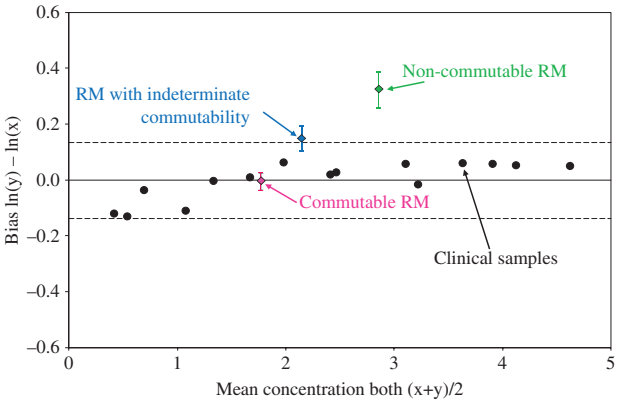

Figure 3: Schematic diagram showing the assessment of commutability of reference materials according to the recommendation by the IFCC Working Group on Commutability [27]. The graph displays the difference in bias between reference materials (colored diamonds) and clinical samples (black circles) vs. mean concentration of the pair of measurement procedures. The solid black line is the mean difference between the two measurement procedures for the clinical samples. The black dashed lines represent the commutability criterion, defined by the intended use of the reference materials. The colored diamonds are the mean difference between the two measurement procedures for the reference materials, and the bars are the uncertainty in the difference in bias between reference material and clinical sample mean bias. Note that an indeterminate conclusion (blue color) means that the uncertainty bar is outside of the predetermined maximum allowable bias for the commutability of the reference material. RM, reference material.

commutability assessment of RMs by defining specific operating procedures, establishing criteria for commutability considering the intended use of an RM, and giving guidance on specific information to be provided regarding the commutability of RMs. The WG-C has recently released three recommendations [26–28]. The first report has addressed critical components of the experimental design for commutability assessment, discussing how to select CS (individual or pooled), qualify measurement procedures for inclusion in the assessment, establish criteria to determine commutability and, for the first time, defining the information to be included in the RM certificate [26]. The other papers describe two approaches to assess commutability. The first approach consists in verifying how close the systematic difference between the two measurement procedures for the tested RM is to the average bias for CS (Figure 3) [27]. Examples applying this approach have been recently published [13, 22]. We compared this IFCC recommended approach with the CLSI one in checking commutability of the ERM-DA470k/IFCC material for serum IgA [13]. Some minor differences in defining the commutability of the RM were seen, which could be expected considering the different underlying theory of the two approaches. In the study, the sample pools used conformed to the CLSI approach to include a large part of the measuring interval for a regression statistical analysis. However, we observed a nonconstant relative bias over the measuring interval for several of the measurement procedure pairs that contributed to larger uncertainty at the concentration of the RM and indeterminate conclusions when using the IFCC approach. The data suggested that a different experimental design is optimal for the IFCC approach to cluster the concentrations of the CS closer to that of the RM to minimize the influence of nonconstant bias and improve the statistical analysis and conclusions regarding commutability [13].

The second IFCC approach is based on the effectiveness of an RM used as a calibrator to improve harmonization among measurement procedures [28]. The candidate RM is used to recalibrate each measurement procedure and is considered commutable if it can reduce the inter-assay CV within an acceptable level of equivalence based on medical requirements. On the contrary, the RM is declared non-commutable for measurement procedures for which, after recalibration, the CS results do not agree with those from other assays. However, other causes of disagreement, including lack of calibration fit, should be investigated before concluding that the RM is non-commutable.

Both IFCC approaches work with preset specifications that are suitable for the intended use of the RM

(commutability criterion). In establishing criteria for commutability validation, the intended use of the material is central. In general, RMs used as calibrators in traceability chains should be validated for commutability using tighter goals, whereas the adoption of wider goals could be enough when assessing commutability of control materials (see below). In selecting commutability criteria, the models defined during the EFLM conference held in Milan in 2014 should be employed [29].

Finally, the IFCC WG-C defined the information regarding commutability assessment that should be documented for a certified RM [26]. Criteria for selecting individuals from whom CS were obtained, together with their number, collection, processing and storage conditions, should be disclosed. Thorough descriptions of the experimental design and of commutability criterion are also requested. Finally, measuring systems for which RM commutability was tested, including the specific models of platforms and the employed lots of reagents and calibrators, should be recorded.

Commutability of control materials

The EQA programs are optimal tools for evaluating the reliability of commercial measuring systems and the clinical suitability of measurements provided by clinical laboratories. However, EQAs must be appropriately structured [30]. Efforts by EQA providers should be made to meet criteria allowing the evaluation of the performance of participating laboratories in terms of traceability of their measurements. This requires assigning values (and uncertainty) to control materials with reference measurement procedures, defining and applying clinically allowable performance specifications for judging the quality of results and using materials of proved commutability [2]. Only materials with proved commutability allow directly transferring of participating laboratory performance to the measurement of CS [31]. Unfortunately, EQA samples are frequently not assessed for commutability because of technical (i.e. the complicated logistics of preparation and distribution of frozen samples) and economic concerns [31, 32]. Usually, the commutability of EQA materials is just assumed based on how they are prepared. It may be reasonable for single donation, while potential limitations exist for spiked or supplemented pools or for materials that are more artificial. The use of single-donor samples, which is preferable to overcome commutability problems, may however limit the achievement of adequate volumes of samples needed for preparing sufficient amount of control materials. On the other hand, pooled samples have the potential limitation that interactions of components such as proteins may cause modification of the matrix. The CLSI has described a rigorous protocol to collect blood, obtain serum, prepare a pool and freeze aliquots under conditions that do not alter the commutability characteristics [33].

Given the pivotal importance of commutability of EQA materials for reflecting laboratory performance for patient results, it was surprising to see the demonstration of commutability of materials as the last item in the list of factors influencing choice of EQA programs by laboratory professionals [34]. For this reason, the EFLM has recently stressed the need that the EQA material matrix and its commutability should be specified by providers, because the interpretation of differences between results in an EQA program is strongly dependent on the nature of the employed material [35]. What appears clear from the published experiences is that sometimes we probably have an optimistic perception of analytical quality in clinical laboratories, due to the traditional approaches of EQA for evaluating their performances, among which the quality of samples is often not a concern [31]. In 2012, Stepman et al. [36] in a survey using single-donation samples, demonstrated the need for improvement even for simple clinical chemistry analytes, such as creatinine and urate. In another project using commutable samples targeted with reference measurement procedures, authors from various European countries demonstrated that, for six out of 17 evaluated general chemistry analytes, the available measuring systems were unable to meet the minimum analytical quality specifications, concluding that manufacturers should improve their performance for these analytes [37]. Finally, a study performed using 20 native single-donation serum samples demonstrated that the analytical bias of four commonly employed immunoassays (cobalamin, ferritin, thyroid-stimulating hormone and free T4) still exceeds the desirable performance specifications derived from biological variation of tested measurands [38]. Therefore, it is clear that the use of commutable samples in EQA is mandatory in order to add substantial value to the practice of laboratory medicine [39]. To avoid illusory perception of the analytical quality of current measuring systems, it is essential to discontinue conventional EQA using non-commutable materials, consensus 'peer' group assessment and not clinically oriented analytical performance specifications and make efforts to provide programs that meet metrological criteria whose benefits have been incontrovertibly proved [31].

Commutability also matters for the internal quality control (IQC) materials that should be used by clinical laboratories to derive the random component of

the uncertainty of measured CS results. We previously described the characteristics for an IQC material to be used to estimate the measurement uncertainty due to random effects, which includes the analytical system imprecision together with the individual laboratory performance in terms of variability [40]. In particular, the material evaluating the random uncertainty must be different from control material used for checking the alignment of the measuring systems and should be commutable, closely resembling to CS, in order to provide adequate information about the imprecision performance of the assay [40]. Hage-Sleiman et al. [41] have elegantly showed the misleading results obtained in the estimate of precision profile when using a non-commutable IQC material, taking as example a highly sensitive troponin assay.

Conclusions

In this paper, we provided an overview of the practical importance of using commutable materials, when they are employed either as common calibrators for implementing metrological traceability or as control materials in EQA and IQC programs. The use of non-commutable RMs may introduce a significant bias in the calibrated procedures producing incorrect results for CS. The use of non-commutable materials in EQA programs prevents the transferability of participating laboratory performance to the measurement of patient samples. Finally, only commutable control materials may provide the proper information for the estimate of measurement uncertainty. Providers of reference and control materials should definitively take the responsibility to assess the commutability of those materials before their use. In this regard, reliable guidelines are now available in the literature. A proper understanding of the importance of commutability represents a central step forward to standardization in laboratory medicine, proving consistent clinical decisions and, ultimately, improving patient outcomes.

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