Opinion Paper

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Implementation of metrological traceability in laboratory medicine: where we are and what is missing

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Abstract

Background: The Joint Committee on Traceability in Laboratory Medicine (JCTLM) has recently created the Task Force on Reference Measurement System Implementation (TF-RMSI) for providing guidance on traceability implementation to in vitro diagnostics (IVD) manufacturers. Using serum creatinine (sCr) as an example, a preliminary exercise was carried out by checking what type of information is available in the JCTLM database and comparing this against derived analytical performance specifications (APS) for measurement uncertainty (MU) of sCr.
Content: APS for standard MU of sCr measurements were established as a fraction (≤0.75, minimum quality; ≤0.50, desirable quality; and ≤0.25, optimum quality) of the intra-individual biological variation of the measurand (4.4%). By allowing no more than one third of the total MU budget for patient samples to be derived from higher-order references, two out of the four JCTLM reference materials (RMs) at least allow minimum APS to be achieved for the MU of patient samples. Commutability was explicitly assessed for one of the JCTLM-listed matrixed RMs, which was produced in compliance with ISO 15194:2009 standard, whereas the remaining three RMs were assessed against the ISO 15194:2002 version of the standard, which only required the extent of commutability testing to be reported. Regarding the three listed reference methods, the MU associated with isotopic dilution-mass spectrometry coupled to gas chromatography (ID/GC/MS) and isotopic dilution-mass spectrometry coupled to liquid chromatography (ID/LC/MS) would allow APS to be fulfilled, while the isotope dilution surface-enhanced Raman scattering (ID/SERS) method displays higher MU.
Summary: The most recently listed RM for sCr in the JCTLM database meets the ISO 15194:2009 requirements with MU that would allow APS to be fulfilled and has had commutability demonstrated for use as a common calibrator in implementing traceability of sCr measurements. Splitting clinical samples with a laboratory performing ID/GC/MS or ID/LC/MS provides an alternative but would also require all components of uncertainty of these materials to be assessed.
Outlook: Using appropriately derived APS to judge whether reference measurement system components are fit for purpose represents a novel approach. The TF-RMSI is planning to review a greater number of measurands to provide more robust information about the state of the art of available reference measurement systems and their impact on the ability of clinical measurements to meet APS.

Keywords: creatinine; measurement uncertainty; metrological traceability; standardization.

Background

Very often, only a brief description of metrological traceability is provided with commercial calibrators. The information is frequently limited to the name of the higher-order reference material (RM) and/or reference measurement procedure (RMP) to which the assay calibration is traceable, without any description of implementation steps. Information such as the applied calibration hierarchy, the measurement uncertainty (MU) associated with the calibrator, and the employed acceptable uncertainty limits is often partly available [1]. On the other hand, accumulated experience shows that standardization projects not only have to address metrological traceability but should also consider the efficacy of its implementation [2]. Previous analyses highlighted how strongly MU may be dependent on the type of traceability chain adopted by the in vitro diagnostics (IVD)

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manufacturers to implement the traceability of commercial calibrators [1, 3, 4]. The selection of different types of traceability chains (no matter if they all employ certified RMs and approved RMPs) may lead to different combined uncertainties at the level of commercial calibrators, not always permitting to fulfill the suitable uncertainty budget at the level of clinical sample measurements [1, 3–5]. Therefore, to aid IVD manufacturers in the traceability implementation, the identification and definition of available reference measurement systems (RMS) and of metrological traceability chains in their entirety and not just in their main components (i.e. RMs and RMPs) can be extremely helpful. The Joint Committee on Traceability in Laboratory Medicine (JCTLM) recently created the Task Force on Reference Measurement System Implementation (TF-RMSI) with the aim to provide guidance on traceability implementation to the IVD community. The objectives of the Task Force are: (a) to identify and describe available RMS and traceability chains in their entirety, based on the information present in the JCTLM database; (b) to illustrate the evolution of MU through the entire metrological traceability chains; and (c) to identify those measurands for which further advancements to existing RMS are needed or some RMS components are lacking. Here, using creatinine as an example, we illustrate details of the current situation of what is listed in the JCTLM database to enable metrological traceability of this measurement, highlighting merits and some limitations.

Data extraction from the JCTLM database

We accessed the JCTLM database (https://www.bipm.org/jctlm/) on July 1, 2019, searching for RMs and RMPs for creatinine. In addition to two primary RMs (National Institute of Standards and Technology [NIST] SRM 914a and National Metrology Institute of Japan CRM6005-a), four secondary (matrixed) RMs and three reference method principles were identified (Table 1). According to the metrological traceability theory, to transfer trueness from higher-order references to commercial calibrators, IVD manufacturers have two possibilities: (a) directly calibrating their internal procedure with a suitable secondary RM or (b) aligning their internal procedure to an RMP by a comparison study [6].

Available secondary RMs

To confirm that providers of secondary (matrixed) RMs intended to offer them as higher-order calibrators for implementing traceability of IVD measuring systems, we checked the intended use on the certificates of RMs listed in Table 1. For all RMs, the scope was similar, including assessment of accuracy and validation of calibration of field methods used in medical laboratories for the determination of serum creatinine. Therefore, to be used according to their intended use, RMs should be validated for commutability [7, 8]. This is essential to guarantee an unbroken sequence of calibrations needed to achieve the traceability implementation to the International System of Units (SI). The use of non-commutable RMs may introduce a significant bias in the calibrated procedures producing incorrect results for clinical samples.

We investigated the availability and quality of information regarding the commutability of listed secondary RMs, noting that the requirements for demonstrating commutability of RMs have strongly evolved between the 2002 and 2009 versions of the ISO 15194 standard, which have been used for the JCTLM assessment of RMs. For the more recently listed RM (Laboratoire National de Métrologie et d'Essais [LNE] CRM Bio 101a) the commutability was investigated and the related information documented in the certificate of analysis [9]. For the remaining three RMs, the commutability was not mentioned in their certificates, having been produced and assessed at the time when ISO 15194:2002 was in place, and this is clearly indicated in the JCTLM listing of the RMs. It should also be noted that as the production methods of some of the RMs rely on the preparation of frozen materials, these could in principle be commutable to a greater or lesser extent, but this would need to be demonstrated. We previously noted that for many RMs released in previous decades the commutability with laboratory measurement procedures was not recognized as an issue and was typically not assessed (8). Today, for newer materials that should be compliant with the ISO 15194:2009, a statement about their commutability with clinical samples for all measurement procedures with which they may be potentially used as common calibrators for implementing metrological traceability represents a major step forward.

The information about the traceability of assigned creatinine values for RMs retrieved from the database are reported in Table 1. The nominal values of all but one of the materials were assigned by using RMPs listed in the JCTLM database [isotopic dilution-mass spectrometry coupled to gas chromatography (ID/GC/MS) or isotopic dilution-mass spectrometry coupled to liquid chromatography (ID/LC/MS), calibrated with NIST SRM 914 or 914a]. The exception was represented by the Joint Research Centre BCR-573/574/575 for which two different procedures, i.e.

Table 1: Synopsis of higher-order matrixed reference materials (RMs) and reference measurement procedures (RMPs) for serum creatinine listed in the Joint Committee on Traceability in Laboratory Medicine (JCTLM) database, including their main characteristics for implementing traceability and fulfilling specifications for suitable uncertainty.

Secondary RM/RMP	Traceability of assigned values	Nominal value, µmol/L	Combined standard uncertainty, %[a]	Commutability information
JRC BCR-573 (lyophilized human serum)	By ID/GC/MS and HPLC[b] calibrated with the NIST SRM 914a	68.7	*1.02*	Not available
JRC BCR-574 (lyophilized human serum)	By ID/GC/MS + HPLC[b] calibrated with the NIST SRM 914a	105.0	**0.62**	Not available
JRC BCR-575 (lyophilized human serum)	By ID/GC/MS + HPLC[b] calibrated with the NIST SRM 914a	404.1	*0.88*	Not available
LGC ERM-DA250a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	358.0	5.87	Not available
LGC ERM-DA251a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	197.0	5.58	Not available
LGC ERM-DA252a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	27.5	15.6	Not available
LGC ERM-DA253a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914	449.0	3.56	Not available
LNE CRM Bio 101a level 1 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 914a	53.04	*1.09*	Available
LNE CRM Bio 101a level 2 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 914a	550.54	**0.56**	Available
CENAM DMR-263a (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 914a	66.4	2.18	Not available
ID/GC/MS	By calibration with high purity crystalline creatinine	151.9[c] 352.9[c]	**0.49**[c] **0.50**[c]	By definition
ID/LC/MS	By calibration with high purity crystalline creatinine	152.1[d] 350.5[d]	*0.82*[d] **0.40**[d]	By definition
ID/SERS	By calibration with high purity crystalline creatinine	345.7[e] 492.0[e]	1.23[e] 2.24[e]	By definition

JRC, Joint Research Centre; ID/GC/MS, isotopic dilution-mass spectrometry coupled to gas chromatography; NIST, National Institute of Standards and Technology; ID/LC/MS, isotopic dilution-mass spectrometry coupled to liquid chromatography; LNE: Laboratoire National de Métrologie et d'Essais; CENAM, Centro Nacional de Metrologia; ID/SERS, isotope dilution surface-enhanced Raman scattering. [a]Higher-order references fulfilling minimum quality specification for uncertainty (1.10%) are in italics and those fulfilling desirable quality specification (0.73%) are in bold. The others do not fulfill specifications. [b]Not listed in the JCTLM database as a higher-order RMP. [c]Derived from RELA 2017, Labcode 1, available at http://www.dgkl-rfb.de:81/4Daction/g_search_RELA?selectAnalyte=Creatinine&submitplot=show+result+plot&session_id=00000000000000000000&cur_year=2017&LabCode=000 (Accessed July 2019). [d]Derived from RELA 2017, Labcode 18, available at http://www.dgkl-rfb.de:81/4Daction/g_search_RELA?selectAnalyte=Creatinine&submitplot=show+result+plot&session_id=00000000000000000000&cur_year=2017&LabCode=000 (Accessed July 2019). [e]Derived from RELA 2010, Labcode 111, available at http://www.dgkl-rfb.de:81/4Daction/g_search_RELA?selectAnalyte=Creatinine&submitplot=show+result+plot&session_id=00000000000000000000&cur_year=2010&LabCode=000 (Accessed July 2019).

ID/GC/MS and high-performance liquid chromatography (HPLC), were used, the latter not listed as an RMP.

Available RMPs

The alternative to the use of a commutable certified RM (ISO 15194 compliant) as a calibrator is to use a panel of native (commutable by definition) or pooled (validated for commutability) human samples (the homogeneity and stability including the associated uncertainty have been measured), and whose values have been assigned by an RMP [6]. This is usually done through a comparison experiment between a reference laboratory performing RMP and the IVD manufacturer performing its own internal procedure. This makes it possible to correct systematic bias, if any, and ensure the alignment of the calibration of the manufacturer's selected measurement procedure to the higher-order references and the assignment of traceable values to the end-user IVD calibrators.

Three reference methods are listed in the JCTLM database: ID/GC/MS, ID/LC/MS and the isotope dilution surface-enhanced Raman scattering method (ID/SERS).

Fulfillment of goals for suitable uncertainty

In addition to the correct transfer of trueness from higher-order references to IVD calibrators, we would like to emphasize that the definition of appropriate analytical performance specifications (APS) for the total uncertainty budget that should be fulfilled at the level of patient results is essential to ensure that laboratory measurements are clinically usable [3, 10]. For MU we believe that the relevant goal that should be fulfilled is that related to the allowable random variability of patient results, as the correct trueness transfer along the metrological traceability chain should allow the achievement of unbiased (or negligibly biased) results [11].

According to concepts for deriving APS established at its 2014 Strategic Conference [12], the European Federation of Clinical Chemistry and Laboratory Medicine has worked on the criteria for assigning laboratory measurands to different models [13]. Serum creatinine was assigned to the biological variation-based model that should be applied when the measurand has stable concentrations, i.e. is in a "steady state" status when a subject is in good health, and deviations from these concentrations will not in itself cause symptoms [14]. By using published data about the intra-individual biological variation (CV_I) of serum creatinine (4.4%) [15] and the classical formulae for deriving APS for random variability [11], APS for standard MU of serum creatinine measurement on clinical samples are 3.3% ($\leq 0.75CV_I$, minimum quality), 2.2% ($\leq 0.50CV_I$, desirable quality), and 1.1% ($\leq 0.25CV_I$, optimum quality).

The higher-order references represent the first contribution to the overall MU budget and, therefore, the MU of references may significantly affect the MU of the patient's results. Due to error propagation in the calibration hierarchy, it is intuitive that this contribution in terms of MU should be sufficiently small to allow to fulfil APS for MU at the clinical sample level, when IVD calibrator and random uncertainties have been added [3, 10]. Accordingly, it has been recommended to turn the approach upside down by focusing first on the established APS of the field measurement results and then to defining the goal for MU of the RM for a given measurand by the performance needs of the clinical assays for that measurand [5]. We conventionally recommended that no more than one third of the total uncertainty budget should be consumed by higher-order references [3]. Therefore, using APS for standard MU of serum creatinine measurement on clinical samples mentioned above, the standard MU associated to higher-order references should be ≤1.10%, ≤0.73%, and ≤0.37% at minimum, desirable, and optimum quality levels, respectively.

Two out of four secondary RMs listed in the JCTLM database would allow at least the minimum quality level for APS related to MU to be fulfilled (Table 1). As expected, fulfillment of minimum or desirable APS was also dependent on the creatinine concentration levels in the same type of RM, the MU being higher when the measurand concentration becomes lower. The LGC ERM-DA materials display relative MU far greater (an order of magnitude) than other materials, and while certificates of the materials indicate that the uncertainty contribution added to account for long-term stability of the material is by far the largest component, the uncertainty from characterization is not negligible [16]. It is not generally expected that such a large difference in uncertainties should be evident for very similar materials, and as such general conclusions should not be drawn based on these materials. Regarding the listed RMPs, the MU associated with ID/GC/MS and ID/LC/MS should allow APS for clinical measurements to be fulfilled, while ID/SERS displays higher MU that would make it difficult for IVD manufacturers using this RMP as a higher-order reference to produce measuring systems able to fulfill MU APS at the level of clinical samples.

Conclusions

In this brief commentary, we focused on an example of what the JCTLM database is offering in terms of practical help to IVD manufacturers for implementing traceability to higher-order references and to end-users in terms of MU of different options for their clinical use. Using creatinine as the example, the overall characteristics reported in Table 1 show that the most recently listed RM, LNE CRM Bio 101a, which was developed and reviewed against ISO 15194:2009 requirements, appears to be suitable for correctly implementing traceability to SI (with commutability explicitly assessed) and has suitably small MU, considering the impact of the error propagation in the calibration hierarchy, to allow APS to be met for measurements on patient samples. Splitting clinical samples with a laboratory performing ID/GC/MS or ID/LC/MS provides an alternative route to establishing a calibration hierarchy, but also requires all components of uncertainty to be

assessed. Using APS to judge whether reference measurement system components are fit for purpose certainly represents a novel approach that should be more widely tested. In our paper, it was only applied for creatinine, so the conclusions about the general status of the traceability implementation could be limited. The JCTLM TF-RMSI is planning a review of a greater number of measurands, chosen based on their frequency of measurement in clinical laboratories, for providing more robust information about the state of the art of available reference measurement systems and their impact on the ability of clinical measurements to meet APS.

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