

Feasibility of Metrological Traceability Implementation Using the Joint Committee on Traceability in Laboratory Medicine Database Entries Including the Fulfillment of “Fit-for-Purpose” Maximum Allowable Measurement Uncertainty

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BACKGROUND: In previous publications, the Task Force on Reference Measurement System Implementation proposed a procedural approach combining a critical review of entries available in the Joint Committee on Traceability in Laboratory Medicine (JCTLM) database with a comparison of this information against analytical performance specifications for measurement uncertainty (MU) and applied it to a group of 13 measurands.

CONTENT: Here we applied this approach to 17 additional measurands, of which measurements are frequently requested. The aims of the study were (a) to describe the main characteristics for implementing traceability and the potential to fulfill the maximum allowable MU (MAU) at the clinical sample level of certified reference materials and reference measurement procedures listed in the JCTLM database; (b) to discuss limitations and obstacles, if any, to the achievement of the required quality of laboratory measurements; and (c) to provide a gap analysis by highlighting what is still missing in the database. Results were integrated with those obtained in the previous study, therefore offering an overview of where we are and what is still missing in the practical application of the metrological traceability concept to 30 common biochemical tests employed in laboratory medicine.

SUMMARY: Our analysis shows that for 28 out of 30 measurands, conditions exist to correctly implement metrological traceability to the International System of units and fulfill at least the MAU of the minimum quality level derived according to internationally recommended models. For 2 measurands (serum albumin and chloride), further improvements in MU of higher-order references would be necessary.

Introduction

The Joint Committee for Traceability in Laboratory Medicine (JCTLM) provides a database of higher-order certified reference materials (CRM), higher-order reference measurement procedures (RMPs), and accredited reference measurement services, for which quality is verified by third-party independent review of their compliance with appropriate normative standards developed and published by the International Organization for Standardization (ISO) (1). As a result, the JCTLM database is central to implementing metrological traceability in laboratory medicine and fulfilling the requirements of the ISO 17511:2020 standard by in vitro diagnostic (IVD) manufacturers, which is now also referenced in

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A lack of information about the procedural implementation of the calibration hierarchy by IVD manufacturers has, however, been noted, as well as limited context on the use of providers of higher-order references to establish traceability (3, 4). Simply describing an assay as “traceable” is not enough, as it does not mean that the manufacturer has transferred trueness successfully and that the measurement uncertainty (MU) of the IVD medical device (IVD-MD) meets clinical needs. Given this scenario, the JCTLM created a Task Force on Reference Measurement System Implementation (TF-RMSI) to provide guidance on metrological traceability implementation for the IVD community. In previous publications, the TF-RMSI proposed a procedural approach combining a critical review of what is available in the JCTLM database with a comparison of this information against analytical performance specifications (APS) for MU (5) and applied it to a first group of 13 measurands (6). In the present paper, we expand this analysis to an additional group of 17 measurands, for which measurements are frequently requested for testing in laboratory medicine. The aims of this study were (a) to describe the main characteristics of CRMs/RMPs listed in the JCTLM database for implementing traceability and their potential to permit fulfillment of the maximum allowable MU (MAU) at the clinical sample level; (b) to discuss major limitations and obstacles, if any, to the achievement of the required quality of laboratory measurements; and (c) to provide a gap analysis by highlighting what is still missing in the database and stimulate reference providers to focus their activities on these areas.

Materials and Methods

The procedural steps used in this study were previously described in detail (6). According to ISO 17511:2020, the material (m.3) that should be selected to transfer trueness from the top of the calibration hierarchy to commercial calibrators can be a commutable CRM or a panel of human samples, whose values are assigned by the RMP, in a comparison experiment between a reference measurement service performing the RMP and the IVD manufacturer performing its own internal measurement procedure (2, 7). Accordingly, both secondary (matrix) CRMs and RMPs were identified in the JCTLM database for each of the selected measurands, and the corresponding reference measurement systems to which they belong were described. The MU of

CRM-certified values and the experimental MU of a given clinical sample characterized as a reference material by a RMP listed in the JCTLM database were examined for their potential to be small enough to avoid significantly affecting the combined MU of clinical samples when uncertainties from the IVD calibrator and end-user IVD-MD are combined and compared to MAU (8).

For matrix CRMs, the intended use as stated in the material’s certificate of analysis was checked to confirm that the CRM provider considered the use as a common calibrator or for the assessment of trueness and validation of the calibration of field methods used in medical laboratories. To address this, the CRM’s certification report was examined for information about commutability with clinical samples for commercial procedures. The specific edition of the ISO 15194 standard used in the JCTLM review process (2002 or 2009 versions) was also identified, as only ISO 15194:2009 explicitly requests information about CRM commutability (9).

The ISO 17511:2020 standard also requires that the MU within a calibration hierarchy is well defined and retains the concept of “fit-for-purpose” MAU needed in clinical sample analysis. This requirement aims to ensure that measurement results in clinical samples are not only traceable to available higher-order references but also have a MU of the reported values that is meaningful and relevant in patient care (2). To achieve this goal, a model for the definition of limits for combined MU across the entire metrological traceability chain was proposed, suggesting that the higher-order references should display a MU (u_{ref}) at most equal to one-third of MAU (10). Although empirical, this concept and suggested requirements have been shown to work at least in some situations and significantly contribute to understanding whether laboratory measurements are clinically usable by identifying measurands for which the MU associated with the higher levels of the calibration hierarchy must be reduced (11, 12). Considering this approach as a reasonable starting point, in our study we employed one-third as the proposed MAU fraction for u_{ref} , using both minimum and desirable quality levels of APS as defined by the APERTURE study, a project for establishing Analytical Performance Specifications for Measurement Uncertainty of common laboratory measurands using models and criteria for measurand allocation proposed by the European Federation of Clinical Chemistry and Laboratory Medicine Strategic Conference (12–14). Table 1 reports the model allocation and MAU for the standard MU for the 17 measurands included in this study, and these values were used to investigate whether the status of the MU budget associated with a given calibration hierarchy may significantly affect clinical interpretation. APS for u_{ref} are also displayed.

Table 1. Model allocation and recommended APS for standard MU for clinical samples and at higher-order reference levels for the 17 evaluated measurands.^a

Measurand	Type of calibration hierarchy described by ISO 17511:2000	APS model	APS for standard MU for clinical samples, % ^b		Allowable standard MU for higher-order references, % ^c	
			Desirable	Minimum	Desirable	Minimum
S-Total cholesterol	CH1	Outcome-based	3.00	7.00	1.00	2.33
S-HDL cholesterol	CH1	Outcome-based	2.90	5.60	0.97	1.87
S-Triglycerides	CH1	Outcome-based	6.10	12.4	2.03	4.13
S-Albumin	CH1	BVTemp ^d	1.25	1.88	0.42	0.63
S-Creatine kinase	CH2	BVTemp	7.25	10.9	2.42	3.63
S-Pancreatic amylase	CH2	BVTemp	3.15	4.73	1.05	1.58
S-Alkaline phosphatase	CH2	BV	2.65	3.98	0.88	1.33
S-Aspartate aminotransferase	CH2	BV	4.75	7.13	1.58	2.38
S- γ -Glutamyl transferase	CH2	BV	4.45	6.68	1.48	2.23
S-Lactate dehydrogenase	CH2	BV	2.60	3.90	0.87	1.30
S-Total protein	CH1	BV	1.30	1.95	0.43	0.65
S-Immunoglobulin G	CH1	BV	2.20	3.30	0.73	1.10
S-Immunoglobulin A	CH1	BV	2.50	3.75	0.83	1.25
S-Immunoglobulin M	CH1	BV	2.95	4.43	0.98	1.48
S-Magnesium	CH1	BV	1.44	2.16	0.48	0.72
S-Uric acid	CH1	BV	4.16	6.24	1.39	2.08
S-Digoxin	CH1	Model 1 and 2 ^e	6.00	9.00	2.00	3.00

S, serum; HDL, high-density lipoprotein; CH1, full metrological traceability chain to SI; CH2, measurand procedurally defined; BV, biological variation.

^aNote that all MU data are reported as standard MU, i.e., the uncertainty of the result of a measurement expressed as SD. They can be expanded by multiplying by a coverage factor of 2 (95.45% level of confidence).

^bDerived from (12).

^cEstimated as one-third of APS for standard MU for clinical samples.

^dIndicates measurands temporarily allocated to the biological variation model because outcome-based data are lacking.

^eA hybrid model specifically developed for drugs was proposed [see (13) for more details].

Results and Discussion

Table 2 provides a synopsis of higher-order matrix CRMs and RMPs retrieved from the JCTLM database for the selected measurands, including their main characteristics for implementation of metrological traceability and potential fulfillment of MAU. Results showed that, with few exceptions discussed later, for most of the evaluated measurands traceability to the highest metrological levels can be established by IVD manufacturers within the defined MAU using the JCTLM available information. This confirms the outcome previously obtained in the first part of this TF-RMSI project (6). For the sake of completeness, we will comment here on our results by integrating them with those obtained in the previous study. This will provide insights about the practical applicability of metrological traceability for 30 of the most common biochemical tests employed in laboratory medicine.

MEASURANDS FOR WHICH TRACEABILITY CAN BE IMPLEMENTED AND MAU FULFILLED

For 24 out of 30 evaluated measurands, CRMs and/or RMPs listed in the JCTLM database offer a practical option for implementation of traceability of clinical results in agreement with the ISO 17511:2020 recommendations, including the fulfillment of MAU derived according to internationally recommended models. In particular, for 10 measurands (i.e., serum calcium, creatine kinase, creatinine, γ -glutamyl-transferase, glucose, total cholesterol, triglyceride, urea, uric acid, and blood glycosylated hemoglobin), both CRM and RMP options exist for transferring trueness to IVD calibrators. In these cases, it is recommended that, in making a choice, IVD manufacturers should consider the available higher-order references in terms of u_{ref} operating to reduce as much as possible MU of the calibration hierarchy and consequently MU of commercial calibrators, especially when

Table 2. Synopsis of CRMs and RMPs listed in the JCTLM database, intended for transferring trueness from the highest order references available to IVD-MD calibrators, including their characteristics for fulfilling analytical performance specifications for suitable MU.

CRM/RMP	Basis for traceability	Nominal value	Standard MU ($k = 1$) ^a (%)	Stated intended use in the CRM certificate of analysis	Commutability information
S-Total cholesterol					
LINECRM Bio 101a level 1 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 911c cholesterol crystalline material	3.61 mmol/L	0.83	For use as quality control material to assess the bias or MU of measurement procedures	Available ^b
LINECRM Bio 101a level 2 (frozen human serum)		5.93 mmol/L	1.10		
ID/GC/MS	By calibration with high-purity crystalline cholesterol	3.222 mmol/L	0.50^c		By definition
ID/LC/MS	By calibration with high-purity crystalline cholesterol	2.972 mmol/L	0.72^c		By definition
HPLC	By calibration with high-purity crystalline cholesterol	3.436 mmol/L	0.76^d		By definition
Spectrophotometry	By calibration with high-purity crystalline cholesterol	4.206 mmol/L	0.75^d		By definition
	By calibration with high-purity crystalline cholesterol	3.185 mmol/L	0.39^e		By definition
	By calibration with high-purity crystalline cholesterol	2.951 mmol/L	0.90^e		By definition
S-HDL cholesterol	By CDC ultracentrifugation/selective precipitation calibrated with the NIST SRM 911c cholesterol crystalline material	3.504 mmol/L	0.26^f		By definition
	By CDC ultracentrifugation/selective precipitation calibrated with the NIST SRM 911c cholesterol crystalline material	4.312 mmol/L	0.30^f		By definition
	By CDC ultracentrifugation/selective precipitation calibrated with the NIST SRM 911c cholesterol crystalline material	1.28 mmol/L	3.13	For use as quality control material to assess the bias or MU of measurement procedures	Available ^b
LINECRM Bio 101a level 1 (frozen human serum)		1.49 mmol/L	1.68		
LINECRM Bio 101a level 2 (frozen human serum)		1.17 mmol/L	1.87^g		By definition
Spectrophotometry (after ultracentrifugation for removing VLDL and pretreatment with heparin/Mn ²⁺ for non-HDL removal)	By calibration with high-purity crystalline cholesterol	1.45 mmol/L	1.06^g		By definition
S-Triglycerides (as measurand defined as the sum of triglycerides, diglycerides, monoglycerides, and free glycerol in serum = "total glycerol")					
LINECRM Bio 101a level 1 (frozen human serum)	By ID/GC/MS calibrated with the NIST SRM 1951b or NIST SRM 909c in turn	0.74 mmol/L	1.35	For use as quality control material to	Available ^b

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Standard MU ($k=1$) ^a (%)	Stated intended use in the CRM certificate of analysis	Commutability information
LNE CRM Bio 101a level 2 (frozen human serum) ID/GC/MS	value-assigned by ID/GC/MS calibrated with high-purity tripalmitin By calibration with high-purity tripalmitin	1.61 mmol/L 1.321 mmol/L 1.466 mmol/L	1.55 0.49 ^c 0.51 ^c	assess the bias or MU of measurement procedures –	By definition
S-Albumin EU-JRC ERM-DA470k/IFCC (lyophilized human serum)	By immunonephelometry/immunoturbidimetry to US National Reference Preparation no. 12-0575C through ERM-DA470	37.2 g/L	1.61	For the calibration of immunoassay-based IVD devices or control products for serum albumin	Not available ^b
S-Creatine kinase GPHCM GBWE)091042 (frozen human serum) Kinetic spectrophotometry IFCC RMP (37°C)	By IFCC primary RMP at 37°C Procedurally defined	374.8 U/L 247.2 U/L 589.2 U/L	1.27 1.46 ⁱ 1.32 ⁱ	For use as calibrator or control material – –	Available ^b By definition
S-Pancreatic amylase ERM-AD456/IFCC (buffered solution with human serum albumin)	By IFCC primary RMP for total amylase at 37°C	274.0 U/L	1.28	For use as trueness control or external quality control material for routine measurement systems if commutability has been proven for the assay concerned	Available ^b
S-Alkaline phosphatase GPHCM GBWE)091042 (frozen human serum) Kinetic spectrophotometry IFCC RMP (37°C) S-Aspartate aminotransferase Kinetic spectrophotometry IFCC RMP (37°C)	By IFCC primary RMP at 37°C Procedurally defined	267.0 U/L 148.3 U/L 410.6 U/L 113.3 U/L 331.8 U/L	1.59 1.29 ^j 1.15 ^j 1.11 ^k 1.08 ^k	For use as calibrator or control material – – – –	Available ^b By definition By definition

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Standard MU ($k=1$) ^a (%)	Stated intended use in the CRM certificate of analysis	Commutability information
S-γ-Glutamyl transferase ERM-AD452/IFCC (purified from pig kidney)	By IFCC primary RMP at 37°C	114.1 U/L	1.05	For calibration of lower-order procedures provided they have the same or similar analytical selectivity as the RMP used for the certification	Not available ^b
GPHCM GBW(E)091042 (frozen human serum)	By IFCC primary RMP at 37°C	242.1 U/L	1.65	For use as calibrator or control material	Available ^b
Kinetic spectrophotometry IFCC RMP (37°C)	Procedurally defined	145.7 U/L 178.0 U/L	1.26 ^l 1.25 ^l	– –	By definition
S-Lactate dehydrogenase					
Kinetic spectrophotometry IFCC RMP (37°C)	Procedurally defined	185.2 U/L 250.0 U/L	1.15 ^m 1.15 ^m	– –	By definition
S-Total protein					
Biuret spectrophotometry	By calibration with NIST SRM 927e (bovine serum albumin, 7% solution)	53.3 g/L 53.8 g/L	1.22 ^l 1.21 ^l	– –	By definition
S-Immunoglobulin G					
EU-JRC ERM-DA470k/IFCC (lyophilized human serum)	To US National Reference Preparation no. 12-0575C through ERM-DA470	9.17 g/L	0.98	For the calibration of immunoassay-based IVD devices or control products for serum immunoglobulin G	Not available ^b
S-Immunoglobulin A					
EU-JRC ERM-DA470k/IFCC (lyophilized human serum)	To US National Reference Preparation no. 12-0575C through ERM-DA470	1.80 g/L	1.39	For the calibration of immunoassay-based IVD devices or control products for serum immunoglobulin A	Not available ^b
S-Immunoglobulin M					
EU-JRC ERM-DA470k/IFCC (lyophilized human serum)	To US National Reference Preparation no. 12-0575C through ERM-DA470	0.723 g/L	1.87	For the calibration of immunoassay-based IVD devices or control products for serum immunoglobulin M	Not available ^b

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Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Standard MU ($k=1$) ^a (%)	Stated intended use in the CRM certificate of analysis	Commutability information
P-Magnesium EU-JRC BCR-304 (lyophilized human serum)	By atomic absorption spectrometry (6 labs), ICP-MS (2 labs), ICP-OES (1 lab), and ID/MS (1 lab), calibrated with NIST SRM 929 magnesium gluconate dihydrate	1.85 mmol/L	0.81	For use as calibration material and as quality control standard for the evaluation of routine methods	Not available ^b
NIM CRM GBW09124 (frozen human serum)	By ICP-MS calibrated with the NIM GBW(E)080126 high-purity magnesium	1.160 mmol/L	1.45	For calibration and validation of procedures in clinical analyses	Not available ^b
NIM CRM GBW09125 (frozen human serum)		0.857 mmol/L	1.47		
NIM CRM GBW09126 (frozen human serum)		0.693 mmol/L	1.52		
Ion chromatography	By calibration with high-purity magnesium gluconate dihydrate	1.205 mmol/L	0.62 ⁿ	–	By definition
Atomic absorption spectrophotometry	By calibration with high-purity magnesium gluconate dihydrate	1.599 mmol/L	0.53 ⁿ	–	By definition
ICP-MS	By calibration with high-purity magnesium solution	1.18 mmol/L	0.72 ^o	–	By definition
		1.57 mmol/L	0.70 ^o	–	By definition
		0.970 mmol/L	0.52	–	By definition
ICP-OES	By calibration with high-purity magnesium gluconate dihydrate	1.475 mmol/L	0.51 ^l	–	By definition
		0.954 mmol/L	0.84 ^k	–	By definition
		1.440 mmol/L	0.83 ^k	–	By definition
S-Uric acid HSA HRM-3007A STY-0018-097 level 1 (frozen human serum)	By ID/LC/MS calibrated with the NIST SRM 913b crystalline uric acid	323.4 µmol/L	1.27	For validation of methods or as quality control material	Available ^b
HSA HRM-3007A STY-0018-097 level 2 (frozen human serum)		500.0 µmol/L	1.30		
ID/GC/MS	By calibration with high-purity crystalline uric acid	247.8 µmol/L	0.59 ^c	–	By definition
		397.2 µmol/L	0.50 ^c	–	By definition

Continued

Table 2. (continued)

CRM/RMP	Basis for traceability	Nominal value	Standard MU ($k=1$) ^a (%)	Stated intended use in the CRM certificate of analysis	Commutability information
ID/LC/MS	By calibration with high-purity crystalline uric acid	242.0 µmol/L 400.9 µmol/L	0.64^P 0.70^P	–	By definition
S-Digoxin					
LGC ERM-DA200a (frozen human serum)	By ID/LC/MS calibrated with the ERM-AC200a pure digoxin	2.14 µg/L	3.50	For use in the validation of new methods and monitoring the performance of methods commonly used in clinical laboratories	Not available ^b
LGC ERM-DA201a (frozen human serum)		0.868 µg/L	2.94		
ID/LC/MS	By calibration with high-purity digoxin	0.952 µg/L 2.049 µg/L	1.27^I 1.26^I	–	By definition

LNE, Laboratoire National de Métrologie et d'Essais; ID/GC/MS, isotopic dilution-mass spectrometry coupled to gas chromatography; NIST, National Institute of Standards and Technology; SRM, Standard Reference Material; ID/LC/MS, isotopic dilution-mass spectrometry coupled to liquid chromatography; HDL, high-density lipoprotein; CDC, Centers for Disease Control and Prevention; VLDL, very low-density lipoprotein; Mn, manganese; EU-JRC, European Commission-Joint Research Centre; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; GPHCM, Guangdong Provincial Hospital of Chinese Medicine; U/L, enzymatic activity of a procedurally defined measurand; ICP-MS, inductively coupled plasma-mass spectrometry; ICP-OES, inductively coupled plasma-optical emission spectrometry; NIM, National Institute of Metrology of China; HSA, Health Sciences Authority; LGC, Laboratory of the Government Chemist; RELA, External quality assessment scheme for reference laboratories in laboratory medicine.

^aHigher-order references fulfilling minimum quality APS for MU are in italics, and those fulfilling desirable quality APS are in bold. The others do not fulfill specifications.

^bReviewed for compliance with ISO 15194:2009 standard.

^cFrom RELA 2022, Labcode 1 (15).

^dFrom RELA 2021, Labcode 18 (15).

^eFrom RELA 2022, Labcode 98 (15).

^fFrom RELA 2021, Labcode 30 (15).

^gCDC Lipids Reference Laboratory.

^hReviewed for compliance with ISO 15194:2003 but has not been reviewed against ISO 15194:2009.

ⁱFrom RELA 2022, Labcode 87 (15).

^jFrom RELA 2022, Labcode 6 (15).

^kFrom RELA 2022, Labcode 3 (15).

^lFrom RELA 2022, Labcode 27 (15).

^mFrom RELA 2022, Labcode 138 (15).

ⁿFrom RELA 2021, Labcode 87 (15).

^oFrom RELA 2021, Labcode 25 (15).

^pFrom RELA 2022, Labcode 51 (15).

Table 3. Average standard MU associated with different RMP for serum ions listed in the JCTLM database.

RMP	Sodium (Na), 130 mmol/L	Potassium (K), 5.0 mmol/L	Chloride (Cl), 145 mmol/L	Calcium (Ca), 2.0 mmol/L	Magnesium (Mg), 1.5 mmol/L
Flame emission (Na, K) and atomic absorption spectrophotometry (Ca, Mg)	0.57%	0.84%	–	0.66%	0.70%
Coulometry	–	–	0.75%	–	–
ICP-MS	0.46%	0.44%	0.51%	0.51%	0.51%
ICP-OES	0.75%	0.81%	–	0.76%	0.83%
Ion chromatography	0.19%	0.28%	0.25% ^b	0.23%	0.53%
Minimum allowable standard MU for higher-order references ^a	0.13%	0.98%	0.25%	0.45%	0.72%

Data adapted from the International Federation of Clinical Chemistry and Laboratory Medicine External Quality Assessment Scheme for Reference Laboratories in Laboratory Medicine according to the approach described in (6).
ICP-MS, inductively coupled plasma-mass spectrometry; ICP-OES, inductively coupled plasma-optical emission spectrometry.
^aEstimated as one-third of MAU for clinical samples at the minimum quality level, from (12).
^bPreliminary estimate obtained from (19). Note that this RMP is currently not present in the JCTLM database.

MAU is stringent, to allow enough MU budget for medical laboratories to produce clinically suitable results (12). For 3 measurands (i.e., serum C-reactive protein, immunoglobulin G, and pancreatic amylase), only a CRM from one source is available. Except for pancreatic amylase, for which the pertinent CRM was just recently released (16), evidence exists that this is enough to ensure the needed harmonization of clinical results (17, 18). Finally, for 11 measurands, splitting clinical samples with a reference service performing a RMP provides the only practical option for establishing a calibration hierarchy permitting the fulfillment of MAU for clinical samples. In this latter group of measurands, 2 subgroups can be further distinguished: measurands that have only a RMP available (serum 25-hydroxyvitamin D₃, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, total bilirubin, and blood hemoglobin) and measurands that also have CRMs but for which the potential of fulfilling MAU is higher when a comparison with the available RMP is established for the IVD calibrator alignment (serum alkaline phosphatase, digoxin, high-density lipoprotein cholesterol, magnesium, and potassium).

ALL RMPs ARE NOT CREATED EQUAL

For serum ions (i.e., sodium, potassium, chloride, calcium, magnesium), RMPs based on different analytical principles are available in the JCTLM database, all of which are able to assign values to commercial calibrators that are traceable to the International System (SI) of units and lay the foundations of result equivalence for clinical samples. However, as shown in Table 3, the associated u_{ref} is different among RMPs for the same measurand.

Using the total MU budget as the key concept for managing the analytical quality of laboratory measurements, it is now clear that the u_{ref} produced by different RMPs may significantly influence the MU at the bottom level of the calibration hierarchy associated with clinical results and therefore affect the achievement of MAU, especially if this target is tight as for serum ions where circulating concentrations are under strict homeostatic control (10–12). Ion chromatography appears to be the RMP approach, which has the lowest impact in terms of MU for implementation of traceability of an IVD-MD (19, 20). By using this RMP approach in the ion value-assigning process for IVD calibrators, the combined MU of clinical samples can be more realistically reduced to values close to the proposed MAU, in particular for ions such as sodium and chloride for which reaching MAU is otherwise difficult if not impossible (12, 21). In this regard, it should be noted that a RMP based on the ion chromatography principle is currently not available in the JCTLM database for serum chloride, and developing and nominating this type of RMP for chloride may represent a target for the work of developers of RMPs and for providers of reference measurement services.

REDUCING AS MUCH AS POSSIBLE MU ALONG THE ENTIRE CALIBRATION HIERARCHY SHOULD BE A PRIMARY GOAL

If assessing the suitability of u_{ref} according to MAU is one of the requirements for characterizing higher-order references, the proposed one-third fraction of MAU assigned to u_{ref} is intended as a suggestion that may be modified depending on the situation. In general, u_{ref} should be set in the context of the downstream

Table 4. Examples of measurands for which accurate alternate allocations of MU sources in the calibration hierarchy may permit reaching the goal of MAU, even if the standard MU of the higher-order reference (u_{ref}) listed in the JCTLM database exceeds the one-third MAU goal.

Measurand	Minimum MAU on clinical samples (%)	u_{ref} (%)	Fraction of MAU used by u_{ref} (%)	Remaining MU margin in the calibration hierarchy to fulfill MAU ^a (%)
S-Total protein	1.95	1.21	62.0	1.53
S-Immunoglobulin A	3.75	1.39	37.1	3.48
S-Immunoglobulin M	4.43	1.87	42.2	4.02

^aMargin calculated as $(MAU^2 - u_{ref}^2)^{1/2}$.

traceability chain and related MU. Accordingly, IVD manufacturers may allocate the MU budget into various parts, as appropriate, to the selected hierarchy as long as the final combined MU does not exceed MAU as required to achieve fit-for-purpose performance at the level of clinical samples. Therefore, it is necessary to accurately define all of the MU contributions and to determine how much of the total MU budget can be used across the different steps of the calibration hierarchy (22). In the evaluated group of measurands, there are at least 3 examples (i.e., serum total protein, immunoglobulin A, and M) in which alternate allocations of MU in the calibration hierarchy could allow the goal of MAU to be reached, even if the u_{ref} formally exceeds the one-third MAU goal (Table 4). A previous study involving all marketed IVD-MDs for immunoglobulin A measurements experimentally confirmed this possibility, providing that a calibration bias was appropriately removed (23).

THE CASE OF SERUM ALBUMIN

In our evaluation, in addition to serum sodium and chloride, serum albumin represents the only measurand among those studied for which a significant reduction of u_{ref} is certainly needed. Although this measurand has indisputable clinical value, it is perplexing to note the lack of harmonization and the large MU in its measurements shown in well-conducted studies (14, 24–26). The situation is worsened further by the lack of analytical selectivity of chromogenic methods, which are unfortunately still employed by the great majority of medical laboratories worldwide (27). Accordingly, the approach needed for the implementation of metrological traceability to the SI for this essential protein should probably be completely redesigned, starting with the reduction of u_{ref} to the levels recommended in Table 1 by employing alternative methods for CRM characterization (24). For instance, using a better-characterized albumin reference preparation at the top of the traceability chain for calibrating RMP together with a performance improvement of RMP used to assign

values and MU to the secondary CRM could work as an effective alternative. Reducing u_{ref} will, however, not solve the issue of method selectivity.

FURTHER HIGHLIGHTS AND GAP ANALYSIS

Despite the first description of commutability 50 years ago (28), for many years the concept, although pivotal in the correct implementation of metrological traceability, was poorly understood and appreciated. Publications dealing with this aspect started to exceed 20 per year only in 2012 (29, 30). This relatively recent awareness of the importance of commutability is mirrored in the approach to evaluation of JCTLM nominations, where the requirements for demonstrating commutability of CRMs intended to be used as common calibrators of IVD-MDs have markedly evolved between 2002 and 2010 in accordance with the use of the 2 versions of the ISO 15194 standard for the CRM assessment (5, 6). Accordingly, all the CRMs listed before 2010 have (with very few exceptions) not been assessed for commutability (for specific information, refer to Table 2 in this paper and Table 2 in ref. 6), and this should be considered by potential users as they must assess commutability before using those CRMs as trueness-transferring calibrators. To create awareness about the limitations of the oldest matrix-based CRMs for value-assigning calibrators of IVD-MDs, the specific edition of the ISO 15194 standard used in the JCTLM review process is clearly indicated in the JCTLM listing of CRMs.

We also noted that the measurand definition (an essential element of a comprehensive reference measurement system) can still be a confusing issue in the JCTLM database, even for some common biochemical tests. While the glycosylated hemoglobin definitions according to the International Federation of Clinical Chemistry and Laboratory Medicine system [i.e., molecules of hemoglobin having a hexapeptide in common, which is the stable adduct of glucose to the N-terminal valine of the hemoglobin β -chain (β N1-deoxyfructosyl-hemoglobin)] and the National Glycohemoglobin Standardization Program

system (i.e., area under the curve of the chromatographic peak) are well described, the same was not observed for “serum triglycerides.” After an analysis of the JCTLM database, 3 types of listed triglyceride-related RMPs with selectivity for different measurands were retrieved: (a) total glycerol, (b) total glycerides, and (c) triglycerides only (Supplemental Table). Therefore, there was a need to modify the definition of available entries in the JCTLM database to improve the clarity and consistency of the information. In particular, we believe that “total glycerol,” as the sum of triglycerides, diglycerides, monoglycerides, and free glycerol in serum is the measurand definition that mirrors the analytical selectivity of the majority, if not all, of marketed IVD-MDs. Using the total glycerol RMPs as higher-order references, therefore, assures the practicality of traceability of IVD-MDs to SI through a whole reference measurement system.

From data obtained in our evaluation, we can also provide a gap analysis by highlighting what remains missing in the JCTLM database. This information provides possible targets for CRM producers, RMP developers, and providers of reference measurement services, helping them to prioritize their activities on gaps. In particular, our analysis showed that suitable commutable matrix CRMs to be used as common calibrators of IVD-MDs are still lacking for clinically important measurands, such as blood hemoglobin, the 2 aminotransferases, lactate dehydrogenase, total protein, total bilirubin, and 25-hydroxyvitamin D₃. For some of these, a CRM nomination can be expected in one of the next JCTLM review cycles (31–33). Comparison studies with RMP are often the only way to suitably implement metrological traceability, although the availability of proper CRMs would be desirable as they would be less expensive and of more practical use. Nominations of RMPs with better performance in terms of u_{ref} , such as ion chromatography for serum chloride, would also be welcome.

Conclusion

The TF-RMSI study was planned to answer the question “How many, among 30 common biochemical measurands, have sufficient entries in the JCTLM database to permit the practical implementation of metrological traceability according to the ISO 17511:2020 requirements, including the fulfillment of ‘fit-for-purpose’ MAU?” Our analysis shows that, with the exception of 2 measurands (serum albumin and chloride) for which further improvements in u_{ref} would be necessary, for the remaining 28 measurands conditions exist to correctly implement metrological traceability to SI and fulfill at least the minimum MAU. Although use of the JCTLM database is not mandated by any regulatory body and can be sometimes incomplete, we show for

the first time the important practical impact and the value added by the information provided by JCTLM. In an editorial written in 2010, the steps of the process and different responsibilities for implementing metrological traceability of patient results and defining their MU were described (34). In these steps, the JCTLM was considered to be the voice of the laboratory profession responsible for defining analytical objectives represented by the description of reference measurement systems (traceability chain) and associated clinically acceptable MAU. In this paper, we believe we have demonstrated that JCTLM has largely fulfilled this role for the measurands included in this study, and it is now the responsibility of other stakeholders, above all IVD manufacturers, to implement IVD-MDs using the information available. Founding global organizations, such as the International Federation of Clinical Chemistry and Laboratory Medicine, with their distinct role as drivers of standardization of prioritized medical tests, retain also a key role in the adoption and implementation of metrological traceability/MAU concepts.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: JCTLM, Joint Committee on Traceability in Laboratory Medicine; CRM, certified reference material; RMP, reference measurement procedure; ISO, International Organization for Standardization; IVD, in vitro diagnostic; MU, measurement uncertainty; IVD-MD, in vitro diagnostic medical device; TF-RMSI, Task Force on Reference Measurement System Implementation; APS, analytical performance specification; MAU, maximum allowable measurement uncertainty; SI, International System.

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