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The JCTLM Task Force on Reference Measurement System Implementation: mission and first results

Mauro Panteghini
TF-RMSI Chair

Premise

- IVD manufacturers usually provide only a short description of how metrological traceability was established for their commercially available measuring systems
- However, ISO 17511:2020 requires appropriate documentation of the implementation steps for the calibration hierarchy as well as documentation of how metrological traceability to higher-order references was verified

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Identify and describe available reference measurement systems and **complete traceability chains, based on the information present in JCTLM database**

Illustrate the **propagation of measurement uncertainty** through the entire calibration hierarchy

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Use **analytical performance specifications derived according to an internationally recommended model** to judge whether reference system components are fit for purpose

Identify those **measurands for which further advancements** to existing reference systems **are needed or where some components of the reference system are lacking [gap analysis]**

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TF-RMSI at a glance

- Give to IVD manufacturers clarifications and recommendations for selecting the optimal approach for correctly implementing traceability and identifying areas for improvement.
- Be a stimulus for higher-order reference providers for improving the suitability of their products, if needed, and to assist with prioritizing future efforts.
- Help lab professionals in defining the quality of their results.

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TF-RMSI Membership

Ref4U GHENT UNIVERSITY

National Center for Clinical Laboratories

NIST National Institute of Standards and Technology U.S. Department of Commerce

LABORATOIRE NATIONAL DE MÉTROLOGIE ET D'ESSAIS LNE

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

Clin Chem Lab Med 2020; 58(8): 1200–1204 DE GRUYTER

Opinion Paper

Mauro Panteghini and Federica Braga*

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

↓

TF-RMSI procedural indications

Using serum creatinine as a case study, a preliminary exercise was carried out by employing an approach combining:

a) a critical review of what is available in the JCTLM database with
b) a comparison of this information against derived APS for MU

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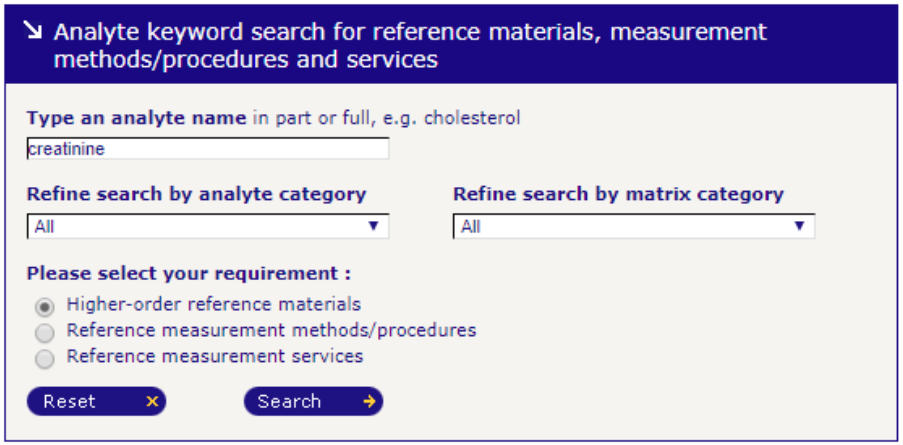
1) SELECTED MEASURAND: DATA EXTRACTION FROM THE JCTLM DATABASE
Available reference materials & reference measurement procedures



https://www.bipm.org/jctlm/

<u>Purified reference materials</u>:

1. **XXX** (Certified XXX Mass Fract.: 99.7±0.3%)
2. **YYY** (Certified YYY Mass Fract.: 0.999 kg/kg ±0.2%)

<u>Secondary (matrix) reference materials</u>:

1. **AAA** (lyophilized human serum)
2. **BBB** (frozen human serum)
3. **CCC** (frozen human serum, 3 levels)

<u>Reference measurement procedures</u>:

1. **ABC**
2. **DEF**

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2A) DESCRIBE THE REFERENCE MEASUREMENT SYSTEM TO WHICH EACH RECRUITED HIGHER-ORDER CRM BELONGS [with a focus on the certified values and their associated uncertainty]

EXAMPLE

NIST SRM 914a

High-purity crystalline creatinine
Mass Fraction: 99.7% ± 0.3%

↘

GC-IDMS + HPLC

↙

- **BCR-573**

Lyophilized human serum
Nominal value: 68.7 µmol/L
Combined u: 0.7 µmol/L (1.02%)

- **BCR-574**

Lyophilized human serum
Nominal value: 105.0 µmol/L
Combined u: 0.65 µmol/L (0.62%)

- **BCR-575**

Lyophilized human serum
Nominal value: 404.1 µmol/L
Combined u: 3.55 µmol/L (0.88%)

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2B) DESCRIBE THE REFERENCE MEASUREMENT SYSTEM TO WHICH THE RECRUITED HIGHER-ORDER RMP BELONGS [including associated uncertainty]

High-purity crystalline creatinine

↘ ID-LC-MS
[reference laboratory]

↓

Nominal value: 152.1 µmol/L
Combined u: 1.25 µmol/L (0.82%)

Nominal value: 350.5 µmol/L
Combined u: 1.41 µmol/L (0.40%)

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According to ISO 17511:2020, to transfer trueness from higher-order references to commercial calibrators, IVD manufacturers have 2 possibilities:

a) directly calibrating their internal procedures for calibrator value assignment with a suitable CRM,

b) aligning to an RMP by a comparison study.

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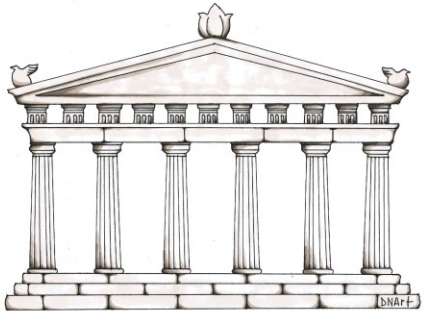
Option a) requires commutable CRM for calibration



Use of a noncommutable CRM to achieve implementation of calibration traceability will cause:

- bias in values assigned to commercial calibrators
- incorrect results for clinical samples and incorrect medical decisions

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3) CHECK THE INTENDED USE OF MATRIX CRMs AS STATED IN THE MATERIALS' CERTIFICATES TO CONFIRM THAT PROVIDERS INTENDED THEM AS HIGHER-ORDER CALIBRATORS FOR IMPLEMENTING IVD MEASURING SYSTEM TRACEABILITY

If the scope of intended use included *use as common calibrators and/or the assessment of trueness of results obtained by field methods*, the CRM's certificate of analysis was examined for information provided regarding commutability.

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Special Reports

Table 1. Information to be included in the documentation of an RM that is commutable for a stated number of MPs.

• Selection criteria for individuals from whom CSs were obtained for the commutability assessment
• Number of CSs used in the commutability assessment and their collection, processing, storage, and distribution conditions
• Description of the experimental design used to assess commutability; state the reference MP if included in the experimental design
• Criteria used to conclude that an RM was commutable with clinical samples
• Summary of the results of the commutability assessment in sufficient detail that the conclusions can be verified; complete experimental results and data analysis must be available to a user on request
• MPs for which commutability was demonstrated, including the specific models of instruments and the part numbers and lot numbers of reagents, calibrators, and calibration confirmation materials

Important remark

- The requirements for demonstrating commutability of CRMs have significantly evolved between the 2002 and 2009 versions of the ISO 15194 standard, which have been used for the JCTLM assessment of CRMs.
- Only when assessing a CRM for compliance with ISO 15194:2009 is a statement explicitly requested about commutability of the CRM with clinical samples for all measurement procedures with which it may be potentially used as a common calibrator for implementing metrological traceability.
- Because of this, the specific edition of the ISO 15194 standard used in the JCTLM review process is clearly indicated in the JCTLM listing of CRMs

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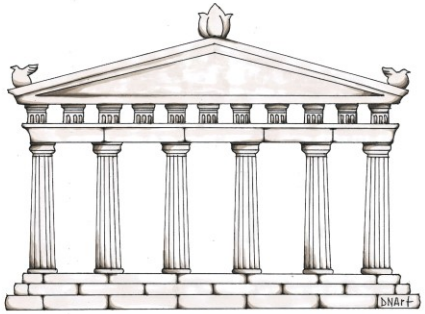
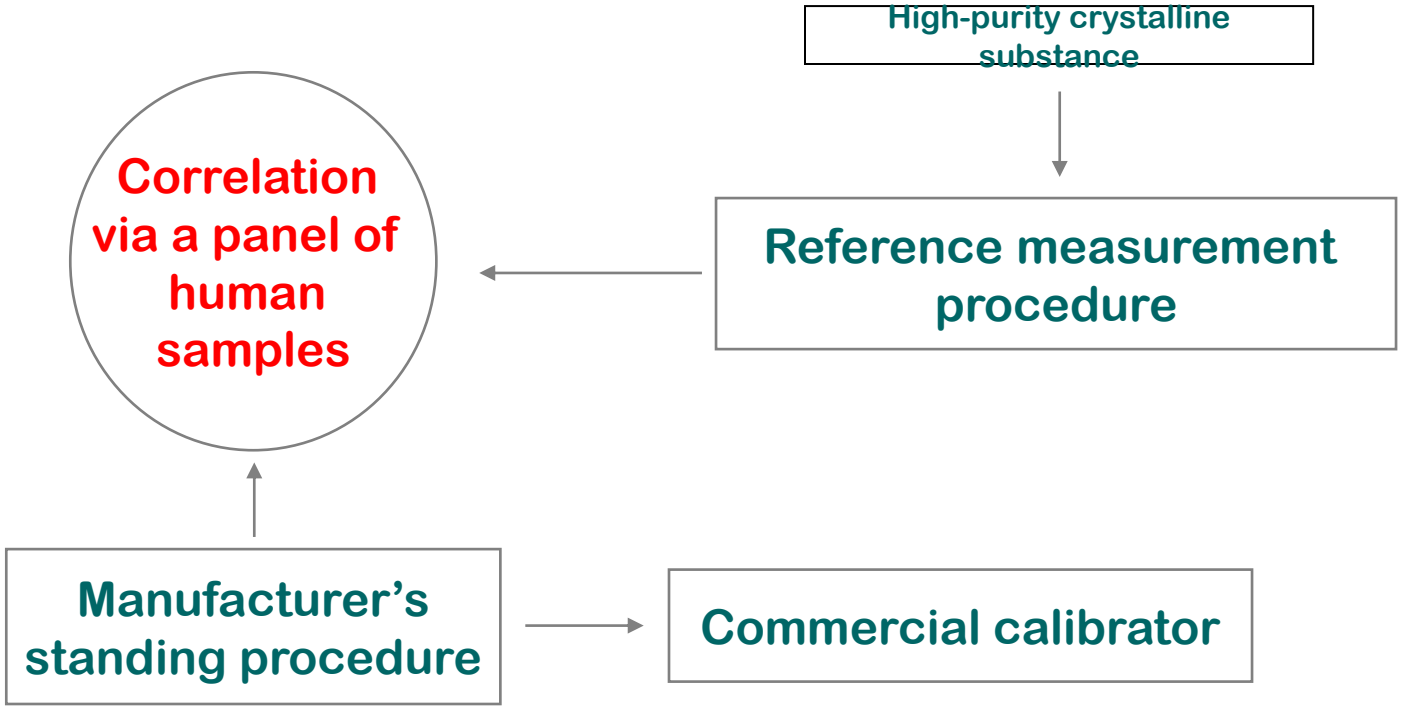
Option b) asks for use of an appropriate panel of clinical samples, whose values are assigned by the RMP, and their resulting MU based on the inherent MU characteristics of the RMP and the specific value transfer protocol employed.





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In our study, the information from the IFCC RELA was used to estimate a mean experimental MU on a given sample characterized as a reference material by an RMP listed in the JCTLM database. As such, the MU of the RELA samples, as reported in the RELA database, was assumed to be representative of the MU of higher-order reference materials in the calibration hierarchy.

High-purity crystalline creatinine

↘

ID-LC-MS
[reference laboratory]

Nominal value: 152.1 µmol/L
Combined u: 1.25 µmol/L (0.82%)*

Nominal value: 350.5 µmol/L
Combined u: 1.41 µmol/L (0.40%)*

*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

Manufacturer's standing procedure

↓

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4) THE MU OF CRM CERTIFIED VALUES AND THE TRUENESS AND REPRODUCIBILITY CHARACTERISTICS OF RMP MEASUREMENTS WERE EXAMINED FOR THEIR POTENTIAL TO BE SMALL ENOUGH TO AVOID SIGNIFICANTLY AFFECTING THE MU OF CLINICAL SAMPLES, WHEN UNCERTAINTIES FROM IVD CALIBRATOR AND END-USER MEASURING SYSTEMS ARE COMBINED AND COMPARED TO APS FOR TOTAL MU BUDGET DERIVED ACCORDING TO INTERNATIONALLY RECOMMENDED MODELS.

Model 1: Based on the effect of analytical performance on clinical outcomes a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcomes; b. Done by indirect outcome studies – investigating the impact of analytical performance of the test on clinical classifications or decisions and thereby on the probability of patient outcomes, e.g., by simulation or decision analysis.
Model 2: Based on components of biological variation of the measurand.
Model 3: Based on state of the art of the measurement (i.e., the highest level of analytical performance technically achievable).

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DE GRUYTER Clin Chem Lab Med 2017; 55(2): 189–194

Opinion Paper

Ferruccio Ceriotti*, Pilar Fernandez-Calle, George G. Klee, Gunnar Nordin, Sverre Sandberg, Thomas Streichert, Joan-Lluis Vives-Corrons and Mauro Panteghini, on behalf of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications (TFG-DM)

Criteria for assigning laboratory measurands to models for analytical performance specifications defined in the 1st EFLM Strategic Conference

APS model 1: outcome-based → The measurand has a central role in diagnosis and monitoring a specific disease

APS model 2: biological variation → The measurand is under strict metabolic control

APS model 3: state-of-the-art → The measurand has neither central diagnostic role nor sufficient homeostatic control

Grading minimum and desirable levels for APS is also important because it stimulates the IVD community to improve the quality of their products to move, if necessary, from unacceptable or minimum performance to a desirable level.

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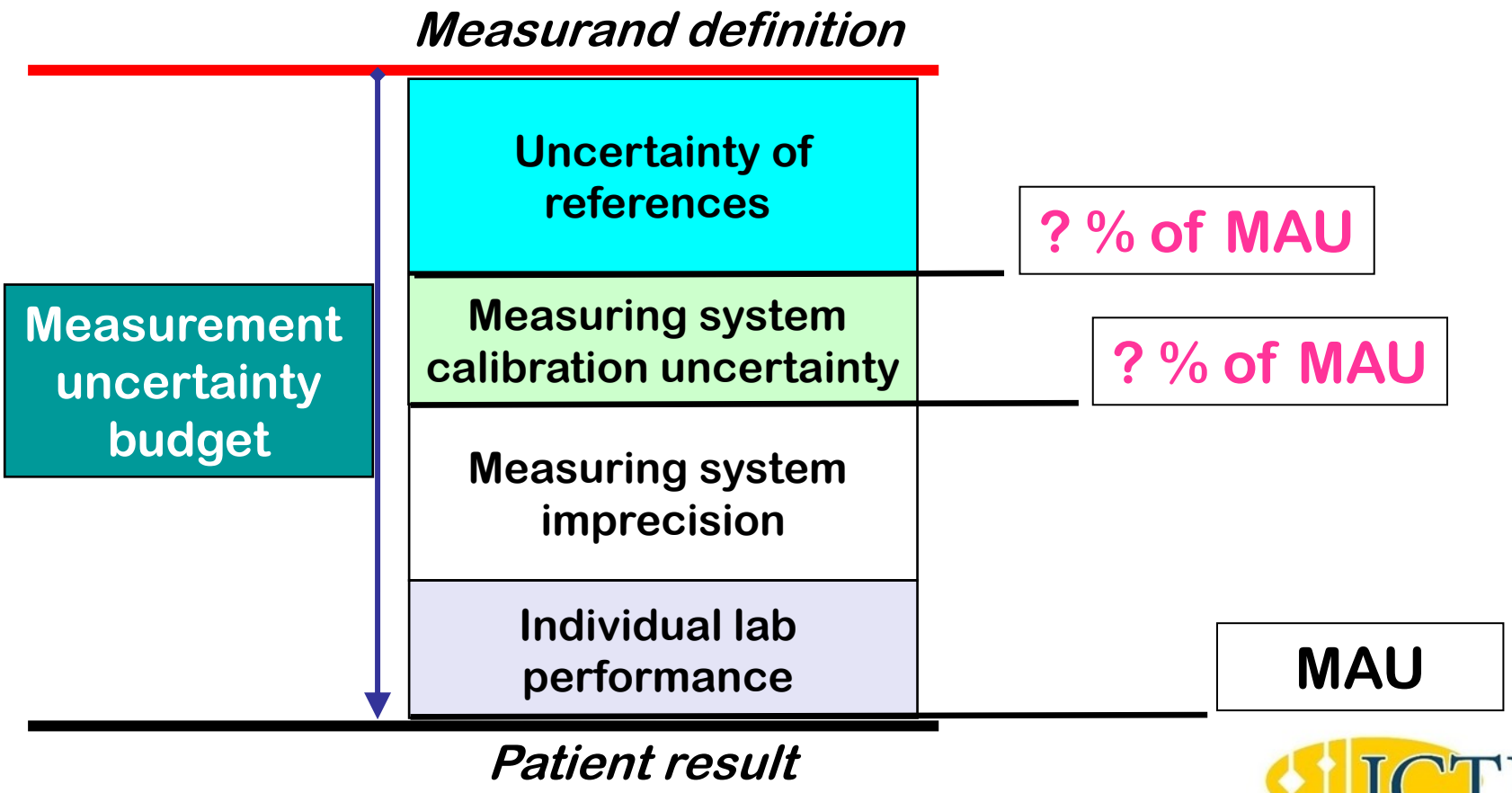
How much of the maximum allowable uncertainty [MAU] should be used across the different steps of metrological traceability chain?



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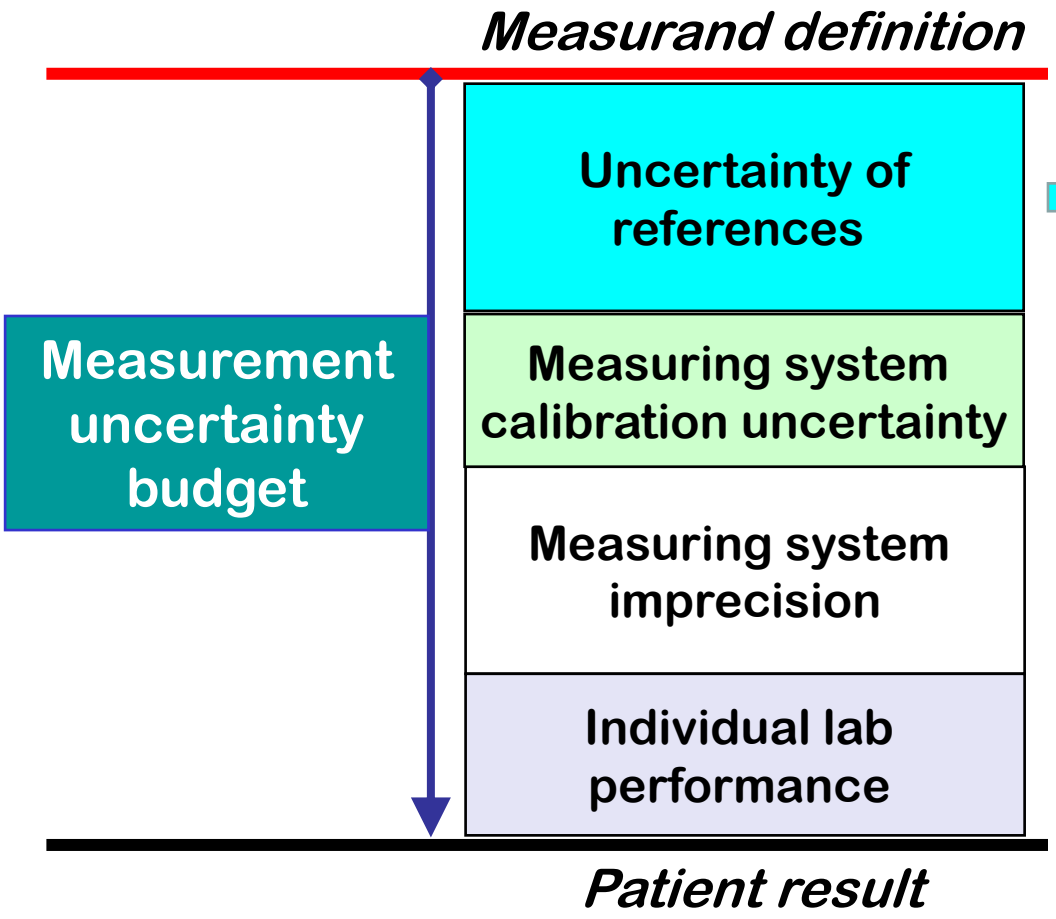
Higher-order reference contribution to the MU budget



Reference provider

Due to propagation of MU in the calibration hierarchy, the uncertainty of the certified value should be significantly lower than recommended performance specifications for routine procedures.

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Turning the problem upside-down: focus first on the APS for field assays

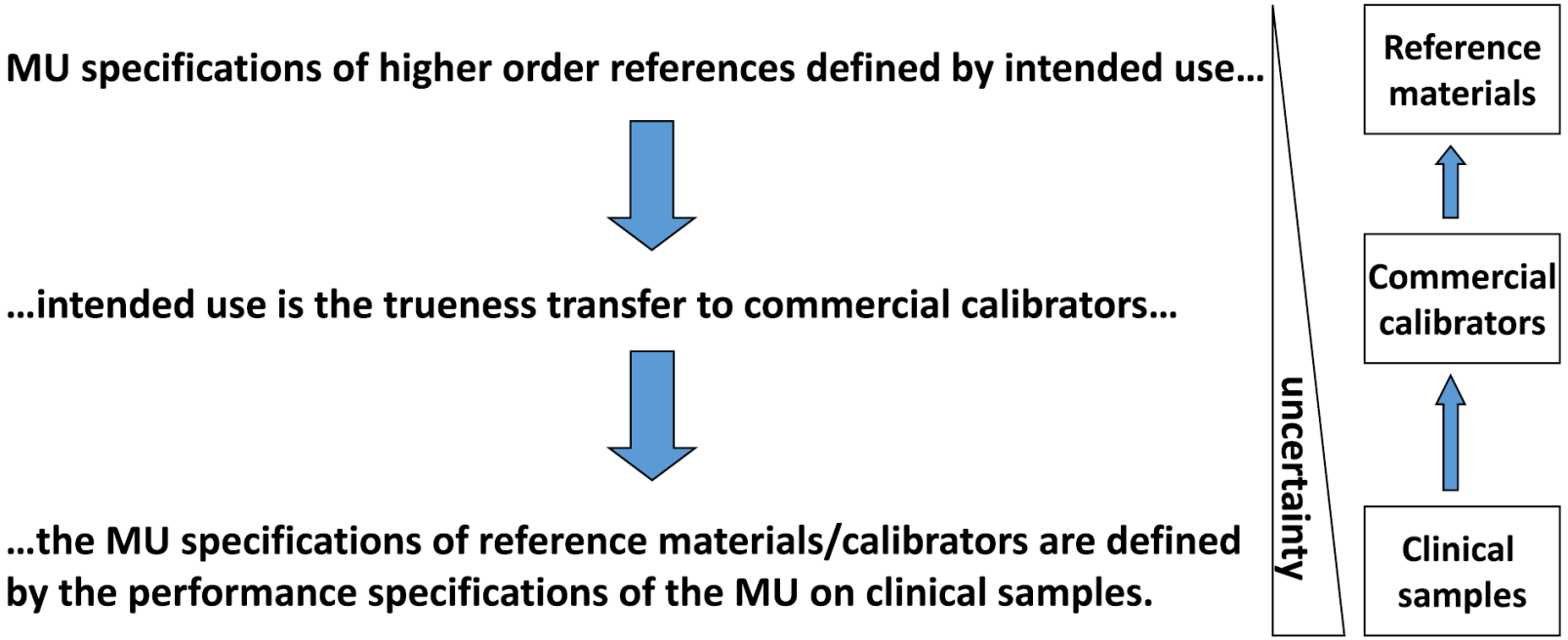
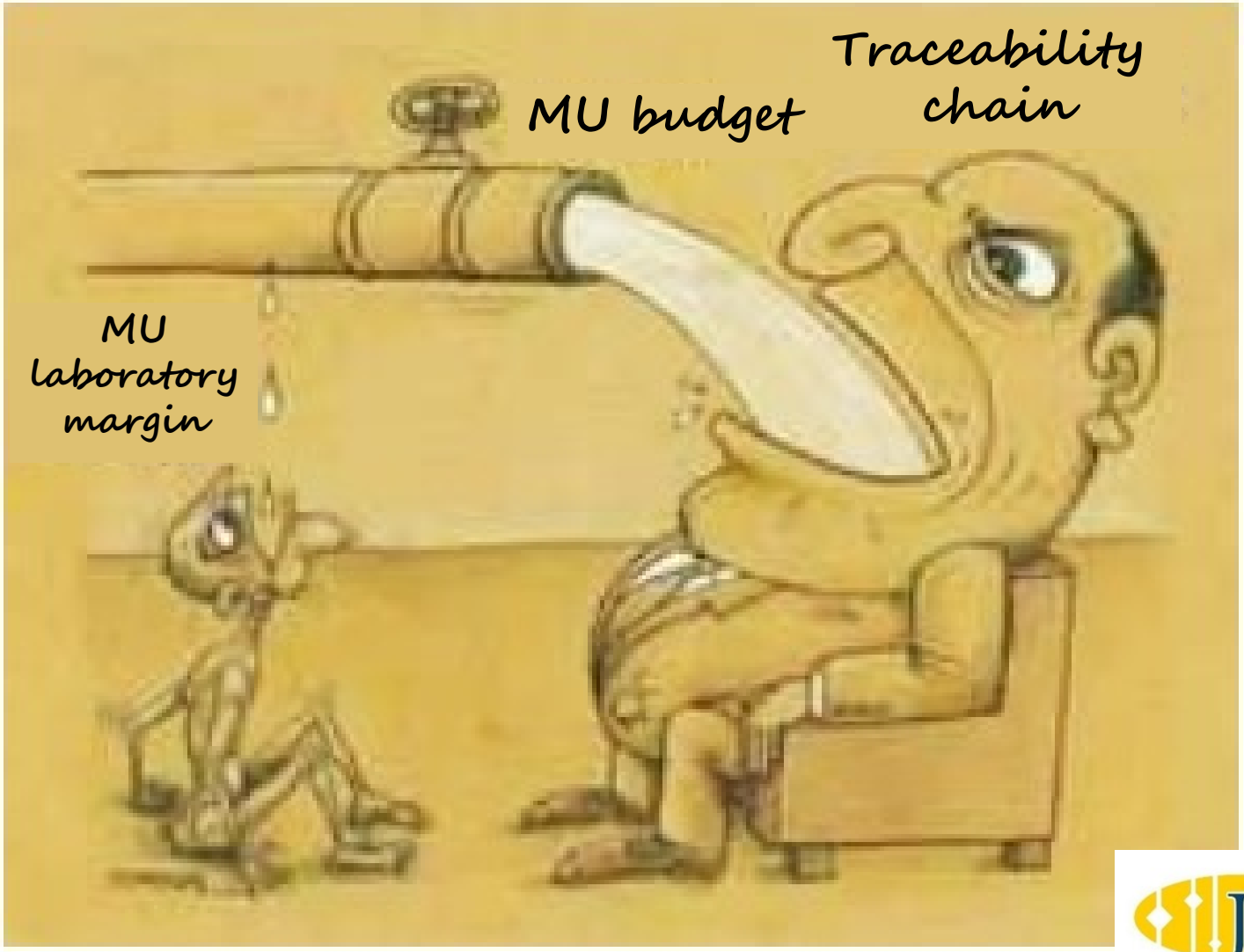


Fig. 3. Defining the suitability of the measurement uncertainty (MU) of higher order references by turning the approach upside down, focusing first on the established performance specifications for MU of clinical samples.

This 'uncertainty budget approach' is useful for identifying measurands for which the MU associated with the higher levels of the calibration hierarchy must be reduced



Adapted from M. Thelen, 10th CIRME International Scientific Meeting – Milan, IT – Nov 2016

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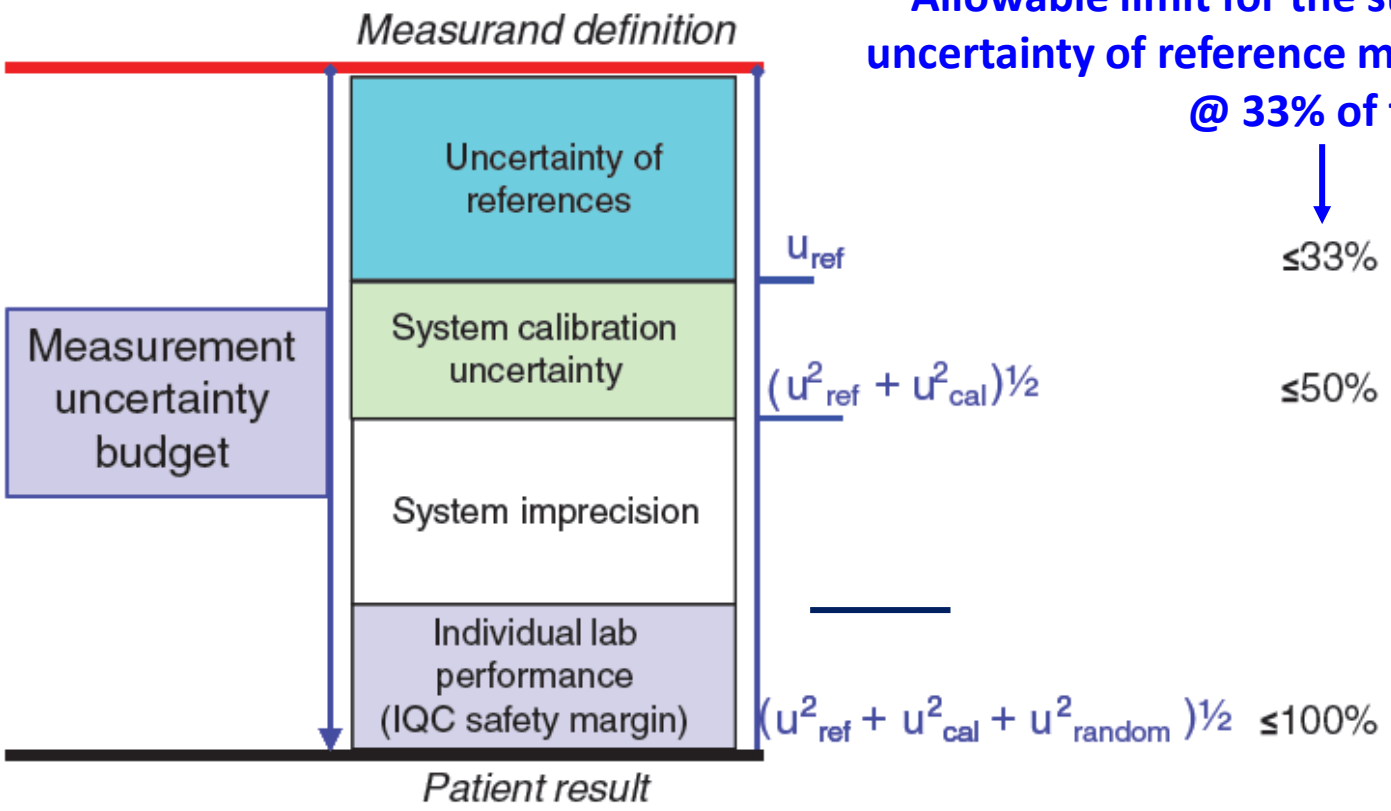
DE GRUYTER Clin Chem Lab Med 2015; 53(6): 905–912

Opinion Paper

Federica Braga*, Ilenia Infusino and Mauro Panteghini

Performance criteria for combined uncertainty budget in the implementation of metrological traceability



Allowable limit for the standard uncertainty of reference materials @ 33% of the APS

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Selection of measurands

- 13 common measurands covered by the JCTLM database selected among:

  1) the most requested tests in a hospital laboratory [Milan];

  2) measurands for which the Consultative Committee for Amount of Substance (CCQM) comparisons were or are planned to be performed;

  3) different biochemistry categories.

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Table 1. Milan model allocation and recommended analytical performance specifications (APS) for standard measurement uncertainty (MU) on clinical samples and at higher-order reference level for the selected measurands.

		APS for standard MU on clinical samples, %[a]		Allowable standard MU for higher-order references, %[b]	
Measurand	APS model	Desirable	Minimum	Desirable	Minimum
B-Total hemoglobin	Outcome-based	2.80	4.20	0.93	1.40
P-Potassium	Biological variation	1.96	2.94	0.65	0.98
P-Sodium	Biological variation	0.27	0.40	0.09	0.13
P-Chloride	Biological variation	0.49	0.74	0.16	0.25
P-Alanine aminotransferase	Biological variation	4.65	6.98	1.55	2.33
P-C-reactive protein	State of the art	3.76	5.64	1.25	1.88
P-Glucose	Outcome-based	2.00	3.00	0.67	1.00
P-Creatinine	Biological variation	2.20	3.30	0.73	1.10
P-Urea	Biological variation	7.05	10.6	2.35	3.53
P-Total calcium	Biological variation	0.91	1.36	0.30	0.45
P-Total bilirubin	Biological variation	10.5	15.7	3.50	5.23
B-HbA_{1c}	Outcome-based	3.00	3.70	1.00	1.23
S-25-hydroxyvitamin D3	Outcome-based	10.0	15.0	3.33	5.00

B, blood; P, plasma; S, serum.
[a]Derived from (33).
[b]Estimated as one-third of APS for standard MU for clinical samples.

A synopsis of higher-order matrixed CRMs and RMPs retrieved from the JCTLM database for the selected measurands, including their main characteristics for implementing metrological traceability and fulfilling APS for suitable MU, is available in:

Clinical Chemistry 67:12
1590–1605 (2021)

Special Report

Optimizing Available Tools for Achieving Result Standardization: Value Added by Joint Committee on Traceability in Laboratory Medicine (JCTLM)

Mauro Panteghini,[a,*] Federica Braga ,[a] Johanna E. Camara,[b] Vincent Delatour,[c] Katleen Van Uytfanghe ,[d] Hubert W. Vesper,[e] and Tianjiao Zhang,[f] for the JCTLM Task Force on Reference Measurement System Implementation

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Summary of results (I)

Traceability to the highest metrological levels can be established by IVD manufacturers within the defined APS for most measurands:

1. Glucose ☺
2. Creatinine ☺
3. Total hemoglobin (RMP) ☺
4. ALT (RMP) ☺
5. Urea (RMP) ☺
6. Total bilirubin (RMP) ☺
7. HbA1c (RMP) ☺
8. 25(OH)D3 (RMP) ☺
9. Potassium (RMP) ☺

For the majority of the listed measurands, splitting clinical samples with a laboratory performing a reference service provides however the sole practical option for establishing a calibration hierarchy that fulfils the desirable APS for the total MU budget on clinical samples.

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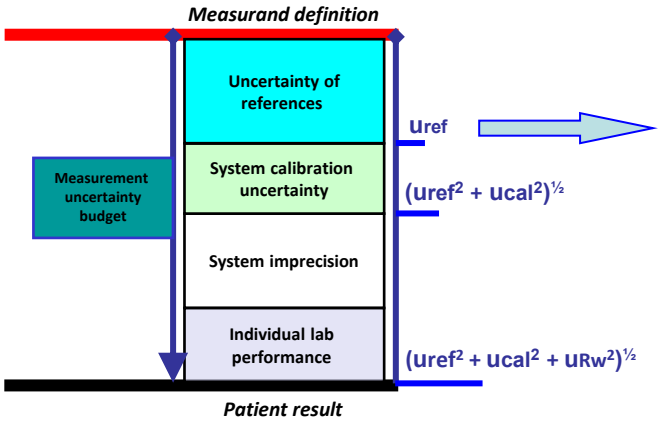
Summary of results (II)

- When different options are available in making a choice, IVD manufacturers should consider the suitability of higher-order references in terms of MU by selecting ones with less impact on the total MU budget.

EXAMPLE



Traceability chain X = 0.73% vs. chain Y = 1.63%

Glucose uncertainty

3.0% minimum

2.0% desirable

The quality of glucose measurement may be dependent on the type of traceability chain selected for trueness transferring, sometimes making more difficult to achieve the desirable limits for MU on clinical samples

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Summary of results (III)

- **Serum sodium and calcium** are similar showing that **traceability** of an IVD measuring system **to ion chromatography** is the only approach giving a realistic possibility to fulfil the APS for the total MU budget.

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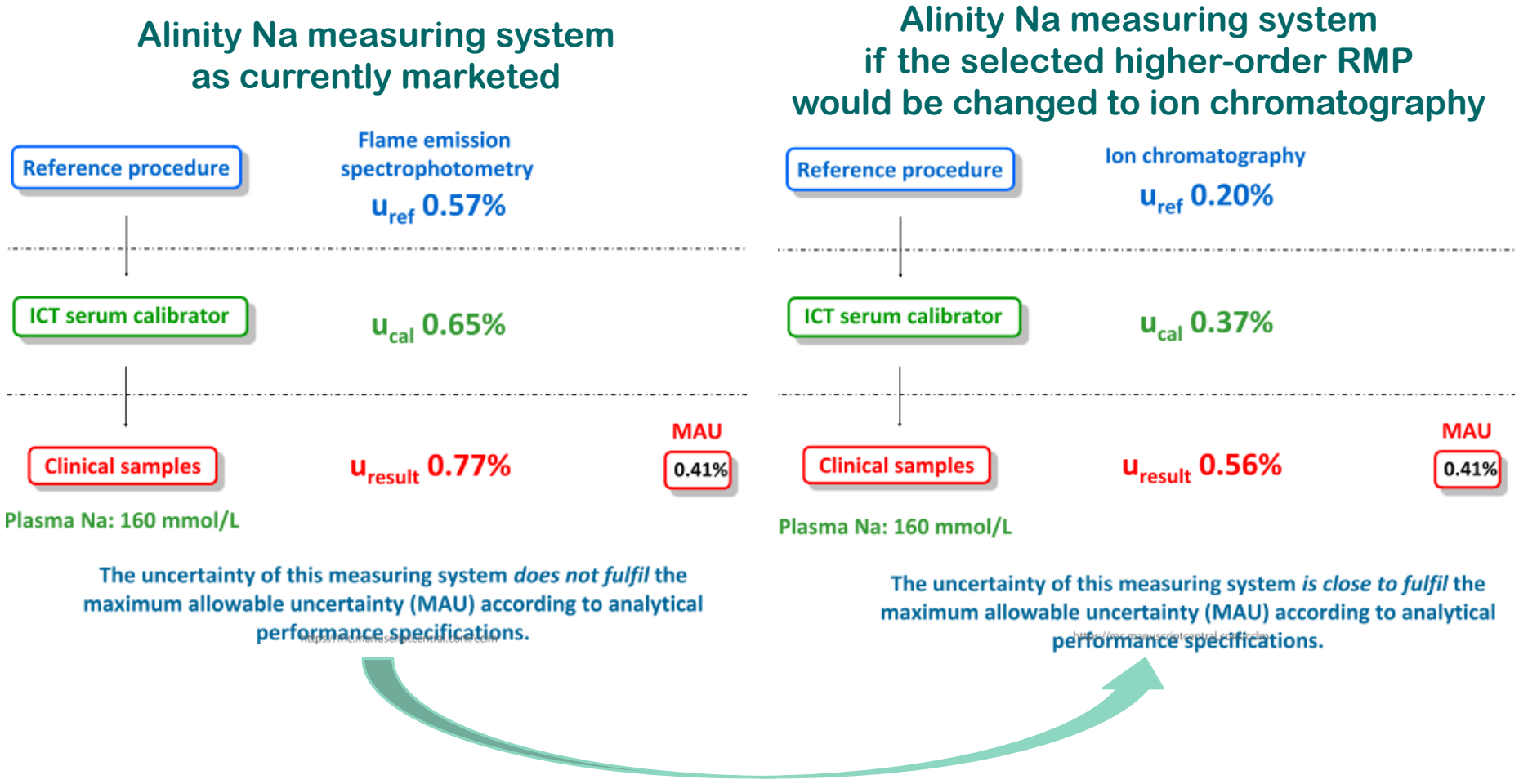
“By replacing flame emission spectrophotometry with ion chromatography in the Na value-assigning process of Abbott calibrators, u_{result} on Alinity measuring system could be improved from about 0.80% to 0.55%.”



Pasqualetti S et al, Clin Chem Lab Med 2021;59:e129

IVD manufacturers should not only direct their efforts on improving instrument performance but operate to reduce as much as possible u_{ref} and consequently u_{cal}, especially when APS are stringent.

P-Chloride

Secondary RM/RMP	Basis for traceability	Nominal value	Combined standard uncertainty
NIM CRM GBW09124 (frozen human serum)	By ICP-MS + ion chromatography* calibrated with NIM GBW(E)080268	100.8 mmol/L	1.23%
NIM CRM GBW09125 (frozen human serum)		112.8 mmol/L	1.30%
NIM CRM GBW09126 (frozen human serum)		126.0 mmol/L	1.12%
Coulometry	By calibration with high purity crystalline sodium chloride	118.6 mmol/L	0.75%
		143.4 mmol/L	0.75%
ICP-MS	By calibration with high purity crystalline sodium chloride	119.5 mmol/L	0.50%
		146.2 mmol/L	0.51%

* Not listed in the JCTLM database as higher-order RMP.

MAU on clinical samples	
Desirable	Minimum
0.49%	0.74%

The MU of the current IVD measuring systems has almost **no possibility to fulfil APS** for the total MU budget on clinical samples, regardless of the higher-order reference selected.

To this regard, it would be interesting to determine whether the use of a **RMP based on the ion chromatography principle** may improve the associated MU and permit the MU for chloride to get close to the APS as already observed for other plasma/serum ions.

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Gap analysis: finding what is still not in the JCTLM database

- Possible targets for
  - Producers of CRMs
  - Developers of RMPs
  - Providers of reference measurement services
- Matrix CRMs for:
  - Total hemoglobin
  - ALT
  - Urea
  - Bilirubin (even purified RM)
  - 25(OH)D3 commutable for immunoassays (even purified RM)
- RMP for:
  - Chloride (Ion chromatography)

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Measurand
Serum total cholesterol
Serum albumin
Serum HDL cholesterol
Serum triglycerides
Serum alkaline phosphatase
Serum aspartate aminotransferase
Serum creatine kinase
Serum γ-glutamyltransferase
Serum lactate dehydrogenase
Serum pancreatic amylase
Serum total proteins
Serum immunoglobulin G
Serum immunoglobulin A
Serum immunoglobulin M
Serum prostate-specific antigen
Serum magnesium
Serum urate
Serum digoxin

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