

Editorial

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The development of reference measurement procedures to establish metrological traceability

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Standardisation is the pinnacle of analytical measurement in laboratory medicine, facilitating comparability of patient results over time. The important goal of achieving comparability (via standardisation or harmonisation) for pathology tests has become essential in the twenty first century as we rapidly advance the electronic sharing of data from electronic health records, cloud technology, and mobile devices offered by multiple providers. The outcome is more integrated and personalised healthcare, while the risk of inaction is the clinical misinterpretation of results. Therefore, initiatives to contribute to standardisation across a broader set of clinical measurands to promote agreement are important for laboratory medicine.

In this special issue of *Clinical Chemistry and Laboratory Medicine* a collation of six methodology papers describing developed candidate reference measurement procedures (RMP)s (and also one opinion paper) are presented for publication [1–7]. The papers reported in this issue are all from Roche Diagnostics. We congratulate Roche on this initiative to address the need for a greater number of Systeme International (SI)-traceable RMPs for small molecules. The papers present single analyte isotope dilution mass spectrometry (ID-LC-MS/MS) methods for the quantification of aldosterone, lamotrigine, gabapentin, methotrexate, levetiracetam and topiramate, in human serum and plasma. Often, from a workflow and green perspective, an ideal situation would be to have multianalyte methods available [8]. However, these methods are presumably designed for use within Roche to allow the authors to claim traceability

to SI, in line with ISO 15193:2009, and as such they are fit for their intended purpose [9].

A critical factor in achieving SI-traceability is the availability of appropriate pure organic calibration materials with SI-traceable assigned purity values. The papers in this special issue utilise the technique of quantitative nuclear magnetic resonance (qNMR) spectroscopy to value assign commercial pure materials in order to provide SI-traceable calibrants for the traceability chains for each measurand. It is pleasing to see the application of this technique, as it can potentially provide SI-traceable values when appropriately applied. In the technique of qNMR, the internal standard is actually the calibrant and its SI traceability is critical. The importance of the internal standard in this role is not always explicitly acknowledged in the publications. qNMR can also produce biased purity value estimates when each application of qNMR is not carefully assessed. For the qNMR methods used to assign the calibrants in the candidate RMPs, a single resonance and set of conditions is provided to support the measurement uncertainties associated with the determined purity values. The claimed uncertainty values are equivalent to world best practice, which would typically require rigorous validation of the qNMR approach. We refer the reader to recent literature on the application of qNMR in a metrological manner that describes its best practice application [10–12].

The measurement uncertainties associated with RMPs are important with respect to ensuring they are appropriately assessed and fit for clinical purpose [13]. ISO 15193:2009 section 4.16 quotes “systematic assessment of factors influencing the result” [9] and the rigour of this helps to define a good RMP that will be robust and effective [14]. The aim is to eliminate biases [9] and whilst it can be suggested that the bias associated with a measurement procedure can be nil [3], in practice this is difficult to achieve and the sole assessment of the bias associated with the reference material (RM) may be insufficient. Additional components of the RMP would typically be assessed to encompass all possible bias factors. Such assessments of bias estimates should be included (or corrected for) in uncertainty budgets.

The robustness of methods to minimise interference is another important factor for methods to be truly assessed as

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RMPs. Assessment vs. orthogonal methods or via the adjustment of aspects within the RMP can provide invaluable information on otherwise unseen affects. In the case of the aldosterone measurement presented, the authors utilised the technique of heart-cutting 2D-LC-MS/MS, which is an excellent approach likely to minimise interferences [1]. The use of this technique is important to support the robustness of the aldosterone method as there are isomeric steroids (cortisone and prednisolone) that share a molar mass of approximately 360.2 g/mol. Other approaches presented in the candidate RMPs to determine method robustness included an assessment of method performance against matrix CRMs and associated RELA materials.

This issue also includes an opinion paper describing the general establishment of metrological traceability for small molecule measurands in laboratory medicine [6]. The manuscript describes aspects of traceability and approaches to standardisation and harmonisation. These concepts are important and outlining them in conjunction with the candidate reference measurement papers is useful. The opinion paper discusses the role of National Metrology Institutes (NMIs) ideally leading in providing relevant standards to establish traceability to SI and RMPs. However, due to the number of measurands within the chemical field, other parties also contribute to developments. In this case, Roche has taken on the initiative of assigning SI-traceable values to pure calibrators and developing associated RMPs for their specific needs.

The importance of publishing these methods is to demonstrate current approaches in working to achieve the development of candidate RMPs that may be appropriate for Joint Committee for Traceability in Laboratory Medicine (JCTLM) submission.¹ Each paper has undergone peer review for publication, but this does not guarantee that the manuscripts have met all of the requirements of ISO 15193:2009, which will be ascertained in the next step [9]; this being the submission to the JCTLM for consideration of formalising these methods as RMPs [15]. To do this, the authors will need to collate their method validation documents,

submit the published manuscript, and complete a checklist against the requirements of ISO 15193:2009 for each submission. These papers will then undergo a subsequent independent review process, which is important for transparency and robustness of proposed RMPs. As we move into cycle 20 of the JCTLM review process in 2023, there are currently 285 RM, 217 RMP and 247 RMS listed in the database [15]. With the acceptance of these candidate RMPs, the authors and Roche will make a significant contribution to supporting standardisation in laboratory medicine for the benefit of patient care.

In conclusion, we congratulate the authors on preparing these papers in order to progress them to JCTLM listed RMPs. These RMPs will help with alignment for clinical decisions related to these measurands and thus will also assist with effective therapeutic interventions. This is an important goal of the clinical community.

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¹ The JCTLM database was formed in 2002 as an initiative of the International Bureau of Weights and Measures (BIPM), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), and the International Laboratory Accreditation Cooperation (ILAC) to create a reference. When these services are applied following the models described in ISO 17511:2020, 'In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples' they can be used to establish metrological traceability and standardisation may be achieved.

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