European Partnership on Metrology
Call 2023 –Fundamental Metrology, Industry, Normative and Research Potential

Selected Research Topic number: **SRT-i19**
Version: 1.0

Title: Manufacturing of commutable calibrators and quality control materials for standardisation and post-market surveillance of IVD tests

Abstract

A key challenge for the in vitro diagnostic industry posed by the new regulation EU/2017/746 is that the metrological traceability of calibrators or control materials shall be assured through suitable reference measurement procedures and/or reference materials of a higher metrological order. This project aims to address the lack of commutable materials in Laboratory Medicine and to support post-market surveillance of IVD tests by establishing a European Metrology infrastructure working in close cooperation with EQA (External Quality Assessment) providers. This will be achieved by developing more efficient and cost-effective ways of conducting commutability studies enabling the identification of manufacturing processes consistently leading to high commutability levels.

Keywords

In Vitro Diagnostic (IVD), In vitro diagnostic medical devices regulation, metrological traceability, calibration, performance verification, commutability, manufacturing, reference materials, external quality assessment, measurement uncertainty.

Background to the Metrological Challenges

As 70 % of medical decisions depend on in vitro diagnostics results, manufacturers of IVD products have a major responsibility to ensure that clinical measurements are accurate, useful, and comparable. A well-recognised approach to obtain comparable and accurate results is to establish their metrological traceability to internationally recognised references. According to the new in vitro diagnostic medical devices regulation (EU) 2017/746 (IVDR)) and ISO 17511:2020, the metrological traceability of values assigned to calibrators and/or control materials shall be assured through suitable reference measurement procedures and/or suitable reference materials of a higher metrological order. The Joint Committee for Traceability in Laboratory Medicine (JCTLM) maintains a database of these higher order materials and methods. Although IVD tests exist for several thousands of biomarkers, the JCTLM database includes Certified Reference Materials (CRMs) for only 160 analytes and Reference Measurement Procedures (RMPs) for 180 measurands. In laboratory medicine, there is, therefore, a significant lack of CRMs and RMPs.

In December 2021, a workshop was jointly organised by the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine), the JCTLM and the ICHCLR (International Consortium for Harmonization of Clinical Laboratory Results) to identify and overcome challenges to global standardisation of clinical laboratory testing. Achieving equivalent results in laboratory medicine is reliant in part on the development and global availability of secondary CRMs with properly assessed commutability and fit for purpose measurement uncertainties. The availability of External Quality Assessment (EQA) schemes was also judged as essential to properly monitor the accuracy of IVD tests. These needs were largely confirmed by the stakeholders' consultations conducted by the EMN TraceLabMed (European Metrology Network) including IVD manufacturers, EQA providers, international organisations and regulators. It was pointed out that addressing the expressed needs requires a coordinated metrological response quality control of life science products. The EMN on Advanced Manufacturing also pointed out the need for improved and new metrology methods to assess the quality of bio-based materials and reference materials for quality control of life science products.

The commutability of calibration and quality control materials has emerged as a key requirement for establishing the metrological traceability of clinical measurements and verifying their accuracy and comparability. Although commutability assessment frameworks have been established by the IFCC working group on commutability, evaluating commutability is cumbersome and to date, very few data are available to

inform the extent to which processed and spiked materials properly mimic real patient samples. Therefore, there is a need of improving the ability to scale up production of materials, e.g., by using purified chemicals, as opposed to biological materials to produce commutable materials. This will allow identifying manufacturing processes making it possible to consistently produce calibration and quality control materials of high commutability levels and therefore to better predict commutability. To get this done in a cost-effective manner and to cover a wide range of measurands, a high level of coordination and integration of capabilities of several institutes is essential and will have an added value far beyond capabilities of a single institute. The creation of an infrastructure able to jointly assess commutability of calibration and quality control materials for various measurands appears as highly beneficial to gather the data needed to better predict materials commutability. Additionally, developing alternative strategies for commutability assessment will make commutability assessment simpler.

As evaluating commutability is demanding, most EQA schemes currently rely on materials of unknown commutability whose target values often consist of peer group consensus means instead of value assigned by a RMP. Therefore, the ability to properly evaluate results accuracy and comparability is compromised and IVD manufacturers lack adequate ways to verify the performance of their products. Improved availability of EQA materials of proven commutability make it possible to properly evaluate the accuracy of IVD tests through accuracy-based programs relying on commutable EQA materials with SI-Traceable target values assigned using an RMP. Mutualising and coordinating the resources of a network of reference measurement service providers would make this more cost-effective and open the door to gather sufficiently large datasets that could merge to evaluate accuracy and comparability of clinical results at a larger scale. Indeed, collecting, and aggregating results from different EQA schemes has recently emerged as a promising way to evaluate harmonisation of measurement results on an international basis. To support the use of aggregated data from different EQA schemes the European Organisation for External Quality Assurance Providers in Laboratory Medicine (EQALM) has established for this purpose a central database. However, work remains to be done on harmonising coding systems and establishing metrological traceability in EQA programs. The ICHCLR and the EQALM have joined forces to form the HALMA (Harmonization of measurands in Laboratory Medicine through data Aggregation) initiative, but this effort is limited by the fact that EQA materials should be commutable. Therefore, there is a need to better predict commutability of EQA materials will make EQA data aggregation more secure and support the HALMA initiative.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on metrology research necessary to support the manufacturing of commutable calibrators and quality control materials for standardisation and post-market surveillance of IVD tests.

The specific objectives are

1. To improve the availability of fit for purpose calibrators and quality control materials that are prioritised and can be used by IVD manufacturers and EQA providers for establishing and verifying metrological traceability of clinical measurements. To address a commutability assessment and SI-traceable value assignment of existing or new materials for various types of measurands to support comparability and traceability of IVD tests for clinically relevant biomarkers, such as bilirubin, cyclosporine, PTHx and hCMV.
2. To identify manufacturing processes and to source and produce (e.g., by matrix-based or synthetic materials subject to freezing and lyophilization) calibration and quality control materials of high commutability levels. This includes the identification of critical quality attributes and target uncertainties for calibration and quality control materials. To evaluate and compare the commutability of these materials as well as to identify improved understanding of key common causes of limiting materials commutability. To consider measurement uncertainty at each level of the calibration hierarchy and its impact on the overall quality of laboratory tests.
3. To develop more efficient and cost-effective ways of conducting commutability studies by e.g., mutualising the resources and capabilities of reference measurement service providers forming a coordinated metrology network acting under the umbrella of the European Metrology Network TraceLabMed as well as to develop alternative strategies in order to make commutability assessment straightforward.

4. To build a coordinated European metrology infrastructure working in close cooperation with EQA providers and IVD manufacturers with the aim of supporting post-market surveillance of IVD tests by organising an of accuracy-based program relying on commutable EQA materials with reference method target values as well as to develop novel approaches for EQA data aggregation to evaluate harmonisation of measurement results on an international basis.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (accredited laboratories, instrumentation manufacturers, EMN TLM), standards developing organisations (e.g., ISO, CEN, CLSI), and end users (e.g., international organisations, assay manufacturers, material producers, EQA providers and medical associations).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes. Proposers shall give priority to work that meets documented industrial needs and include measures to support transfer into industry by cooperation and by standardisation. An active involvement of industrial stakeholders is expected in order to align the project with their needs – both through project steering boards and participation in the research activities.

Proposers should establish the current state of the art and explain how their proposed project goes beyond this.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.9 M€ and has defined an upper limit of 2.3 M€ for this project.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the 'end user' community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the "end user" community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Facilitate improved industrial capability or improved quality of life for European citizens in terms of personal health, protection of the environment and the climate, or energy security,
- Transfer knowledge to the commutable calibrators and quality control materials' manufacturing for standardisation and post-market surveillance of IVD tests sector.

You should detail other impacts of your proposed JRP as specified in the document "Guide 4: Writing Joint Research Projects (JRPs)"

You should also detail how your approach to realising the objectives will further the aim of the Partnership to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

Timescale

The project should be of up to 3 years duration.