European Partnership on Metrology
Call 2025 – Health, Integrated European Metrology, Regulation and Research Potential

Selected Research Topic number: **SRT-s17**
Version: 1.0

Title: Enabling international comparisons of primary radioactivity standards for short-lived radiopharmaceuticals

Abstract

National Metrology Institutes (NMIs) and Designated Institutes (DIs) must support their calibration and measurement capabilities (CMCs) for primary radioactivity standards on the Key Comparison Database (KCDB), via linkage to the international realisation of the becquerel though the BIPM. For short-lived radiopharmaceuticals, this has to be undertaken on-site using the transportable BIPM international reference system transfer instrument (BIPM-SIRTI). However, long waiting times prevent European NMIs and DIs from demonstrating such linkage in support of the rapidly emerging fields of nuclear medicine and molecular radiotherapy. Therefore, a portable EURAMET-SIRTI needs to be developed, which will provide additional capacity to enable all European NMIs/DIs to provide traceable calibration services to nuclear medicine clinics, thus underpinning effective dosimetry and diagnostic procedures.

Keywords

BIPM international reference system (BIPM-SIR), BIPM international reference system transfer instrument (BIPM-SIRTI), calibration, comparisons, EURAMET-SIRTI, molecular radiotherapy, Monte-Carlo models, nuclear medicine, primary standards, radiopharmaceuticals, short half-life, traceability, uncertainty

Background to the Metrological Challenges

The need for improved measurement traceability in clinical settings has been identified in the orientation statements of the European Metrology Network for Radiation Protection and the EURAMET Technical Committee for Ionising Radiation WG1 [1,2]. Although legislation varies between European countries, it is a general requirement that the devices used to measure the administered activity (typically radionuclide calibrators) are traceable to national standards of radioactivity for the radionuclide of interest. The provision of clinical measurement traceability is ultimately the responsibility of each European NMI and DI and they usually demonstrate the international equivalence of primary standards for a gamma-ray emitting radionuclide by submitting a BIPM glass ampoule of standardised material to the International Reference System (BIPM-SIR) where the standard is compared to primary standards from other NMIs/DIs using a high-stability ionization chamber. The results are reported in the KCDB and can be used to support CMC claims. However, the BIPM-SIR cannot be used for radionuclides with short half-lives, of ≤ 1 day, as the samples decay in transit. To address this issue, an on-site comparison service using the transportable BIPM international reference system transfer instrument (BIPM-SIRTI) has been developed. The measurement reproducibility of the BIPM-SIRTI is around 0.05 %. Measurements of the same radioactive solution in both the BIPM-SIRTI and the BIPM-SIR provide the linkage, and the BIPM-SIRTI provides linkage to the SIR for the following radionuclides: 13N, 11C, 18F, 56Mn, 99mTc, 64Cu, 123I, 153Sm. The BIPM are currently working on expanding this list to include 68Ga and 166Ho.

In support of the rapidly evolving field of nuclear medicine, the H2020 PRISMAP project is actively producing a portfolio of 28 medical radionuclides for use in research into the introduction of novel radiopharmaceuticals in clinical trials worldwide. However, maximising the impact and reach of this work will require the involvement of European NMIs/DIs, which will be able to provide the necessary traceability for activity measurements in a clinical environment. This is a key component in underpinning effective dosimetry in molecular radiotherapy and diagnostic clinical procedures.

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European Partnership Co-funded by the European Union
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As the BIPM can only visit one laboratory per year, there are long waiting times for access to the BIPM-SIRTI. Consequently, other regional metrology organisations (RMOs) (APMP and SIM) are currently developing their own RMO-SIRTIs, as direct clones of the BIPM-SIRTI, for their own use. The RMO-SIRTI comparisons will be linked to the BIPM-SIR through the BIPM-SIRTI, requiring the linking measurements to be carried out in the RMOs. The BIPM workplan includes support to RMOs (including EURAMET) in the validation of RMO-SIRTIs. In 2023, the Consultative Committee for Ionizing Radiation (CCRI) of the International Committee for Weights and Measures (CIPM) agreed that an RMO instrument can be named “RMO-SIRTI” and run RMO.RI(II)-K4 comparisons if the instrument is ‘sufficiently similar to the BIPM-SIRTI so that the same measurement procedure can be used’.

Although radionuclide calibrators are used for activity measurement in clinical settings, they do not provide the precision required for meaningful comparisons of primary standards of radioactivity, which are required by NMI/DIs to support their CMC claims in the KCDB. A more robust approach is required through the creation of a European SIRTI. However, in contrast to the other RMO-SIRTIs being developed, the planned design of the EURAMET-SIRTI will not be limited to the creation of a clone of the BIPM-SIRTI. One option is to use a different type of detector (i.e. CeBr3) in the design. Therefore, Monte-Carlo modelling work needs to be performed due to the enhanced energy resolution (useful for verifying impurity corrections), faster response time (for handling high count rates) and the lower intrinsic background noise. Bespoke pulse processing and dead-time handling algorithms also need to be developed for the EURAMET-SIRTI. These enhancements are needed to deliver a world-leading instrument that will be capable of precision measurements on the novel suite of radiopharmaceuticals supplied by the H2020 PRISMAP project. The EURAMET-SIRTI will need to meet the technical criteria for an RMO-SIRTI, as defined by the BIPM, and it will be required to exhibit a similar or better measurement reproducibility (in the order of 0.05 %) as that currently exhibited by the BIPM-SIRTI. There will also need to be robust linkage to the BIPM-SIR (via linkage measurements with the BIPM-SIRTI or direct submission to the BIPM-SIR) for a suite of short-lived novel radiopharmaceuticals. Once commissioned, the potential stewards of this device will need to be trained in its operation, under the auspices of EURAMET-TC-IR.

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 proposal shall focus on enabling international comparisons of primary radioactivity standards for short-lived radiopharmaceuticals.

The specific objectives are

1. To design and develop a precise, robust and portable radioactivity measurement instrument for use with key clinical short-lived radiopharmaceuticals. This instrument, which will be known as the international reference system transfer instrument (EURAMET-SIRTI), must exhibit excellent measurement reproducibility (in the order of 0.05 %) to enable European NMI/DIs to compare national primary standards and thus demonstrate linkage to the International Reference System (BIPM-SIR) and ultimately to support their CMC claims in the KCDB.
2. To generate a Monte-Carlo model of radiation transport in the EURAMET-SIRTI, in order to (i) help to establish an efficiency curve for various photon energies and (ii) to provide a robust mechanism for deriving the associated uncertainty budget. Monte-Carlo methods should also be developed to simulate detector pulses from the EURAMET-SIRTI, with rapidly decreasing count rates, in order to test and validate the analysis routines that are used for handling dead-times with short-lived radionuclides.
3. To generate robust linkage factors to the BIPM-SIR (via linkage measurements with the BIPM-SIRTI or direct submission to the BIPM-SIR) for a suite of short-lived novel radiopharmaceuticals. For radionuclides with half-lives of < 1 hour, the NMI/DIs should perform primary standardisations at the production site and create linkages in-situ. This objective should include the validation and augmentation of the efficiency curve from Objective 2 using the highly characterised longer-lived radionuclides held at the BIPM.
4. To provide training, under the auspices of EURAMET-TC-IR, on the operation of the EURAMET-SIRTI to potential stewards of this device. The training should cover (i) the use of the extensive database of operational data, and (ii) best practice in the robust dissemination of each

NMI/DI's primary standard(s) in order to support local nuclear medicine clinics via the use of secondary standards.

5. To demonstrate the establishment of an integrated European metrology infrastructure and to facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (accredited laboratories, measurement equipment manufacturers, EMN for Radiation Protection), standards developing organisations (ISO, IAEA), and end users (EURAMET-TC-IR-WG1, clinical stakeholders, manufacturers of medical and healthcare products).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes. To enhance the impact of the research work, the involvement of the larger community of metrology R&D resources both within and outside Europe, plus engagement with existing European research infrastructures and European Partnerships is recommended. A strong industry involvement is expected in order to align the project with their needs and guarantee an efficient knowledge transfer into industry and end users. Where relevant, proposals are encouraged to build on, or seek collaboration with, existing projects and develop synergies with other relevant European, national or regional initiatives and funding programmes. In particular, links are encouraged with (i) the projects funded under earlier relevant topics of the Horizon Europe programme; or (ii) other relevant European Partnerships.

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

In the case that the proposal includes costs of equipment associated with the development of a robust, portable, radioactivity measurement transfer instrument, proposers should provide a clear rationale for the equipment, explain how this contributes a sustainable metrology infrastructure within Europe and how the facility will be supported in the future. Proposers shall ensure that the cost eligibility conditions applicable to the respective cost categories are fulfilled. In addition, proposers should note that funds for any other required infrastructure and capital equipment must be provided from other sources.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 2.1 M€ and has defined an upper limit of 2.6 M€ for this proposal.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 25 % 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 proposal's 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 healthcare 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 Metrology 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.

Additional information

The links provided in this section are only correct at the time of publication up until the end of the Call year.

The references below were provided by PRT submitters; proposers should therefore establish the relevance of any references.

[1] EMN for Radiation Protection orientation statement on the Call 2025. https://www.metpart.eu/applicants-2025/integrated-metrology-call-2025-s1.html

[2] EURAMET TC IR WG1 Orientation Page 2025 IEM and Health. https://www.metpart.eu/applicants-2025/integrated-metrology-call-2025-s1.html