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

Selected Research Topic number: **SRT-h16**
Version: 1.0

Title: Metrology for standardising nucleic acids preparation approaches for reliable biomedical analysis

Abstract

Advances in early detection, prognosis, and therapies suffer from the lack of standards to assess sub-molecular interaction across multiple techniques. The characterisation of nucleic acids unveils genes regulation and how alterations relate to pathologies and treatments. Proposals addressing this topic should establish the metrology and standardisation basis for easy-to-use physiologically compatible preparation techniques for the physical and chemical analysis of nucleic acids (NA), enabling precise comparisons of healthy and ligand-affected samples. By addressing critical metrological challenges for reliable data collection and methods compatibility, submitted proposals should enhance high-throughput techniques and improve the accuracy of biomedical applications.

Keywords

Physiological reliable preparation, superhydrophobic devices, nucleic acids, sub-molecular metrology

Background to the Metrological Challenges

Toxic pollutants, particularly heavy metals, are known to interact with nucleic acids, disrupting their structure and functionality. The classification of these toxic elements, and a thorough understanding of the damage they cause at the sub-molecular level remain unclear and are essential for assessing analytical methods and ligand activity control. Therefore, the need for quantitative reference methods to study the interactions between toxic elements and nucleic acids is needed.

The response to pharmacological treatments often displays overlapping characteristics for example, chemotherapy aims to target specific cellular components, yet issues of specificity persist. The toxicity and potential overdose of drugs pose serious life-threatening risks, which are only partially understood for a limited number of pharmaceuticals. This challenge extends to drug discovery, where designing novel drugs that specifically target disease mechanisms without adversely affecting healthy biological processes is complex. Many drug candidates inadvertently disrupt physiological functions, leading to toxicity or ineffective treatments. In addition, a standardised biological preparation protocol will enhance reproducibility across laboratories and promote the use of nucleic acid nanoscale filaments as internal standards for high-resolution electron microscopy, and thus enabling better comparability of data and diagnostics. Moreover, such approach will have a strong impact on the healthcare system of the European Union and therefore, easier sample preparation has the potential to boost precision medicine and personalised therapies.

Considering these challenges, access to reliable sub-molecular information is urgently required to uncover the precise effects of drug administration on cellular biomolecules, particularly nucleic acids. Emerging therapeutic strategies, including gene editing, vaccine development, and advancements in synthetic biology, also require standardised measurements that benchmark the physical and chemical properties of nucleic acids against internal standards, which currently lack consistency.

To ensure the validation and safe application of genetic therapeutic products, metrological standards, interlaboratory consistency, and comprehensive guidelines for nucleic acid analysis (DNA and RNA) during pre-clinical and clinical trials are essential. This infrastructure is critical to accelerate regulatory approvals. However, given the complexity of biological systems, developing a preparation procedure that meets the biological requirements of various molecules while simultaneously providing high-resolution access to sub-

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molecular details remains a significant obstacle. Furthermore, technical limitations associated with different instruments further complicate this effort and therefore, a clear and urgent need for advancements in methodologies to overcome these hurdles in nucleic acid analysis and therapeutic development.

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.

Proposals should focus on the development of metrology to enable reliable biomaterials preparation, based on the combination of a one-step drop casting procedure of the biomolecules and the microfabrication of superhydrophobic-based devices (SHS).

The specific objectives are

1. To develop a well-controlled and standardised biological preparation for sub-cellular subcomponents. This includes biomaterials preparation comparing established techniques to testing of ligands effect to pristine molecules while minimizing preparation time up to 1 hour as well as reducing process control parameters to room temperature (RT) and relative humidity (RH). In addition, the platform biomolecules-SHS obtained will reproducibly provide a statistically relevant number of nominally identical NA filaments.
2. To develop measurement capability and metrology for nano-dimensional characterisation of physical and chemical properties of nucleic acids. This includes i) Secondary Ion Mass (SIMS) and X-Ray Spectrometry to quantify ligands presence in NA filaments through characteristic target atoms (e.g., Pt, Ni) at nanogram level and counting NA helices by using selected elements for targeting; ii) X-ray absorption spectrometry to quantify the chemical state changes of NA by micro- or nano-sized synchrotron radiation beam; iii) X-ray diffraction (XRD) to evaluate structural modification in the NA filaments; iv) Energy Dispersive X-ray Spectroscopy (EDS) for elemental characterisation combined with electron microscopy methods.
3. To develop traceable chemical and structural characterisation of nucleic acids to assess ligands presence and effects to native helices. This includes developing a traceable quantification of morphological, chemical and structural properties of ligands local effects through: i) scanning microscopies (SEM, AFM) for statistical analysis of the diameters of the suspended NA filaments (5 nm to 200 nm range) and insights in their morphology and Young moduli (5 GPa to 15 GPa); ii) vibrational spectroscopies (microRaman, FTIR); iii) Transmission electron microscopy (TEM) for direct images down to 0.15 nm resolution; mass spectroscopy for 3D structures.
4. To provide interlaboratory comparison through the repetition of statistically relevant number of the preparation of suspended NA across several research and clinical laboratories to assess reproducibility of the result under controlled environment. Ideal working conditions envisage a 20 °C RT and 55 % RH, tailored on sample outcomes.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (EURAMET TC-MC, CIPM CCQM (Cellular Analysis Working Group and Nucleic Acid Working Group), Joint Committee for Traceability in Laboratory Medicine, standard developing organisations (ISO TCs 194, 229, 276 and 334) and end users (e.g. 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, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development. 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.

Proposers should note that the programme funds the activity of researchers to develop the capability, not the required infrastructure and capital equipment, which 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 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 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 pharmaceutical 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.