European Partnership on Metrology
Call 2022 – Digital Transformation, Health, Integrated European Metrology, Normative and Research Potential

Selected Research Topic number: **SRT-h03**
Version: 1.0

Title: Metrology for innovative nanotherapeutics

Abstract

Nanotherapeutics has the potential to aid in responding to societal and medical challenges related to aging populations and an increase in chronic diseases. With a large number of new products being approved, there are pressing regulatory and industrial needs for preclinical characterisation of innovative nanotherapeutics, focusing on synthetic lipid-based and metal oxide nanoparticles used as medicinal products and as radio enhancers. Development and validation of fit-for-purpose traceable methods are required to measure their stability, surface properties, biotransformation in biological fluids and for their identification and quantification in cells and tissues. Moreover, well characterised representative testing materials should be produced to enable method development and measurement quality control. A robust metrological framework for the assessment of nanotherapeutic products will improve their regulation and safety as well as further facilitate their development.

Keywords

Nanomedicine, liposomes, lipid-based nanoparticles, metal oxide nanoparticles, radiotherapy, critical quality attributes, surface properties, biological matrices

Background to the Metrological Challenges

In Europe, ageing and an increase in chronic diseases like cancer, diabetes, heart disease, and brain conditions that require complex types of treatment are increasing healthcare costs to potentially unsustainable levels. Nanotherapeutics offers significant promise for tackling these societal challenges, providing versatile technical solutions. Currently, more than 50 nanomedical products are on the market and hundreds more are in clinical trials.

The rapid development and increasing complexity of innovative nanotherapeutics have given rise to significant analytical challenges, highlighting the need to develop, validate and harmonise fit-for-purpose measurement methods and standards to support industry and regulation bodies. The European Medicines Agency, in EMA Regulatory Science to 2025 Strategic Reflections, has pointed to “new testing methods for quality and safety assessment of nanomedicines” and an understanding of “the critical quality attributes (CQA) of a given product and the relationship between those and the biological activity and in-vivo behaviour of the product” as necessary for an “understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals”. Specific gaps in the metrology related to nanotherapeutics include the need for methods to measure (i) the surface properties of the nanocarriers, (ii) their physico-chemical stability and kinetic properties in biological media, and (iii) particle uptake, absorption and distribution in cells and tissues.

The great diversity of materials and structures with unique and distinct features makes it essential to consider and identify strategies for the unique characteristics of various nanomaterials (e.g., new polymer mixtures, composite metal core nanoparticles, etc). In order to determine the CQAs of nanotherapeutic products and to understand their link with product safety and efficacy, it is crucial to develop ad hoc measurement strategies for each class of nanomaterials, and to control the uncertainties of measurements. This will only be possible by harmonising, and validating, metrologically robust protocols and by developing fit-for purpose representative testing materials (RTM) that respond to explicit regulatory needs. Importantly, only integrated cooperation among all the stakeholders with NMIs and standardisation bodies will guarantee optimal knowledge transfer to targeted groups and full exploitation of the results of such work.

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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 the traceable measurement and characterisation of innovative nanotherapeutics, focusing on synthetic lipid-based and metal oxide nanoparticles.

The specific objectives are

1. To develop representative testing materials (RTM) for synthetic lipid-based and metal oxide nanoparticles and to measure their chemical composition, particle size distribution, polydispersity and particle concentration with a controlled uncertainty using existing methods.
2. To develop and harmonize traceable methodologies for measuring
    a. particle size and concentration of small (<10 nm) nanoparticles and of aggregated non-spherical objects,
    b. lipid composition and structural integrity of lipid-based nanoparticles,
    c. nanoparticle surface properties, including the amount, chemical composition, and homogeneity of the surface coating.
3. To develop and harmonise robust and efficient sample preparation methods for the measurements of the nanoparticle stability and their biotransformation in biological matrices, and to minimise matrix interferences. Fractionation methods, including size exclusion chromatography (SEC), field flow fractionation (AF4) and ultracentrifugation (UC) that are used to separate nanoparticles from free proteins in plasma, reach a demonstrated recovery of the analyte of interest above 70 %, as required by ISO/TS 21362:2018 and CEN/TS 17273:2018.1,2
4. To improve correlative methods and model tissue phantoms to measure nanoparticle uptake and distribution in single cells and tissues associated to their biodistribution profile, safety, and efficacy. This includes using a combination of complementary techniques (e.g., MS, single cell ICP-MS, EM; Raman- and fluorescence-based approaches) with the aim to reduce the uncertainty in the detection, localization, and quantification of nanoparticles in single cells and tissues. The developed methods, RTM and model tissue phantoms to be consolidated through the performance of an interlaboratory comparison.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (NMIs, accredited laboratories), standards developing organisations (e.g., CEN/TC 352-Nanotechnologies, ASTM E56, ISO TC 229, VAMAS TWA 2 and TWA 34) and end users (e.g., the pharmaceutical industry, regulators, clinicians, nanomedical product manufacturers, nanomedicine research community)

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.

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 2.6 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,
- Transfer knowledge to the pharmaceutical industry, regulators, clinicians, nanomedical product manufacturers, and nanomedicine research community.

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.

Time-scale

The project should be of up to 3 years duration.