

Title: Metrology to support sustainable development of nanomedicines for therapy and theranostics

Abstract

Nanomedicines have the potential to revolutionise European healthcare through safer and more efficacious treatments for chronic diseases such as cardiovascular, neurological, inflammatory, musculoskeletal and cancer, which are forecasted to cause > 80 % of global deaths by 2030. However, there are no validated methods for characterisation of: i) drug concentration within nanocarriers, ii) drug transformation and stability upon encapsulation or storage, or iii) drug loading variability across particle populations, even though clinical outcomes highly depend on these parameters. Proposals are sought to develop validated methods to support safe and sustainable development of nanomedicines, successful translation to the clinic and regulatory compliance.

Keywords

Nanomedicines, nanotherapeutics, nanotheranostics, drug delivery, encapsulation, simulated drug release, clinical translation, artificial intelligence, regulatory compliance, sustainability.

Background to the Metrological Challenges

By the end of 2030, over 80% of global deaths are expected to be caused by chronic diseases such as cardiovascular, neurological, inflammatory, musculoskeletal, and cancer. Increasing prevalence of chronic diseases, coupled with other health challenges arising from an ageing population, are placing unprecedented socioeconomic pressure on the worldwide and European healthcare systems, adversely impacting patient prognosis and quality of life. For this reason, the 2030 United Nations Agenda for Sustainable Development has recognised chronic diseases as a major challenge for sustainable development. As part of the agenda, heads of states and governments have committed to achieve a 30% reduction in premature mortality from chronic diseases by 2030, through better prevention and treatment. To address these goals and unmet clinical needs, safer and more sustainable medicines are urgently needed.

Following the success of global uptake of nanoparticle-based immunisation during the COVID-19 pandemic, nanomedicines have emerged as potential candidates that could revolutionise the European healthcare and contribute to addressing challenges associated with chronic diseases. This is due to increased efficiency of the treatment, reduction of side-effects, and improved cost-effectiveness of nanotherapies in comparison with more conventional approaches. To overcome some technical barriers, (such as the lack of expected clinical efficacy and nanomedicines failures associated with the occurrence of adverse effects), and ultimately prevent unprecedented rate of failures in clinical trials, robust methods for: i) characterisation of the encapsulated (vs unencapsulated) drug, ii) in vitro characterisation of the drug release, iii) in-line (real-time) testing and development of automated process control and quality assurance, and iv) improved procedures for mid- and long-term storage, are urgently needed to support the sustainable development of nanomedicines, nanotherapeutics and nanotheranostics. Such methods will also support compliance with regulatory testing requirements for healthcare applications (e.g. EU IVD Directive 98/79/EC and EU Regulations on medical devices 2017/745 and in-vitro diagnostic 2017/746) and contribute to addressing the needs described by the European Medical Agency (EMA) in the recently published guidelines on nanomedicines. The critical need for development, validation, harmonisation and ultimately standardisation of methods for characterisation of nanomedicines, nanotherapeutics and nanotheranostics has been also expressed by the EURAMET EMNs in the orientation papers for the Metrology Partnership Health Call 2025, including EMN Traceability in Laboratory

Medicine [1] and EMN Advanced Manufacturing [2], as well as various European Committees (e.g. Nanomedicine European Technology Platform ETPN), CIPM CCQM (e.g. CCQM Working Group on Nucleic Acid Analysis), reference materials producers (e.g. JRC), public sector (e.g. The UK Medicines and Healthcare products Regulatory Agency), Standards Developing Organisations (e.g. ISO TC 229, ISO TC 276) and relevant industrial Stakeholders.

To date, validated, harmonised and standardised methods for characterisation of nanomedicines have been limited to a few selected measurands (e.g. ASTM E56.02 - WK83164). These, mostly involve determination of particle size, or quantification of the total drug content using indirect or bulk approaches. There are only limited number of examples of standardisation efforts focused on specific formulations, such as liposomal doxorubicin (e.g. ISO/PWI 3181) or RNA containing (e.g. ASTM E56.08 - ASTM WK75607) lipid nanoparticles (LNPs). Interlaboratory comparisons (ILCs), which are essential pre-normative requirements for methods validation, have also been scarce and limited to a few selected measurands (e.g. CIPM CCQM-P244). Consequently, certified reference materials (CRM), representative of nanomedicines loaded with relevant drugs are currently lacking and the CRMs which have been made available so far are limited to empty liposomes (e.g. ALIPO-1, NRC Canada) or LNPs (e.g. ALPN-1, NRC Canada) characterised for particle size only. Method transfer from empty lipid-based carriers to fully functional drug-containing nanomedicines as well as other clinically relevant formulations is challenging, since there is a lack of consensus on how to address critically important measurands related to encapsulated drugs. Currently ongoing European projects, e.g. the Metrology Partnership project 22HLT04 MetrIno, although significantly contributing to the development, validation and harmonisation of methods for nanomedicines characterisation, are not addressing challenges associated with quantification of the drug within delivery systems. Although some methods have been proposed for the simultaneous characterisation of both encapsulated and free drug content (e.g. multidetector field flow fractionation (FFF), measurement of the mass of encapsulated drug either in bulk (e.g., high performance liquid chromatography (HPLC)-based) or at single particle level, as well as drug integrity, none of these methods have been metrologically validated and/or correlated with the expected in vivo behaviour and physiological effect of the drug. There is also a lack of validated in vitro methods for simulated drug release and post-release potency assessment. Ultra-fast methods and machine learning algorithms required for the development of in-line manufacturing process control and assurance are also currently lacking. Moreover, innovative solutions for improved storage stability are also currently underdeveloped.

There is a documented urgent demand for development and validation of robust measurement methods for characterisation of nanomedicines, to support their sustainable development and accelerate their clinical translation. Development and metrological validation of such methods can only be effectively realised as a collaborative approach involving metrology institutes, nanotherapeutics producers, instrument manufacturers, academics, and clinicians.

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 the validation of methods for quantification of encapsulated/immobilised drug within nanomedicines and the drug's transformation and stability upon encapsulation and storage.

The specific objectives are:

1. To develop at least three test materials representing different classes of nanomedicines in pre-clinical phase trials (such as synthetic lipid- or polymer-based, inorganic solid or mesoporous, and/or extracellular vesicles derived from bioprocessing) or / as well as encapsulating therapeutically relevant model drugs representative of therapeutic / theranostics applications (including nucleic acid, metal-based and/or optically detectable compounds). The materials shall come with characterised values of particle size, number concentration, as well as mass of total and encapsulated drug, and be sufficiently homogenous and stable in a predefined time period to serve as candidate reference materials.
2. To develop and harmonise traceable methodologies for characterisation of (i) mass of total versus encapsulated drug (ii) mass of drug per particle/vesicle and drug loading distribution across particle/vesicle populations (iii) chemical, structural and functional integrity of the drug pre- and post-encapsulation, and following storage, using multiparameter, hybrid and hyphenated techniques such as multidetector FFF (e.g. AF4/PTA(sp)ICP-MS) or HPLC/ESI-MS, combination of light scattering with backscattering interferometry or differential refractometry, or other fluorescence-based

(SAXS/FCCS), and Raman-based (e.g. FCM/Raman, AF4/MALS/Raman, SEM/Raman or AFM/Raman).

3. To develop, validate and harmonise in vitro methods for simulated drug release and post-release potency assessment, which represent in vivo behaviour and hence can serve as predictors of clinical success, with the aim to reduce probability of adverse effect occurrence and late-stage failure during clinical trials, improving the overall safety and efficacy of nanotherapies.
4. To develop and validate ultra-fast measurement methods and artificial intelligence models for in-line process monitoring and control and eventual automation of continuous manufacturing processes, to facilitate sustainable development of nanomedicines and regulatory compliance. To identify suitable metrics for evaluating machine learning models and to define the robustness limits of these metrics (and thus of the models) under operational conditions relevant to end users. To generate training data sets and guidelines for nano-therapeutic and theranostic communities.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (accredited and testing laboratories, instrument and device manufacturers), standards developing organisations (CEN/TC 352, ISO TC 229, ISO/TC 276), and end users (pharmaceutical industry, regulators, clinicians and manufacturers).

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. In particular, proposers should outline the achievements of the Partnership 22HLT04 MetriNo project and how their proposal will build on those.

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 participants will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of the 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 sectors and manufacturers of nanomedicines.

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 Traceability in Laboratory Medicine Strategic Research Agenda
<https://metpart.eu/applicants-2025/health-call-2025-s1.html>
- [2] EMN Advanced Manufacturing Strategic Research Agenda
<https://metpart.eu/applicants-2025/health-call-2025-s1.html>