

Title: Radionuclide metrology for improved diagnosis and treatments in nuclear medicine

Abstract

Nuclear medicine as a tool to fight cancer is in need of metrological support. New emerging radionuclides as well as some known radionuclides used for diagnosis and treatment need an established traceability chain to primary standard laboratories. Traceable radioactivity measurements of radiopharmaceuticals and on patient monitoring after radionuclide administration should be established. Particular attention should be paid to therapeutical nuclides decaying via alpha- and beta- particle emission chain. On-site measurement techniques for accurate activity determination of very short-lived positron emission tomography isotopes should be developed.

Keywords

Nuclear medicine, positron emission tomography (PET), single photon emission tomography (SPECT), radiopharmaceuticals, radionuclide therapy, theranostics.

Background to the Metrological Challenges

Malignant tumour diseases, generally denoted as cancer, are causing death to almost two million people per year in Europe. Lowering this number is one of Europe's main health challenges. Nuclear medicine as a tool to fight cancer is in need of high level metrological support. Currently several measurements in nuclear medicine are based on calibration factors provided by manufacturers, or simply estimated from factors with similar decay scheme (e.g. O-15, N-13). Such measurements are not traceable to primary standards.

New emerging radionuclides as well as some known radionuclides used for diagnosis and treatment need an established traceability chain to primary standard laboratories. This includes radionuclide impurities determination and nuclear data improvement. New or improved activity measuring devices must be developed suitable for on-site use. They must enable traceable on-site activity measurement of radiopharmaceuticals and radionuclide impurities, including pure beta- and alpha-emitting radionuclides. This will generate more accurate determinations of radiopharmaceuticals activities which in turn will improve diagnosis and treatment of patients. Furthermore, treatment protocols employing monoclonal antibodies and other low-molecular compounds radiolabelled with therapeutical radionuclides need traceable dosimetric surveillance. The same applies to *in vivo* monitoring of individual patients (PET, SPECT functional imaging), particularly in multistage protocols, where patient immune reaction to the antibody may significantly influence its *in vivo* biological distribution and proper dose targeting.

Insufficient measuring systems also create problems when monitoring patients after treatment. Because they cannot cover the wide range of activity measurement, from kilobecquerels to gigabecquerels, they do not enable systematic measurement. Moreover, current methods require patients moving to each consecutive retention measurement for several days after the treatment, an uncomfortable, impractical and stressful situation for them. Measurements that yield the most effective diagnosis and treatment planning must be performed until complete decay of the respective radionuclide. This should be done in a way that is convenient for the patient.

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 traceable radioactivity measurements of radiopharmaceuticals and on patient monitoring after radionuclide administration.

The specific objectives are

1. To develop activity standardisation techniques for short-lived isotopes with half-lives in the order of minutes (e.g. C-11, N-13 and O-15) in order to establish the missing traceability chain.

This requires new instruments for primary measurements and activity measurements at the production site before administering radiopharmaceuticals to the patient. A transfer to secondary instruments, such as gas-filled re-entrant ionisation chambers, should enable clinics to carry out traceable measurements in the future.

2. To determine nuclear decay data and to establish new activity standards for radioisotopes which are already in use or considered to be used in nuclear medicine for diagnosis and treatment.

The decay data to be determined comprise half-lives and emission probabilities for photons and alpha- or beta- particles. Decay data should be determined for established PET radionuclides, such as C-11, N-13, O-15, F-18, Cu-64, Ga-68, and I-124, and emerging PET/SPECT and theranostic isotopes / isotope pairs, such as Cu-61/Cu-67, Sc-44/Sc-47, Ga-66/Ga-67, Br-76, Rb-82, Y-90/Y-86, Zr-89 and Tc-94m. Activity measurement techniques need to be improved and better decay data should be established for radionuclides used for different types of therapy and preclinical research (e.g. palliative medicine, tumours and/or metastases treatment), such as Re-186, Tb-161, Ho-166, At-211, Bi-212, Bi-213, Ac-225, and Th-227. A priority list should be established among these nuclides of interest to be studied in close cooperation with producers and end users.

3. To develop measuring systems for patient monitoring after treatment, allowing:
 - (i) The determination of the time dependence of high activities up to gigabecquerels with target standard uncertainties less than 10 %,
 - (ii) The determination of the distribution of activity in a treated organ with high sensitivity and resolution.

An investigation of systems for patient monitoring based on different detectors (e.g. MOSFET or NaI(Tl)), and for activity distribution determination (e.g. GAMMAPIX or multimodular MEDIPIX) should be performed and the best developed.

4. To facilitate the take up of the technology and measurement infrastructure developed by the project by healthcare professionals (nuclear medicine clinics, PET centres) and industry (radiopharmaceuticals producers and instrumentation 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.

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 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution to the project. Any deviation from this must be justified.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded 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 radiopharmaceutical sector.

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

You should also detail how your approach to realising the objectives will further the aim of EMPIR 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.