

**Statement of the European Association of Nuclear Medicine (EANM)
for a better inclusion of the particularities of Radiopharmaceuticals
within the Review of Directive 2001/83EC on Pharmaceutical Legislation
December 2021**

About EANM:

Founded in 1985, the European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. As largest organisation dedicated to nuclear medicine in Europe, EANM is an umbrella organisation for individuals and national societies, representing more than 9,000 specialists, and aiming at advancing science and education in nuclear medicine for the benefit of public health.

Summary:

In the context of the upcoming review of the European Pharmaceutical Legislation (Directive 2001/83 EC), this statement has been written by members of the EANM Radiopharmacy Committee and the EANM Board and is intended to provide input for the consideration of specificities of Radiopharmaceuticals within this review. The document addresses current regulatory challenges, aiming at ensuring quality and safety of radiopharmaceuticals as well as a harmonised framework and efficient supply chains.

INTRODUCTION

What are radiopharmaceuticals

Radiopharmaceuticals (RPs) are a special type of drug that contain a radioactive component and are used in nuclear medicine for **diagnostic** as well as **therapeutic applications** (radionuclide therapy or radioligand therapy), in contrast to other imaging specialties focused on diagnostic applications only.

The combination of diagnostic with therapeutic radionuclides is referred to as the “**theranostic**” approach. Theranostics in nuclear medicine means using the same chemical structure for radiopharmaceuticals to both diagnose and treat disease. It is considered the gold standard of personalised medicine and has paved the way for targeted care of particularly oncological patients. While the theranostics approach has been successfully applied by nuclear medicine physicians since decades in the treatment of thyroid disease already, recent innovations in the field of RPs have helped to expand its application to other tumour entities such as neuroendocrine tumours and prostate cancer.

How are radiopharmaceuticals used

The RPs are injected into the patient and are detected within the body using specific technologies, such as planar gamma cameras, **SPECT-** (Single Photon Emission Computed Tomography) or **PET-** (Positron Emission Tomography) scanners. These scanners produce a highly accurate image of the processes within the individual patient. Therefore, nuclear medicine is considered to be “**functional imaging**” rather than “anatomical imaging” like diagnostic-focused sister-modalities such as ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT). Both imaging methods are nowadays combined in multi-modality imaging scanners.

RPs can also be used for therapeutic purposes in nuclear medicine. In this case, RPs are injected into the patient, diffuse in the body, and attack specifically the diseased (cancer) cells in a highly targeted approach, significantly limiting damage to healthy tissue as compared to e.g. external radiotherapy.

Fields of clinical application for nuclear medicine and hence RPs cover both adults and children and help to diagnose and treat conditions on patients related to:

- Oncological diseases
- Endocrinology
- Cardiovascular system
- Neurological systems
- Respiratory system
- Nephro-urinary system
- Infections and inflammations
- and many more

What else there is about radiopharmaceuticals

- RPs have an excellent safety profile. Due to the extreme sensitivity of the scanners and the high efficiency of radionuclides, RPs are applied in trace amounts, only once or a few times in a patient’s lifetime and are always administered in a controlled environment by a nuclear medicine physician. A RP is never given directly to a patient but always delivered to a trained nuclear medicine physician who needs to justify its use and remains fully responsible for the procedure.
- Most RPs have a very short shelf life: they need to be prepared extemporaneously *in-house*, e.g. in the institution where they are used normally within minutes or hours after preparation, for them not to lose their radioactive potentials by physical decay.
- The radioactive nature of the products requires handling and preparation in dedicated facilities complying with radiation protection standards (e.g. Clinical Nuclear Medicine Departments, PET centres) and not in standard hospital pharmacies.
- The high diversity of RPs combined with small total patient numbers leads to a lack of commercial interest and availability of some RPs

Radiopharmaceuticals now and then: a success story

Back in the 1980s when the Directive 2001/83 EC was developed, nuclear medicine was significantly different to the nuclear medicine practice we know today. This includes technological advancements such as more sensitive scanners and improved algorithms but was moreover driven by the advancements in molecular biology, radiochemistry and radiopharmacy changing the possibilities for production, preparation and use of RPs in diagnosis and treatment.

	1980s	Today
Type of radionuclides in clinical use	<p>Diagnostics One main RP – Technetium-99m</p> <p>Therapy / Theranostics One main RP – Iodine-131</p>	<p>Diagnostics Technetium-99m Fluorine-18 Gallium-68 Etc.</p> <p>Therapy / Theranostics Iodine-131 Lutetium-177 Etc.</p>
Application	<ul style="list-style-type: none"> • Vastly diagnostic • Limited treatment options 	<ul style="list-style-type: none"> • Diagnostic use steady • Treatment options rapidly growing
Production & preparation	<ul style="list-style-type: none"> • “Kit-based” 	<ul style="list-style-type: none"> • “Kit-based” • Complex production

Table 1 Radiopharmaceuticals through the ages - 1980s versus nowadays

The EANM is proud of the **tremendous innovations** in the field of nuclear medicine in general and in the advancement of RPs specifically. These developments have substantially improved patient care especially in oncology globally and **have their roots in Europe**. The evolution of new RPs have paved the way for a new paradigm in patient care, opened new opportunities in basic research and **underpin the potential and value of nuclear medicine**.

It is with pleasure that the EANM supports the European Commission's efforts and commitment to ensure that the regulatory **framework for medicinal products including RPs** is not only adapted to support the current practice, but also to foster innovation and secure patient access to be fully future-proof and ready for the challenges ahead.

CONSULTATION FEEDBACK

Challenges for radiopharmaceuticals within the Directive 2001/83 EC

Given the above outlined innovations in nuclear medicine, it is reasonable that the requirements laid out in the Directive 2001/83 EC, which is also applicable for RPs, are not adequate anymore. The challenges posed by the implementation of this outdated regulatory framework manifest in different ways:

- Uncertainties among Member State authorities as well as producers and users in how to interpret the Directive
- Resulting in an increased level of heterogeneity in the interpretation of the Directive among Member States
- Negative impact on the availability of RPs due to unsure legal basis

Proposals for consideration to the revision of Directive 2001/83 EC

In line with **recital 17**, page 5 of the Directive 2001/83 the EANM proposes to **further elaborate on specific provisions for RPs** to create a legislative framework that takes the latest developments into consideration. The EANM strongly believes that this will not only help to **increase the level of compliance** among Member States but will also **support harmonisation** across Europe while **safeguarding patient access** and **ensuring robust supply chains** as well as ample research opportunities.

The EANM sees the need for adaption of the Directive 2001/83 in the following areas:

- Definition of terms to reflect today's nuclear medicine and radiopharmacy practices
- Differentiation in regulations between kit-based RP preparation and complex RP preparation
- Differentiation in regulations considering production settings (commercial vs in-house)
- Evaluation if dedicated guidelines for the in-house preparation of RPs for non-commercial use within healthcare establishments could be implemented in the revision

EANM has identified the following points for consideration in the context of a review of the Directive 2001/83 EC:

1. Issues relating to the Marketing authorisations for radiopharmaceuticals and starting materials

a) Rationale

As outlined above in Table 1 the current Directive 2001/83 is based upon one RP production method only, which is the traditional *kit-based preparation*. Based on former needs, the **Directive requires marketing authorization** for each of the used starting materials, namely radionuclide generators, (radionuclide) kits and radionuclide precursors/radionuclide precursor radiopharmaceuticals. Meanwhile, however, scientific and technological developments have led to another form of preparation for RPs in addition, that is commonly referred to as *complex preparation* – the elements of which (= starting materials for complex RP preparation) are not specifically considered in the Directive. This gap in legislative guidance has led to the interpretation that marketing authorization has to be fully applied also to the starting materials used in the novel complex RP preparations that did not exist at the time the Directive was written, including e.g. disposable cassettes used for automated synthesis procedures or reagents.

This leads to:

- De-facto overregulation and unnecessary additional administration
- In consequence to a significant increase in need of resources (financial, staff etc.)
- Resulting in a lack of commercial interest to provide some of the starting materials impacting its supply negatively

Excursus – Kit-based RP preparation

In this traditional type of RP preparation a non-radioactive part (= precursor; a chemical molecule) and a radioactive part (= radionuclide) are combined. The formulation in which the precursor is provided (containing all necessary reagents and additives such as buffers) enables/facilitates an easy combination process hence the name “kit”.

While non-radioactive kits are purchased from commercial vendors, the radionuclides can either be obtained from an external supplier or produced at the healthcare establishment by means of a radionuclide generator.

The kit-based RP preparation can easily be compared with a reconstitution process (even if it is not a reconstitution in the strict sense of the word, as the active pharmaceutical ingredient is only formed during the process). As such the risk of any microbiological contamination during these kit-based RP preparations is minimal. Usage instructions for the kit are based on the methods

developed and validated by the marketing authorisation holder of the kit including limited but adequate quality control procedures and have to be strictly followed by the user. **Consequently, the kit-based RP preparation using licensed starting materials that have a marketing authorisation do not require a marketing authorisation of the final product when prepared by professionals who are allowed to do so according to national laws and are also exempted from the scope of Annex 3 defining GMP requirements for RPs.**

Excursus - Complex RP preparation

These novel RP preparation procedures are - as the name already suggests – more advanced and involve typically not only multiple processing steps but also different starting materials as compared to the traditional kit-based RP preparation.

The complex RP preparation process involves several synthesis and purification steps and a sterilization procedure and are (in most member states) either subject to a manufacturing authorization or are performed within the practices of pharmacy.

The RPs that are prepared by these complex procedures are subject to extensive quality control measures as defined by the applicable **European Pharmacopoeia** monographs before application to the patient.

The need for a dedicated marketing authorization for starting materials that are used in this type of preparations is a clear overregulation and leads to restricted availability of the starting materials.

b) What EANM is calling for relating to Marketing authorisations for radiopharmaceuticals and starting materials

Based on the above, the EANM suggests considering the following in the revision of the Directive 2001/83:

- A revision of existing definitions relating to especially the radionuclide generator, (radionuclide) kit, the radionuclide precursor, and the radionuclide precursor radiopharmaceutical
- A clear distinction between kit-based RP preparations and complex RP preparations in the entire document

In specific, the EANM suggests that

- For the novel complex RP preparations only the final product (= the actual RP delivered to the patient) and not the individual starting materials shall be subject to a marketing authorisation if intended for commercial distribution through industrial providers. For

complex in-house preparation¹ of RPs for non-commercial use in the healthcare establishment no marketing authorisation shall be required for the final product, as already established for kit-based preparations in Article 7 of the current directive

- Only for kit-based RP preparations that are carried out under facilitated conditions the need for a marketing authorization of the starting materials shall be kept, as it is justified.

In regard to manufacturing authorization, it has to be mentioned that Member States regulate these requirements on national level. Some Member States recognise the particularities of RP preparation to the extent that they grant explicit exceptions for RP preparations.

2. Issues relating to the Good Manufacturing Practice (GMP) for in-house preparation of Radiopharmaceuticals

a) Rationale

The Directive 2001/83/EC applies broadly “to industrially produced medicinal products for human use intended to be placed on the market in Member States” (Article 2), stating that the development of all these medicinal products must comply (Article 8) with the current standards of Good Manufacturing Practice (GMP), developed in Commission Directive 2003/94/EC.

The GMP guidelines ensure the highest standards of quality in any process that involves the manufacture of health products and are a necessary condition for the permission to produce pharmaceuticals for human use (manufacturing authorisation).

While the Directive is also applicable to RPs (at least the commercially produced RPs), the need for a special regulatory framework was acknowledged by the European Commission for GMP handling by the adoption of **Annex 3 to the EU Guidelines to Good Manufacturing Practice specifically on the Manufacture of RPs (2008), setting specific requirements in terms of GMPs for RPs**, which was very much welcomed by EANM.

The current GMP regulations are, however, not fully fit for purpose, in particular given the above outlined scientific and technological advancements relating to the novel complex RP preparations. Overall, compliance with general GMP in the clinical settings is highly challenging with the framework being unsuitable as it was not intended for this type of in-house preparation.

This resulted in:

- Disproportional increase of quality assurance processes that are not fit-for-purpose
- Slowing down and hindering innovations

¹ In-house preparation and use of RPs are a vital part of the clinical routine for various nuclear medicine applications. A detailed description and analysis as well as professional guidance will be given in a separate statement on in-house production of RPs that will be available in early 2022.

- Ultimately impacting negatively on patients not receiving innovative diagnostic or therapeutic treatments in certain member states

Excursus: RPs in the Clinical Trials Regulation

In this context, the EANM welcomed the introduction of the new European Clinical Trials Regulation in 2014, which recognised for the first time the special characteristic of RPs and relaxes some of the GMP requirements for investigational medicinal products in the case of preparation of diagnostic radiopharmaceuticals, mainly applicable to in-house preparations. However, a dedicated definition of the quality framework for this type is generally missing in the EU legislation.

b) What EANM is calling for relating to GMP for radiopharmaceuticals

Based on the above, the EANM suggests considering the following in the revision of the Directive 2001/83:

- Adding and adopting **specific articles** concerning RPs that are prepared **in-house, non-commercially** outside the usual marketing authorisation track, defining a dedicated quality framework for this practice².
- Some memberstates enforce GMP for kit-based RP preparation, we believe **GMP regulations should not apply to preparations using marketing authorised kits with marketing authorised radionuclide generators**³.

3. Adequate training for responsible persons

The current education and training requirement laid down in the Article 49 of the Directive on qualified healthcare professionals are not fitting the needs of the nuclear medicine services any more. Indeed, (small-scale) preparation of radiopharmaceuticals requires in-depth knowledge of radiochemistry, radiation safety, automated procedures and other aspects in particular for the persons responsible, which are not required for Qualified Persons as defined in the Directive.

Recognising that the nuclear medicine sector needs an adequately trained workforce and that such training is uneven across the European Union, EANM is supporting for more than two decades a

² Specifically we would like to highlight that the EANM has published guidance documents related to good practices in the small-scale preparation of RPs. These guidelines on current good radiopharmacy **practice (cGRPP) for small-scale preparation of radiopharmaceuticals** provide guidance to the community, while following the layout of the EU GMP guidelines. It is specifically intended for non-commercial sites such as hospital radiopharmacies, nuclear medicine departments, research PET centres and in general any healthcare establishment. The intention is that the guideline will assist radiopharmacies in the preparation of diagnostic and therapeutic RPs safe for human administration. **This professional guidance document could be the basis for specific regulations for RPs outside the marketing authorisation track.**

³ In this case the RP preparation follows exactly the steps and processes of the usage instructions that are intended by the marketing authorization holder and have been subject to review and approval during the previous marketing authorization process which process the safety of the procedure. Consequently, GMP/manufacturing regulations applied in this case are only reiterating the marketing authorisation process and are considered unnecessary.

dedicated European wide [Post Graduate educational programme](#) that intends to provide the minimum basic educations for specialists being responsible for the preparation of in-house RPs. **Recognition of such dedicated, highly specialised programmes within the Directive would ensure appropriate qualifications of the responsible person in this setting.**

4. Varia

In addition to the review of the Directive 2001/83, other legal frameworks should be adapted by better implementation in order to facilitate the delivery of the new generation of RPs.

- **EMA guideline on radiopharmaceuticals** issued by the committee for human medicinal products in 2008 requests the definition of a **single** radioactivity concentration at time of calibration. Given the fact that the amount of radioactivity obtained in the manufacturing process (radiosynthesis) is subject to the radiochemical yield, the concentration can only be altered by volume adjustment, i.e. dilution. This otherwise unnecessary dilution process is technically demanding and implies further handling of the product solution, which is in principle associated with technical failure possibilities and risk of contamination. For radiopharmaceuticals with very short half-lives of the radioisotope (minutes to hours), the adjustment to a defined radioactivity concentration is of no further use since the adjusted concentration value will be valid only for the specific time point at the end of the dilution process. The dosage for the individual patient is exclusively prepared based on radioactivity measurement at the time of application and not based on the activity concentration declared by the manufacturer. EANM therefore suggests to revise the EMA guideline with regard to this point and suggests the definition of a concentration **range** instead. By defining suitable minimum and maximum values for the radioactivity concentration the minimum and maximum volumes required for a patient dose can easily be controlled and especially the problem of instability of the drug substance due to radiolysis can adequately be addressed by an upper concentration limit.
- **The Clinical Trial Regulation 536/2014** Article 68 already acknowledged that the general rules on labelling are inappropriate in view of the very controlled setting of the use of radiopharmaceuticals. The same considerations should also apply to in-house produced radiopharmaceuticals outside clinical trials.
- A **harmonisation of RP nomenclature** (EANM has published guidance documents in this respect) on labels would be useful.

The European Association of Nuclear Medicine would be pleased to further develop suggestions and recommendations with regard to the review of the European Pharmaceutical legislation.