European Association of Nuclear Medicine (EANM) suggested amendments on Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

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Radiopharmaceuticals (radioactive medicinal products) have seen a tremendous development over the past two decades and are becoming ever more important for many clinical applications in both diagnosis and therapy. Therefore, the European Association of Nuclear Medicine (EANM) has proposed adaptation of the regulatory framework, namely the Directive 2001/83/EC.

However, the recent proposal for the revision of the EU Pharmaceutical Legislation by the European Commission as well as the compromised amendments voted by the European Parliament in April 2024 do not contain any changes regarding radiopharmaceuticals reflecting these developments.
The EANM therefore proposes three changes to the current proposal aiming at refining definitions and paragraphs relating to radionuclides, kits and starting materials with the aim:

1.) To **ensure patient access** to radiopharmaceuticals by overcoming unclear requirements for the local preparation in hospitals and Nuclear Medicine departments leading to significant national differences and health care practices.
2.) **To harmonise regulatory views** and requirements in the preparation of radiopharmaceuticals that cannot be centrally supplied and, therefore, have to be prepared locally.
3.) To **clarify legal requirements for producers** providing novel technologies (including radionuclides and starting materials), ensuring Europe`s leading role in this field

Technical details and extended justifications can be found in the below table with the proposed amendments.

European Commission legislative proposal		EANM suggested amendment	Rationale/Justification
Article 4 - Definitions	(20) 'kit' means any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration;	(20) 'kit **for radiopharmaceutical** preparation' **means a pre-formulated medicinal product containing all ingredients required to directly prepare a** radiopharmaceutical**, with the exception of the radionuclide;**	The short half-life of radionuclides in radiopharmaceuticals, and/or instability of the radiolabelled compound (by e.g. radiolysis), often results in a very short shelf-life of the final product. This requires unique strategies for industry to develop and provide a drug product with high and consistent quality. A kit for radiolabelling provides a safe and effective solution for this unique situation, with the preparation of the final radiopharmaceutical conducted close to the patient. Manufactures of kits provide a fully developed medicinal product, with a specific formulation of defined quality and clinical studies ensuring safety and efficacy (performed with the final radiolabelled formulation), which is the basis for a marketing authorization for the kit. Since there are immediate consequences resulting from the use of "kits" (exemption from the need for a marketing authorization of the final product in Article 16, Nr. 2 of both the commission's proposal and the "old" directive (Dir 2001/83, Article 7)), a **clear and unambiguous definition** of a "kit" is mandatory. The current definition of "kit" is based on the practices available at the time of the 2004 directive amendment but does not reflect the technological advances and future developments in the field, in particular in the context of "complex radiopharmaceutical preparations", where chemical precursor alone or technical tools for radiosynthesis such as reagent sets or cassettes are being used, which **should not fall under exemption of Art. 16, No2,** but be supervised via the final product. Additionally, without a clear **distinction between "kits" and other starting materials** providers of these types of starting materials (reagent sets, cassettes etc.) will withdraw their products, in particular related to the need to provide safety and efficacy data. This is, from a scientific point of view, not appropriate and often not possible for starting materials, which often are not linked to a specific final product.

			Impact: So called "kits" rightfully require a marketing authorization by the manufacturer based on clinical data to show safety and efficacy thereby exempting the final product prepared locally. A large number of other starting materials should clearly **not fall** under this umbrella. This proposal ensures that clinically established diagnostic radiopharmaceuticals and their supply will remain **available for patients in need of these products in many member** states and **innovation and development** in this field, in which Europe is playing a leading role, **is not hampered**. .
Article 16 - Radiopharmaceuticals	1. A marketing authorisation shall be required for radionuclide generators, kits, and radionuclide precursors, unless they are used as starting material, active substance or intermediate of radiopharmaceuticals ~~covered by a marketing authorisation under Article 5.~~	1. A marketing authorisation shall be required for radionuclide generators, kits, and radionuclide precursors, unless they are used as starting material, active substance or intermediate of radiopharmaceuticals.	The suggested change removes the link to the marketing authorisation of the final product for which the radionuclide, kit or radionuclide generator is a starting material. The proposal by the Commission would exempt only starting materials from the need for a marketing authorization if the final product is covered by a marketing authorization. A large number of radiopharmaceuticals has to be prepared in-house in a hospital pharmacy (or equivalent department) for immediate application to the patient due to reasons of stability and physical half-life. These radiopharmaceuticals are **by nature not covered** by a marketing authorization. Even if these preparations are performed under a manufacturing license and GMP, the **starting materials are often not available** if the supplier does not apply for a marketing authorization. There is no scientific reason for the link to the marketing authorisation process in this context, as starting materials are to be processed and not applied directly to patients without full quality control of the final product. A need for a marketing authorization for starting materials represents a clear overregulation for radiopharmaceutical products that is not existing for any other types of medicinal products! Impact: The supply of a large number of radionuclides that are needed as **starting materials** for in-house production of commercially not available radiopharmaceuticals is in threat. The

			proposed change will ensure that patients will have **access to radiopharmaceuticals that need to be prepared locally** and lead to a more harmonized regulatory view on this topic.
Article 142 – Manufacturing Authorisation	1.Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to authorisation (the "manufacturing authorisation"). <...>	1.Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to authorisation (the "manufacturing authorisation"). <...> **6. A manufacturing authorisation shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorised, according to national legislation, to use such radiopharmaceuticals in an approved healthcare establishment exclusively from authorised radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.**	Radiopharmaceuticals prepared from kits with marketing authorisation are intended to be used within the facility where it is being used (usually the healthcare establishment), which works under the umbrella of national legislation covering such practices. **No additional manufacturing authorization requirement should be in place.** This would also be in line with Article 61 Nr. 5 b) of the Clinical Trial Regulation, in which the radiopharmaceutical production of an investigational medicinal product does not require a manufacturing authorisation. Impact: This clarification would help users in member states, avoid unnecessary bureaucracy and **ensure patient access to locally prepared radiopharmaceuticals**, especially **in small health care centres** providing nuclear medicine services. In addition, if this clarification is **not added**, there will be the **contradicting situation,** that for **routine preparations** a manufacturing authorization **is needed** while the preparation of diagnostic radioactive **investigational medicinal products** is possible **without manufacturing authorization**.