The new EU Pharmaceuticals Law is a very important legislation for the future of healthcare in the European Union and we, the **German Society for Nuclear Medicine** (**DGN**) and the **Professional Association of German Nuclear Medicine Practitioners (BDN)** together with the **European Association of Nuclear Medicine (EANM)** would like to emphasise some specific aspects that touch on the field **of in-house production** of radiopharmaceuticals.

The **EANM**, as the largest organisation dedicated to Nuclear Medicine in Europe and representing **Nuclear Medicine healthcare professionals**, jointly with DGN and BDN representing the majority of the **German Nuclear Medicine practitioners**, have been following closely the **revision of the EU general pharmaceuticals legislation**, as well as all related European initiatives pertaining to medical applications of ionising radiation.
Together, we aim at **advancing science and education in Nuclear Medicine for the benefit of public health**, and therefore welcome the attention that Nuclear Medicine has been receiving in the recent years as an effective way to manage many diseases.

As a medical application of nuclear technology, Nuclear Medicine uses radioactive drugs (radiopharmaceuticals)**,** which are employed to diagnose (by imaging) or to treat patients. **Every year, more than 9 million patients in Europe benefit from the use of radiopharmaceuticals** in Nuclear Medicine for unique diagnostic procedures and specific targeted treatment options, with a large number of different radiopharmaceuticals in clinical use in Europe.
Radiopharmaceuticals are a very diverse class of medicinal products with radioactivity as the common denominator. The **radioactive decay** requires **unique logistical challenges** for radiopharmaceuticals due to short (days) to very short (minutes) half-lives of the radionuclides, thus keeping ready-available stocks impossible. Therefore, a considerable fraction of all radiopharmaceuticals that are applied to patients must be prepared **on-site in the hospital**, often for a single patient only, and used immediately, i.e. within minutes after production and quality testing is finished, justifying the need for special consideration for radiopharmaceuticals.

The preparation of radiopharmaceuticals in hospitals mostly takes place at the immediate point of use, in the Nuclear Medicine department, i.e. **outside** the legal framework associated with a hospital pharmacy. Therefore, the preparation of radiopharmaceuticals often is not covered by the (hospital) pharmacy exemption (i.e. magistral and officinal preparation, (Article 1, 5. (a) and (b) of the Commission's proposal). Nevertheless, the hand-over from the radiopharmacist to the Nuclear Medicine physician is in some Member states - from a (national) regulatory point of view - considered as a “placing on the market” situation. Being outside the pharmacy exemption has considerable impact on the regulatory aspects of both the **process** (preparation of) and the **medicinal product** (the

radiopharmaceutical): in principle, the former would need a manufacturing authorization, the latter would need a marketing authorization.
Since the Community Code Directive was restricted to industrial processes, and the in-house preparation of radiopharmaceuticals is to be seen as "non-industrial", this type of manufacturing could be individually regulated outside the scope of the directive in the different member states.
The Commission's proposal for a **new directive** is **no longer restricted to industrial processes**. Although this change of the directives scope was intended for a different type of medicinal products it will have an (unintended) impact on the in-house preparation of radiopharmaceuticals as well, thus threatening the availability of those products for patients in need.

Therefore, EANM, DGN and BDN urge the legislators to **adapt the Directive 2023/0132 (COD) and** to ameliorate the proposal in the following aspects:

- In-house production of radiopharmaceuticals in healthcare establishments should be **included** in the general pharmacy exemptions and thus be outside the scope of the new directive, despite the fact, that (in many member states) it is not the hospital pharmacy **but radiochemists and –pharmacists allocated in Nuclear Medicine departments** who are providing the radiopharmaceuticals to the Nuclear Medicine physician.

In addition, the radiopharmaceutical landscape has changed dramatically over the last two decades with a wave of new therapeutic and diagnostic radiopharmaceuticals having been developed, that are holding the promise to represent **a new pillar of cancer care**[1] and offering new opportunities in terms of **personalised medicine**. These advances now need to be adequately supported by a **tailored regulatory framework** in order to maintain Europe's leadership position in this field. Adaptive regulatory frameworks as proposed in Article 28 in the Commission proposal, should therefore also be considered for radiopharmaceuticals. As a foundation, this includes a revision of very basic concepts such as the **definitions** that are used to characterise and regulate the medicinal product, i.e. the radiopharmaceutical, including the preparation process and the starting materials that are needed.
EANM, DGN and BDN therefore welcome the inclusion of revised definitions touching the field of radiopharmaceuticals in the first draft report on the commission's proposal by the European Parliament Committee on the Environment, Public Health and Food Safety (ENVI-PR-753470_EN). However, one definition that was proposed is missing in this context:
The current legislation is ambiguous about the term "kit" and does not clearly define that a kit is a fully developed medicinal product, with a specific final radio-labelled formulation backed up by clinical studies (which are performed with the final radiolabelled formulation) in contrast to the chemical precursor alone or technical tools for radiosynthesis such as reagent sets or cassettes. Therefore, the inclusion of a new definition for a kit[2] was highly appreciated.
However, the process of preparing a radiopharmaceutical from a kit needs a clear definition as well.
Therefore, we strongly recommend to add the following definition on "kit-radioabeling" to the defintions in Article 4.

[1] European Commission (2021). Europe's Beating Cancer Plan, COM (2021/44), p. 19.

[2] (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;

(20a) 'preparation of a radiopharmaceutical from a kit (kit-radiolabeling)' means reconstitution and subsequent radiolabeling of the pre-formulated sterile medicinal product according to the instructions including specified quality control requirements outlined in the Summary of Product Characteristics (SmPC).

The suggested definition would clarify that 'kit-radiolabelling' is the combination of sterile components (kit for radiopharmaceutical preparation and eluate from radionuclide generator or a radionuclide for radiolabelling) in a direct way, i.e., a clear description of the concept of a "kit for radiopharmaceutical preparation". It is of high importance to consistently implement this concept and encourage innovation even in cases where a centralised production of the radiopharmaceutical is technically and logistically not achievable. It is therefore important to add a definition specifically for radiolabelling of a kit, setting it apart from "manufacturing" thereby correcting differences in local requirements for a manufacturing license for the radiolabelling of an authorized kit.

The EANM, DGN and BDN strongly believe that the above points will not only help to increase the level of compliance among Member States but will also **support harmonisation across Europe** while ensuring patient's safety and patient access to radiopharmaceuticals, supporting robust supply chains as well as ample research opportunities.

Since in Germany (in contrast to other European member states) the reconstitution-like kit-based compounding of radiopharmaceuticals from exclusively authorized starting materials (i.e. licensed "kit" and generator eluate from licensed radionuclide generators) is considered "manufacturing", we strongly recommend that the new Directive should explicitly state that
Kit-based radiopharmaceutical compounding are **exempted from the need of a manufacturing authorization** regardless of taking place within a hospital pharmacy or a Nuclear Medicine department.

References:

- Joint statement of the European Association of Nuclear Medicine (EANM) and Nuclear Medicine Europe (NMEU) on the revision of the EU Pharmaceutical Legislation – Time to Act for Nuclear Medicine (October 2023)
- Joint Statement of the European Association of Hospital Pharmacists (EAHP) and the European Association of Nuclear Medicine (EANM) on the availability of radiopharmaceuticals in the context of the revision of the general pharmaceutical legislation (December 2022)
- The revision of the pharmaceutical legislation — it is time to act for nuclear medicine in Europe: https://link.springer.com/article/10.1007/s00259-023-06472-1

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, also taking into consideration the ENVI draft report dated from October 3rd

European Commission legislative proposal		**European Parliament draft negotiating position**		**EANM suggested amendment**	**Rationale/Justification**
Recital 19	This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom, ~~including with respect to justification and optimisation of protection of patients and other individuals subject to medical exposure to ionising radiation. In the case of radiopharmaceuticals used for therapy, marketing authorisations, posology and administration rules have to notably respect that Directive's requirements that exposures of target volumes are to be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended therapeutic purpose of the exposure.~~	Amendment 5 – Recital 19	This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom.	**Any rules governing radiopharmaceuticals must take into account the provisions of COUNCIL DIRECTIVE 2013/59/EURATOM of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation (2) and subsequent directives, the objective of which is to prevent the exposure of the general public, workers, volunteers or patients to excessive or unnecessarily high levels of ionising radiation, and in particular of Article 28 (a) and (c) thereof, which subjects the use of radioactive source to regulatory control of such medicinal products and Article 56 requiring for all medical exposure of patients for radiotherapeutic purposes, that exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.**	The introduction of Directive 2013/59/Euratom (BSS directive) requires to update the reference regarding specific authorization of the use of radioactivity in the context of medical applications (and with it radiopharmaceuticals), as rightly indicated by Article 4.1 of the Directive 2001/83/EC, i.e., community rules on medicinal products should not contradict the BSS Directive. Additionally the BSS directive has introduced the requirement to individually plan treatment involving ionising radiation, which includes therapy with radiopharmaceuticals. The missing alignment of the current directive 2001/83/EC with this requirement in the BSS directive has caused an unclear situation in Member States and should be clarified. It is acknowledged that in Recital 19 of the proposed legislation reference is made to the Basic Safety Standards Directive (Council Directive 2013/59/Euratom) which needs to be taken into consideration for Radiopharmaceuticals. However, neither the positioning (as a Recital) nor the verbatim quote of the Euratom Directive (which in the spirit of the European Commission's own pledge for regulatory harmonisation through SAMIRA Action Plan should be avoided) are expected to help in establishing a clear and feasible approach for radiopharmaceuticals which takes into account the major innovations in the field and aligns the regulatory provisions of BSSD and pharma legislation.

Recital 137	To achieve a better security of supply for medicinal products in the internal market and to contribute thereby to a high level of public health protection, it is appropriate to approximate the rules on monitoring and reporting of actual or potential shortages of medicinal products, including the procedures and the respective roles and obligations of concerned entities in this Regulation. It is important to ensure continued supply of medicinal products, which is often taken for granted across Europe. This is especially true for the most critical medicinal products which are essential to ensure the continuity of care, the provision of quality healthcare and guarantee a high level of public health protection in Europe.	Ø	Ø	To achieve a better security of supply for medicinal products in the internal market and to contribute thereby to a high level of public health protection, it is appropriate to approximate the rules on monitoring and reporting of actual or potential shortages of medicinal products, including the procedures and the respective roles and obligations of concerned entities in this Regulation. It is important to ensure continued supply of medicinal products, which is often taken for granted across Europe. This is especially true for the most critical medicinal products which are essential to ensure the continuity of care, the provision of quality healthcare and guarantee a high level of public health protection in Europe. **To combat shortages and ensure wide accessibility for patients, medicinal products prepared for individual patients in a pharmacy according to a medical prescription "magistral formula", or according to the pharmacopoeia and intended to be supplied directly to patients served by the pharmacy "officinal formula", may be used. This should also be applicable to radiopharmaceuticals. Since radiopharmaceuticals often are prepared in Nuclear Medicine departments (outside the (hospital) pharmacy practice) the applicability of magistral and officinal formulae**	Compounding, preparing and manufacturing are unique activities of the pharmacy profession. Compounding is essential for patient care since it closes the gap between licensed medicinal products manufactured by the industry and the lack of treatment options for certain patient groups and individual patients with unmet medical conditions or needs. This includes situations where there are shortages. To further enhance patient care in Europe, EANM calls on health systems to create an environment which enables the provision of compounding services by hospital pharmacists based on the European Statements of Hospital Pharmacy. Thus, it should be specified that pharmacy preparations are one of the options to address certain medicine shortages. This also includes radiopharmaceuticals.

				has to be extended to Nuclear Medicine departments.	
Article 1 - Subject matter & scope	(2) This Directive shall apply to medicinal products for human use intended to be placed on the market.	Ø	Ø	***Please refer to Amendment 57 – Article 16***	The previous Directive only applied to "medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process". With this new wording, the revised Directive would also cover non-industrial manufactured radiopharmaceuticals. EANM is aware that the change reflects the commitment of the European decision-makers to have an all encompassing legislation. However, the current wording will very likely create numerous uncertainties with regards to in-house production, which is non-industrial, but can, in some member states interpreted as "placement to the market". Therefore, the EANM has identified numerous consequences triggered by this change, and has therefore developed a proposal to mitigate this change of scope. Non-industrial processes are an important practice for radiopharmaceuticals, and because of the absence of specific considerations for radiopharmaceuticals, we believe that this practice should be exempt from the scope of the Directive to allow further innovation, as it was initially intended to. The European Commission´s proposal wording will certainly lead to numerous uncertainties, with regards to the meaning of placement on the market. In the case of the in-house production of radiopharmaceuticals, this could be understood, in some EU countries, as the handing over of the radiopharmaceutical from the radiopharmacist to the physician.

					As such, and to mitigate this uncertainty, the EANM has proposed an amendment to Article 16, clarifying the meaning of placement on the market for radiopharmaceuticals.
	(4) In cases where, taking into account all its characteristics, a product falls within the definition of a 'medicinal product' and within the definition of a product covered by other Union law and there is a conflict between this Directive and other Union law, the provisions of this Directive shall prevail.	Ø	Ø	4. In cases where, taking into account all its characteristics, a product falls within the definition of a 'medicinal product' and within the definition of a product covered by other Union law and there is a conflict between this Directive and other Union law, the provisions of this Directive shall prevail. **(a) Nothing in this directive shall in any way derogate from Council Directive 2013/59/Euratom.**	See the rationale for Recital 19.
	(5) The Directive shall not apply to: (a) medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient ('magistral formula'); (b) medicinal product prepared in a pharmacy in accordance with a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question ('officinal formula'); (c) investigational medicinal product as defined in Article 2, paragraph 5, of Regulation (EU) No 536/2014.	Ø	Ø	5. The Directive shall not apply to: (a) medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient ('magistral formula'); (b) medicinal product prepared in a pharmacy in accordance with a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question ('officinal formula'); (c) investigational medicinal product as defined in Article 2, paragraph 5, of Regulation (EU) No 536/2014; **(d) radiopharmaceuticals, prepared in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process or in accordance with a pharmacopoeia and if the**	Due to the short half-life of the radionuclides used, radiopharmaceutical preparation in-house is an essential practice for nuclear medicine. It is usually regulated nationally and carried out in accordance with "good radiopharmaceutical practices". In light of this, the preparation of radiopharmaceuticals for in-house use should be exempted. The wording of this exemption is aligned with the wording included in the Clinical Trial Regulation No 536/2014. The magistral and officinal formula mentioned in (a) and (b) do not cover this type of preparation in several Member States, since the preparation is performed outside of the hospital pharmacy (i.e. in the Nuclear Medicine department).

				radiopharmaceutical is intended to be used in-house.	
Article 4 - Definitions	(2) 'substance' means any matter irrespective of origin, which may be: <...> (d) chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis; <...>	Amendment 38 – Article 4	(2) 'substance' means any matter irrespective of origin, which may be: <...> (d) chemical, e.g. elements, **including radioactive isotopes thereof (radionuclides)**, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis;	Ø **The EANM has been extremely pleased to see numerous amendments related to the definitions of Radiopharmaceuticals in the EP draft negotiation position. We firmly believe that such updated definitions will lay the foundation of an updated regulatory framework with adjustments for unique aspects of radiopharmaceuticals and radiopharmacy practices.**	The common denominator which sets radiopharmaceuticals apart from all other medicinal products is the radioactive component. So far this radioactive component (= radionuclide) is not accounted for under the definitions for "substances", and a proposal is made to fill this gap.
	(4) 'starting material' means any material from which an active substance is manufactured or extracted;	Amendment 39 – Article 4	(4) 'starting material' means any material, **including radioactive materials**, from which an active substance is manufactured or extracted;		The radionuclide may be the active substance of the radiopharmaceutical, however, more often it is only part of an active substance comprised of a chemical (carrier molecule) to which the radionuclide is bound. In such cases the radionuclide is a starting material, hence it is proposed to add radionuclides to the "starting material" definition.
	(18) 'radiopharmaceutical' means any medicinal product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose;	Amendments 40, 41 & 42 – Article 4	(18) 'radiopharmaceutical' means any medicinal product that, when ready for use, contains **a radioactive component and that is intended to treat or diagnose a disease, including radionuclide radiopharmaceuticals and complex radiopharmaceuticals, not including**		Radiopharmaceuticals are diverse and constantly evolving. Ambiguity in the current definitions has resulted in variability in Member State interpretations for this product class, introducing inconsistencies in authorisation and impeding progress in this innovative area in the EU. While in the past most radiopharmaceuticals were used to diagnose a disease (= diagnostic radiopharmaceuticals or imaging agents), today's innovation lies to a great extent with the use of radiopharmaceuticals for treatment of diseases (therapeutic radiopharmaceuticals). In addition, specific imaging agents now play an important role in the targeted selection of patients for treatment

			radionuclides **used only for radiolabelling purposes, medical devices and in-vitro diagnostic devices;** **(18a) 'radionuclide radiopharmaceuticals' means a radiopharmaceutical where the radionuclide or its salt is the active substance;** **(18b) 'complex radiopharmaceutical' means a radiopharmaceutical where the radionuclide is bound to or within a carrier molecule to achieve the targeted accumulation, including ready-to-use dosage forms and kits for radiopharmaceutical preparation;**		(radioactive and non-radioactive), something that previously was only done with *in vitro* diagnostic tests. These proposed definitions are to ensure that future guidelines appropriately address potential uses of diagnostic and therapeutic radiopharmaceuticals. This also avoids potential confusion of an *in vivo* imaging agent for patient selection (drug) with an *in vitro* diagnostic test (device) There is a wide diversity of radiopharmaceuticals coming from both different radionuclides[1] and targets . The proposed sub-definitions allow a clear link to specific regulatory pathways/guidelines for the different types of radiopharmaceuticals thereby preventing ambiguous interpretation. For regulatory purposes, the different role of the radionuclide in the radiopharmaceutical product is of major importance, thus it is proposed to include this differentiation as overarching framework in the directive and specify two categories: - "radionuclide radiopharmaceuticals" where the radionuclide is the active substance - "complex radiopharmaceuticals" where the radionuclide is bound to or within a carrier molecule. The medicinal use of radiopharmaceuticals is based on targeted accumulation of the radionuclide (and thus the radioactivity) in certain parts of the body (e.g. cancer lesions or inflamed tissue). The radionuclide sometimes accumulates on its own (e.g., ^{123}/^{131}Iodide accumulates in the thyroid gland), in which case the radionuclide is the active substance (radionuclide radiopharmaceuticals). But more

[1] Radionuclides emit different types of radiation, i.e. photons (= gamma emitters, used for imaging), positrons (=beta plus emitters, used for imaging), electrons (= beta minus emitters, mostly used for therapy) or alpha particles (= alpha emitters, always used for therapy)

-The technology to produce radionuclides ranges from reactors, over cyclotrons to radionuclide generators, with constant work on new technologies to improve quality and yield.

					recently innovative targeted products rely on the radionuclide attached to a "carrier molecule" (or ligand) which, once in the body, binds to a specific target (e.g., on cancer cells) or accumulates and brings the radioactivity to these cells. In the latter case the active substance consists of a chemical and a radioactive portion (carrier molecule and radionuclide; ("complex radiopharmaceuticals). Innovation driven by "complex radiopharmaceuticals" is not well-supported by the current regulatory framework which results in inconsistencies in presently authorised products. These variabilities create major uncertainty for industry which has the potential to hinder innovation in the field of radiopharmaceuticals in Europe. With radioactivity being a unique concept for medicinal products, there is also uncertainty where to draw the boundary to what really constitutes a radiopharmaceutical. To avoid such questions, it is proposed to spell out clearly products which are <u>not</u> radiopharmaceuticals in the sense of being a medicinal product. This includes radionuclides which are solely used for radiolabelling of a carrier molecule, i.e., they are solely the radioactive component of the active substance of a "complex radiopharmaceutical", which further highlights and clarifies the different roles a radionuclide plays in the radiopharmaceutical requires different regulatory pathways.
	(19) 'radionuclide generator' means any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical;	Amendment 43 – Article 4	(19) 'radionuclide generator' means any system incorporating a fixed parent radionuclide from which a daughter radionuclide **is produced, where the daughter radionuclide is used either as a medicinal product**		The current definition was based on the only common practice at the time of development of directive 2001/83, i.e., using 99Mo/99mTc-radionuclide generators in combination with kits. Since then tremendous development has happened and generators are used also in the context of "complex radiopharmaceuticals".

			or as a radionuclide for radiolabelling purposes;		A radionuclide generator is a system with fixed parent radionuclides which provides certain radionuclides locally at the time of use through radioactive decay. From a regulatory perspective, they need a specific definition and respectively adjusted regulatory pathways, as they neither can be seen as typical medicinal product, nor as typical device, nor as typical "substance". Some generator-produced radionuclides can be used as "radionuclide radiopharmaceutical" as defined under Art 4(18), in which case it is most appropriate to register the radionuclide generator as a medicinal product, as is presently the practice in Europe (e.g., ^{99m}Technetium generators). Other generator-produced radionuclides can only be used for radiolabelling of various carrier molecules (e.g. ^{68}Gallium), and are therefore not a medicinal product as per the proposed definitions. To ensure availability of, in case of ^{68}Ga very short-lived radionuclides (i.e., 68 minutes) for radiolabelling close to the patient, an appropriately adjusted regulatory pathway needs to be established which ensures the quality of the radionuclide and necessary access to it. This adjusted framework would be more aligned with the purpose of use (radionuclide used for radiolabelling).
	(20) 'kit' means any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration;	Amendment 44 – Article 4	(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;**	(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; **(20a) 'preparation of a radiopharmaceutical from a kit (kit-radiolabeling)' means reconstitution and subsequent radiolabeling of the pre-formulated sterile medicinal product according to the**	The short half-life of radionuclides in radiopharmaceuticals, and/or radio-instability of the radiolabelled compound (e.g.radiolysis), often results in a 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 radiolabelling step conducted close to the patient. The current definitions do not reflect the technological advances and future developments in the field, in particular in the context of "complex

				instructions including specified quality control requirements outlined in the Summary of Product Characteristics (SmPC). **Suggestion for a recital:** The preparation of a radiopharmaceutical is distinct from "manufacturing" as the specification of the final radiopharmaceutical product has been developed and tested by *the kit manufacturer and is ensured by the instructions for reconstitution and radiolabeling of the kit*.	radiopharmaceutical preparations". The current definition was based on the only practice available at the time of the 2004 directive amendment. The current legislation is ambiguous about the "kit" and does not clearly define that a kit is a fully developed medicinal product, with a specific final radio-labelled formulation backed up by clinical studies (which are performed with the final radiolabelled formulation) in contrast to the chemical precursor alone or technical tools for radiosynthesis such as reagent sets or cassettes. The legislation update provides the unique opportunity to fill this gap and provide a basis for harmonisation where the current legislation led to different interpretation and thus highly variable local implementations. As described above, the suggested definition would clarify that 'kit-radiolabelling' is the combination of sterile components (kit for radiopharmaceutical preparation and eluate from radionuclide generator or a radionuclide for radiolabelling) in a direct way, i.e., a clear description of the concept of a "kit for radiopharmaceutical preparation". It is of high importance to consistently implement this concept and encourage innovation even in cases where a centralised production of the radiopharmaceutical is technically and logistically not achievable. It is therefore important to add a definition specifically for radiolabelling of a kit, setting it apart from "manufacturing" thereby correcting differences in local requirements for a manufacturing license for the radiolabelling of an authorized kit.
	(21) 'radionuclide precursor' means any other radionuclide produced for the radio-labelling of another substance prior to administration;	Amendment 45 – Article 4	deleted	Ø **The EANM has been extremely pleased to see numerous amendments related to the definitions of Radiopharmaceuticals**	With the addition of the radionuclide to Article 4 (2) definition of substance, and Article 4 (4) definition of starting material, together with the clarification added under Article 4 (18) that a radionuclide which is solely used for radiolabelling is not a radiopharmaceutical, the current definition of a

				in the EP draft negotiation position. We firmly believe that such updated definitions will lay the foundation of an updated regulatory framework with adjustments for unique aspects of radiopharmaceuticals and radiopharmacy practices.	radionuclide precursor is no longer necessary and should be deleted. In addition, the term precursor should be avoided with regards to radioactive starting materials. In common radiopharmaceutical language, the term precursor is dedicated to the non-radioactive molecule that is used in a preparation/manufacturing of a "complex radiopharmaceutical". This confusion has led to different interpretations and practices across the EU Member States.
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.**	Amendment 57 – Article 16	1. A marketing authorisation shall be required for radiopharmaceuticals.	A marketing authorisation shall be required for radiopharmaceuticals **to be placed on the market.** **Placement on the market does not refer to radiopharmaceuticals, prepared in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process or in accordance with a pharmacopoeia and if the radiopharmaceutical is intended to be used in-house.**	There has been a tremendous development within radiopharmaceutical preparations since the introduction of the Directive 2001/83. Since many years, it has become common standard to use automated modules for many radiopharmaceutical preparations, mainly to adhere to radiation safety requirements, but also to accommodate "multi-step radiopharmaceutical preparations". This automation process has led to some confusion related to the term "industrial". Therefore, the distinction should rather be made between preparation intended to be placed on the market and in-house preparations (to be exclusively used within e.g. a hospital). The proposed change in Article 16(1) intends to clarify this context and also to align to the proposed change of definitions. Article 16(2) of the proposed Directive should be aligned with the wording used in the Clinical Trials Regulation No 536/2014 and the tremendous development of radiopharmaceuticals since the adoption of Directive 2001/83/EC. An exemption for "in-house" preparation in general is also in line with the specified exemptions of Article 1 of the proposed Directive, therefore leading to harmonisation. Additionally, it is clearer to state that radionuclide generators not intended for combination with kits with marketing authorisation are exempted from the
	2. A marketing 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 radiopharmaceutical in an approved healthcare establishment exclusively from authorised radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.	Amendment 58 – Article 16	2. A marketing authorisation shall not be required **for radionuclides or radionuclide generators solely used for radiolabelling purposes, or** for a radiopharmaceutical prepared at the time of use by **an authorised** person or establishment **using an** authorised kit for radiopharmaceutical **preparation in combination with a** radionuclide or radionuclide **generator** in		

			accordance with the **summary of product characteristics of the kit ('kit-radiolabelling').**		requirement for marketing authorization. Radionuclide Precursors are anyway suggested to be removed from the requirement for Marketing Authorization
Article 28 - Adapted frameworks due to the characteristics or methods inherent to the medicinal product	1. Medicinal products listed in Annex VII shall be subject to specific scientific or regulatory requirements due to the characteristics or methods inherent to the medicinal product, when: (a) it is not possible to adequately assess the medicinal product or category of medicinal products applying the applicable requirements due to scientific or regulatory challenges arising from characteristics or methods inherent to the medicinal product; and (b) the characteristics or methods positively impact the quality, safety and efficacy of the medicinal product or category of medicinal product or provide a major contribution to patient access or patient care.	Ø	Ø	Ø	The adapted regulatory framework mentioned in Article 28, for products whose categorisation poses regulatory and scientific challenges, could be a promising tool to accommodate the specific of in-house production of radiopharmaceuticals. Considering the high innovation pace, the theranostic developments - highly questioning the definition of radiopharmaceuticals, radiopharmaceuticals would benefit from specific regulatory requirements. Therefore the EANM very much welcomed this Article, and would welcome the inclusion of radiopharmaceuticals in Annex VII when revised, along with phage-containing medicinal products.
Article 68 – Labelling and instruction leaflet of radionuclides and radiopharmaceuticals	4. The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with Article 64(1). In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.	Ø	Ø	4. The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators or ~~radionuclide~~ kits for radiopharmaceutical preparation ~~or radionuclide precursors~~. The text of this leaflet shall be established in accordance with Article 64(1). In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special	Provided that definitions of Article 1 are amended to account for the tremendous innovation in nuclear medicine, the wording of Article 68(4) would need to be amended appropriately.

				precautions for the disposal of the packaging and its unused contents.	
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"). The manufacturing authorisation shall be required also if the medicinal products manufactured are intended for export. 2.The manufacturing authorisation referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation. 3. By derogation from paragraph 2, the manufacturing authorisation shall not be required for the following: (a) preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes; or (b) decentralised sites carrying out manufacturing or testing steps under the responsibility of the qualified person of a central site referred to in Article 151. 4. A manufacturing authorisation shall also be required for imports of medicinal products coming from third countries into a Member State. This Chapter and Articles 195 and 198 shall apply to imports of medicinal	Ø	Ø	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 by kit-radiolabelling and for radiopharmaceuticals to be used exclusively in-house.**	Radiopharmaceuticals prepared by kit-radiolabelling 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 requirement should be in place, also as such products are not intended to be placed on the market, which is also the case for other radiopharmaceutical preparations for individual patient`s needs. This would be in line with Article 16(2) of the Clinical Trial Regulation, in which the radiopharmaceutical production does not require a manufacturing authorisation; This should applied to established radiopharmaceuticals which are monographed in the Pharmacopeia (in line with recital 93).

	products from third countries. 5. Member States shall enter the information relating to the manufacturing authorisation referred to in paragraph 1 in the Union database referred to in Article 188.				
Article 160 - Rules applicable to medicinal products and active substances	The Commission may adopt implementing acts in accordance with Article 214(2) to supplement this Directive by specifying: (a) the principles of good manufacturing and good distribution practices for medicinal products complemented, where relevant, by specific measures applicable notably to pharmaceutical forms, medicinal products or manufacturing activities in line with good manufacturing principles; (b) the principles of good manufacturing and good distribution practices for active substances. Where relevant, these principles shall be specified in coherence with any principles of good practices established under any other Union legal framework.	Ø	Ø	The Commission may adopt implementing acts in accordance with Article 214(2) to supplement this Directive by specifying: (a) the principles of good manufacturing and good distribution practices for medicinal products complemented, where relevant, by specific measures applicable notably to pharmaceutical forms, medicinal products or manufacturing activities in line with good manufacturing principles; (b) the principles of good manufacturing and good distribution practices for active substances~~.~~**;** **(c) the principles of good radiopharmaceutical practices for the preparation of radiopharmaceuticals including multi-step radiopharmaceutical preparations to be used exclusively in-house.** Where relevant, these principles shall be specified in coherence with any principles of good practices established under any other Union legal framework.	While the proposed Directive is also applicable to radiopharmaceuticals (at least the commercially produced radiopharmaceuticals), the need for a special regulatory framework was acknowledged by the European Commission through the adoption of Annex 3 to the EU Guidelines to Good Manufacturing Practice (GMP) specifically on the Manufacture of Radiopharmaceuticals (2008), setting specific requirements in terms of GMPs for radiopharmaceuticals. 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 multi-step radiopharmaceutical 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 and ultimately impacting negatively on patients not receiving innovative diagnostic or therapeutic treatments in certain member states The new European Clinical Trials Regulation in 2014, recognised for the first time the special characteristic of radiopharmaceuticals and adjusts 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. The proposed name of “good radiopharmaceutical practices” (instead of “good manufacturing practices”) would also help to clarify that the scope of such guideline would cover the practices outlined above.

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-023-06472-1

EDITORIAL

The revision of the pharmaceutical legislation — it is time to act for nuclear medicine in Europe

Marianne Patt[1] · Clemens Decristoforo[2] · Amélie de Martini[3] · Michel Koole[4] · Wim J. G. Oyen[5,6,7] · Oliver C. Kiss[8]

Introduction

In the context of the reform of the European Union Pharmaceutical Framework, a very important legislation for the future of healthcare in the European Union, the European Association of Nuclear Medicine (EANM), has conducted regular advocacy efforts to bring specific aspects of nuclear medicine to the attention of the European decision-makers. This editorial aims at highlighting these aspects of the revision of the European Pharmaceutical Package that touch on the field of nuclear medicine.

The last decades have yielded tremendous advances in nuclear medicine with the advent of clinical positron emission tomography (PET) in the 1990s and the early 2000s [1], starting with the widespread use of [^{18}F]FDG and further expansion by other PET radiopharmaceuticals and the clinical establishment of ^{68}Ga-labelled somatostatin analogues in the mid-2000s [2], in combination with ^{90}Y- and ^{177}Lu-based analogues for targeted radionuclide therapy (RNT) [3], which finally lead to the approval of [^{177}Lu]Lu-DOTATATE (Lutathera™) by EMA in 2017 and, of course, the tremendous clinical success of a number of PSMA-binding ligands for PET imaging and RNT of patients with prostate cancer, resulting in the recent EMA and FDA approval of [^{177}Lu]Lu-PSMA-617 (Pluvicto™) [4].

All these developments were primarily driven by European academic institutes and clinical facilities within a regulatory environment defining these radiopharmaceuticals as medicinal products and therefore governing their use by the pharmaceutical legislation. The legal inclusion of radiopharmaceuticals into the pharmaceutical legislation was originally implemented in the Directive 89/343/EEC of 3 May 1989 [5] that also covered radionuclide generators, kits and radionuclide precursor and their authorisation requirements. The main points of this directive were incorporated into the current "Community Code Directive" Directive 2001/83/EC [6], which, together with regulation 726/2004/EC, has laid down the basic rules for manufacturing and marketing of medicinal products in the European Union for the last two decades. Despite several amendments, it has not undergone relevant changes in relation to radiopharmaceuticals since its release in 2001. At that time, nuclear medicine practice was dominated by the use of ^{99}Mo/^{99m}Tc-generators in combination with cold kits and by externally supplied, ready for use, radiopharmaceuticals. However, this situation has meanwhile changed considerably over the years with, e.g. increasing importance of in-house production [7], which currently is enabled by specific national exceptions from Directive 2001/83/EC, thus causing large heterogeneity in nuclear medicine practice and availability of radiopharmaceuticals throughout Europe. Despite the tremendous new developments of nuclear medicine having an irrefutable positive impact on the daily care of our patients and, specifically, the emerging successful applications of theranostics for both the diagnosis and treatment of cancer patients, radiopharmaceuticals were never in the focus of the European Commissions' pharmaceutical strategy.

✉ Oliver C. Kiss
o.kiss@hzdr.de

1 Section Radiopharmacy, Department of Nuclear Medicine, University Hospital Augsburg, Augsburg, Germany

2 Department of Nuclear Medicine, Medical University Innsbruck, Innsbruck, Austria

3 European Association of Nuclear Medicine, Vienna, Austria

4 Nuclear Medicine and Molecular Imaging, Department of Imaging and Pathology, KU Leuven, Louvain, Belgium

5 Department of Biomedical Sciences and Humanitas Clinical and Research Centre, Department of Nuclear Medicine, Humanitas University, Milan, Italy

6 Department of Radiology and Nuclear Medicine, Rijnstate Hospital, Arnhem, The Netherlands

7 Department of Medical Imaging, Nuclear Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands

8 Department of Targetry, Target Chemistry and Radiopharmacy, Institute for Radiopharmaceutical Cancer Research, Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Dresden, Germany

Published online: 23 October 2023

History, from the pharmaceutical strategy to the pharmaceutical package: the EANM advocacy efforts

Boosted by the COVID-19 crisis and as part of a whole package of measures put in place to build a strong European Health Union in 2020, the European Commission published a communication on a Pharmaceutical Strategy for Europe which was announced as an ambitious long-term project in the area of health, "intended to make the European pharmaceutical system more patient-centred, future-proof and crisis-resistant" [8]. Overall goals were to create a suitable legal environment for innovation, secure supply, address shortages and contribute to the overall aims of Europe's Beating Cancer Plan while maintaining high quality and safety standards, as well as reducing the overall environmental footprint, in summary an ambitious plan with well-justified rationales. Based on the above pillars, it included several legislative and non-legislative actions, with the main flagship action being the reform of the EU pharmaceutical legislation. The Pharmaceutical Strategy initially sets the goal to have a proposal for the revision of the EU pharmaceutical legislation ready in 2022. To succeed in this ambitious goal, the European Commission conducted a series of consultations and meetings to inform on the design of the reform and took account of the positions and priorities raised by stakeholders, including the EANM, interested parties and the general public.

A first public consultation in the second half of 2021 invited all stakeholders, interested parties and EU citizens to provide feedback via a questionnaire with the objective to evaluate the general pharmaceutical legislation and assess the impacts of possible changes in legislation. The EANM, as a scientifically orientated society, provided feedback to the questionnaire and took advantage of the possibility to upload a general statement emphasising the relevance of the in-house preparation of radiopharmaceuticals to address the special needs of nuclear medicine and its patients and to drive innovation. At that time, the EANM highlighted that the regulatory framework for in-house radiopharmaceuticals production is not harmonised throughout Europe and has resulted in unbalanced access to innovative radiopharmaceuticals based on national legislative particularities. The EANM therefore called for any future revision to consider the importance of in-house production of radiopharmaceuticals and ensuring quality and safety with harmonised standards and dedicated rules, such that the particular needs of nuclear medicine are taken into account.

In addition to EANM's own reply to the consultation, the statement was shared with the nuclear medicine national societies across Europe who were encouraged to provide harmonised feedback to raise awareness at the European Commission level. These efforts were well received by the European Commission, resulting in nuclear medicine practitioners being identified as one of the top ten campaigns of the public consultation, mainly thanks to the efforts of the German nuclear medicine community [9].

Furthermore, the input of EANM to the consultation resulted in an invitation by the Directorate-General for Health and Food Safety, DG Santé (which is the directorate of the European legislative body in charge of developing the revised directive) to the EANM to provide advice on how to revise the Community Code Directive in order to address the special needs of nuclear medicine and specifically radiopharmaceuticals. The EANM gratefully accepted this invitation and provided detailed suggestions on the revision, including the specific suggestion to distinguish between the two major classes of radiopharmaceutical preparation types, i.e. those that make use of licenced kits and licenced radionuclides (kit-based radiopharmaceutical compounding) on the one hand and more complex radiopharmaceutical preparations on the other hand. This proposed differentiation was accompanied by the suggestion for a revision of the existing definitions of kit and radionuclide precursor in order to restrict the need for a manufacturing authorisation to those starting materials that are used for kit-based radiopharmaceutical compounding activities which, from a regulatory point of view, are (already in the currently applicable legal framework) to be treated differently than "ordinary manufacturing practices" carried out outside a hospital pharmacy (Article 7 of Dir 2001/83/EC).

Following this extensive consultation process, the European Commission published on April 26, 2023, the legislative proposal for the review of pharmaceutical regulations. The publication, which is to be considered the most extensive reform in the pharmaceutical sector in more than 20 years, was very much welcomed by the health community. However, certain passages of the new legislation have sparked public criticism. Notably for the EANM, despite the extensive contribution to the consultation process, the legislative proposal did not include the aforementioned suggestions provided by EANM, most likely because of timelines that were too restrictive to be achieved and because of the conflictual nature of the legislative dossier.

EANM proposal/intention

Now, with the publication of the legislative proposal, the general public as well as all other stakeholders (industry, patients, national regulatory bodies, national scientific communities and EANM) is once again invited to comment and provide feedback. Since harmonised suggestions supported by many stakeholders will have by nature better chances to

be recognised, EANM has gone to great lengths to align with many other important stakeholders such as national nuclear medicine societies, patient representations, European hospital pharmacists (EAHP) and industry represented by Nuclear Medicine Europe (NMEU), hoping that this joint advocacy effort will allow the nuclear medicine community to have a much stronger impact on the ongoing and upcoming debates by speaking with a unified and common voice.

Three main topics have been identified by EANM

1. As was stated above, developments in radiopharmacy within the last two decades have shown that the current definitions with regard to radiopharmaceutical preparations are no longer fully applicable as they were intended to cover the radiopharmaceutical practice when Directive 2001/83/EC came into force. In particular, the ascent of complex radiopharmaceutical preparations now leads to a higher availability of individual, patient-centred radiopharmaceuticals in healthcare establishments (in-house preparations), that cannot be served by large-scale manufacturers. To further improve the availability of these in-house prepared radiopharmaceuticals, EANM proposes to restrict the need for marketing authorisation solely to those radionuclide precursors and radionuclide generators that are used either in kit-based radiopharmaceutical compounding or directly as medicinal products and to embrace radionuclide precursors or radionuclide generators that are used in complex radiopharmaceutical preparations as starting materials. This would highly increase the availability of radionuclides and radiopharmaceuticals to radiopharmacy and nuclear medicine departments for the benefit of our patients [11].
2. The second topic is related to the very heterogeneous landscape of radiopharmaceutical preparations within Europe. Due to the short half-life of the radionuclides used, in-house radiopharmaceutical preparation is an essential practice for nuclear medicine. Radiopharmaceutical preparation has been based on pharmacy practice (commonly known as the *magistral and officinal formula*) in some member states, whereas in other member states pharmacy practice does not cover radiopharmaceuticals [12]. Depending on the member states, preparations are either carried out in "classical" hospital pharmacies or, in nuclear medicine departments, research institutes and other entities to accommodate the specificities of radiopharmaceuticals. This is most of the time covered by specific national legislation, originating from the current wording of the Directive 2001/83/EC. This heterogeneity has already been identified in the revision of the Clinical Trial Directive and within the new Clinical Trial Regulation No. 536/2014 [10], by including the exemption for manufacturing authorisation for the "Preparation of radiopharmaceuticals, if this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such process, and if the radiopharmaceutical is intended for 'in-house' use" (introduced in 2014 and with effect from 2023). The EANM proposes a similar provision for the revision of Directive 2001/83/EC.
3. The Council Basic Safety Standards Directive 2013/59/Euratom (BSSD) [13] has introduced the requirement to individually plan treatment involving ionising radiation, which includes treatment with radiopharmaceuticals. The missing alignment of the Directive 2001/83/EC with this requirement in the BSS Directive has caused an unclear situation in member states and should be clarified with the revision. As such, the EANM was pleased to see the point (19) of the recital in the proposed revision of Directive 2001/83/EC, stating that the revised Pharmaceutical Legislation Directive should be without prejudice to any provisions of Council Directive 2013/59/Euratom. It is very clearly stated that for all aspects related to radiation protection, and to posology and administration of radiopharmaceuticals, the BSS Directive should prevail over the Pharmaceutical Legislation Directive. However, this key statement is only included in the Recital of the Directive, which does not have any binding consequences (only setting the rationale behind the legal text). This means and this is of the utmost importance, that in the amendment process, similar provisions are included in relevant articles. A typical example here is Article 4 of the revised Directive, stating that for any medicinal product, the Directive should always prevail, hence contradicting Recital (19). To align with the Recital, Article 4 should be transformed to clearly state that nothing in this Directive shall in any way derogate from Council Directive 2013/59/Euratom.

A delicate negotiation, with potential long-lasting impact on nuclear medicine: "nothing is finalised until everything is finalised"

After the publication of the legislative proposal by the European Commission, it is now in the hands of the co-legislators (the European Parliament and the Council). Following the Ordinary Legislative Procedure, the European Parliament and the Council of the EU, as co-legislators, have been preparing their positions on the overhaul of the EU medicines legislation ahead of discussions that are expected to take between 2 and 3 years.

Indeed, the main characteristic of the ordinary legislative procedure is the adoption of legislation jointly and on an

equal footing by Parliament and the Council. It starts with a legislative proposal from the Commission and consists of up to three readings, with the possibility for the co-legislators to agree on a joint text — and thereby conclude the procedure — at any reading. Due to translation issues (i.e. the texts of the proposals cannot be formally presented to the European Parliament and Council until they have been translated into all of the EU's official languages), the Parliament and Council have started to examine in parallel the Commission's proposal only in September 2023.

While they are examining in parallel the Commission's proposal, it is up to the Parliament to act first, voting by a simple majority and on the basis of a report prepared by one of its committees, in most cases either amending the Commission's proposal or adopting it without amendments. It will only after that the Parliament has adopted its position that the Council will decide to accept Parliament's position, in which case the legislative act is adopted, or it may adopt a different position at first reading and communicate it to Parliament for a second reading.

In the European Parliament, the Committee on Environment, Public Health and Food Safety (ENVI) is responsible for the file, guided by Pernille Weiss (EPP, Denmark), the rapporteur for this Directive. Work within the European Parliament on the legislation reform package has officially started on September 20th when the ENVI Committee Members met in Brussels and opened both the Commission's proposal for a new directive and regulation. Overall, the proposal to revamp the European Union's regulatory framework for pharmaceuticals was welcomed, but Members the European Parliament (MEPs) did not refrain from criticising certain aspects. Now MEPs, with the support of the Rapporteurs and Shadow Rapporteurs, will prepare their amendments to the Commission's proposal and present them by November 14th back to ENVI, aiming to reach a common position and move the discussion to the plenary.

Considering both the Commission's delay in presenting the file in spring and the delay in delivering the translations of the proposal, as well as taking into account that these discussions are expected to be delicate and conflictual, it therefore seems unlikely that the file will be approved within this mandate. Indeed, with the European Parliament election coming up in 2024, this leaves little time for the legislative process to take shape before the elections for the new European Parliament are held in June next year.

When adopted in plenary by the European Parliament, and then approved by the Council, likely somewhere in 2024, the procedure will move to the implementation stage. For the Directive, member states will receive a guideline and timetable for the implementation of the intended outcomes. With regard to the regulation, most likely, implementing regulations will be needed to ensure uniform implementation.

Thus, in light of the upcoming European elections in 2024, the negotiation process may well continue into the next mandate. Furthermore, in addition to health being a competence of the member states, the extensive and sensitive nature of the file will likely lead to lengthy negotiations in the Council of the EU. Therefore, there is no clear timeline for the adoption of the file, but the process is likely to go on until 2026 or even beyond.

In terms of immediate next steps opened to all stakeholders, a feedback consultation has been opened until November 2023, with all comments being summarised by the European Commission and presented to the European Parliament and the Council to feed into the legislative debate. In addition, at the level of the European Parliament, all stakeholders have the possibility to bring comments and feedback and suggested amendments to MEPs involved in the dossier.

The EANM is currently in discussion with several MEPs in order to suggest some amendments that would further strengthen the radiopharmaceutical provisions within the pharmaceutical package. Likewise, the EANM is replying to the European Commission's feedback consultation and is encouraging the nuclear medicine community to do the same. For the whole nuclear medicine community, it is time to act now on the national level as well!

This revised pharmaceutical package has the potential to substantially modify the way radiopharmaceuticals are prepared and delivered in the decades to come, so is the time for the nuclear medicine community to raise any challenges and concerns we might have, the EANM is welcoming comments and suggestions on this topic.

Funding Open Access funding enabled and organized by Projekt DEAL.

Data availability Not applicable.

Declarations

Ethical approval Not applicable to this editorial.

Consent to participate Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Deutsch E. Clinical PET: its time has come? J Nucl Med. 1993;34(7):1132–3.
2. Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med. 2007;48(4):508–18.
3. Krenning EP, Kwekkeboom DJ, Valkema R, Pauwels S, Kvols LK, De Jong M. Peptide receptor radionuclide therapy. Ann N Y Acad Sci. 2004;1014:234–45.
4. Hennrich U, Eder M. [177Lu]Lu-PSMA-617 (PluvictoTM): the first FDA-approved radiotherapeutical for treatment of prostate cancer. Pharmaceuticals (Basel). 2022;15(10):1292.
5. Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals. Official Journal of the European Communities. 1989. http://data.europa.eu/eli/dir/1989/343/oj/eng. Accessed 27 Aug 2023.
6. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Communities. 2001. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML. Accessed 27 Aug 2023.
7. Hendrikse H, Kiss O, Kunikowska J, Wadsak W, Decristoforo C, Patt M. EANM position on the in-house preparation of radiopharmaceuticals. Eur J Nucl Med Mol Imaging. 2022;49:1095–8.
8. A pharmaceutical strategy for Europe. European Commission. 2023. https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en. Accessed 27 Aug 2023.
9. Have your say - revision of the EU general pharmaceuticals legislation. European Commission. 2023. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation/F_en. Accessed 27 Aug 2023.
10. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union. 2014. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf. Accessed 27 Aug 2023.
11. Neels O, Patt M, Decristoforo C. Radionuclides: medicinal products or rather starting materials? EJNMMI Radiopharm Chem. 2019;4(1):22.
12. Decristoforo C, Penuelas I, Patt M, Todde S. European regulations for the introduction of novel radiopharmaceuticals in the clinical setting. Q J Nucl Med Mol Imaging. 2017;61(2):135–44.
13. Konijnenberg M, Herrmann K, Kobe C, Verburg F, Hindorf C, Hustinx R, et al. EANM position paper on article 56 of the Council Directive 2013/59/Euratom (basic safety standards) for nuclear medicine therapy. Eur J Nucl Med Mol Imaging. 2021;48(1):67–72.