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**

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Continuing to meet the needs of patients across Europe should, in the opinion of the European Association of Hospital Pharmacists (EAHP) and the European Association of Nuclear Medicine (EANM), be one of the guiding principles for the revision of the general pharmaceutical legislation.

Nuclear medicine is an essential treatment area for which radiopharmaceuticals are of utmost importance. Such low-volume products that are in-house manufactured or single-batch personalised medicines require particular attention in the context of the revision of the general pharmaceutical legislation. Radiopharmaceuticals are a subtype of medications 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 specialities focused on diagnostic applications only. The main fields of application for radiopharmaceuticals include oncology, endocrinology, cardiovascular and respiratory diseases and neurology. A large proportion of radiopharmaceutical development is performed by non-commercial entities like hospitals, research institutions and universities[1]. Since the availability of commercially available radiopharmaceuticals is limited, most applications of radiopharmaceuticals in daily practice are highly dependent on small-scale preparations that are compounded in-house (e.g. within hospitals) under the responsibility of the nuclear medicine department or a hospital pharmacy.

[1] European Association of Nuclear Medicine (2021). Statement of the EANM for a better inclusion of the particularities of Radiopharmaceuticals within the Review of Directive 2001/83EC on Pharmaceutical Legislation: https://www.eanm.org/content-eanm/uploads/2021/12/EANM_Radiopharmaceuticals-Directive-2001-83_Final.pdf

1) A flexible regulatory framework for low volume products

Distinguishing commercial and non-commercial preparations of medical products

Industrial Good Manufacturing Practice (GMP) principles[2] are not intended and, therefore, not suitable for low-volume products. Thus, the revision of the pharmaceutical legislation should establish clear non-industrial standards for this type of small-scale preparations that take into account, on the one hand, the scientific and technological advancements related to novel and complex radiopharmaceutical preparations and, on the other hand, the specificities of preparations in hospital pharmacies or nuclear medicine departments. While patient safety and high-quality standards for the in-house preparation of radiopharmaceuticals by non-industrial entities should be upheld, a disproportional increase of quality assurance requirements not fitting for the purpose and further measures that impede innovation should be avoided.

Due to the difference between commercial and non-commercial preparations of radiopharmaceuticals, EAHP and EANM are calling for a specific approach to the regulation of small-scale preparation of radiopharmaceuticals.

Supporting healthcare professionals and investing in education

The patient-oriented preparation of medicines is anchored deeply in pharmacy practice. Since the establishment of the profession, pharmacies have manufactured, prepared and compounded medicines to adequately respond to patient needs, especially for those individual patients or patient groups whose medical requirements cannot be met by industrially manufactured medicines. The reasons why hospital pharmacies have to prepare and compound medicines in-house stem directly from the necessity to personalise care and customise interventions to address patients' special needs. The area of application for compounding is vast. Paediatric and elderly patients particularly benefit from compounding, which offers the possibility of age-adapted drug formulation[3]. Other areas of application include patients with adherence or ingestion difficulties or allergies to components present in industrially manufactured products, as well as the preparation of radiopharmaceuticals. On the latter, due to radioactive decay, the majority of radiopharmaceuticals used for medical applications have a very short half-life and, therefore, need to be prepared extemporaneously in-house, e.g. in radiopharmacies of hospitals. For them not to lose their radioactivity and depending on their physical half-life, they are usually used and delivered to patients within minutes or a few hours after preparation, respectively.

The role and responsibilities of healthcare professionals, in particular hospital pharmacists or radiopharmacists, in the field of compounding need to be strongly anchored in the legislation so that compounding opportunities to offer adequate patient care should be enhanced. National particularities regarding those authorised to compound medicinal products should be taken into

[2] Annex 3 to the EU Guidelines to Good Manufacturing Practice on the manufacture of radiopharmaceuticals (2008) – European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

[3] Breitkreutz, Jörg & Boos, Joachim. (2007). Pediatric and geriatric drug delivery. Expert opinion on drug delivery. 4. 37-45. 10.1517/17425247.4.1.37.

account in this regard. Hospital pharmacists and radiopharmacists are indeed facing similar challenges related to recognition and education, as well as to operating in an environment which enables timely and equal access of patients to a safe supply of medication and high-quality (radio) pharmaceutical care in the hospital sector.

To further improve patient care, **EAHP and EANM encourage (health) authorities to invest in in-house production services, including compounding services and the preparation of radiopharmaceuticals, and the provision of training tailored to specific preparations, including the expansion of training opportunities.** With respect to radiopharmaceuticals, in-depth knowledge of radiochemistry, radiation safety automated procedures and radiation measurement technology are of particular importance.

Reducing the regulatory burden for small-scale preparations

Both hospital pharmacists and radiopharmacists are challenged by overregulation and the unnecessary additional administrative burden related to the requirement for marketing authorisations of certain starting materials, resulting in a significant increase in the need for resources and in a lack of interest of industrial manufacturers to provide some of the starting materials and active ingredients for complex radiopharmaceutical preparations[1].

Similarly to reconstitutions ("manipulation to enable the use or administration of a medicinal product with a marketing authorisation") that are carried out by hospital pharmacists in accordance with the instructions given in the summary of product characteristics, radiopharmacists use authorised kits and combine them with authorised radionuclide precursors in order to compound the final radiopharmaceutical ready for application[4]. These kit-based radiopharmaceutical preparations[5] are developed and validated by the marketing authorisation holder of the kit, including adequate quality control procedures. Therefore, kit-based preparations of radiopharmaceuticals are treated in a special way by current legislation: the final radiopharmaceutical does not need a separate marketing authorisation when prepared in-house, and the preparation process is exempted from the scope of Annex 3 to the EU Guidelines to Good Manufacturing Practice on the manufacture of radiopharmaceuticals[6].
However, with the development of more complex preparations aside from kit-based reconstitution processes, a clear distinction between starting materials for kit-based preparations and complex radiopharmaceutical preparations has to be introduced. In this regards, current gaps in legislative guidance have led to misinterpretations of such requirements even by competent authorities directly in charge, ultimately impacting the actual supply.

[4] Even if it is not a reconstitution in the strict sense of the word, the active pharmaceutical ingredient is only formed during the process. It is under the aspect of sterility or microbiological safety, even identical.
[5] In this traditional type of radiopharmaceutical preparation, a non-radioactive part (= precursor; 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".
[6] – European Commission, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

The review of the Pharmaceutical Legislation should consider that, within hospital pharmacies and radiopharmacies, the demand for marketing authorisation should be strictly limited to starting materials and radionuclide precursors used in kit procedures and not for starting materials and radionuclide precursors if used in complex radiopharmaceutical preparations [7].

2) Enhancing the security of the supply of medicines and addressing shortages

More generally, the problems caused by medicines shortages are serious, threaten the well-being of patients and have far-reaching consequences for European health systems. To minimise patient impact, all supply chain actors, including healthcare professionals, wholesalers, manufacturers and competent national authorities, have the obligation and responsibility to collaborate more closely in terms of resolving the shortage problem. All supply chain actors, especially wholesalers and manufacturers, must communicate more effectively about likely and current shortages. Such communication should be carried out in a timely manner and contain insights on how imminent the issue is, the expected duration of the shortage and whether alternatives are available. Timely notification of shortages is also essential for patients whose treatment is dependent on radionuclides that are not generated widely across Europe and beyond.

Thus, EAHP and EANM call for improved information exchange between authorities and supply chain actors and the relay of information to the end-users. For combatting medicine and radionuclide shortages, best practice sharing is essential, and implementation support for shortage management strategies needs to be provided in the interest of patient safety.

Recent initiatives, such as the new European Shortages Monitoring Platform and the planned extension of the mandate of the European Observatory on the Supply of Medical Radioisotopes, should consider the specificities of in-house preparations related to shortages and the technical requirements of radiopharmaceuticals to ensure that all patients across can have timely access to needed medical products.

[7] European Association of Nuclear Medicine (2021). Statement of the EANM for better inclusion of the particularities of Radiopharmaceuticals within the Review of Directive 2001/83EC on Pharmaceutical Legislation: https://www.eanm.org/content-eanm/uploads/2021/12/EANM_Radiopharmaceuticals-Directive-2001-83_Final.pdf