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Key elements of the

European Association of Nuclear Medicine's response

to the European Commission's Consultation on Revision of the EU general pharmaceuticals legislation

As part of the EU pharmaceuticals strategy, and drawing lessons from the COVID-19 pandemic, the European Commission plans to evaluate and revise the EU's general legislation on medicines for human use to ensure a future-proof and crisis-resistant medicines regulatory system.

Legal proposals to review Directive 2001/83/EC and Regulation EC/726/2004 are to be expected for end of 2022.

All stakeholders are invited to share their views and perspectives here.

Due to the fast pace of innovation and progress pertaining to Radiopharmaceuticals (RPs) in the last decade, the general pharmaceutical legislation, which is also applicable for RPs, is 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 The challenges posed by the implementation of this outdated regulatory framework manifest in different ways: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
- Negative impact on the availability of RPs due to unsure legal basis

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**

1. Issues related to the Marketing authorisations for RPs and starting materials

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**:
  - ✓ *For complex in-house preparation of RPs for non-commercial use in the healthcare establishment no marketing authorisation shall be required for the*

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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.*

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

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 practice**
  - ✓ Some Member States 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.
  - ✓ Ideally a dedicated legal text that covers the in-house production of RPs should be established in a way that it does not impose additional requests raised by the radioactive nature but clearly states alleviations from the general industrial regime. It should no longer refer to existing annexes to the EU GMP guideline but clearly define the appropriate measures needed to ensure the quality of the preparation for a safe patient dose.

3. Issues related to supply chains

- Due to the short life of RPs, time management and having access to transportation hubs that understand the need for quick and swift processing is key. The transport of radioactive material is regulated by various regulatory frameworks and national requirements, being major hurdles for an efficient and unbureaucratic supply of RPs.
- The EANM is concerned with the Europe-wide issue of aging research reactors. While the number of accelerators is increasing, the supply of medical radioisotopes relies on an increasingly limited number of research reactors**.**
  - ✓ **This review of the Pharma Legislation should include new and necessary measures to support a robust supply chain for radioisotopes which goes beyond irradiation of targets and includes the supply of target material and processing capabilities.**

4. Call for more recognition of in-house preparation and academic research

A major aspect to be addressed is bedside/in-house preparation of RPs. The current Pharma Legislation mainly focuses on industrial/large scale manufacturing intended to be distributed commercially, leaving behind an important part of the pharmaceutical innovation.

- Development of innovative RPs often takes place in radiopharmacies or research centres: all recent major breakthroughs were based on the use of in-house preparations of these innovative RPs.

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- ✓ **It is of the outmost importance that this review includes specific provisions and incentives for academic research and hospital preparations.**

➢ EANM welcomes the acknowledgement of the current shift towards bedside/hospitals and more individualized preparations in the pharmaceutical ecosystem and is pleased to see that the European Commission understands that innovative solutions challenging the definition of medicinal product are testing the limit of the current regulatory system.

- ✓ **The review of the pharmaceutical legislation should consider adaptations to the current system of authorizations and new regulatory pathways to accommodate to new products, such as innovative RPs.**