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EANM Reply to the public consultation on the European Medicines Agency Concept paper on clinical evaluation of therapeutic radiopharmaceuticals in oncology.

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Concept paper available here.

1. General Comments

1.1. Introductory remarks

The EANM appreciates the opportunity to review this concept paper and commends the proposed guideline, which has the potential to further strengthen the field of nuclear medicine and to underline the evolving role of nuclear medicine therapies.

The EANM respectfully underscores that the issues raised in the concept paper regarding the implementation of dosimetry for personalized radioligand therapy remain a matter of debate within the field. First, it must be noted that radioligand therapy (RLT) is already inherently personalized to a certain degree when a theranostic approach is applied. In this setting, patients are stratified for a specific type of RLT based on the results of pre-therapeutic molecular imaging, proving that the lesions can be adequately targeted with the treatment. But also, information from other imaging modalities such as CT or MRI, as well as clinical parameters such as blood values, histology, kidney function, and the patient's previous treatments, are considered before proceeding with RLT. In addition, extensive consultations are held with other specialists in multidisciplinary tumour boards, to determine whether RTL is the optimal choice of therapy.
However, divergent opinion persists among stakeholders, not on the efficacy of RLT but on how RLT could be made more personalized, with a recurrent concern being the lack of sufficiently robust evidence demonstrating that personalizing administered activities based on dosimetry provides tangible benefits either in terms of enhanced efficacy or decreased toxicity to patients, compared to simplified approaches or even fixed-activity posology. Such robust evidence is needed to establish dosimetry not merely as a tool for regulatory compliance, but also as a critical approach for optimizing patient care in clinical practice.

The EANM states that the generation and availability of such evidence would significantly enhance the acceptance of dosimetry for individualized treatment optimization. Given the current lack of conclusive clinical evidence, however, the EANM does not hold a definitive position on recommending either extensive individual dosimetry, simplified approaches or fixed-activity posology. Instead, it supports initiatives that would make individualized treatment planning using dosimetry in nuclear medicine more accessible and foster the generation of evidence data to support broad clinical use.
In addition, efforts should be supported to tailor and harmonize dosimetry for each type of RLT to ensure uncertainties related to tumour and organ absorbed dose estimates are within an acceptable range to be clinically useful, while RLT remains accessible to patients with limited additional burden. Equally important, these efforts should be accompanied by initiatives to further improve traceability of administered activities to patients by ensuring adequate calibration of activity meters and imaging devices. Meanwhile, challenges related to image-based dosimetry should also be addressed for therapies using radionuclides such as Actinium 225 where the limited imaging potential of current nuclear imaging devices warrants other strategies or new technological developments. This way, evidence-driven and clinically feasible standardized dosimetry practice can be established not as a

barrier, but as an enabler for broad access and individualized RLT, leading to improved patient outcomes and cost effective RLT.

To this end, the EANM encourages wider stakeholder collaboration to identify and implement measures that facilitate the collection of high-quality evidence data on individual treatment planning for radiopharmaceutical therapies, while considering other factors such as patients' clinical condition, prior anticancer treatment regimens, etc. For instance, establishing a unified database to collect dosimetric data from centres across Europe could be an important step in this direction.

The EANM also wishes to draw attention to concerns raised during the SIMPLERAD workshop in December 2023. Some stakeholders expressed apprehension that mandating extensive dosimetry protocols might severely restrict patient access to radionuclide therapies in Europe and deter industry investment in the development and marketing of such therapies within the EU due to the perceived complexity of dosimetric requirements. On the other hand, other stakeholders argued that the absence of a mandate for dosimetric optimization is itself a barrier to generating high-quality evidence data on the potential superiority of personalized treatment approaches over fixed-activity administration.

In this context, the EANM suggests that the EMA prioritizes stakeholder engagement as an essential step before issuing any formal guidance. A balanced and inclusive approach will be critical to achieve consensus and ensure that any proposed measures effectively support both patient care and the continued advancement of nuclear medicine therapies.

1.2. **Evaluating dosimetry's role in Radioligand Therapy: EANM's perspective**

While radiation is the primary driver of therapeutic effects of RLT, the EANM wants to point out that robust and extensive clinical evidence is still missing when it comes to the added clinical value of dosimetry.

In early phase clinical trials, it is essential that data are collected to provide clear evidence supporting this approach. While acknowledging that more reports linking absorbed dose with therapeutic effects are being published, current data are still scattered and limited such that there is no compelling evidence that "individualised" activities will greatly enhance therapeutic efficacy of RLT. That said, a fixed-dose approach without considering any individual factors is probably an oversimplification, although proven effective. Obviously, the clinical context remains a critical consideration in all cases.

With the current limited clinical evidence, the EANM recommends that the guideline does not try to mandate radiopharmaceuticals to be prescribed by planned tumour absorbed dose, but to rather define which data are required for such an approach to be used in clinical routine and which methods should be recommended for clinical dosimetry.

1.3. **Distinct roles of biomarkers and treatment planning**

Additionally, treatment personalisation and optimization can also be achieved through other measures than absorbed dose.

It is of the utmost importance that the concept paper does not mix the role of a biomarker with that of a treatment planning tool, which are distinct in their purposes and applications. A target biomarker as detected by e.g. molecular imaging in the treatment evaluation can be the base for the treatment

decision and should be used for individualization. Moreover, the argument grounded in the role of absorbed dose in external radiotherapy cannot be transferred as such to the planning of radioligand therapy.

1.4. Ensuring Radiopharmaceuticals market competitiveness

Additionally, the EANM highlights that, in this context, it is also important to address the necessity of enhancing competitiveness and preventing monopolistic practices in the radiopharmaceutical market. This issue is increasingly prevalent and varies across Europe; while some countries benefit from broader access to radiopharmaceuticals from multiple manufacturers, others experience a clear monopoly by a single vendor. This matter should be appropriately addressed ahead of a thorough implementation of this guideline.

1.5. Considering clinical practice

To ensure a successful implementation across Europe, while not increasing the bureaucratic burden on healthcare professionals and not threatening innovation, it is important that the proposed guideline develops recommendations for the design of clinical studies that remain clinically manageable and cost effective.

1.6. Considering workforce

The EANM would like to flag that there is a huge discrepancy in installed infrastructure and skilled workforce across EU member states for nuclear medicine procedures. Like many other medical specialties, the nuclear medicine sector faces significant shortages that threaten both patient care and innovation.
In the context of a workforce shortage, the EANM would like to bring to the attention of European regulators that an increase in mandatory dosimetry procedures will further increase the disparities across Europe, unless it is applied in a cost effective and resource efficient way.

2. Specific comments on text

2.1. Introduction

No comments.

2.2. Problem statement

24-25: If any, the pharmacologically active part of the radiopharmaceutical is not the radioisotope, but the ligand which carries the radioisotope. Furthermore, it must be clearly stated that there is no pharmacological effect from the radiopharmaceutical as such because the administered amount is too low but that therapeutic effect is induced by radiation that is generated by the carried radionuclide.

33: The paper states that “A basic radiobiological principle is that the higher the AD delivered to the tissues the greater the expected biological effect “. However, we would like to invite EMA to consider that for the commonly recognised radiobiological models for absorbed dose – effects are sigmoidal.

2.3. Discussion on the problem statement

61-63: The EANM states that the "Incorporation of systematic evaluation of dosimetry in the clinical development of tRPs" would be a potential alternative to prescription of injected activities, but not a replacement. This would imply a definition of the clinical data that are needed from a clinical trial to allow one to prescribe an absorbed dose and not an injected activity. As long as the data from the clinical trial do not support the prescription of an absorbed dose, there is no scientific basis to change the current standard.
The EANM very much welcomes clarification on this point, confirming that the data from the clinical trial do not support the prescription of an absorbed dose.

2.4. Recommendation

No comments.

2.5. Proposed timetable

No comments.

2.6. Resource required for preparation

No comments.

2.7. Impact assessment

No comments.

2.8. Interested parties

No comments.

2.9. References to literature, guidelines…

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This reply has been endorsed by the European Association of Urology.

European Association of Urology