

**Statement by the European Association of Nuclear Medicine (EANM)
Posology for Radiopharmaceuticals: contradictory legal requirements
between BSS Directive 2013/59/Euratom and EMA marketing authorisations
schemes
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About EANM:

Founded in 1985, the European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. As largest organisation dedicated to nuclear medicine in Europe, EANM is an umbrella organisation for individuals and national societies, representing more than 9,000 specialists, and aiming at advancing science and education in nuclear medicine for the benefit of public health.

Summary:

The last few years have seen important changes in the development and composition of radiopharmaceuticals introduced in clinical practice. These technical changes have led to new delivery requirements: nowadays, posologies need to be more patient centric. However, EU requirements for the use of radiopharmaceuticals in patients, based on their respective posologies, which are issued as part of their marketing authorization by the European Medicine Agency (EMA), are currently not fitting the needs and are partially in contradiction to the Council Directive 2013/59/Euratom, which leads to complex situations in clinical practice.

EANM is keen to provide input on this challenging situation and is offering suggested solutions.

In the near future, the new developed therapeutic radiopharmaceuticals will very likely need a patient-specific tailoring of the activities to administer such that the absorbed dose limits for normal organs and tissues are considered while achieving high absorbed doses for the treatment target.

Individually planned doses within EURATOM Directive: the ways forwards

While the Article 56 of the Council Directive 2013/59/Euratom, the European Basic Safety Standard Directive, states that *“For all medical exposure of patients for radiotherapeutic purposes, 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”*, a 2015 European survey on radionuclide therapies showed that the implementation of individual dose planning was far from being optimal across the European Union. Compliance with the BSS Directive would mean personalised doses for radiopharmaceuticals for each patient. However, in daily practice, the implementation of such directive is complicated due to lack of financial resources, lack of infrastructure, lack of dosimetry tools as well as lack of training for healthcare professionals. In this respect, EANM has published guidance on compliance with the BBS directive.

EMA fixed posology schemes

However, the BSS directive is not aligned with the EMA suggested posologies for therapeutic radiopharmaceuticals. Indeed, EMA marketing authorizations for radiopharmaceuticals follow traditional posology schemes, mainly following the posologies of chemotherapies. Such an approach is not fitting the needs of radiopharmaceuticals, for which dosing need to be patient centric. Most radiopharmaceuticals are administered either as a one-time administration with the option of later retreatment or in several repeated cycles. For EMA-approved package inserts, the dosing often follows a fixed activity scheme, sometimes stratified according to body weight; however, patient-specific dosimetry or post-therapeutic verification of the absorbed doses is mostly not part of the posology. Furthermore, the posologies issued by regulatory agencies for recently authorized radiopharmaceuticals provide only very general data on absorbed doses, very often obtained from few subjects during phase I or, sometimes, phase II of clinical trials. These values are mean values and show a high inter-patient variability.

There are several consequences of administering radiopharmaceuticals for therapy purposes according to fixed posologies, and not based on patient centric dosimetry. First, the treatment with radiopharmaceuticals is subject to the optimization principle as it applies ionizing radiation. However, it is acknowledged that patient throughput might be increased or access to treatment might become easier for a fixed activity dosing scheme. Secondly, the administration of radiopharmaceutical following the EMA posology puts the responsibility of the treatment to the drug company and not to the treating physician.

How to reconcile these conflicting regulations?

These contradictory applications between EMA and EURATOM are making the delivery of radiopharmaceuticals to patients very complex. In this respect, EANM would welcome a **reconciliation between these differing requirements**.

1. DG Energy and the EURATOM treaty article 31 group of experts should acknowledge the fact that treatment with radiopharmaceutical is different as compared to external beam therapy for the following reasons:
 - For some radionuclides pre-therapeutic treatment planning or post-therapeutic absorbed dose verification is not possible due to technical limitations in quantitative imaging procedures for dosimetry (e.g. ^{223}Ra or ^{90}Y)
 - For some radiopharmaceuticals absorbed dose limits for organs-at-risk derived from data on external beam therapy are not well established
 - For some treatments the variability in the pharmacokinetics, and consequently, in the absorbed doses is low; thus reducing the necessity for treatment planning
 - The relative biological effectiveness (RBE) for therapeutically administered radiopharmaceuticals labelled with alpha emitters are not established. The determination of absorbed doses only, in particular for treatment planning, might not reflect the dose-effect relationship correctlyThese considerations could be embedded a future revision of the BSS.

2. EMA marketing authorizations schemes for radiopharmaceuticals should be adapted, to follow patient-centric dosimetry, instead of traditional posology schemes. In this respect:
 - Early stage clinical trials (phase I/II) for new radiopharmaceuticals should be requested to collect and monitor patient-specific dosimetry data and absorbed doses in order to improve the safety and efficacy of new therapies. These trials should follow the requirement to develop patient-specific prescription of radiopharmaceuticals for an improved assessment of patient dosing in later phases for obtaining marketing authorisations.
 - Such requirement for collection of patient-specific dosimetry data in phase III would also support the precise establishment of absorbed dose, which is crucial to limit side-effects.
 - Such requirement to gather sufficient dosimetry data from early clinical trials will limit uncertainties in patient treatments in case dosimetry cannot be performed because of technical reasons.
 - With such requirement, posologies will contain more detailed and verified information on dosimetry data including the expected uncertainties and range of absorbed dose to organs-at-risk
 - For all marketing authorization applications concerning therapeutic radiopharmaceuticals, an external advisor who is knowledgeable in this kind of treatment should be closely involved.

Overall, EANM would welcome the establishment of a close working relation between DG Energy and DG SANTE and the respective European agencies for improved harmonizing requirements and regulations for therapeutically used radiopharmaceuticals.