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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on clinical evaluation of therapeutic radiopharmaceuticals in Oncology

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. Introduction

Radiopharmaceuticals are a special type of medicinal products as they are regulated by both the pharmaceutical legislation (2001/83/EC) and the radiation protection legislation (Directive 2013/59/Euratom). A radiopharmaceutical is defined as any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes). Radiopharmaceuticals can be further divided into those intended for diagnostic use, and those with therapeutic indications. This concept paper concerns ready-to-use therapeutic radiopharmaceuticals (tRPs).

The objective of this concept paper is to identify aspects that are specific for tRPs that need to be addressed in the future guideline, to complement the more general Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6). The scope of the guideline is to provide specific guidance on how the key concepts from the two areas of legislation should be applied to the clinical development of tRPs for marketing authorisation application.

2. Problem statement

The particularities of radiopharmaceuticals derive from the fact that the pharmacologically active moiety of the drug is a radioisotope. The posology is therefore expressed in terms of the amount of administered (radio)activity to the patient (with the SI-unit Becquerel, Bq), rather than milligrams or millilitres. Furthermore, radiopharmaceuticals can be imaged in the patient after administration to quantify the absorbed (radiation) dose (AD, with the SI-unit Gray, Gy) to both tumours and normal organs/tissues. This process of relating the administered amount of radioactivity to the resulting AD is called dosimetry.

The mechanism of action of tRPs is based on the targeted delivery of cytotoxic ionising radiation to tumour cells, with limited irradiation of normal cells. A basic radiobiological principle is that the higher the AD delivered to the tissues the greater the expected biological effect. The AD can thus be seen as an image-based biomarker that is predictive of both toxicity and anti-tumour effect that can be used for individualized dosimetry-based treatment planning. Although simple in theory, in practice there are several challenges related to its implementation that need to be systematically addressed.

The current practice of administering fixed amounts of activity to the patients in a fixed number of treatment cycles[1,2] has been shown to lead to highly variable ADs to both tumour lesions and normal organs (Lawhn-Heath et al., 2022; Ells et al., 2024; Nautiyal et al., 2022). This might lead to sub-optimal anti-tumour effect and late radiation-induced toxicity, both of which are potentially preventable by adjusting the administered activity to the ADs observed in the individual patient.

The current radiation protection legislation[3] requires "all medical exposures of patients for radiotherapeutic purposes" to be optimised and individually planned in terms of the radiation exposure of target volumes vs non-target volumes. It specifically includes nuclear medicine therapies in the definition of "radiotherapeutic".

There is a growing number of requests for scientific advice, marketing authorisation applications (MAA), variations and clinical trials applications dealing with tRPs. The experience gained during the assessment of these procedures indicates that guidance on how to fulfil the requirements for Marketing Authorisation is urgently needed to ensure harmonised interpretations and to deal with recent developments and practices in the field of radiopharmaceuticals.

[1] https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf
[2] https://ec.europa.eu/health/documents/community-register/2022/20221209157605/anx_157605_en.pdf
[3] EU Directive 2013/59/Euratom, also known as the Basic Safety Standards Directive (BSSD)

3. Discussion (on the problem statement)

The following items have been identified as the key points that will be addressed in the future Guideline on the Clinical Evaluation of Therapeutic Radiopharmaceuticals in Oncology:

- Standardisation of relevant terminology, i.e., "dose" in relation to "administered activity" and "absorbed dose"; "activity" in relation to anti-tumour effect and amount of tRP.
- Incorporation of systematic exploration of a wide range of administered activity early in the development program (phase I/II trials) to establish the maximum tolerated activity/ AD, identify (acute) dose-limiting toxicities (DLTs), understand the relationship between administered activity and ADs, and begin to gather data on dose-response for (late) radiation-induced toxicity.
- Incorporation of systematic evaluation of dosimetry in the clinical development of tRPs and a specification of the data requirements allowing definition of posology for individualized planning of the ADs in clinical routine. The posology should include a recommended target AD (range) to the tumour lesions and a recommended AD limit (range) to the main risk organs.
- Guidance for management of acute toxicity in order to achieve short- and long-term treatment optimization, i.e., high likelihood of efficacy and tolerability with an acceptable risk of late toxicity.
- Guidance for specific tRPs/situations (e.g., alpha-emitters and beta-emitters with low photon emissions) for which challenges are identified in performing direct dosimetry analyses.
- Discussion of development strategies with implementation of study designs adapted for specific aspects/needs of tRPs to achieve optimisation of patient treatment and swift approval. This will include a discussion on collection of post-approval data with long-term follow up to identify late toxicity, and possible tRP-specific risk mitigation strategies.
- Discussion on the objectives of individually optimised treatment and how they may vary depending on the treatment setting. In late-stage symptomatic disease tumour shrinkage and symptom control might be prioritized above the risk of long-term toxicity given the limited expected survival. At the other end of the spectrum, in a curative setting, relatively high rates of acute and reversible toxicity are generally accepted, while the acceptability of long-term, irreversible toxicity depends on its frequency and impact on quality of life and survival.

To deliver individually optimised radionuclide therapy some core resources, which are currently not standard, are needed to ensure high quality and safety of the treatment. These include, but are not limited to, adequate imaging equipment and CE-marked software for internal dosimetry, staff specifically trained in nuclear medicine therapy and dosimetry and specific treatment areas adapted according to radiation protection principles. Such aspects are, however, out of the scope of this concept paper and the future guideline.

4. Recommendation

The Working Party/Committee recommends drafting a guideline on the clinical requirements specific for marketing authorisation of tRP which addresses the critical issues identified above. The guideline should also provide guidance on emerging issues in view of recent developments and changing practices in the field of radiopharmaceuticals.

5. Proposed timetable

The concept paper will be published for a three-month public consultation period. ONCWP will take into account all comments received during the public consultation on the concept paper when preparing the draft guideline. The draft guideline will be published for a three-month public consultation period. ONCWP will take into account all comments received during the public consultation on the draft guideline when preparing the final guideline text. It is expected that the final guideline will come into operation six months after publication following adoption by CHMP.

6. Resource requirements for preparation

The development of the guideline will involve the EMA-ONCWP Secretariat, the EMA Oncology (EMA-ONC) European Specialised Expert Community (ESEC) specialised Interest Area (SIA) Radiopharmaceuticals Secretariat, and the temporary Drafting Group appointed by the ONCWP.

7. Impact assessment (anticipated)

This proposed guideline on the clinical development of tRPs will address specific regulatory and methodological aspects of radiopharmaceutical therapies with regard to clinical trial design and marketing authorisation. This includes, but is not limited to, the impact and role of implementing patient-specific dosimetry in clinical trials and in clinical practice with the purpose of optimising safety and efficacy of these treatments. These aspects, which are not covered by the current anticancer guideline, will improve the development and marketing authorisation process of this class of medicinal products for the benefit of all stakeholders.

8. Interested parties

Pharmaceutical Industry, Healthcare, Professionals associations, EU Competent Authorities.

9. References to literature, guidelines, etc.

Directives of the European Atomic Energy Community (EURATOM) (Directive 2013/59/Euratom).

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 as amended

Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6)

Guideline on the non-clinical requirements for radiopharmaceuticals - Draft (EMA/CHMP/SWP/686140/2018)

Guideline on radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) and Concept paper on the revision of the Guideline on Radiopharmaceuticals (EMA/CHMP/QWP/298182/2023)

Core summary of product characteristics (SmPC) and package leaflet for radiopharmaceuticals - Scientific guideline

Ells Z, Grogan TR, Czernin J, Dahlbom M, Calais J. Dosimetry of [(177)Lu]Lu-PSMA-Targeted Radiopharmaceutical Therapies in Patients with Prostate Cancer: A Comparative Systematic Review and Metaanalysis. J Nucl Med. 2024;65:1264-1271.

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