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Quality Working Party (QWP)

Concept paper on the revision of the Guideline on Radiopharmaceuticals

Agreed by Quality Working Party	June 2023
Adopted by CHMP for release for consultation	20 July 2023
Start of public consultation	21 July 2023
End of consultation (deadline for comments)	31 October 2023

The proposed guideline will replace 'Guideline on Radiopharmaceuticals' (EMEA/CHMP/QWP/306970/2007).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Radiopharmaceuticals; Pharmaceutical and chemical documentation; Development; Manufacture; Quality control; Stability.

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1. Introduction

The time elapsed since its adoption and the growing experience gained during the last years has lead to the identification of the need to update the current Guideline on radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007).

2. Problem statement

Radiopharmaceuticals are a special type of medicinal products that were the subject of a specific guideline covering their particular requirements very early after their inclusion in the Pharmaceutical legislation framework by Council Directive 89/343/EEC. A few guidelines explicitly exclude radiopharmaceuticals from their scope; nevertheless, the grounds/principles of these guidelines can, in some cases, be a useful guide also for radiopharmaceuticals. Those guidelines not excluding radiopharmaceuticals are, in principle, applicable, although in many cases will require appropriate interpretation.

The particularities of radiopharmaceuticals derive mainly from the fact that, when ready for administration to the patient, they contain one or more radionuclides, that the strength is expressed in terms of the radioactivity (radioactivity concentration for liquid dosage forms or total radioactivity per dosage unit in some cases), the posology is expressed in terms of the amount of radioactivity administered to the patient and not in terms of mass (or amount of substance) and finally, that the amount of radioactivity decreases with time. This has led to the need of defining, along with 'radiopharmaceutical', three additional specific types of medicinal products: radionuclide generator, radionuclide precursor and kit (for radiopharmaceutical preparation).

The current Guideline on radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) is a quality guideline adopted in 2008 as an update of the original guideline dated back in 1990. The experience gained during the assessment of the (growing) number Marketing Authorisation Applications (MAA), Variations and Clinical Trials dealing with radiopharmaceuticals, shows that the revision that lead to the current guideline was particularly necessary and has demonstrated to be very useful. Nevertheless, the same experience made it clear that non harmonised interpretations, lack of coverage of some issues and poorly detailed treatment of some others requires a new update to cope with these problems and to deal with recent developments and practices in the field of radiopharmaceuticals. Moreover, Ph.Eur. texts on radiopharmaceuticals have been the subject of significant changes since the adoption of the current guideline.

The revision of the current guideline has to be done maintaining the alignment with the provisions on radiopharmaceuticals of the current Community code relating to medicinal products for human use (Directive 2001/83/EC), with the current texts of the Ph.Eur. on radiopharmaceuticals and with other relevant legal and regulatory framework.

The guideline is not intended to cover the in-house preparation of non-licensed radiopharmaceuticals.

According to the BWP work plan for 2023, the guideline 3AQ21a 'Radiopharmaceuticals based on Monoclonal Antibodies' is being updated in parallel.

3. Discussion (on the problem statement)

The following items have been identified as the key ones that need to be dealt with in the revision of the Guideline on Radiopharmaceuticals:

1. Provide more detailed guidance on the documentation requirements for each of the four types of medicinal products covered by the guideline (radiopharmaceuticals, radionuclide generators, radionuclide precursors and kits). For each one, clarify what are the substances/preparations that should be the subject of module 3.2.S and of module 3.2.P. and clarify accordingly the separation between the manufacturing processes of the active substance and of the finished product.
2. Consider if it could be useful to separate under different sections of the guideline the requirements for the dossier of each of the four types of medicinal products covered by the guideline.
3. If deemed advisable, introduce additional definitions or provide guidance on the use of terms commonly found in the field of radiopharmaceuticals but not always used with the same meaning.
4. For the production of the radionuclide and for the manufacture of the active substance of a kit and of the chemical precursor, clarify the steps of the processes that should be included in the dossier and in which sections. Moreover, clarify which of the involved manufacturers need to be stated in the dossier and which of them need to be included also in administrative data and comply with GMP requirements.
5. Indicate minimum requirements for the description of the different manufacturing operations.
6. Provide guidance on the substances, solutions or any other materials that should be considered starting materials in the manufacture of the drug substance and of the finished product.
7. Explain what additional or specific information need to be provided on the description and validation of radioanalytical test procedures, in particular for therapeutic radionuclides.
8. Make clear the applicability and use of the different texts of the Ph.Eur. specific for radiopharmaceuticals.
9. Provide guidance on the tests and acceptance criteria (if relevant) that are required for the active substances and for the finished products of the four different types of medicinal products covered by the guideline.
10. Discuss the problem of the lack of general thresholds applicable for chemical, radiochemical and radionuclidic impurities.
11. Provide details on what is expected on stability protocols for active substances and for finished products containing radionuclides and the storage conditions that can be granted depending on the stability protocol and results.
12. Provide guidance on the data required to demonstrate the accuracy of administered dose, e.g. in the case of small doses and relative dilution to be performed by the user before administration or in the case of therapeutic radiopharmaceuticals. Required information to be stated in the SmPC related to accuracy of the administered dose will also be dealt with.

4. Recommendation

The QWP recommends revising the current Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007). The aim of the revision is:

- To further clarify a number of issues that have been the subject of non-harmonised interpretations.
- Address some issues not covered or poorly detailed in the current guideline.
- Provide guidance on new issues raised after recent developments and new practices in the field of radiopharmaceuticals.

5. Proposed timetable

The concept paper will be published for a three-month public consultation period.

QWP will take account of all comments received during the public consultation on the concept paper when preparing the draft guideline.

The draft guideline will be published for a six-month public consultation period.

QWP will take account of 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-QWP Secretariat, the Joint CHMP/CVMP Quality Working Party, the CHMP BWP and GMP/GDP Inspectors Working Group, who would be consulted, as necessary. The QWP should appoint a rapporteur and a drafting group.

7. Impact assessment (anticipated)

The revision of the guideline will contribute to a more harmonised interpretation, both for regulators and for industry, of the regulatory requirements related to the quality part of the dossier for radiopharmaceuticals.

No adverse impact on industry with respect to either resources or costs is foreseen.

The guideline will not introduce new requirements on medicinal products already authorised and on the market.

8. Interested parties

Pharmaceutical Industry, EU Competent Authorities, GMP/GDP Inspectors Working Group.

9. References to literature, guidelines, etc.

Directive 2001/83/EC, as amended

Guideline on radiopharmaceuticals (*EMEA/CHMP/QWP/306970/2007*)

Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (*EMA/CHMP/QWP/545525/2017 Rev. 2*)

Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals, (EMA/CHMP/167834/2011)

European Pharmacopeia, current edition, in particular:

- Ph.Eur 2.2.66 Detection and measurement of radioactivity
- Ph.Eur 2902 Chemical precursors for radiopharmaceutical preparations
- Ph.Eur. 0125 Radiopharmaceutical preparations)

Guide for the elaboration of monographs on radiopharmaceutical preparations, Edition 2018 (EDQM).

Other general texts and monographs of the Ph.Eur. and other Guidelines not specific for radiopharmaceuticals but also applicable, should be considered too.