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COMMITTEE FOR HUMAN MEDICINAL PRODUCTS (CHMP)

GUIDELINE ON RADIOPHARMACEUTICALS

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EXECUTIVE SUMMARY

This guideline describes the specific additional information that needs to be submitted in relation to radiopharmaceuticals, in the context of applications for marketing authorisations or variations to authorised medicinal products.

1. INTRODUCTION (background)

Applications for marketing authorisation in respect of radiopharmaceuticals should be accompanied, as in the case of all medicinal products, by the particulars and documents referred to in Directive 2001/83/EC, as amended. This guideline provides information about specific requirements for radiopharmaceuticals. The relevant provisions of the current European Pharmacopoeia should be observed. Due account must be taken of relevant CHMP guidelines which should be applied with special interpretation, recommendation or completion for radiopharmaceuticals, as discussed in this guideline. Radiopharmaceuticals are exempted from a number of guidelines, but with special interpretation they could still give the necessary guidance on the matter.

Radiopharmaceuticals are used for diagnostic and therapeutic purposes. They are usually given only once, or sometimes on a few occasions, and contain only small amounts of the active substances with a radionuclide attached to them to allow scintigraphic imaging, measurement of biodistribution or therapeutic treatment. Such radiopharmaceuticals do often not show any measurable pharmacodynamic effect. Radiation is a general property of all radiopharmaceuticals, which when administered gives the patient an inevitable radiation dose. In the case of therapeutic radiopharmaceuticals, the radiation effect is the wanted property.

Radiopharmaceuticals have decreasing content of radioactivity with time, as a consequence of the radioactive decay. The physical half-life of the radionuclide is often short for radiopharmaceutical diagnostics. In these cases, the final preparation has to be done shortly before administration to the patient. This is in particular the case for positron emitting radiopharmaceuticals for Tomography (PET radiopharmaceuticals). It often leads to the use of semi-manufactured products such as radionuclide generators, radioactive precursors and kits.

2. SCOPE

This guideline covers the following products:

- ready-for-use radiopharmaceuticals, including PET radiopharmaceuticals;
- non-radioactive components (kits and chemical precursors including those for positron emission Tomography) for combination with a radioactive component (e.g. eluate from a radionuclide generator or a cyclotron produced radionuclide);
- radionuclide generators;
- radionuclide precursors used for radiolabelling other substances prior to administration.

Article 3.5 of Directive 2001/83/EC specifically mentions radionuclides in sealed sources as being outside the requirements of the Directive, and therefore outside the scope of this guideline.

Concerning radiopharmaceuticals based monoclonal antibodies, a separate guideline exists (3AQ21a).

Concerning radiopharmaceuticals intended in the conduct of clinical trials (investigational medicinal products), the principles of this guideline expressed in eudralex vol 10 have to be applied.

3. LEGAL BASIS

Directive 2001/83/EC, as amended:

- TITLE II, Articles 2, 3 and 4
- TITLE III, Chapter 1, Article 6.2 & Article 7
- Annex I , introduction and general principles (4), and part 2

4. DRUG SUBSTANCE (3.2.S)

In a radionuclide generator, both mother and daughter radionuclides are to be considered as active substances.

For radiopharmaceutical kits, the active substance is considered to be that part of the formulation that is intended to carry or bind the radionuclide or to permit its binding. In addition, the radiolabelled form obtained after radiolabelling with a suitable radionuclide should be described.

The active substance of a radiopharmaceutical kit and the chemical precursor for the synthesis of PET radiopharmaceuticals should satisfy the *Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier (CHMP/QWP/297/97 Rev. 1)*. Information on chemical precursors including those for synthesis of PET radiopharmaceuticals may be presented in a separate section 3.2.S.

Radioactive drug substances are as a rule not isolated; they are usually presented as solutions. This gives advantages when handling and reduces the effect of radiolysis.

For radiopharmaceuticals prepared from kits, documentation on the chemistry of the active substance can in some cases be obtained and presented differently from what is described in the relevant note for guidance (e.g. some technetium complexes). It should however be ensured that all information necessary to evaluate the active substance specifications (e.g. information on related substances and residual solvents) is available.

Radioactivity should only be expressed in Becquerel at a given date, and time if appropriate. If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET). Where practicable, specific radioactivity, carrier free, non carrier added or carrier added should be stated.

General Information (3.2.S.1)

Structure (3.2.S.1.2)

The structural formula should indicate the position of the radionuclide where possible.

For radiopharmaceutical kits the structure of the radiolabelled compound should be described if possible.

General Properties (3.2.S.1.3)

For radionuclides, their source must be specified, i.e. whether fission or non fission, the decay characteristics of the radionuclide e.g. half-life, type, energy and probability of its emission should be stated for the most frequent. Information on whether the radionuclide is carrier-free, carrier-added or not-carrier-added should be provided.

Manufacture (3.2.S.2)

Manufacturer(s) (3.2.S.2.1)

For radionuclides this should include the source of any irradiation target materials and site(s) at which irradiation occurs.

Description of Manufacturing Process and Process Controls (3.2.S.2.2)

For radioactive components, a full description is required of the production process of the radionuclide (isolation or manufacturing of the radioactive starting material).

Control of Materials (3.2.S.2.3)

Requirements for the target material (specifications and control methods) should be described.

Manufacturing Process Development (3.2.S.2.6)

For radionuclides this should include nuclear transformation, including unwanted transformations that may occur under the irradiation conditions used due to isotopic impurities present in the target material; irradiation conditions, including effect of variations on nuclear reactions; description and validation of separation processes; influence of geometry of the target chamber and its material.

Characterisation (3.2.S.3)

Elucidation of Structure and other Characteristics (3.2.S.3.1)

For radiopharmaceutical kits the structure of the radiolabelled compound should be described where possible.

Impurities (3.2.S.3.2)

Radionuclidic impurities should be described and their physical characteristics should be stated. Radiochemical impurities should be discussed. The effect of radiolysis on the purity should be addressed.

Where an active substance is not isolated during the production process, information on impurities may be presented in section 3.2.P.5.5., Characterisation of impurities.

Control of Drug Substance (3.2.S.4)

Specification (3.2.S.4.1)

For radioactive substances the specification should include radionuclidic identity and purity, radiochemical identity and purity, specific radioactivity and radioactive concentration.

Where an active substance is not isolated during the production process, information on specification may presented in section 3.2.P.5.1. Drug Product Specification(s).

Validation of Analytical Procedures (3.2.S.4.3)

For radioactivity measurement procedures information should be given on calibration of equipment.

Justification of Specification (3.2.S.4.5)

The specification for the amount of radioactivity and radiochemical impurities may deviate from general principles of assay and related substances due to limitations of the measurement procedures, the special chemistry involved and the small chemical amounts present.

Reference Standards or Materials (3.2.S.5)

Information on calibration standards used in radioactivity measurements should be provided. If an appropriate traceable standard of the isotope is not available, justification for the use of another method of calibration should be included.

Container Closure System (3.2.S.6)

The shielding container is secondary packaging and should only be briefly described.

Stability (3.2.S.7)

The shelf life and the storage conditions for the active substance should be specified and justified. The general stability guidelines are fully applicable to the non-labelled active substance applied in radiopharmaceutical kits and chemical precursors for the production of PET radiopharmaceuticals. They are not fully applicable for drug substances used in ready-for-use radiopharmaceuticals, radionuclide generators and radioactive precursors due to the radioactive nature of these substances. Stress testing of radioactive substances is often not feasible. In some cases simulated stress testing may be performed on the non radioactive chemical form.

5. DRUG PRODUCT (3.2.P)

Description and Composition of the Drug Product (3.2.P.1)

Radioactivity should only be expressed in Becquerel at a given date, and time if appropriate. If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET). Where practicable, specific radioactivity, carrier free, non carrier added or carrier added should be stated.

Only one radioactive concentration (volumic activity in Bq/mL) may be included in the application of radiopharmaceuticals presented as solutions. However, diagnostic and therapeutic products should be in separate applications.

Pharmaceutical Development (3.2.P.2)

Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96) and *Note for Guidance on Pharmaceutical Development (ICH Q8) (EMEA/CHMP/167068 /2004).*

Drug Substance (3.2.P.2.1.1)

Influence of radioactivity on the excipients should be discussed.

Formulation Development (3.2.P.2.2.1)

Data on stability of particles (e.g. of colloidal size), after reconstitution, should be presented, as appropriate.

Manufacturing Process Development (3.2.P.2.3)

For radiopharmaceutical kits the suitability of the proposed radiolabelling procedure should be fully demonstrated, using the extremes of volume and radioactivity recommended. The specification of the radioactive material necessary for labelling kits should be established, where necessary, in this section (and referred to elsewhere as necessary). Specification should include i.e. content of radioactivity, volume, purity and pH. Instructions for final preparation (the reaction time and any manipulation necessary during final preparation, including dilution prior to administration where relevant should be detailed and justified). Any special quality requirement for the diluent should be stated here if appropriate. Quality control procedures to be applied by the end-user should be justified during the development pharmaceutics. Reproducibility and robustness must be demonstrated. Moreover, the

quality control method as recommended by the manufacturer in the SPC should be cross-validated against the quality control method applied for batch release by the manufacturer.

For a radionuclide generator a general description of the system must be given, with a detailed description of those components that could have an influence on the composition of the eluate. The materials supplied with the generator to permit elution (e.g. eluent and evacuated vials) should be described. The recommendations for use of the generators should be discussed and documented. Measures to take to avoid malfunctioning due to misuse (e.g. during transportation or drying) should be discussed.

Influence of the purity of any substance (e.g. reagents and materials such as tubes, filters, column materials) used in the production of radiopharmaceuticals in automated units (e.g. PET radiopharmaceuticals) and of the parameters of this process on the quality of the final preparation should be discussed.

Potential and actual impurities should be considered not only for any direct effect on the patient but also for their possible influence on the radiochemical purity and/or biodistribution of the product.

Container Closure System (3.2.P.2.4)

Compatibility of the radiolabelled product with the container and closure should be considered and validated where appropriate. It should be described if compatibility problems between the product and representative syringe materials or container closures used for patient doses are observed or expected.

Manufacture (3.2.P.3)

Note for Guidance on Manufacture of the Finished Dosage form (CPMP/QWP/ 486/95).

Batch Formula (3.2.P.3.2)

Batch sizes of radiopharmaceuticals containing radionuclides may vary from batch-to-batch. The minimum and maximum batch size that can be applied in commercial manufacturing should however be defined in the dossier and justified by process validation data.

Description of Manufacturing Process and Process Controls (3.2.P.3.3)

Apart from the manufacturing process, in addition the following, should be described in the dossier for radiopharmaceuticals:

- For radiopharmaceutical kits a detailed description of the radiolabelling procedure should be given.

- For radionuclide generators a detailed description of the elution procedure should be included. Because of the complexity of the production of radiopharmaceuticals such as generators**,** special attention should be paid to methods for obtaining and maintaining sterility during manufacture (preparation and assembly).

- For radiopharmaceuticals containing radionuclides of short physical half-life (e.g. PET radiopharmaceuticals), that can be released before all results on finished product testing are available, special attention should be devoted to the purity and control methods for all starting materials, reactants, chemicals, reagents and solvents used in synthesis and purification.

- For radiopharmaceuticals, which are synthesised in automated units, including PET radiopharmaceuticals, the unit and all production steps in this unit should be described in detail, including cleaning and steps to avoid contamination where relevant. Indicators of malfunctioning computer control should be stated.

- In the case of radiopharmaceutical suspension information on particle size distribution should be provided.

Controls of Critical Steps and Intermediates (3.2.P.3.4)

For radiopharmaceuticals containing radionuclides of short physical half-life (e.g. PET radiopharmaceuticals), that need to be released before all results on finished product testing are available, special attention should be devoted to in-process controls for critical parameters of the production process. The filter used in final filtration should be tested for integrity before release of the product in accordance with Ph.Eur. requirements (5.1.1 Methods of Preparation of Sterile Products - Filtration).

Process Validation and/or Evaluation (3.2.P.3.5)

When radiopharmaceuticals are manufactured in situ for direct administration to the patient (e.g. PET radiopharmaceuticals with physical half life of the radionuclide ≤ 20 min), the consistency of the production process has a particularly great importance.

For radiopharmaceuticals containing radionuclides of short physical half-life, that can be released before all results on finished product testing are available (e.g. PET radiopharmaceuticals), the manufacturing process should be fully validated.

Control of Excipients (3.2.P.4)

Note for Guidance on Excipients in the dossier for application for marketing authorisation of a medicinal product (CHMP/QWP/396951/06).

Control of Drug Product (3.2.P.5)

Specification(s) (3.2.P.5.1)

The specifications should cover the generally required tests for the specific dosage form (such as dissolution for capsules and sterility and endotoxins for parenteral products).

Specifications for radiopharmaceuticals should also include radiochemical identity and purity, chemical purity and, where relevant specific radioactivity, radionuclidic identity and purity. Special attention should be paid to impurities that influence the radiochemical purity or biodistribution of the product. Acceptance limits for the radioactive concentration for diagnostic radiopharmaceuticals should be within 90 to 110% of the label claim. For therapeutic radiopharmaceuticals, acceptance limits should be within 95 to 105% of the label claim. Wider limits must be conclusively justified (e.g. inferior accuracy of radioactivity measurement).

For kits, the specifications of the finished product shall include tests on the quality of products after radiolabelling. Appropriate controls on the identification, radiochemical purity, radionuclidic purity, content of radioactivity and (where relevant) specific radioactivity of the radiolabelled compound shall be included. Radionuclidic purity testing of the radiolabelled product may be omitted if this test is performed on the eluate or the radioactive precursor applied for the labelling and this is justified. Any material essential for radiolabelling shall be identified and assayed (e.g. stannous chloride).

For radionuclide generators, details on testing for mother and daughter radionuclides are required. For generator-eluates, tests for specific activity, mother radionuclides, daughter radionuclides and for other radionuclidic and chemical impurities from the generator shall be provided. Specifications shall also be presented for materials delivered with the generator to permit elution (e.g. eluent and evacuated vials).

For radiopharmaceuticals described in a Ph. Eur. monograph, the suitability of the monograph should in all cases be demonstrated. If certain impurities (e.g. from new routes of production) are not covered by the monograph, methods are to be provided which control these impurities.

For some radiopharmaceuticals it may not be possible to obtain the results of certain tests, e.g. sterility test, before the product is released. However, these tests are important in the validation of the manufacturing process. It should be stated which tests are normally undertaken before the release of the product for use and which are undertaken after release. The latter should be justified.

Analytical Procedures (3.2.P.5.2)

Quality control tests carried out after labelling of kits to be performed by the end-user, should be described where relevant. These methods should be validated versus the methods applied by the manufacturer (cross validation).

Characterisation of Impurities (3.2.P.5.5)

If information on impurities is transferred from section 3.2.S.3.2 to section 3.2.P.5.5 all impurities should be considered, not only degradation products.

Justification of Specification(s) (3.2.P.5.6)

Radionuclidic impurities likely to be present and the changes in the levels of those impurities during the in-use lifetime of the product should be discussed.

For generators the potential of mother radionuclide breakthrough as well as other potential impurities from the generator systems should be discussed.

Release of drug products before all test results are obtained should be justified in each case.

Reference Standards or Materials (3.2.P.6)

Information should be provided on radioactive standards used in the calibration of radioactivity measurement equipment. If an appropriate traceable standard of the isotope is not available, justification for the use of another method of calibration should be included.

Container Closure System (3.2.P.7)

The shielding container is secondary packaging and should only be mentioned briefly.

Stability (3.2.P.8)

The general stability guidelines are not fully applicable for ready-for-use radiopharmaceuticals, radionuclide generators and radioactive precursors.

However, when applying the stability guidelines to radiopharmaceuticals the following aspects should be taken into consideration.

- In stability testing of ready-to-use radiopharmaceuticals, including PET radiopharmaceuticals, the minimum and maximum amount or concentration of radioactivity at the time of manufacture should be taken into account.

- In the selection of batches for radiopharmaceuticals containing radionuclides, one should not refer to pilot scale or production scale because it is generally not possible to define a fixed production scale size. Due to the short shelf-lives, batch sizes are determined by the market request. Stability results should be presented on three batches for which the applied manufacturing process meaningfully simulates that which will be applied for marketing, taking into account the upper limits for the batch size.

- The specifications and test procedures to apply should take into account the specific characteristics for radiopharmaceuticals (see also section 3.2.P.5.1)

- The minimum time periods covered at submission defined in the stability guidelines (12 months long term testing, 6 months accelerated testing, etc.) cannot be applied for radiopharmaceuticals with a proposed shelf life of less than one year. In these situations, the testing frequency should be adapted and justified based on shelf-life, and presented at submission.

- The guideline on Evaluation of Stability Data is generally not applicable to radiopharmaceuticals containing radionuclides.

For radiopharmaceutical kits, the shelf life and recommended storage conditions of the prepared product should additionally be defined and justified. Data should be provided on the stability (including radiolabelling and biodistribution performance) of the kit (for shelf-life estimation) and of the reconstituted radiolabelled product using maxima and minima of radionuclide content and volume of reconstituting medium (to establish the maximum radiolabelled shelf-life).

For radionuclide generators, the shelf life and recommended storage conditions of the eluate and of the different materials to permit elution (e.g. eluent and evacuated vials) should additionally be defined and justified. The influence of ageing and elution frequency on eluate quality should be discussed.

For ready-for-use radiopharmaceuticals, the shelf life after the time of manufacture should be established. Establishing the shelf life after the time of calibration can also be accepted, provided that the time period between manufacture and calibration is strictly defined. The relationship between the production date, the calibration date and the use date should be stated. Moreover, the influence on product specification (e.g. radionuclidic purity) and performance should be discussed.

Stress testing as generally described is not applicable for radiopharmaceuticals except for radiopharmaceutical kits.

The storage conditions should be declared using the storage statements given in the relevant Note for Guidance.

For radiopharmaceuticals prepared in multiple-dose vials, the stability following removal of successive doses, simulating the real use of the product, should be investigated over the proposed in-use shelf life. Sterile radiopharmaceutical products are often unpreserved, maximum shelf life should usually be 8 hours after first use or following reconstitution, unless adequately justified by data.

In-use stability in syringes may be included here if available but is usually the responsibility of the end user.

REFERENCES (scientific and / or legal)

Directive 2001/83/EC, as amended

Note for Guidance on Summary of Requirements for Active Substances in Part II of the Dossier (CHMP/QWP/297/97 Rev. 1)

Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)

Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068 /2004)

Note for Guidance on Manufacture of the Finished Dosage form (CPMP/QWP/ 486/95)

Note for Guidance on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product (CHMP/QWP/396951/06)

Eudralex Vol 4: Good Manufacturing Practice, Annex 3 - Radiopharmaceuticals.