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Guideline on quality of radiopharmaceuticals

Draft

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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

Guideline on quality of radiopharmaceuticals

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Executive summary

This guideline describes the specific additional information that needs to be submitted in relation to the chemical, pharmaceutical and biological information for radiopharmaceuticals based on synthetic chemical substances, in the context of applications for marketing authorisations or variations to authorised medicinal products.

1. Introduction (background)

Radiopharmaceuticals are a special type of medicinal products. 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 as a consequence of the radioactive decay.

Radioactivity should only be expressed in Becquerel and is always expressed at a given date, and time if appropriate (*Activity Reference Date/Time*, see glossary). If a time is stated, the time zone used should be stated (e.g. GMT/CET). Where practicable, specific radioactivity, non-carrier added or carrier added should be stated.

Radiopharmaceuticals may be administered orally, by injection or inhalation and are used for diagnostic or for therapeutic purposes. They are usually given only once, or sometimes on a few occasions, and contain only small amounts of the *radiolabelled active substance* (see glossary), that contains a radionuclide to allow imaging, measurement of biodistribution or therapeutic treatment. 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.

The physical half-life of the radionuclides in radiopharmaceuticals is short, especially those used for diagnostic purposes, in particular for positron emitting radiopharmaceuticals for Tomography (PET radiopharmaceuticals). In these cases, the final preparation has to be done shortly before administration to the patient.

According to Directive 2001/83/EC radiopharmaceuticals are considered medicinal products and, as such, cannot be placed on the market unless they hold a valid marketing authorisation.

The short physical half-life of most radionuclides in radiopharmaceuticals (along with the inherent instability of many radiolabelled active substances) has led to the need to use and define, along with *ready for use radiopharmaceutical*s (see glossary), three additional special types of substances/preparations: radionuclide generator, radionuclide precursor and kit (for radiopharmaceutical preparation). When they are placed on the market intended to be used by the end user as described in article 7 of Directive 2001/83, they also need to hold a valid marketing authorisation. On the other hand, when a substance/preparation covered by the definition of radionuclide generator, radionuclide precursor or kit is used as starting material, active substance or intermediate in the manufacture of a radiopharmaceutical subject of a marketing authorisation application, they do not need to hold a marketing authorisation. Nevertheless, the documentation on their quality should be in line with that requested for marketed products and included in the dossier of the radiopharmaceutical in which manufacture they are used.

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. This guideline provides information about specific requirements for the quality part of the dossier for radiopharmaceuticals, essentially the content of Module 3.

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, these could still offer useful guidance for Radiopharmaceuticals.

2. Scope

This guideline provides guidance on the quality documentation required for the following medicinal products:

- Ready-for-use radiopharmaceuticals, including PET radiopharmaceuticals
- Kits (for radiopharmaceutical preparation)
- Radionuclide generators
- Radionuclide precursors

The following substances used in the manufacture of radiopharmaceuticals are also covered:

- Active substances in kits
- Chemical precursors
- Radionuclide precursor (used as a starting material).

The main body of the guideline clarifies what are the substances/medicinal products that should be the subject of modules 3.2.S and 3.2.P and the specific requirements for their content. Due to the significant differences between the four types of medicinal products, the specific requirements are separated in different subsections covering substances/medicinal products that share most of the requirements.

Concerning radiopharmaceuticals based on monoclonal antibodies, a separate guideline exists.

Concerning radiopharmaceuticals intended to be used in the conduct of clinical trials (investigational or auxiliary investigational medicinal products), the principles of this guideline are also applicable but allowing flexible and phase appropriate interpretation. *Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017 Rev. 2)* is the key regulatory reference regarding this topic.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- TITLE I, Article 1
- TITLE II, Articles 2, 3 and 4
- TITLE III, Chapter 1, Article 6.2, Article 7, Article 9 and Article 11.12
- Annex I, Introduction and general principles (3), and part III.2

4. Active substance (3.2.S)

In most medicinal products, the subject of module 3.2.S of the dossier is the active substance finally administered to the patient and intended to exert the proposed 'medical action', or a derivative (e.g. a salt) that contains the complete active moiety.

In a ready for use radiopharmaceutical, the active substance presented in the finished product and administered to the patient is a radiolabelled substance; it is synthetised during the manufacture of the finished product and cannot be isolated, characterised, tested and stored. Thus, ensuring the quality of the radiolabelled active substance requires go upstream in the process and get to the closest precursors that can be isolated, characterised, tested and, eventually, stored. These will be the chemical precursor (a non-radioactive chemical substance intended to bind or carry the radionuclide)and the radionuclide precursor (a radionuclide usually in the form of a solution for radiolabelling containing the radionuclide in a suitable form for the radiolabelling process, in most cases a simple aqueous solution of the radionuclide). The radionuclide precursor and the chemical precursor will be the subject of complete modules 3.2.S.

Regarding the kits, radionuclide generators and radionuclide precursors, they do not contain the radiolabelled active substance as they are placed on the market. In these cases, the radiolabelled active substance is prepared by the end-user shortly before administration by radiolabelling a kit (or patient's blood cells) with a radionuclide precursor or with the eluate of a generator (in a few cases, the eluate of a generator might be administered directly to the patient without further preparation). In the case of kits, the active substance, subject of module 3.2.S, is that component of the formulation that is intended to bind or carry the radionuclide. In case of radionuclide precursors, the subject of module 3.2.S is the radionuclide prior to its final formulation into the marketed radionuclide precursor Finally, in the case of radionuclide generators the subject of module 3.2.S is the parent radionuclide (although both parent and daughter radionuclides are considered active substances because the parent is always in equilibrium with daughter radionuclide).

The substances subject of modules 3.2.S in the dossier of a radiopharmaceutical should be considered similar to an active substance or an active substance intermediate from a regulatory point of view: their manufacturers need to be stated in section 3.2.S.2.1 of the dossier and relevant documents of Module 1, their manufacture should be made in compliance to GMPs for active substances and they have to be included in the QP declaration among the audited sites.

4.1. Radionuclide precursor (for ready for use radiopharmaceuticals, for radionuclide precursors or for radionuclide generators)

Radioactive substances are as a rule not isolated as pure substances; they are usually presented as solutions. Accordingly, radionuclide precursors are almost always in the form of a solution (in most cases containing a simple salt of the radionuclide).

In ready for use radiopharmaceuticals the radionuclide precursor is a solution that contains the intended radionuclide in a chemical form suitable to be combined with the chemical precursor. In case it can be isolated, characterised and tested it should be the subject of a complete specific module 3.2.S.

In the case of radionuclide precursors, the radionuclide used as starting material is a solution of the radionuclide, in some cases with the same composition that is present in the final radionuclide precursor as it is placed on the market and in other cases containing the radionuclide in the same chemical form but at a different concentration or even with different composition. It should also be the subject of a module 3.2.S.

In a radionuclide generator, both parent and daughter radionuclides are to be considered as active substances. The parent radionuclide is always in equilibrium with the daughter radionuclide and should be the subject of a module 3.2.S. The quality of the daughter radionuclide, once separated from the parent, should be dealt with in section 3.2.P.

General Information (3.2.S.1)

When presented as a solution, the composition of the solvent (including any additive used) should be stated. When applicable, the position of the radionuclide in the substance should be clearly stated in the structure and in the chemical name.

Section on general properties should describe the source of the radionuclide, whether accelerator, nuclear reactor (fission or non-fission) or mass separation produced. Decay properties of the radionuclide (half-life and decay chain as well as nature, energy and intensity of most relevant emissions) and, where relevant for the intended use, physico-chemical properties (e.g. solubility).

Manufacture (3.2.S.2)

Sites where manufacturing steps that, according to GMP regulations, need to be conducted under GMP for active substances, should be stated as manufacturers of the radionuclide precursor in section 3.2.S.2.1 of the dossier.

In section 3.2.S.2.2, description of the manufacturing process should start with the step where the radionuclide is produced (cyclotron or other accelerators, nuclear reactor or mass separation). The irradiation and, if relevant, mass separation parameters applied at any of the proposed sites should be stated. The nuclear transformation that yields the desired radionuclide should be stated.

All manufacturing steps after irradiation or mass separation should be described with full details. This includes any step of the processing of the irradiated target or of the implantated target material in case of mass separation, aimed to separate the intended radionuclide and put it in the desired chemical form. If these process steps, or any part of them, are conducted in an automated unit (synthesis module), the module used should be stated and described. Each manufacturing step that takes place on it should be described with detail.

Sources of any irradiation target material as well as sites conducting only irradiation and mass separation should be stated in section 3.2.S.2.3 of the dossier as well as composition and specifications of any target material and of the implantation target material for mass separation, used in the production of the radionuclide. A brief summary of the target preparation process (e.g. enrichment method, measures taken to avoid impurities that could impact the quality of the radionuclide precursor) should be provided.

In section on Manufacturing process development, the Applicant should provide a discussion on unwanted transformations that may occur under the irradiation or mass separation conditions due to impurities present in the target material, including isotopic impurities. The impact of variation of irradiation or mass separation parameters on nuclear reactions and the influence of geometry of the target chamber and its material should be discussed.

Characterisation (3.2.S.3)

Results of relevant studies conducted to characterise a representative batch of the radionuclide precursor should be provided. Typically, a characterisation of the radioactive properties of the radionuclide (half-life, nature, energy and intensity of the emitted radiations) has to be provided. When relevant for the intended use, physico-chemical properties should be determined (e.g. pH).

In section 3.2.S.3.2 a discussion on potential and actual radionuclidic and radiochemical impurities and the control strategy to minimise the risk of its presence should be provided. The effect of radiolysis on the purity should be addressed.

Control of Active Substance (3.2.S.4)

The specification of the radionuclide precursor should be provided, even when the radionuclide precursor is not isolated and controlled during routine manufacture. E.g. compliance with the specification should be demonstrated during manufacturing process development, during process validation, when target and/or manufacturing method is changed, and as part of GMP related maintenance activities to demonstrate the process remain in control. When tested, the radionuclide precursor must comply with the specification. See annex 1 for specification parameters to be included.).

Where a Ph.Eur. monograph exist for a radionuclide precursor (solution for radiolabelling, parent radionuclide of a generator, radionuclide used as starting material for a radionuclide precursor) it should be applied.

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. For therapeutic radionuclides (beta and alpha emitters) the suitability of the calibration standard and calibration method should be demonstrated with experimental validation data at the manufacturing site. Whenever available, a calibration standard sourced from an official metrological institution should be used.

Container Closure System (3.2.S.6)

Justification that the container closure system has been demonstrated suitable for storage of the radionuclide precursor should be provided.

Stability (3.2.S.7)

Where a radionuclide precursor is not isolated during the manufacturing process, information on stability may be presented in section 3.2.P.8 Stability (of the finished product). When the radionuclide precursor is isolated and can be stored, the shelf life and the storage conditions should be specified and justified. Data on stability should cover the shelf-life period proposed and should be provided for at least three batches representative of the worst-case scenario (highest radioactivity). The general stability guidelines are not fully applicable for radionuclide precursors used in the manufacture of ready-for-use radiopharmaceuticals, radionuclide generators and radionuclide precursors due to the radioactive nature of these substances; however, stability studies should be conducted such that the stability profile can be established. Stress testing of radioactive substances is often not feasible. Storage at different relative humidity conditions is not deemed necessary. Regarding the storage temperature during stability studies of radionuclide precursors, it is not required either to follow the general stability guidelines (e.g. storage at 25ºC and 40ºC) but the actual storage conditions used should be stated.

4.2. Active substance (for kits for radiopharmaceutical preparation) and chemical precursor (for ready-for-use radiopharmaceuticals)

For kits, the active substance is considered to be that part of the formulation that is intended to carry or bind the radionuclide. Also, for kits, the radiolabelled active substance obtained after radiolabelling with the intended radionuclide should be described as well.

Chemical precursors for ready for use radiopharmaceuticals should be selected as the structurally closest non-radioactive precursors of the radiolabelled active substance that can be isolated, characterised and tested. In most cases they already contain almost the complete structure of non-radioactive part of the radiolabelled active substance. In any case they should be substances that are incorporated as significant structural fragments into the structure of the radiolabelled active substance.

The documentation on active substance of a radiopharmaceutical kit and on the chemical precursor should satisfy the *Guideline on summary of requirements for active substances in the quality part of the dossier (CHMP/QWP/297/97 Rev. 1)*. Information on chemical precursors, including those for synthesis of PET radiopharmaceuticals, should be presented in a separate module 3.2.S.

Manufacture (3.2.S.2)

The synthesis of the active substance of a kit and of the chemical precursor for a ready for use radiopharmaceutical should include all synthesis steps necessary to build up-the structure and functional groups of the substance essential to obtain after radiolabelling the desired radiolabelled active substance. The guideline on the Chemistry of active substances excludes radiopharmaceuticals and radiolabelled products from its scope but their principles as well as the guideline ICH Q11 can help to decide the starting point of the manufacture of active substances of kits and chemical precursors.

Control of Active Substance (3.2.S.4)

When there is a monograph in the Ph. Eur. specific for a given active substance of a kit or for a chemical precursor, the respective monograph is to be applied.

In the absence of a specific Ph. Eur, monograph, limits should be based on batch and stability data and consider the principles outlined in the currently available guidelines and compendial texts pertaining to the control of impurities in active substances and drug products, as applicable. An overall safety evaluation of the levels of impurities delivered with each dose to the target patient population should be taken into account (e.g. whether the manufacturing/preparation process includes or not a purification step).

4.3. Radiolabelled active substance (for ready for use radiopharmaceuticals)

Even in cases where the radiolabelled active substance is not isolated, a reduced module 3.2.S with the following minimum information should be presented.

General Information (3.2.S.1)

When applicable, the position of the radionuclide in the substance should be clearly stated in the structure and in the chemical name.

Section on general properties should describe the source of the radionuclide, whether accelerator, nuclear reactor (fission or non-fission) or mass separation produced. Decay properties of the

radionuclide (half-life and decay chain as well as nature, energy and intensity of most relevant emissions) and, where relevant for the intended use, physico-chemical properties (e.g. solubility).

Manufacture (3.2.S.2)

If the manufacturing process of the ready for use radiopharmaceutical is a continuous process and the radiolabelled active substance is not isolated at any time, the information on its manufacture should be provided in section 3.2.P.3 Manufacture (of the finished product).

Characterisation (3.2.S.3)

Information on the characterisation of the non-radioactive analogue of the radiolabelled active substance should be provided.

Control of Active Substance (3.2.S.4)

The specification of the radiolabelled active substance should be provided, even when the radiolabelled active substance is not isolated and controlled during routine manufacture. E.g. compliance with the specification should be demonstrated during manufacturing process development, during process validation, when target and/or manufacturing method is changed, and as part of GMP related maintenance activities to demonstrate the process remain in control. When tested, the radionuclide precursor must comply with the specification. See annex 1 for specification parameters to be included.

5. Drug product (3.2.P)

A radiopharmaceutical is: Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

5.1. Drug product (for ready for use radiopharmaceuticals and radionuclide precursors)

Radionuclide precursor is any other radionuclide produced for the radiolabelling of another substance prior to administration.

Ready for use radiopharmaceuticals are in most cases manufactured from chemical precursor(s) by combination with the radionuclide present in a radionuclide precursor, resulting in the radiolabelled active substance which is generally not isolated but further processed as a solution into the finished product in a continuous process.

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

A composition table should be presented. It should state the amount of each ingredient of the medicinal product as it is placed on the market. The amounts of each ingredient should be expressed per dosage unit (e.g. capsules) or, in the case of solutions, per volume unit. If the amount of an ingredient is variable, the maximum and minimum amounts should be stated. The finished product should have a strength suitable for application. For the radiolabelled active substance, the maximum amount in terms of mass or of amount of radiolabelled active substance should be stated in addition to the amount of radioactivity.

In most cases, a range of strengths for the finished product is not acceptable. Nevertheless, more than one strength can be applied for in a single dossier provided each strength is clearly defined and stated along the dossier. For radiopharmaceuticals containing a radionuclide with a physical half-life shorter than two hours and presented as a solution, a range of strengths for the finished product could be

acceptable. Nevertheless, the proposed range should be supported by process validation data and justified with detail under pharmaceutical development in terms of the foreseen time of administration to the patient. The proposed range should allow the administration to the patient in a suitable volume without further dilution to reduce the exposure of the user to the radiation. Unjustified high radioactive concentrations are not acceptable.

Pharmaceutical development (3.2.P.2)

Influence of radioactivity on the stability and function of active substance itself (if not already discussed under 3.2.S.2) and on the excipients and container closure material should be discussed.

The proposed strength(s) or range of strengths should be justified with detail. The proposed strength should take into account the posology and ease of administration.

The effect of radiolysis on the purity should be addressed.

Choice, quality and amounts of excipients acting as inhibitors of radiolysis/radical scavengers/stabilizers should be justified by development data.

In the case of solutions for parenteral administration, osmolarity of the preparation should be addressed.

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

The specifications of materials used in the manufacture should be justified in relation to the purge of potential and actual impurities by the process in order to ensure a consistent quality of the finished product.

The Applicant should discuss the influence on the quality of the finished product of the purity of any raw material (e.g. reagents and materials such as tubes, filters, columns) used in the manufacturing process, also in automated units (e.g. PET radiopharmaceuticals). The impact of manufacturing process parameters on the quality should also be addressed.

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.

For parenteral preparations, filling the final container by piercing the stopper of closed pre-sterilised containers (in a class A environment) is as a general rule not acceptable. Nevertheless, for radiopharmaceuticals containing a radionuclide with a shelf-life shorter than 24 hours (e.g. PET radiopharmaceuticals), this could be accepted if properly justified (and supported by validation data).

Compatibility of the radiolabelled active substance 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)

Batch formula should be provided. The batch formula is a list of all starting materials (reagents, solvents, catalysers, excipients…), and their amounts, used in the manufacture of a batch of the finished product. When a starting material is used as a ready for use solution, its quantitative composition should be stated including quality standard of each component, e.g. Ph. Eur. If all or some of the raw materials are sourced as a set of substances/preparations or other materials provided together for a particular purpose this should be stated, the components described, and its' provider specified. The word «kit» to refer to such a set is strongly discouraged to avoid confusion with the kit

as defined in Directive 2001/83. If any solution is prepared in-house by the manufacturer, the components of that solution are considered starting materials, and the preparation of the solutions is to be considered part of the manufacturing process. Specifications of starting materials should be set and justified in this section, except for excipients, which should be presented in 3.2.P.4.

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 and stability data. The batch size should generally be defined in terms of the total radioactivity, and volume in case of solutions, as well as in terms of the number of containers per batch.

For sterile filtered radiopharmaceuticals where bioburden is not routinely monitored during manufacture, bioburden specification limits in the specifications of raw materials used in the manufacture should be set to ensure a consistent bioburden of NMT 10 CFU/100 ml before sterile filtration.

In the description of the manufacturing process, the following should be considered for radiopharmaceuticals containing a radionuclide:

- Any disposable single use material used (e.g. purification cartridges, tubes, containers, syringes, cassettes) should be described and suitable specifications provided. For purification cartridges, the amount and chemical composition of the filling material should be stated, and specifications should include parameters relevant for their intended use (e.g. particle size, retention capacity).

- 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 the synthesis and purification. In addition, special attention should be devoted to in-process controls for critical parameters of the production process. The sterilising filter used in final filtration should be tested for integrity before release of the product in accordance with *Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015)*.

- For radiopharmaceuticals which are manufactured in automated units (e.g. synthesis modules, dispensing modules), including PET radiopharmaceuticals, the automated unit should be stated 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. If two or more automated units are proposed as alternative, it should be fully justified, and demonstrated by suitable validation data, that the manufacturing process followed in each unit is essentially similar (same sequence of manufacturing operations conducted under the same conditions) and that they yield a product of the same composition and quality.

When ready for use 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 and process validation data demonstrating that the process is in control and consistently provides a compliant product should be provided.

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

radiopharmaceuticals manufactured using sterile-filtration, bioburden results from process validation batches (non-released surrogate batches manufactured without the final sterile filtration) should be provided to demonstrate adequate control of the microbiological quality of the materials and equipment used for manufacture such that a bioburden of NMT 10 CFU/100 ml is presented to the sterile filter.

Control of excipients (3.2.P.4)

Additional specifications to those described in Ph. Eur. for excipients may be applicable to ensure consistent product quality (e.g. metal impurities where this is critical to the finished product, bioburden when the finished product is sterile filtered).

Control of the Drug Product (3.2.P.5)

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).

Specification limits should be set according to product performance, i.e. according to batch and stability data to ensure a consistent quality.

Specifications for radiopharmaceuticals containing radionuclides 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 final product administered to the patient. 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 radiopharmaceuticals described in a Ph. Eur. monograph, the monograph should be applied, and 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.

For minimum specification parameters to be included in the specification, see Annex 1.

Radioactivity detectors should be appropriately validated with respect to sensitivity to ensure that radiochemical impurities can be detected and quantified at the requested reporting threshold also at the end of shelf-life by taking into account the decay.

Ph. Eur. "General monograph Radiopharmaceutical preparations (0125)" applies and analytical procedures given in Ph. Eur. general chapter "2.2.66 Determination and detection of radioactivity" are used. The "Guide for the elaboration of monographs on Radiopharmaceutical preparations" may be also helpful for the development and validation of the analytical methods.

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. As a general rule, limits for radiochemical impurities and radionuclidic impurities should be based on batch and stability results of clinical batches. For diagnostic radiopharmaceuticals, limits of NLT 95% for radiochemical purity and of NLT 99.9% for

radionuclidic purity could be accepted without further justification if supported by batch and stability data and unless there are specific concerns of relevant impact on safety or efficacy.

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 in justification of specifications.

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.

For therapeutic radiopharmaceuticals (beta and alpha emitters) the suitability of the calibration standard and calibration method should be demonstrated with experimental validation data at the manufacturing site. Whenever available, a calibration standard sourced from an official metrological institution should be used.

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.

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. 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 (highest radioactivity).
- For radiopharmaceuticals presented as solutions, samples stored upside down should be included in stability studies.
- Stress testing of radioactive substances is often not feasible.
- Storage at different relative humidity conditions is not deemed necessary.
- Regarding the storage temperature during stability studies of radiopharmaceuticals containing radionuclides, stability studies should be conducted at 25ºC and 40ºC to allow the setting appropriate storage conditions. When a medicinal product is manufactured at multiple manufacturing sites, stability at 25ºC should be tested at all manufacturing sites but stability at accelerated temperature condition can be conducted at only one site, but in all proposed container closure systems, if they are different in different sites. The selection of stability indicating parameters and test procedures to apply should be justified and take into account the specific characteristics of radiopharmaceuticals.
- 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. Data on stability should cover the complete shelf-life proposed and presented at submission.

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

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

For radiopharmaceuticals containing radionuclides 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 in-use shelf life should usually be 8 hours after first use or following removal of the first dose or dilution, unless adequately justified by data.

SmPC

Section 2

For radiopharmaceuticals presented as a solution, in addition to the strength (radioactive concentration) the total activity per container should be stated.

If relevant for the intended use, the production method of the radionuclide should be declared, e.g. nuclear reactor (fission or non-fission), accelerator produced and, if required, nuclear reaction. The decay properties of the radionuclide have to be described (half-life, types and energies of the main radiations emitted).

Section 6

If the finished product can be diluted before administration, the shelf life after dilution should be stated.

Section 12

If the finished product can be diluted before administration, the dilution instructions should be provided (diluent to be used, maximum dilution).

5.2. Drug product (for radionuclide generator)

A radionuclide generator is: Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

Radionuclide generators are used in most cases in combination with kits for radiolabelling of the active substance in a kit prior to administration into the patient.

In a generator, both parent and daughter radionuclides shall be considered as active substances. The parent radionuclide is always in equilibrium with the daughter radionuclide. The documentation on the parent radionuclide should be described in the S-part of the dossier, whereas the documentation on

the daughter radionuclide is included in the 3.2.P part together with the finished product. The eluent should be described in a separate 3.2.P part.

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

The finished product of a generator includes always the generator itself (that contains the parent radionuclide in equilibrium with the daughter radionuclide) and the eluent.

For the generator, section 3.2.P.1 should include a general description of the system, including a statement of the composition of column and amount of the stationary phase. The table of the composition of the generator should state the total amount of the parent radionuclide and the quantitative composition and amount of the solvent.

All the materials supplied with the generator to permit its elution should be stated and described. The composition of the eluent should be provided, and its container closure system briefly described.

Different defined strengths can be approved for a radionuclide generator.

Pharmaceutical Development (3.2.P.2)

Influence of radioactivity of the active substance on the stability and function of excipients and the column/container closure material should be discussed.

In formulation development, the choice of column stationary phase, specific activity and eluent (composition and volume) in relation to number of elutions, with acceptable yield of the daughter radionuclide, which can be performed during the shelf-life before break-through of the parent radionuclide is observed should be described and justified.

Regarding the manufacturing process development, 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 and purity 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 microbial contamination or malfunctioning due to misuse (e.g. during transportation or drying) should be discussed.

The choice of manufacturing method should ensure sterility, e.g. terminal sterilisation of the column and eluent is expected.

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 finally administered to the patient (e.g after radiolabelling with the eluate).

Compatibility of the parent and daughter radionuclides with the stationary phase and with the column material should be discussed and validated where appropriate. Any container supplied for the elution (e.g. that of the eluent and evacuated vials) should be described.

Manufacture (3.2.P.3)

The batch formula should be provided also for the manufacture of the eluent.

Because of the complexity of the production of generators, the description of the manufacturing process should pay special attention to methods for obtaining and maintaining sterility during manufacture (preparation and assembly).

For radionuclide generators a detailed description of the elution procedure and the materials to be used should be included in 3.2.P.3.3 and in the SmPC section 12. Illustrative figures should be used to ease the understanding of the procedure and to avoid microbial contamination or malfunction.

The manufacture of the eluent should also be described, including its sterilisation process. If the eluent is manufactured by a different manufacturer, the manufacturer of the eluent should be stated as manufacturer of the finished product.

Control of Excipients (3.2.P.4)

Additional specifications to those described in Ph. Eur. for excipients may be applicable to ensure consistent product function and quality, e.g. particle size and parent radionuclide retention capacity of the column stationary phase.

Control of Drug Product (3.2.P.5)

Considering the particularities of the manufacture and assembling of generators, each generator has to be tested before release.

The specifications should be provided for the eluate containing the daughter radionuclide and should include tests for sterility and endotoxins.

Specification limits should be set according to product performance, i.e. according to batch- and stability data to ensure a consistent quality.

For radionuclide generators, details on testing for parent and daughter radionuclides are required. For generator-eluates, tests for specific activity, parent radionuclides, daughter radionuclides and for other radionuclidic and chemical impurities from the generator shall be provided. 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).

Specifications shall also be presented for materials delivered with the generator to permit elution (e.g. eluent and evacuated vials). The eluent is expected to be sterile.

If the Ph. Eur. Includes a monograph for the eluate of a generator, it should be applied, and the suitability of the monograph should in all cases be demonstrated. If certain impurities (e.g. from different production methods) are not covered by the monograph, methods are to be provided which control these impurities.

For specification parameters to be included in the specification of radionuclide generators, see Annex 1.

Ph. Eur. "General monograph Radiopharmaceutical preparations (0125)" applies and analytical procedures given in Ph. Eur. general chapter "2.2.66 Determination and detection of radioactivity" are used. The "Guide for the elaboration of monographs on Radiopharmaceutical preparations" may be also helpful for the development and validation of the analytical methods.

Radioactivity detectors should be appropriately validated with respect to sensitivity to ensure that radiochemical impurities can be detected and quantified at the requested reporting threshold also at end of shelf-life by taking into account the decay.

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.

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

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

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.

The container of the eluent should also be described.

Stability (3.2.P.8)

The general stability guidelines are not fully applicable for radionuclide generators.

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

- 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. 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 (higher radioactivity).
- 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. Data should be provided that covers the complete proposed 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.

Stress testing as generally described is not applicable for generators.

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

SmPC

Section 2

If more than one strength (total radioactivity) is to be commercialised, the individual available strengths have to be stated.

A general description of the system should be provided (parent and daughter radionuclides, physico-chemical nature of the eluate, etcetera) and a mention of the eluent provided for elution.

If relevant for the intended use, the production method of the parent radionuclide should be declared, e.g. nuclear reactor (fission or non-fission), accelerator produced and, if required, nuclear reaction. The decay properties of both the parent and the daughter radionuclide have to be described (half-life, types and energies of the main radiation emitted).

Section 3

The appearance of the generator is to be provided.

The nature and appearance of the eluate should be stated.

Section 6

Among the components of the generator, those substances that are part of or are in contact with the parent and the daughter radionuclides are considered excipients. In general, these are the material of the filling of the chromatographic column and the components of the eluent.

In addition to the shelf-life of the generator itself, the shelf-life of the eluent has also to be stated.

If the eluate is not for immediate use, the shelf-life after elution should be stated.

In section 6.5 a detailed description of the generator is to be provided with mention of all the components that are relevant for the proper functioning and use. All accessories provided with the generator need to be mentioned (e.g. eluent containers, containers for collection of the eluate, tubes, adapters)

Drawings of the generator and its relevant parts and accessories are to be provided as necessary for a proper use.

Section 12

Detailed description of the elution procedure should be provided. The description of the elution should be accompanied by drawings and/or pictures to facilitate the proper use.

If any quality control test needs to be conducted on the eluate before use, it should be described in detail and the acceptable limits stated.

5.3. Drug product (for kits for radiopharmaceutical preparation)

A kit for radiopharmaceutical preparation is: Any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

The radiolabelled product resulting from combination of the marketed kit for radiopharmaceutical preparation with a marketed radionuclide precursor or with the eluate of a radionuclide generator is prepared immediately before use by the end user by a validated radiolabelling procedure described in detail in the SmPC. By following the procedure in the SmPC, the predefined quality of the resulting radiolabelled kit is obtained.

The documentation on the active substance in the kit is included in the S-part and the kit in the P-part. An additional P-part should be included for diluents for reconstitution, if included in the kit.

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

The strength of a radiopharmaceutical kit is given as the content of the active substance in terms of the mass of the active substance.

Pharmaceutical Development (3.2.P.2)

Influence of radioactivity on the stability and function of the active substance and excipients should be discussed.

Data on the particle size distribution of particles (e.g. of colloidal size), after reconstitution and radiolabelling, should be presented, as appropriate, in formulation development.

The choice and amounts of excipients used as stabilisers or as essential for radiolabelling should be described.

In section 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 as well as kits at start and end of shelf-life. The specification of the radioactive preparation necessary for labelling the kits should be established. The specification should include i.e. content of radioactivity, volume, purity and pH. Reference should be given to the marketed radionuclide precursor or radionuclide generator to be used for radiolabelling and to the specifications in Ph. Eur., if available. 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. Tests procedures to be applied by the end-user after radiolabelling should be justified in Manufacturing process development. Reproducibility and robustness must be demonstrated. Moreover, the test procedures as recommended by the manufacturer in the SmPC should be properly described and cross-validated against the quality control method applied for batch release by the manufacturer.

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

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)

Apart from the manufacturing process of the kit, section 3.2.P.3.3 of the he dossier for a kit should include a detailed description of the radiolabelling procedure. It should be clearly stated which marketed radionuclide precursors/radionuclide generators should be used, i.e. those that have been demonstrated to be suitable. The radiolabelling procedure should also be described in the SmPC section 12.

Control of Drug Product (3.2.P.5)

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

Specification limits should be set according to product performance, i.e. according to batch- and stability data to ensure a consistent quality.

For kits, the specifications of the finished product shall also include tests on the quality of the product after radiolabelling. If there is a Ph. Eur. monograph for the radiolabelled preparation it should be applied, and the suitability of the monograph should in all cases be demonstrated. If certain impurities (e.g. from specific components of the kit) are not covered by the monograph, methods are to be provided which control these impurities.

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 of the generator or the radionuclide precursor applied for the radiolabelling and this is justified. Any component essential for radiolabelling shall be identified and assayed (e.g. stannous chloride). In the case of a radiopharmaceutical suspension, information on particle size distribution should be provided and particle size distribution should be included in the specification.

For specification parameters to be included in the specification of kits for radiopharmaceutical preparations, see Annex 1.

Radioactivity detectors used in the analytical procedures should be appropriately validated with respect to sensitivity to ensure that radiochemical impurities can be detected and quantified at the requested reporting threshold also at end of shelf-life by taking into account the decay.

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 in the characterisation of impurities, not only degradation products.

Chemical impurities likely to be present and the changes in the levels of those impurities during storage should be discussed in justification of specifications with respect to the resulting impact on the radiochemical purity and the in-use time of the radiolabelled kit

Stability (3.2.P.8)

The general stability guidelines are fully applicable to kits as they are placed on the market.

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

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

For kits, the shelf life and recommended storage conditions of the radiolabelled preparation should be defined and justified. To establish the maximum shelf-life after radiolabelling, data should be provided on the stability of the radiolabelled product using maxima and minima of radioactive concentration and volume of radiolabelling solution and considering the expected changes in the radionuclidic impurities with time.

When the radiolabelled product is a multiple-dose preparation, the stability following removal of successive doses, simulating the real use of the product, should be investigated over the proposed in-use shelf life. The proposed in-use shelf-life should not be longer than what is needed in actual practice. In most cases, the radiolabelled preparations are unpreserved, and the in-use stability will always be shorter than 24 hours. The shelf-life and storage conditions of the radiolabelled preparation should be stated as follows in the SmPC:

Chemical, radiochemical and physical stability has been demonstrated for x hours at y ºC.

From a microbiological point of view, unless the method for radiolabelling precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user

SmPC

Section 6

In addition to the shelf-life of the kit as placed on the market (before radiolabelling), the shelf-life of the preparation obtained after radiolabelling should be stated.

The composition of the radiolabelled preparation will be provided (identity of the radiolabelled active substance, qualitative composition of the radiolabelled preparation)

Section 12

The solution for radiolabelling (radionuclide precursor or eluate of a generator) that is to be used should be clearly defined along with any specific quality requirement that has to comply with (compliance with a specific Ph. Eur. monograph if relevant, volume and activity ranges etcetera)

Detailed description of the radiolabelling procedure has to be provided.

The quality control test(s) that need to be conducted by the user after radiolabelling (e.g. appearance, radiochemical purity, pH) should be described in detail and the acceptable results stated.

6. Glossary

Definitions stated in the Pharmaceutical legislation and in the Ph. Eur. are not included in this glossary.

Activity reference date/time: The date and, if required, the time to which the radioactivity of a radiopharmaceutical is referred.

Radiolabelled active substance: In a radiopharmaceutical, the radioactive substance finally administered to the patient and intended to exert the proposed pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

Ready for use radiopharmaceutical: A radiopharmaceutical that is ready for administration to the patient as it is placed in the market, as such or after a simple dilution.

7. References

Directive 2001/83/EC, as amended

European Pharmacopeia, current version

Guideline on summary of requirements for active substances in the quality part 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, ICH guideline Q8 (EMEA/CHMP/167068 /2004)

Guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015).

Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015)

Guideline on process validation for finished products - information and data to be provided in regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1

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

Note for guidance on stability testing: Stability testing of new drug substances and products, (CPMP/ICH/2736/99)

798 Guideline on declaration of storage conditions, CPMP/QWP/609/96/Rev 2

799 Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning
800 investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017 Rev. 2)

801 Ph. Eur. General monograph "Substances for Pharmaceutical use" (2034)

802 Ph. Eur. General monograph "Radiopharmaceutical preparations (0125)

803 Ph. Eur. General monograph "Chemical precursors for radiopharmaceutical preparations (2902)

804 Ph. Eur. General chapter "2.2.66. Detection and measurement of radioactivity"

805 Guideline on core summary of product characteristics and package leaflet for radiopharmaceuticals,

806 Guidelines on the product-specific core SmPC and product leaflet.

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Annex 1 List of specification parameters applicable for radiopharmaceutical preparations

Ready for use radiopharmaceutical				
specification parameter	*Radiolabelled active substance*[§]	*chemical precursor*	*radionuclide precursor*	*finished product*
radionuclidic ID	✓		✓	✓ *
radionuclidic impurities	✓		✓	✓ *
radiochemical ID	✓		✓	✓
radiochemical purity	✓		✓	✓
radioactive concentration	✓		✓	✓
specific activity	✓			
chemical purity	✓	✓	✓	✓
chemical ID		✓		
assay		✓		
residual solvents		✓		✓
terility**				✓
bacterial endotoxins**		✓		✓
microbial contamination		✓		
[§] May be tested on the finished product, when the radiolabelled active substance is not isolated during routine manufacture				
* if not tested on radiolabelled active substance				
** If required by the specific dosage form				

Radionuclide precursor		
	active substance	*finished product*
specification parameter		
radionuclidic ID	✓	✓
radionuclidic impurities	✓	✓
radiochemical ID	✓	✓
radiochemical purity	✓	✓
radioactive concentration	✓	✓
specific activity	✓	✓
chemical purity	✓	✓
particulate matter		✓
sterility		✓
bacterial endotoxins		✓

Radionuclide generator		
specification parameter	*active substances (parent radionuclide -in equilibrium with daughter* radionuclide-)*	*finished product/eluate*
radionuclidic ID	✓	✓
radionuclidic impurities	✓	✓
radiochemical ID	✓	✓
radiochemical purity	✓	✓
radioactive concentration	✓	✓
specific activity	✓	✓
chemical ID	✓	✓
chemical purity	✓	✓
residual solvents	✓	
particulate matter		✓
sterility		✓
bacterial endotoxins		✓
* daughter radionuclide tested in the finished product (eluate)		

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Kit for radiopharmaceutical preparations			
specification parameter	*active substance*	*finished product*	*radiolabelled product*
radionuclidic ID			✓§
radionuclidic impurities			✓§
radiochemical ID			✓
radiochemical purity			✓
radioactive concentration			✓
chemical purity	✓	✓	
chemical ID	✓	✓	
assay	✓	✓	
ID of excipient essential for radiolabeling		✓	✓
assay of excipient essential for radiolabeling		✓	✓
residual solvents	✓	✓	
particulate matter			✓
sterility		✓	
bacterial endotoxins	✓	✓	
microbial contamination	✓		
§ may be performed on radionuclide precursor or the eluate of the generator if justified			

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