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NOTE ON THE GENERAL CHAPTER

A first draft of this general chapter was presented in Pharmeuropa 23.4 with the title 'Compounding of radiopharmaceutical preparations'.

The chapter generated a large number of comments, all of which were considered in the preparation of this new draft. As a result: the scope and definition section has been redrafted completely to clarify the subject; the section on automated systems has been revised in order to focus less on cassettes and more on the different means that are used in automatisation; the section on analytical control has been extended considerably; and a glossary has been added.

The section on sterilisation was the most difficult to deal with, since the regulation and guidance in place in the different countries varied a lot. It was not possible to meet fully everybody's needs.

It is remarked that the requirements laid down in this chapter are not legally binding for users of the European Pharmacopoeia as long as the chapter is not cross-referenced in a monograph (e.g. in the general monograph Radiopharmaceutical preparations (0125)). It should be interpreted as guidance.

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5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICAL PREPARATIONS

This chapter is published for information.

1. SCOPE AND DEFINITION

Many radiopharmaceutical preparations are prepared on-site on a regular basis, typically as individual doses for a few patients based on specific clinical needs (extemporaneously prepared radiopharmaceutical preparations, EPRPs). Whereas the manufacture of radiopharmaceutical preparations and of investigational medicinal products is well covered by existing regulations, this general chapter only covers EPRPs, which are also to be considered in the light of any existing national competent authority requirements.

EPRPs are either prepared in accordance with a medical prescription for an individual patient, or prepared in accordance with a monograph of a pharmacopoeia and intended to be supplied directly to the patients (commonly known as the officinal formula). The concerned radiopharmaceutical preparations are used on the day of preparation and include kit-based preparations (from licensed and unlicensed kits) and unlicensed preparations containing radionuclides for positron emission tomography (PET), single photon emission computed tomography (SPECT) or therapeutic applications.

For the purpose of this general chapter, the preparation of radiopharmaceutical preparations is considered as a process involving all or some of the following steps: purchase of materials and products; production of radionuclides for radiolabelling; radiolabelling; chemical modification and/or purification; formulation; dispensing of the pharmaceutical form; sterilisation; analytical control; packaging; labelling; and release. Drawing patient doses for immediate application (e.g. from a multidose vial) is not considered part of the preparation of radiopharmaceutical preparations, but of clinical practice.

EPRPs require an appropriate framework to ensure the desired quality, hereinafter referred to as the quality system. The extent of the quality system is driven by risks for the patient concerned, such as microbial contamination, failure of chemical reactions and its consequences, malfunctioning of equipment involved in the preparation process, and inappropriate storage conditions. Risk assessment is employed to justify the extent of the quality system. Examples for quality systems can be found in guidance documentation such as: *EudraLex Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 3: Manufacture of radiopharmaceuticals*; *Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide PE 010-3: Guide to good practices for the preparation of medicinal products in healthcare establishments*; *European Association of Nuclear Medicine (EANM) guidelines: Guidance on current good*

1 *radiopharmaceutical practice (cGRPP) for the small-scale preparation of radiopharmaceuticals;*
2 and national guidelines from the competent authority. Guidance on risk assessment can be found
3 in, for example, ICH Guideline Q9: Quality Risk Management.

4 Particular attention is to be paid to:

- 5 – qualified personnel with appropriate training;
- 6 – adequate premises;
- 7 – qualified and suitable equipment for production and analysis;
- 8 – validated procedures for all critical production steps;
- 9 – environmental monitoring;
- 10 – appropriate documentation;
- 11 – procurement of starting materials and services;
- 12 – analytical methods/quality control.

14 All steps in the preparation of radiopharmaceutical preparations have to be designed to meet the
15 radiation safety requirements of the involved personnel and the environment, thereby complying
16 with national or international regulations. This includes appropriate shielding, measures to avoid
17 radioactive contamination, and radiation contamination monitoring.

18 2. PREMISES AND EQUIPMENT

19 The relevant premises and equipment must be designed, built, maintained, cleaned and sanitised
20 so that they protect product quality, protect the environment from particulates and microbial
21 contamination and protect staff and the environment from the effects of radiation.

22 Radiopharmacies may characteristically prepare a wide variety of radiopharmaceutical
23 preparations, often in the same session and place. Facilities and equipment are designed and
24 controlled to reflect the specific risk of all preparations concerned, taking into account the potential
25 of microbial contamination of the preparation. Additional considerations have to be taken into
26 account when handling biological material.

27 Detailed knowledge of process parameters, workflow, environmental conditions and microbial
28 aspects of the preparation helps to avoid possible chemical, radiochemical, radionuclidic and
29 microbial contamination. In the particular case of blood-cell radiolabelling, movement of operators
30 between the blood-labelling area and the pharmaceutical area of the laboratory is prevented by an
31 appropriate design and layout of the premises. Any animal- or human-derived biological material
32 is stored and handled separately from other substances for pharmaceutical use, pharmaceutical
33 preparations or starting materials.

34 Measurement of radioactivity is carried out as described in general chapter 2.2.66. *Detection and*
35 *measurement of radioactivity*. Measurement equipment must be properly shielded, particularly
36 when high levels of radioactivity are handled in adjacent areas. A system to ensure proper
37 performance of this equipment including daily checks and periodic calibration is implemented. All
38 deviations, such as changes to the range of linearity, calibration for energy and efficiency and
39 unexpected changes in background readings must be investigated.

38 3. PREPARATION PROCESS

39 In the case where a licensed product is being used as a part of the preparation process,
40 the licensed product must comply with the requirements of its marketing authorisation. The
41 holder of the marketing authorisation is responsible for the licensed product complying with
42 the requirements in the marketing authorisation. The radiopharmacy preparing licensed
43 radiopharmaceutical preparations according to the instructions for use carries the responsibility
44 for the quality of the preparation and handling of these radiopharmaceutical preparations at its
45 site, but no specific risk assessment on radiolabelling and chemical quality is needed. If the
46 instructions for use of a licensed radiopharmaceutical preparation are not strictly followed or if
47 one or more components used for the preparation do not have a marketing authorisation, risk
assessment is undertaken and documented. It is the responsibility of the radiopharmacy to
demonstrate that the quality of the final preparation is suitable for the intended use.

1 The bioburden of ingredients/excipients is an important factor in maintaining a low bacterial
2 endotoxin content and achieving a high sterility assurance level in subsequent operations.
3 Opened or partially used packages of ingredients intended for subsequent use must be properly
4 indicated (labelled) and stored, under restricted access conditions. Shelf-life periods are defined
5 for non-opened, opened and dissolved starting materials, as well as excipients, especially in
6 view of the microbiological background in the specific working conditions. The use of single-use
7 packages is recommended.

8 Monitoring of the environment and personnel during the extemporaneous preparation of
9 radiopharmaceutical preparations is essential in defining the quality of the final preparation,
10 irrespective of the origin of material used in the preparation. Recommended monitoring
11 frequencies can be found in guidance documents such as PIC/S Guide PE 010-3. Deviations
12 from the recommended frequency are risk-assessed and justified. When a sterile preparation is
13 to be obtained and terminal sterilisation or sterile filtration is not possible, all starting materials
14 must be sterile. Components of the equipment that come into direct contact with the preparation
15 during the preparation process must be sterile and disposable or reused only after a validated
16 cleaning and sterilisation procedure is carried out.

15 3-1. *PRODUCTION OF RADIONUCLIDE PRECURSORS*

16 The procedure for production of the radionuclide clearly describes major parameters, such as:

- 17 – target material;
- 18 – nuclear reaction;
- 19 – construction and material of the holder for the target material;
- 20 – maintenance of the holder for the target material and transfer lines;
- 21 – irradiation data, such as beam energy and intensity;
- 22 – typical radionuclidic contaminants for the adopted conditions (excitation function);
- 23 – separation/purification process of the desired radionuclide;

24 and evaluates all effects on the efficiency of the production in terms of quality and quantity of
25 the produced radionuclide.

26 Radionuclide precursors and radiolabelled molecules comply with the requirements of the general
27 monograph *Radiopharmaceutical preparations (0125)* and of their individual monographs where
28 available.

29 3-2. *CHEMICAL PRECURSORS*

30 Chemical precursors are usually obtained by synthesis. They can be combined or pre-loaded with
31 other substances in the form of pre-prepared sets for radiolabelling procedures and/or used as
32 starting materials in cassettes or kits.

33 Chemical precursors, either in isolated form or in the form of starting material sets, have an
34 acceptable, low degree of microbial contamination, irrespective of whether the final product is
35 terminally sterilised or sterile-filtered. Sterilisation is to be considered if there is a risk that the
36 chemical precursors support microbial growth.

37 Quality requirements for chemical precursors are stated in their respective monographs. In case
38 no monograph is available, the general monograph *Substances for pharmaceutical use (2034)*
39 applies and a programme to test the quality is implemented. However, it is to be noted that
40 certain provisions of the general monograph *Substances for pharmaceutical use (2034)* are not
41 applicable to radiopharmaceutical preparations or chemical precursors. These provisions are
42 covered by the general monograph *Radiopharmaceutical preparations (0125)*.

43 A shelf-life for starting material sets is defined, with consideration given to the degradation of
44 ingredients, microbial contamination and the stability of packaging materials, taking into account
45 the permeability of plastic and elastomeric packaging. Shelf-life is indicated and justified by
46 stability studies reflecting the mode of use.

46 3-3. *RADIOLABELLING*

47 The radiolabelling step is the reaction of the radionuclide precursor with a chemical precursor.
Biological materials such as proteins or cells can also be substrates for direct radiolabelling.

1 The radiolabelling includes the mixing of starting materials in controlled conditions (i.e.
2 temperature or pressure). After radiolabelling, subsequent steps may be involved to remove
3 protecting groups or to couple the radiolabelled compound to another molecule, which may be an
4 organic moiety or a more complex structure such as a peptide or an antibody.

5 Risks for radiolabelling efficiency, quality, safety and efficacy of the radiopharmaceutical
6 preparation, associated with the chemical and physical composition of the kit/components/starting
7 materials, must be evaluated. Chemical and physical stability and risks of microbial contamination
8 must be examined closely.

9 The source and quality of ingredients (e.g. metal contaminants), quantitative and qualitative
10 composition (e.g. concentration, pH, sterility, osmolarity, viscosity, solubility, stability) and
11 operating conditions (e.g. use of inert gas, temperature, pressure) are considered when
12 developing the synthesis. Special attention is also paid to possible side products of the synthesis.
13 Automation and/or use of cassettes are possible ways of improving the reliability of synthesis
14 processes, reducing the risk of microbial contamination and increasing radiation safety.

15 Before introducing a new synthesis in clinical practice, the synthesis process is validated by
16 suitable controls during the preparation (in-process control) and extensive quality control of the
17 final preparation using at least 3 batches. Once the process is validated, the routine controls
18 that need to be performed before patient administration depend on the risk assessment based
19 on different factors such as chemical complexity, factors affecting the efficacy of the product
20 and radiation dose concerns for the patient, for example through the control of radiochemical
21 and radionuclidic impurities.

22 3-3-1. Radiopharmaceutical preparations without a purification step

23 This type of synthesis is characterised by combining a radionuclide precursor with a mixture of
24 starting materials. This addition is followed by a quantitative reaction of the radionuclide with
25 the chemical precursor, so that this extemporaneous preparation process does not require
26 a purification step. Open procedures are to be avoided due to the elevated risk of microbial
27 contamination. All components are co-injected with the resulting radiopharmaceutical active
28 ingredient. The risk assessment focuses on the chemical, radiochemical and microbiological
29 quality of all starting materials, including the radionuclide precursor. In case of multiple additions,
30 the risk assessment also focuses on the conditions of addition and reaction of the different starting
31 materials, especially on the reaction container.

32 3-3-2. Radiopharmaceutical preparations requiring purification

33 This type of synthesis is characterised by a single addition of a radionuclide solution to a mixture
34 of starting materials or by multiple additions of different starting materials, which then requires
35 subsequent purification (see also section 3-5). An efficient purification of the desired radioactive
36 compound from the reaction mixture is necessary in order to ensure low levels of radionuclidic,
37 chemical and/or radiochemical impurities. Physico-chemical and chemical separation of
38 intermediates or the final product is essential to yield a radiopharmaceutical preparation that
39 meets the desired quality specifications. If possible, the preparation process, including the critical
40 separation steps, is monitored with suitable detectors. Controls are performed considering
41 radiation safety. The risk assessment focuses on the same points as in section 3-3-1, as well
42 as on the conditions of purification, especially the efficiency of separation and the effect of
43 chromatographic media on the subsequent microbiological quality of the product (endotoxin
44 content).

45 3-3-3. Cell radiolabelling

46 Cross-contamination, cross-infection, mix-up of blood and blood components and integrity and/or
47 viability of the cells after radiolabelling are all specific points of attention for the risk assessment
48 for cell radiolabelling. This type of radiolabelling is considered more extensively in section 3-14.

49 3-4. AUTOMATED SYSTEMS

50 Some of the steps described above can be subject to automation. An automated module usually
51 consists of a combination of power supplies, actuators, pumps, heaters and sensors that are used
52 in combination with an interconnected network of containers, reactors, tubing, syringes, solid
53 phase cartridges and/or preparative high-performance liquid chromatography (HPLC) systems.

1 The automated module can be a commercial piece of equipment or can be custom made. It is
2 common for different radiopharmaceutical preparations to be made on the same automated
3 module.

4 Within the synthesis process, the automated module controls process parameters in such a
5 way that a bulk solution of a radiopharmaceutical preparation is produced. The containers and
6 purification system used with the automated module can be single-use ('radiopharmaceutical
7 cassette') or used in multiple production runs.

8 It must be shown by validated cleaning protocols that the quality of the produced
9 radiopharmaceutical preparation is not negatively affected when used in multiple production runs.
10 The potential for cross-contamination is assessed and, if necessary, monitored.

11 The containers and purification systems (for example the column of a preparative HPLC system)
12 are considered part of the synthesiser.

13 The electronic components of the synthesiser are resistant to high radiation levels.

14 Components that come into contact with the starting materials, solvents and/or
15 radiopharmaceutical preparation are chemically inert. Special care must be taken with
16 components that may degrade under the influence of radiation and that come into contact with
17 the starting materials, solvents and/or radiopharmaceutical preparation, as they may release
18 impurities over time.

19 Automated modules may also control formulation and dispensing of the radiopharmaceutical
20 preparation, usually by using volume- or weight-measuring devices and radioactivity detectors
21 in order to measure and dispense the correct quantities. For dispensing, single-use tubing
22 systems are used unless a validated cleaning protocol is performed. The measuring systems
23 must be calibrated.

24 For an automated synthesis and/or dispensing module, 2 levels of qualification/validation are
25 required. The automated module itself is qualified by the supplier and/or the user. After the
26 qualification of the automated module, the extemporaneous preparation/dispensing process is
27 validated.

28 The synthesis process on the synthesiser is usually controlled by software and must be validated.
29 The user of the automated system has the list of the sequence steps used in the synthesis and a
30 history of changes made to them. Changes to the software are controlled and documented. The
31 software is under access control. Guidance on the use of computerised systems can be found
32 for example in EudraLex Volume 4, Annex 11.

33 Manual interventions or adjustments of parameters (e.g. manual operation of valves) are
34 documented and investigated as a process deviation. The version of the software used for a
35 production is recorded as a batch parameter. When changes are made to the software, the old
36 version of the software is archived for the same period as the documentation of the batches
37 made with that version.

38 Automated systems may involve the use of radiopharmaceutical cassettes and other disposable
39 devices. A radiopharmaceutical cassette is defined as a system of single-use production
40 hardware (such as tubes, valves and filters). It is used with a set of starting materials (such as
41 precursors, solvents, catalysts, etc.), which may be contained in the cassette (prefilled cassette)
42 or provided separately (empty cassette).

43 Cassettes can be made by commercial manufacturers or assembled in-house. The requirements
44 apply to both, and the related information is directed towards the users of the cassette to help
45 them establish their user requirements.

46 All materials of the system that come into contact with reagents or product exhibit suitable stability
47 during storage and use. The compatibility of the plastic and the chemical process must be
48 proven. Glass components are at least type I (see general chapter 3.2.1. *Glass containers for
49 pharmaceutical use*).

50 Before human use of a preparation prepared with the aid of cassettes, it must be validated
51 that the combination of the cassette and the automated system consistently produces the
52 radiopharmaceutical preparation of the desired quality.

53 The quality of the chemicals used complies with the requirements mentioned above in section 3-2.

1 The cassette must be able to synthesise the radiopharmaceutical preparation to the agreed
2 specification during the entire shelf-life of the cassette.

3
4 In order to maintain a low bacterial endotoxin content and achieve a high sterility assurance
5 level for the radiopharmaceutical preparation prepared with the use of a cassette, the cassette
6 must have a low initial bioburden.

7 The user must be assured of the suitability of the manufacturing process and must ensure the
8 final product quality by appropriate analytical tests.

9 The user of the automated system must have the necessary information about the chemicals and
10 reaction processes applied within the system to evaluate the potential deviations that may occur
11 during the production of the radiopharmaceutical preparations. In the case of suboptimal reaction
12 or system malfunction, yields might be lower and additional impurities might occur. Sufficient
13 information about potential malfunctions of the system must be made available to the user to set
14 up appropriate release specifications.

14 3-5. *PURIFICATION*

15 Purification of the product from the reaction mixture is often required, particularly when organic
16 chemical reactions are carried out. Since the purification step ensures the final quality of the
17 radiopharmaceutical preparation, separation efficiency has to be carefully evaluated in terms of
18 final radiochemical, radionuclidic and chemical purity. Special attention must be paid to residual
19 solvents (see general chapter 5.4. *Residual solvents*). All purification procedures must be
20 validated.

21 A microbial contamination risk exists when using chromatographic media, especially in the case of
22 multiple-use liquid chromatography columns. Risk assessment focuses on cleaning/conditioning
23 procedures and conditions of storage of chromatographic media. Bioburden and endotoxin
24 content are maintained below suitable limits to allow sterilisation in case of parenteral dosage
25 forms.

26 For biological materials such as blood cells, centrifugation is an important purification step. If the
27 purification step cannot provide a reproducible quality of a product, the radiolabelling process
28 must be redeveloped.

29 3-6. *FORMULATION*

30 After purification of the labelled compound, the radiolabelled molecule is formulated into a suitable
31 form for administration to patients.

32 The source and quality of excipients and additives are documented.

33 When an in-house ingredient/excipient starting material set is used, the use of components with
34 no microbial contamination (or an acceptably low level) is recommended, irrespective of whether
35 the final product is terminally sterilised or sterile-filtered.

36 In case different types of radiopharmaceutical preparation from kits are to be prepared in the
37 same period, individual vials of diluent are used to prevent cross-contamination.

38
39 Most radiopharmaceutical preparations are intended for parenteral administration. In this respect,
40 pH, osmolarity, viscosity, ionic strength and solubility must be appropriately addressed when
41 radiopharmaceutical preparations and in-house starting material sets are developed.

42 3-7. *DISPENSING*

43 Dispensing is the process of aliquoting bulk solution into final product dosage forms, subject
44 to release before medical administration (see section 3-12). It includes preparation of a batch
45 consisting of one or more final product vials or syringes from the bulk solution. In order to keep
46 the bioburden as low as possible, components used in the dispensing process are sterile. If these
47 are not available, components are sterilised by a validated process. If components are reused,
it must be ensured by a validated cleaning procedure that no cross-contamination from one
product to another can take place.

3-8. STERILISATION

Radiopharmaceutical preparations for parenteral administration must be sterile. Terminal sterilisation provides the highest level of assurance that a product will be sterile. In most cases only sterile filtration steps or even no sterilisation (e.g. when autologous cells are radiolabelled) can be performed. These are to be considered as aseptic preparations. The methods of sterilisation that can be used are described in general chapter 5.1.1. *Methods of preparation of sterile products*.

Aseptic manipulations take place in a grade A environment. The grade of the surrounding environment will depend on the containment system used, the risk of contamination for the preparation, the shelf-life of the preparation and the number of units prepared during a preparation run.

The complexity of operation and the shelf-life determine the measures that need to be taken to ensure a sterile product, for example:

- simple operations in a closed system requiring little handling (e.g. preparing radiopharmaceutical preparations from licensed kits and generators) are undertaken in a grade A air-supply area located in at least a grade D area with respect to air cleanliness;
- more complex operations (e.g. open-vial preparation or vial filling after sterile filtration, aseptic preparation, labelling of autologous cells) are undertaken in a grade A air-supply area located in a grade C area with respect to air cleanliness or in an isolator (class A air-supply area located in a class D area).

Closed procedures for dispensing are used whenever possible as an alternative to open-vial filling, especially for very small batches or individual patient preparations. The dispensing set (sterilising filter and vials) that is used in closed aseptic dispensing operations must be sterile. This can be achieved by sterilisation of the dispensing set. Sterile components of the dispensing sets, such as sterilising filters, tubes and vials, are assembled and connected in a grade A air-supply area located in a grade C area with respect to air cleanliness. The process of closed aseptic dispensing can be performed in at least a grade C area with respect to air cleanliness.

Monitoring of the critical grade A air-supply areas and background environment for particulates and microbial contamination is carried out on a regular basis. When sterile filtration is used to sterilise the preparation, the filter is tested for integrity before administration of the preparation to the patient. Filter-integrity testing for each type of preparation, for example by bubble-point determination, must be validated.

Preparations that contain as active ingredient a radioisotope with a half-life shorter than 5 min are exempt from filter integrity testing before release of the product.

Where the administration is performed directly from the equipment to the patient, the filter used is suitable for direct human use.

Compatibility of the filter membrane and housing with the product solution is verified experimentally using the supplier specifications. In some cases it is not possible to find acceptable certified filters for certain applications (e.g. for hydrophobic radiopharmaceutical preparations). In these cases filters need to be tested for bacterial endotoxin content, efficiency and product recovery.

3-9. ANALYTICAL CONTROL

All analytical systems are qualified and all methods validated according to the recognised standards (e.g. ICH Guideline Q2: Validation of Analytical Procedures: Text and Methodology).

3-9-1. Ingredients and starting materials

Ingredients used for extemporaneous preparation comply with the general monograph *Substances for pharmaceutical use (2034)* and with their individual monographs where available.

For starting materials that are not present in the radiopharmaceutical preparation (e.g. reagents removed by purification, catalysts, solvents, cartridges), specifications are verified by evaluation of the certificate of analysis provided by the manufacturer, completed if necessary by specific tests. Specifications are adapted to the level of chemical and microbiological purity needed to ensure a suitable quality for the intended purpose in the radio-synthesis.

The identity of unlicensed excipients included in the final formulation is also verified by a suitable analytical method. Specifications are adapted to the level of purity needed to ensure a quality suitable for a component of a pharmaceutical for injection, especially bioburden and bacterial endotoxin content.

Some radionuclide precursors cannot be systematically evaluated by analysis before use in the radiosynthesis process. The suitability for the intended purpose is established each time a new batch of the target material is used or a modification of the radionuclide manufacturing process takes place.

For chemical precursors, (i) identity is verified by a suitable analytical method, (ii) suitability for radiosynthesis is verified for each batch by performing a complete radiosynthesis with a final radiopharmaceutical product complying with all its specifications (run test), and (iii) specifications are verified by evaluation of the certificate of analysis provided by the manufacturer, completed if necessary by specific tests.

3-9-2. Radiopharmaceutical preparations

Extemporaneously prepared radiopharmaceutical preparations comply with the general monograph *Radiopharmaceutical preparations (0125)* and with their individual monographs where available. Moreover, other applicable general monographs and general texts must also be followed, especially *Pharmaceutical preparations (2619)*, 5.1.1. *Methods of preparation of sterile products* and 5.4. *Residual solvents*.

Where no individual monograph exists, specifications and corresponding test methods are established for each radiopharmaceutical preparation. Table 5.19.-1 provides a basis for determining the suitable analytical parameters and methods. Details on the measurement of radioactivity in test methods can be found in general chapter 2.2.66. *Detection and measurement of radioactivity*. For each scheduled test, it must be stated whether the result has to be available before release for use of the radiopharmaceutical preparation. When a test is delayed until after the release for use, this must be justified and a maximum period of delay for performing the test must be established.

Table 5.19.-1. – *Analytical parameters and methods for release of an extemporaneously prepared radiopharmaceutical preparation*

Test or parameter	Equipment or method
Characters, appearance	Visual inspection
Identity of radionuclide	Ionisation chamber (half-life), gamma-ray spectrometry
Identity of radiopharmaceutical preparation	Liquid chromatography, thin-layer chromatography
Identity of pharmaceutical substance	Liquid chromatography, thin-layer chromatography
Radiochemical purity	Liquid chromatography, thin-layer chromatography
Chemical purity	Liquid chromatography, thin-layer chromatography, ultraviolet/visible absorption spectrophotometry
Residual solvents	Gas chromatography
Pharmaceutical or physiological parameters	pH, osmolality
Microbiological parameters	Bacterial endotoxins, sterility
Radionuclidic purity	Gamma-ray spectrometry
Radioactivity content, concentration	Ionisation chamber
Specific radioactivity	Liquid chromatography, ionisation chamber
Enantiomeric purity	Chiral liquid chromatography

3-10. PACKAGING

The immediate packaging material is compatible with the preparation.

3-11. LABELLING

Where a radiopharmaceutical preparation is prepared and used on the same site, the labelling of the immediate packaging contains as a minimum the following information:

- the name of the preparation/active substance and/or its reference;
- an unequivocal reference to the preparation (batch number or date of the EPRP);
- where applicable, a serial number for the dispensed unit (where several units are dispensed);
- the radioactive trefoil.

Where applicable, the shielding labelling contains a reference to the patient (identification number or name).

For liquid and gaseous preparations, the total radioactivity in the container, or the radioactive concentration per millilitre at a stated date and calibration time, and the volume of liquid in the container are stated.

For solid preparations (such as capsules), the total radioactivity at a stated date and, if necessary, time are stated.

The labelling can be adapted in certain cases where, due to the extremely short half-life of the product, the preparation is used before all of the information is available.

In addition, the label on the outer package states:

- where applicable, the name of any excipients;
- the name of the manufacturer (site where the preparation was made);
- the route of administration;
- the period of validity or the expiry date;
- where applicable, any special storage conditions.

3-12. RELEASE

The decision to release a pharmaceutical preparation as suitable for administration is dependent on the conformance of the analytical results to the specifications, and process data related to its preparation, especially in process controls and environmental monitoring. However, due to the short-lived nature of radiopharmaceutical preparations not all quality parameters of the preparation can be known at the time of release for administration. The list of analytical tests to be performed before release for administration is established according to section 3-9-2. A written procedure detailing all preparation and quality control data (preparation, quality control, assessment of deviations, etc.) that is required to be available before release for administration is consulted before the preparation is released. The review and the release of the preparation before administration by the responsible person is confirmed in writing in the batch documentation.

A written procedure also describes the actions to be taken by the responsible person (recall of the preparation or provision of information to its users, depending on the time of discovery), should unsatisfactory test results be obtained after the preparation has been released.

The final review and final release of the preparation by the responsible person is confirmed in writing in the batch documentation.

3-13. RETENTION SAMPLES

In case of preparations without marketing authorisation, retention samples are kept for a period of 1 month after the time all testing is completed or 1 month after expiry of the preparation, whichever is the longer. In the case of single vial dispensing, retention samples may not be available; this must be carefully considered in any risk assessment. No retention samples are needed for preparations of radiolabelled blood cells.

3-14. PREPARATION OF RADIOLABELLED BLOOD CELLS

During cell manipulation and radiolabelling, it is necessary to maintain both cell viability and sterility. Operator protection is of paramount importance. Operator exposure to biological and radiation hazards must be avoided.

1 3-14-1. **Collection of blood cells and cellular components for radiolabelling and reinjection**
2 **into the original donor/patient**

3 Blood cells and cellular components are collected in such a way as to preserve their function (use
4 of a wide-bore needle, use of a syringe pre-coated with an appropriate anticoagulant, avoiding
5 excessive centrifugation). The containers are suitably labelled with the patient's information in
6 order to prevent mix-up. Quality requirements for all substances used in the separation of the cells
7 are stated in the respective monographs. Where no individual monograph is available, the general
8 monograph *Substances for pharmaceutical use (2034)* applies. Further precautions may be
9 necessary where the use of heterologous cells is required, as provided in respective regulations.

10 A centrifuge, constructed to ensure containment in case of spills and/or breakage (with closed
11 buckets), is required for blood-cell components separations. The equipment used in the labelling
12 of cells is only used for 1 procedure at a time. Single-use utensils are the preferred choice for use.
13 Separation in time and a cleaning/disinfection process for utensils and equipment that ensures
14 the destruction of blood-borne pathogens and viruses are implemented between the processing
15 of samples from different subjects.

16 3-14-2. **Radiolabelling of the cells**

17 Precautions are taken to prevent cross-contamination, cross-infection or mix-up of blood and
18 introduction of microbial contamination. Radiolabelling conditions must not impair the integrity
19 and/or viability of the cells. Since terminal sterilisation is not possible, radiolabelling of cells is
20 considered as an aseptic preparation (see section 3-8).

21 3-14-3. **Quality control**

22 The identity, calculation of the labelling yield and absence of aggregation or clumping of cells is
23 assessed to verify the suitability of radiolabelled cells before release and reinjection/administration.
24 At regular time intervals, testing for cell viability/integrity is performed.

25 Validation of the preparation of radiolabelled blood cells includes testing of cell viability,
26 morphology or function, depending on the cell type. Any changes to the standard procedure for
27 preparation of radiolabelled cells is validated.

28 GLOSSARY

29 **Automated module for synthesis and/or dispensing.** Electromechanical device controlled by
30 software to perform automatically a sequence of operations needed for radiolabelling, purification,
31 formulation, dispensing and/or sterilisation of a radiopharmaceutical preparation.

32 **Cassette.** Pre-assembled network of containers, valves and syringes, including or not the starting
33 material set, intended to be mounted on a synthesis module in order to prepare the EPRP.

34 **Responsible person.** Person designated as responsible for the release of a radiopharmaceutical
35 preparation, meeting the conditions provided by the national legislation.

36 **Starting material set.** Set of reagents, solvents and precursors in their usable forms for the
37 EPRP. Usable forms are mostly either a weighed amount of a solid or a volumetric sample of a
38 suitable solution. Solids and liquids are often dispensed in closed vials for storage before use.
39 Starting material sets may be available commercially or be prepared on-site from commercial or
40 locally synthesised chemicals and packaging materials.

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