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5.19. EXTEMPORANEOUS PREPARATION OF RADIOPHARMACEUTICALS

This general chapter is published for information.

1. SCOPE AND DEFINITION

Many radiopharmaceuticals are prepared on-site on a regular basis, typically as doses for a few patients based on specific clinical needs (extemporaneously prepared radiopharmaceuticals, EPRs). Whereas the manufacture of radiopharmaceuticals and investigational medicinal products is well covered by existing regulations, this general chapter only covers EPRs, which are also to be considered in the light of any national competent authority requirements. Radiopharmaceuticals are pharmaceutical preparations, and the provisions and terminology of the general monograph *Pharmaceutical preparations (2619)* apply.

EPRs are either prepared in accordance with a medical prescription for an individual patient, or in accordance with a pharmacopoeial monograph, and intended to be supplied directly to patients. The radiopharmaceuticals concerned are used within their specified expiration time, and include both 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 for therapeutic applications.

For the purpose of this general chapter, the preparation of radiopharmaceuticals is considered as a process involving some or all 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 considered as part of clinical practice, and not part of the preparation of radiopharmaceuticals.

EPRs 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 the 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 determine the level of risk and the required level of quality assurance to achieve appropriate product quality and to assure radiation safety. Examples of quality systems can be found in the following guidance documents or any subsequent revisions: *Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S): Guide to good practices for the preparation of medicinal products in healthcare establishments (PE 010); EudraLex Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use; European Association of Nuclear Medicine (EANM) guideline: Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals*; and national guidelines from the competent authority. Guidance on risk assessment can be found in, for example, *ICH Guideline Q9 Quality Risk Management*.

Particular attention is to be paid to:

- qualified personnel with appropriate training;
- adequate premises;
- qualified and suitable equipment for production and analysis;
- validated procedures for all critical production and testing steps;
- environmental monitoring;
- appropriate documentation;
- procurement of materials and services used in the preparation;
- analytical methods / quality control.

All steps in the preparation of radiopharmaceuticals are designed to meet the radiation safety requirements for the personnel involved and the environment, thereby complying with national or international regulations. This includes appropriate shielding, and measures to avoid and monitor radioactive contamination.

2. PREMISES AND EQUIPMENT

The relevant premises and equipment are designed, built, maintained, cleaned and sanitised so that they protect product quality, ensure a low level of particulates and microbial contamination and protect staff and the environment from the effects of radiation.

Radiopharmacies may characteristically prepare a wide variety of radiopharmaceuticals, often in the same session and place. The premises, equipment and workflow are arranged in order to minimise the risk of cross-contamination and mix-up. Facilities and equipment are designed and controlled to reflect the specific risk of all preparations concerned, taking into account the potential for microbial contamination of the preparation. Additional considerations are taken into account when handling biological material.

Detailed knowledge of process parameters, workflow, environmental conditions and microbial aspects of the preparation helps to avoid possible chemical, radiochemical, radionuclidic and microbial contamination. In the particular case of blood cell radiolabelling, movement of operators within the laboratory between the area for blood cell labelling and the area for the preparation of other radiopharmaceuticals is prevented by the appropriate design and layout of the premises. Any biological hazardous material is stored and handled separately from other substances for pharmaceutical use, pharmaceutical preparations or starting materials.

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

3. PREPARATION PROCESS

In the case of a licensed product used as a part of the preparation process, it is the responsibility of the marketing authorisation holder to ensure that the licensed product complies with the requirements of its marketing authorisation. The radiopharmacy preparing licensed radiopharmaceuticals according to the instructions for use carries the responsibility for the quality of the preparation and the handling of these radiopharmaceuticals at its site.

If the instructions for use of a licensed radiopharmaceutical are not strictly followed or if one or more components used for the preparation do not have a marketing authorisation, risk assessment (including rationales and pharmaceutical equivalence, if applicable) 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.

In general for ERPs, the bioburden of starting materials is an important factor in maintaining a low bacterial endotoxin content and achieving a high sterility assurance level in subsequent operations. Opened or partially used packages of starting materials intended for subsequent use are properly indicated (labelled) and stored under restricted

access conditions. Shelf-life periods are defined for opened, unopened and dissolved starting materials, especially in light of the microbiological background in the specific working conditions. The use of single-use packages is recommended. A shelf-life for starting material sets is defined with consideration given to the degradation of ingredients, microbial contamination and the stability of packaging materials, taking into account the permeability of plastic and elastomeric packaging. Shelf-life is indicated and justified by stability studies reflecting the mode of use.

Monitoring of the environment and personnel during the extemporaneous preparation of radiopharmaceuticals is essential in defining the quality of the final preparation, irrespective of the origin of material used in the preparation. Recommendations for the frequency of monitoring can be found in guidance documents such as PIC/S Guide PE 010 or any subsequent revisions. Deviations from the recommended frequency are made based on risk assessment and justified. When a sterile preparation is to be obtained and terminal sterilising filtration is not possible, all starting materials are sterile. Components of the equipment that come into direct contact with the preparation during the preparation process are sterile and disposable or re-used only after a validated cleaning and sterilisation procedure has been carried out.

3-1. *PRODUCTION OF RADIONUCLIDES*

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

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

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

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

3-2. *CHEMICAL PRECURSORS*

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

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

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

3-3. *RADIOLABELLING*

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

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

Risks to radiolabelling efficiency, quality, safety and efficacy of the radiopharmaceutical, associated with the chemical and physical composition of the kit, the components or the starting materials, are evaluated and documented. Chemical and physical stability and risks of microbial contamination are examined closely.

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

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

3-3-1. **Radiopharmaceuticals not requiring a purification step**

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

3-3-2. **Radiopharmaceuticals requiring purification**

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

3-3-3. **Cell radiolabelling**

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

3-4. *AUTOMATED SYSTEMS*

Some of the steps described above can be subject to automation. An automated module (synthesiser) usually consists of a combination of power supplies, actuators, pumps, heaters and sensors that are used in combination with an interconnected network of containers, reactors, tubing, syringes, solid phase cartridges and/or preparative liquid chromatography systems. The automated module can be a commercial piece of equipment or can be custom made. It is common for different radiopharmaceuticals to be made on the same automated module.

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

When using consecutive production runs, the risk of cross-contamination is considered. Appropriate measures are taken to prevent cross-contamination by using dedicated components or equipment or by assessing the effectiveness of the cleaning procedure.

The containers and purification systems (e.g. the column of a preparative liquid chromatography system) are considered part of the synthesiser.

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

Components of the automated module that come into contact with the starting materials, solvents and/or the radiopharmaceutical are chemically inert. Special care is taken with components that may degrade under the influence of radiation and that come into contact with the starting materials, solvents and/or the radiopharmaceutical, as they may release impurities over time.

Automated modules may also control formulation and dispensing of the radiopharmaceutical, usually by using volume- or weight-measuring devices and radioactivity detectors in order to measure and dispense the correct quantities. For dispensing, single-use tubing systems are used. The measuring system is calibrated.

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

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

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

Automated systems may involve the use of radiopharmaceutical cassettes and other disposable devices. Cassettes are used with a set of starting materials (such as precursors, solvents, catalysts, etc.), which may be contained in the cassette (prefilled cassette) or provided separately (empty cassette).

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

All materials in the system that come into contact with reagents or product exhibit suitable stability during storage and use. The compatibility of the materials (e.g. plastics) with the chemical process is assessed and documented. Glass components are at least type I (see general chapter *3.2.1. Glass containers for pharmaceutical use*).

Before administration of a preparation produced with the aid of cassettes, it is validated that the combination of the cassette and the automated system consistently produces the radiopharmaceutical of the desired quality.

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

The cassette is able to synthesise the radiopharmaceutical to the agreed specification during the entire shelf-life of the cassette.

In order to maintain a low bacterial endotoxin content and achieve a high sterility assurance level for the radiopharmaceutical prepared with the use of a cassette, the cassette has a low initial bioburden.

The suitability of the manufacturing process is assured and the user confirms the final product quality by appropriate analytical tests.

The user of the automated system has the necessary information on the chemicals and reaction processes applied within the system in order to evaluate potential deviations that may occur during the production of the radiopharmaceuticals. In the case of suboptimal reaction or system malfunction, yields might be lower and/or additional impurities may occur. Sufficient information about potential system malfunctions is made available to the user in order to set up appropriate release specifications.

3-5. *PURIFICATION*

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

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

The radiolabelling process for biological materials such as blood cells are developed in such a way that the purification step, typically centrifugation, guarantees a reproducible quality of product.

3-6. *FORMULATION*

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

The source and quality of excipients and additives are documented.

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

In case different types of radiopharmaceuticals from kits are to be prepared in the same period, separate vials of diluent are used to prevent cross-contamination.

Most radiopharmaceuticals are intended for parenteral administration. In this respect, pH, osmolarity, viscosity, ionic strength and solubility are appropriately addressed when radiopharmaceuticals and in-house starting material sets are developed.

3-7. *DISPENSING*

Dispensing is the process of aliquoting formulation solution into final product dosage forms, subject to release before medical administration (see section 3-12). It includes preparation of a batch consisting of one or more final product vials or syringes. In order to keep the bioburden as low as possible, components used in the dispensing process are sterile. If unavailable, components are sterilised by a validated process. If components are reused, it is ensured by a validated cleaning procedure that no cross-contamination from one product to another can take place.

3-8. *STERILISATION*

Radiopharmaceuticals for parenteral administration are sterile. Terminal sterilisation provides the highest level of assurance that a product will be sterile. In most cases, only sterilising filtration steps can be performed, but in others, no sterilisation is possible (e.g. when autologous cells are radiolabelled). 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 (class A zone). 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. With respect to air cleanliness, a grade C surrounding area for open workstations, or a grade D surrounding area for isolators is typically acceptable.

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

– for simple operations in a closed system requiring little handling (e.g. preparing radiopharmaceuticals from licensed kits and generators), suitable control of the immediate surrounding area of a workstation may provide the appropriate level of air cleanliness when additional measures (e.g. gowning flow) are in place; a risk assessment is crucial in this respect;

– for complex operations (e.g. open-vial preparation or vial filling after sterile filtration, aseptic preparation, labelling of autologous cells), additional measures may be required in the immediate surrounding area of an open workstation to ensure a sterile product.

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, needles, tubes and vials) that is used in closed aseptic dispensing operations is sterile. This can be achieved by sterilisation of the dispensing set, or by using sterile components. These sterile components 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 an area that is at least grade C with respect to air cleanliness.

Monitoring of critical grade A air-supply areas and the background environment for particulates and microbial contamination is carried out on a regular basis. When sterilising 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, is validated.

Preparations that contain a radionuclide with a half-life shorter than 10 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 radiopharmaceuticals). 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*). Wherever possible, quality control testing is carried out by a person other than the person who prepared the radiopharmaceutical.

3-9-1. **Starting materials**

Starting materials 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 (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. If testing is not possible from a technical point of view, for example when using commercially available prefilled cassettes, testing can be omitted provided that the omission is backed up by a risk assessment. Specifications are adapted to the level of chemical and microbiological purity needed to ensure a suitable quality for the intended purpose in the radiosynthesis.

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

Some radionuclides 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 preparation process takes place.

For chemical precursors, (i) identity is verified by a suitable analytical method, (ii) suitability for radiosynthesis is verified by performing a complete radiosynthesis with a final radiopharmaceutical product complying with all its specifications (test synthesis), 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. **Radiopharmaceuticals**

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

Where no individual monograph or authorised summary of product characteristics exists, specifications and corresponding test methods need to be established for each radiopharmaceutical. Table 5.19.-1 provides examples 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 is

stated whether the result has to be available before release for use of the radiopharmaceutical. When a test is delayed until after release for use, this must be justified and a maximum period of delay for performing the test is established.

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

Test or parameter	Equipment and/or method
Characters, appearance	Visual inspection
Identity of radionuclide	Half-life determination; alpha spectrometry; beta spectrometry; gamma-ray spectrometry
Radiochemical identity	Liquid chromatography, thin-layer chromatography
Radiochemical purity	Liquid chromatography, thin-layer chromatography
Chemical purity	Liquid chromatography, thin-layer chromatography
Radionuclidic purity	Half-life determination; gamma-ray spectrometry, alpha spectrometry, beta spectrometry
Residual solvents	Gas chromatography
Pharmaceutical or physiological parameters	pH, osmolality
Microbiological contamination	Bacterial endotoxins, sterility
Radioactivity content, concentration	Ionisation chamber
Specific radioactivity	Liquid chromatography, ionisation chamber
Enantiomeric purity	Chiral chromatography

3-10. *PACKAGING*

The primary packaging material is compatible with the preparation.

3-11. *LABELLING*

Where a radiopharmaceutical is prepared and used on the same site, the labelling of the primary packaging of the radiopharmaceutical indicates the identity and ensures traceability. It complies with the relevant national and European legislation.

The label typically states:

- the name of the preparation/active substance and/or its reference;
- an unequivocal reference to the preparation (batch number or date of the EPR);
- where applicable, a serial number for the dispensed unit (where several units are dispensed);
- the international symbol for radiation (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 measurement time, and the volume of liquid in the container are stated on the shielding labelling.

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

The labelling can be adapted in certain cases where, due to the extremely short half-life (i.e. less than 10 min) of the product, the preparation is used before all of the information is available.

In addition, the label on the shielding or 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 radiopharmaceutical as suitable for administration is dependent on the conformance of the analytical results to the specifications, and to the process data related to its preparation, especially in-process controls and monitoring (e.g. particle, microbial, environmental). However, due to the short-lived nature of radiopharmaceuticals, 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. Release for administration follows a written procedure indicating all relevant data (preparation, quality control, assessment of deviations, etc.) required. This procedure is based on a risk assessment. Retrospective examination of analytical results is acceptable in cases where the test results can technically not be obtained before administration of the radiopharmaceutical and is based on a risk assessment. 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 in case unsatisfactory test results are obtained after the preparation has been released (recall or provision of information to users of the preparation, depending on the time of discovery).

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 the case of preparations without a marketing authorisation, retention samples are kept for a period of 1 month from 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 is carefully considered in any risk assessment. Where technically possible, the same approach is applied to chemical precursors and starting materials. 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, and operator exposure to biological and radiation hazards is avoided.

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

Blood cells and cellular components are collected in such a way as to preserve their function (use of a wide-bore needle, use of a syringe pre-coated with an appropriate anticoagulant, avoiding excessive centrifugation). The containers are suitably labelled with the patient's information in order to prevent mix-up. Quality requirements for all substances used in the separation of the cells are stated in the respective individual monographs, if available. The general monograph *Substances for pharmaceutical use (2034)* applies, whether or not an individual monograph is available. Further precautions may be necessary where the use of heterologous cells is required, as provided in respective regulations.

A centrifuge, constructed to ensure containment in case of spills and/or breakage (with closed buckets), is required for blood-cell component separations. The equipment used in the labelling of cells is only used for one procedure (one patient) at a time, and single-use utensils are the preferred choice. The processing of samples from different patients

is separated by a suitable period of time, and includes a cleaning/disinfection process for utensils and equipment that ensures the destruction of blood-borne pathogens and viruses.

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

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

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

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

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

GLOSSARY

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

Cassette. Single use production hardware consisting of a pre-assembled network of containers, valves and syringes, including or not the starting material set, intended to be mounted on a synthesis module in order to prepare an EPR.

Closed method for radiosynthesis. Method where a solution is never directly exposed to the environment during the radiosynthesis process, but is contained within the synthesis system (e.g. a cassette).

Closed vial dispensing. Method of dispensing, in which the solution to be filled after sterile filtration is not in direct contact with the environment and no aseptic connections are made in the system after the sterilising filter during the dispensing process.

Open method for radiosynthesis or dispensing (open vial filling). Method where at some point during the process, a solution is directly exposed to the environment (*NOTE*: for dispensing, contact with the environment through a sterilising air filter is not considered a direct exposure).

Responsible person. Person designated as responsible for the release of a radiopharmaceutical, who meets the requirements provided by the national legislation.

Starting material. Substance used for the preparation of a medicinal product. Generators, chemicals for synthesis, ion-exchange resins, packing components and consumables are considered as starting materials.

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