Draft Monographs and General Texts for Comment

IMPORTANT NOTICE

This section contains proposals for new and revised monographs and general texts that are intended for inclusion in the European Pharmacopoeia and are submitted for public comment.

According to the Guide for the work of the European Pharmacopoeia:

- *for manufacturers and other interested parties from member states of the Ph. Eur. Convention:*
  - *comments on Pharmeuropa texts should be submitted via the national pharmacopoeia authority;*
- *for manufacturers and other interested parties from non-member states of the Ph. Eur. Convention, and for multinational interested parties:*
  - *comments on Pharmeuropa texts should be submitted preferably via the national pharmacopoeia authority of the member state where the product is authorised;*
  - *in cases where comments are submitted to the EDQM HelpDesk (preferably as attachments to the enquiry form), please indicate the member state(s) where the product is authorised;*
- *for industry associations or other associations: communications should be made via the EDQM secretariat (see the address on the back cover of this issue).*

In order to facilitate the processing of comments received by the secretariats of the national authorities and the EDQM, please mention in any correspondence the PA/PH reference number indicated at the beginning of each text. Comments that propose modifications of limits should be supported by analytical data obtained on a significant number of batches. Proposed changes of methodology should be supported by experimental results of a comparative trial of the method published in Pharmeuropa for comment and the proposed alternative.

Only comments sent before ***31 December 2011*** *will be considered for the preparation of the final version.*

It is stressed that these proposals have not been adopted by the European Pharmacopoeia Commission and must not be regarded as official texts.

In the case of proposals for revision, text to be deleted is crossed out and replacements or additions are underlined.

Reference: PA/PH/Exp. CRP/T (11) 2 ANP

NOTE ON THE GENERAL CHAPTER

In Europe, radiopharmacies have existed in many academic institutions for over 20 years. Typical examples are radiopharmacies in nuclear medicine departments and PET-centres, and particularly in university hospitals. As in the academic environment, the clinical applications and the compounding processes show great variations. Moreover, differences between European countries are extraordinarily high. Therefore a document to bridge these differences is essential.

In many cases, radiopharmaceuticals are prepared in a daily routine for in-house use or in some cases also for neighbouring hospitals (satellite concept). Characteristically, individual doses for a few patients based on individual prescriptions are prepared to be used within the same working day. This is in contrast with industrial manufacturing where batches for a great number of patients are produced.

For the industrial manufacturing of radiopharmaceuticals, GMP guidelines have been well established for a long time. This document tries to summarise the expectations for the compounding of radiopharmaceuticals. The in-house preparations of radiopharmaceuticals involve radiochemical methods and procedures that have been in use for several decades, particularly in academic institutions. It is noteworthy that the radioanalytical procedures are highly sensitive, well standardised and commonly used. This document also tries to summarise and document the current state of the art of compounding of radiopharmaceuticals, taking into account this well-established knowledge.

The general monograph Radiopharmaceutical preparations (0125) is currently under revision. The parts of this monograph that are related to the production of radiopharmaceuticals have been taken out of the general monograph and transferred to this general chapter. These parts concern mainly the description of the production procedure, including automation and the analytical control of precursors.

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5.19. COMPOUNDING OF RADIOPHARMACEUTICALS

1. SCOPE AND DEFINITION

This general text specifically addresses radiopharmaceutical compounding and preparation in radiopharmacies. For the purpose of this text, compounding of radiopharmaceuticals is considered as a process involving the following steps: production of radionuclides for radiolabelling, synthesis of non-radioactive precursors, radiolabelling, purification, formulation, dispensing, sterilisation, analytical control, packaging, labelling and release. The preparations concerned include kit-based preparations, preparations made on-site such as PET preparations and others involving short-lived radionuclides. The manufacture of ready-to-use radiopharmaceuticals that have a marketing authorisation is not within the scope of this general text.

It is advised that the respective guidelines for good radiopharmaceutical practices (as described in, for example, in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) PE 010-3 Guide to good practices for the preparation of medicinal products in healthcare establishments and the European Association of Nuclear Medicine (EANM) Guidelines on current Good Radiopharmacy Practice (cGRPP) for the small-scale preparations of radiopharmaceuticals) will have been observed in the design of the compounding process including, in particular, the use of:

- qualified personnel with appropriate training;
- adequate premises;
- suitable equipment;

– validated procedures for all critical production steps;
– environmental monitoring;
– appropriate documentation systems;
– sourcing.

The different types of radiopharmaceuticals are each compounded in their own specific way. Each requires an appropriate procedure that is designed to ensure the desired quality, hereinafter referred to as 'the quality framework'. The extent of the quality framework is driven by risks due to failure and consequences of the chemical reactions or malfunctioning of equipment involved in the preparation process. In the following sections, for each of the compounding steps the critical issues and the requirements are addressed. In the case where a licensed product is being used as a part of the compounding process, the product must comply with the requirements of its licence. In this case it is the responsibility of the holder of the kit's marketing authorisation that the licensed product complies with the requirements. The radiopharmacy compounding licensed radiopharmaceuticals according to the Summary of product characteristics carries the responsibility of the quality of the compounding/handling of these radiopharmaceuticals at its site.

The workflow of the preparation of a radiopharmaceutical follows the principles of the reactions applied and subsequent handling that is necessary for the particular synthesis. Detailed knowledge of reaction parameters, workflow, environmental conditions and microbial aspects of the preparation help to avoid possible chemical, radiochemical and microbial contamination. In the particular case of blood-cell labelling, movements of operators between the blood-labelling area and the pharmaceutical area of the laboratory is kept to a minimum by an appropriate design and layout of the premises. The storage and handling of any animal- or human-derived biological material should be segregated from other substances for pharmaceutical use, pharmaceutical preparations or starting materials.

All steps in the compounding of radiopharmaceuticals have to be designed to meet the requirements of radiation safety of the involved personnel and the environment. This includes appropriate shielding, measures to avoid radioactive contamination, and radiation monitoring. National regulations thereby have to be observed and followed.

2. PREMISES AND EQUIPMENT

The relevant premises (radiopharmacy) and equipment must be designed, built and maintained so that they do not bear any negative impact on or represent any hazard to the product, personnel or immediate surroundings.

Radiopharmacies may characteristically prepare a wide variety of radiopharmaceuticals, often in the same session, and the batch size may be 1 vial and subsequent numbers of patient doses may be low. Facilities and equipment should be designed and controlled to reflect the specific risk of all preparations concerned, taking into account the radiation safety to the operator and the potential of microbial contamination of the preparation. Additional considerations have to be taken when handling biological material.

Measurement of radioactivity should be done as described in the general monograph *Radiopharmaceutical preparations (0125)*. Equipment must be 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 should be implemented. All deviation must be investigated, in particular unexpected changes in background readings.

3. COMPOUNDING PROCESS

Monitoring of environment and personnel during compounding of radiopharmaceuticals is essential in defining the quality of the final preparation irrespective of the origin of the kits and any material used in the preparation. The frequency of environmental monitoring should reflect the specific risk of the preparation concerned. When a sterile preparation is to be obtained and terminal sterilisation or sterile filtration is not possible, all starting materials have to be sterile. Components of the equipment that come in direct contact with the preparation should be disposable or reused after a validated cleaning procedure is performed.

3-1. *PRODUCTION OF RADIONUCLIDE PRECURSORS*

Radionuclide precursors for the synthesis of radiopharmaceuticals can be produced by accelerators, mainly cyclotrons, by nuclear reactors or subsequently obtained from a mother radionuclide (a generator system). As part of the overall quality assurance the production procedure of the radionuclide should clearly describe major parameters, such as:

– target material;
– nuclear reaction;
– excitation function;
– construction and material of the holder for target material;
– irradiation data, such as beam energy and intensity;
– typical radionuclidic contaminants for the adopted conditions;
– separation/purification of the desired radionuclide;

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

Radionuclide precursors and radiolabelled molecules should comply with the demands of the general monograph *Radiopharmaceutical preparations (0125)* and of their monograph if a monograph is available.

3-2. *SYNTHESIS OF NON-RADIOACTIVE PRECURSORS AND OTHER NON-RADIOACTIVE STARTING MATERIALS*

Non-radioactive precursors are usually obtained by organic chemical reactions. They can be combined or pre-loaded with other substances in the form of pre-prepared sets for simplification of radiolabelling procedures and/or used as starting materials in cassettes or kits (i.e. in-house starting material set).

Quality requirements for non-radioactive precursors and starting materials are stated in the respective monographs. In case no monograph is available, the general monograph *Substances for pharmaceutical use (2034)* applies and a programme to test the quality should be implemented. However, it is to be noted that certain provisions of the general monograph *Substances for pharmaceutical use (2034)* are not applicable to radiopharmaceuticals and to non-radioactive precursors. These provisions are covered by the general monograph *Radiopharmaceutical preparations (0125)*.

The use of starting materials (including in-house starting material sets) with acceptable, low degree of microbial contamination is recommended, irrespective of whether the final product is terminally sterilised or sterile-filtered. Bioburden and bacterial endotoxin levels of starting materials are important factors for the successive operations and must be kept at a low level. Sterilisation should be considered.

A time for storage of in-house starting material sets should be defined under consideration of the degradation of ingredients, microbiological contamination and stability of packaging materials including effects on permeability of plastic and elastomeric packaging. Time for storage should be indicated and be justified by stability studies reflecting the mode of use.

3-3. *RADIOLABELLING*

The radiolabelling step is the reaction of the radionuclide with a non-radioactive precursor. This step is generally performed on the basis of chemical reactions that are adapted in such a way as to meet appropriate radiochemical conditions. Biological materials such as proteins or cells are also substrates for direct radiolabelling.

After radiolabelling, subsequent steps may be involved to remove protecting groups or to couple the radiolabelled compound to another molecule that can be an organic moiety or a more complex form such as a peptide or an antibody.

In some cases, the final radiolabelled structure may need purification using solid phase extraction or liquid chromatography or a combination of these processes. See also section 3-5. Purification.

Risk assessment is based on 2 main features to be considered successively: regulatory aspects and synthesis complexity.

For radiopharmaceuticals prepared following a marketing authorisation, it is the responsibility of the marketing authorisation holder that marketed items (such as kits for radiopharmaceutical preparations, radionuclide generators, radionuclide precursors and other starting materials) comply with the requirements of their authorisation.

In the case of preparation of radiopharmaceuticals from such authorised system and/or components, strictly following the instructions given by the marketing authorisation holder, no specific risk assessment on radiolabelling and quality is needed.

If the instructions given by the marketing authorisation holder are not strictly followed or if one or more components used for the preparation do not have a marketing authorisation, risk assessment must be undertaken and documented. It is the responsibility of the radiopharmacy/compounding unit to prove that the quality of the final preparation is suitable for human use.

Risks for radiolabelling efficiency, quality, safety and efficacy of the radiopharmaceutical, generated by chemical and physical composition of the kit/components/starting materials must be evaluated. Chemical and physical stability and risks of microbiological contamination must be examined closely.

Before introducing a new synthesis in clinical practice, the synthesis process should be validated successfully by means of suitable controls during the preparation (in-process control) and extensive quality control of the final preparation. Once the process is validated, the routine controls to be performed before patient application depend on the risk assessment based on chemical complexity, efficacy of the product and radiation safety concerns.

As indicated before, synthesis complexity is to be considered in the risk assessment.

Source and quality of ingredients (e.g. metal contaminants), quantitative and qualitative composition (concentration, pH, sterility, osmolarity, viscosity, solubility, stability), operating conditions (atmosphere, heating and cooling) should be considered when planning/executing the synthesis. Special attention should also be paid to the possible side products of the synthesis.

The synthesis step includes the mixing of starting materials, the labelling step in controlled conditions (i.e. temperature or pressure) and the subsequent modifications of radiolabelled product (i.e. removal of protecting groups or coupling with another moiety). A successive formulation is not considered as part of the synthesis step.

Automation and use of cassettes are possible ways of improving synthesis processes and increasing radiation safety.

3-3-1. **Radiopharmaceutical preparations without purification step**

This type of synthesis is characterised by combining a radionuclide precursor with a mixture of starting materials. This addition is followed by a quantitative reaction of the radionuclide with the chemical precursor, so that this compounding process does not require a purification step. All components are co-injected with the resulting radiopharmaceutical active ingredient. The risk assessment should focus on the chemical, radiochemical and microbiological quality of all starting materials, including the radionuclide precursor. In case of multiple additions, risk assessment should also focus on the conditions of addition and reaction of the different starting materials, especially the type of reaction container (closed or open).

3-3-2. **Radiopharmaceutical preparations requiring a purification step**

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 steps (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 final product is essential to yield a radiopharmaceutical preparation that meets the desired quality specifications. If possible, the separation process should be monitored with suitable detectors. In-process controls should be performed with respect to radiation safety considerations. The risk assessment should focus 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 subsequent microbiological quality of the product (i.e. endotoxins levels).

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

Cross contamination, cross infection, mix-up of blood and integrity and/or viability of the cells to be radiolabelled should be specific points of attention for the risk assessment for cell radiolabelling. This type of radiolabelling is considered more extensively in section 3-14 of this text.

3-4. *AUTOMATED SYSTEMS*

Some of the steps described above can be subject to automation. An automated synthesis/dispense module is defined as an electromechanical device controlled by software to automatically perform a sequence of operations needed to synthesise and/or formulate and/or dispense a radiopharmaceutical. It 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 HPLC systems. The automated synthesis/dispense 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 synthesis/dispense module.

Within the synthesis process, the automated synthesis/dispense module controls the mixing of starting materials and reaction parameters in such a way that a bulk solution of a radiopharmaceutical is produced. The containers and purification system used with the automated synthesis/dispense module can be single-use ('radiopharmaceutical cassette') or used in multiple production runs. It must be shown by appropriate cleaning protocols that the quality of the produced radiopharmaceutical is not negatively affected when used in multiple production runs. Cross contamination must be prevented.

The containers and purification systems (i.e. the column of a preparative HPLC system) are considered part of the synthesiser.

The electronic components of the synthesiser should be resistant to high radiation.

Components that come into contact with the starting materials, solvents and/or the radiopharmaceutical should be chemically inert. Special care should be taken with components that may degrade under the influence of radiation and come into contact with the starting materials, solvents and/or the radiopharmaceutical, as they may release impurities upon aging.

Automated dispensing modules control formulation and dispensing of the radiopharmaceutical. This is usually done 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 should be used unless a validated cleaning protocol is performed. The measuring systems should be calibrated.

For an automated synthesis/dispense module, 2 levels of qualification/validation are required. The automated synthesis/dispense module itself should be qualified by the supplier and/or the user. After the qualification of the automated synthesis/dispense module, validation of the compounding process should take place following accepted rules (such as Rules governing medicinal products in the European Union, Volume 4, Good Manufacturing Practice, Part I, Chapter 5).

The synthesis process on the synthesiser is usually controlled by software containing specific time lists for each process. A description and the history of the software should be part of the validation documentation. Changes to the software should be controlled and documented. The software should be under access control.

The version of the time list used for a production should be recorded as a batch parameter. When changes are made to the time list, the old version of the software should be archived for the same period as the documentation of the batches made with this time list.

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

The materials used for the cassette should comply with general chapter *3.2.2. Plastic containers and closures for pharmaceutical use* in case of plastic materials and must be suitable for the intended purpose. The compatibility of the plastic and the chemical process must be proven. Glass components should be minimum Glass Type I (see general chapter *3.2.1. Glass containers for pharmaceutical use*).

Before human use of the preparation prepared with the aid of cassettes, it should be 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 in the cassette should comply with the requirements mentioned above in 3-2.

The cassette should be 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 level and achieve a high sterility assurance level for the radiopharmaceutical prepared with the use of a cassette, the cassette should have a low bioburden. Solutions of starting materials should be sterile or prepared aseptically.

The user should be assured of the suitability of the manufacturing process and the employed cassette system and has to ensure the final product quality by appropriate analytical testing.

The user of the cassette should have the necessary information about chemicals and reaction processes applied within the system (combination of cassette and automated synthesis equipment) to evaluate the 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 additional impurities might occur. The information gathered during the development of a cassette system on potential impurities and potential malfunctions of the system should be made available to the user as well as information towards analytical testing supporting the user of the cassette system to establish appropriate release specifications.

3-5. *PURIFICATION*

Purification of the product out of the reaction mixture is often required, particularly when organic chemical reactions are applied. Solid state extraction by use of cartridges is a method of choice and is often combined with semi-preparative radio-liquid chromatography. Since the purification step ensures the final quality of the radiopharmaceutical preparation, separation efficiency has to be carefully evaluated in terms of final radiochemical, radionuclidic and chemical purity. A microbiological risk exists when using chromatographic media, especially in the case of multiple-use liquid chromatography columns. Risk assessment should focus on cleaning/conditioning procedures and conditions of storage of chromatographic media. Microbiological burden and endotoxin content should be maintained within suitable limits, in correlation with the method used to obtain sterility in the case of parenteral form. In case of single-use cartridges, pre-sterilisation should be considered.

In working-up procedures of biological materials such as blood cells, centrifugation remains to be an important purification step. In any case, the extent of the purification procedure directly depends on the type of chemical reaction applied in the radiopharmaceutical preparation. A highly efficient procedure with a good reproducibility assures a permanent good quality of the radiopharmaceutical. If that is not the case, it may be advisable to decide on the development of a different labelling procedure.

3-6. *FORMULATION*

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

Special attention should be paid to residual solvents (see general chapter *5.4. Residual solvents*) and bioburden of the material used. Source and quality of excipients and additives should be documented.

Before the use of such substances it should be established that they comply with their quality requirements. See also section 3-9. Analytical control.

Quality requirements for ingredients (active substances, excipients and additives including antimicrobial preservatives or other substances used for the formulation of radiopharmaceuticals) are stated in the respective monographs. In case no monograph is available, the general monograph *Substances for pharmaceutical use (2034)* applies and a programme to test the quality should be implemented. When an in-house ingredient/excipient starting material set is used, the use of components with no microbiological contamination (or an acceptably low level) is recommended, irrespective of whether the final product is terminally sterilised or sterile-filtered. Bioburden of ingredients/excipients is an important factor to maintain a low bacterial endotoxin level and to achieve a high sterility assurance level in successive operations. Opened or partially used packages of ingredients for subsequent use should be properly indicated (labelled) and stored, under restricted access conditions. Shelf-life periods should be defined for non-opened, opened and dissolved starting materials, as well as excipients, especially in view of the microbiological background in the specific working conditions. The use of single-use packages is recommended.

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

3-7. *DISPENSING*

Dispensing is the fractionation of the bulk solution into final product forms, subject to release before use for medical applications (see section 3-12). It includes preparation of a batch consisting of 1 final product vial from the bulk solution. Drawing syringes for individual patients for injection has to be seen as a separate process not defined as dispensing but as administration following clinical practice.

In order to keep the bioburden as low as possible, components used in the dispensing process should be sterile. If these are not available, components should be sterilised by means of a validated process. If components are reused, it must be ensured that no cross contamination from one product to another product can take place.

3-8. *STERILISATION*

Radiopharmaceutical preparations must be sterile when used parenterally. 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) is 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*.

The complexity of operation determines the measures that need to be taken to ensure a sterile product:

- simple operations (for example preparing radiopharmaceuticals from licensed kits and generators) are undertaken in a class A air supply area located in a class D area with respect to air cleanliness;
- more complex operations (for example open-vial filling after sterile filtration, aseptic preparation, labelling of autologous cells) should be done in a class A air supply area located in a class C area with respect to air cleanliness.

Closed procedures for dispensing should be used whenever possible as an alternative to open-vial filling, especially for very small batches or individual patient preparations. The assembly (sterilising filter and vials) used with closed aseptic dispensing should be sterile. This can be achieved by sterilisation of the assembly or by aseptic preparation of the set in a class A air supply area located in a class C area with respect to air cleanliness. The process of closed aseptic dispensing can be performed in a class C area with respect to air cleanliness.

Monitoring of the critical class A zone and background environment for particulates and microbial contamination should be carried out on a regular basis. The frequency of monitoring is determined by the level of cleanliness of the environment.

When sterile filtration is used to sterilise the preparation, the filter should be tested for integrity before administration of the preparation to the patient, as the preparation will be administered to a patient before the result of the final sterility test is known. In order to perform a correct filter-integrity test, for each type of preparation the bubble point at a filter rating of 0.22 µm should determined as part of process verification.

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

3-9. *ANALYTICAL CONTROL*

The identity and purity is assessed to verify the suitability of the preparation for the intended application.

The quality specifications for the radiopharmaceutical preparations, excipients and other materials used in the compounding process and the methods used to determine these must be documented.

It is accepted that not all specifications of excipients and other materials that are being used in the compounding of radiopharmaceutical preparations are tested directly. Compliance with the requirements may be demonstrated by verification of the Certificate of Analysis (CoA) provided by the manufacturer. The identity of each lot of components and starting materials should be verified by defined methods or documented CoAs, as appropriate. At least 1 identity test for precursors should be performed.

When a pharmacopoeial monograph on the preparation exists the preparation should be analysed by the methods described and should comply with the requirements mentioned in the monograph. Any deviations from the described method should be validated/verified.

In case no monograph on the preparation is available, the methods and procedures used to assess the quality of the preparation need to be validated/verified.

Radiopharmaceutical preparations made by compounding comply with the general monograph *Radiopharmaceutical preparations (0125)*.

3-10. *PACKAGING*

The primary packaging material should be compatible with the preparation to be dispensed.

3-11. *LABELLING OF THE PRIMARY PACKAGING/CONTAINER*

When a radiopharmaceutical preparation is prepared and used within the same site, the labelling of the primary packaging should as a minimum contain the following information:

- the name of the preparation and/or its reference;
- an unequivocal reference to the preparation (batch number or date of compounding) and, when applicable, a serial number for the dispensed form (when several vials are dispensed);
- when applicable, 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, if necessary, calibration time, and the volume of liquid in the container (for more complex compounding reactions, it can be difficult to predict the exact yield of the process. In these cases it can be justified to not have the total radioactivity in the container, or the radioactive concentration per millilitre on the label. The vials should be traceable to a log in which the total radioactivity in the container, or the radioactive concentration per millilitre is noted);
- for solid preparations (such as capsules): the total radioactivity at a stated date and, if necessary, the calibration time.

The labelling can be adapted in certain cases when, 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:

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

3-12. *RELEASE*

The decision to release a pharmaceutical preparation as suitable for administration is dependent on the analytical results and other data characteristically related to the processes involved in its preparation. However, due to the nature of radiopharmaceutical preparations not all quality parameters of the preparation can be known at the time of release. A written procedure detailing all preparation and quality control data should be available and should be consulted before the preparation is released. A written procedure should also describe the measures to be taken by the responsible person, should unsatisfactory test results be obtained after the preparation has been released.

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

3-13. *RETENTION SAMPLES*

In case of preparations without marketing authorisation retention samples should be kept for a period of 3 months or 10 times the half-life, whichever is longer. 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's exposure to biological and radiation hazard should be 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, preventing excessive centrifugation) and 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 monographs. In case no monograph is available the general monograph *Substances for pharmaceutical use (2034)* applies. Further precautions may be necessary where the use of heterologous cells is required, as given in respective regulations.

A centrifuge, constructed to ensure containment in case of spills and/or breakage (with closed buckets) is required for blood-cell components separations. The equipment used in the labeling of cells should only be used for one procedure at a time. Separation in time and a cleaning process for utensils and equipment that ensures the destruction of blood-borne pathogens and viruses should be used.

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

Cross contamination, cross infection or mix-up of blood should be prevented at all times and the necessary precautions should be taken. Reaction/synthesis conditions should not impair the integrity and/or viability of the cells to be labelled.

When autologous or donor cells are radiolabelled, no final sterilisation sterilisation step is possible, thus radiolabelling of cells is considered as an aseptic preparation (see also section 3-8).

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

The identity, 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 should be performed.

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

ADDRESSES OF THE NATIONAL PHARMACOPOEIA AUTHORITIES

parties to the European Pharmacopoeia Convention

Correspondence relating to the draft monographs submitted for comment in the present issue are to be sent to the relevant authority.

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