

Annex 3

Guidelines on Good Manufacturing Practices for radiopharmaceutical products

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1. **Scope of these guidelines**

These guidelines are intended to complement those already available for pharmaceutical products (1,2) as well as those for sterile pharmaceutical products (3).

The regulatory procedures necessary to control radiopharmaceutical products are in large part determined by the sources of these products and the methods of manufacture. Manufacturing procedures within the scope of these guidelines include:

- The preparation of radiopharmaceuticals in hospital radiopharmacies.
- The preparation of radiopharmaceuticals in centralized radiopharmacies.
- The production of radiopharmaceuticals in nuclear centres and institutes or by industrial manufacturers.
- The preparation and production of radiopharmaceuticals in positron emission tomography (PET) centres.

Radiopharmaceuticals can be classified into four categories:

1. Ready-for-use radioactive products.
2. Radionuclide generators.

3. Non-radioactive components (“kits”) for the preparation of labelled compounds with a radioactive component (usually the eluate from a radionuclide generator).
4. Precursors used for radiolabelling other substances before administration (e.g. samples from patients).

Radiopharmaceutical products include inorganic compounds, organic compounds, peptides, proteins, monoclonal antibodies and fragments, and oligonucleotides labelled with radionuclides with half-lives from a few seconds to several days.

2. Principles

Radiopharmaceuticals must be manufactured in accordance with the basic principles of good manufacturing practices (GMP). The matters covered by these guidelines should therefore be considered as supplementary to the general requirements for GMP previously published (1,2) and relate specifically to the production and control of radiopharmaceuticals. In the preparation of these guidelines, due consideration was given to national or international radiation safety guidelines (4).

Because of their short half-lives, many radiopharmaceuticals are released and administered to patients shortly after their production, so that quality control may sometimes be retrospective. Strict adherence to GMP is therefore mandatory.

3. Personnel

3.1 The manufacturing establishment, whether a hospital radiopharmacy, centralized radiopharmacy, nuclear centre or institution, industrial manufacturer or PET centre, and its personnel should be under the control of a person who has a proven record of academic achievement together with a demonstrated level of practical expertise and experience in radiopharmacy and radiation hygiene. Supporting academic and technical personnel should have the necessary post-graduate or technical training and experience appropriate to their function.

3.2 Personnel required to work in radioactive, clean and aseptic areas should be selected with care, to ensure that they can be relied on to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product. Health checks on personnel should be requested before employment and periodically thereafter. Any changes in personal health status (e.g. in haematology) may require the temporary exclusion of the person from further radiation exposure.

3.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Access to these areas should be restricted during the preparation of radiopharmaceuticals, kits or sterile set-ups. Inspection and control procedures should be conducted from outside these areas as far as possible.

3.4 During the working day, personnel may pass between radioactive and non-radioactive areas only if the safety rules of radiation control (health physics control) are respected.

3.5 The release of a batch may be approved only by a pharmacist or a person with academic qualifications officially registered as a suitably qualified person, and with appropriate experience in the manufacture of radiopharmaceuticals.

3.6 To ensure the safe manufacture of radiopharmaceuticals, personnel should be trained in GMP, the safe handling of radioactive materials and radiation safety procedures. They should also be required to take periodic courses and receive training to keep abreast of the latest developments in their fields.

3.7 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

3.8 All personnel engaged in production, maintenance and testing should follow the relevant guidelines for handling radioactive products and be monitored for possible contamination and/or irradiation exposure.

4. Premises and equipment

4.1 As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials must be specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility. Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks; they should not shed matter and should permit easy cleaning and decontamination. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas.

4.2 Specific disposal systems should be mandatory for radioactive effluents. These systems should be effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility.

4.3 Sinks should be excluded from aseptic areas. Any sink installed in other clean areas should be of suitable material and be regularly

sanitized. Adequate precautions should be taken to avoid contamination of the drainage system with radioactive effluents.

4.4 Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity to ensure the comfort of personnel working in protective clothing. Buildings should be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space for the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms should be clean, sanitary and free from radioactive contamination.

4.5 Ventilation of radiopharmaceutical production facilities should meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Suitable pressure and airflow patterns should be maintained by appropriate isolation/enveloping methods. Air handling systems for both radioactive and non-radioactive areas should be fitted with alarms so that the working personnel in the laboratory are warned of any failure of these systems.

4.6 Dedicated facilities and equipment should be used for the manufacture of any radiopharmaceutical product derived from human blood or plasma. Autoclaves used in production areas for radiopharmaceuticals may be placed behind a lead shield to minimize the radiation exposure of the operators. Such autoclaves should be checked for contamination immediately after use to minimize the possibility of cross-contamination by radioactivity of the products in the next autoclave cycles.

4.7 All containers of radiopharmaceutical substances, regardless of the stage of manufacture, should be identified by securely attached labels. Cross-contamination should be prevented by the adoption of some or all of the following measures:

- processing and filling in segregated areas;
- avoiding the manufacture of different products at the same time, unless they are effectively segregated;
- containing material transfer by means of airlocks, air extraction, changing clothes and careful washing and decontamination of equipment;
- protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;
- using “closed systems” of manufacture;

- taking care to prevent aerosol formation;
- using sterilized containers.

4.8 Positive pressure areas should be used to process sterile products. In general, any radioactivity should be handled within specifically designed areas maintained under negative pressures. The production of sterile radioactive products should therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met.

4.9 Separate air-handling units should be used for radioactive and non-radioactive areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance.

4.10 Pipework, valves and vent filters should be properly designed to facilitate validated cleaning and decontamination.

5. **Production**

5.1 Standard operating procedures (SOPs) must be available for all operating procedures and should be regularly reviewed and kept up to date for all manufacturing operations. All entries on batch records should be initiated by the operator and independently checked by another operator or supervisor.

5.2 Specifications for starting materials should include details of their source, origin and (where applicable) method of manufacture and of the controls used to ensure their suitability for use. Release of a finished product should be conditional on satisfactory results being obtained in the tests on starting materials.

5.3 Careful consideration should be given to the validation of sterilization methods.

5.4 A wide variety of equipment is used in the preparation of radiopharmaceuticals. Equipment for chromatography should, in general, be dedicated to the preparation and purification of one or several products labelled with the same radionuclide to avoid radioactive cross-contamination. The life span of columns should be defined. Great care should be taken in cleaning, sterilizing and operating freeze-drying equipment used for the preparation of kits.

5.5 A list of critical equipment should be drawn up, including any equipment such as a balance, pyrogen oven, dose calibrator, sterilizing filter, etc., where an error in the reading or function could potentially cause harm to the patient being given the final product. These devices should be calibrated or tested at regular intervals and should

be checked daily or before production is started. The results of these tests should be included in the daily production records.

5.6 Specific equipment for radioactive measurements may be required as well as radioactive reference standards. For the measurement of very short half-lives, national central laboratories should be contacted to calibrate the apparatus. Where this is not possible, alternative approaches, such as documented procedures, may be used.

5.7 In the case of labelling kits, freeze drying should be carried out as an aseptic procedure. If an inert gas such as nitrogen is used to fill vials, it must be filtered to remove possible microbial contamination.

5.8 The dispensing, packaging and transportation of radiopharmaceuticals should comply with the relevant national regulations and international guidelines (5).

6. Labelling

6.1 All products should be clearly identified by labels, which must remain permanently attached to the containers under all storage conditions. An area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling, the label should appear on its package. Information on batch coding must be provided to the national and/or regional authorities.

6.2 The labels of radiopharmaceuticals must comply with the relevant national regulations and international agreements. For registered radiopharmaceuticals, the national control authority should approve the labels.

6.3 The label on the container should show:

- (a) the name of the drug product and/or the product identification code;
- (b) the name of the radionuclide;
- (c) the name of the manufacturer or the company and/or the person responsible for placing the drug on the market;
- (d) the radioactivity per unit dose:
 - for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in the container;
 - for solid preparations, such as freeze-dried preparations, the total radioactivity at a stated date and, if necessary, hour;

- for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour, and the number of capsules in the container;
- where relevant, the international symbol for radioactivity.

6.4 The label on the package should state:

- (a) the qualitative and quantitative composition;
- (b) the radioactive isotopes and the amount of radioactivity at the time of dispatch;
- (c) the route of administration;
- (d) the expiry date;
- (e) any special storage conditions;
- (f) mandatory information related to transport regulations for radioactive materials.

6.5 The leaflet in the package should contain the specific product information and indications for use. This information is especially important for preparation kits (cold kits), and should include:

- (a) the name of the product and a description of its use;
- (b) the contents of the kit;
- (c) the identification and quality requirements concerning the radio-labelling materials that can be used to prepare the radiopharmaceutical, namely:
 - the directions for preparing the radiopharmaceutical, including the range of activity and the volume, together with a statement of the storage requirements for the prepared radiopharmaceutical;
 - a statement of the shelf-life of the prepared radiopharmaceutical;
 - the indications and contraindications (pregnancy, children, drug reactions, etc.) in respect of the prepared radiopharmaceutical;
 - warnings and precautions in respect of the components and the prepared radiopharmaceutical, including radiation safety aspects;
 - where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical, including the route of elimination and the effective half-life;
 - the radiation dose that a patient will receive from the prepared radiopharmaceutical;
 - the precautions to be taken by users and patients during the preparation and administration of the product and the special precautions for the disposal of the container and any unconsumed portions;

- a statement of the recommended use of the prepared radiopharmaceutical and the recommended dosage;
- a statement of the route of administration of the prepared radiopharmaceutical;
- if appropriate for particular kits (i.e. those subject to variability beyond the recommended limits), the methods and specifications needed to check radiochemical purity.

7. **Production and distribution records**

7.1 The processing records of regular production batches must provide a complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the written procedures.

7.2 Separate records for the receipt, storage, use and disposal of radioactive materials should be maintained in accordance with radiation protection regulations.

7.3 Distribution records should be kept. Since the return of radioactive products is not practical, the purpose of recall procedures for such products is to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with international and national transport regulations.

8. **Quality assurance and quality control**

8.1 Radiopharmaceuticals are nearly always used before all quality control testing (e.g. tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential.

8.2 Quality assurance and/or quality control should have the following principal responsibilities:

- (a) the preparation of detailed instructions for each test and analysis;
- (b) ensuring the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination;
- (c) ensuring that environmental monitoring and equipment and process validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
- (d) the release or rejection of starting materials and intermediate products;
- (e) the release or rejection of packaging and labelling materials;
- (f) the release or rejection of each batch of finished preparation;

- (g) the evaluation of the adequacy of the conditions under which the starting materials, intermediate products and finished radiopharmaceutical preparations are stored;
- (h) the evaluation of the quality and stability of the finished products and, when necessary, of the starting materials and intermediate products;
- (i) the establishment of expiry dates on the basis of the validity period related to specified storage conditions;
- (j) the establishment and revision of the control procedures and specifications;
- (k) assuming the responsibility for retaining samples of radiopharmaceutical products;
- (l) assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceutical products.

8.3 Whenever the size of the establishment permits, quality assurance and quality control duties should be organized in separate groups. Quality assurance should also include the monitoring and validation of the production process.

8.4 A manufacturer's quality control laboratory should be separated from the production area. The control laboratory should be designed, equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, the preparation of records and the performance of the necessary tests.

8.5 The performance of all qualitative and quantitative tests mentioned in the specifications for the starting materials may be replaced by a system of certificates issued by the supplier of these materials, provided that:

- (a) there is a history of reliable production;
- (b) the producer or supplier is regularly audited;
- (c) at least one specific identity test is conducted by the manufacturer of the finished radiopharmaceutical.

8.6 Samples of the intermediate and final products should be retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control. These samples should be kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g. for radiopharmaceuticals with a short half-life.

8.7 Sampling procedures may be adapted to the purpose of the sampling, the type of controls being applied, and the nature of the mate-

rial being sampled (e.g. a small batch size and/or its radioactive content). The procedure should be described in a written protocol.

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