SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

SAHPRA
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RADIOPHARMACEUTICAL MANUFACTURING

This document has been prepared to serve as a recommendation for manufacture of radiopharmaceuticals. It represents the South African Health Products Regulatory Authority's current thinking on the subject.

This guideline should be read in conjunction with the SA Guidelines for Good Manufacturing Practices.

CHIEF EXECUTIVE OFFICER
(CEO)

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1. INTRODUCTION

Radio pharmaceutical products should be manufactured in accordance with the Good Manufacturing Practices, described in the current South African Guide to Good Manufacturing Practices, this guidance document and the supplementary guidelines such as those for sterile preparations where appropriate. Some points are nevertheless specific to the handling of radioactive products and are modified by or detailed in these supplementary guidelines.

2. GENERAL

2.1 Radio pharmaceutical preparations are preparations containing one or more radionuclides. They may be formulated in any of the pharmaceutical formulations covered in this guide and the general and specific guidance should be followed at all times, but considerations must be given to the special requirements of radiation work.

2.2 The manufacturing and handling of RADIO PHARMACEUTICALS is potentially hazardous. The level of risk depends in particular on the types of radiation emitted and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants and to waste disposal. Special consideration may be necessary with reference to small batch sizes made frequently for many RADIO PHARMACEUTICALS. Due to their short half-life, some RADIO PHARMACEUTICALS are released before completion of certain Quality Control tests. In this case, the continuous assessment of the effectiveness of the Quality Assurance system becomes very important.

3. REGISTRATION REQUIREMENTS

3.1 Care should be taken to comply with national and local regulations concerning production, supply, storage, use and disposal of radioactive products.

3.2 Premises in which radioactive work is conducted must be licensed by the Department of Health.

3.3 RADIO PHARMACEUTICALS, produced by a nuclear reactor or cyclotron, may only be used by physicians who are qualified by specific training in the safe use and handling of radioisotopes, and whose experience and training have been approved by an appropriate governmental agency authorised to licence the use of radionuclides.

3.4 All people engaged in radioactive work are required by law to be registered as radiation workers. Maximum permitted radiation doses for radiation workers are prescribed by the International Atomic Energy Agency and are monitored by film badges and pocket dosimeters or TLD. At all times the ALARA principle (i.e. as low as reasonably attainable dose) applies to any person working with radioactivity.

4. PERSONNEL

4.1 All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive additional training specific to this class of products. In particular, they should be given detailed information and appropriate training on radiation protection.

5. PREMISES AND EQUIPMENT

5.1 Radioactive products should be stored, processed, packaged and controlled in dedicated and self-contained facilities. The equipment used for manufacturing operations should be reserved exclusively for RADIO PHARMACEUTICALS**.**

5.2 In order to contain the radioactive particles, it may be necessary for the air pressure to be lower where products are exposed than in the surrounding areas. However, it is still necessary to protect the product from environmental contamination.

5.3 For sterile products, the working zone where products or containers may be exposed should comply with the environmental requirements described for Sterile Products. This may be achieved by the provision within the work station of a laminar flow of HEPA-filtered air and by fitting air-locks to entry ports. Total containment work stations may provide these requirements. They should be in an environment conforming to at least a grade D.

5.4 Air extracted from areas where radioactive products are handled should not be recirculated; air outlets should be designed to avoid possible environmental contamination by radioactive particles and gases.

5.5 There should be a system to prevent air entering the clean area through extraction ducts e.g. when the extraction fan is operating.

6. PRODUCTION AND HANDLING OF RADIOACTIVE PREPARATIONS

6.1 Each isotope should be worked in a separate specially shielded, contained work station to prevent cross-contamination of the radionuclide. Production of different radioactive producers in the same workstations and at the same should be avoided in order to minimize the risk of cross-contamination or mix-up. The operator must be shielded from the radiation which must be contained in the work station.

6.2 Radioactive materials should be handled in a contained work station operated at an air-pressure below that of the room in which it is sited. Air admitted to the work station should still have passed through terminal filters of appropriate porosity so that the required class conditions are maintained at the point of greatest risk, where products are exposed.

6.3 All operations should be carried out in such a manner as to minimize the risk of microbial or particulate contamination.

6.4 All sterile products are terminally sterilised before despatch either by autoclave or filtration.

NOTE: The radiation in the Radio pharmaceutical is not sufficient to effect sterilisation.

6.5 Process validation, in-process controls and monitoring or process parameters and environment assume particular importance in cases where it is necessary to take the decision to release or reject a batch or a product before all the tests are completed.

7. QUALITY CONTROL

7.1 When products have to be dispatched before all the tests are completed, this does not obviate the need for a formal recorded decision to be taken by the Qualified Person on the conformity of the batch. In this case there should be a written procedure detailing all production and Quality Control data which would be considered before the batch is dispatched. A procedure should also describe the measures to be taken by the Qualified Person if unsatisfactory test results are obtained after dispatch.

7.2 Unless otherwise specified in the marketing authorization, reference samples of each batch should be retained.

8. PACKAGING OF RADIOPHARMACEUTICALS

8.1 Due to the short half-life of certain RADIO PHARMACEUTICALS it may be necessary to despatch the products before all the tests are completed. This does not reduce the need for a formal recorded decision to be taken by an authorized person as to whether or not the product should be released based on the production and quality control data available at the time. Specifications should define at which stage of testing a decision on release may be taken.

8.2 All containers must be checked by a Health Physicist for radioactive contamination before packaging and the radiation levels emanating from the package monitored by a Health Physicist.

8.3 IAEA transport regulations prescribe the maximum acceptable levels of radiation measured at the surface of the package and one metre from the package permitted on road and air transport. The conditions under which the packages may be transported are also prescribed.

9. NON-RADIOACTIVE KITS

9.1 Non-radioactive chemicals are supplied as kits to be reconstituted with the radioactive eluate from a radionuclide generator such as a Molybdenum-99 / Technetium-99m generator at the hospital. These kits must conform to the requirements of pharmaceuticals as listed in the chapter on guidelines for small volume parenterals.

9.2 The preparation of these RADIO PHARMACEUTICALS at the hospital must be carried out using aseptic technique. It may be acceptable to carry out this work under environmental conditions of a lower grade than those prescribed for aseptic work when the following situation pertains:

- the preparation is done entirely by transference of materials between closed containers, for example by use of syringe and hypodermic needle penetrating a rubber closure (so-called 'closed procedures')
- manipulations are performed within a contained work station which, whilst giving the required degree of operator protection, also maintains the critical working zone at the standard of Class 1
- the product is administered within a few hours of preparation.

10. DISTRIBUTION AND RECALLS

10.1 Detailed distribution records should be maintained and there should be procedures which describe the measures to be taken for stopping the use of defective RADIO PHARMACEUTICALS. Recall procedures should be shown to be operable within a very short time.

11. CONTACT DETAILS

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12. UPDATE HISTORY

Date	Reason for update	Version & publication
Oct 2019	Authority: “MCC” to “SAHPRA” Authority Logo: “MCC Logo” to “SAHPRA Logo” Registrar of Medicines to Chief Executive Officer (CEO) Medicines Control Council to South African Health Products Regulatory Authority	v1.1 Oct 2019