International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2019): 7.583

A Review on Good Manufacturing Practices for Radiopharmaceuticals

Jadhav Pradnya Santosh

Abstract: ***According to WHO, they are classified as Ready-for-use radioactive products, Radionuclide generators, Non-radioactive components ("kits") for the preparation of labeled compounds with a radioactive component and Precursors used for radio labeling other substances before administration they are classified into three groups: Preparations which are supplied as a radioactively-labelled product in a ready-to- inject form, Inactive products which are made radioactive immediately prior to patient injection and Radionuclide preparations that are combined with an inactive preparation to produce the final product for injection. They are characterized by their chemical and physicochemical properties and by the radiation properties of the radionuclide which they contain. Radiopharmaceuticals consist of pharmaceutical component as well as radioactive component Radiopharmaceuticals are considered a safe class of agents, in part due to the small chemical quantities administered in most cases. However, if a study had to be repeated because of a poor quality radiopharmaceutical, the patient would receive an unnecessary radiation dose with useless consequences. The preparation of radiopharmaceuticals is generally reliable. The reliability of radiopharmaceuticals depends on both, the design of preparation procedures. Objectives: a) To explain the importance of radiopharmaceuticals b) To explain the basic requirement necessary for radiopharmaceutical's like personnel's, premises, equipment, qualification and validation. c) To explain the material which are required for packaging of radiopharmaceuticals products. d) To understand the key parameters which are necessary on labels on primary packaging and secondary packaging and packaging material. e) To explain quality assurance and quality control for radiopharmaceuticals***

1. Introduction

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 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 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. These guidelines are intended to provide a general overview of the minimum Good Manufacturing Practices (GMP) requirements for radiopharmaceuticals. The main principles of GMP are described in detail in the chapters for pharmaceutical products as well as those for sterile pharmaceutical Unless otherwise specified, the GMP requirements for radiopharmaceuticals described in this guidance should take precedence over the GMP requirements for pharmaceutical procedures necessary to manufacture and control radiopharmaceutical products are in large part 8 determined by the nature of these products, the methods of manufacture and their intended use. The recommendations in these guidelines are applicable to the followingscenarios:

- The production or compounding of radiopharmaceuticals in hospital radio pharmacies, including diagnostic and therapeuticproducts.
- The production or compounding of radiopharmaceuticals in centralized radio pharmacies.
- The production or compounding of radiopharmaceuticals in nuclear centres and institutes.
- The production of radiopharmaceuticals by industrialmanufacturers.
- The production of cyclotron-based positron emission tomography (PET) radiopharmaceuticals.

2. Content

2.1 Personnel

1) The manufacturing establishment, whether a hospital radiopharmacy, centralized radio pharmacy, 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 postgraduate or technical training and experience appropriate to theirfunction.
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 radiationexposure.
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 aspossible.
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) arerespected.
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.

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.
7) Training records should be maintained and periodic assessment of the effectiveness of training programmes should be made.
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

2.2 Premises and equipment

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 asepticareas.
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 thefacility.
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 radioactiveeffluents.
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 radioactivecontamination.
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 thesesystems.
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 autoclavecycles.
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 followingmeasures:
   - Processing and filling in segregatedareas;
   - Avoiding the manufacture of different products at the same time, Unless they are effectivelysegregated;
   - Containing material transfer by means of airlocks, air extraction, Changing clothes and careful washing and decontamination ofEquipment;
   - Protecting against the risks of contamination caused by recirculation Of untreated air, or by accidental re-entry of extractedair;
   - Using “closed systems” of manufacture;
   - Taking care to prevent aerosolformation;
   - Using sterilized containers
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.
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 forperformance.
10) Pipe work, valves and vent filters should be properly designed to Facilitate validated cleaning and decontamination.

2.3 Qualification and Validation

1) Qualification of instruments/equipment and validation of methods/procedures are essential to prove that the critical aspects of their operation are controlled.
2) Validation and qualification activities should be planned in an orderly manner and documented.
3) Qualification of premises, supporting utilities, production and QC equipment should demonstrate that they have been designed (if applicable), installed, operated and perform in accordance with the requirements of GMP and arefit-for-purpose.
4) The planning of qualification and validation activities should consider the complexity and critical aspects of the intended radiopharmaceutical production. A schedule of planned preventive maintenance should be established for instruments/equipment as well as regular verifications and/or calibrations as appropriate. These commitments must be documented in a written and approved standard operating procedure (SOP).
5) Process validation should be carried out after all other qualification and validation have been successfully completed.
6) Process validation should include an adequate number

of productions of the intended radiopharmaceutical(s), prepared following the same procedures, covering the intended batch size range and with the same production, quality specifications and acceptance criteria as of typical intended routine batches. The number of batches and the batch size range should be pre-determined as part of a risk assessment performed prior to processvalidation

7) Cleaning validation should be especially focused on critical production areas, such as working surfaces, and in general surfaces which come into direct contact with the operators or with starting materials, intermediates and finishedproducts.
8) Analytical methods should be validated in case they are not described in any recognized source (e.g. apharmacopoeia). Compendial analytical methods, already described in a recognized source, are not required to be validated; however, method suitability under actual conditions of use should be performed and documented.
9) General principles on validation of analytical methods may be found following suitable guidelines; however, the unique nature of radioactivity should be considered, and specific adaptations should be made, ifjustified.
10) Re-validation of critical processes (e.g. media fill studies) should be performed on a periodic basis. These commitments must be documented in a written and approved SOP. Re-validation of any process or requalification of equipment may be warranted under certain circumstances (e.g. in case of significant changes and/or of deviations which may affect the quality of theproduct)

2.4 Equipment

1) Equipment used should be qualified for the intended purpose through appropriate design, specifications, installation, calibration, operation, and maintenance. Critical factors, including minimizing the risk of product contamination, minimizing the risk of staff radiation exposure and optimised ergonomics, should be considered during equipment
2) Equipment used for radiopharmaceutical manufacture and QC should be periodically calibrated andmaintained.
3) Equipment maintenance, qualification, and calibration operations should be recorded and archived in properlog-books.
4) Equipment controlling software may be considered as part of the equipment and, therefore, may be included in the process of equipmentqualification.
5) SOP's should be established for the operation, calibration, and planned preventative maintenance (PPM) of theequipment
6) The dose calibrator (also known as activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dialsetting.

3. Material

1) Written specification, testing procedure and suitable storage condition and expiry date should be established for all material and component used in manufacture of product.
2) All material should be purchase from qualified suppliers where all possible certificate of analysis ,performance testing should be obtained from suppliers if these not available complete test should be carriedout.
3) For raw material there is not standard available it is necessary to establish necessary standards. Their use has to be appropriately validated byexperiments.

Container and Closure

1) Flint neutral borosilicate glass should be used fordispensing
2) Sterile kit formulation, gelatine capsules, rubber stopper with split ends should be used for freeze dryingoperation

Packaging Material

1) Packaging material should include thermocol boxes, cardboard boxes, tin container, absorbent cotton, lead container, labels.
2) Printed material and cut labels and other loose printed material should be stored separately to avoided mixup
3) There should be procedure to test integrity of packaging material prior toshipment
4) These material should be issued by an authorized person following documented procedure

Packaging

1) When setting up a program for packaging operation attention should be given to avoid cross contamination mix up or substitution
2) Different packaging operation should not be packaging in close proximity to each others
3) Before packaging operation are begun steps should be taken to ensure that the working area and packaging lines printing machines and others equipment are clean and free from leftmaterial
4) Printed and embossed information on packaging should be resistance to fading or erasing

Labelling

1) 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.
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.
3) The label on the container shouldshow:

a) The name of the drug product and/or the product identificationcode;
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 themarket;

4) The label on the package shouldstate:
a) The qualitative and quantitative composition;
b) The radioactive isotopes and the amount of radioactivity at the time ofdispatch;
c) The route of administration;
d) The expiry date;
e) Any special storage conditions;
f) Mandatory information related to transport regulations forradioactivematerials.

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 shouldinclude:
a) The name of the product and a description of itsuse;
b) The contents of the kit;
c) The identification and quality requirements concerning the radiolabelling materials that can be used to prepare theradiopharmaceutical

Production

1) Standard operating procedures (SOPs) must be available for all operating procedures and should be regularly reviewed and kept upto date for all manufacturing operations. All entries on batch records should be initiated by the operator and independently checked by another operator orsupervisor.
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.
3) Careful consideration should be given to the validation of sterilization methods.
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 ofkits.
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.
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 beused.
7) In the case of labeling 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 microbialcontamination.
8) The dispensing, packaging and transportation of radiopharmaceuticals should comply with the relevant national regulations and internationalguidelines

Production and distribution records

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.
2) Separate records for the receipt, storage, use and disposal of radioactive materials should be maintained in accordance with radiation protectionregulations.
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. IfNecessary, the return of radioactive products should be carried out in accordance with international and national transportregulations.

Quality assurance and quality control

1) Radiopharmaceuticals are nearly always used before all quality control testing (e.g. tests for sterility, endotoxin, radionuclide's purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential.
2) Quality assurance and/or quality control should have the following principal responsibilities:
   a) The preparation of detailed instructions for each test andanalysis;
   b) Ensuring the adequate identification and segregation of test samples to avoid mix- ups andcross-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 intermediateproducts;
   e) The release or rejection ofpackaging and labelling materials;
   f) The release or rejection of each batch of finishedpreparation;
   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 intermediateproducts;
   i) The establishment of expiry dates on the basis of the validity period related to specified storageconditions;
   j) The establishment and revision of the control procedures andspecifications;
   k) Assuming the responsibility for retaining samplesof radiopharmaceutical products;
   l) Assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceuticalproducts.

4. Quality Controls of Starting Materials

Incoming Radioactive Starting Materials
Regarding radionuclides, the minimum quality controls should be performed for incoming Material acceptance: radionuclide identity confirmation and activity confirmation via inspection Of CoA, and verified by activity measurement if possible. Additional acceptance criteria may need to be established if required. In addition to these requirements, conformance to the parent Radionuclide breakthrough acceptance criteria should be established for the generator.

Radiochemical Purity

1) Chromatographic methods

A) Thin and instant layerchromatography
The aim is to determine the radiochemical purity of a radiopharmaceutical. The method is as follows:

Apply a sample of the radiopharmaceutical (5 µL or a suitable volume) on a TLC plate/ITalk paper and dry the spot in a stream of air; Insert the TLC/iTLC paper into a chamber containing a suitable solvent (mobile phase) which is added a few minutes before into the chamber for the saturation; Allow the mobile phase to migrate to the top of the TLC/iTLC paper. The mobile phase level must be below the test spot on the TLC/iTLC paper; RCP is established depending on the distribution of components between the stationary (TLC/iTLC paper) and the mobile phase; Therefore, the radioactivity distribution is determined by using a radioactivity scanner (plate Or paper strip) or by counting small pieces in the case of iTLC (paper). RCP is defined as the ratio of counts in the product peak (or product counts in the pieces) compared to total counts on the plate / paper. RCP (%) = 100x (counts in product/total counts on plate or paper). If the RCP is less than the specification (typically 95% or recommended value in related monograph), the batch is rejected.

B) Size Exclusion High Performance Liquid Chromatography
The aim is to provide information on radio labelled macromolecules protein integrity (i.e. the existence of high mass aggregates or low molecular weight species in protein solutions). The methods refer to the Radiochemical Identity by SEC-HPLC section above for details on how to Analyse samples. As the sample components interact with the SEC-HPLC column matrix, larger size molecules such as aggregated proteins (also known as high molecular weight species or HMWS) pass through the column quicker; these molecules are then detected by the detectors and produce peaks with relatively shorter retention times; Smaller molecules such as pieces of protein (also known as low molecular weight species or LMWS) interact with the column for longer periods of time and produce peaks with relatively longer retention times, once it is eluted from the column and detected by the detectors; Therefore, one can use the impurity peak retention times, relative to the known peak retention time, to determine whether the impurity has either higher molecular weight or smaller molecular weight than the molecule of interest. For example, if the radio labelled. Ig Ganti body produces a peak at 8.5 minutes, any peaks detected prior to 8.5 minutes indicate presence of high molecular weight species (aggregates in some cases) and any peaks present after 8.5 minutes indicate presence of low molecular weight species; Integrating the areas under the curve for every peak present on the radioactivity trace and then dividing the area under the curve for the peak of interest by the sum of all peak AUC's and multiplying the result by 100 provides the percent value for the radiochemical purity. It is product specific and it may vary. Values of ≥80% monomer, ≤10% of high molecular Weight species, and ≤10% of low molecular weight species have been used. The values are based on the radioactivity detector signal as formulation may affect the ability to interpret the UV signal if UV absorbing species are present in the final formulation.

Enantiomeric purity
The aim is to determine the enantiomeric purity of a radiopharmaceutical that exists in two Forms using chiral HPLC. The method is as follows: Inject a sample of the radiopharmaceutical into a validated HPLC system, for example a system equipped with a chiral column, Crown pack-CR, and radioactivity and UV detector; Record the chromatogram and determine the radiopharmaceutical peak area ratio versus Land -D isomers peaks areas detected by UV. The specification establishes that the radioactive area corresponding to the specified (usually) L-isomer of radiopharmaceutical should represent at least 90% of total radioactive peak areas belonged to bothenantiomers.

5. Conclusion

Radiopharmaceuticals are regulated differently indifferent countries and the time it takes for radiopharmaceutical to shiftfrom bench side to bedside of suffering humanity is lengthy and cumbersome. Lack of harmonized guideline is clearly evident for radiopharmaceuticals. Therefore it has become pertinent to address all the issues related to development, manufacturing, dispensing, ADR reporting, transport, disposal, and Labeling requirements concerning radiopharmaceuticals. The implementation of strict regulatory guidelines to assess quality, safety, and efficacy of radiopharmaceuticals is need of the hour. This will lead to public trust and insight into the safety of the radiopharmaceutical use. A comparative study of different regulatory bodies can help develop harmonized guidelines which could enable free exchange of radiopharmaceuticals across the globe in the most cost efficient manner agent. The recent trend in increase of cancer cases, their detection and treatment has been a major factor drawing the attention of researchers towards radiopharmaceuticals which can be suitably exploited for such purposes. Scientific fraternity worldwide is continuously working in search of newer radiopharmaceutical of increased efficacy and minimum hazard.

6. Outcomes

- Produce radiopharmaceutical products conforming to the predeterminedspecification
- Produce radiopharmaceutical products of consistentquality

- Minimize radiation contamination andexplosion
- Eliminate theerrors
- Ensure the consistency of products only by approved starting material and standardized allaction

References

[1] G.C.Harts and A.H.Smith, Eds Quality Standards For Radiopharmacutics institution of physical science in medicines, 1992,report no65
[2] Quality assurance in nuclear medicines, World health organization,1982
[3] Hyonsoo Han, Van soole, shaharuddinmohd for good manufacturing practices of radiopharmaceuticals, IAEA RTC, January2001,112
[4] Guidelines on good manufacturing practices for radiopharmaceuticals, WHO technical report series no 908,2008,annex3
[5] K Kristen, preparation and controls of radiopharmaceuticals, IAEA, 1979,194.
[6] GyPreparation of radiopharmaceuticals ,EANM radiopharmacycommittee,2007,19
[7] Radiopharmaceutical preparation, Indianpharmacopeia(2014)3383-3411
[8] Monographs for radiopharmaceutical preparation, Indian pharmacopeia,2014,3314- 343