Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Review Article

Received on: 25-03-2017
Accepted on: 09-04-2017
Published on: 15-04-2017

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An Insight on the Emerging Regulations for Radiopharmaceuticals by Europe and India

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ABSTRACT

Radiopharmaceuticals are the radioactive substances or radioactive drugs for diagnostic or therapeutic interventions. The formulation of radiopharmaceuticals is different from ordinary pharmaceuticals. Many radiopharmaceuticals are released and administered to patients shortly after their production because radiopharmaceuticals may decompose during process and labeling steps due to variation in environmental conditions, indicating serious stability concerns. So, administrative prerequisites must be taken for the formulation of the radiopharmaceuticals. Radiopharmaceuticals production, unlike conventional pharmaceuticals production, is still raw and processing at a full fledged speed. Hence, implementing the cGMP guidelines which are applicable for the drugs industry is both difficult and expensive. The present article introduces radiopharmaceuticals in an effective and useful way. Herein, the radiopharmaceuticals are described as a trustworthy aid for curing the life threatening diseases. It demonstrates a brief investigation of the guidelines constituted by the regulatory bodies for the radiopharmaceuticals. It emphasizes on understanding the mandatory regulations to be taken for the radiopharmaceuticals in various countries. It includes the regulations framed for radiopharmaceuticals by Europe and India. The present work provides information on the guidelines used by Europe and India for the regulation of radiopharmaceuticals by the special committees. The regulations in Europe are stringent whereas, in several countries, like India, the regulations are still to get illumination. It withholds the names of the guidelines in the world to be alluded for the radiopharmaceuticals and the regulatory bodies responsible for the regulation.

Key-words: Radiopharmaceuticals, regulations, Europe and India.

Cite this article as:
Shrutay Mehta, Dilip Maheshwari, An Insight on the Emerging Regulations for Radiopharmaceuticals by Europe and India, Asian Journal of Pharmaceutical Technology & Innovation, 05 (23); 86-96, 2017. www.asianpharmtech.com

Introduction

Radiopharmaceuticals:[1][2][3][4]

- A drug is generally chemical substance which provides biological effects on humans as well as on animals. In the broadcast of pharmacology term; drug is defined as a chemical substance used for diagnosis of disease or to enhance mental or physical well-being.
- Drugs are producing a physiological effect when ingested or otherwise introduced into the body.
- A radiopharmaceutical is a pharmaceutical formulation containing radioactive compound which is used for the diagnosis and therapeutic treatment of human diseases.
- In designing a radiopharmaceutical, a pharmaceutical is first chosen on the basis of its preferential localization in a given organ or its participation in the physiologic function of the organ. Then a suitable radionuclide is tagged onto the chosen pharmaceutical such that after administration of the radiopharmaceutical, radiations emitted from it are detected by a radiation detector.
- Once administered to the patient they can localize to specific organs or cellular receptors.

Classification of Radiopharmaceuticals:

Radiopharmaceuticals can be classified into four categories as follows:

1. Radiopharmaceutical preparation
2. Radionuclide generator
3. Radiopharmaceutical precursor
4. Kit for radiopharmaceutical preparation

Summary

1. Regulatory Requirements for Radiopharmaceuticals in Europe.

1.1 Definition of Radiopharmaceutical:[5]

Radiopharmaceutical means any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

Examples of Radiopharmaceuticals in Europe

Sr No.	Radiopharmaceuticals	Uses
1	Fluorine-18 fludeoxyglucose	Diagnosis in oncology, neurology, inflammatory diseases
2	Sodium Flouride	Diagnosis of bone metastase

Table 1: Examples of radiopharmaceuticals

1.2. Marketing Authorization:

1.2.1 Centralized Procedure:[6]

Procedure of auditing and evaluating the dossier to bolster a therapeutic product in view of its marketing, clearly concluded by granting of a document also called marketing authorization.This procedure is performed inside an authoritative structure which characterizes the prerequisites important for application to the concerned regulatory authority, details on the assessment procedure (based on quality, safety and efficacy criteria) and the grounds for approval or rejection of the application, and also the circumstances where a marketing authorization officially allowed may be withdrawn, suspended or renounced.

The application dossier for marketing authorization is called Marketing Authorization Application (MAA) in the European Union and other countries. Essentially, this comprises of a dossier with information demonstrating that the medication has quality, viability and security properties suitable for the proposed utilization, extra authoritative archives, tests of completed products or related substances and reagents important to perform

examinations of finished product as depicted in that dossier. The content and format of the dossier must follow ICH CTD guidelines and other changes given by regulatory authority.

Radiopharmaceuticals are regulated under centralized marketing Authorization procedure. In the Centralized Procedure, the applicant applies to the EMEA for marketing authorization and finally receives one European approval, which is valid in all 27 countries in the community, as well as Norway, Iceland and Liechtenstein. At least seven months before submission, the applicant should notify the EMEA of their intention to submit an application. Applicants have the opportunity to meet the EMEA in a pre-submission meeting, to discuss any procedural or regulatory issues. The applicant's request for eligibility for evaluation via the Centralized Procedure, together with a justification and other documents is presented to all CHMP members. Following discussion at CHMP, the EMEA informs the applicant of the CHMP position, whether the medicinal product is eligible for evaluation via the Centralized Procedure. Content is mainly reviewed by CHMP but here for radiopharmaceutical, Dossier is reviewed by CAT reporters and then they give scientific opinion to the CHMP. Whole process is as follows.

Table 2: Centralized Procedure

Review Timeline(Days)	Progresses	Regulatory Authority
1	Start of the procedure.	
80	Receipt of the Assessment Report from CAT Rapporteurs to CHMP Coordinators, CAT and CHMP members and EMEA.EMEA sends the Assessment Reports to the applicant making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CAT and CHMP.	CAT Co Rapporteurs
100	CAT Rapporteurs, other CAT and/or CHMP members and EMEA receive comments from CHMP Coordinators, Members of the CAT and the CHMP (incl. peer reviewers).	CHMP Coordinators, CHMP and CAT members
115	Receipt of draft list of questions (including the recommendation and scientific discussion) from CAT Rapporteur and CAT Co-Rapporteur, as discussed with the CHMP Coordinators, peer reviewers, by CAT and CHMP members and EMEA.	CAT Rapporteurs
120	CAT adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMEA. The CHMP Coordinators can attend the CAT meeting during the product discussion.	CAT adopts the list of questions CHMP Coordinators to present the major objections and points of interests to the CHMP
120	At the latest by Day 120, adoption by CAT of request for GMP/GLP/GCP inspection, if necessary (Inspection procedure starts).	CAT
Clock stop		
121	Submission of the responses, including revised summary of product characteristics labelling and package leaflet texts in English, and restart of the clock.	Applicant
150	Joint response Assessment Report from CAT Rapporteurs received by CHMP Coordinators, CAT and CHMP members and the EMEA.EMEA sends joint Assessment Report to the applicant making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CAT / CHMP. When applicable,	CAT (Co)-Rapporteurs

	Inspection to be carried out. EMEA sub-group meeting for the review of English product Information with participation of the applicant (when applicable).	
160	Deadline for comments from CAT and CHMP Members to be sent to CAT (Co)-Rapporteurs, CHMP Coordinators, EMEA and other CAT and CHMP Members.	CAT and CHMP members
170	CAT discussion and decision onthe need for adoption of a list of "outstanding issues" (LoOI) and/or an oral explanation by the applicant.The major objections and Point of interests from the LoOIare presented to the CHMP. In the event that the CHMP identifies supplementary issues (i.e. upgrade to major objection or identification of important scientific questions), such issues will be added to the LoOIs after consultation of the CAT Chair and sent to the applicant by EMEA secretariat for the applicant to address in the scheduled oral explanation, which will be held in front of the CAT. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation.Submission of final inspection report to EMEA, CAT (Co)-Rapporteurs, CHMP Coordinators by the inspections team (at the latest by day 170).	
171	CAT oral explanation	CAT
171	Discussion on the draft opinion and identification of the recommendations for Marketing Authorization/refusal which will be transmitted to CHMP.	CAT
171	The applicant provides the final draft of English summary of product characteristics, labeling and package leaflet, and where needed an updated Risk Management Plan and traceability system.	Applicant
180	The CHMP will discuss the Grounds for approval/refusal as adopted by CAT.The outcome of the discussions will be transmitted to the CAT via the CHMP Coordinator or the joint CAT and/or CHMP Members.	CHMP
200	CAT adopts the draft opinion and draft assessment report and transmits it to the CHMP.	CAT
By 210	Adoption of CHMP Opinion and CHMP Assessment Report (and timetable for the provision of product information translations)	CHMP
215 at the latest	Applicant provides the EMEA with summary of product characteristics, Annex II, labelling and package leaflet and Annex A in the 20 languages (All EU languages including Norwegian). EMEA circulates draft translations to Member States for review.	
232 at the latest	Applicant provides EMEA with final translations of summary of product characteristics, Annex II, labeling and package leaflet in the 20 languages, taking account comments received from Member States by Day 229.	
By 237	Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland.	
By 246	Applicant provides EMEA with one final full colour 'worst-case' mock-up of outer and inner packaging for each pharmaceutical form.	

1.2.2 Decentralized Procedure:[7][8]

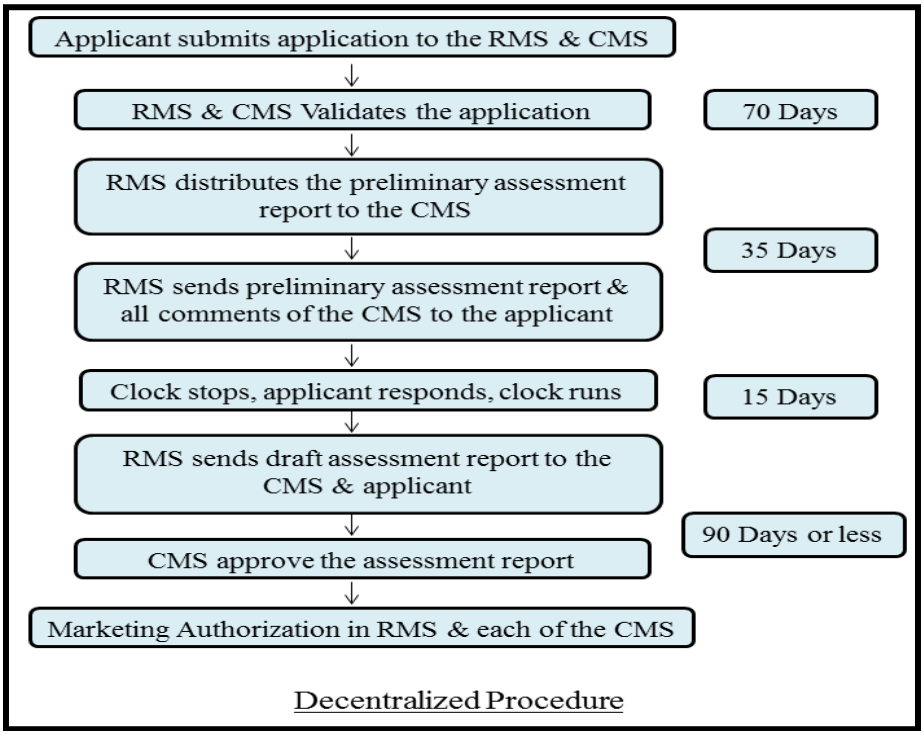


Figure 1: Decentralized Procedure

The decentralized procedure will probably remain the main route for most applications for a marketing authorization. In this case, the application is made to one Member state, which appoints a rapporteur and follows a similar procedure to that of the centralized procedure. Application may be made to the one State will undertake the evaluation procedure. Once a marketing authorization has been granted by one Member State, it can be used as grounds for registration in the other Member States. At this time other states have 90 days to review the dossier and raise objections. A binding arbitration procedure (CPMP) is available to applications appealing against licensing decisions. It is perhaps pertinent to emphasize that the registration is still in fact a State by State procedure.

The dossier should be possible to obtain a Draft Committee Decision on a marketing authorization in 270 days via the centralized procedure and in 330 days by means of the decentralized procedure. In practice it would appear unlikely that the authorization could be obtained in less than one year.

1.3Good Manufacturing Practices for Radiopharmaceuticals:

1.3.1 Preparation:

- A change control procedure should be in place to deal with all changes that may affect the quality of the radiopharmaceutical. This includes changes in the preparation method as well as in QC, equipment, software, manufacturing and suppliers.
- Process controls should include monitoring of all measurable parameters such as pressures, temperatures, radioactivity levels, and gas and liquid flow rates at relevant process locations and times, to ensure that the materials arecontrolled until required tests or other verification activities have been completed, or necessary approvals are received and documented.
- Microbiological control of aseptic processing and sterile filtration.
- Integrity testing of the membrane filter should be performed by performing a pressure-retaining test or bubble-point test.

- Aseptic processing of RPs should involve microbiological control over various types of components. Additionally the bioburden of the processing system and/or critical steps in the process should be analyzed.

1.3.2 Laboratory Controls:[9]

- Each QC laboratory should have and follow written procedures for the conduct of each test and for the documentation of results.
- Each laboratory should keep complete records of all tests necessary to ensure compliance with established specifications.
- The records should include:
    - A description of the sample received for testing including its source, batch or lot number, date and time the sample was taken, date and time the sample was received for testing, and its quantity.
    - A description of each method used in the testing of the sample, a record of all calculations performed in connection with each test and a statement of the weight or measure of the sample used for each test.
    - Relevant data obtained in the course of each test, including graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, in-process material, or radiopharmaceutical for each lot tested. Raw test data (such as chromatograms, spectra, and printouts) and any calculations performed can be documented and become part of the batch preparation and control record. Laboratory controls should be followed and documented at the time of performance.
    - A document, which should include the results of tests and whether the results comply with established acceptance criteria, signed by the person responsible for QC.
    - Deviation from written procedures should be documented and justified. Any out-of-specification results obtained should be investigated and documented.

1.3.3 Stability Testing:

- For radiopharmaceutical kits, the shelf life of the prepared product should be defined; in this case, data should be submitted which detail the minimum and maximum levels of radioactivity (and maximum and minimum volumes) and other relevant factors that are recommended for use in the preparation of the product to be administered to the patient.

1.3.4 Quality Assurance:

- There has to be a quality assurance unit that can oversee preparation operations to ensure that a radiopharmaceutical of sufficient quality is prepared.
- The quality assurance unit should have the authority to examine and approve or reject components, containers, closures, in-process materials, packaging materials, labelling and finished product to ensure compliance with procedures and specifications affecting the identity, concentration, quality and purity of a radiopharmaceutical.
- The quality assurance unit should also be able to approve or reject procedures or specifications and any changes to a specification, method, process or procedure that affect the identity, concentration, quality or purity of a radiopharmaceutical before they are implemented. It should also assess the need for revalidation after a change has been made.
- If errors have occurred, or a production batch or its components fail to meet any of its specifications, the quality assurance unit should ensure that the errors or failures have been fully investigated and corrective action taken.

1.3.5 Packaging and labelling:[10]

1.3.5.1 Labelling:

The label on the container should state:

- The name of the product and the name of the radionuclide;

- Any product identification code;
- The name of the manufacturer;
- An identification number (batch number);
- 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 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.

In addition, the label on the package should state;

- Qualitative and quantitative composition;
- The route of administration;
- The expiry date;
- Any special storage conditions.

Information on batch coding should be provided to the authorities.

1.3.5.2 Package leaflets:

Package leaflets play a particularly important role for semi-manufactured products such as preparation of kits and should include:

- The name of the product and a description of its use;
- A list of the contents of the kit; the name and the address of the manufacturer of the kit; identification and quality requirements concerning the radiolabelling materials that can be used to prepare the radiopharmaceutical;
- Directions for preparing the radiopharmaceutical including range of activity and volume and a statement of the storage requirements for the prepared radiopharmaceutical;
- A statement of the useful life 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 route of elimination and effective half-life;
- The radiation dose to the patient from the prepared radiopharmaceutical;
- Precautions to be taken by the user and the patient during the preparation and administration of the product and special precautions for the disposal of the container and its unused contents;
- A statement of the route of administration of the prepared radiopharmaceutical;

2. Regulatory Requirements for Radiopharmaceuticals in India.

2.1 Definition of Radiopharmaceutical:[11]

Radiopharmaceuticals are any medicinal or pharmaceutical product, which contains radioactive substances (radioisotopes and molecules labeled with radioisotopes), which are intended for human use either in diagnosis or therapy. Radiopharmaceuticals are essential components, administered to patients for diagnosing, managing and treating number of diseases.

Examples of Radiopharmaceuticals in India

Sr No.	Radiopharmaceuticals	Uses
1	Chromium-51sodium chromate	For labelling RBCs
2	Fluorine-18 flucicovine	A radioactive diagnostic agent indicated for PET imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen levels following prior treatment

Table 3: Examples of radiopharmaceuticals

2.2 Marketing Authorization:

For the approval of a new drug, one has to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population it has to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format. But a provision is there in Rule - 122A of Drugs and Cosmetics Act 1940 and Rules 1945 that the licensing authority may waive certain trails if he considers that in the interest of public health he may grant permission for import of new drugs basing on the data of the trials done in other countries. Also, as it is the case of radiopharmaceuticals, the DCGI has to refer to the Bhabha Atomic Research Centre for the approval of the concerned radiopharmaceutical.

Similarly there is another provision in Rule - 122A which says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries. Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required. Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials. Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that the licensing authority may require pharmacokinetic studies (Bioequivalence studies) first to show that the data generated in Indian population is equal to data generated abroad and then require him to proceed with Phase III trials.

In summary, the exact requirements of Clinical trials may change from case to case and depend on the extent to which licensing authority is satisfied about its safety and efficacy. The process of approval of new drug in India is a very complicated process, which should meet necessary requirements along with NDA to FDA.

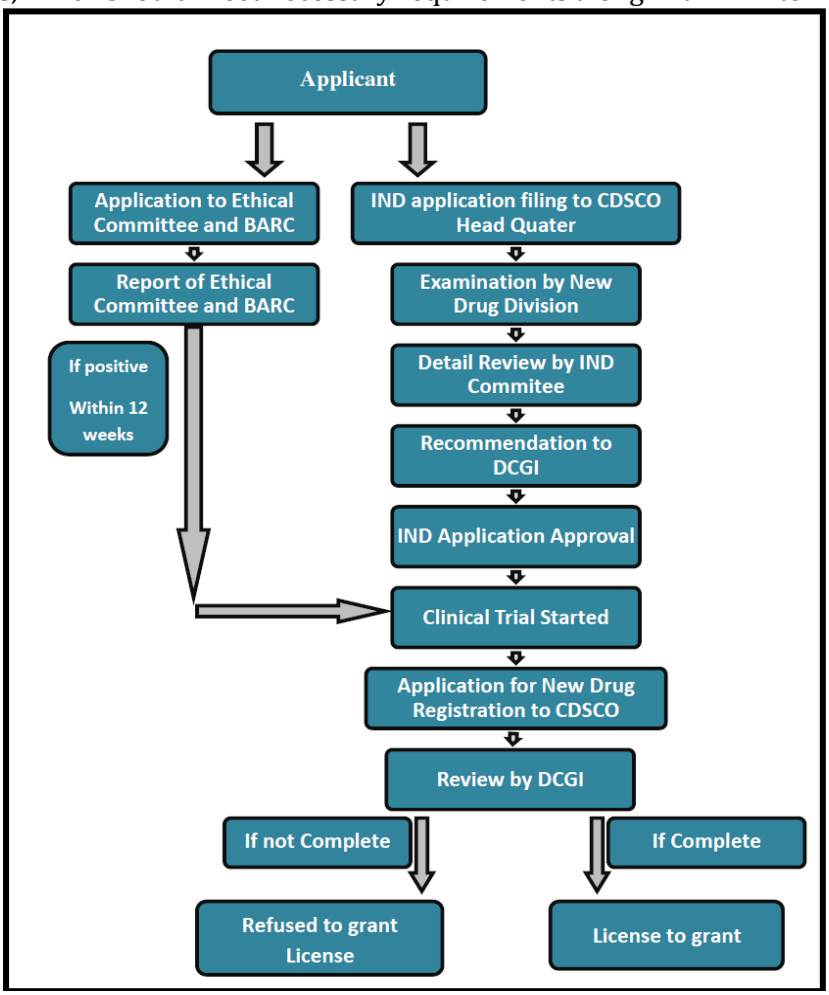


Figure 2: Drug Approval Procedure[12]

2.3 Good Manufacturing Practices for Radiopharmaceuticals:

2.3.1 Preparation:

All operations, from the preparation of the target to the dispensing of the final radiopharmaceutical preparation, must be clearly documented including their impact on the purity of the final product and the efficiency of the procedure. Wherever possible, in-process controls are performed and the results recorded at each production step to identify at which level a possible deviation from the normal production procedure may have occurred.

- For radiopharmaceutical preparations containing short-lived radionuclides, such as certain positron emitters, remotely controlled production and automated radiosynthesis are generally used. For radionuclides with a very short half-life (less than 20 min), the control of the performance of the production system is an important measure to assure the quality of the radiopharmaceutical preparation before its release.
- All conditions which may affect the quality of the product (e.g. radiochemical purity, sterility etc) must be clearly defined and must include appropriate measures for radiation protection.

2.3.2 Quality Control:

- For certain radiopharmaceutical preparations a test for bacterial endotoxins is prescribed, taking the necessary precautions to limit radiation exposure to the personnel carrying out the test.
- The limit for bacterial endotoxins is indicated in the individual monograph.
- When the nature of the radiopharmaceutical preparation results in interference by inhibition or activation and it is not possible to eliminate the interfering factor(s), the test for pyrogens may be specifically prescribed.

2.3.3 Quality Assurance:

- The determination of radiochemical purity requires separation of the different chemical substances containing the radionuclide and estimating the percentage of radioactivity associated with the declared chemical substance.
- In principle, any method of analytical separation may be used in the determination of radiochemical purity. For example, the monographs for radiopharmaceutical products may include paper chromatography, thin-layer chromatography, instant thin-layer chromatography, electrophoresis, size-exclusion chromatography, gas chromatography and liquid chromatography.
- Radioactivity may be measured by integration using an automatic-plotting instrument or a digital counter.

2.3.4 Packaging and labelling:

2.3.4.1 Labelling:

Apart from the general labelling requirements, the label on the direct container should state:

- Notification that the product is radioactive in nature,
- The name of the preparation and/or its reference,
- The name of the manufacturer,
- An identification number,
- For liquid and gaseous preparations: the total radioactivity in the container, or the radioactive concentration per milliliter at a stated date and stated time, and the volume of liquid in the container,
- For solid preparations (such as freeze-dried preparations): the total radioactivity at a stated date and stated time. After reconstitution with the appropriate solution, the preparation is considered as a liquid preparation,
- For capsules: the radioactivity per capsule at a stated date and time and the number of capsules in the container,
- Route of administration.

The labelling can be adapted in certain cases (e.g. radiopharmaceutical preparations containing short-lived radionuclides).

The label on the outer package states, in addition to those on the direct container:

- The route of administration,
- The validity period or the expiry date,
- The name and concentration of any added antimicrobial preservative,
- Where applicable, any special storage conditions.

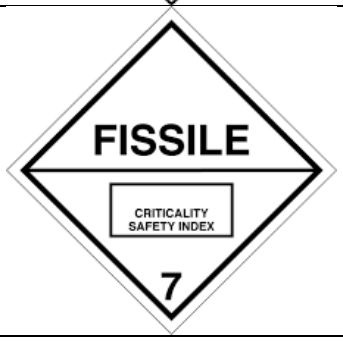
Pictogram	Symbol	Background
	Trefoil in black Black in lower half of label: **"RADIOACTIVE"**	White
	Upper half of label: **"FISSILE"** Lower half of label: **"CRITICALITY SAFETY INDEX"**	White

Table 4: Labelling Requirements

2.3.4.2 Packaging:

Drugs packages, containers, storage and bins areas for radiopharmaceuticals must bear characteristic labels identifying these drugs as it requires great handling precautions as described below:

- Inner packaging must be packed in an outer packaging in such a way that, under normal conditions of transport, they are protected from breakage, puncture or leakage.
- They are packed into either of the three packing groups in accordance with the degree of danger they present which is described as below:
  - Packing group I: substances presenting high danger
  - Packing group II: substances presenting medium danger
  - Packing group III: substances presenting low danger

Conclusion

Radiopharmaceuticals are more precise dosage form and require to have limited exposure for the safety of the patients. As they are used in the life threatening diseases, no misconduct must be observed in the application of radiopharmaceuticals. Moreover, radiopharmaceuticals should be considered as the most regulated materials administered to patients because they are controlled both as drugs and as radioactive substances. Hence, the regulation for radiopharmaceuticals is compulsory, as it is used in life threatening conditions. Also, the regulations framed, help for the better manufacturing and administration of the radiopharmaceuticals. The guidelines framed, itself, shows the need and the importance for the regulation of the radiopharmaceuticals in the world. By providing with the regulations, the awareness about the effectiveness and usefulness of radiopharmaceuticals can also be brought to the limelight.

Acknowledgements
The authors are thankful to Dr. K. Pundarikakshudu, Director of L. J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities to carry out work.

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