A Comparative Study of Pharmacopoeial Quality Standards and Regulations of Radiopharmaceuticals

Abstract

Radiopharmaceutical preparations are the important pharmaceutical dosage forms used for the diagnosis and therapeutic purposes. Various pharmacopoeias are having methods for the quality control of these preparations in the form of monographs. Indian Pharmacopoeia (IP) also included these monographs in IP 2014 first time with the help of an experts’ group on radiopharmaceutical, drawing expertise from elite stakeholder institutions and the core team of Indian Pharmacopoeia Commission. Since then, these standards are regularly updated through the IP addendum and bringing out new edition of IP. IP is a book of official methods as per Drugs and Cosmetic Act, 1940. These standards can be used in government laboratories, private laboratories, or academia in India and abroad. This review provides an overview of the journey of radiopharmaceuticals’ standard setting in IP. A comprehensive comparative information of regulatory perspectives of radiopharmaceuticals in different jurisdictions such as the US, EU, and India is also presented.

Keywords: Indian Pharmacopoeia, quality control, radiopharmaceutical standards

Introduction

Pharmaceutical preparations containing radioactive substances (like radioisotopes) are termed as radiopharmaceuticals, which are formulated for diagnosis, cure, and mitigation of diseases.[1] These are integral formulations used in nuclear medicine practice which are administered to patients for diagnosis and treatment of various types of diseases. Radiopharmaceuticals are either formulated in house or reconstituted through radioisotopes from generators and radiators from cold kits. Any necessary ligand required to formulate the radiopharmaceuticals are synthesized at hospital radiopharmacy center or procured commercially. All formulations undergo appropriate quality control checks to establish that the radiopharmaceuticals fulfill the criteria of sufficient radioactive activity, safety, and efficacy in line with the conditions set out in the relevant legislature.[2] Short-lived radiopharmaceuticals, including positron-emission tomography (PET) drugs, are subject to sterility testing; however, they may be released prior to completion of this test (parametric release) mainly to save time and resources.

Radiopharmaceuticals play a vital role in nuclear medicine practice. Nuclear medicine is the medical discipline in which radiopharmaceuticals are used for diagnosis, treatment, and mitigation of various diseases.[3-5] Radiopharmaceuticals differ from other pharmaceuticals mainly due to the short half-life of the radionuclide, as radiopharmaceuticals degenerate or decay with time. Due to a limited shelf life, the final preparation should be formulated just before administrating to the patient. Therefore, every nuclear medicine facility should be assisted by a radiopharmacy setup to ensure a timely and continuous supply of radiopharmaceuticals. A competent radiopharmacist is required to formulate the various radiopharmaceutical preparations of standard quality. These preparations can then be used only under the guidance of a qualified medical professional during the health-care services.[2]

The application of radioactive material requires careful and safe administration by competent and designated personnel, in authorized radiopharmaceutical setup in accordance with guidelines specified by regulatory body (Atomic Energy Regulatory Board [AERB] in India).[6]

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Production of radiopharmaceuticals involves various stages which include processing of active chemical entity in a laboratory in compliance with good manufacturing practices, good laboratory practices, good radiation practices, and quality management system including regulatory approvals.

In nuclear medicine or radiotherapy laboratories, various types of electronic magnetic radiation are used. Proper radiation protective mechanisms are required to be put in place while formulating radiopharmaceuticals. Emission of $\gamma$-rays is the rare property of radioactive isotopes and this promotes radiopharmaceuticals to provide useful anatomic and/or functional information on organ or tissue under study. $\beta$-rays emitted from radioisotopes are used in nuclear medicine therapy to partly or completely destroy the impaired tissues or organ.\[2]\n
Radiopharmaceuticals, as the name suggests, are essentially unique preparations wherein a particular radioisotope is tagged with a pharmaceutical so that it acquires the specificity. The nonradioactive component acts as a carrier of the radioisotope to the specific organs, tissues, or cells within the living organism, thereby allowing tracing of the biodistribution pattern of radioactivity. This property of diagnostic radiopharmaceuticals enables the evaluation of physiology underlying the disease process and organ/tissue functions. Therapeutic radiopharmaceutical accumulation at the target site allows localized therapeutic applications of the radioisotope for destruction of diseased body cells.

Radiopharmaceuticals mainly differ from the conventional pharmaceuticals as regards their stability, this is due to disintegration/decay of radionuclide with time, resulting in their limited shelf life. This distinctive nature of radiopharmaceuticals necessitates them to be freshly used within their shelf life, cater to regulatory requirement of two regulatory bodies – pharmaceutical (efficacy, purity, sterility, pH, ionic strength, microbiological control, bacterial endotoxin test, particle size and number, apyrogenicity, and isotonicity to ensure patient safety, etc.) as well as nuclear concerned with radiation safety both for the patients and occupational workers. Due to their short physical half-life, their parametric release for use is permitted for clinical use after satisfactory basic tests. As compared to conventional drugs, RPs require more careful handling and administration procedure.

In the Indian technological regime, radiopharmaceuticals have not been given the full status of a drug despite their diverse roles in biomedical research and health care.\[7]\n
Radiopharmaceuticals are listed in Schedule K of the Drug and Cosmetic Act, 1940, and are exempted from the provisions of rules of its Chapter IV which concern the manufacture, sale, and distribution of drugs and cosmetics.

**Definitions and Terminology**

Any elemental molecule represented by (a) its mass number “A” (in nucleus total number of neutrons and protons), (b) its atomic number “Z” (neutral atom with equal number of electrons and protons), and also by (c) its nuclear energy (nuclide).

Isotopes are defined as the elements with the same atomic number “Z” and different mass numbers “A”. In the periodic table, they occupy the same place and contain the same chemical properties.

**Radioactivity**

The emission of radiation from radioactive substances is due to spontaneous decay of radioisotopes or the voluntary transformation or fragmentation of a radionuclide by releasing alpha, beta, and gamma rays. Nonetheless, the term radioactivity is more used to explicit the physical strength or activity. The number of nuclear disintegrations or transformations per unit time is the radioactivity of a preparation.

**Half-life period**

The time taken for a radionuclide to decay to half of its original strength is termed as half-life ($T_{1/2}$).

**Radionuclide**

An isotope with excess energy leads to unstable nuclide, improper arrangement of neutrons and protons that alter either a stability or conversion of energy to electron or by discharge of radiation. The initial unstable nuclide is parent radionuclide which emits radiation, transformed into daughter nuclide; this conversion is referred to as radioactive disintegration/transmutation/radioactive decay.

**Radionuclide generator**

It is a device that contains longer-lived parent radionuclide which undergoes decay process and gives short-lived daughter radioactive substance, which are generally used for therapy and diagnosis in nuclear medicine. For example, commonly used radionuclide generator in radiopharmacy is $^{99m}$Mo-$^{m+}$Tc generator.

**Radionuclidic purity**

It is defined as the ratio of radioactivity of the radionuclide of interest to that of radioactivity of the radioactive formulation, which is expressed as a percentage. Quality and purity are the two important attributes of standards of pharmaceuticals. In addition, it sets the limits of the impurities in the preparations. Basically, radionuclidic impurities derive during the production of radionuclide and also dependent on route of production. For each monograph of radiopharmaceuticals in the Indian Pharmacopoeia (IP), radionuclide tolerable limits are specified in the individual monographs.

**Radiochemical purity**

Radiochemical Purity can be expressed as the ratio of radioactivity of the chemical entity to that of radionuclide present in the preparation. Any radioactive preparation should follow the official standard as specified in
monographs of radiopharmaceutical in the IP. Purity is an important attribute to assess the quality of radiochemical.

**Isotopic carrier**
The stable isotope present in element or its addition to the radioactive isotope of the same element is called isotopic carrier. In general, radionuclides consist of isotopic carriers and their quantity determined based on the method followed in the generation of the radionuclide.

**Radiopharmaceutical preparation kit**
Prior to administration of final radiopharmaceutical formulations, it contains a pair of nonradioactive reagents which is to be combined with radionuclides as per the protocol provided by the marketing authorization holder, it is called as radiopharmaceutical preparation kit; these are also often called to as “cold kits,” which do not have any radioactivity.

**Development of Radiopharmaceutical Preparation Standards in Indian Pharmacopoeia**
A pharmacopoeia contains methods for checking the quality of a drug or its formulations used in a country in which it is applicable. IP is a legal book of drug standards as per Drugs and Cosmetic Act 1940 and Rules 1945 thereunder.[4] The monographs published in the IP are the minimum standards to be complied with by the stakeholders/manufacturers. Trend of drug standards developed over time by the IPC in IP is mentioned in Figure 1.

The IP Commission has initiated efforts to include radiopharmaceuticals used in the field of nuclear medicine and radiotherapy, as tracers in the diagnosis and treatment of various diseases. IP Commission included a senior scientist from DRDO in its scientific body. After due deliberations, an Expert Committee on Radiopharmaceuticals was constituted in the meeting of the scientific body. The experts belong to various organizations in India as under Institute of Nuclear Medicine and Allied Sciences, Delhi, Bhabha Atomic Research Centre (BARC), Mumbai, Board of Radiation and Isotope Technology, Department of Atomic Energy, Mumbai, Radiation Medicine Centre, Tata Memorial Hospital Annex Building, Parel, Mumbai, and National Institute of Pharmaceutical Education & Research, Mohali, Punjab.[8,9] The group had its first meeting at IP Commission and developed a monograph template. Subsequently, the expert group finalized the list of radiopharmaceuticals and prioritized those developing monographs over a period of time. The draft was critically discussed with BARC’s Radiopharmaceutical Committee and was also deliberated in various professional meetings. [8,9] Trend of radiopharmaceutical drug standards developed in IP is mentioned in Figure 2.

**Content of general chapter**
There is an elaborative general chapter included in IP 2014 with 19 monographs of radiopharmaceutical preparations.[8,9] The general chapter on radiopharmaceuticals was finalized by the expert committee meeting after sustained deliberations/inputs obtained from nuclear medicine and radiopharmacy fraternity in India and scientists connecting to other International Pharmacopoeias. The general chapter contains introduction, definitions and terminology, phenomenon of radioactive decay, modes of radioactive decay, the units of radiation dose and radiation exposure, production of radionuclides, identification, storage, and labeling on harmonization with other pharmacopoeias. The general chapter also covers some special interest matters like Techno Legal Regime in the use of Radiopharmaceuticals in Indian Scenario, Dose Limits for exposures from Ionizing Radiations for workers and members of public as per AERB safety code No.AERB/RF-med/Sc-2 (Rev.2), Physical Characteristics of Radionuclides and Positron Emission Tomography Radiopharmaceuticals (PET-RPs) and Associated Radiopharmacy Practices. It defines nuclide, isotopes, radionuclide, radioactivity, units of radioactivity, half-life period, radionuclide generator, radionuclidic purity, isotopic carrier, radiochemical purity, chemical purity, specific radioactivity, radioactive concentration, etc.[8,9]

**Template for radiopharmaceutical monographs**
Radiopharmaceutical monographs contain isotopes of various elements such as technetium, iodine, gallium, and strontium. Various parameters of the monographs are
names of the monograph, structure, category description, production, identification, radioactivity assay, radionuclidic purity, radiochemical purity, sterility, bacterial endotoxin test, storage, and labeling, etc.[8,9]

**Journey of radiopharmaceutical standards in Indian Pharmacopoeia**

For quality control of radiopharmaceuticals preparations, IP Commission incorporated one general chapter and 19 monographs on radiopharmaceuticals for the first time in IP-2014 [Table 1]. Thereafter, 10 more monographs have been included in the addendum 2015[10] of IP-2014 by rigorous consultation with the IP expert subgroup of radiopharmaceuticals, as shown in Table 2.

New radiopharmaceutical monographs added in addendum 2016[11] to IP 2014 are listed in Table 3.

A list of new radiopharmaceutical monographs added in IP 2018 and its addendum 2019 is given in Tables 4 and 5, respectively.

As of date, IP is having a total of 37 monographs of radiopharmaceutical preparations, of which 30 monographs are for radiopharmaceuticals used for diagnostic category, 6 fall in the therapeutic category, and one monograph used in both diagnosis and in therapy. Sixteen monographs are based on technetium (Tc), 07 are iodine-based preparations, and others are sodium, gallium, strontium based, etc.[12]

**A Comparison of Pharmacopoeial Quality Standards of Radiopharmaceuticals**

**Indian pharmacopoeia**

IP is listed in the index of World Pharmacopoeias and pharmacopoeial authorities.[13] IP has the policy to harmonize the drug standards in line with other pharmacopoeias of the world and at the same time keeping their feasibility in the Indian context.

**International pharmacopoeia**

International Pharmacopoeia is the most leading pharmacopoeias of the world having 27 monographs of radiopharmaceutical preparations[14] that include technetium ([99mTc]) monographs, sodium iodide ([131I]) monographs, and monographs of sodium pertechnetate and iobenguane. Monographs of fluorodeoxyglucose, gallium citrate, sodium iothalamate, sodium phosphate, samarium lexidronam, strontium chloride, thallous chloride, and yttrium silicate are also present.[14]

**British pharmacopoeia**

British pharmacopoeia (BP) contains about 79 monographs on radiopharmaceutical preparations. All these 79 monographs are also available in European Pharmacopoeia (EP) 10.0 (2020) edition, in which technetium (99mTc), sodium iodide (131I), sodium iodide (123I), iobenguane, indium (111In), and cyanocobalamin (57Co and 58Co) monographs are available. Other monographs are ammonia, carbon monoxide, chromium edentate, fluoroxyglucose, flumazenil, fluoride, fluorodopa, gallium citrate, human albumin (iodinated), iomethylonorcholesterol, krypton, medronic acid, L-methionine, oxygen, pentetate calcium trisodium, raclopride, sodium acetate, sodium chromate, sodium fluoride, sodium iodohippurate (123I and 131I), sodium pertechnetate (fission and nonfission), sodium phosphate, strontium chloride, tetra-O-acetyl-mannose

| Name of monograph | Category                  |
|-------------------|---------------------------|
| Technetium ([99mTc]) DTPA injection | Diagnostic                  |
| Technetium ([99mTc]) EC injection    | Diagnostic                  |
| Technetium ([99mTc]) ECD injection   | Diagnostic                  |
| Sodium pertechnetate ([99mTc]) injection (fission) | Diagnostic                  |
| Sodium pertechnetate ([99mTc]) injection (nonfission) | Diagnostic                  |
| Technetium ([99mTc]) MIBI injection  | Diagnostic                  |
| Technetium ([99mTc]) glucoheptonate injection | Diagnostic                  |
| Fluodeoxyglucose 18F injection fluoride oxyglucose ([18F]) injection | Diagnostic                  |
| (131I) Meta-iodobenzylguanidine injection | Therapeutic                  |
| (131I) Meta-iodobenzylguanidine injection | Therapeutic                  |
| Samarium ([153Sm]) EDTMP injection | Therapeutic                  |
| Sodium phosphate ([32P]) injection | Therapeutic                  |
| Sodium fluoride 18F injection sodium fluoride ([18F]) injection | Diagnostic                  |
| Sodium iodide (131I) solution | Diagnostic and therapeutic |
| Sodium iodide (131I) capsules | Diagnostic                  |
| Sodium iodide (131I) capsules | Therapeutic                  |
| Injection technetium ([99mTc]) DMSA injection | Diagnostic                  |
| Technetium ([99mTc]) mebrofenin injection | Diagnostic                  |
| Technetium ([99mTc]) medronate complex injection | Diagnostic                  |

EDTMP: Ethylenediamine tetramethylene phosphonate
radiopharmaceuticals and some of these monographs are also common in BP, Ph.Eur and International Pharmacopoeia published by WHO. Among these monographs, some monographs are technetium (\(^{99}\)Tc)-based and others are indium- (\(^{111}\)In), sodium iodide-, and urea-based monographs. Apart from these, it includes some other monographs that are Yttrium (\(^{90}\)Y) ibritumomab tiuxetan), \(^{99}\)Tc oxidonate injection, \(^{99}\)Tc lidofenin injection, \(^{99}\)Tc arcitumomab injection, rubidium chloride \(^{82}\)Rb injection, samarium \(^{153}\)Sm leixidronam injection, etc.[17]

Harmonization of Radiopharmaceutical Standards

Harmonization of drug standards to the extent possible is today’s requirement. In general, all the pharmacopoeial bodies are working toward this to prevent the duplication in testing and sparing resources. The WHO is working on harmonization of standards of the world pharmacopoeias by the formation of Pharmacopoeial Discussion Group.[18] The WHO when developing monographs for International Pharmacopoeia is taking opinion/comments from various pharmacopoeias of the world. When Radiopharmaceutical Standards for IP were developed, International Pharmacopoeia has been referred, taking into consideration of Indian scenario. Sometime during harmonization, more than one method has been adopted for a particular test so that Indian quality control laboratories follow these standards without compromising the quality of medicines.[19,20] The applicable regulatory requirements in a particular country are to be adhered. The current comparative table of various RP monographs present in different pharmacopoeias is presented in Table 6.

Current Regulatory perspectives of Radiopharmaceuticals

Radiopharmaceuticals are specific and diverse from current pharmaceutical products; these are combinations of both pharmaceutical and radionucleotide components.[21] In contrast to current conventional pharmaceutical products, the RPs require two regulatory authorities, namely authority governing pharmaceutical preparations as well as the regulatory authority governing radioactive materials for licensing the production, use, and storage. Moreover, it may also require additional regulations for transportation or dispensing.[22,23]

USA

Under the administrative control of the US, Food and Drug and Administration (FDA), Center for Drug Evaluation and Research division, regulates the use of radiopharmaceuticals in the USA. Comparatively, US FDA has a sound regulatory structure for use and control of radiopharmaceutical than that of other regulatory authorities because of vast research in this field and also regulatory process exists since development phase and continues around its lifecycle by ADR reporting. Before
| Name of the RP monograph | Ph Eur-2020 | BP-2020 | USP-2020 | IP-2018 | Ch Phar-2015 | International Pha-2019 |
|--------------------------|-------------|---------|----------|--------|---------------|-----------------------|
| Albumin aggregated and stannous chloride for injection | X | X | X | X | √ | X |
| Alovudine (¹⁸F) injection | ✓ | ✓ | X | X | X | X |
| Ammonia (¹⁴N) injection | ✓ | ✓ | X | X | X | X |
| Carbon monoxide (¹⁵O) | ✓ | ✓ | X | X | X | X |
| Choline ([¹³C] methyl) injection | ✓ | ✓ | X | X | X | X |
| Chromium ([⁶¹Cr] edentate injection | ✓ | ✓ | X | X | X | X |
| Colloidal chromium phosphate[³²P] injection | X | X | X | X | ✓ | ✓ |
| Copper tetramibi tetrafluoroborate for radiopharmaceutical preparations | ✓ | ✓ | X | X | X | X |
| Cyanocobalamin ([⁵⁷Co] capsules | ✓ | ✓ | X | X | X | X |
| Cyanocobalamin ([⁷⁷Co] solution | ✓ | ✓ | X | X | X | X |
| Cyanocobalamin ([⁵⁸Co] capsules | ✓ | ✓ | X | X | X | X |
| Cyanocobalamin ([⁸⁶Co] solution | ✓ | ✓ | X | X | X | X |
| Etifenin and stannous chloride injection | X | ✓ | X | X | ✓ | ✓ |
| Fludeoxyglucose (¹⁸F) injection | ✓ | ✓ | X | X | X | X |
| Flumanezil (N-[¹¹C] methyl) injection | ✓ | ✓ | X | X | X | X |
| Fluoride solution (¹⁸F) for radiolabelling | ✓ | ✓ | X | X | X | X |
| Fluorocholine (¹⁸F) injection | ✓ | ✓ | X | X | X | X |
| Fluorodopa (¹⁸F) (prepared by electrophilic substitution) injection | ✓ | ✓ | X | X | X | X |
| Fluorodopa (¹⁴F) (prepared by nucleophilic substitution) injection | ✓ | ✓ | X | X | X | X |
| Fluoroethyl-L-tyrosine (¹⁴F) injection | ✓ | ✓ | X | X | X | X |
| Fluoromisonidazole (¹⁸F) injection | ✓ | ✓ | X | X | X | X |
| Gallium ([⁶⁷Ga] citrate injection | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Gallium ([⁶⁸Ga] chloride solution for radiolabelling | ✓ | ✓ | X | ✓ | X | X |
| Gallium ([⁶⁸Ga] edotreotide injection | ✓ | ✓ | X | ✓ | X | X |
| Human albumin injection, iodinated ([¹²⁵I]) | ✓ | ✓ | X | X | X | X |
| Indium ([¹¹¹In] capromab pendetide injection | X | X | ✓ | X | X | X |
| Indium ([¹¹¹In] chloride solution | ✓ | ✓ | ✓ | X | X | X |
| Indium ([¹¹¹In] oxine solution | ✓ | ✓ | X | X | X | X |
| Indium ([¹¹¹In] oxyquinoline solution | X | X | ✓ | X | X | X |
| Indium ([¹¹¹In] pentetate injection | ✓ | ✓ | ✓ | X | X | X |
| Indium ([¹¹¹In] pentetreotide injection | X | X | ✓ | X | X | X |
| Iobenguane ([¹²³I]) injection | ✓ | ✓ | ✓ | X | X | X |
| Iobenguane ([¹³¹I]) injection for diagnostic use | ✓ | ✓ | X | X | X | X |
| Iobenguane ([¹³¹I]) injection for therapeutic use | ✓ | ✓ | X | X | X | X |
| Iobenguane sulfate for radiopharmaceutical preparation | ✓ | ✓ | X | X | X | X |
| Iodine ([¹²⁵I]) brachytherapy source | X | X | X | ✓ | X | X |
| Iodinated albumin ([¹³¹I]) injection | X | X | ✓ | X | X | X |
| Iodomethylcholesterol ([¹³¹I]) injection | ✓ | ✓ | X | X | X | X |
| Iothalamate sodium ([²⁵¹I]) injection | X | X | ✓ | X | X | X |
| Krypton ([¹³³Kr]) inhalation gas | ✓ | ✓ | X | X | X | X |
| Lutetium ([¹⁷⁷Lu]) solution for radiolabelling | ✓ | ✓ | X | X | X | X |
| Medronic acid for radiopharmaceutical preparation | ✓ | ✓ | X | X | X | X |
| Meta-iodobenzyl guanidine injection for diagnostic use | ✓ | ✓ | X | X | X | X |
| Meta-iodobenzyl guanidine injection for therapeutic use | X | X | ✓ | X | X | X |
| Methylenediphosphonate and stannous chloride for injection | X | X | X | ✓ | X | X |
| L-Methionine ([¹⁴C] methyl) injection | ✓ | ✓ | X | X | X | X |

Contd...
| Name of the RP monograph                                          | Ph Eur-2020 | BP-2020 | USP-2020 | IP-2018 | Ch Phar-2015 | International Pha-2019 |
|------------------------------------------------------------------|-------------|---------|----------|---------|---------------|-------------------------|
| Oxygen (¹⁵⁰O)                                                     | ✓           | ✓       | X        | X       | X             | X                       |
| Pentetate sodium calcium for radiopharmaceutical preparations   | ✓           | ✓       | X        | X       | X             | X                       |
| Pentetate and stannous chloride for injection                    | X           | X       | X        | X       | ✓             | X                       |
| Raclopride [¹¹C] methoxy) injection                              | ✓           | ✓       | X        | X       | X             | X                       |
| Samarium (¹⁵⁴Sm) EDTDMP injection                                  | X           | X       | ✓        | X       | ✓             | ✓                       |
| Samarium (¹⁵⁴Sm) lexidronam complex injection                     | X           | X       | ✓        | X       | ✓             | ✓                       |
| Samarium phosphate (³²P) colloid injection                       | X           | X       | ✓        | X       | X             | X                       |
| Sodium acetate-[¹⁻¹¹C] injection                                 | ✓           | ✓       | X        | ✓       | ✓             | X                       |
| Sodium chromate (⁶⁵Cr) injection                                  | ✓           | ✓       | X        | ✓       | ✓             | ✓                       |
| Sodium fluoride (⁹⁹F) injection                                   | ✓           | ✓       | X        | ✓       | X             | X                       |
| Sodium iodide (¹²³I) capsules                                    | X           | X       | ✓        | X       | X             | X                       |
| Sodium iodide (¹²³I) injection                                   | ✓           | ✓       | X        | ✓       | X             | X                       |
| Sodium iodide (¹²³I) solution for radiolabelling                 | ✓           | ✓       | ✓        | ✓       | X             | X                       |
| Sodium iodide (¹³¹I) capsules for diagnostic use                 | ✓           | ✓       | ✓        | ✓       | ✓             | ✓                       |
| Sodium iodide (¹³¹I) capsules for therapeutic use                | ✓           | ✓       | ✓        | ✓       | ✓             | ✓                       |
| Sodium iodide (¹³¹I) injection                                   | X           | X       | X        | X       | ✓             | ✓                       |
| Sodium iodide (¹³¹I) solution                                    | ✓           | ✓       | ✓        | ✓       | ✓             | ✓                       |
| Sodium iodide (¹³¹I) solution for radiolabelling                 | ✓           | ✓       | ✓        | ✓       | X             | X                       |
| Sodium iodide (¹³¹I) dihydrate for radiopharmaceutical preparations | ✓           | ✓       | X        | X       | X             | X                       |
| Sodium molybdate (⁹⁹Mo) solution (fission)                       | ✓           | ✓       | X        | X       | X             | X                       |
| Sodium pertechnetate (⁹⁹mTc) injection (accelerator produced)     | ✓           | ✓       | X        | ✓       | ✓             | X                       |
| Sodium pertechnetate (⁹⁹mTc) injection (fission)                  | ✓           | ✓       | ✓        | ✓       | X             | ✓                       |
| Sodium pertechnetate (⁹⁹mTc) injection (nonfission)               | ✓           | ✓       | ✓        | ✓       | X             | X                       |
| Sodium phosphate (³²P) injection                                  | ✓           | ✓       | X        | ✓       | X             | X                       |
| Sodium phosphate (³²P) Oral Solution                             | X           | X       | X        | ✓       | ✓             | ✓                       |
| Sodium pyrophosphate and stannous chloride for injection         | X           | X       | X        | X       | ✓             | X                       |
| Sodium pyrophosphate decahydrate for radiopharmaceutical preparations | ✓           | ✓       | X        | X       | X             | X                       |
| Strontium (⁹⁰Sr) chloride injection                              | ✓           | ✓       | ✓        | ✓       | ✓             | ✓                       |
| Technetium (⁹⁹mTc) albumin aggregated injection                   | X           | X       | ✓        | X       | ✓             | X                       |
| Technetium (⁹⁹mTc) bicisate injection                             | ✓           | ✓       | ✓        | X       | ✓             | ✓                       |
| Technetium (⁹⁹mTc) colloidal rhenium sulfide injection            | ✓           | ✓       | X        | ✓       | X             | X                       |
| Technetium (⁹⁹mTc) colloidal sulfur injection                     | ✓           | ✓       | X        | X       | ✓             | X                       |
| Technetium (⁹⁹mTc) colloidal tin injection                        | ✓           | ✓       | X        | X       | ✓             | ✓                       |
| Technetium (⁹⁹mTc) Disofenin injection                            | X           | X       | ✓        | X       | X             | X                       |
| Technetium (⁹⁹mTc) DMSA injection                                 | X           | X       | ✓        | X       | X             | X                       |
| Technetium (⁹⁹mTc) DTPA injection                                 | X           | X       | ✓        | X       | X             | X                       |
| Technetium (⁹⁹mTc) EC injection                                  | X           | X       | ✓        | X       | X             | X                       |
| Technetium (⁹⁹mTc) ECD injection                                 | X           | X       | ✓        | X       | X             | X                       |
| Technetium (⁹⁹mTc) etifenin injection                             | ✓           | ✓       | X        | X       | ✓             | X                       |
| Technetium (⁹⁹mTc) L, L-ethylene dicysteine Injection             | X           | X       | X        | ✓       | X             | X                       |
| Technetium (⁹⁹mTc) exametazime injection                          | ✓           | ✓       | ✓        | ✓       | X             | X                       |
| Technetium (⁹⁹mTc) gluconate injection                            | ✓           | ✓       | X        | X       | X             | X                       |
| Technetium (⁹⁹mTc) glucoheptonate injection                       | X           | X       | ✓        | X       | X             | X                       |
1997, FDA exempted some requirements for focus on PET drugs and then these are focused, regulated by the commencement of FDA Modernization Act (Public Law 105‑115), under section 21 of this act guided FDA to enact appropriate regulatory approval process along with current good manufacturing practices (CGMPs) for PET drugs.

Furthermore, US FDA had published PET Drugs‑Current Good Manufacturing Practices (Small Entity Compliance Guide) in 2009 (accessed from: https://www.fda.gov/files/drugs/published/PET‑Drugs‑Current‑Good‑Manufacturing‑Practice‑%28CGMP%29‑‑Small‑Entity‑Compliance‑Guide.pdf). Subsequently, various significant regulatory guidelines started addressing on NDA and ANDA matters and its contents and formats. Again, USFDA has come up recently with current guidelines addressing compounding and repacking of radiopharmaceuticals by contract agency as well as and state-licensed nuclear pharmacy.\(^{[22,23]}\)

### European Union

All member states across Europe have their own regulatory framework for radiopharmaceuticals. The European Medicine Agency (EMA) is a foremost medicine regulatory authority that inspects medicines across Europe, which is a regionalized authority of the European Union (EU) and is answerable for the scientific assessment, control, and safety monitoring of medicines in the EU. At EMA, the Committee for Medicinal Products for Human Use established the radiopharmaceuticals drafting group having the prime responsibility of drafting guidelines pertaining to radiopharmaceuticals.\(^{[25]}\) EMA released different guidelines starting from Good Radio Pharmacy Practice to Early Phase Clinical Trials, Good Manufacturing Practices, and Clinical Evaluation and Regulations on Market Authorization for Radiopharmaceuticals. EMA has addressed Guidelines on Investigational Medicinal Product Dossier issues related to

### Table 6: Contd...

| Name of the RP monograph                                      | Ph Eur‑2020 | BP‑2020 | USP‑2020 | IP‑2018 | Ch Phar‑2015 | International Pha‑2019 |
|---------------------------------------------------------------|-------------|---------|----------|---------|--------------|------------------------|
| Technetium (⁹⁹mTc) human albumin injection                     | ✓           |         | X        | X       | X            | X                      |
| Technetium (⁹⁹mTc) HYNIC-TOC injection                         | X           | X       | X        | ✓       | X            | X                      |
| Technetium (⁹⁹mTc) labeled human serum albumin nanocolloid injection | X           | X       | ✓        |         | X            | X                      |
| Technetium (⁹⁹mTc) macrosalb injection                         | ✓           | ✓       | X        | ✓       | X            | X                      |
| Technetium (⁹⁹mTc) mebrofenin injection                        | ✓           | ✓       | ✓        |         | X            | ✓                      |
| Technetium (⁹⁹mTc) medronate injection                         | ✓           | ✓       | ✓        |         | X            | ✓                      |
| Technetium (⁹⁹mTc) mertiatide injection                        | ✓           | ✓       | ✓        |         | X            | ✓                      |
| Technetium (⁹⁹mTc) MIBI injection                              | X           | X       | ✓        |         | X            | X                      |
| Technetium (⁹⁹mTc) methylenediphosphonate injection             | X           | X       | X        | ✓       | ✓            | X                      |
| Technetium (⁹⁹mTc) microspheres injection                      | ✓           | ✓       | X        | X       | X            | X                      |
| Technetium (⁹⁹mTc) oxidorane injection                         | ✓           | ✓       | ✓        |         | X            | X                      |
| Technetium (⁹⁹mTc) pentetate injection                         | ✓           | ✓       | ✓        | X       | ✓            | ✓                      |
| Technetium (⁹⁹mTc) pyrophosphate injection                     | X           | X       | ✓        |         | X            | ✓                      |
| Technetium (⁹⁹mTc) (pyro and trimeta) phosphate injection       | X           | X       | ✓        |         | X            | X                      |
| Technetium (⁹⁹mTc) red blood cells injection                   | X           | X       | ✓        |         | X            | X                      |
| Technetium (⁹⁹mTc) sestamibi injection                         | ✓           | ✓       | ✓        | X       | ✓            | ✓                      |
| Technetium (⁹⁹mTc) succimer injection                         | ✓           | ✓       | ✓        |         | X            | ✓                      |
| Technetium (⁹⁹mTc) sulfur colloid injection                    | X           | X       | ✓        |         | X            | X                      |
| Technetium (⁹⁹mTc) Tetrofosmin complex injection               | X           | X       | ✓        |         | X            | ✓                      |
| Technetium (⁹⁹mTc)-TRODAT-1 Injection                          | X           | X       | ✓        |         | X            | X                      |
| Technetium (⁹⁹mTc) tin pyrophosphate injection                 | ✓           | ✓       | X        |         | X            | ✓                      |
| Tetra-O-acetyl-mannose triflate for radiopharmaceutical preparations | ✓           | ✓       | X        |         | X            | X                      |
| Thallous (²⁰¹Tl) chloride injection                            | ✓           | ✓       | ✓        | ✓       | ✓            | ✓                      |
| Tritiated (3H) water injection                                 | ✓           | ✓       | X        | X       | X            | X                      |
| Urea (¹⁴C) Capsules                                           | X           | X       | ✓        |         | X            | X                      |
| Water (¹⁵O) injection                                         | ✓           | ✓       | X        | X       | X            | X                      |
| Xenon (¹³³Xe) injection                                       | ✓           | ✓       | X        |         | ✓            | X                      |
| Yttrium (⁹⁰Y) chloride solution for radiolabeling              | ✓           | ✓       | X        |         | X            | X                      |
| Yttrium Y 90 ibritumomab Tiuxetan injection                   | X           | X       | ✓        |         | X            | X                      |
| Yttrium (⁹⁰Y) silicate injection                               | X           | X       | X        |         | X            | ✓                      |

USP: United States Pharmacopoeia, IP: Indian Pharmacopoeia, EDTMP: Ethylenediamine tetramethylene phosphonate
radiopharmaceuticals during developmental phase. Moreover, stringent Guideline on Package Leaflet and core Summary of product characteristics (SmPC) for radiopharmaceuticals persists that guides marketing authorization holders and regulators with integrated guidance on the information which should be published in the SmPC for radiopharmaceuticals.

**India**

AERB which is an essential board of the Department of Atomic Energy, Government of India, primarily governs radiopharmaceuticals in India. In November 1983, AERB was established by the President of India by exercising the powers conferred by Section 27 of the Atomic Energy Act, 1962, and brings out different regulatory and safety functions of Atomic Energy Act, 1962. The rules and notifications published under the Atomic Energy Act, 1962, and Environment (Protection) Act, 1986, help in the creation of various functions of AERB. Under the same Department of Atomic Energy, BARC oversees usage of radioactive material and develops its utilization in medicine. AERB made available various publications like codes and guides, annual reports, newsletter, booklet, and AERB bulletin to stakeholders.

In addition to AERB, Central Drug Standard Control Organization under Director General of Health Services, Ministry of Health and Family Welfare, Government of India, regulates the radiopharmaceuticals under its Drug and Cosmetic Act 1940 and Rules framed there, it is also a fundamental national drug regulatory agency monitoring drugs and pharmaceuticals in India. The Office of the Drug Controller General of India has issued a few notices related to import of radiopharmaceuticals. However, these notices have resulted in several challenges among the nuclear medicine community.

**Ethical issues on Radiopharmaceuticals Research in India**

Indian Council of Medical Research has recently revised National Ethical Guidelines for Biomedical and Health Research involving Human Participants in 2017, in which it enlightens radiopharmaceuticals as one of the attributes to carry out a clinical trial in any research study. The guidelines are designed for human participants or patient groups to one or more health-related investigation(s) to evaluate the consequence on outcomes. In addition, these guidelines provide insight for research on radiopharmaceuticals both as diagnostic and therapeutic agents, if it is used for therapeutic purposes, section 7.15 applies to a diagnostic agent. The permissible exposure limit of the radiopharmaceuticals or radioactive material used in a clinical study must be in compliance with the guidelines specified by BARC, Mumbai. Besides this, the following considerations must be applied.

- The investigating site should have a license from the competent authority to store, handle, and dispense the radioactive substance
- The investigator and clinical trial team must be competent and should have received appropriate training in handling radioactive substances and X-rays
- The protocol and informed consent document (ICD) should clearly state the potential radiation exposure to which participants are likely to be exposed in quantitative terms to the whole body or per organ. This exposure must be within acceptable limits
- The ethical committee (EC) may co-opt relevant expertise to review such protocols
- When a trial involving radioactive substances is planned in healthy participants, they should preferably have completed their family and receive radiation in a dose as low as permitted
- Women of childbearing age, children, radiation workers, or any individual who has received more than the permissible amount of radiation in the past 12 months should be excluded from trials involving radioactive materials or X-rays
- In the event of death of a participant with a radiological implant, due precautions must be taken as per the prescribed radiation guidelines so as to ensure that relatives or close co-habitants are not exposed to radiation
- The protocol should make adequate provisions for detecting pregnancies to avoid risks of exposure to the embryo. Information must be given to the participant in the ICD about possible genetic damage to the offspring.

**Conclusion**

Currently, the impact of radiopharmaceuticals in diagnosis and management of various medical ailments is clearly visible. The inherent quality of Radiopharmaceuticals may have a direct impact on safety of the patient and on the outcome of diagnosis and therapy. Radiopharmaceuticals are regulated differently in various countries and inclusion of RPs in different pharmacopoeias will legally support the national medicines regulatory authorities in regulatory inspections improving the quality of such preparations and thereby promote the patient safety.

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**Conflicts of interest**

There are no conflicts of interest.

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