**RECENT ADVANCES IN RADIOPHARMACEUTICALS: EXPANDING HORIZONS IN NUCLEAR MEDICINE - A BRIEF REVIEW**

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**ABSTRACT**

In recent times, there has been a remarkable surge in the utilization of radiopharmaceuticals, both as diagnostic tools and therapeutic agents. This growth can be attributed to several key factors. Firstly, their non-invasive nature has made them highly appealing for medical applications. Additionally, the increasing population of cancer patients has driven the demand for these pharmaceuticals. Notably, alpha radio-immunotherapy has developed as a targeted cancer treatment approach, offering exceptional accuracy and precision. India, known for its varied weather conditions and genetic variability, has been a thriving hub for innovative research. Consequently, substantial advancements have been achieved in the domain of nuclear medicine and molecular imaging within the Indian market. However, in spite of these developments, there are certain regulatory challenges. The Drugs & Cosmetic act of 1940 and its accompanying regulations, which control the Indian pharmaceutical business, have granted exemptions to radiopharmaceuticals from certain provisions. As a result, these vital pharmaceuticals do not enjoy the full recognition and status of traditional drugs. To address this issue, it is crucial to delve into the accessible literature on regulations concerning radiopharmaceuticals in India. Furthermore, there is an urgent need to enhance endeavors aimed at establishing standardized regulatory guidelines for conducting studies on the bioequivalence and bioavailability of radiopharmaceuticals. Such guidelines, with global acceptance, would facilitate the process of obtaining marketing authorization for these critical medical products, making them more accessible to those in need. The primary intent for this study is to produce inclusive regulatory guiding principle for the storage and dumping of radiopharmaceuticals that align with global standards. To accomplish this, a comprehensive technique was used that involved a thorough review of the Atomic Energy Regulatory Board's (AERB) current rules, with a focus on how radiopharmaceuticals should be stored and disposed of in India. The goal was to find and take into account certain parameters that might not have been expressly mentioned in the current rules. The resulting set of guidelines is designed to encompass all essential aspects, including proper documentation, clear allocation of responsibilities, strategies for waste prevention, and the implementation of various mechanisms to handle radiopharmaceutical waste in all forms. This chapter offers valuable perspectives on the application, preparation, labeling, storage, and regulatory aspects concerning radiopharmaceuticals.

**Keywords:** nuclear medicine, radionuclide, diagnosis, radiopharmaceutical, regulatory

1. **INTRODUCTION**

Radiopharmaceuticals play a fundamental role in nuclear medicine, forming the foundation of molecular imaging and precision medicine. These substances provide cutting-edge means of early disease detection and treatment. A radiopharmaceutical's basic components are a radionuclide and a carrier molecule having a high affinity for a particular organ or bodily function [1]. Both imaging and treatment methods depend heavily on radiopharmaceuticals. These medications are given orally, intravenously, or inhaled during the imaging procedure to enable the visualization of various organs utilizing their radioactive tracers. Nearly 95% of radiopharmaceuticals employed in nuclear medicine are utilized for diagnostic procedures, with the remaining 5% being used for therapeutic therapy. Because they are often employed in tracer quantities, radiopharmaceuticals typically have little pharmacologic impact. They are different from traditional medications in these situations because they do not exhibit a dose-response connection. Since they are given to humans, they ought to remain sterile, pyrogen-free, and subject to all quality control procedures required for a conventional drug. An example of a radiopharmaceutical is 133Xe, a radioactive element. Other examples of labeled substances include 131I-iodinated proteins and 99mTc-labelled substances. Drugs that restrain radioactive materials are recognized as radiopharmaceuticals. These medications can be externally scanned because they contain a radioactive substance called a radionuclide. For instance, radionuclide-labelled red and white blood cells can act as ligand or carriers to direct the radioactivity to a certain organ [1,2]. The radiopharmaceutical's radioactive portion emits radiation, which are identified by specialized scanners during imaging procedures. The radioisotope and the ligand both possess a role in a radiopharmaceutical's appropriateness. A radiopharmaceutical should have a high target-to-background ratio and display quick clearance from surrounding tissues (such as blood) while selectively concentrating in the target organ [2]. The precise targeting of particular organs, tissues, or cells inside the body is made possible by these radioisotopes attached to biological molecules, making accurate diagnosis and focused treatments possible [3].

When used at the proper doses, diagnostic radiopharmaceuticals are intended to have no pharmacological effects on the body, which means they won't change physiological processes or cause any obvious clinical adverse effects. However, due to their radioactive nature, their usage in clinical settings entails inherent dangers connected to radiation exposure during the formulation and manufacturing of radiopharmaceuticals. To reduce the risk of exposure, the employees handling these compounds must adhere to strict safety procedures. The majority of diagnostic radiopharmaceuticals are supplied intravenously, necessitating careful administration and handling techniques to protect patients and avoid unintentional radioactive material exposure. The key distinction between medicines and radiopharmaceuticals is that regular medications have therapeutic effects, meaning they are intended to treat or alleviate medical conditions. In contrast, radioactive compounds lack any therapeutic effect themselves; instead, they are used for diagnostic purposes and medical imaging [2,5].

Pharmaceuticals are also defined as pharmaceutics preparations labelled with radionuclides in therapeutic concentrations or tracer forms [7]. The short half-life of radiopharmaceuticals, which is caused by the radioactive element's quick decay, is one distinctive quality that sets them apart. Radionuclides are substances with the same number of protons but differing numbers of neutrons. An unstable radionuclide undergoes nuclear rearrangement as it transforms into a stable state, releasing energy in the process [8]. Due to the radioactive nature of radiopharmaceuticals, their preparation and use require a high level of safety and expertise. Medical professionals and operators handling these substances must follow strict protocols to protect themselves and patients from potential radiation exposure. Proper handling, administration, and degradation of radioactive are essential to ensure the safety and well-being of everyone involved in the process. Overall, it is crucial to provide accurate medical diagnoses while minimizing any hazards associated with their usage through the safe and competent use of radiopharmaceuticals. However, they have a special quality to emit radiation that makes it possible to detect and track them. When one or more atoms in a compound are replaced with radioisotopes, the compound becomes a radioactive tracer or labelRadioisotopes have revolutionized our ability to explore and understand complex biological and chemical processes, providing valuable insights into the functioning of living organisms and offering essential tools for medical diagnosis and research. The foremost metal complexes intended as radiopharmaceuticals encompass a variety of compounds, each with its specific applications in nuclear medicine for diagnostic imaging [3,4,7].

1. **SOME OF THE PROMINENT RADIOPHARMACEUTICALS**
2. **Technetium-99m**

One of the radiopharmaceuticals employed in radiological treatments is technetium-99m. The atomic weight and atomic number of this material is 99, is among its fundamental characteristics. Due to its ability to change the number of oxidation states, techenetium-99m induces a wide range of biologically reactive chemicals to be produced. In order for it to react with the interest of the organ, it must collaborate with the biological molecule. Bone scans are utilized to treat skeletal injuries directly, and in rare circumstances, they can detect bone tumors by allowing techenetium-99m to react with them. Brain scanning is another method it uses to find strokes. The Technetium-99m radioisotope's characteristics make it possible to pinpoint the lymph nodes that breast cancer uses to spread. In order to detect abnormal lymph node activity, the radioisotope will be employed in conjunction with the antimony sulphide colloid as a radioactive maker in our body. By using a shielding syringe, this radioactive maker is injected into the lymph node drain area and the area that has been identified as having abnormal activity as the site of cancer growth. In addition, Technetium-99m is combined with a tin component to identify areas of gastrointestinal bleeding. By tying them to red blood cells and mapping the circulatory system's problems, the detection takes place. What is referred to as a metastable state nuclide is technetium-99m [9].

In comparison to the usual state, it has greater energy in the atomic nucleus. Technetium-99m is one among the radioactive transition metals used as a radioactive maker. It is routinely used to determine whether several organs, including the brain, thyroid, heart muscle, and bones, have been injured. One among the nuclear transition metals that's utilized as a radioactive maker is technetium-99m. Due to its short half-life, it can serve as a preparation, cellular absorption, imaging, and agent removal. Numerous organs, such as the brain, thyroid, heart muscle, and skeleton, can be diagnosed with technetium-99m. A radioisotope called technetium-99m emits gamma rays. This enables the use of Technetium-99m for SPECT (single photon emission computed tomography). Nuclear imaging methods like SPECT employ gamma to be detected by a gamma camera. When a radioisotope is given through injections into a patient, the concentrated form will stick to the patient's target organ and send out a signal that a gamma camera can pick up [9,10].

1. **Thallium (201Tl) compounds**

Tl-201 is effective in separating benign from malignant bone lesions. Tl-201 uptake and chemotherapy response have been originated to be highly correlated. Tumor necrosis is indicated by low Tl-201 uptake in a mass, and tumour response is accompanied with declining Tl-201 uptake. Ga-67 and Tc-99m MDP are inferior to Tl-201 for imaging tumours of the bone and soft tissues [6].

1. **Gallium (67Ga, 68Ga) Compounds**

Gallium-based radiopharmaceuticals are extremely valuable for screening lymphomas and several other cancer types. A novel radioactive substance for PET that shows promise is the radionuclide 68Ga. PET might be sold without a cyclotron because it is produced using a 68Ge/68Ga-generator. To make 68Ga-labeled radiopharmaceuticals, different BCAs have been attached to peptides, or tiny biological molecules utilizing active esters, isothiocyanates, maleimides, and hydrazides. 68Ga-1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid-Tyr3-octreotide (DOTA-TOC), 68Ga-DOTA-1-Nal-octreotide (DOTA-NOC), 68Ga-DOTA-bombesin, and 68Ga-1,4,7-triazacyclon are some instances of such [11,12].

1. **67Ga-citrate**

One of the earliest radiopharmaceuticals used for infection scintigraphy was 67Ga-citrate. After being administered intravenously (i.v.), 67Ga-citrate mostly binds with the iron-binding proteins lactoferrin, ferritin, and bacterial siderophores. Throughout the first 24 hours of injection, the kidneys excrete a sizable part, while the intestines excrete only a minor portion throughout the first 7 days. As a result, lactoferrin-rich organs including the breasts and eyes that are used for breastfeeding contain radioactivity as well as the kidneys, bladder, and abdomen [13,14].

1. **Palladium-103**

Palladium-102's neutron was absorbed to create palladium-103. It was Pd-102 decay brought on by electron capture. Because radiation changes cellular DNA, it has been utilized to cure prostate cancer. There are two types of radiation healing therapy for prostate cancer: internal and external. Interstitial is another name for it. Additionally, palladium is more easily fused and tougher than platinum. It is also primarily utilized in dental alloys and as a catalyst. Palladium was used in radiopharmaceutical therapy, nevertheless. Medication is given from "within the tissue" during interstitial brachytherapy. Pd-103 has also been used in medical procedures, particularly to identify cancer. Its interstitial brachytherapy (prostate) therapeutic application is represented by seed model. Greek in origin, the term "brachy" signifies "close" or "short distance." The term "therapy that is administered from a close distance" is brachytherapy, which is employed for prostate cancer. Since the early 20th era, the idea of treating prostate cancer with internal radiation therapy has been around. Direct implantation of radioactive Palladium-103 or Iodine-125 seeds into the prostate gland is used to treat prostate cancer. Surgery is needed for this treatment. The rare element palladium was a member of the platinum group of metals. Palladium-103 was produced by absorbing the neutron from palladium-102. It was electron capture-induced Pd-102 decay. Applications of Pd-103 were used as prostate cancer seeds [15].

1. **Strontium- 89**

Strontium 89 is frequently administered to cancer patients whose disease progresses to bone metastases. Bone metastasis is the process through which cancer cells depart from the main tumour and go to the bones. The decay of strontium-89 results in beta emission, which has a half-life of 50.5 days. The greatest beta energy is 1.463 MeV, or 100%, and the average decay energy is 0.58 MeV. Strontium-89 is a frequently used medication for the bone discomfort that some tumours induce. Strontium-89 will be absorbed by the malignant bone tissue and release radiation that reduces pain. A physician with substantial training in nuclear medicine or radiation oncology will administer the prescription, either directly or indirectly. In the human body, active osteogenesis frequently involves the uptake of strontium 89. Therefore, compared to nearby normal bone, primary bone cancers and areas of metastatic involvement may acquire higher strontium amounts. Strontium 89, though decrease discomfort, did not cure cancer. A dose will remain in a metastatic bone lesion for about two weeks longer than it would in healthy bones. More than half of the dosage will remain in the bones in patients with substantial skeletal metastases. Urine and faeces are the two ways that strontium 89 departs from a human body. The first two days after the injection are the most significant for urinary excretion in patients without bone abnormalities. Strontium 89 emits beta and selectively irradiates areas of metastatic bone involvement while exposing the soft tissue surrounding the bone lesions to the least amount of radiation possible. In a multicenter Canadian placebo-controlled trial involving 126 people, a single injection of Metastron was found to significantly reduce pain compared to a specific administration of a placebo [16].

1. **Rubidium-82**

With a concentration of about 90 parts per million, rubidium is an abandoned element in the crust of earth and one of our more frequent elements. In nuclear medicine, rubidium, the second-most electropositive metal, is employed since it is non-toxic and has no known biological activities. The average person has around a half-gram's equivalent of storage of rubidium in their body, similar to potassium, and it can be absorbed via meals. The progress of the rubidium generator has led to its safe usage in clinical nuclear medicine, immunological response, and breast cancer PET scans. Because we rarely utilize rubidium to treat ailments, its use is still rather low in Malaysia. Keeping a hygienic and pyrogen-free eluate for secure intravenous injection, having a sufficient supply of Sr-82 at a reasonable price, having interchangeable inorganic ion exchange columns charged with 100-200 mCi of Sr-82, and being able to operate the generator simply and dependably over prolonged elution volumes are a few examples of Rb-82's importance in nuclear medicine. Advanced intracoronary imaging methods such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) provide superior sensitivity for exposing cardiac allograft vasculopathy (CAV), but their use is limited by their high cost, a lack of expertise, and their ability to evaluate only the epicardial vessels. Furthermore, intrusive instrumentation is needed for both advanced intracoronary imaging techniques and coronary angiography, which carries a small but significant risk for consequences. Due to its outstanding picture quality, low cost, and wide range of applications, rubidium is a good application to replace. In contrast to on-site specialised cyclotrons, radionuclide generators, like Rb -82, offer a less expensive option for producing short-lived positron-emitting radionuclides. In a commercial Rb-82 generator, a radioactive detector can be employed as a backup plan to integrate the provided dose of Rb-82 and electronically activate a bypass or shutdown valve to stop the infusion of radioactivity at the required level. Concentrated pee is a good indicator of rubidium exposure because rubidium is discharged in the urine. Rubidium may be absorbed from food, and an average individual has around a half-gram's worth of reserves in their body, similar to potassium. The rubidium generator has advanced to the point that it may now be used safely in PET tests for breast cancer, immunological response, and clinical nuclear medicine. Since we seldom ever employed rubidium to cure illness, utilisation of the metal is still minimal in Malaysia [17].

1. **Iodine compounds (123I and 131I)**

The iodine isotopes encompass iodine-123, iodine-124, iodine-125, and iodine-131. In the area of thyroid imaging and the therapy of thyroid-related disorders, radiotherapeutics utilizing iodine are commonly employed. The prospect of formulating radiopharmaceuticals for the diagnosis and management of numerous illnesses through the tagging of organic substances with iodine isotopes holds great promise. Iodine-125 Iothalamate sodium is used in diagnostic techniques to assess kidney filtration rates and analyze deep vein thrombosis within the leg [18,19]. It is also widely used in radioimmuno tests to detect hormones in extremely low concentrations. Iodine is a chemical element with an atomic number of 53. It is much heavier and a halogen. Only one of the 37 recognized isotopes is found naturally. Iodine is necessary for preserving human health, particularly since it aids in the production of thyroid hormones by the body. Mostly employed iodine isotopes as radioactive are iodine-123, having half-life of 13 hours and produces telurrium-123 through electron capture while also generating gamma rays. For imaging procedures like X-ray computed tomography (CT) scans and Single Photon Emission Computed Tomography (SPECT), it is mostly worn in nuclear medicine. Iodine-123 is produced using a cyclotron. By delivering a proton bombardment to a tellurium target during SPECT, iodine-123 is created. Nuclear reactions also produce iodine. The radioactive target's inert Xenon-123 gas was chemically removed from it before decomposing into Iodine 123 [18,19,20].

1. **Lutetium-177**

 One stable isotope of the naturally occurring element lutetium-177 exists. After injection, stable Lutetium-177 is chemically attached to the malignant region as part of targeted therapy. Lutetium-177 will release low energy gamma photons when it decays. The tissue will be traversed by the low energy gamma photons, which will be used for targeting visualisation by external imaging. The beta particle emission will cause the cancerous tissue to absorb energy. Even though the energy only travels a short distance into the tissue, it will then kill the cancer cells. Additionally, neuroendocrine tumours develop when malignancies develop in the cells of the endocrine and neurological systems. Lutetium-177 can be used to treat this illness. Lutetium-177 PSMA Therapy, also known as prostate-specific membrane antigen therapy, is one of the treatments for cancer patients. For men with prostate cancer, a targeted radionuclide therapy like lutetium-177 PSMA may be employed as a treatment option. The cancer area must be compatible with the emission properties of a therapeutic radionuclide in order to treat the cancer accurately rather than the surrounding tissue. The medium beta emitter energy of lutetium-177 is 490 keV, the maximum energy is 0.5 MeV, and the tissue penetration depth is 2 mm. In comparison to shorter beta-range, longer beta-range is poorer because it does not sufficiently irradiate small tumours. Ex vivo imaging is possible through lutetium-177's gamma emission. As a result, a lot of data is acquired and used to determine dosimetry and the location of the malignancy. When treating Lutetium-177 PSMA, the kidney, salivary, and lacrimal glands are of special concern [19].

1. **Iridium-192**

Iridium is a silvery-white metal that received its name from the Latin term for "rainbow" due to the vibrant colours of its salts. Iridium is extremely challenging to manufacture and form due to its brittleness, hardness, and low ductility. It is quite thick—roughly twice as dense as lead—and has two stable isotopes in nature, Ir-191 and Ir-193. Around 63% of iridium that occurs naturally is iridium-193, with iridium-191 making up the remaining 4%. In a nuclear reactor, the non-radioactive metal iridium is utilised to produce the radioactive element radioisotope Ir-192. The strength (or specific activity) of the resulting Ir-192 is determined by the amount of neutron irradiation and the length of exposure to the naturally occurring iridium metal. In the field of medicine, Ir-192 implants are useful. They are used to treat breast and head issues in addition to curing diseases. These implants are carefully inserted and fashioned to resemble wires [20].

1. **Carbon-11**

Radiation is used in nuclear medicine to diagnose diseases or to offer information on how a person's specific organs are functioning. The information is used by doctors to quickly diagnose the patient's illness. To find functional problems, it is straightforward to image the thyroid, bones, heart, liver, and many other organs. Radiation may occasionally be used to treat tumours or diseased organs. Despite only occasionally being used in therapy, radioisotopes are important. Radiation harm to malignant growths can be severe. Irradiating the location of the malignant growth as a result can occasionally treat or eradicate the tumour. The use of a gamma beam for teletherapy or external radiation therapy is possible with a cobalt-60 source. Carbon 11 is used as a gamma-emitting tracer in Positron Emission Tomography (PET) machines for medical imaging. For the initial disclosure of cancer, tracking the therapeutic response to cancer treatment, and studying the pharmacokinetics of anticancer medicines, carbon-11 radiotracers are frequently utilised. In the medical sector, carbon 11 is used. In PET, which is used to diagnose cancer predominantly, carbon 11 is used as a radioisotope to radioactively label molecules. This serves as a guide for the therapeutic response to cancer treatment and pharmacokinetics. Analyses of anti-cancer medications based on how the body responds to the drug [21].

1. **Samarium**

Samarium, which is radioactive, is absorbed in the region affected by bone cancer and emits radiation that aids in pain alleviation. Only medical professionals with specialised expertise in nuclear medicine or radiation oncology are permitted to administer samarium (Sm-153) lexidronam, either directly or indirectly. This medication is offered in dose forms for injection and solution. Chemical element samarium has the atomic number 62 and the letter Sm after it. The primary constituent of the drug samarium (153Sm) lexidronam (Quadramet) is the radioactive isotope of samarium known as samarium-153 (Sm). Breast, prostate, lung, and osteosarcoma cancer cells are all treated with this isotope. Another isotope, samarium-149, is intended in reactor control rods as it is a tough neutron absorber. It is among the essential elements taken into consideration during the design and operation of the reactor and is also produced as a decompose material when the reactor is in operation. Additionally, samarium is utilised in X-ray lasers, radioactive dating, and chemical reactions as a catalyst. The management of a cancer patient does not lend itself to the diagnostic philosophy that we are accustomed to in nuclear medicine. It's crucial to evaluate the patient overall. Given their age range, individuals are more probable to have concomitant diseases, and the tumor may affect multiple organ systemsNuclear physicians are knowledgeable about how labelled phosphonates and elemental strontium are absorbed. The future of systemic radioisotope treatment is quite promising. One or more therapeutic medicines that target bone, such as 89Sr-chloride and one or more of the labelled phosphornates, should be made accessible in the upcoming. These advancements must be understood by the nuclear physician, who must then implement bone-seeking radiopharmaceuticals into his or her practise as soon as they become accessible. Patients have access to a safe and efficient therapy alternative with Sm-153. It is a systemic, straightforward, and well-tolerated single-session technique that frequently results in good pain relief and occasionally pain-free periods lasting many months [22].

1. **Nitrogen-13**

Nitrogen-13 proves to be an exceptionally valuable radionuclide in the medical field, playing a considerable part in numerous medical procedures, particularly in PET for imaging myocardial perfusion. Its uses include the early detection of coronary artery disease, measurement of myocardial blood flow, and coronary flow monitoring using streamlined PET procedures. In the body, N-13 acts as a radio tracer to help deliver the radionuclide to specific region enabling the detection and treatment of tumors and arterial abnormalities with greater ease. Ammonia-13 nitrogen PET imaging intended to measure the absolute and relative myocardial blood flow using tomographic pictures. However, its accessibility is restricted, imaging techniques are intricate, and it need an on-site cyclotron. Due of this, this clinical approach is not frequently used. Depending on the size of the patient, typical scanning doses for relative MPI are for descriptions of rest, use 10 to 15 mCi (370 to 555 MBq), and for stress imaging, use 30 mCi (1110 MBq). Due to the physical half-life of roughly 10 minutes, exercise stress is achievable; nevertheless, pharmacologic stress is preferred and more beneficial. Imaging is performed 3 to 5 minutes after injection, and each imaging series acquisition may take 10 to 15 minutes [24].

1. **Iodine compounds**

Iodine-125 is a medical isotope which emits gamma rays. It is primarily employed in medical applications for radiation therapy and medical imaging. It is often utilised for brachytherapy in nuclear medicine to treat a variety of malignancies, including brain tumours, prostate cancer, and breast cancer. Implantation of radioactive iodine-125 seed tissue demonstrates to be a practical, effective, and secure management technique. It provides a safe and effective method for managing local tumour growth and pain relief. Patients with an overactive thyroid and those with papillary thyroid carcinoma receive iodine-131 therapy. Iodine-131 therapy assists in the targeted destruction of certain thyroid gland components in cases of an overactive thyroid, when one gland generates extra thyroid hormone. This restores the thyroid glands normal function. Iodine-131 cancer treatment has a success rate that ranges from 75% to 100% [26, 27].

1. **Indium (111In) compounds**

**a. Indium- 111**

Indium-111 finds widespread application in radiology for diagnostic imaging through the radiolabeling of target molecules. It is used to image lymph nodes, localise tumours, and do WBC scans for bone evaluation. Nuclear medicine, for instance, uses indium-111 chloride solution to bind antibodies. Typically, a chelating agent is used to connect the radionuclide to the target molecule, producing the desired outcome. The indium 111-tagged WBC scan is one imaging technique used to help find sites of inflammation and subsequently infections when other imaging studies are equivocal or inappropriate. Indium-111 has a half-life of 67 hours for a number of uses. Additionally, it possesses the proper gamma photon energies (173 keV-89% and 247 keV-94%) enabling detection from outside utilising detectable equipment that is readily available for purchase. Diethylenetriamine pentaacetic acid (DTPA)-folate labelled with indium-111 was examined as a radiopharmaceutical for focusing on tumor-associated folate receptors [23].

**b. Indium-111 Chloride**

Since there is no beta emission, indium-111 decays by electron capture. With a physical half-life of 67 hours, it is suitable for a variety of in vivo applications. Gallium is more suitable for detection than Indium 111, despite the latter's larger abundance. As a result, it receives less use in clinical settings. The compounds made with indium-111 for use in living things are not found naturally in the body, so it is anticipated that they will behave differently in living things than chelating agents.

**c. Indium-II1 labeled ferric hydroxide**

Although indium hydroxide is extremely hazardous, it does co-precipitate with ferric hydroxide, which is far less harmful as a result; carrier-free Lymph node scanning has been done using colloidal ferric hydroxide that has been tin-labeled. Per gramme of a lymph node that was removed, more than 20% of the prescribed amount had accumulated. Larger particles called macroaggregates, which are stabilized with gelatin and utilized for lung scintigraphy, form when the iron concentration and pH of the solution are elevated.

**d. Indium-111 labeled bleomycin**

The limited effectiveness of indium chloride as a tumor localizing agent led researchers to continue looking for a more effective substance. The radionuclide's physical properties were approved for this use. However, a reliable carrier was required in order to deliver the radionuclide to the intended tissue. Bleomycin, a concoction of closely related antibiotics, has been demonstrated to have antitumor effects on artificially created tumours and cytostatic effects on cancer cells in culture animals.

Bleomycin given intravenously leaves the bloodstream quickly and is eliminated in the urine within 24 hours. These properties of the substance make it a particularly effective tool for locating tumours. Two other crucial requirements must be met, though. For radioactivity to be transported to the target, bleomycin must first mix with a radionuclide that has adequate thermodynamic stability. Second, the newly synthesized chemical should retain the biological properties of the original organic molecule.

**e. Indium-111 Oxine**

Specialised diagnostic applications employ indium-111, such as when indium-111 tagged antibodies are utilised. Labelling the constituents of blood cells can also be done with indium-111 oxine. Platelets can be marked for thrombus identification, while leukocytes can be labelled for the localization of inflammation and abscesses **[**10].

1. **SUPERLATIVE CHARACTERISTIC OF RADIONUCLIDE'S**
* **Energy Emissions-** The radionuclide's decay should emit specific energy ranges that align with the requirements of the imaging modality used. For instance, PET demands radionuclides emitting 511 keV gamma rays, while SPECT imaging typically requires energy emissions in the 100-200 keV range.
* **Absence of Particulate Radiation-** Radiopharmaceuticals utilized for imaging should not emit particulate radiation, such as beta emissions. This is essential to prevent excessive radiation doses in patients and avoid undesired side effects.
* **Short Half-Life-** The half-life of the radionuclide is expected to be only a few hours on average. This guarantees a quick decrease in radioactivity following injection, minimising the patient's needless exposure to radiation.
* **Carrier-Free and Non-Contaminated-** Radiopharmaceuticals should be carrier-free, meaning they contain no stable isotopes of the same constituent or other radionuclides. This purity ensures that the emissions solely originate from the radioisotope, enhancing accuracy and reducing interference from other isotopes.
* **High Specific Activity** - With carrier-free radionuclides, specific activity, which measures the radioactivity per unit mass of the radiopharmaceutical, should be high. This enables the radiopharmaceutical to be administered at lower doses, perhaps minimising side effects.
* **Non-Toxic and Non-Physiologically Active-** Radiopharmaceuticals should be non-toxic and devoid of any physiological effects on the body. This ensures patient safety and avoids unwanted reactions during imaging procedures. Readily Available and Easy to Compound: Radiopharmaceuticals should be easily accessible and simple to prepare or compound in clinical settings. This streamlines imaging procedures, minimizing delays in patient care.
* **Accurate Targeting-** Radiopharmaceuticals should efficiently reach the target organ or tissue relevant to the specific imaging application. This ensures that the obtained images precisely represent the physiological or pathological condition under investigation.

By adhering to these criteria, radiopharmaceuticals have developed into requisite tools in clinical imaging, enabling precise diagnoses, treatment evaluations, and effective patient management. Their application in nuclear medicine has revolutionized medical practices, providing valuable insights into various diseases and significantly improving patient outcomes [28,29,30].

1. **TERMINOLOGY**
* **Radioactivity-** Radiation from radioactive materials is produced by the radioisotopes' spontaneous decay as well as by the deliberate modification or fragmentation of radionuclides. The emission of alpha, beta, and gamma radiation results from this process. To express the degree of physical vigour or activity in such substances, the word "radioactivity" is more frequently used. It clearly states how many nuclear disintegrations or transformations take place within a certain preparation per unit of time.
* **Radionuclide-** An isotope that has too much energy transforms into an unstable nuclide with an unnatural arrangement of neutrons and protons. Changes in stability, the conversion of energy into electrons, or the emission of radiation are all effects of this instability. The parent radionuclide, which undergoes radioactive disintegration, transmutation, or decay and emits radiation in the process, is the original unstable nuclide.
* **Half-life Period-** The time it takes for a radionuclide to decay to half of its initial strength is known as its "half-life" (T1/2).
* **Radionuclide Generator-** In nuclear medicine, radionuclide generators are frequently used for therapy and diagnosis. It contains a parent radionuclide with a longer half-life, which goes through a decay process to create a daughter radioactive material with a shorter half-life. The 99Mo-99mTc generator is an illustration of such a radionuclide generator in radiopharmacy.
* **Radionuclide Purity-** By contrasting a chemical entity's radioactivity with that of the radionuclide included in the preparation, one can ascertain the radiochemical purity. Any radioactive preparation must adhere to the official requirements outlined in the monographs of radiopharmaceuticals in the IP (International Pharmacopoeia). An important factor in determining the superiority of the radiochemical process is purity.
* **Isotopic Carrier-** The stable isotope that is present in an element or that is combined with the radioactive isotope of the same element is referred to as an isotopic carrier. Typically, radionuclides contain isotopic carriers, the amount of which depends on the process used to create the radionuclide [3,31,32,33]
1. **HISTORICAL ORIGIN OF RADIOACTIVITY AND NUCLEAR MEDICINE**

Wilhelm Roentgen's groundbreaking research on X-rays served as an inspiration for other researchers, including Henri Poincaré, who delved into X-ray emission and fluorescence concepts. The first researcher who validated Poincaré's theories was Charles Henry, who used zinc sulphide as an X-ray intensifier. According to his research, the substance's actions caused radiographs to become sharper in the presence of light. Henri Becquerel experimented with uranium salts on photographic plates in 1896, producing amazing radiographs even in the absence of light. After that, in 1905, Marie and Pierre Curie suggested using radium to cure cancer, heralding the start of contemporary nuclear medicine. The cyclotron, which Ernest Lawrence created in 1931, made it possible to artificially produce new radioactive elements, many of which are now extensively employed for medical and biological research. The Oak Ridge reactor in the United States allowed for the global production of during World War II radionuclides, having the way for medical applications. Hal Anger's development of the image-scintillation chamber in 1958 improved imaging resolution and enabled the acquisition of different projections of radiopharmaceutical distributions. Nuclear medicine achieved significant diagnostic capabilities with the introduction of the 99mTc radionuclide by Paul Harper and his team. 99mTc possesses ideal characteristics for imaging studies, emitting 140 keV gamma-type radiations, having a short half-life, and reasonable study intervals. It is consequent from the parent element 99Mo through decay in 99Mo/99mTc generators. The commercialization of radiopharmaceuticals began in the 1950s, with 131Iodine being the first isotope available for medical use, produced by Abbott Laboratories [34,35].

1. **DIAGNOSTIC TECHNIQUES USED IN NUCLEAR MEDICINE**

Based on the half-life of their radionuclides, radiopharmaceuticals can be divided into two groups: one with a half-life of less than 2 hours and another with a half-life of more than 2 hours. Cameras used in nuclear medicine are specialized tools used to find and classify radioactive particles [2], PET cameras can detect the pair of gamma rays released after a positron decays, SPECT cameras are used to identify nuclides that undergo decay by generating single gamma rays directly. Radioactive tracers used in nuclear medicine diagnostic procedures cause the body to emit gamma radiation. A specialized camera records the radiation points that are released, producing an image that is magnified on a computer and shown on a monitor to help find any irregularities. For better anatomical visualisation, nuclear medicine procedures such as Single Photon Emission Computerised Tomography (SPECT), PET, and computed tomography-PET (PET-CT) are available. Additionally, microcomputerized axial tomography (micro-CAT) and micro-PET with ultra-high resolution are used [2,36]. Despite producing images with great intensity, SPECT and PET methods have a restricted spatial resolution because of their surface-directed visualisation. Magnetic resonance imaging (MRI) and computerised tomography (CT) give a higher spatial resolution but less sensitivity. Techniques are coupled to obtain superior spatial resolution and high sensitivity in order to get beyond these restrictions. The three-dimensional images produced by X-ray CT are more detailed and have a greater resolution [2,37,38].

1. **APPLICATIONS OF RADIOPHARMACEUTICALS**

Advancements in radiation detection technology have led to a fundamental increase in the exercise of radioisotopes in medicine. Both the diagnosis and therapy of diseases use radioactive substances. Monitoring blood flow to organs such the liver, brain, lung, heart, and kidney requires the use of diagnostic radiopharmaceuticals. A carrier molecule is necessary for the majority of radioisotopes to be transported throughout the body and localised in the desired tissue or organ. The introduction of radioisotopes, which find extensive usage in numerous applications, has significantly changed medical practice. More than 10 million nuclear medicine treatments and more than 100 million nuclear medicine tests are performed annually in the US alone. Notably, the use of four radioactive tracers—technetium-99 (99mTc), thallium-201 (201Tl), iodine-131 (131I), and sodium-24 (24Na) has come to be standard. These radionuclide-labeled biologically active substances are useful tools for both therapeutic and diagnostic applications [39,40].

1. **Some specific applications of radiopharmaceuticals include**
2. **Diagnostic Imaging**

For non-invasive visualisation of physiological processes and disease situations, radiopharmaceuticals are worn during medical imaging procedures like positron emission tomography (PET) scans and single-photon emission computed tomography (SPECT) scans.

1. **Therapeutic Purpose**

Certain radioisotopes can be employed for therapeutic purposes, such as targeted radiation therapy for cancer treatment (radiopharmaceutical therapy).

1. **Cardiac Imaging**

Radiopharmaceuticals help evaluate heart function, blood flow, and myocardial perfusion in patients with cardiovascular diseases.

1. **Bone Imaging**

Radiopharmaceuticals are used to evaluate bone health, identify fractures, and detect bone metastases in cancer patients.

1. **Neurological Imaging**

Radiopharmaceuticals aid in diagnosing neurological disorders like Alzheimer's disease, and epilepsy by mapping brain activity and identifying abnormalities.

1. **Radioimmunoassays**

In laboratory settings, they are intended in radioimmuno assays in order to gauge attentiveness of various substances (e.g., hormones, drugs) in biological samples [42].

1. **In vivo applications of radiopharmaceuticals**

While accomplishing in-vivo operations to acquire clinical data, radiopharmaceuticals are essential. These treatments entail measuring the drug's spatial delivery inside an organ (scintigraphy) or analysing the drug's intake or output inside the organ to determine how well it functions. A tumour may be present or certain organ parts may have decreased viability if abnormal areas are seen during radioactivity scans. The thyroid's ability to remove radioactive iodide from the bloodstream is one prominent application of uptake analysis, as it reveals important details about the physiological status of the gland. The rate of accretion of a radiopharmaceutical, such as 197 Hg chlormerodrin, in both kidneys at the same time can be used to assess kidney function. Less than 50 radiopharmaceuticals are being used frequently for in vivo delivery. Many of them are used for comparable diagnostic procedures, and the choice of radiopharmaceutical is frequently based on the practitioner's personal preferences. The goal of ongoing, rigorous research in several labs across the world is to create radiopharmaceuticals that are more effective. Over the next 10 to 20 years, there will likely be major improvements and adjustments to the medications used in radiology [41].

1. **In vitro applications of radiopharmaceuticals**

In the area of in vitro clinical tests involving radioactive reagents, one stands out as particularly significant: the radioimmunoassay for body hormones. This method revolves around the utilization of labeled hormone preparations and binding proteins, allowing for the separation of bound and unbound hormone components. By gauging the radioactivity in every portion, a bound-to-unbound ratio is derived, which is then compared against a ordinary curve to determine the hormone concentration in the plasma. The radioimmunoassay boasts remarkable sensitivity, enabling the measurement of most hormones at nanogram to picogram levels. Its specificity is also noteworthy, as the antibodies selectively bind to their corresponding hormones with great precision. This technique proves remarkably versatile, facilitating the assessment of a wide range of hormones and other antigens. Notable examples include insulin, thyroxine, prostaglandins, digitoxin, human growth hormone, and the "hepatitis-associated" antigen. The latter, in particular, plays a crucial role in pre-testing blood donors to minimize the risk of hepatitis transmission through blood transfusions [41].

1. **CONTRASTING RADIOPHARMACEUTICALS DERIVED FROM NATURAL COMPOUNDS WITH OTHER RADIOPHARMACEUTICALS**

In radiopharmaceuticals made from natural sources, natural compounds are ligands. The ligand's subsequent selective engagement with the target tissues is what allows radionuclides to be distributed in a targeted manner. This interaction, which may take place immunologically, pharmacologically, or metabolically, is typically reversible. After the contact occurs and the ligand connects with its target, the resulting bound radiopharmaceutical can be internalised and stored within the target cells. Therefore, even at low doses, the ligand must effectively stop any pharmacological action or negative effects on the target. When compared to radiopharmaceuticals made from natural substances, conventional radiopharmaceuticals frequently use small molecules, peptides, and proteins as ligands. A suitable radiopharmaceutical synthesis reaction is then selected, and the synthesised radiopharmaceutical is then assessed. However, radiopharmaceuticals made from natural substances typically go through a longer development stage. An appropriate radiopharmaceutical synthesis reaction is then selected, and the synthesised radiopharmaceutical is then assessed. However, radiopharmaceuticals made from natural substances typically go through a longer development stage. Finding the natural chemicals themselves is the first step in creating such radiopharmaceuticals. Research often commences with the exploration of natural product sources in the environment. After that, the lead compound will be identified, and the natural compounds will be isolated and identified by their structure elucidation. Subsequently, the molecular targets and pharmacological activities will be identified. Afterward, the subsequent phase involves choosing a suitable radiopharmaceutical synthesis reaction, considering both the structure and target of the natural compounds. In certain cases, structural modifications may be necessary to achieve optimal radiopharmaceutical synthesis outcomes. Following a similar pattern to other radiopharmaceuticals, those derived from natural compounds undergo characterization and evaluation based on several criteria, including stability, physicochemical characteristics, cellular uptake, preclinical studies, dosimetry prediction, and clinical studies [43,44,45].

1. **PREPARATION OF RADIONUCLIDE**

The preparation involves three essential steps: radionuclide production, synthesis of the non-radioactive compound, and the subsequent reaction of the radionuclide with the non-radioactive compound.

1. **Radionuclide Production**

The initial stage in the preparation of radiopharmaceuticals focuses on generating the appropriate radionuclide. There are two primary sources for obtaining radionuclide suitable for nuclear medicine procedures: primary and secondary sources. The primary source involves directly producing radionuclide using either a nuclear reactor or a particle accelerator. On the other hand, the secondary source employs an indirect method by utilizing a radionuclide generator scheme to produce the desired radionuclide.

1. **Primary source**
2. **Nuclear reactors**

Nuclear reactors are widely employed as a primary method for generating radioactive materials utilized in various industries, academic research, and medical applications. Through the fission reaction of uranium, a significant number of neutrons are produced. One neutron is utilized to sustain the fission reaction for each uranium atom involved. The residual neutrons are employed to generate plutonium or to interact with specific substances, inserted into the reactor, to produce radioactive products. This end method is known as neutron activation. This technique enables the creation of isotopes such as Xe133, Mo99, and I131. The fission reaction can be symbolically depicted by the following equation [46]:



Within a nuclear reactor, a stable nucleus of compounds undergoes bombardment by low-energy or thermal neutrons. As these neutrons are absorbed, the nucleus of the bombarded atom undergoes rearrangement, resulting in its transformation into an unstable, or radioactive, state. This instability is subsequently followed by the emission of particles such as protons or alpha particles, as well as gamma rays or fission. This nuclear reaction can be represented symbolically as follows:

(n, p),(n, 4He),(n, γ ) or (n, f)

In this symbolic representation, n represents a neutron, p denotes a proton, 4He represents an alpha particle or helium nucleus, γ signifies a gamma ray emission, and f represents fission. Within the realm of nuclear medicine procedures, the (n, γ) and (n, f) reactions are the crucial methods for producing radionuclide within a nuclear reactor.

(n, γ) process- This process can be depicted schematically as:



In this representation, 'X' represents an element, 'A' denotes its mass number, and 'Z' represents its atomic number. This process is depicted as:



Molybdenum-98 is irradiated in the aforementioned (n, γ) reaction to create molybdenum-99. The area of the cross-section of thermal neutrons is 0.13 barns, while the natural abundance of 98Mo is 24.13 %. For 3–7 days, radiation is applied at a neutron flux of 1013 n/cm2/s. Using highly enriched 98Mo is crucial for producing 99Mo that has excellent specific activity and less radioactive contamination, and the recommended chemical composition is trioxide (MoO3) [47].

In summary, radiopharmaceutical production involves managing numerous complexities to ensure adherence to regulatory standards, safety measures, and quality control during the whole production process. For small-scale manufacturers, implementing cGMP guidelines presents specific challenges that require careful attention to various aspects of production, from personnel qualification to documentation and product release [48]. The majority of radioactive materials used in industry, academic research, and medicine today are produced in nuclear reactors, commonly referred to as nuclear piles. These reactors employ the process of uranium fission to generate a substantial number of neutrons. The remaining neutrons have two main purposes: they can be utilized to generate plutonium or directed towards specific substances inserted into the reactor, leading to a process called neutron activation. Neutron activation involves the interaction of neutrons with targeted substances present in the reactor. This interaction results in the production of radioactive isotopes. By carefully selecting and introducing specific materials into the reactor, isotopes such as 133Xe, 99Mo, and 131I can be generated using this neutron activation process [49].

1. **Particle accelerators**

Particle accelerators come in two main types: linear accelerators and cyclotrons. In the case of radiopharmaceutical preparation, the stable nucleus of the chemical complex is bombarded through charged particles like electrons, protons, deuterons, and alpha particles. In a linear accelerator, the charged particles are accelerated along a linear path by utilizing controlled electric current and voltage for precise regulation. Conversely, in a cyclotron, the charged particles follow a circular path while being accelerated, thanks to interplay of controlled electric current and magnetic fields [50].



1. **Secondary sources**
2. **Radionuclide Generator**

The radioisotope generating system is an ion exchange column with resin or alumina that has been adsorbed with a long-lived parent nuclide. It comprises of a glass or plastic column with adsorbent material at the bottom, upon which the parent nuclide is adsorbed. The daughter nuclide expansion is eluted in the carrier-free condition using the right solvent after 4-5 half-lives. Using this process, Ga68, Kr81, Rb82, Tc99, and In113 are produced. Around 85% of all imaging procedures in the US are favored after the injection of Tc99 because of its optimal imaging energy, physical half-life, and wide range of ligand. Due to its optimal imaging energy, suitable physical half-life, and its ability to bind to a wide range of compounds, around 85% of all imaging procedures utilize 99mTc. The diverse chemistry of technetium, which can exist in eight different oxidation states, combined with an understanding of the relationship between its structure and biological activity, has led to the improvement of numerous products for morphological and functional imaging of various organs. Recent advancements have focused on creating 99mTc -labeled compounds for assessing receptor or transporter functions. In addition, bi-functional chelating agents have been developed to enable the labeling of proteins and peptides with 99mTc, resulting in high in vivo stability and radiochemical yields [51].

An ideal generator system for radiopharmaceutical production should possess the following characteristics:

* Sterile and Progeny-Free Output: If intended for clinical use, the output of the generator must be free from any contaminants or progeny to ensure its sterility.
* Differential Chemical Properties: The chemical features of the daughter isotope must be distinct from those of the parent to facilitate their separation. Chromatographic techniques are commonly employed for this purpose.
* Elution Process: The generator should be eluted with a 0.9% saline solution, which should not involve any violent chemical reactions. It is desirable to minimize human intervention to reduce radiation exposure.
* Short-Lived Gamma-Emitting Daughter Isotope: The daughter isotope should have a comparatively short physical half-life, typically spanning hours to days, and emit gamma radiation.
* Versatile Daughter Chemistry: The daughter isotope should have suitable chemical properties for the manufacturing of a extensive range of compounds, particularly those in kit form.
* Stable Granddaughter: The generator system should contain a very long-lived or stable granddaughter isotope to ensure that no additional radiation dose is conveyed to the patient through subsequent generations of decay.
* Effective Shielding: The generator should be equipped with inexpensive and effective shielding to minimize radiation exposure for users and ensure their safety.
* Ease of Recharging: Although some generators, such as Mo/Tc generators, are not rechargeable and are stored in decompose areas after their valuable life is over, an ideal generator system should allow for easy recharging or replacement when necessary.

Various generators are accessible, and these comprise molybdenum-99-technetium-99m (99Mo-99mTc), tin-113-indium-113m (113Sn-113In), rubidium-81-keypton-81m (81Rb-81mKr), strontium-82-rubidium-82 (82Sr-82Rb) and germanium-68-gallium-68 (68Ge-68Ga). Molybdenum-99-technetium-99m (99Mo-99mTc) is most significantly used radioactive generator [52].

1. **Thermal Neutron Reactor**

The radioisotopes employed are primarily synthetic in nature. In the case of radioisotopes produced in thermal neutron reactors, the reactor serves as a source of thermal neutrons. An atomic reaction takes place, resulting in an increase in atomic weight by one unit while the atomic number remains unchanged. Consequently, the same element is retained, for example, Mo98 produces Mo99 following the reaction.

The yield of radioisotopes in a reactor depends on various factors, including:

* Neutron Flux: The intensity of neutron flux within the reactor, measured in neutrons per second per square centimeter (n/sec/cm²).
* Nuclear Capture Cross Section: The probability of nuclear capture, which refers to the likelihood of a nucleus capturing a neutron and undergoing a reaction.
* Number of Target Atoms: The quantity of target atoms available for neutron capture within the reactor.
* Decay of Product: The rate at which the produced radioisotope undergoes radioactive decay after its formation.
* Length of Irradiation: The duration for which the target material is exposed to the neutron flux within the reactor.
* Isotope Enrichment of the Target: The degree of enrichment or concentration of the specific isotope targeted for radioisotope production.

These factors collectively influence the yield and production efficiency of radioisotopes in thermal neutron reactors for use in nuclear medicine applications [52, 53].

1. **Cyclotron-Produced Radionuclides**

Cyclotrons and similar particle accelerators are specifically designed for the acceleration of charged particles such as electrons, protons, and deuterons. These machines rely on the interaction of magnetic and/or electrostatic fields with the charged particles to facilitate their acceleration. By employing a magnetic field for control and an electric current for acceleration, a beam of charged particles is generated as the ions traverse an expanding circular path. Various separation techniques are available to divide the preferred product from the target material. Notably, this method is utilized for the manufacturing of isotopes such as C11, N13, O15, and F18.

The yield of cyclotron-desired radionuclide depends on several factors [54]:

* Number of Target Atoms: The quantity of target atoms available for interaction with the accelerated particles.
* Energy of Particles: The energy at which the particles are accelerated within the cyclotron.
* Decay of Product: The rate at which the produced radionuclide undergoes radioactive decay after its formation.
* Length of Irradiation: The duration for which the target material is exposed to the accelerated particles.
* Isotope Enrichment of the Target: The degree of enrichment or concentration of the specific isotope targeted for production [55].
1. **Synthesis of non-radioactive compounds for radiopharmaceuticals**

The second crucial stage in the production of radiopharmaceuticals involves the organic or inorganic synthesis of non-radioactive compounds. This synthesis can range from a straightforward, one-step process involving the mixing and refluxing of suitable reagents to a more intricate, multi-step procedure with varying physicochemical conditions. The choice of synthesis depends on the specific requirements of the clinical study. The non-radioactive compounds serve different purposes based on the nature of the clinical study. It may act as a carrier compound, such as methylene diphosphonate, responsible for transporting the radionuclide to the target organ or tissue. Alternatively, it can function as a complexing or chelating agent (ligand) that interact with the radionuclide to form the new compound with distinct chemical and biological properties such as, iminodiacetate derivatives [56].

1. **Radiopharmaceutical kit preparation**

The preparation of a radiopharmaceutical kit enables the radio pharmacist to convert the radioactive isotope acquired from the generator into the preferred radiopharmaceutical. This kit consists of a vial containing freeze-dried and sterile non-radioactive components, into which the appropriate radionuclide is either added or diluted before its medical use. The non-radioactive ingredients in a typical formulation include ligands, reducing agents, stabilizers, buffers, and antioxidants. To prepare the kit, the freeze-dried contents are reconstituted by aseptically transferring the required dosage of the radioactive isotope using a sterile syringe or needle. The amount of activity withdrawn for reconstitution depends on the number of patient doses to be produced. Once reconstituted, the kit is divided aseptically to provide each patient with a dose containing the necessary activity. It is imperative to note that radiopharmaceutical preparations resulting from these kits are typically proposed for utilization within 12 hours of their preparation [57].

The radiopharmaceutical kit consists of the following components:

* Methylene diphosphonate (MDP): MDP is a ligand that forms a complex with Technetium. It acts as a chelating agent, binding to Technetium to create a stable radiopharmaceutical compound.
* Stannous ions: The kit includes stannous ions, which occurred in the form of stannous chloride or stannous fluoride. Stannous ions serve as reducing agents that enhance the complexation of the ligand (MDP) with Technetium. They facilitate the proper binding of Technetium to the ligand, ensuring the stability and effectiveness of the radiopharmaceutical.
* Stabilizers, buffers, and antioxidants: The kit may contain additional compounds such as stabilizers, buffers, and antioxidants. These ingredients help maintain the integrity and stability of the radiopharmaceutical formulation. Stabilizers prevent degradation or breakdown of the radiopharmaceutical over time, while buffers help maintain the desired pH level. Antioxidants protect the radiopharmaceutical from oxidation, ensuring its quality and potency [58].
1. **LABELING AND PACKAGING OF RADIOPHARMACEUTICALS**

The label on the package of a radiopharmaceutical should include the following information:

* **Product Name:** Clearly state the name or generic description of the radiopharmaceutical.
* **Strength or Activity:** Specify the strength or activity of the radiopharmaceutical, typically expressed in units such as milligrams (mg) or Becquerels (Bq).
* **Batch or Lot Number:** Provide a unique recognition number specified to the definite batch or lot of the radiopharmaceutical for traceability and quality control purposes.
* **Expiration Date:** Indicate the date until which the radiopharmaceutical is guaranteed to remain within the specified potency and quality standards.
* **Radiation Warning Symbols:** Display internationally recognized radiation warning symbols, such as the trefoil symbol, to alert individuals about the presence of radioactive material.
* **Precautionary Statements:** Include necessary precautionary statements to guide individuals on the safe handling, storage, and disposal of the radiopharmaceutical. This may include instructions on radiation protection, proper shielding, and any specific handling precautions.
* **Storage Conditions:** Specify the recommended storage conditions, such as temperature, light exposure, and humidity, to maintain the stability and integrity of the radiopharmaceutical.
* **Manufacturer Information:** Provide the name and contact information of the producer or distributor responsible for radiopharmaceutical.
* **Regulatory Information:** Include any necessary regulatory information, such as the registration or approval number, to ensure compliance with applicable regulations and standards.
* **Barcodes or QR Codes:** Incorporate barcodes or QR codes for efficient tracking, inventory management, and electronic documentation [59, 60].
* **For liquid preparations**, the label on the package should provide the subsequent instructions regarding the radionuclide concentration:
* Total Volume in the Vial: Clearly state the total capacity of the liquid radiopharmaceutical solution present in the vial. This indicates the overall quantity of the solution contained in the vial.
* Total Concentration of Radionuclide: Specify the total concentration of the radionuclide within the vial. This indicates the quantity of radionuclide present in the entire volume of the liquid radiopharmaceutical solution in the vial.
* Concentration per Milliliter at the Date and Time of Manufacturing

By including this information on the label, healthcare professionals can accurately determine the concentration of the radionuclide in the liquid radiopharmaceutical solution, enabling them to calculate and administer the appropriate dosage to patients [61].

* **For solid preparations** (lyophilized powder) of radiopharmaceuticals, the label on the package should include the following information regarding the radionuclide content:

Total Amount of Radionuclide: Clearly state the total amount of radionuclide present in the lyophilized powder at the date and time of manufacturing. This indicates the overall quantity of the radionuclide contained in the solid radiopharmaceutical preparation [62].

* **For radiopharmaceutical capsules**, the label on the package should include the following information regarding the radionuclide content:
* Total Number of Capsules in the Package: Clearly state the total number of capsules contained within the package. This provides information about the quantity of capsules available for use.
* Amount of Radionuclide in every Capsule: Specify the quantity present in each individual capsule. This indicates the quantity of the radionuclide enclosed within each capsule [63].
1. **PACKAGING**

The packaging for radiopharmaceuticals should be appropriate for the specific product and its conditions. This includes using materials that ensure the integrity, stability, and safety of the product throughout its shelf life. Packaging should also provide adequate protection against radiation and contamination [64].

**Package Leaflets**

The package leaflets accompanying radiopharmaceutical kits or products should contain the following information:

* Name and Usage of the Radioactive Product: Clearly state the name of the radiopharmaceutical and its intended use, providing an overview of its medical purpose.
* Ingredients: List the names of all ingredients present in the radiopharmaceutical product, including both radioactive and non-radioactive components.
* Manufacturer Information: Provide the name and address of the company responsible for producing the kits or radiopharmaceuticals.
* Method of Preparation: Describe the procedure for preparing the radiopharmaceutical from the provided kits, ensuring clarity and accuracy in the instructions.
* Shelf-Life: Specify the shelf-life or expiration date of the prepared radiopharmaceutical, indicating the duration during which it remains suitable for use.
* Route of Administration and Effects: Detail the recommended route of administration for the radiopharmaceutical and provide information on its pharmacological and toxicological effects.
* Dose Information: Specify the dosage.
* Precautions: Highlight the precautions that patients and nuclear pharmacists should take during the administration and preparation of the radiopharmaceutical. This may include handling precautions, radiation protection guidelines, and any special considerations.
* Disposal: Provide guidance on the proper disposal of the container and any unused contents, ensuring compliance with regulations for radioactive waste disposal.
* Recommended Dose: Include the recommended dosage information for the prepared radiopharmaceutical, emphasizing the importance of adhering to prescribed doses [65, 66].
1. **STORAGE OF RADIOPHARMACEUTICALS**

When it comes to the storage of radiopharmaceuticals, adherence to international standard guidelines is crucial. After undergoing appropriate pretreatment, the waste should be reserved in designated waste storage facilities until it has adequately decayed to its nonradioactive form. The storage process should allow for easy scrutiny, monitoring, preserving and maintenance throughout the storage period. The recommended supervision approach involves placing the waste in suitable waste storage facilities equipped with acceptable shielding, depending on the intricacy of the operation. This method follows the 'decay in storage' program and is equally applicable to waste in all physical states. It aligns with the International Atomic Energy Agency's guidelines, especially for waste with half-lives shorter than 100 days [67]. The storage or clearance of waste should be based on its specific chemical state, as detailed below:

1. **Proper Management of Solid Radioactive Wastes:**

To ensure safe storage of solid radioactive wastes, it is essential to adhere to the following guidelines:

1. Sharp Radioactive Items: These objects should be firmly dispatched in lead-lined bins and labeled with vigilance about radioactivity. Before disposal, each container's exterior should be swiped and experienced for radioactivity using a well counter. To prevent breakage, the radioactive sharp materials container must be positioned in a designated safe area for sufficient decay. Additionally, a secondary container may be used with an absorbent pad to prevent any potential leakage.
2. Radioactive Absorbent Materials (paper and gloves): These should be segregated and sited in appropriately shielded and labeled containers.
3. Carcasses of Experimental Animals and Blood-Contaminated Wastes: For such wastes, hermetically preserved polyethylene drums should be used as an alternative of plastic bags. Before storage, it is advisable to disengage the waste. Subsequently, the waste should be stored in a freezer.
4. Reuse and Recycling of Lead Pots: Before reusing or recycling lead pots as non-radioactive waste, suitable decontamination procedures should be applied.
5. Radionuclide Generator Disposal: The preeminent practice is to choose the "decay in storage" option for radionuclide generators. Before dismounting the elution column from its shield, it is essential to ensure that the activity and dose rate are low [67, 68].
6. **Management of Liquid Radiopharmaceutical Waste:**

Liquid radiopharmaceutical waste should be disposed of or stored in accordance with the following guidelines:

1. Segregation based on Half-Life: The initial step in disposal is to segregate liquid waste based on its half-life. Short half-life radiopharmaceuticals, such as Tc99m and F18, should be separated from long half-life ones, which may contain Lutetium 177. Intermediate half-life radionuclides like I131, I123, and Ga67 should follow the decay in storage approach.
2. Discharge into Sewerage System: Excreta from patients undergoing diagnostic scans with short half-life radiopharmaceuticals can be discharged directly into the sewerage system if it is centrally connected to the hospital's sewerage management system.
3. Separate Storage for Radioactive Organic and Aqueous Wastes: Radioactive organic and aqueous wastes, even if they contain the same radionuclide, should be stored and disposed of separately.
4. Contaminated Rinsing Solutions: Contaminated solutions from rinsing radioimmunoassay kit apparatus can be diluted and discharged through the hospital's sewerage system to municipal waste. The solubility of the material in water is crucial for such disposal.
5. Managing Inpatients' Excreta: For inpatients receiving radiopharmaceutical therapy in the hospital's nuclear medicine department, the outlet of their toilets should be designed to route to delay tanks via leak-proof pipes. These delay tanks, adequately shielded and potentially using the Biochroma technique, can hold the excreta until the radioactivity decays to a safe, nonradioactive level.
6. Decay in Concrete Delay Tanks: Radioactive liquid waste can also undergo decay into a nonradioactive form using concrete delay tanks with suitable shielding. After an adequate decay period, the activity in these tanks should be measured through sampling. If the activity is within permissible limits, the waste can be discharged into the community sewerage system [69].
7. **Gaseous Radioactive Waste Management:**

Radioactive gaseous waste should be treated directly at its point of origin using a specific setup. The setup should include a condenser, pre-filter, and HEPA filters. The process begins with the condenser, which is responsible for condensing the radioactive gaseous waste. The condensed waste is then passed through the pre-filter to remove any additional impurities. Finally, the pre-filtered gas undergoes a final filtration process by passing through a HEPA filter, which is installed at the exhaust end of a chimney set at an appropriate height. This comprehensive system ensures the effective treatment and containment of radioactive gaseous waste, safeguarding the environment and public health [70].

1. **REGULATION OF RADIOPHARMACEUTICALS**

Radiopharmaceuticals stand apart from conventional pharmaceutical products as they are a combination of pharmaceutical and radio nucleotide components. Unlike regular pharmaceuticals, the production, use, and storage of radiopharmaceuticals necessitate approval from two regulatory authorities: one overseeing pharmaceutical preparations and the other managing radioactive materials. Additionally, there may be supplementary regulations pertaining to transportation and dispensing [71].

1. **India**

Radiopharmaceuticals in India are primarily governed by the essential board of the Department of Atomic Energy, Government of India, known as AERB. AERB was recognized in November 1983 by the President of India, empowered by Section 27 of the Atomic Energy Act, 1962, to oversee various authoritarian and safety functions related to atomic energy. AERB's role is complemented by the Central Drug Standard Control Organization, operating under the Director General of Health Services, Ministry of Health and Family Welfare, Government of India. This organization regulates radiopharmaceuticals under the Drug and Cosmetic Act 1940 and its associated rules. It serves as a crucial national drug regulatory agency responsible for monitoring drugs and pharmaceuticals throughout India.

### While AERB and the Central Drug Standard Control Organization play vital roles in regulating radiopharmaceuticals, challenges have arisen within the nuclear medicine community due to certain notices issued by the Office of the Drug Controller General of India regarding the import of radiopharmaceuticals [72].

To support stakeholders, AERB provides various publications, including codes, guides, annual reports, newsletters, booklets, and the AERB bulletin. Meanwhile, under the same Department of Atomic Energy, BARC oversees the usage of radioactive materials and their development for medical applications. In India, the regulation of RPs falls under the authority of the "Atomic Energy Regulatory Board" (AERB), which operates as the supreme board under the "Department of Atomic Energy, Government of India". AERB was established in November 1983 through the President of India's exercise of powers granted by Section 27 of the Atomic Energy Act, 1962. AERB is responsible for carrying out various regulatory tasks and disseminating safety information in accordance with the provisions of the Atomic Energy Act, 1962. Its administrative role involves formulating rules and issuing notifications under both the Atomic Energy Act, 1962 and the Environment (Protection) Act, 1986. The Board of Radiation and Isotopic Studies (BRIT) operates as an autonomous division within the Government of India's Department of Atomic Energy (DAE) and serves the radiation and isotope-related needs within the country [73]. Working in collaboration with the RPs Division of the Bhabha Atomic Research Center (BARC) in Mumbai, BRIT is responsible for the development, production, and distribution of RPs to various nuclear medicine centers across India. BARC supplies radioisotopes produced by reactors to BRIT, where they are processed to create RPs for diverse applications in healthcare and industry. In February 2018, during the 78th Meeting of the Drugs Technical Advisory Board (DTAB) held at DGHS, Nirman Bhawan in New Delhi, the establishment of a dedicated wing at the Central Drugs Standard Control Organization (CDSCO) was discussed. This proposed wing would collaborate with the DAE to enforce regulatory controls on RPs. The inclusion of RPs in the Indian Pharmacopeia-2014 involved extensive consultations with the Indian Pharmacopoeia Expert Committee on Radiopharmaceuticals (ECRP), resulting in the introduction of one general chapter and 19 monographs for RPs. An additional 10 RPs were added in the 2015 addendum, followed by three more in the 2016 addendum. The Indian Pharmacopeia 2018 saw the inclusion of three further radiopharmaceutical monographs [74, [75].

1. **USA**

The exploit of radiopharmaceuticals in the USA is governed by the Center for Drug Evaluation and Research (CDER), a division of the US Food and Drug Administration (FDA). Compared to other regulatory authorities, the US FDA has a well-established regulatory constitution for the use and control of radiopharmaceuticals, supported by extensive research in this field. The regulatory process begins during the development phase and continues throughout the lifecycle of the product through Adverse Drug Reaction (ADR) reporting. Prior to 1997, certain requirements were exempted by the FDA for PET drugs to focus on their development. However, with the commencement of the FDA Modernization Act (Public Law 105-115), section 21 of this act directed the FDA to establish an appropriate regulatory approval process, along with CGMPs, for PET drugs. In 2009, the US FDA published the PET Drugs-Current Good Manufacturing Practices (Small Entity Compliance Guide). Over time, various significant regulatory guidelines have been developed, addressing matters related to New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA), including their contents and formats. Recently, the US FDA has introduced guidelines specifically addressing the compounding and repacking of radiopharmaceuticals by contract agencies and state-licensed nuclear pharmacies [76, 77].

### European Union

### Throughout Europe, each member state has possession of regulatory agenda for handling radiopharmaceuticals. The European Medicine Agency (EMA) plays a crucial role as the primary medicine regulatory authority overseeing medicines across the region. As a regionalized authority of the European Union (EU), the EMA is accountable for the scientific estimation, control, and security supervision of medicines within the EU. Within the EMA, the Committee for Medicinal Products for Human Use has established a dedicated radiopharmaceuticals drafting group. This group is entrusted with the accountability of creating guidelines specifically related to radiopharmaceuticals. Over time, the EMA has released various guidelines covering a range of topics, including Good Radio Pharmacy Practice, Early Phase Clinical Trials, Good Manufacturing Practices, and Clinical Evaluation, as well as Regulations on Market Authorization for Radiopharmaceuticals. During the developmental phase, the EMA has addressed issues related to radiopharmaceuticals in its Guidelines on Investigational Medicinal Product Dossier. Additionally, the EMA has set forth stringent Guidelines on Package Leaflet and core Summary of Product Characteristics (SmPC) for radiopharmaceuticals. These guidelines offer comprehensive guidance to marketing authorization holders and regulators, outlining the essential information that should be included in the SmPC for radiopharmaceuticals [78].

1. **Regulatory challenges for RPs in India:**

India's growing demand for RPs necessitates a robust regulatory framework. Initially, the production of RPs was primarily undertaken by the Radiation Medicine Centre (RMC) of BARC at Tata Memorial Centre, Parel, and the Institute of Nuclear Medicine and Allied Science (INMAS) of the Defense Research and Development Organization (DRDO). To regulate RPs, BARC has been assigned the responsibility through the Radiopharmaceutical Committee (RPC), with representation from CDSCO. However, the existing regulatory arrangement has certain contradictions and gaps, which complicate matters and discourage investment in the radiopharmaceutical sector. One major challenge in Indian regulations is that RPs is exempted from the purview of the D & C Act of 1940 and the associated rules, which apply to other drug and cosmetic products. RPs is listed under Schedule K of the Act, exempting them as a class from the provisions of Chapter IV and related rules governing their manufacture and sale [79]. However, in the 21st century, private players, including health facilities with hospital cyclotrons, have entered the market, necessitating amendments to accord full drug status to RPs due to their expanding roles in diagnosis and treatment. Currently, manufacturing permission must be obtained from AERB, while DCGI approval is required to launch the product in the Indian market. RPs has now been officially recognized through the inclusion of various monographs in the Indian Pharmacopoeia over the past decade. However, the non-implementation by drug control organizations remains a significant ambiguity that requires urgent attention. The lack of coordination between nuclear regulators (AERB) and pharmaceutical regulators (CDSCO), who have attempted to exercise regulatory control over RPs in recent times, has had far-reaching consequences within the nuclear medicine community. The guidelines governing RPs in India require clear data to initiate preclinical and clinical studies, clinical trials, and various bioavailability and bioequivalence assessments [80].

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**Figure 1. The approval procedure of RPs in India 81**

1. **The Regulatory Requirement for Radiopharmaceutical Handling**

Individuals responsible for managing radioactive substances in medical applications must possess a comprehensive understanding of the legal guidelines outlined in the Atomic Energy (Radiation Protection) Rules, G. S. R. 303, 2004, the Atomic Energy (Safe Disposal of Radioactive Waste) Rules, G. S. R. 125, 1987, as well as stay updated with the Security directives regularly issued by relevant authorities and promptly adhere to any instructions issued by the competent authority [82].

**Some specific features of radiopharmaceuticals include the following aspects:**

* A straight forward distribution chain, where the finished product is directly delivered.
* Manufactured specifically for nuclear medicine departments.
* Small batch sizes.
* Short shelf life
* Quality control (QC) samples that represent the entire batch.
* Diagnostic radiopharmaceuticals are administered at micro-dose levels, often resulting in minimal remedial or toxic effects.
* These are sometimes dispensed earlier than all QC examinations are accomplished.
* Certain examinations, such as sterility testing, and post-release radionuclide purity testing, may be required.
* Hence, adhering to Good Manufacturing Practice (GMP) becomes crucial to reduce potential risks.
* Instrument and equipment qualification, along with the validation of methods and processes, are essential to show controlled handling of hazardous elements [83, 84].
1. **The Regulatory Requirement for Radiopharmaceutical Disposal**

In India, it is essential to conduct exhaustive and unswerving research on the accessible guidelines of the "Atomic Energy Regulatory Board" (AERB) concerning the proper dumping of radiopharmaceuticals. AERB is the primary regulatory authority for Radiopharmaceuticals in India and operates under the Department of Atomic Energy (DAE) of the Government of the Republic of India [85]. To ensure effective regulation of radio-pharmaceuticals in the country, AERB has established mandatory requirements through various guidelines. Regarding clearance, the Atomic Energy Regulations, G. S. R. 125, 1987, and the code-named Radioactive Waste Management, 2007 have been issued. Additionally, Nuclear Medicine services have a security code issued in 2010 that covers the entire range of operations, from site consent to setup and the overall declassification process. AERB has also provided disposal provision and other pertinent guiding principle, though only some of these regulations specify the exact method of radiopharmaceutical disposal. However, they do conform to international standards [86].

**Table 1 Radiopharmaceuticals commercially available in India**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S.NO.** | **Radiopharmaceutical**  | **Manufacturer**  | **Trade name** | **Approved indications for adults use (pediatric usage as specified)** |
|  | Carbon-14- urea | Halyard Health | PYtest | Identification of gastric urease as a supportive measure for diagnosing H. pylori infection in the stomach [87] |
|  | Copper-64 dotatate | Curium  | Detectnet  | Recommended for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult patients [88] |
|  | Fluorine-18 florbetapir  | Life molecular imaging | Neuraceq  | Intended for PET imaging of the brain in adult patients with cognitive impairment, to assess β-amyloid neuritic plaque density during evaluation for Alzheimer's disease (AD) or other potential causes of cognitive decline [89] |
|  | Fluorine-18 florbetaben  | Eli Lilly | Tauvid | Recommended for PET imaging of the brain to check the density and distribution of aggregated tau neurofibrillary tangles (NFTs) in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) [89] |
|  | Fluorine-18 flucicovine  | Blue earth Diagnostics  | Axumin  | Recommended for positron emission tomography (PET) imaging in men [90] |
|  | Fluorine-18 fluoroestradiol | Zionexa  | CERIANNA | Recommended for PET imaging to detect estrogen receptor (ER)-positive lesions as a supplementary tool to biopsy in patients with recurrent or metastatic breast cancer [91] |
|  | Gallium-67 citrate | Curium  | - | Used in demonstration of presence of Hodgkin’s disease, lymphoma and bronchogenic carcinoma [92] |
|  | Gallium-68 dotatate | Advanced AcceleratorApplications  | NETSPOT | A radiopharmaceutical diagnostic agent recommended for both adult and pediatric patients, to be used in conjunction with positron emission tomography (PET) [93] |
|  | Indium-111 chloride | Curium  | - | Recommended for radiolabeling in the context of an in vivo diagnostic imaging procedure using ProstaScint [94] |
|  | Indium-111 oxyquinoline | BWXT/ GE Healthcare | - | Intended for the radiolabeling of autologous leukocytes, serving as a supplementary aid in identifying inflammatory processes that leukocytes migrate to, such as those related to abscesses or other infections [95]. |
|  | Indium-111 pentetate | GE Healthcare | - | Intended for radionuclide cisternography [95] |
|  | Indium-111 pentetreotide | Curium  | Octreoscan  | A radiopharmaceuticals intended for scintigraphic localization of somatostatin receptor-bearing primary and metastatic neuroendocrine tumors [96] |
|  | Iodine I-123 iobenquane | GE Healthcare | AdreView | Recommended as an addition to other diagnostic tests for the recognition of primary or metastatic pheochromocytoma [97] |
|  | Iodine I-123 ioflupane | Curium  | DaTscan  | Recommended as a supplementary aid to other investigative assessments for visualizing striatal dopamine transporter using SPECT brain imaging in adult patients [98] |
|  | Iodine I-125 human serum albumin | IsoTex Diagnostics  | Jeanatope  | Employed for the determining of total blood and plasma [99] |
|  | Iodine I-125 iothalamate | IsoTex Diagnostics  | Glofil-125  | Recommended for evaluation of glomerular filtration [100] |
|  | Iodine I-131 human serum albumin  | IsoTex Diagnostics  | Megatope  | Recommended for use in determination of Total blood and plasma volumes [101] |
|  | Lutetium Lu-177 dotatate | Advanced AcceleratorApplications | LUTATHERA  | Recommended for the cure of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [102] |
|  | Lutetium Lu- 177 vipivotide tetraxetan | Advanced AcceleratorApplications | Pluvicto  | In the treatment of adult patients with prostate-specific membrane antigen (PSMA)- positive metastatic castration-resistant prostate cancer (mCRPC) against androgen receptor (AR) and taxane- based chemotherapy [102] |
|  | Molybdenum Mo- 99 generator | Curium  | Ultra-TechneKow V4 | Formation of Tc-99m sodium pertechnetate for administration or radionuclide production [103] |
|  | Nitrogen-13 ammonia | Various  | - | For the diagnostic purpose in positron emission tomography (PET) imaging of the myocardium during rest or stress conditions [104] |
|  | Radium-223 dichloride | Bayer Healthcare pharmaceutical Inc. | Xofigo  | Induced for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease [105] |
|  | Strontium-89 chloride | Q Biomed | - | In painful skeletal metastases it is use to relief bone pain [106] |
|  | Technetium-99m bicisate | Lantheus Medical Imaging | Neurolite  | SPECT imaging as an adjunct to conventional CT or MRI imaging in the localization of stroke in patients [107] |
|  | Technetium-99m exametazime | DRAXIMAGE | - | In the detection of altered regional cerebral perfusion in stroke [108] |
|  | Technetium-99m macroaggregated albumin | Curium  | Pulmotech  | An adjunct in the assessment of pulmonary perfusion both in adults and pediatric [109] |

**RESULT AND DISCUSSION**

Radiopharmaceuticals have emerged as a prominent focus in the pharmaceutical industry, representing a hallmark of modern medicine and a high-tech sector. Their exponential growth can be accredited to their dual relevance as both diagnostic and advantageous agents. Traditionally, radiopharmaceuticals have been worn for diagnostic measures, but current research has expanded their exploitation as therapeutic agents as well. The worldwide radiopharmaceuticals market is primarily ambitious by an aging population and the prevalence of cardiovascular, oncological, and neurological disorders. Additionally, regulatory advancements now allow for the use of radiopharmaceuticals in pediatric populations, contributing to their widespread application. Continuous availability of radioisotopes and local production has fostered generous research on novel radiopharmaceuticals and a scuttle of products into the market. Nuclear imaging, offering non-invasive, static, and dynamic images of the body's organs, is the main application for most radiopharmaceuticals. Key players in the global radiopharmaceuticals market include Bayer Healthcare AG, Cardinal Health, Inc., GE Healthcare, IBA Molecular Imaging, Mallinckrodt PLC, Medtronic PLC, Nordion, Inc., Siemens Healthcare, and Jubilant Pharma. Market research forecasts by Transparency Market Research indicate a rapid expansion of the global radiopharmaceuticals market, with North America holding over 40% market share. Revisions are necessary in existing national laws and policies to establish a cohesive, inclusive, and internationally standardized framework for effectively managing regulatory issues related to the storage and dumping of radiopharmaceuticals. A primary focus should be directed towards exploring waste management options and seeking improved alternatives. To accomplish this, a detailed assessment of the annual nuclear medicine procedures conducted in India, along with the generated waste, must be undertaken. This evaluation will help understand the capacity of various hospitals in handling radiopharmaceutical waste, leading to the establishment of waste repositories at regional and national levels. To achieve this goal, researchers need to devise suitable synthesis reactions that enable stable binding of radionuclides to the selected natural compounds.

**CONCLUSION**

In the present era, a wide array of radiopharmaceuticals is available, playing a crucial role in disease diagnosis. Notably, the field of nuclear medicine has witnessed remarkable growth with the introduction of novel radionuclides and radiopharmaceuticals for treating conditions such as metastatic bone pain, neuroendocrine tumors, and others. This exciting phase has positioned radionuclide therapy for even more substantial advancement in the years ahead.

However, the escalating demand for radiopharmaceuticals has exposed the necessity for a robust regulatory framework that expedites their journey from laboratory development to bedside application. Unfortunately, the current regulatory setup is fraught with shortcomings, making it perplexing for manufacturers and investigators to invest in the radiopharmaceutical domain. To address these issues effectively, it is imperative to establish a powerful regulatory structure that facilitates the swift and secure transition of radiopharmaceuticals from research to clinical use. Additionally, radiation safety and associated risks need to be addressed adequately. In India, radiopharmaceuticals fall under Schedule K of the Drug and Cosmetic Act 1940, which exempts them from certain provisions. However, it is essential to thoroughly regulate radiopharmaceuticals to maintain their safety and efficacy. Developing explicit, evidence-based guidelines will significantly enhance the healthcare process and outcomes. These guidelines will be grounded in rigorous scientific principles, ensuring the well-being of patients and healthcare personnel alike. By prioritizing a strong and comprehensive regulatory framework, we can foster progress and innovation in the radiopharmaceutical domain while guaranteeing the highest standards of patient and personnel health and safety. Additionally, we highlight the specific applications of radiopharmaceuticals in disease diagnosis. The field of nuclear medicine has experienced significant growth, primarily due to the introduction of various recent radionuclides and radiopharmaceuticals. The development of radiopharmaceuticals through radionuclides is currently in an exciting and critical phase, with even greater progress anticipated in the years to come. This evolution promises substantial advancements in the field of nuclear medicine, paving the way for better diagnostic and therapeutic options. Currently, the field of radionuclide therapy is in a captivating and dynamic phase, holding immense promise for substantial growth and advancement in the foreseeable future.

**FUTURE PROSPECTS**

Radiopharmaceutical is mounting into more vital field of medicine. There is a considerable increase in the global insist in radiopharmaceutical field, with the augment of disease related to cardiac, neurological and cancer disease. The global usage of radiopharmaceuticals has surged, with the total value of these drugs approaching $(US) 100,000,000 per year, and more than two-thirds of the production handled by private companies. The worldwide adoption of these drugs is escalating at a rate of 15 to 20% annually. This significant expansion highlights the critical role radiopharmaceuticals play in modern medicine. High effect 68Ga-labeled radiopharmaceuticals are anticipated in the near future. The pioneering radiopharmaceutical, iodine-131, was widely used in the late forties as a diagnostic tool for certain thyroid disorders. Its administration as an oral solution earned it the nickname "Atomic Cocktail" in the press. Since then, nuclear medicine has seen remarkable growth in most developed nations. Annually, around 10,000,000 people in the United States alone undergo diagnostic tests using radioactive drugs, whether in vivo or in vitro. In recent years, radiopharmaceuticals (RPs) have emerged as a crucial tool for both diagnosing and treating various medical conditions. These pharmaceuticals have not only found increasing use in diagnosing critical diseases but have also achieved significant success in therapeutically treating conditions like cancer, bone pain palliation from skeletal metastasis, and hyperthyroidism. Despite these recent advancements, there are certain challenges related to design and regulatory hurdles that need to be addressed to fully harness the potential of these agents. Regulatory authorities play a significant role in overseeing various aspects of RPs. Upon reviewing the available literature, it becomes evident that there is a pressing need to reassess the existing limited regulatory guidelines for RPs, especially in the context of India, where they remain insufficient compared to standards in the US and EU. To design more effective radiotherapeutic agents, close coordination between radiopharmaceutical industries, regulatory bodies, and nuclear medicine associations within each respective country is essential. Overall, the rise of radiopharmaceuticals has brought about significant advancements in medical diagnostics and treatment. However, to unlock their full potential, it is crucial to address regulatory gaps and foster collaboration among key stakeholders in the field of nuclear medicine.

**REFERENCES**

1. Cherry, S. R., Sorenson, J. A., Phelps, M. E., & ScienceDirect (Online service). (2003). *Physics in nuclear medicine* (Vol. 3). Saunders.
2. Payolla, F. B., Massabni, A. C., & Orvig, C. (2019). Radiopharmaceuticals for diagnosis in nuclear medicine: A short review. *Eclética Química*, *44*(3), 11-19.
3. Saha, G. B., & Saha, G. B. (1998). Radiopharmaceuticals and methods of radiolabeling. *Fundamentals of nuclear pharmacy*, 80-111.
4. Chakraborty, K., Mondal, J., An, J. M., Park, J., & Lee, Y. K. (2023). Advances in Radionuclides and Radiolabelled Peptides for Cancer Therapeutics. *Pharmaceutics*, *15*(3), 971.
5. Marengo, M., Martin, C. J., Rubow, S., Sera, T., Amador, Z., & Torres, L. (2022, March). Radiation safety and accidental radiation exposures in nuclear medicine. In *Seminars in Nuclear Medicine* (Vol. 52, No. 2, pp. 94-113). WB Saunders.
6. Ziessman, H. A., O'Malley, J. P., & Thrall, J. H. (2014). *Medicina nuclear*. Elsevier Brasil.
7. Othman, S. A., Bakar, N. F. A., Azman, N. F. A. N., & Jasrin, N. S. (2019, June). Future of nuclear medicine-an overview. In *IOP Conference Series: Materials Science and Engineering* (Vol. 555, No. 1, p. 012032). IOP Publishing.
8. Loveland, W. D., Morrissey, D. J., & Seaborg, G. T. (2017). *Modern nuclear chemistry*. John Wiley & Sons.
9. Duatti, A. (2009). Role of 99m Tc in diagnostic imaging. Chapter 1. In *Technetium-99m radiopharmaceuticals: Status and Trends*.
10. Yusof N.F. Indium-111. Chapter 7. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
11. Thakur, M. L. (1977). Gallium-67 and indium-111 radiopharmaceuticals. *The International journal of applied radiation and isotopes*, *28*(1-2), 183-201.
12. Hoffend, J., Mier, W., Schuhmacher, J., Schmidt, K., Dimitrakopoulou-Strauss, A., Strauss, L. G., ... & Haberkorn, U. (2005). Gallium-68-DOTA-albumin as a PET blood-pool marker: experimental evaluation in vivo. *Nuclear medicine and biology*, *32*(3), 287-292.
13. Lavender, J. P., Lowe, J., Barker, J. R., Burn, J. I., & Chaudhri, M. A. (1971). Gallium 67 citrate scanning in neoplastic and inflammatory lesions. *The British journal of radiology*, *44*(521), 361-366.
14. Salmanoglu, E., Kim, S., & Thakur, M. L. (2018, March). Currently available radiopharmaceuticals for imaging infection and the holy grail. In *Seminars in nuclear medicine* (Vol. 48, No. 2, pp. 86-99). WB Saunders.
15. Saufi N.M. Palladium-103. Chapter 2. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
16. Mat Radzi S.F. Strontium-89. Chapter 8. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
17. Nor Azman N.R. Rubidium-82. Chapter 9. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
18. Ferris, T., Carroll, L., Jenner, S., & Aboagye, E. O. (2021). Use of radioiodine in nuclear medicine—A brief overview. *Journal of Labelled Compounds and Radiopharmaceuticals*, *64*(3), 92-108.
19. Zulhazmi A.N. Lutetium- 177. Chapter 3. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
20. Ahmad Asri N.A. Iridium-192. Chapter 4. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
21. Nor Azman N.R. Carbon-11. Chapter 6. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
22. Baharuddin N.Q. Samarium-153. Chapter 1. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
23. Mohd Yusof N.M .Indium-111. Chapter 7. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
24. Mettler, F. A., & Guiberteau, M. J. (2018). *Essentials of Nuclear Medicine and Molecular Imaging E-Book*. Elsevier Health Sciences.
25. Ghazali A.I. Iodine 123. Chapter 13. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
26. Mustafha, S.K. Iodine-125. Chapter 14. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
27. Malike, S.S. Iodine-131. Chapter 15. In *Applications of Radiopharmaceutical in Nuclear Medicine*.
28. Stokke, C., Kvassheim, M., & Blakkisrud, J. (2022). Radionuclides for targeted therapy: Physical properties. *Molecules*, *27*(17), 5429.
29. Bakker, C. J. (1955). Production and physical properties of radioisotopes. *Recueil des Travaux Chimiques des Pays‐Bas*, *74*(3), 281-293.
30. Khan, N. T. (2017). Radioisotopes and their biomedical applications. *J. Biomol. Res. Ther*, *6*, 156.
31. Dash, A., Pillai, M. R. A., & Knapp, F. F. (2015). Production of 177 Lu for targeted radionuclide therapy: available options. *Nuclear medicine and molecular imaging*, *49*, 85-107.
32. Kim, Y. S., & Brechbiel, M. W. (2012). An overview of targeted alpha therapy. *Tumor biology*, *33*, 573-590.
33. Brandt, M., Cardinale, J., Aulsebrook, M. L., Gasser, G., & Mindt, T. L. (2018). An overview of PET radiochemistry, part 2: Radiometals. *Journal of Nuclear Medicine*, *59*(10), 1500-1506.
34. Malley, M. C. (2011). *Radioactivity: a history of a mysterious science*. OUP USA.
35. L'Annunziata, M. F. (2016). *Radioactivity: introduction and history, from the quantum to quarks*. Elsevier.
36. Wells, R. G. (2016). Instrumentation in molecular imaging. *Journal of Nuclear Cardiology*, *23*, 1343-1347.
37. Townsend, D. W. (2008, August). Combined positron emission tomography–computed tomography: the historical perspective. In *Seminars in Ultrasound, CT and MRI* (Vol. 29, No. 4, pp. 232-235). WB Saunders.
38. Sharma, P., & Mukherjee, A. (2016). Newer positron emission tomography radiopharmaceuticals for radiotherapy planning: an overview. *Annals of translational medicine*, *4*(3).
39. Rothchild, S. (1973). Radioactive drugs in clinical medicine. *Div. Of Research and Laboratories, IAEA*.
40. Akgun, E., Ozgenc, E., & Gundogdu, E. (2021). Therapeutic Applications of Radiopharmaceuticals: An Overview. *FABAD Journal of Pharmaceutical Sciences*, *46*(1), 93-104.
41. Munjal, A., & Gupta, N. (2020). Radiopharmaceuticals.
42. Jalilian, A. R., Beiki, D., Hassanzadeh-Rad, A., Eftekhari, A., Geramifar, P., & Eftekhari, M. (2016, July). Production and clinical applications of radiopharmaceuticals and medical radioisotopes in Iran. In *Seminars in Nuclear medicine* (Vol. 46, No. 4, pp. 340-358). WB Saunders.
43. Vermeulen, K., Vandamme, M., Bormans, G., & Cleeren, F. (2019, September). Design and challenges of radiopharmaceuticals. In *Seminars in nuclear medicine* (Vol. 49, No. 5, pp. 339-356). WB Saunders.
44. Pelletier-Galarneau, M., Sogbein, O. O., Dinh, L., & Zuckier, L. S. (2015). Superiority of digital subtraction for analysis of simultaneously-acquired dual-radiopharmaceutical parathyroid scintigraphy. *Open Journal of Medical Imaging*, *5*(02), 42.
45. Nurhidayah, W., Setyawati, L. U., Daruwati, I., Gazzali, A. M., Subroto, T., & Muchtaridi, M. (2022). Future prospective of radiopharmaceuticals from natural compounds using iodine radioisotopes as theranostic agents. *Molecules*, *27*(22), 8009.
46. Alsharef, S., Alanazi, M., Alharthi, F., Qandil, D., & Qushawy, M. (2020). Review about radiopharmaceuticals: preparation, radioactivity, and applications. *Int J App Pharm*, *12*(3), 8-15.
47. Cooper, J. F. (1981). Preparation and Control of Radiopharmaceuticals in Hospitals: K. Kristensen. Vienna, International Atomic Energy Agency, 1979, 119 pp, Austrian Schillings 185.
48. Hu, J., Li, H., Sui, Y., & Du, J. (2022). Current status and future perspective of radiopharmaceuticals in China. *European Journal of Nuclear Medicine and Molecular Imaging*, *49*(8), 2514-2530.
49. Dobrescu, L., Stanciu, S., Pleșca, C., & Ropot, A. (2017). Towards an integrated medical system for radiological medical imaging investigations. *Res J Med Med Sci*, *120*, 5.
50. Akgun, E., Ozgenc, E., & Gundogdu, E. (2021). Therapeutic Applications of Radiopharmaceuticals: An Overview. *FABAD Journal of Pharmaceutical Sciences*, *46*(1), 93-104.
51. Ferris, T., Carroll, L., Jenner, S., & Aboagye, E. O. (2021). Use of radioiodine in nuclear medicine-A brief overview. *Journal of Labelled Compounds and Radiopharmaceuticals*, *64*(3), 92-108.
52. Hung, J. C., Ponto, J. A., Gadient, K. R., Frie, J. A., Aksamit, C. M., Enquist, C. L., & Carrels, K. E. (2004). Deficiencies of product labeling directions for the preparation of radiopharmaceuticals. *Journal of the American Pharmacists Association*, *44*(1), 30-35.
53. Lange, R., ter Heine, R., Decristoforo, C., Peñuelas, I., Elsinga, P. H., van der Westerlaken, M. M., & Hendrikse, N. H. (2015). Untangling the web of European regulations for the preparation of unlicensed radiopharmaceuticals: a concise overview and practical guidance for a risk-based approach. *Nuclear medicine communications*, *36*(5), 414-422.
54. Ziessman, H. A., O’Malley, J. P., Thrall, J. H. (eds.). Radiopharmaceuticals, In: Nuclear Medicine, 4th ed., W. B. Saunders: Philadelphia, USA, 2014, ch. 1.
55. Othman, S. A., Bakar, N. F. A., Azman, N. F. A. N., & Jasrin, N. S. (2019, June). Future of nuclear medicine-an overview. In *IOP Conference Series: Materials Science and Engineering* (Vol. 555, No. 1, p. 012032). IOP Publishing.
56. Owunwanne, A., Patel, M., Sadek, S., Owunwanne, A., Patel, M., & Sadek, S. (1995). Ideal characteristics of radiopharmaceuticals. *The Handbook of Radiopharmaceuticals*, 16-17.
57. Payolla, F. B., Massabni, A. C., & Orvig, C. (2019). Radiopharmaceuticals for diagnosis in nuclear medicine: A short review. *Eclética Química*, *44*(3), 11-19.
58. Willowson, K. P. (2019). Production of radionuclides for clinical nuclear medicine. *European Journal of Physics*, *40*(4), 043001.
59. Cherry, S. R., Sorenson, J. A., Phelps, M. E., & ScienceDirect (Online service). (2003). *Physics in nuclear medicine* (Vol. 3). Saunders.
60. Crestoni, M. E. (2018). Radiopharmaceuticals for diagnosis and therapy.
61. Del Guerra, A., & Panetta, D. (2019). Fundamentals of Natural and Artificial Radioactivity and Interaction of Ionizing Radiations with Matter. *Nuclear Medicine Textbook: Methodology and Clinical Applications*, 3-19.
62. Magill, J., & Galy, J. (2005). *Radioactivity, radionuclides, radiation* (Vol. 259). Berlin: Springer.
63. Santos-Oliveira, R., Smith, S. W., & Carneiro-Leão, A. M. A. (2008). Radiopharmaceuticals drug interactions: a critical review. *Anais da Academia Brasileira de Ciências*, *80*, 665-675.
64. Satav, K.R., Shangrapawar, T.P., Bhosle A. (2019). Illustrative Review on Radiopharmaceuticals, *International Journal of Trend in Scientific Research and Development*, 4(1).
65. International Atomic Energy Agency (IAEA). Operational guidance on hospital radiopharmacy : a safe and effective approach. Vienna: International Atomic Energy Agency, 2008. ISBN 978-92-0-106708-1.
66. Malley, M. C., Radioactivity: a history of a mysterious science, Oxford University Press, New York, 2011, ISBN 978-0-19-976641-31.
67. Khan, S., Syed, A. T., Ahmad, R., Rather, T. A., Ajaz, M., & Jan, F. A. (2010). Radioactive waste management in a hospital. *International journal of health sciences*, *4*(1), 39.
68. Meher, B. R. (2020). Inclusion of radiopharmaceuticals in the Indian pharmacopeia: A step forward. *Indian Journal of Nuclear Medicine: IJNM: The Official Journal of the Society of Nuclear Medicine, India*, *35*(1), 1.
69. Keresztes, A., Borics, A., & Tömböly, C. (2015). Therapeutic and diagnostic radiopharmaceuticals.
70. Kar, N. R. (2019). Production and Applications of Radiopharmaceuticals: A Review. *International Journal of Pharmaceutical Investigation*, *9*(2).
71. Sharma, S., Baldi, A., & Sharma, R. K. (2017). Radiopharmaceuticals regulations on bioavailability and bioequivalence: present status and future requirements. *Mod. Appl. Bioequiv. Bioavail*, *1*, 1-4.
72. Sharma, S., Baldi, A., Singh, R. K., & Sharma, R. K. (2018). Drafting of comprehensive harmonized regulatory guideline for storage and disposal of radiopharmaceuticals. *Journal of Drug Delivery and Therapeutics*, *8*(6-s), 279-286.
73. Sharma, S., Baldi, A., Singh, R. K., Sharma, R. K., & Sharma, R. K. (2018). Regulatory framework of radiopharmaceuticals: current status and future recommendations. *Res J Life Sci Bioinform Pharm Chem Sci*, *4*, 275-90.
74. Sharma, S., Jain, S., Baldi, A., Singh, R. K., & Sharma, R. K. (2019). Intricacies in the approval of radiopharmaceuticals–regulatory perspectives and the way forward. *Current Science*, *116*(1), 47-55.
75. Le, D. (2022). Regulatory Oversight of Radiopharmaceuticals. In *Radiopharmaceuticals in the Management of Leptomeningeal Metastasis* (pp. 199-213). Cham: Springer International Publishing.
76. Drozdovitch, V., Brill, A. B., Callahan, R. J., Clanton, J. A., DePietro, A., Goldsmith, S. J., & Simon, S. L. (2015). Use of radiopharmaceuticals in diagnostic nuclear medicine in the United States: 1960–2010. *Health physics*, *108*(5), 520.
77. Haswika, R. and Vinod K. (2022). A review on regulatory framework of radiopharmaceuticals in pharmaceutical industry: current scenario and future aspects. *International Journal of Pharmaceutical Science and Research*, 13(4): 1499-1507.
78. Boschi, S., & Todde, S. (2023). Radiopharmaceutical need between the clinic and regulatory agencies: how philosophy could explain'the road taken'. *European Journal of Nuclear Medicine and Molecular Imaging*, 1-4.
79. Lika, S. A., Idrizi, E. A., Bexheti, D., Dauti, M., & Ivanovska, E. J. Overview of the Regulatory Framework for Radiopharmaceuticals.
80. Kristensen, K. (1992). European regulations and guidelines for the registration of radiopharmaceuticals. In *Progress in Radiopharmacy* (pp. 171-180). Dordrecht: Springer Netherlands.
81. Kaushik, D., Jangra, P., Verma, R., Purohit, D., Pandey, P., Sharma, S., & Sharma, R. K. (2021). Radiopharmaceuticals: An insight into the latest advances in medical uses and regulatory perspectives. *Journal of Biosciences*, *46*, 1-25.
82. Kumar, R., Kalaiselvan, V., Kumar, R., Verma, R., & Singh, G. N. (2016). Pharmacovigilance in radiopharmaceuticals. *Indian journal of nuclear medicine: IJNM: the official journal of the Society of Nuclear Medicine, India*, *31*(2), 89.
83. Debnath, S., & Babu, M. N. (2015). Radiopharmaceuticals and their therapeutic applications in health care system. *Asian Journal of Research in Pharmaceutical Science*, *5*(4), 221-226.
84. Ercan, M. T., & Caglar, M. (2000). Therapeutic radiopharmaceuticals. *Current pharmaceutical design*, *6*(11), 1085-1121.
85. Salvadori, P. A. (2008). Radiopharmaceuticals, drug development and pharmaceutical regulations in Europe. *Current Radiopharmaceuticals*, *1*(1), 7-11.
86. Wadsak, W., & Mitterhauser, M. (2010). Basics and principles of radiopharmaceuticals for PET/CT. *European journal of radiology*, *73*(3), 461-469.
87. Dahl, K., Halldin, C., & Schou, M. (2017). New methodologies for the preparation of carbon-11 labeled radiopharmaceuticals. *Clinical and Translational Imaging*, *5*, 275-289.
88. Jalilian, A. R., & Osso Jr, J. (2017). The current status and future of theranostic Copper-64 radiopharmaceuticals. *Iranian Journal of Nuclear Medicine*, *25*(1), 1.
89. Goud, N. S., Joshi, R. K., Bharath, R. D., & Kumar, P. (2020). Fluorine-18: A radionuclide with diverse range of radiochemistry and synthesis strategies for target based PET diagnosis. *European Journal of Medicinal Chemistry*, *187*, 111979.
90. Romagnolo, C., Cottignoli, C., Palucci, A., Biscontini, G., Fringuelli, F. M., & Burroni, L. (2021). Pictorial essay: incidental findings on 18 F-fluciclovine PET/CT scan. *Clinical and Translational Imaging*, *9*, 189-198.
91. Zhou, D., Lin, M., Yasui, N., Al‐Qahtani, M. H., Dence, C. S., Schwarz, S., & Katzenellenbogen, J. A. (2014). Optimization of the preparation of fluorine‐18‐labeled steroid receptor ligands 16alpha‐[18F] fluoroestradiol (FES),[18F] fluoro furanyl norprogesterone (FFNP), and 16beta‐[18F] fluoro‐5alpha‐dihydrotestosterone (FDHT) as radiopharmaceuticals. *Journal of Labelled Compounds and Radiopharmaceuticals*, *57*(5), 371-377.
92. Kolenc Peitl, P., Rangger, C., Garnuszek, P., Mikolajczak, R., Hubalewska‐Dydejczyk, A., Maina, T., & Decristoforo, C. (2019). Clinical translation of theranostic radiopharmaceuticals: Current regulatory status and recent examples. *Journal of Labelled Compounds and Radiopharmaceuticals*, *62*(10), 673-683.
93. L’Annunziata, M. F., Radioactivity: introduction and history, from the quantum to quarks, Elsevier, 2nd ed., 2016. eBook ISBN: 9780444634962.
94. Mettler, F. A., & Guiberteau, M. J. (2018). *Essentials of Nuclear Medicine and Molecular Imaging E-Book*. Elsevier Health Sciences.
95. Nurhidayah, W., Setyawati, L. U., Daruwati, I., Gazzali, A. M., Subroto, T., & Muchtaridi, M. (2022). Future prospective of radiopharmaceuticals from natural compounds using iodine radioisotopes as theranostic agents. *Molecules*, *27*(22), 8009.
96. RADIOISOTOPES, I., & No, R. S. (2021). Guidance for Preclinical Studies with Radiopharmaceuticals. International Atomic Energy Agency. 4-11.
97. Radvanyi, P., & Villain, J. (2017). The discovery of radioactivity. *Comptes Rendus Physique*, *18*(9-10), 544-550.
98. Ramamoorthy, N. (2018). Impact of nuclear medicine and radiopharmaceuticals on health-care delivery: Advances, lessons, and need for an objective value-matrix. *Indian Journal of Nuclear Medicine: IJNM: The Official Journal of the Society of Nuclear Medicine, India*, *33*(4), 273.
99. Rothchild, S. (1973). Radioactive drugs in clinical medicine. *Div. Of Research and Laboratories, IAEA*.
100. Saha, G. B., & Saha, G. B. (1992). Uses of radiopharmaceuticals in nuclear medicine. *Fundamentals of Nuclear Pharmacy*, 227-304.
101. Saha, G. B., & Saha, G. B. (1998). Radiopharmaceuticals and methods of radiolabeling. *Fundamentals of nuclear pharmacy*, 80-111.
102. Banerjee, S., Pillai, M. R. A., & Knapp, F. F. (2015). Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications. *Chemical reviews*, *115*(8), 2934-2974.
103. Ahmad, M., Vandegrift, G., & Cristini, P. (2014). Molybdenum-99 (99 Mo): past, present, and future. *Science and Technology of Nuclear Installations*, *2014*.
104. Saha, G. B., MacIntyre, W. J., & Go, R. T. (1992, July). Cyclotrons and positron emission tomography radiopharmaceuticals for clinical imaging. In *Seminars in nuclear medicine* (Vol. 22, No. 3, pp. 150-161). WB Saunders.
105. Salmanoglu, E., Kim, S., & Thakur, M. L. (2018, March). Currently available radiopharmaceuticals for imaging infection and the holy grail. In *Seminars in nuclear medicine* (Vol. 48, No. 2, pp. 86-99). WB Saunders.
106. Bauman, G., Charette, M., Reid, R., Sathya, J., & of Cancer, T. R. G. G. (2005). Radiopharmaceuticals for the palliation of painful bone metastases—a systematic review. *Radiotherapy and oncology*, *75*(3), 258-E1.
107. Boschi, A., Martini, P., Pasquali, M., & Uccelli, L. (2017). Recent achievements in Tc-99m radiopharmaceutical direct production by medical cyclotrons. *Drug development and industrial pharmacy*, *43*(9), 1402-1412.
108. Duatti, A. (2009). Role of 99m Tc in diagnostic imaging. Chapter 1. In *Technetium-99m radiopharmaceuticals: Status and Trends.*