**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 Molecular Imaging and Nuclear Medicine within the Indian market. However, in spite of these developments, there are certain regulatory challenges. The Drugs & Cosmetic Act of 1940 and its associated rules, which govern the pharmaceutical industry in India, 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 objective of this study is to develop inclusive regulatory guiding principle for the storage and dumping of radiopharmaceuticals that align with global standards. To achieve this, a meticulous methodology was adopted, involving an extensive examination of existing guidelines provided by the Atomic Energy Regulatory Board (AERB) specifically focusing on storing and disposing of radiopharmaceuticals in India**.** The aim was to identify and incorporate various parameters that may not have been explicitly covered within the existing guidelines. 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. This makes it possible to evaluate the heart, kidney, lung, thyroid, and blood circulation functions. Radiopharmaceuticals are used in the therapeutic modality to treat diseases like cancer and hyperactive thyroid glands. They target the damaged area and help with treatment by delivering a concentrated, high dosage of radiation to the sick organ [2]. 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. They should be sterile, pyrogen-free, and subject to all quality control checks necessary for a conventional medicine because they are provided to humans. 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. To enable precise targeting inside the body, this radionuclide is combined with a non-radioactive component, such as a biologically active substance, medication, or cell. 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 suitability of a particular radiopharmaceutical depends on both the radioisotope and the ligand. An ideal radiopharmaceutical should exhibit selective concentration in the target organ with rapid clearance from surrounding tissues (e.g., blood), ensuring a high target-to-background ratio [2].

For diagnostic imaging, the preferred isotope is a gamma or positron emitter, as their emissions are capable of penetrating the body and can be detected externally by imaging equipment. Additionally, the isotope should have a short half-life to minimize radiation exposure to the patient. For diagnostic imaging, the preferred isotope is a gamma or positron emitter, as their emissions are capable of penetrating the body and can be detected externally by imaging equipment. Additionally, the isotope should have a short half-life to minimize radiation exposure to the patient. The target tissue or organ can learn important things about itself from this radiation. In contrast, the radiopharmaceutical's pharmaceutically active component is in charge of identifying the precise activity within the body, enabling a more precise diagnosis and evaluation of the medical condition. These elements combine to produce effective molecular imaging and accurate medicinal therapies. Mili Curie (mCi) or Mega Becquerel (MBq) units are frequently used to express radioactivity in radiopharmaceuticals, with 1 mCi equal to 37 MBq.

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 [2,4]. 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 [2,5]. In contrast, radioactive compounds lack any therapeutic effect themselves; instead, they are used for diagnostic purposes and medical imaging.

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. The chemical characteristics of stable isotopes of an element are the same for radioactive isotopes, also referred to as radioisotopes [7,8]. 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 label. The use of radioactive tracers is highly valuable in scientific research, medicine, and various industries. By incorporating these tracers into compounds, scientists can monitor their movement and behavior within biological systems or chemical reactions. This enables researchers to pursue the paths of biochemical reactions, study metabolic processes, and understand how substances are distributed within organisms. Radioisotopes 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. It can lower the patient's exposure to radiation, resulting in less tissue damage. Technetium-99m was produced by its generators, which greatly influenced its use in radioactive medicines. It is widely applied in the medical field. Gamma rays with energy of 140 keV or greater are suitable for use as radioactive tracers in diagnosis. In addition to being used to picture the skeleton, techenetium-99m can moreover be used to image the brain, liver, lungs, thyroid, spleen, gall bladder, and bone marrow. 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. **Indium (111In) compounds**

Indium-111 has an estimated physical half-life of 67 hours, but the majority of earlier work on the synthesis of radioactive indium compounds for medicinal uses used a generator that produced indium-113. Additionally, it possesses the proper gamma photon energies (173 keV-89% and 247 keV-94%) enabling detection from outside utilizing detectable equipment that is readily available for purchase. Imaging investigations employ 67GaIndium-based radiopharmaceuticals to evaluate diseases such infection, inflammation, and tumor location. Although indium co-precipitates with the much less poisonous ferric hydroxide, indium hydroxide is nonetheless exceedingly hazardous. Consequently, carrier-free Colloidal ferric hydroxide that has been tin-labeled has been utilized for lymph node scanning. Per gramme of an excised lymph node, more than 20% of the given dose had been accumulated. Larger particles, called macro aggregates, are generated when the iron concentration and pH of the solution are elevated. These aggregates are stabilized with gelatin and have been utilized for lung scintigraphy.

**a. 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. Since none of the compounds created with Indium-111 for use in living organisms are naturally present in the body, it is expected that they will behave differently in living organisms than chelating agents (perform several roles: have suitable functional groups in their molecules, maintain biological activity even during complex formation, carry a significant part of the radioactivity injected .

**b. 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.

**c. 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. Bleomycin must first combine with a radionuclide that has sufficient thermodynamic stability to allow it to transport radioactivity to the target. Second, the biological characteristics of the original organic molecule should be carried over into the newly created compound.Two other crucial requirements must be met, though. Bleomycin must first combine with a radionuclide that has sufficient thermodynamic stability to allow it to transport radioactivity to the target. Second, the biological characteristics of the original organic molecule should be carried over into the newly created compound .

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

Tl-201 is effective in separating benign from malignant bone lesions. Tl-201 uptake and chemotherapy response have been originate 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**

67Ga-citrate was one of the first radiopharmaceuticals used for infection scintigraphy. 67Ga-citrate mostly adheres with the iron-binding proteins lactoferrin, ferritin, and  bacterial siderophores after being injected intravenously (i.v.). A significant portion is excreted by the kidneys in the first 24 hours after injection, and a relatively small amount is eliminated by the intestines in the first week. 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.

For the first half of the 20th era, rays were injected into the prostate gland using 15 different procedures. These treatments have a meager amount of success. Pd-103 applications were employed as prostate cancer seeds. What patients can anticipate from Palladium-103 brachytherapy or seed implantation for prostate cancer was the subject of a study. Prostate cancer is treated by directly implanting radioactive Palladium-103 or Iodine-125 seeds into the prostate gland. For this treatment, surgery is required. The metal platinum group included the uncommon element palladium. The neutron from palladium-102 was absorbed to create palladium-103. It was Pd-102 decay caused by electron capture. Pd-103 applications were employed as prostate cancer seeds. What patients can anticipate from Palladium-103 brachytherapy or seed insertion for prostate cancer was the subject of a study. A radioactive seed of Palladium-103 or Iodine-125 is injected straight into the prostate gland as a therapy for prostate cancer. For this sort of therapy, surgery is required. Either preloaded needles or needles that had been loaded with a special "gun" were used to advance. Both of these seeds emit low-energy X-rays, and the vast majority of the radioactivity is emitted within a short amount of time [15].

1. **Strontium- 89**

Strontium 89 is frequently administered to cancer patients whose disease progresses to bone metastases. When cancer cells separate from the primary tumor and migrate to the bones, they undergo a process known as bone metastasis. Patients discovered that their customers had positive opinions about the product. With a half-life of 50.5 days, beta emission is produced as strontium-89 decays. The average decay energy is 0.58 MeV, and the highest beta energy is 1.463 MeV, or 100%. A common treatment for the bone pain that some cancers cause is strontium-89. The cancerous bone tissue will absorb strontium-89 and release radiation that helps to relieve pain. The prescription will be administered, either directly or indirectly, by a doctor with extensive preparation in nuclear medicine or radiation oncology. 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. The exact mechanism of action of strontium-89 is unknown; some think local irradiation prevents the tumour from generating pain-causing enzymes, while others think it might function by inhibiting tumour growth.

Despite the fact that strontium 89 could lessen pain, it could not treat cancer. A dose injected into a metastatic bone lesion will stay there for roughly two weeks longer than in normal bones. In patients with significant skeletal metastases, more than half of the dose will be retained in the bones. Two ways that strontium 89 leaves the human body are through the urine and through the excrement. Two thirds of the dose will be eliminated by the urinary system, and the residual one third will be eliminated via faeces. Patients without bone lesions often excrete through the urine, and the first two days following the injection are the most significant for urinary excretion. With minimal radiation exposure to the soft tissue surrounding the bone lesions, strontium 89 emits beta and selectively irradiates regions of metastatic bone involvement. An injection of Metastron single dose has been shown to relieve a higher percentage of pain than a particular injection of a placebo in a multicenter Canadian placebo-controlled trial involving 126 participants [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. A few examples of Rb-82's importance in nuclear medicine include maintaining a hygienic and pyrogen-free eluate for secure intravenous injection, having a sufficient priced supply of Sr-82, 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 extended elution volumes. Intravascular ultrasound [IVUS] and optical coherence tomography are two examples of advanced intracoronary imaging techniques that offer superior sensitivity for the exposure of cardiac allograft vasculopathy (CAV), but their application is constrained by high cost, a lack of expertise, and their limited ability to assess 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. A radioactive detector can be used as a backup strategy in a commercial Rb-82 generator to integrate the supplied dose of Rb-82 and to electronically activate a shutdown or bypass valve to halt the infusion of radioactivity at the desired level. Rubidium is expelled, and concentrated urine is an excellent measure of rubidium exposure. Due to the incidence of rubidium salts in the bodily fluids, the acid poisons pouring out of the tumour mass were neutralized and made harmless. Rubidium levels in whole blood are significantly lower in colorectal patients than they are in patients who are healthy controls. The tumor has sequestered the rubidium, so there is little of it in the patient's serum or urine. Because it is the second large electropositive metal, intended in radiology because it is non-toxic and has no recognized biological functions. 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. The iodine isotopes will be transported to the target using natural substances functioning as pharmacotherapeutic agents. The resultant radiation emitted by these iodine isotopes will then serve as a versatile tool for either diagnosis or treatment. Iodine-125 Iothalamate sodium is used in diagnostic techniques to assess kidney filtration rates and analyze deep vein thrombosis within the leg [18,19]. Additionally, it is frequently employed in radioimmuno assays to reveal the presence of hormones at minuscule amounts. Chemical element iodine has an atomic number of 53. It is a halogen and significantly heavier. In the halogen family, it is the heaviest member. 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. Iodine-123 is used in nuclear medicine for pheochromocytoma, carcinoid tumours, no secreting paragangliomas, and neuroblastoma, which is examined with an injection of iobenguane. Iodine is renowned for its usage in thyroid metastases and thyroid gland imaging. Iodine is consumed as a solution and capsule of sodium iodide. Each of the many follicles that make up the thyroid gland is coated by colloid-filled epithelial cells [18].

Thyroglobulin, the building block for the synthesis and storage of thyroid hormones, makes up colloid. In taken iodine is absorbed by the blood, where it oxidises and interacts with tyrosine residues in thyroglobulin to produce thyroid hormone, which is then deposited in the colloid. Through a feedback mechanism, the hypothalamic-pituitary axis regulates the thyroid gland. Thyrotropin-releasing factor, which is secreted by the brain as thyroid hormone levels fall, causes the anterior pituitary to release Thyroid Stimulating Hormone (TSH), which in turn initiates the thyroid gland to create more thyroid hormone. When there is an overabundance of a hormone, the thyroid hormone creates a negative feedback loop that lowers thyroid hormone synthesis and raises TSH levels. A patient is given the capsule to check their thyroid function. The patient's capsule is counted as the standard count for radioactive iodine uptake tests (RAIU). The thyroid gland count for the patient is compared to the typical count. Every capsule that is administered raises the bar. The gastrointestinal tract quickly absorbs the radioiodine at a rate of 5% per minute. Depending on whether food is available, the absorption takes between one and two hours to complete. The majority of the radioiodine is eliminated within 24 hours after being broadly dispersed throughout the body. The thyroid gland is where the residue is concentrated. The thyroid gland is a crucial organ for radioiodine to function. The supplied radionuclide and gland uptake determine how much radiation is delivered to the gland, other organs, and the entire body. The thyroid gland absorbs 13 Rad of radiation from iodine-123 as opposed to the body as a whole, which receives 0.029 Rad. The given activity of iodine-123 is 200–400 Ci. It is consumed orally, and the 24-hour imaging period follows the dose. The dosage for the thyroid is 0.013 Ci. Due to the radioiodine's short half-life, there are no safety concerns for iodine-123 after ingestion. The radioiodine is eliminated in the urine [18,19,20].

1. **Lutetium-177**

Lutetium-177 is a naturally occurring element with one stable isotope. Targeted therapy involves chemically attaching stable Lutetium-177 to the cancerous area after injection. During its decay, Lutetium-177 emits low-energy gamma photons that can be utilized for targeted visualization through external imaging as they travel through the tissue. The PSMA radionuclide therapy, employing Lutetium-177, is utilized to treat prostate cancer in men. Lutetium-177 PSMA therapy has shown to be highly effective and well-tolerated in men with end-stage metastatic disease, boasting low toxicity. The targeted therapy includes the chemical attachment of stable Lutetium-177 to the cancer area after injection. During decay of Lutetium-177, it will emit low energy gamma photons.

The low energy gamma photons will travel across the tissue and utilized for targeting visualization by external imaging. The cancer area will absorb energy from the emission of beta particle. Then, the energy will kill the cancer cells even though it travels in short distance in the tissue. Furthermore, neuroendocrine tumors occur when neoplasms arise from the cells of endocrine and nervous system. This disease can be treated by using Lutetium-177. Prostate-Specific Membrane Antigen Therapy or known as Lutetium- 177 PSMA Therapy is among the treatment for cancer patient. A targeted radionuclide therapy, such as Lituteium-177 PSMA, may be used as a treatment option for males with prostate cancer. To treat the cancer accurately rather than the surrounding tissue, the cancer area must be compatible with the emission properties of a therapeutic radionuclide. Lutetium-177 has medium beta emitter energy of 490 keV, a greatest energy of 0.5 MeV, and tissue penetration depth of 2 mm, respectively. Longer beta-range is inferior to shorter beta-range because the final does not adequately irradiate tiny tumors. Ex vivo imaging can be conducted due to gamma emission from Lutetium-177. As a result, there is a lot of information gathered that are used to know the position of the cancer and dosimetry. Kidney, salivary and lacrimal glands are the particular concern in Lutetium-177 PSMA treatment [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 has two stable isotopes in nature, Ir-191 and Ir-193, and is quite dense—roughly twofold as dense as lead. Iridium-193 makes up around 63% of naturally occurring iridium, with iridium-191 making up the remaining 4%. Iridium metal, which is not radioactive, is used to create the radioactive element radioisotope Ir-192 in a nuclear reactor. The quantity of neutron irradiation and duration of exposure to the naturally abundant iridium metal determine the strength (or specific activity) of the ensuing Ir-192. Ir-192 implants have useful medical uses in the healthcare sector. They are primarily used to cure illnesses, and they are frequently utilized to treat breast and head disorders. These implants are made in the shape of wires and are carefully put through a catheter into the desired location [20].

1. **Carbon-11**

Nuclear medicine uses radiation to diagnose illnesses or to provide details on how a person's individual organs are working. Physicians utilize the data to quickly determine the disease of the patient. It is simple to image the thyroid, bones, heart, liver, and many other organs to identify functional issues. In some circumstances, radiation is intended to cure tumors or sick organs. Despite being utilized in therapy only sometimes, radioisotopes are crucial. Radiation damage can be devastating to cancerous growths. As a result, irradiating the area where the malignant growth is located can sometimes manage or remove the malignancy. A gamma beam from cobalt-60 source can be used for external radiation therapy or teletherapy. When using a Positron Emission Tomography (PET) machine for medical imaging, Carbon 11 is employed as a tracer that emits gamma rays. This nuclear medicine functional imaging method makes it possible to monitor the body's metabolic processes, which helps with disease diagnosis. A radionuclide that emits positrons causes pairs of gamma rays to be indirectly detected by the PET system. The body's tracer concentration is then depicted in three dimensions using computer analysis. This three-dimensional imaging is frequently supplemented in contemporary PET-CT scanners by a CT X-ray scan that is carried out on the patient concurrently on the same device. In addition to its use in medicine, PET with Carbon-11 is a useful research tool. It is crucial for clinical medical imaging to find tumours, look for metastases, and diagnose certain brain conditions that lead to various dementias. Additionally, it helps with drug development and the mapping of typical human heart and brain activity. 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. While the carbon 11 radiotracer enables a hot/cold biological substitution of active molecules, PET imaging offers a non-invasive (without requiring the introduction of devices into the body) way to monitor metabolic processes, molecular targets, and chemically caused tumors.

Carbon 11 is used as a gamma-emitting tracer in PET machines for medical imaging. When a positron is launched and totally annihilates with an electron nearby, two gammas are produced back-to-back. PET is a nuclear medicine functional imaging technique that aids in disease diagnosis by using observations of the body's metabolic processes. The device picks up pairs of gamma rays that are indirectly released by a radionuclide that emits positrons. Three dimensional imaging is typically achieved with the aid of a CT X-ray scan, which is completed on the patient during the same session in the same machine. It can be used in research and medicine. It is widely utilised for further clinical diagnosis of several diffuse brain illnesses, such as those producing various types of dementias, and for clinical imaging of tumours and the search for metastases [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.

Average beta particle ranges for samarium-153 in water are 0.5 mm and 3.0 mm, correspondingly. Samarium-153 has a definite gamma-ray constant for external radiation of 0.46 R/mCi-hr (1.24x10-5 mSv/MBq-hr at 1 Metre). Samarium-153-based quadramet must be kept frozen until use in a lead-protected container. Samarium-153 for the management of bone cancer and other tumours that have progressed to the bone, lexidronam is a radiopharmaceutical that is used as a radioactive material. Samarium is present in it in a radioactive form, and it also contains ethylenediamine tetra (methylene phosphonic acid), a chelator for tetra phosphonates, which makes it a therapeutic agent. Following administration, it builds up in the bone and releases radiation that may be able to find and destroy cancer cells.

The patient must be given advice by the treating physician on how to avoid exposing friends, family, and the general public to unneeded radiation. Patients should completely elude getting pregnant for at least 6 months after receiving 153Sm-lexidronam and 186Re-etidronate, and even longer after receiving 89Sr. It is improbable that women who are of childbearing age will qualify for this therapy in reality. Patients need to drink enough water both before and after therapy. Patients should stay in the facility for the first 4-6 hours after the treatment if it is administered on an out-patient basis. After the first 8–12 hours following administration, it is almost finished for 153Sm-lexidronam. Patients need to be instructed to maintain strict hygiene to prevent contaminating vulnerable groups while they share a lavatory. Patients should be informed that heavily soiled clothing should be laundered separately and not to soil undergarments or the region around toilet bowls for one week following injection. It's advised to wash out the toilet twice once urinating. After urinating, patients should wash their hands. 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 advanced expertise in medicine or radiology are authorized to administer samarium (Sm-153) lexidronam, either directly or indirectly. This medication is offered in dose forms for injection and solution. 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 systems. It is necessary to evaluate each patient uniquely. Patients with cancer frequently struggle to manage their pain. Since the nuclear physician usually treats patients with minimal to no soft tissue involvement, we believe an aggressive approach to managing their bone pain is important. Nuclear 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. **Indium- 111**

Indium-111 finds widespread application in radiology for diagnostic imaging through the radiolabeling of target molecules. It serves to localize tumors, conduct WBC scans for bone assessment, and image lymph nodes. For example, Indium-111 Chloride solution is utilized in nuclear medicine to bind antibodies, typically employing a chelating agent to attach the radionuclide to the target molecule, resulting in the desired product. When other imaging investigations are inconclusive or inappropriate, the indium 111-tagged WBC scan is one imaging technique used to assist locates areas of inflammation and consequently infections. For a variety of applications, indium-111 has a half-life of 67 hours. It also has the right gamma photon energies (173 keV-89% and 247 keV-94%) for external detection using commercially available detecting equipment. Although the first mention of a tttln compound for in vivo use was not made until 1969, its appealing physical properties have spurred the creation of a wide range of useful compounds that are more numerous than those created with 67GaIndium-based radiopharmaceuticals and are used in imaging studies to assess conditions like infection, inflammation, and tumor localization. Indium-111-labeled diethylenetriamine pentaacetic acid (DTPA)- folate was evaluated as a radiopharmaceutical for targeting tumor-associated folate receptors [23].

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 myocardial perfusion imaging. Its applications include detecting coronary artery disease, quantifying myocardial blood flow, and monitoring coronary flow through simplified PET techniques. N-13 serves as a radio tracer in the body, facilitating the delivery of the radionuclide to areas of interest, 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 10 to 15 mCi (370 to 555 MBq) for rest descriptions and 30 mCi (1110 MBq) for stress imaging. Exercise stress is possible due to the physical half-life of around 10 minutes, although pharmacologic stress is preferred and more useful. Imaging is done 3 to 5 minutes after injection, and it takes 10 to 15 minutes to acquire each imaging series acquisition might be carried out [24].

1. **Iodine compounds**

Iodine-125 is a medical isotope which emits gamma rays. In medical applications, it serves two key purposes: medical imaging and radiation therapy. In nuclear medicine, it is commonly used for brachytherapy in the management of various cancers like brain tumors, prostate cancer, and breast cancer. Iodine-125 radioactive seed tissue implantation proves to be a viable, efficient, and safe management method. It offers a secure and efficient approach to alleviate pain and control local tumor growth. Iodine-131 therapy is employed for patients with an overactive thyroid and those diagnosed with papillary thyroid cancer. In cases of an overactive thyroid, where one gland produces excessive thyroid hormone, iodine-131 therapy aids in targeted destruction of certain parts of the thyroid gland, restoring its normal function. The success rate of iodine-131 treatment varies between 75% to 100%, showing its effectiveness in managing thyroid conditions and certain types of thyroid cancer [26,27].

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 radionuclide's half-life should be relatively short, generally lasting just a few hours. This ensures rapid reduction in radioactivity after administration, minimizing unnecessary radiation exposure to the patient.
* **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** - Specific activity, representing the radioactivity per unit mass of the radiopharmaceutical, should be high and achieved with carrier-free radionuclides. This allows for lower doses of the radiopharmaceutical to be administered, reducing potential adverse 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-** Radioactive substances emit radiation through spontaneous decay of radioisotopes or intentional transformation or fragmentation of a radionuclide. This process leads to the emission of alpha, beta and gamma rays. However, the term "radioactivity" is more commonly employed to describe the level of physical strength or activity in such substances. It specifically indicates the number of nuclear disintegrations or transformations that occur per unit time within a given preparation.
* **Radionuclide-** When an isotope contains excess energy, it becomes an unstable nuclide characterized by an improper arrangement of neutrons and protons. This instability results in changes in stability, conversion of energy into electrons, or the emission of radiation. The original unstable nuclide is known to as the parent radionuclide, which undergoes radioactive disintegration, transmutation, or decay, emitting radiation and transforming into a daughter nuclide.
* **Half-life Period-** The term "half-life" (T1/2) indicates the time in use for a radionuclide to decay to half of its original strength.
* **Radionuclide Generator-** In nuclear medicine for therapy and diagnosis, a radionuclide generator is commonly utilized. It contains a longer-lived parent radionuclide that undergoes a decay process to produce a short-lived daughter radioactive substance. An example of such a radionuclide generator in radiopharmacy is the 99Mo-99mTc generator.
* **Radionuclide Purity-** The radiochemical purity is determined by comparing the radioactivity of a chemical entity to that of the radionuclide present in the preparation. Adhering to the official standards specified in the monographs of radiopharmaceuticals in the IP (International Pharmacopeia) is crucial for any radioactive preparation. Purity serves as a crucial attribute for evaluating the eminence of the radiochemical.
* **Isotopic Carrier-** An isotopic carrier refers to the stable isotope found in an element or added to the radioactive isotope of the same element. Radionuclides typically include isotopic carriers whose quantity is determined based on the method used to generate 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. Charles Henry was the first scientist to experiment with Poincaré's hypotheses, utilizing zinc sulfide as an X-ray intensifier. His findings revealed that radiographs became sharper in the presence of light due to the substance's effects. In 1896, Henri Becquerel conducted experiments using uranium salts on photographic plates, resulting in remarkable radiographs even without the presence of light. Subsequently, in 1905, Marie and Pierre Curie proposed the use of radium for cancer treatment, marking the early beginnings of modern nuclear medicine [2,34]. Ernest Lawrence's invention of the cyclotron in 1931 allowed for the artificial production of new radioactive elements, many of which are now widely used for medicinal and biological studies. During World War II, the Oak Ridge reactor in the United States facilitated global-scale production of radionuclides, paving 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**

Radiopharmaceuticals can be alienated into two groups based on the half-life of their radionuclides: one group with a half-life of less than 2 hours, and another with a half-life greater than 2 hours. Nuclear medicine cameras are specialized devices designed to detect and identify radioactive particles [2]. The type of camera used depends on the radiation emitted: SPECT cameras are utilized to detect nuclides that undergo decay by emitting single gamma rays directly, while PET cameras are capable of detecting the pair of gamma rays emitted after the decay of a positron. A nuclear medicine diagnostic technique utilizes radioactive tracers that emit gamma radiation from inside the body. A specialized camera captures the emitted radiation points, creating an image that is magnified on a computer and displayed on a monitor, aiding in the identification of any anomalies. Various nuclear medicine techniques include Single Photon Emission Computerized Tomography (SPECT), PET, and computed tomography-PET (PET-CT) for improved anatomical visualization. Additionally, micro-PET with ultra-high resolution and micro computerized axial tomography micro-CAT are used [2,36]. These techniques analyze biochemical dysfunctions, early disease signs, disease mechanisms, and their association with conditions ranging from cancer to cardiovascular diseases and mental disorders. SPECT is primarily used to visualize blood flow in veins and arteries and assess seizures pre-surgery. It is also valuable for diagnosing brain ischemia (blood deprivation), spinal stress fractures (spondylolysis), and tumors. PET imaging detects pairs of gamma rays resulting from the interaction between positrons and electrons in body tissues. The neutralization of the electron and positron produces two gamma rays in opposite directions, which are captured by PET using scintillation crystals to convert the energy released by gamma rays. For gamma cameras, 99mTechnetium is the most suitable radionuclide, while 18fluorine exhibits the most desirable characteristics for PET. Although SPECT and PET techniques produce images with high intensity, their spatial resolution is limited due to their surface-directed visualization. In contrast, computerized tomography (CT) and magnetic resonance offer higher spatial resolution but with less sensitivity. To overcome these limitations, techniques are combined to achieve excellent spatial resolution combined with high sensitivity. X-ray CT employs a computational process to generate three-dimensional images, providing higher resolution and more detailed [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. Radioactive compounds find application in both the diagnosis and treatment of diseases. Diagnostic radiopharmaceuticals play a crucial role in monitoring blood flow to organs such as the liver, brain, lung, heart, and kidney. Most radioisotopes, though not all, require a carrier molecule for transportation throughout the body and localization in the targeted tissue or organ. Medical practice has been profoundly transformed by the preamble of radioisotopes, which find extensive use in various applications. In the US alone, greater than 10 million nuclear medicine procedures and over 100 million nuclear medicine tests are conducted annually. Notably, four radioactive tracers have become typical examples of their use in medicine: technetium-99 (99mTc), thallium-201 (201Tl), iodine-131 (131I), and sodium-24 (24Na). Technetium-99 is employed to target injured tissues in the hepatic, cardiac, and lungs. By detecting the emitted γ rays from the Tc-99 isotope after injection, medical professionals can determine the position of the technetium complex and consequently identify the damaged tissue. Thallium-201, yet, concentrates in healthy heart tissue, and it is often used in conjunction with Tc-99 to study heart tissue effectively. As for iodine-131, it stored in the thyroid gland, the liver and specific regions of the brain [39]. Thus, it serves in monitoring goiter and treating thyroid conditions like Grave’s disease, as well as liver and brain tumors. It is crucial to note that the radioisotopes employed in medicine generally possess short half-lives. For instance, the widely used Tc-99m has a half-life of 6.01 hours, making storage and transportation impractical. Hence, it is generated on-site, with hospitals and medical facilities utilizing Mo-99, extracted primarily from U-235 fission products, to produce Tc-99. Mo-99 decays via β decay with a half-life of 66 hours, yielding the pertechnetate ion, TcO4−, which can be chemically extracted. In addition to their use as tracers, radioisotopes are employed for medical treatment, typically at higher doses. Radiation therapy, for instance, involves using extreme radiation energy to degrade the DNA of malignant cells, either killing them or inhibiting their division. This remedy may be inserting externally through a machine or internally via brachytherapy using a radioactive substance introduced into the body. It is essential to differentiate this form of treatment from chemotherapy, which involves the injection of chemical substances to combat cancer cells rather than using radioisotopes. Radiopharmaceuticals play a crucial role in diagnosing, palliating, and treating various illnesses, including cancer, heart disease, musculoskeletal disorders, and neurological disorders. These biologically active compounds labeled with radionuclides serve as valuable tools for both diagnostic and therapeutic purposes [40,41].

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

Radiopharmaceuticals are worn in medical imaging techniques like single-photon emission computed tomography (SPECT) and positron emission tomography (PET) scans, enabling non-invasive visualization of physiological processes and disease conditions.

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 to measure the concentration of various substances (e.g., hormones, drugs) in biological samples [42].

1. **In vivo applications of radiopharmaceuticals**

Radiopharmaceuticals play a crucial role in obtaining clinical information through in-vivo procedures. These procedures involve measuring the spatial delivery of the drug inside an organ (scintigraphy) or assessing the uptake or output of the drug in the organ to evaluate its function. Abnormal areas detected in radioactivity scans can designate the existence of a tumor or reduced viability in specific parts of the organ. One notable example of the uptake analysis is the thyroid radioiodine intake measurement, where the rate at which the thyroid removes radioactive iodide from the bloodstream provides essential information about the gland's physiological state. Similarly, kidney function can be examined by evaluating the rate of accretion of a radiopharmaceutical, such as 197 Hg chlormerodrin, in both kidneys simultaneously.

Currently, there are fewer than 50 radiopharmaceuticals commonly employed for in vivo administration. Many of these are employed for similar diagnostic tests, and the selection of a particular radiopharmaceutical often depends on the practitioner's preferences. Ongoing intensive research in numerous laboratories worldwide aims to develop more effective radiopharmaceuticals. It is probable that significant changes and advancements in the drugs intended in radiology will occur over the next 10 to 20 years [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. **Isotope generators**

A significant advancement in nuclear medicine over the past few years was due to the commercial introduction of isotope generators. These generators utilize a decay scheme involving a long-lived mother isotope and a short-lived daughter isotope. The mother isotope, with a relatively long half-life, is transported to hospitals. Through simple manipulations, the preferred daughter isotope can be acquired from the originator in a sterile and pyrogenic solution.

The rapid adoption of generators in nuclear medicine can be attributed to the understanding that radiation doses to patients should remain within acceptable levels and be minimized whenever possible. Achieving this is facilitated by employing a radioisotope with a convenient short half-life, allowing the isotope to decay rapidly after obtaining the necessary medical information. Additional beneficial features include the absence of beta ray emission, which can lead to unnecessary radiation exposure and a high degree of localization of the radiopharmaceutical in the target organ or specific body region (high target-to-non-target ratio of incorporation). Moreover, these radiopharmaceuticals should be cleared from the body quickly through biological processes.

The technetium-99m generator is now widely utilized in greater than 2000 hospitals. It utilizes molybdenum-99 (with a half-life of 67 hours) as the parent isotope, absorbed on an alumina column and shipped on a weekly basis. Technetium-99m (with a half-life of 6 hours) can be eluted once or twice daily in the chemical form of pertechnetate ion, allowing for direct applications in brain and thyroid imaging. Several marketable kits have been discovered to convert the pertechnetate into further valuable radiopharmaceuticals under sterile conditions. These include technetium-sulfur colloid for liver scanning, technetium-labeled serum albumin for blood pool studies, and macroaggregated serum albumin for lung scanning. Tc-99m radiopharmaceuticals are the most frequently used agents in nuclear medicine for diagnostic imaging, accounting for more than 80% of all diagnostic procedures. Radionuclide generators have played a pivotal role in advancing the availability and development of these tracers.

Cobalt-60 is a synthetic radioisotope created through neutron activation of Co-59, followed by β decay to form Ni-60, releasing γ radiation in the process. The overall process can be represented as follows

**Co-59 + n → Co-60 → Ni-60 + β- + γ**

Radioisotopes find diverse applications in studying the mechanisms of chemical reactions together in plants and animals. These applications encompass various uses, such as labeling fertilizers to investigate nutrient uptake by plants and crop growth, examining digestive and milk-producing processes in cows, and exploring the growth and metabolism of both animals and plants. One such instance involves the radioisotope C-14, which has been instrumental in unraveling the intricate details of photosynthesis. The general reaction for photosynthesis is represented as:

**6CO2 + 6H2O → C6H12O6(s) + 6O2 (g)**

However, the actual process is much more complex, involving a series of steps leading to the production of various organic compounds. To study this reaction pathway, plants were exposed to CO2 enriched with a high concentration of C-14. At regular intervals, researchers analyzed the plants to establish which organic complex enclosed carbon-14 and the quantity of each compound present. By observing the time series in which the compounds emerged and assessing their amounts at specific time intervals, scientists gained valuable insights into the chemical route of the photosynthesis reaction [40].

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

Radiopharmaceuticals derived from natural compounds utilize natural compounds as ligands for their composition. The ligand will then selectively interact with target tissues; thus, it has the ability to selectively deliver radionuclides. This interaction can take place immunologically, pharmacologically, or metabolically, and it is often reversible. Once the interaction occurs and the ligand binds with its target, the resulting bonded radiopharmaceutical can be internalized and stored within the target cells. It is hence very crucial for the ligand to effectively, at a low concentration, prevent any pharmacological activity or side effects on the target. Contrasting radiopharmaceuticals derived from natural compounds, conventional radiopharmaceuticals typically employ small molecules, peptides, and proteins as ligands. Small molecules such as fats, amino acids, nucleotides, and small inorganic compounds enable the targeting of intracellular regions because small molecules can penetrate semipermeable membranes easily. The examples of radiopharmaceuticals that use small molecules are [123I]NaI, [123I]ioflupane etc. [123I]NaI is a substrate for sodium iodide symporter for thyroid imaging. The presence of a parathyroid adenoma is characterized by areas of cellular tissue which do not exhibit trapping of [123I]NaI . [123I] ioflupane provides sensitive results in the analysis of Parkinson’s disease even in its early stages, based on the pattern of [123I]. They use peptides or proteins typically target specified receptors proteins of tumor or carcinogenic cells. Peptide-based radiopharmaceuticals exhibit swift diffusion into target tissues and prolonged accumulation in tumor cells. Nevertheless, a drawback of utilizing peptides or proteins as ligands is the risk of radio nephrotoxicity, stemming from their significant accumulation in the kidneys. An illustrative case of a protein used as a ligand involves Designed ankyrin repeat proteins (DARPins) labeled with iodine-124, iodine-125, and iodine-131, which aims to assess human epidermal growth factor receptor 2 (HER2) expression levels in breast and gastroesophageal cancer [43,44,45].

The contrast between radiopharmaceuticals derived from natural compounds and other radiopharmaceuticals is also evident in their respective developmental stages, as illustrated below. Typically, the development process of other radiopharmaceuticals involves identifying molecular targets and synthesizing pharmaceutical compounds to serve as ligands (small molecules or peptides). Subsequently, an appropriate radiopharmaceutical synthesis reaction is chosen, followed by the evaluation of the synthesized radiopharmaceutical. On the other hand, radiopharmaceuticals from natural compounds tend to undergo a more extended development stage. The initial phase of developing such radiopharmaceuticals involves the discovery of the natural compounds themselves. 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.

These pharmaceuticals plays an essential function in generating images of specific organs or tissues through scintigraphy, a non-invasive diagnostic technique in nuclear medicine which uses gamma rays emitted by radioactive isotopes to create detailed images of internal body structures [2]. The process involves administering a small amount of a radioactive substance, known as a radiotracer or radiopharmaceutical, which binds to a specific compound. The radiotracer then travels to the target organ or tissue within the body. As the radiopharmaceutical undergoes radioactive decay, it emits gamma rays, which are detected by a specialized camera called a gamma camera. Positioned over the region of interest, the gamma camera captures the allocation of the radiopharmaceutical within the tissues, producing images that reveal the functional status of the investigated organ or tissue. These images offer crucial insights into physiological activity and metabolic processes, aiding in the diagnosis and management of various medical conditions. One notable advantage of this technique is its safety, as radiopharmaceuticals used in scintigraphy emit low doses of radiation and do not cause harm to the body. The imaging process is non-invasive and generally well-tolerated by patients. Additionally, scintigraphy provides valuable information for precise diagnosis, treatment planning, and therapeutic response monitoring. In summary, radiopharmaceuticals and scintigraphy have developed into requisite tools in modern medicine, offering detailed functional information about organs and tissues without pretense harm to patients. Ongoing advancements in radiopharmaceuticals are likely to further enhance diagnostic capabilities, leading to improved patient care and outcomes. Close collaboration between medical professionals is essential to address potential drug-radiopharmaceutical interactions and ensure safe and effective use of these tools in patient care [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 system 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 remaining neutrons are employed to either generate plutonium or to interact with specific substances, inserted into the reactor, to produce radioactive products. This latter process is known as neutron activation. This method 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).

Currently, there is a wide range of more than 100 radiopharmaceuticals evolved using both reactor and cyclotron-produced radioisotopes. These radiopharmaceuticals play a crucial role in diagnosing various common diseases and treating selected conditions, including cancer. However, the production of radiopharmaceuticals involves handling substantial amounts of radioactive substances and requires complex chemical processing. Several important aspects require to be addressed in production, including effective management of radioisotope production, importation, operation, and maintenance of processing facilities. Compliance with the codes of current good manufacturing practices (cGMP) is essential, ensuring high-quality standards and meeting regulatory requirements. This involves establishing robust systems for quality assurance (QA) and quality control (QC), registering products with national/regional health authorities, and ensuring the secure transportation of radioactive materials [47].

One significant challenge faced in radiopharmaceutical production is that it is still relatively small-scale compared to conventional pharmaceuticals production. Implementing cGMP guidelines, which are designed for the larger pharmaceutical industry, can be difficult and expensive for small-scale manufacturers. Ensuring cGMP compliance demands careful attention to various aspects before, during, and after production. This includes developing a well-qualified and competent workforce, employing controlled materials and procedures, ensuring availability of qualified equipment, manufacturing products in designated clean areas, applying validated processes and analytical methods, maintaining comprehensive documentation throughout the production process, and releasing the final product under the supervision of a qualified person.

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].

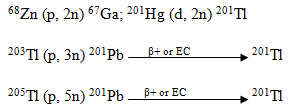
* **Production of Isotopes in Nuclear Reactors**

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. During the uranium fission reaction, one neutron is utilized to sustain the chain reaction for each uranium atom undergoing fission. 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.

The production of these isotopes plays a crucial role in diverse fields, including medical imaging, diagnostics, and industrial applications. Nuclear reactors provide a controlled environment for the assembly of specific isotopes, allowing for a reliable and efficient supply of radioactive materials for various purposes [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. Both linear accelerators and cyclotrons provide the charged particles with ample energy to overcome the barrier enveloping the nucleus, commonly known as the Coulomb barrier. This barrier arises due to the electrostatic repulsion between positively charged particles and necessitates a sufficient energy boost to enable successful collisions and reactions. Examples- the 203Tl is enriched while 205Tl is naturally occurring; the starting material and product have different chemical identities [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.

These efforts have significantly expanded the possibilities for diagnostic imaging, allowing for more precise and targeted evaluation of different physiological processes inside the body. The utilization of 99mTc and the advancement of novel radiopharmaceuticals continue to advance the field of medical imaging and contribute to improved diagnostic capabilities [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:

* 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.
* These factors collectively impact the yield and efficiency of radionuclide production using cyclotrons, providing a range of isotopes for diverse applications, including in nuclear medicine [54].

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.

The non-radioactive compound should possess the following attributes:

* Compatibility with 'kit' formulation.
* Ability to serve as a 'backbone' molecule, facilitating chemical modifications and substitutions.
* Maximized in vivo stability of the final product, unless biotransformation is needed for either prolonged residence time or rapid transit through the target organ.
* Non-toxic and free from adverse effects at the milligram dose level.
* Capability to stabilize any of the lower oxidation states of technetium in an aqueous medium, required for the production of 99mTc radiopharmaceuticals.
* Ability to be easily radiolabeled through simple exchange reactions for iodine radiopharmaceuticals during the final step of preparation.

Furthermore, the non-radioactive compound should undergo comprehensive chemical and structural characterization, employing a range of methods such as melting point determination, elemental analysis, polarography, paper chromatography, thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), electrophoresis, ion exchange, lH and 13C-nuclear magnetic resonance (NMR), infrared (IR), UV-visible and magnetic susceptibilities, field desorption mass spectroscopy, and X-ray crystal analysis. It is vital to consider the intended use of the final radiopharmaceutical when synthesizing the non-radioactive compound. Understanding the biological activities of the radiopharmaceutical is crucial in this process [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.
* It is imperative to consider that once the radiopharmaceutical is prepared by reconstituting the kit, the resulting Technetium complex should be used within 8 hours after production. This time constraint emphasizes the need for timely administration of the radiopharmaceutical to ensure its optimal efficacy and safety [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 details of the manufacturer or distributor responsible for the 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** of radiopharmaceuticals, the label on the package should provide the following information 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: Indicate the concentration of the radionuclide per milliliter (ml) of the liquid radiopharmaceutical solution at the specific date and time of manufacturing. This signifies the amount of radionuclide present in each milliliter of the solution at the time it was prepared [61].

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.

* **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.

Including this data on the label facilitates medical professionals to accurately determine the amount of radionuclide in each capsule, facilitating precise calculation and administration of the appropriate dosage to patients [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 Use 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 manufacturer 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. Explain the process of elimination from the body.
* Dose Information: Specify the dose of the radioactive substance contained in the prepared radiopharmaceutical.
* 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, radiopharmaceutical waste should be stored in designated waste storage facilities until it has adequately decayed to its nonradioactive form. The storage process should allow for easy inspection, monitoring, and preservation throughout the storage period. The recommended management approach involves placing the radiopharmaceutical waste in suitable waste storage facilities equipped with adequate shielding, such as lead or concrete blocks, depending on the complexity 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. The key purpose of storage is to isolate and contain the waste while it undergoes decay, ultimately transforming into regular waste. During storage, meticulous record-keeping must ensure full traceability of waste packages. Regular monitoring of the storage site is essential to ensure safety throughout the storage duration. Adhering to the International Commission on Radiological Protection's recommendation, a dose limit of 1mSv per year at the boundary of the radiological facility should be considered to verify the safety aspect during the storage of radioactive wastes [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 (syringes, scintillation vials, scalpels blades, and hypodermic needles): These items should be securely deposited in lead-lined sharp bins and labeled with caution about radioactivity. Before disposal, each container's exterior should be swiped and tested 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): Radioactive wastes consisting of absorbent materials should be segregated and placed in appropriately shielded and labeled containers.
3. Carcasses of Experimental Animals and Blood-Contaminated Wastes: For such wastes, hermetically sealed polyethylene drums should be used instead of plastic bags. Before storage, it is advisable to deactivate the waste through autoclaving or chemical disinfection. Subsequently, the waste should be stored in a freezer. For putrescible waste (carcasses of experimental animals), a deep freezer should be used to prevent biological decay during the transition to non-radioactive waste. A frost-free deep freezer is recommended to prevent any off-gas phenomenon, which could trap radioactive material in frost buildup.
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 best 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. Proper surveys must confirm total decay, and labels should be removed from the devices. Once the generator's activity has decayed to background levels, it can be disposed of in non-radioactive trash [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 radionucleotide 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. 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 [73, 74].

### The primary aim of the "Therapeutic Goods Amendment (Radiopharmaceuticals and Radiopharmaceutical Active Ingredients) Regulations 2020" (the Regulations) is to modify the TG Regulations and remove the inclusion of certain radiopharmaceuticals and radiopharmaceutical active ingredients from the scope of Part 3-3 of the Act listed in Schedule 7 of the TG Regulations (RAI). The Bhabha Atomic Research Centre (BARC), operating under the Department of Atomic Energy, plays a significant role in overseeing the use of radioactive materials and supporting various applications in radio medicine. The CDSCO, under the Ministry of Health and Family Welfare, Government of India, serves as a crucial entity for regulating RPs in India. With the authority granted by the Drug and Cosmetic Act of 1940 and the rules formulated therein, CDSCO fulfills an important role in monitoring RPs within the country [75].

1. **USA**

The use 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 structure 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].

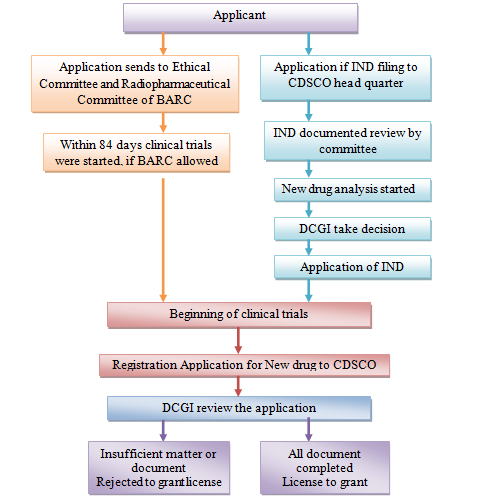
### European Union

### Throughout Europe, each member state has its own regulatory framework 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 assessment, control, and security monitoring 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. This exemption likely stems from the belief that the Drug Controller General of India (DCGI) lacks sufficient expertise to regulate RPs [79]. Since the government sector, including DAE units and INMAS DRDO, was the primary producer of RPs in the past, the RPC adequately handled regulation. 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 India81**

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. Pharmaceutical industries, in the process of preparing radiopharmaceuticals, strictly adhere to their own Standard Operating Procedure (SOP) specific to the manufacturing of radiopharmaceutical products. The handling of radiopharmaceuticals complies with the necessary regulatory guidelines to ensure the safety of workers. This involves adhering to licensing commitments aimed at minimizing exposure levels for the involved personnel to the lowest feasible extent. Radiopharmaceuticals belong to a distinct class of Pharmaceuticals that demand utmost caution in their handling [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, typically ranging from a few minutes to a few days.
* Quality control (QC) samples that represent the entire batch.
* Diagnostic radiopharmaceuticals are administered at micro-dose levels, often resulting in minimal therapeutic or toxic effects.
* Radiopharmaceuticals are sometimes dispensed before all QC examinations are completed.
* Certain examinations, such as sterility testing, endotoxin content determination, 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 demonstrate controlled handling of hazardous elements [83, 84].

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

In India, it is essential to conduct detailed and reliable research on the existing guidelines of the "Atomic Energy Regulatory Board" (AERB) concerning the proper disposal 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. To ensure effective regulation of radio-pharmaceuticals in the country, AERB has established mandatory requirements through various codes, rules, and guidelines. Regarding disposal, the Atomic Energy (Safe) Regulations, G. S. R. 125, 1987, and the code-named Radioactive Waste Management, 2007 have been issued. Additionally, Nuclear Medicine Facilities 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 specifications and other relevant guidelines, though only a few of these regulations or codes specify the exact method of radiopharmaceutical disposal. However, they do conform to international standards. The project's objective was to bridge a regulatory gap in India's current framework for radiopharmaceuticals, leading to the establishment of comprehensive global regulatory guidelines as standard practice. Since radiopharmaceutical waste can be present in various materials, it is crucial for regulatory guidelines to address each type independently. The primary aim of radiopharmaceutical disposal is to safeguard healthcare professionals, radiation workers, patients, the public, and the environment from pollution and radiation exposure. Achieving this necessitates adherence to Good Radiopharmaceutical Practices (GRPs), good manufacturing practices (GMP), and radiation safety, in addition to the rules set forth by the International Atomic Energy Agency (IAEA) [85, 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 | A radiopharmaceutical diagnostic agent recommended for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence, determined by elevated blood prostate-specific antigen (PSA) levels after previous treatment [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 Accelerator  Applications | NETSPOT | A radiopharmaceutical diagnostic agent recommended for both adult and pediatric patients, to be used in conjunction with positron emission tomography (PET) for locating somatostatin receptor positive neuroendocrine tumors (NETs) [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 radiopharmaceutical agent designed for scintigraphic localization of somatostatin receptor-bearing primary and metastatic neuroendocrine tumors [96] |
|  | Iodine I-123 iobenquane | GE Healthcare | AdreView | Recommended as an adjunct to other diagnostic tests for the detection of primary or metastatic pheochromocytoma or neuroblastoma [97] |
|  | Iodine I-123 ioflupane | Curium | DaTscan | Recommended as a supplementary aid to other diagnostic assessments for visualizing striatal dopamine transporter using SPECT brain imaging in adult patients with:   * Suspected Parkinsonian syndromes (PS) or * Suspected dementia with Lewy bodies (DLB) [98] |
|  | Iodine I-125 human serum albumin | IsoTex Diagnostics | Jeanatope | Employed for the determination of:   * Total blood * Plasma volume [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 * Cardiac output * Protein turnover studies * Heart and great vessel delineation * Localization of the placenta * Localization of cerebral neoplasms [101] |
|  | Lutetium Lu-177 dotatate | Advanced  Accelerator  Applications | LUTATHERA | Recommended for the cure of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults. [102] |
|  | Lutetium Lu- 177 vipivotide tetraxetan | Advanced  Accelerator  Applications | 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 evaluation of pulmonary perfusion both in adults and pediatric [109]. |
|  | Technetium-99m mebrofenin | Bracco Diagnostics | Choletec | As a hepatobiliary agent [110] |
|  | Technetium-99m medronate | DRAXIMAGE | MDP-25 | As a bone imaging agent to delineate areas of altered osteogenesis [111]. |
|  | Xenon-133 gas | Curium | - | The evaluation of pulmonary function and for imaging the lungs [112]. |
|  | Yttrium-90 ibritumomab tiuxetan | Acrotech Biopharma | Zevalin | In the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin’s lymphoma (NHL) [113]. |

**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 attributed to their dual application as both diagnostic and therapeutic agents. Traditionally, radiopharmaceuticals have been used for diagnostic procedures, but recent research has expanded their use as therapeutic agents as well. The global radiopharmaceuticals market is primarily driven 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 ample research on new radiopharmaceuticals and a rush 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, comprehensive, and internationally standardized framework for effectively managing regulatory issues related to the storage and disposal 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. The facility for disposing of spent sealed sources with long half-lives using deep geological methods should remain adaptable to accommodate ongoing technological advancements. National authorities should conduct periodic audits, including unplanned inspections, independently, ensuring strict adherence to approved procedures, thus fostering public trust and transparency. A comprehensive study should be conducted for each radiopharmaceutical used in healthcare and nuclear medicine, leading to a consensus on the appropriate activities and activity concentrations for different age groups and acceptable disposal levels concerning landfill, sewer, or the atmosphere. This uniform approach will promote standardized radiopharmaceutical waste disposal practices. A radiopharmaceutical can effectively deliver a radiolabeled substance to a specific target within the body, thanks to its unique and selective affinity for the target enzyme, protein, or receptor. The selection of an appropriate pharmaceutical agent revolves around its ability to maintain its target specificity and selectivity even after being radiolabeled. Common examples of such agents include small molecules like NaI, peptides, and proteins. However, these agents still face challenges related to stability, specificity, and selectivity. To address these issues, ongoing research is exploring new pharmaceutical agents, particularly focusing on compounds derived from natural sources. Natural compounds are promising precursors with diverse pharmacological effects, such as acting as antioxidants, antibacterial agents, and displaying anticancer activities. Their inherent affinity for disease targets makes them attractive candidates for developing pharmaceutical agents. 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. Proper regulation is vital to prevent the administration of non-sterile formulations, ensure accurate dosing for reliable diagnoses, and avoid harmful consequences like overdose. 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.

With the introduction of new radiopharmaceuticals into the market, the issue of their storage and disposal demands significant attention. It is imperative to establish comprehensive regulatory guidelines to ensure the responsible storage and disposal of radiopharmaceuticals, prioritizing the well-being of both individuals and the environment. Every new radiopharmaceutical entering the market must be accompanied by a full life cycle regulatory plan. This plan should encompass strategies to minimize waste throughout its production and usage, culminating in a well-defined approach for its final disposal, following a cradle-to-grave philosophy. This approach ensures that the entire lifecycle of the radiopharmaceutical is managed responsibly, with a focus on waste reduction and environmentally-conscious practices. Various types of radiopharmaceuticals play a crucial role in disease diagnosis. This review focuses on the concept of radioactivity, including the preparation, manufacturing, and regulation of radiopharmaceuticals. 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 developing into more crucial field of medicine. There is a significant increase in the global demand in radiopharmaceutical field, with the increase 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. Overall, the versatility and usefulness of radiopharmaceuticals have revolutionized medical practice and research, contributing to improved diagnostics, more targeted treatments, and a deeper understanding of human physiology and disease processes. Radiopharmaceuticals, or radioactive drugs, have become indispensable in clinical settings for diagnosing, investigating, and occasionally treating various human illnesses. 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. The development of theranostic agents, which combine diagnostic and therapeutic RPs to offer personalized treatment, has been a groundbreaking advancement in the field of nuclear medicine. Additionally, the exploration of artificial intelligence, nano radiopharmaceuticals, and carbon dots has expanded the horizons of research in RPs. 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. In this review, the authors have extensively discussed these aspects of radiopharmaceuticals, with a particular focus on their applications and regulatory information. 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.

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