

RADIOPHARMACEUTICAL SCIENCES

Abstract

The Federal Register of the USA initially described radiopharmaceuticals as radioactive agents—natural substances based on carbon (^{14}C) and potassium (^{40}K)—or biological products that include unstable nuclei that may spontaneously decay and release photons or nuclear particles. In 1960 at the University Of Southern California (USC), USA the demand for the radio labeled drugs has been established, and radiopharmaceutical agents have become the first specialty. Radiopharmaceuticals are those pharmaceutical preparations that contain radioactive materials (radioisotope and compounds tagged with radioisotopes) and are used for either treatment or diagnosis. The radiation effect is the desired properties for the radiopharmaceuticals used for therapeutically. In this chapter the various pharmaceutical applications of radiopharmaceuticals have been describes such as in bone metastasis, in the treatment of hyperthyroidism and thyroid cancer, in neuroendocrine treatment, and myeloproliferative diseases.

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I. INTRODUCTION

The Federal Register of the USA initially described radiopharmaceuticals as radioactive agents—natural substances based on carbon (^{14}C) and potassium (^{40}K)—or biological products that include unstable nuclei that may spontaneously decay and release photons or nuclear particles. These medications could be made using a nonradioactive reagent or a nuclide generator.

The majority of radiopharmaceuticals are employed in medical diagnosis. They are typically administered once, or occasionally more than once, and only include trace amounts of the active ingredients with a radioisotope attached to enable scintigraphic imaging or biodistribution analysis. These radiopharmaceuticals frequently exhibit no discernible pharmacodynamic impact. All radiopharmaceuticals have the general property of radiation, and when delivered, they dose the patient with radiation.

The radiation effect is the desired properties for the radiopharmaceuticals used for therapeutically. In addition to generic characteristics, estimation of the protection and effectiveness of radiopharmaceutical should take into account radiation dosimetry, radiopharmaceutical features, and radiation cleanliness.

Due to the radioactive decay, the composition of radiopharmaceutical agents changes with time. The parameters of generators, kits, and other semi-manufactured items are also taken into consideration while evaluating the safety and effectiveness of radiopharmaceuticals.

Radiopharmaceuticals are those pharmaceutical preparations that contain radioactive materials (radioisotope and compounds tagged with radioisotopes) and are used for either treatment or diagnosis. In nuclear medicine, where radiopharmaceuticals are used to diagnose, treat, and manage a variety of disorders, radiopharmaceuticals are crucial components of the nuclear medicine.

II. HISTORY OF RADIOPHARMACY

In 1960 at the university of Southern California (USC), USA the demand for the radiolabeled drugs has been established, and radiopharmaceutical agents have become the first specialty. This is true even though training on the use and management of labeled compounds is provided in various institutions. In 1969 to 1986 the short –term research courses and training program for radiopharmaceutical technician were also be conducted with master degree courses of radiopharmaceuticals. At that time 15 of these participants received technology certificates, and more than 500 people participated and offered similar expert training.

Clinical requirements may include imaging performances that could be crucial for the staging or projection of the disease. Many instructional and radiopharmaceutical analysis-focused programs have not addressed this issue for a very long time. Without considering its potential applications in the future, the program usually focuses on designating a certain molecule and on its application. Even if a specific biological target has been identified, it is typically not taken into account whether or not it actually meets a therapeutic need.

III. DEFINITIONS AND TERMINOLOGY

1. A nuclide, also known as a nuclear species or a nucleide, is an atomic species that differs from other atomic species by the composition of its nucleus, specifically by the number of protons, Z , the number of neutrons, N , and the nuclear energy state.
2. An unstable atom is referred to as a radionuclide (also known as a radioactive nuclide, radioisotope, or radioactive isotope).
3. The extra energy can be released from the nucleus in one of three ways: as gamma radiation; by being transferred to one of its electrons and then released as a conversion electron; or by being created and released from the nucleus as a new particle (alpha particle or beta particle).

IV. NUCLIDES VS ISOTOPES

1. **Nuclides:** The nuclide is an atom that has a meticulous number of protons and neutrons in the nucleus, e.g. Carbon-13, has (six protons and seven neutrons).

In contrast to the isotope concept, which groups all the atoms of a certain element, the nuclide concept (which refers to specific nuclear species) places more emphasis on chemical than nuclear features. The amount of neutrons has a significant impact on nuclear properties, although for the majority of elements, its influence on chemical reactions is minimal.

2. **Isotopes:** Isotopes are different chemical elements that differ in nucleon number and neutron number, respectively. The number of protons in each atom is the same for all isotopes of a given element, while the numbers of neutron varies. Atoms of the same element with various mass numbers (A) but the same atomic number (Z) are known as isotopes of that element. They both have the same chemical properties and are in the same position on the periodic table.



The amount of protons and neutrons in a given isotope's nucleus determines its mass number, or nucleon number.

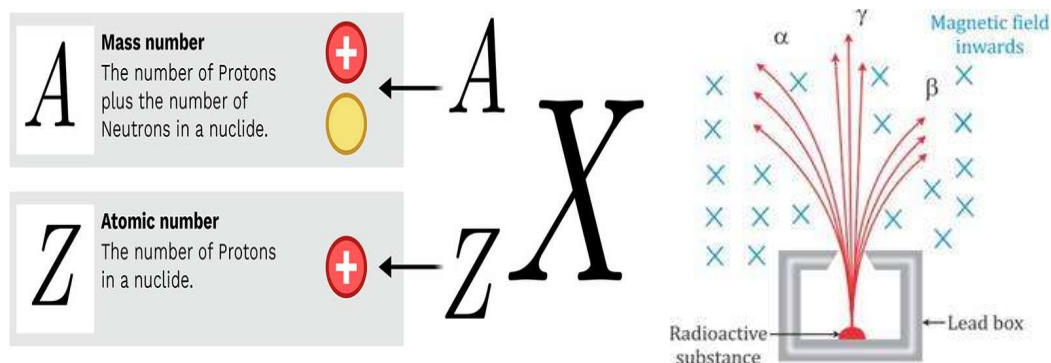


Figure 1: Mass and Atomic Numbers of Chemical Elements

V. RADIOACTIVITY

During any process the energy of an unstable atomic nucleus loses this is known as the radioactive decay or nuclear decay, radioactivity and radioactive or nuclear disintegration. A material that has unsteady nuclei is regarded as radioactive. There are three types of decay -Alpha, beta, and gamma decay and these all involved in the emission of either one or more than one particles.

Decay patterns (**Alpha, Beta and Gamma Radiations**). Three different forms of radioactive rays have been identified:

- Alpha rays were so weak that they hardly penetrated papers.
- Beta rays can pass through aluminum (3mm).
- Gamma rays, may through lead up to several centimeters thick

- **Alpha Decay:**

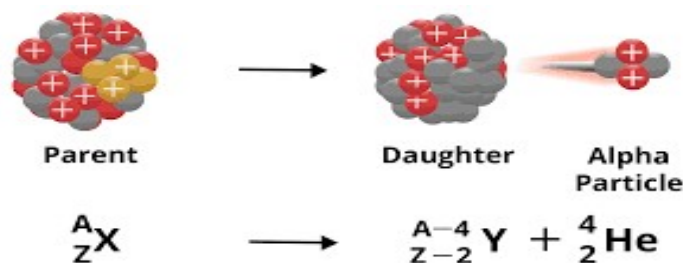
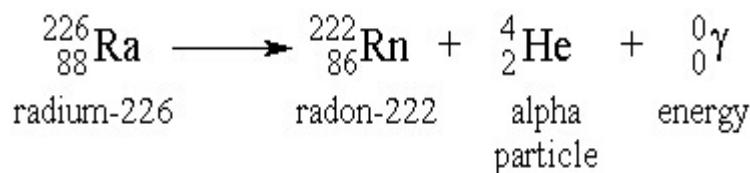


Figure 2: Alpha Decay

A big nucleus cannot be held together by a strong nuclear force because:

- The mass of the parent nucleus is larger than the combined mass of its daughter and alpha particle
- The disintegration energy is the difference between these two values that determines how quickly a nucleus decays by alpha emission.

Radium 226 will alpha decay to radon 222



- **Beta Decay:** When any atomic nucleus emitted beta ray than this phenomenon of particular radioactive decay is known as beta decay. In this decay the proton converted in neutron in any nucleus and vice versa. If proton transformed in neutron than the decay known as β^+ and if any neutron converted in proton than it is called as β^- decay.

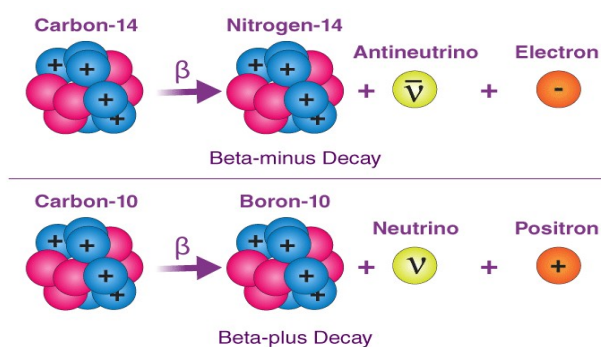


Figure 3: Representation of Beta Decay

- **Gamma Decay:** Gamma rays are electromagnetic rays coming out of a nucleus as a result of the difference in nuclear energy levels of the excited and the ground states of the daughter nuclide when a nuclear transmutation takes place. Most radioactive decays are accompanied by γ rays, although this is not essential. Since γ rays carry the energy arising out of the difference in nuclear energy levels, these are often highly energetic, with energy greater than those of X-rays.

1. Advantages of Radiopharmaceutical Agents

It has the following benefits:

- It may be used to diagnose and treat patients;
- It is a common cure for malignancies;
- It can treat numerous modes of therapy;
- It directly treats tumor, notably useful for bone metastases;
- It can provide quick pain relief;
- For certain patients, a single dose is effective.
- Children can undergo nuclear medicine testing, which is also painless and cost-effective.
- Nuclear medicine procedures are also fully safe with no known negative effects.

2. Disadvantages of Radiopharmaceutical Agents

- Nuclear medicine examination may be dangerous for pregnant women because unborn babies are more sensitive to radiation than children or adults.
- Patient dental braces, permanent bridges, and fillings may deform the mouth.
- Patients may have prolonged discomfort and inconvenience while receiving several fractions.
- Cardiovascular complications, thyroid dysfunction, and pituitary axis dysfunction can all be linked to higher doses of head and neck radiation.
- Possibility of allergic responses.
- There is a risk of radiation.
- Myelosuppression is possible, especially after chemotherapy treatment in the past.

VI. PRODUCTION OF RADIONUCLIDES

The 403 method of radionuclide synthesis is described as precisely as possible in a radiopharmaceutical preparation monograph. The radionuclide remains in radiopharmaceutical preparation as an element in the form of atom or molecule, like [^{133}Xe], [^{15}O]O₂, as an ion, like [^{131}I] iodide or [$^{99\text{m}}\text{Tc}$] pertechnetate, or by covalent bond, like 2-[^{18}F] fluoro-2-deoxy-D-glucose, in or attached to organic molecules.

The following methods are effective for generating radionuclides for utilization or as radiopharmaceutical formulations:

- Bombarding target materials with neutrons (typically in nuclear reactors);
- Bombarding target materials with charged particles (typically in accelerators like cyclotrons);
- Nuclear fission of heavy nuclides of target materials (typically after bombardment with neutrons or charged particles);
- Radionuclide generator.

1. Bombarding Target Materials with Neutrons: The physical properties of the target material, type, energy, and quantity of the confrontation particles, can affect the nuclear reaction and the likelihood that it will occur in a given amount of time.

It is possible to express the nuclear change caused by particle bombardment as follows: target nucleus (bombarding particle, outgoing particle, or radiation) generated nucleus. Examples: $^{58}\text{Fe} (n,\gamma) ^{59}\text{Fe}$; $^{18}\text{O}(p,n)^{18}\text{F}$

Aside from the targeted nuclear reaction, accidental changes could take place. Both the energy of the impacted particle and the purity of the target material will have an impact on these. These accidental changes could result in radionuclidic contaminants.

2. Nuclear Fission: A small number of nuclides with a high atomic number can fission, and the reaction that occurs most frequently in nuclear reactors is the neutron-induced fission of uranium-235. Molybdenum-99, xenon-133, and iodine-131 can all be created through nuclear fission of uranium-235. (c)

3. Radionuclide Generators: A parent radionuclide has relatively longer half-life decays into a daughter radionuclide and it produces a radionuclides. According to the half life of both parent and daughter nuclide they can subsit in either transitory or secular equilibrium. The daughter radionuclide can be separated from parent radionuclide by chemical or physical procedure. Despite having a short half-life, the daughter can be used far from the generators' manufacturing location. The parent radionuclide's T_{1/2} will determine how long the generator can be operated.

4. Target Materials: The proportions of the main radionuclide and radionuclidic impurities depend on the target material's isotopic makeup and purity. The manufacturing yield and purity of the desired radionuclide can be boosted by using target material havinc strong isotopic property, in which the larger quantity of the desirable target nuclide has been artificially raised.

The chemical state and chemical purity of the radionuclides that are created will depend on the chemical form, chemical purity, physical condition, chemical additives, bombardment conditions, and the direct physical and chemical environment.

Before additional processing and the creation of radiopharmaceutical agents, it may not be able to conclude any of these quality standards in the production of radionuclides, especially short-lived radionuclides. To make sure that the target yields the radionuclide in the desired quantity and quality under the specified conditions, for this respectively batches of target material must be tested in test production before used in routine radionuclide production and manufacturing of the radiopharmaceutical formulations.

To be irradiated by a particle beam, the target material must be held in a container in either a solid, liquid or gas form. The target material for neutron bombardment is frequently housed in ampoules (quartz), containers made by highly pure aluminum, or titanium.

The holder for the target substance used in charged particle bombardment should be made up of aluminum or another appropriate metal, which has a low cross section for the irradiating particles. The container should also have strong thermal conductivity to squander the heat produced. The target material should have cooling systems around it, inlet and exit ports, and typically a thin metal foil target window. The quality and thickness of this window have effect on the purity of radionuclide and also in the yield of nuclear reaction.

VII. APPLICATION OF RADIOPHARMACEUTICALS

The various applications of radiopharmaceuticals have shown in figure 4.

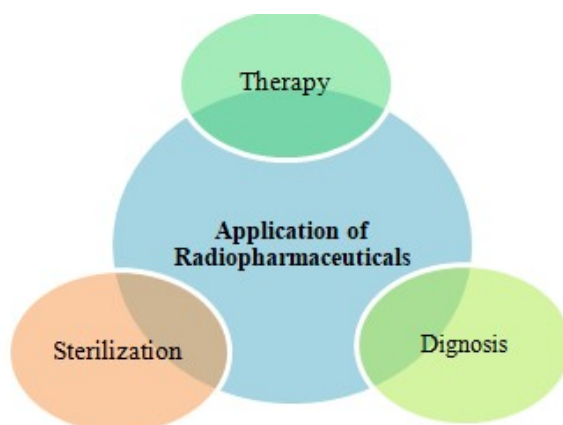


Figure 4: Application of Radiopharmaceuticals

- 1. Therapeutic Application of Radiopharmaceuticals:** The radiopharmaceutical formulations therapeutically projected to target the radiolabeled molecules to certain affected areas inside the body. Emission of charged beta particles at the target site provides therapeutic effects, such as in cancers. Some radiopharmaceuticals and their therapeutic uses are shown in table (1).

Table 1: Therapeutic Applications of Radionuclide Agents

Radionuclide	The Therapeutic Use
Iodine-131, Yttrium-90	Used to treat non-Hodgkins lymphoma
Americum-241, Californium-252, Cobalt-60, Gold-194	For the treatment of cancers and tumors
Holmium-66	Used in liver cancers
Iodine-131	Used as antineoplastic, and for Grave' disease
Rhenium-186	Used to reduce the pain allied with bone metastasis
Samarium-153, Strontium-89	Palliative treatment of bone metastasis
Samarium-153	Used in bone cancer, prostate and breast cancer to reduce the pain

The superlative properties of radiopharmaceuticals used as therapeutic agents are:

- Significantly uptake at one location
- Blood activity should be low
- There should not be any retention tissues or organs other than target,
- Should be excreted via the renal pathway

The therapeutic radiopharmaceuticals have a variety of applications, including myocardial perfusion in cardiology, tumors in oncology, and cerebral perfusion in neurology.

- **Application of Radiopharmaceuticals in the Treatment of Hyperthyroidism and Thyroid Cancer:** thyrotoxicosis, a clinical condition caused by hyperthyroidism, is when the thyroid gland produces excessive amounts of thyroid hormone. Iodine-131 administration orally has been a widely acknowledged method for treating benign and malignant thyroid disorders as well as hyperthyroidism. A radioisotope with an 8-day half-life is iodine-131. Gamma rays and beta particles are produced as a result of its decay. The capacity of iodine to retain in the thyroid gland determines the therapeutic impact of iodine-131. If hyperthyroidism reoccurs after the treatment of antithyroid medicine or surgery in such case the radiolabeled iodine-131 may be applied as a first line treatment.

In thyroid cancer, radiolabeled iodine-131 accumulates specifically in the affected tissue of the gland. The decays emitted an alpha particles, which is responsible for destroying the tumor tissue. For patients who have difficulty in swallowing or vomit, radiolabeled iodine-131 may be given i.v. route or some time in an oral dosage form (liquid or pill).

- **Application of Radiopharmaceuticals in Bone Metastasis:** The bone metastasis is associated with numerous consequences, such as hypercalcemia, bone fractures bone and spinal cord compression. The treatment by using the analgesics, anti-inflammatory medicines, radiation therapy, and surgery required palliative care. Samarium-153 (Sm-153), phosphorus-32 (P-32), and strontium-89 (Sr-89) are only a few of the radionuclides that are utilized to treat bone metastases. Due to the radionuclide samarium-153's 1.9-day half-life and ability to emit both beta particles

and gamma radiation, it can be utilized to detect and treat bone metastases. Samarium-153 has the capacity to specifically target bone tumors, reaches to cancer infected bone, and produces beta particles that improve pain. Some time most of the patients suffered by pain alleviation within the first week of treatment.

Phosphorous-32 was utilized to restrain excessive cell growth. It releases beta particles having physical half-life of 14.3 days and a maximal energy of 1.71 MeV which makes phosphorous-32 helpful in the treatment of bone metastases.

After being injected intravenously, strontium-89 chloride decays and releases beta particles. Strontium-89 has a physical half-life of 51 days. Greater concentrations of metastatic bone lesions can build up in it comparatively in healthy bone. When strontium-89 intravenous administered intravenously, it behaves like calcium, which is localized in the bone minerals and selectively removed from the blood.

- **In Neuroendocrine Tumors Treatment:** Meta iodo benzyleguanidine have similar structure as guanethidine a adrenergic neuron blocker and nor- adrenaline. Due to this similarity, Meta iodo benzyleguanidine received by the tissues having sympathetic innervations and also by adrenal medulla. But it is slowly metabolized and excreted unchanged in large amount in the urine.

¹³¹I-metaiodobenzyleguanidine (¹³¹I-MIBG) has been used successfully to treat various severe diseases such as neuroendocrine tumors e.g. neuroblastoma, carcinoid tumors and medullary carcinoma of the thyroid. There are some other radiopharmaceutical agents are being investigated as alternatives to ¹³¹I-MIBG, ¹⁶¹-Terbium-diethylenetriaminepentaacetic acid-octreotide and ¹¹¹Indium-diehylnetriaminepentaacetic acid (¹¹¹In-DTPA) for tumors containing somatostatin receptors.

- **In the Treatment of Myeloproliferative Diseases:** A number of haematological illnesses have been treated with ³²P for more than 50 years. Following intravenous injection, bone uptake occurs and quickly growing tissue selectively concentrates ³²P, the orthophosphate. This result in the haemopoetic cell lines' proliferation being retarded and delivers a large radiation dosage to the bone marrow. In the treatment of polycythaemia rubra vera, ³²P is primarily used. The amount of red cells in the circulation has an abnormally high increase in this illness. On the other hand, chemotherapy, radioactive phosphorus, and phlebotomy all significantly lengthen life expectancy.
- 2. The Diagnostic/ Imaging Application of Radiopharmaceuticals:** The different organs of the body have various functions. Medical professionals discovered the chemicals that each organ can absorb during the study. Examples include the selective uptake of iodine by the thyroid gland, glucose by the brain, and calcium by the bones. According to this concept, when radiopharmaceutical agents enter in the body certain organs uptake the radioisotopes from it. The nuclide that have concise half-life and decays by the emission of the gamma radiation can be consider as best diagnostic radionuclide such as Technetium-99 m has short half-life (6 h), exclusive gamma radiation emission during decay, and effective gamma camera detection.

Curtis et al. employed fluorine-18 for the diagnosis of early Alzheimer's disease. Radioactive Holmium-166 was utilized by Vente et al. to identify and classify liver cancer. Radioiodene-131 was utilized by Maxon et al. to identify metastatic thyroid cancer. Iodine-123 was utilized by Mandel et al. to scan thyroid remains in people with differentiated thyroid carcinoma. Elmotaleb et al. synthesized radiopropanol by using Iodine-125 for the scanning of Lung perfusion.

- **CT (Computer Tomography):** By measuring the spatial distribution of physical material which can be viewed from various angles the superposition- free images can be calculate and this is the basic idea behind CT. It is essentially an X-ray photography technique which helps to scan the single patient's plane from different angles and produces a cross-sectional image of that plane's interior structure. There are numerous clinical diagnostic uses for a CT scan. By outlining the particulars of the organs, together with the soft tissues and bones, it increases the accuracy of the diagnosis. A CT scan can also be helpful for the surgical procedures, biopsies, and radiotherapies by providing information on the spread of an infection or tumor to various body parts.
- **MRI (Magnetic Resonance Imaging):** An MRI creates cross-sectional images of the body, much like a Computerized Topography (CT) scanner. Cross-sectional imaging of the body can be compared to slicing up a loaf of bread to see the inside. MRI does not utilize X-rays, in contrast to a CT scan. Instead, it creates extremely precise and in-depth digital images of the inside of the body using a powerful magnetic field and radio waves. The gut, pelvis, joints, brain, and spine are frequently examined with MRI technology. The blood vessel is examined using a specialized MRI test called Magnetic Resonance Angiography (MRA).

Heart and vascular imaging in cardiac imaging, radiopharmaceuticals agents help to make available details about the regional myocardial blood perfusion. The patient will either be subjected to treadmill activity or an intravenous dipyridamole injection as part of the trial. Then, an imaging procedure is performed using a technetium-99m (^{99m}Tc) labeled methoxy isobutyl isonitrile injection or thallium chloride injection.

- **Bone Imaging:** Bone tumors, both primary and metastatic, can be diagnosed with this technique in both benign and malignant cases. A diagnostic agent (often a single photon emitter) plus a therapeutic agent make up radiopharmaceuticals used for bone imaging. In contrast to single photon bone imaging agents, therapeutic radiopharmaceuticals are used based on their particle emissions (mainly Beta). Polyclonal human immunoglobulin labeled by ^{99m}Tc was utilized to demonstrate arthritic lesions by gamma scintigraphy in the in vivo investigations. The DS loaded radio labeled microspheres were directly injected into the articular cavity of knee joints of rabbits and induced with arthritis. After that the gamma scintigrams were taken at different time intervals to identify the habitation duration of the microspheres in the joints of knee. This allowed researchers to establish the effects of the injections on the rabbits' knees.

- **Lung Imaging:** Lung imaging is primarily used to diagnose pulmonary emboli, test pulmonary function prior to pneumonectomy, and measure pulmonary perfusion and ventilation. Iseri et al. prepared microsphere by using albumin and gelatin which contains the rifampicin (tuberculostatic drug), and they evaluated the drug's in vivo distribution by inducing it to accumulate in the lung, the target organ. ^{99m}Tc labeled microspheres having the size range 25-27nm were administered in Swiss mice by IV route and biodistribution was examined. When the radioactivity of the liver, spleen, kidney, stomach, and heart were compared with that of the lungs it was found the percentage accumulation of microspheres was greater in the lungs than in the other organs.
 - **Renal Imaging:** Renal imaging is require to appraise renal shape, renal vascular flow, and renal function. The examination of kidney transplant recipients for complications such blockage, infarction, leakage, tubular necrosis, and rejection also makes use of these tests. Common radiopharmaceuticals include ^{131}I -ibdohippurate and ^{99m}Tc -diethylene triaminepenta acetic acid.
3. **Application of Radiopharmaceuticals in Sterilization:** Radiation sterilizes the thermolabile compounds such as hormones and vitamins. Some medicines, surgical dressings and disposable syringes are also thermo sensitive materials which can be sterilized with the help of radiopharmaceuticals. For this, radioisotopes are employed which decays by gamma radiation and utilizes for the sterilization of thermo labile compounds i.e. cobalt-60.

VIII. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS AND DEVELOPMENT PHARMACEUTICS

1. **Control of Starting Materials:** For the purposes of this section, "starting materials" refers to all of the components of the medicinal product, all of its containers and closures, and, if applicable, all of the radionuclide source's components, as well as any other materials used in the administration process's final stages. Separation of radionuclides, control of radionuclide purity, and particular activity (with regard to contaminants and degradation products) must all be fully described. Details about the container's parts, including the names of authorized producers, should be provided. The finished products should also have any radiation shielding described in detail. It can be challenging to discern between control of the raw ingredients and control of the completed product when it comes to some radiopharmaceuticals.
2. **Control Tests on the Finished Product:** No matter the volume, goods planned for intrathecal injection must undergo a suitable endotoxin test unless doing so can be fully and convincingly explained. Process parameter release*, also known as parametric release, may be appropriate for products that have undergone terminal sterilization. A sterility test is necessary for an aseptically built product. Before the product is released, it might not be possible to get the results of various testing, such as sterility and pyrogenicity tests, for some radiopharmaceuticals. These tests should be carried out as a manufacturing process monitor, nevertheless. In addition to any direct effects on the patient, potential and real impurities should be taken into account for any potential impact on the product's radiochemical purity or biodistribution.

- **Radioactive Decay:** Each radionuclide exhibits radioactivity, which degrades at an exponential pace with a unique decay constant.

The equation: describes the exponential decline (decay curve).

$$A_t = A_0 e^{-\lambda t}$$

A_t = the radioactivity at time t ,

A_0 = the radioactivity at time $t = 0$,

λ = the decay constant characteristic of each radionuclide,

e = the base of Napierian logarithms.

The half-life ($T_{1/2}$) is related to the decay constant (λ) by the equation:

$$T_{1/2} = 0.693 / \lambda$$

The radionuclide is generally identified by its half-life or by the nature and energy of 532 its radiation or radiations emitted or by both, as prescribed in the monograph.

- **Measurement of $T_{1/2}$:** With the aid of an appropriate radiation detector, such as an ionization chamber, Geiger-Müller counter, scintillation counter (solid crystal or liquid), semiconductor detector, or scintillation counter, the $T_{1/2}$ is determined. The radiopharmaceutical preparation that will be examined is either used undiluted or diluted and then dried in a capsule. Regarding experimental requirements, the radioactivity chosen must be high enough to permit exposure over numerous predictable $T_{1/2}$, but it should not be too high to reduce count rate losses, such as those caused by dead time. The radioactive source has been prepped to prevent material loss during handling. If the substance is a solution,

It is kept in sealed tubes or bottles. If it is a solid then covered by a sheet of sticky cellulose acetate or another substance. The same source is measured in the same geometry throughout a period of around three half-lives, frequently at intervals equivalent to half of the predictable half-life. Utilizing a source with a long $T_{1/2}$, the effectiveness of the equipment is evaluated.

On graph time may be used as the abscissa, and ordinate can be the logarithm of the relative instrument reading (for example, count rate). Unless specifically indicated otherwise in the pharmacopoeia, the computed $T_{1/2}$ should not deviate from the expected $T_{1/2}$ by more than 5%.

- **Measurement of Radioactivity:** The radioactivity of a radiopharmaceutical is specified at a specific date and time. If the radionuclide's decay pattern is known, it is possible to estimate the radioactivity of a specific sample in absolute terms, although in reality, several corrections are needed to produce reliable findings. This is why using a primary standard source to perform the measurement is usual. For radionuclides with a short half-life, such as α emitters, primary standards might not be readily available. Measurement equipment is calibrated by using standards appropriate for the specific radionuclides. Standards should be offered by laboratories that have been approved by the appropriate authority.

Geiger-Müller counters and ionization chambers can be used to appraise "and" and "/" emitters. Scintillation or semiconductor counters, ionization chambers, or liquid-scintillation counters can be used to measure gamma emitters. Specialized tools and methods are needed for the detection and measurement of emitters. It is crucial that samples and standards are measured under identical circumstances in order to compare radioactive sources accurately.

Liquid-scintillation counting can be used to measure low-energy emitters. The sample is dissolved in a solution which contains one or more organic fluorescent compounds such as primary and secondary scintillators. These compounds convert a portion of the energy of disintegration into photons of light. These photons can be detected by a photomultiplier and after that transformed into electrical impulses. Comparative measurements made with a liquid-scintillation counter are adjusted for the effects of light quenching. Wherever possible, direct measurements are taken of the source being evaluated and the reference source under comparable circumstances (such as volumes and types of solutions).

All radiation measurements must be adjusted by deducting the background caused by radioactivity in the surrounding area and caused by false signals produced by the equipment itself.

Because some equipment's detectors and related electronic components have limited resolving times, it can be essential to compensate for loss by coincidence when it was calculated at higher levels of radioactivity. The correction is as follows for a counting system with a constant dead time after each count:

$$N = N_{\text{obs}} / (1 - N_{\text{obs}} \times \tau)$$

N = true count rate/second,
 N_{obs} = Observed count rate/second,
 τ = dead time, in seconds.

This adjustment can be accomplished automatically with the help of some devices. Prior to making the correction for background radiation, the loss by coincidence corrections needs to be made.

The decay during the measurement period should be taken into consideration if the time of a single measurement, t_m , is not insignificantly small than the half-life, $t_{1/2}$ then the decay correction throughout measurement time is as follows-

$$R_{\text{corr}} = \text{instrument reading corrected to the beginning of the individual measurement,}$$

R = instrument reading before decay correction, but already corrected for background, etc.

The findings of radioactivity measurement vary, mostly due to the unpredictable nature of nuclear transmutation. To account for differences in transformations number per unit of time, a sufficient number of counts must be recorded. The relative standard deviation should not more than 1% (confidence interval: 1 sigma) requires at least 10,000 counts because the sd is equal to the square root of the counts.

The radioactivity of a solution is expressed per unit volume to indicate the radioactive concentration.

- **Sterility:** For parenteral administration, radiopharmaceutical preparations must be made utilizing safeguards intended to prevent microbiological contamination and guarantee sterility. Due to the radiation risks, limited batch sizes, and short half-lives of specific radionuclides, radiopharmaceutical preparations face unique challenges. It is not always practicable to hold out on authorizing the release of the radiopharmaceutical product for patient usage while awaiting the results of the sterility test. In these circumstances, the preferred way is to parametrically release the product produced by a thoroughly approved process. Sterility testing must be done as a quality control measure when aseptic manufacturing is being employed. It may not be necessary to perform sterility test when the quantity of the radiopharmaceutical formulations is only one or a few samples (such as when the radiopharmaceutical preparation is therapeutic or has a very short shelf life). When radiopharmaceuticals sterilized by filtration technique or by aseptic process the process validation is important. The delivery of the radiopharmaceutical preparation to the patient is typically on line with a validated production system when the radionuclide's half-life is relatively brief (less than 20 minutes, for example).
- **Stability Tests:** For the radiopharmaceuticals, supplied by the producer the shelf-life must be specified and justified in appropriate manner. The shelf life of the prepared invention should be specified for radiopharmaceutical kits; in this case, data detailing the minimum and maximum levels of radioactivity (as well as minimum and maximum volumes). The other relevant factors which are suggested for use in the manufacturing of the product to be delivered to the patient should be submitted. The stability after removing successive doses of radiopharmaceuticals manufactured in multiple-dose vials needs to be explored.
- **Toxicological and Pharmacological Tests:** There are some possibility that toxicity could be linked to a radiation dosage is understood. The unwanted property of radiopharmaceuticals employed in therapy results in this toxicity, which is a side effect of their usage in diagnosis. Therefore, considerations for radiation dosimetry as well as general elements of the medical product should be included in the assessment of the safety and effectiveness of radiopharmaceuticals.

Studies on toxicity should focus more on the chemical characteristics of toxicity than the radiation aspects. The toxicity of parent molecules should also be determined, after reacting of ligand with a non-radioactive isotope of the appropriate element. The approach and technique which is used must be justified. With the tagged chemical, distribution and elimination investigations should be conducted. No extra toxicity studies would typically be needed for no-carrier-added radioactive elements and their simple salts if the toxicity of that particular product or simple salt is known and already included in the applications.

In many cases it may be acceptable to employ a bulk preparation for toxicity testing (e.g., kit preparations). The stability testing of the bulk material

also required during the testing period. The estimated timeframe for clinical use will be used to calculate the length of animal toxicological testing. The examination period of the toxicity study may be extended in situations when the radiopharmaceutical's pharmacokinetic characteristics (such as retention in specific organs) may result in long-term exposure.

Radiopharmaceuticals study should be intended to appraise:

- The radionuclide complex's immovability in vivo
- The radionuclide's biodistribution in animals
- Any potential chemical toxicity;
- The radiation revelation of tissues brought on by the radiopharmaceutical's administration.

3. Carcinogenic Potential: It is necessary to evaluate any potential carcinogenicity of the compounds under question. The "Summary of Product Characteristics" must make it abundantly evident if no testing for carcinogenicity were conducted.

- **Pharmacodynamics:** Radiopharmaceuticals are typically not anticipated to have measurable pharmacodynamic effects. The possibility of their absence can be inferred from toxicity tests, but it is important to provide information that no pharmacological effect is observed in the major organ systems to provide customers peace of mind.
- **Pharmacokinetics:** Detail descriptions of the radiolabelled compounds' dispersion and elimination are required. If applicable, details on biotransformation and absorption ought to be provided. It is necessary to analyze significant pharmacokinetic parameters in the animal species used in the toxicological experiments. Data from the pharmacokinetic studies on animals should always be available to estimate the tissue and whole body radiation doses that can be extrapolated to humans.
- **Storage:** Store in an airtight container in a location that conform with national and international rules regarding the storage of radionuclides and is sufficiently sheltered to avoid employees from revelation to primary or secondary emissions. Containers may discolor during storage as a result of radiation. This darkening need not necessarily mean that the preparations are becoming worse.

The expiration date of radiopharmaceutical preparations must be made apparent because they are meant to be used quickly. The pharmaceutical purity of radiopharmaceuticals meant for parenteral administration should be preserved during storage.

- **Labelling:** The label on the container should state:
 - Name of the product and radionuclides.
 - It should contain product identification code, identification number (batch number) and manufacturer name.

- The total radioactivity, concentration of radioactive substance (per ml) at a particular date and time, volume of liquid in sample should be mention for the liquid preparations.
- For solid preparations e.g. freeze-dried preparations, the total radioactivity should be clearly written on container at a stated date.
- for capsules, the radioactivity of each capsule at a stated date and total number of capsules in the container;
- The appropriate international symbol for radioactivity should be shown when required.

The label on the package should also state: composition qualitatively and quantitatively, route of administration, expiry date and any special storage conditions if applicable.

➤ **Packaging:**

- The packaging material should be appropriate for the product.
- The labeling procedure should be described.
- It may be necessary to describe special radiation shielding.

Package Leaflets: Package leaflets play an important role for semi-manufactured products and preparation kits which may contain name of the product and a explanation of its uses, content list, manufacturer name and address. It should also contain recognition and quality requirements relating to the radiolabelling material which can be used to manufacture the radiopharmaceutical agents.

Directions to prepare the radiopharmaceutical agent with the range of activity, volume and storage condition for the prepared radiopharmaceutical also be described in leaflets.

Warnings and precautions regarding radiation safety aspects of the prepared radiopharmaceutical should mentioned. Contra-indications, pharmacology and toxicology of the prepared radiopharmaceutical including route of elimination and effective half-life should also shown when applicable.

Safety measures that should be followed by the user and the patient when preparing and administering the product, as well as specific safety measures for the disposal of the container and any unused contents, a statement of the recommended use and dosage for the prepared radiopharmaceutical, a statement of the recommended route of administration, and, if appropriate for specific kits (i.e. those subject to variability beyond the recommended limits), the leaflet should contain the procedures and requirements required to check radiochemical purity.

