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A REVIEW ON REGULATORY FRAMEWORK OF RADIOPHARMACEUTICALS IN PHARMACEUTICAL INDUSTRY: CURRENT SCENARIO AND FUTURE ASPECTS

G. Haswika Reddy * and K. Vinod Kumar

Department of Pharmaceutical Quality Assurance, Raghavendra Institute of Pharmaceutical Sciences (RIPER), Ananthapuramu - 515001, Andhra Pradesh, India.

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Correspondence to Author:
G. Haswika Reddy

Department of Pharmaceutical Quality Assurance, Raghavendra Institute of Pharmaceutical Sciences (RIPER), Ananthapuramu - 515001, Andhra Pradesh, India.

E-mail: haswikareddygangavaran@gmail.com

ABSTRACT: In recent times, the use of radiopharmaceuticals in Medical Imaging and Nuclear medicine has increased. They are a special group of pharmaceuticals with short-shelf life in their final state, and their preparation has been done with utmost care. Due to the inherently hazardous nature of radionuclides on the one hand and the associated concern about radiation safety for patients and staff handling them on the other, this necessitates extreme caution during their manufacture, dispensing, storage and disposal. Therefore there is a need for the implementation of the regulatory guidelines to improvise the quality, safety, and potency of radiopharmaceuticals. This review mainly highlighted the regulatory framework for handling, disposal, and clinical trials of radiopharmaceuticals according to India, Europe Union and USA guidelines. However, in India Cosmetic and Drug act 1940 and rules govern the pharmaceutical industries for the regulatory framework and in Europe and the USA, they follow the EANM and USFDA guidelines. This guideline helps to improvise and remove the barrier for submission to regulatory authorities. The review article is to provide insight into the current regulatory framework surrounding radiopharmaceuticals in major countries around the world, as well as recommendations for delivering high-quality radiopharmaceuticals most cost-effectively.

INTRODUCTION: Why regulatory framework is important for Radiopharmaceuticals. Recently the use of radiopharmaceuticals as diagnostically and therapeutically was increased. The demand for radiopharmaceuticals is growing by the day, fueled by lifestyle disorders and non-communicable diseases such as coronary heart disease [1], Alzheimer's disease [2] and metastasized cancer in the breast and bones.

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The applications of radiopharmaceuticals have been increased day today. The regulatory framework of radiopharmaceuticals has played a crucial role in the part of the pharmaceutical industry for handling, disposal, and most importantly for clinical trials and bioavailability. There are different regulatory guidelines for different countries.

For European countries, the European Association of Nuclear Medicine (EANM) is a professional, non-profit medical organization dedicated to facilitating communication among those working in nuclear medicine to achieve clinical and research excellence. It was established in 1985 [3]. Throughout the world, the global market of

radiopharmaceuticals was increased but still in India by, governing regulatory guidelines faces hurdles and challenges. In India Atomic Energy Regulatory Board (AERB) is charged with developing and implementing appropriate regulatory measures to ensure the radionuclide standard and safe use of ionizing radiation involving radioactive substances [4]. In contrast, the United States of America follows US Food and Drug Administration. Radiopharmaceuticals are a special type of pharmaceutical that must be handled, stored, dispensed, and used with extreme caution. Radioisotopes are distinguished from pharmaceuticals by their short shelf-life, intrinsic hazard, the challenge of maintaining sterility, storage, transport, and waste disposal issues. Even minor dose variations can lead to misdiagnosis or even overexposure. Critical steps must be followed during the preparation of medicines, and extreme caution must be exercised when handling radiopharmaceuticals.

When compared to other pharmaceuticals, radio-pharmaceuticals have more severe side effects. The storage and disposal of radiopharmaceutical waste are critical aspects of waste management throughout the life cycle. The majority of radiopharmaceuticals are made from radio-pharmaceutical waste, primarily composed of radionuclides that lose half their radioactivity in minutes to weeks which emits the beta and gamma radiations. With the end goal of commercialization, *i.e.*, obtaining marketing authorization, the pharmaceutical industry now drives drug development, designing, implementing, and funding controlled clinical trials from Phase I to Phase III. Clinical translation radiopharmaceuticals' initial success, according to history, was related to academic innovations and projects [5]. Many were approved in several European countries without the involvement of national drug regulatory authorities, allowing novel concepts to be used outside of clinical trials for diagnosis and treatment. Most European countries have tightened their regulations in recent years, allowing the use of novel diagnostic and therapeutic radiopharmaceuticals only after national drug authorities have approved a prospective clinical trial application. The introduction of the Clinical Trials Directive in the early 2000s sparked widespread concern, particularly among academic clinical researchers, due to higher costs, a lengthy registration process, and a lack of congruence between countries. The controlled number of clinical studies in Europe has decreased significantly. As a result, efforts to revise the regulatory framework began, and the new Clinical Trial Regulation 536/2014 was born [6, 7]. The diagram below depicts the overall path from the preclinical to the medicinal product.

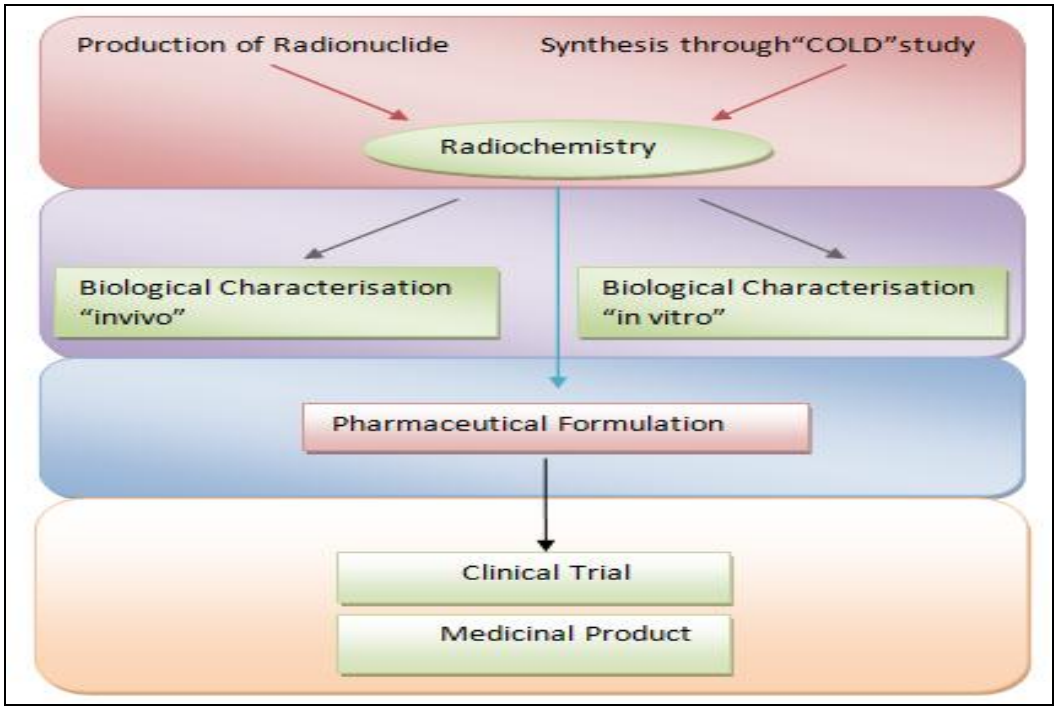

FIG. 1: OVERALL PATHWAY FROM PRECLINICAL TO THE MEDICINAL PRODUCT

This review mainly addresses the regulatory framework of radiopharmaceuticals in handling, disposal, and clinical trials through the European, US, and Indian guidelines and also focuses on the shortcomings of radiopharmaceuticals in light of current regulatory requirements and proposes a path to global harmonization to improve radiopharmaceutical safety evaluations, production quality, and efficacious utilization.

Current Regulatory Advances: The key objective of the "Therapeutic Goods Amendment (Radiopharmaceuticals and Radiopharmaceutical Active Ingredients) Regulations 2020" (the Regulations) is to amend the TG Regulations to exclude such radiopharmaceuticals and radiopharmaceutical active ingredients from the application of Part 3-3 of the Act in Schedule 7 of the TG Regulations (RAI) [7].

The United States Pharmacopeia (USP) is a non-profit organization that establishes drug strength, quality, and purity guidelines. In addition to including all medications and supplements sold in the United States, the regulations also concern radio-pharmaceuticals. A new portion, USP 825, has recently been introduced that sets guidelines for the compounding and handling of radio-pharmaceuticals [8]. CDSCO is involved in regulating radiopharmaceuticals regularly and issues various office orders. On June 29, 2016, office orders were issued stating that all importers must follow the Drug and Cosmetic Act 1940 regulations as revised for importing radiopharmaceuticals [9].

The Regulatory Requirement for the Handling of Radiopharmaceuticals: The person who handles radioactive substances for medical applications is knowledgeable with the legal provisions of 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, Security directives issued regularly by the relevant authorities, and other instructions issued by the competent authority promptly. According to the pharmaceutical industries, during the preparation of radio-pharmaceuticals, they follow the specific or own Standard Operating Procedure (SOP) in the manufacturing of radiopharmaceutical products. The handling of radiopharmaceuticals had been met the regulatory guidelines required for the safety of workers. This entails licensing commitments to keep all exposure levels for the workers involved as low as reasonably possible [10-12]. Radio-pharmaceuticals are a unique class of Pharmaceuticals that must be handled with extreme caution.

Specific Features of Radiopharmaceutical usually include the following [12]:

- Simple distribution chain, with finished product delivered directly from the distribution chain.
- Manufacturer for the nuclear medicine department.
- The batch size is small.
- Shelf life is short, ranging from a few minutes to a few days.
- A sample of quality control (QC) that is representative of the entire batch.
- Due to the micro-dose levels at which diagnostic radiopharmaceuticals are administered, they often have few therapeutic or toxic effects.
- Radiopharmaceuticals are frequently dispensed before all QC examinations are completed.
- Sterility testing, endotoxin content determination, and post-release radionuclide purity testing may be required. As a result, the importance of following Good Manufacturing Practice (GMP) is critical in reducing potential risks.
- Instrument/equipment qualification and validation of methods/processes are necessary to demonstrate that the actions of the hazardous elements are controlled.

SOP for Handling of Radiopharmaceuticals:

- Only trained individuals should be managed for the handling and quality control of radiopharmaceuticals and take part in them.
- Wear eyeglasses and proper gowning when handling the radiopharmaceuticals.

- Radioactive material should not be present in the working areas.
- If the radioactive liquid is to be treated, it must be transported in trays lined with absorbent tissue paper to absorb any spillage.
- When working with radioactive liquids, rubber gloves have to be used.
- Mouth-operated pipettes should never be used. It must be ensured that they have been inactive before making use of glass apparatus.

  The radioactive waste materials must be stored until the low activity before disposal.
- In radioactive activity, smoking, eating, and drinking are prohibited.
- Forceps should be used to handle the radioactive emitter.
- Adequate shielding equipment should be used.
- Radioactive materials must be kept in appropriately labeled containers, brick-shielded containers, and out-of-the-way corners.
- When disposing of radioactive materials, extreme caution is required.
- Radioactivity should be monitored regularly in the storage area for radioactive materials.

The Regulatory Requirement for Disposal of Radiopharmaceuticals: Detailed and reliable research into the existing guidelines of the "Atomic Energy Regulatory Board" (AERB) for the disposal of radiopharmaceuticals is required in India. The AERB is responsible for most of the Radio-pharmaceuticals. Agency and its regulations in India and is part of the Department of Atomic Energy (DAE) of the Government of the Republic of India. To exercise its regulatory effect on radio-pharmaceuticals in India, the AERB has formulated some compulsory requisites in numerous codes, rules, and guidelines. In terms of disposal, the Atomic Energy (Safe) Regulations, G. S. R. 125, 1987 [13] and other code-named Radioactive Waste Management, 2007 have been issued [14]. Aside from that, Nuclear Medicine Facilities issued a security code in 2010 that encompasses the entire spectrum of operations, beginning with the consent of the site, its setup, and the overall declassification layout. The AERB has also mentioned some of the disposal specifications and other relevant guidelines. Very few of these regulations or codes state that radiopharmaceuticals must be disposed of in a specific way. It complies with international standards [15]. The project's goal was to close a regulatory gap in India's current regulatory framework for radiopharmaceuticals, and the development of comprehensive global regulatory guidelines is now standard practice [15]. Because radiopharmaceutical waste can be found in a variety of materials, regulatory guidelines should address each one independently. The primary goal of radiopharmaceutical disposal is to protect radio healthcare professionals, radiation workers, patients, people, and the environment from pollution and radiation exposure. To achieve this, Good Radiopharmaceutical Practices (GRPs), good manufacturing practices (GMP) and radiation safety must be followed in addition to the IAEA's rule.

Radioactive Waste Classification: Radio-pharmaceutical wastes are classified based on various factors, including radiological and physical properties, and are properly disposed of as a result of these classifications.

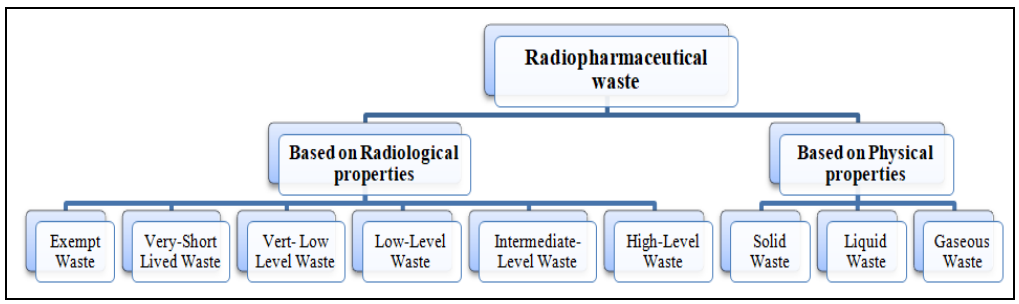

FIG. 2: CLASSIFICATION OF RADIOPHARMACEUTICAL WASTE IN THE PHARMACEUTICAL INDUSTRY

Based on Radiological Properties:

Exempt Waste (EW): Exempt Waste (EW) is a type of low-radioactivity waste that does not need to be regulated by a legal authority. Residues of substances are cleared by the legal authority after radioactivity and are not counted as radioactive waste. There is a small amount of radioactive material in this waste that is safe for human health and the environment.

Very-Short Lived Waste (VSLW): These wastes' radioactivity above the exemption limit and have been stored for a few years falls below the release limit known as VSLWs. These radioactive wastes typically come from applications of radionuclides for scientific and medical purposes.

Very-Low Level Waste (VLLW): VLLW refers to radioactive waste that exceeds the exemption limit, is not classified as VSLW, and has an activity concentration of less than 1/100 of the release limit. The majority of the waste comes from the nuclear power plant's operation, decommissioning, and evacuation phases.

Low-Level Waste (LLW): LLW is made up of components contaminated with nuclear waste or has become radioactive due to exposure to neutron radiation. Contaminated protective clothing, swaps, injectors, laboratory animal carcasses, machinery, and tools contain a significant amount of waste. It is disposed of in a surface landfill.

Intermediate-Level Waste (ILW): These waste materials are subjected to alpha or long-lived radionuclides at a concentration level that necessitates their isolation and long-term storage. Ion-exchange resins, certain radioactive sources used in radiation therapy, and contaminants from reactor disposal are all included in this waste category.

High-Level Waste (HLW): Radioactive Waste Management Regulation HLW defines “radioactive waste produced as a result of reprocessing, which may be reprocessed. Contain fission products and actinides, as well as other radioactive wastes with activities nearby, shall be classified as HLW.” HLWs are radiated substances that are produced as a by-product of nuclear reactor reactions.

Based on Physical Properties:

Solid Waste: Solid radiopharmaceuticals include contaminated swabs, gauntlets, and lancets used in the manufacture of radiopharmaceuticals, as well as radionuclide generator waste from particle accelerators and nuclear reactors, the radio-pharmaceutical set after it has been used and has reached its expiration period, contaminated spoons used by patients, swabs, gloves and lancets used in the manufacture of radiopharmacy pipettes, glassware, plastic containers, blood lancets, contaminated media, disposable radioimmunoassay plastic tips, lead pots used for decay in contaminated storage, and sealed sources used and disused at the end of the cycle, are all examples of this type of waste.

Liquid Waste: The main components of liquid waste are wastewater of contaminated radiation patients waste, instruments, glassware, unutilized and unsealed radiopharmaceuticals, labeled compounds, and sludge from patients receiving radiopharmaceuticals such as 131I, 89Sr, 90Y, and 32P during treatment.

Gaseous Waste: Exhaust systems frequently release gaseous waste such as iodine-123,125,131, and Xenon-133 into the atmosphere. Gases released outside the building are not allowed to re-enter through open windows or ventilation systems.

The regulatory requirements for Clinical Trials:

Requisites for Clinical Trial with Radiopharmaceuticals: The continuing to rise regulatory overburden in the pharmaceutical industry, through extensive, and in the field of radioactive drugs, in particular, is posing a significant barrier to the development of new radiopharmaceuticals for clinical use. According to European regulations, radio-pharmaceuticals are now classified as drugs or "medicinal products" in almost every country and are subject to the same rules. To ensure the potency of a new drug, clinical trials are required before it can be considered suitable for its intended use. Even though some countries permit "compassionate use," which was one of the most common methods for bringing new diagnostic and therapeutic radiopharmaceuticals into clinical use outside of clinical trials, it is poorly regulated. It has become less common in recent years [16]. In addition to nuclear medicine, clinical trials provide information that is accepted

by authorities and other clinical specialties. Such information is also required for the commercial exploitation of experimental drugs, and it must be collected in a well-documented manner throughout the development process. In submitting clinical trial documentation, most of the industry people follow the USA and Europe guidelines [17].

Present Regulatory Framework of Clinical Trials in Europe: Regulation 536/2014, also known as the "Clinical Trial Regulation," will govern clinical trial legislation in the European Union (EU). When comparing this new regulation to the old (but still valid) Directive 2001/20, there are significant differences [18]. Clinical trials are currently governed by the Clinical Trials Directive, which is a unified regulatory framework in the European Union (EU). Individual EU member states must incorporate a directive into their domestic legislation, resulting in minor variations across Europe. Radiopharmaceuticals are referred to as Investigational Medicinal Products (IMPs) when they are used in a clinical trial [19].

In addition to the Clinical Trials Directive, preparation rules ("Good Manufacturing Practices" —GMP) [20] and details for "Good Clinical Practice" (GCP) [21] were established. In the United States, the Food and Drug Administration (FDA), which reviews clinical trials, takes a different approach to submission and approval. The differences in radiopharmaceuticals between Europe and the US have recently been discussed. A clinical trial application dossier, on the other hand, necessitates similar documents, which are discussed in the following chapter.

Application and Documentation Practices: The clinical trial regulatory system determines who is responsible for the trial's application and execution (both "old" and "new"). The sponsor and the principal investigator both play important roles. The sponsor is mostly a pharmaceutical company. The sponsor receives any pertinent trial information from the investigator. The registration process for clinical trials with IMP begins with online registration with Eudra CT (European Union Drug Regulating Authorities Clinical Trials), a European database. After registration generation of Eudra CT number has been generated, this number contains all information of sponsor, investigator, and the total countries included in the clinical trials. The Clinical Trials Directive still governs the rest of the clinical trial application process within the European Union [22]. A national radiation safety body must also approve a clinical trial involving radiation in some countries. Shortening timelines and simplifying the process are two major goals of the new Clinical Trial Regulation 536/2014. The clinical trial protocol, Informed Consent Form (ICF), Case Report Forms (CRFs), and Standard Operating Procedures (SOPs) are all crucial documents. The EU's most important document is the Investigational Medicinal Product Dossier (IMPD). The IMPD is a lamination of pertinent trial conduct information extracted from the IMP. The proposed form for this document is set up in the Fundamental Structure of Trials [23].

Quality Studies: The chemical and structural properties of the new radiopharmaceutical are described in the first section of the IMPD. This part provides information about the starting product and finished product, the data in **Table 1.**

TABLE 1: REQUIRED QUALITY DATA OF RADIOPHARMACEUTICAL TRANSLATIONS

S. no.	Type of Product	Data	Purpose
1	Starting Product	Precursor	Specifications, Stability studies, product and analytical data
		Radionuclide	Specifications, Stability studies, product and analytical data
		Reference material	No purpose
2	Finished Product	Excipients	Controls, Stability, COA and Producer
		Formulation	Development, composition and process
		Stability	Shelf life and storage
		Analytical Control	Validations, Specifications, and impurity profiling

As a result, drug regulators expect a deluge of information about the quality of radionuclides and chemical precursors classified as Active Pharmaceutical Ingredients (API) in the drug substance section. An authorized manufacturer must follow GMP when preparing a chemical precursor, such as a peptide targeting a receptor, notably if substrates are not withdrawn by the

purification process, as is often an instance in theranostic applications with radiometals. One of the most significant expenses associated with translational research.

Here describing test methods, specifications, and also the stability data of finished product and precursor were important in the quality studies of a new radiopharmaceutical. It is also important that the information of excipients in the studies which are under development.

Clinical and Non-Clinical Studies: Data on IMP's safety and efficacy should be included in the second part of the IMPD. Clinical data must be submitted early in the development of new radiopharmaceuticals, followed by expected safety studies, and finally efficacy studies. Pharmacokinetic and pharmacological data were included in the non-clinical data.

This must be supplemented with data on the target interaction, which is typically obtained through functional profile *in-vitro* studies. Animal study data on therapeutic efficacy should also be considered. In the case of theranostics and its application in the context of clinical therapy. Dosimetry studies must be included in non-clinical safety data.

These are an important part of a medication's safety and toxicity assessment. The use of radioactivity is the most common cause of teratogenicity, genotoxicity and carcinogenicity. The ICH guideline M3 describes non-clinical safety data (R2) [24]. This guideline describes the "micro-dosing concept" for evaluating non-radiopharmaceutical compounds in radio-pharmaceuticals.

Radiopharmaceuticals are considered safe because they are only given once at a dose of 100g. The EANM recently published a position paper that develops deeper into the issues surrounding this topic [25, 26]. The conduction of clinical trials has to follow strict regulatory guidelines not only EU guidelines and other national territory guidelines, during the submission. There are different people involved in the authorization of a clinical trial.

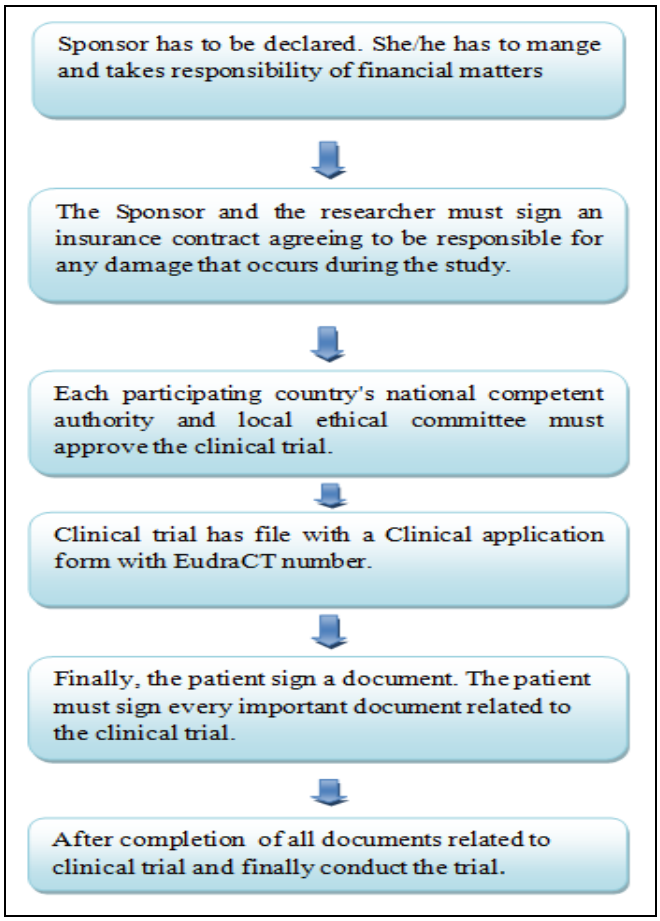

FIG. 3: STEPS INVOLVED IN THE CLINICAL TRIALS PROCESS IN EUROPE

TABLE 2: DOCUMENTS REQUIRED FOR CLINICAL TRIAL SUBMISSION IN EUROPE

S. no.	Documents	Purpose
1	Clinical trial application form (CTA) with Edura CT number	Edura CT number should be specific for clinical trial must used in all authorizations and ethical committee
2	Investigator's Brochure (IB)	It is a collection of clinical and non-clinical data
3	Investigational Medical Product Dossier (IMPD)	It includes all the information on quality, production, pharmacological, toxicological, and the risk and benefits of IMP
4	Informed Consent Form (ICF)	It declares that the patient knows all information about the trial like risks, benefits and alternatives of trial
5	Case Report Form	It is a document for the evaluation of specific data (*eg*. Blood tests, *etc*.,) of patients through entire trials

The Present Regulatory Framework in the United States for Clinical Trials: The Food and Drug Administration (FDA) in the United States is in charge of clinical trials. The following are the two regulatory options for conducting radiopharmaceutical clinical trials:

a. By FDA regulation 21 CFR 312 Investigational New Drug Application, "under an IND application [26].

b. By RDRC" – as part of the institutional Radioactive Drug Research Committee (RDRC) program, by 21 CFR 361.1 Radioactive Drugs for Certain Research Uses, a federal regulation [27].

CONCLUSION: The growing demand for radiopharmaceuticals has illustrated the need for a powerful regulatory framework to help them move as quickly as possible from the work surface to the bedside. Manufacturers and investigators avoid investing in the radiopharmaceutical domain because the current regulatory framework has numerous flaws that make it confusing. For handling, disposal, and clinical trial submission in India, Europe, and the USA has to follow the regulatory guidelines. In India, radio-pharmaceuticals are covered by Schedule K of the Drug and Cosmetic Act 1940, which states that Schedule K drugs are exempt from the provisions of Chapter IV of the act (rule 123). For European countries, the European Association of Nuclear Medicine (EANM) is a professional, non-profit medical organization dedicated to facilitating communication among those working in nuclear medicine to achieve clinical and research excellence and it was established in 1985.

In the USA for the regulatory frame of radiopharmaceuticals has to follow the FDA guidelines. As part of its cradle-to-grave approach, any new radiopharmaceutical should have a regulatory plan that covers the entire life cycle, this includes methods for reducing waste during its production, use, and final disposal. Furthermore, clinical and preclinical studies of radiopharmaceuticals must be prioritized to ensure the radiopharmaceutical's potency. It would boost public confidence in the radiopharmaceuticals' safety and quality.

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