International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 04 (F); April 2019; Page No.18407-18411
DOI: http://dx.doi.org/10.24327/ijcar.2019.18411.3518

Research Article

RADIOPHARMACEUTICALS - REGULATORY FRAMEWORK AND MARKET AUTHORIZATION PROCESS IN US AND INDIA

Ritika Pal, Harvinder Popli and Sumati Randeo

Department, Delhi Institute of Pharmaceuticals Science and Research University
New Delhi 17, India

A R T I C L E I N F O

Article History:
Received 12th January, 2019
Received in revised form 23rd February, 2019
Accepted 7th March, 2019
Published online 28th April, 2019

Key words:

Radiopharmaceuticals,,market authorization ,regulatory guidelines, regulatory approval pathway, regulatory controls.

A B S T R A C T

Radiopharmaceuticals are radioactive sterile and non-sterile drugs that are used to diagnose, monitor, and treat diseases.The exponential rise in use of Radiopharmaceutical in healthcare can be attributed to their twin application as diagnostics and therapeutic agents. They are special group of pharmaceuticals containing a short-lived radionuclide in their final form and are generally administered intravenously. This mandate utmost care coupled with stringent quality and essential safety requirements throughout their production, dispensing, storage and disposal. Further these safety measures are important due to inherent hazardous nature of radionuclide on one side and the associated concern regarding radiation safety for patient as well as staff handling them on the other side. These pertinent safety requirements and unique features associated with the hazardous nature of Radiopharmaceuticals have attributed to increased regulatory controls worldwide and having a complex regulatory market authorization process. Most of the regulatory regimes in the world regulate these drug compounds both under the drug / pharmaceutical regulatory authority as well as atomic nuclear radiation energy regulating authorities. The present article aims at providing insight into current regulatory framework for radiopharmaceuticals in US & India. An attempt has been made to compare the two regulatory models and analyze the impact on regulatory approval pathway with the implementation of India Medical Device Rules 2017.

INTRODUCTION

Evolution of Regulatory Framework For Radiopharmaceuticals In Usa & India

History of Radiopharmaceuticals In India

Use of radiopharmaceuticals started during ninety sixties in India .This period saw the advent of radiopharmaceuticals like iodine-131 labeled molecules which could concentrate in specific organs.99mTc-radiopharmaceuticals were introduced in the early seventies. This began with the production of 99Mo in the CIRUS reactor and development of a solvent extraction generator for producing 99mTc.

Introduction of molybdenum-99-technetium-99m solvent extraction generator and cold kits for preparation of a variety of technetium-99m-radiopharmaceuticals in the early seventies marked an important point in the evolution of radiopharmaceuticals use in India.

The production of 99mTc generators enabled the use of short lived radiopharmaceuticals at nuclear medicine centres far from the reactor sites This became possible due to the development of the speciality of hospital radiopharmacy during late seventies. With the increased use of radiopharmaceuticals for diagnosis in patients, a regulatory body to ascertain the quality of products and address any legal matters became necessary. The "Radiopharmaceuticals Committee" (RPC) comprising members from various organizations such as Professors of pharmaceutical sciences, Drug Controller General of India, Food and Drug Administration (FDA, Maharashtra) along with leaders in Radiopharmaceuticals Programme of BARC, was formed in late seventies.

The next decade witnessed a flurry of activity in this area and as a natural outcome, several 99mTc based radiopharmaceuticals were introduced in the market by BARC. Nearly all the vital organs could be imaged using the indigenous products..By 1980, nearly 12 radiopharmaceutical products based on 99mTc and 131I were being supplied to more than 60 nuclear medicine centres by BARC.

The actual utilization of cyclotron produced radioisotope in medicine has begun with the commissioning and operation of a medical cyclotron at the basement of Tata Memorial Hospital, Parel, in October 2002.

Corresponding author:* **Ritika Pal
Department, Delhi Institute of Pharmaceuticals Science and Research University New Delhi 17, India

The cyclotron has been functioning satisfactorily and over 1200 patients have benefited from the modern technology of "Positron Emission Tomography" (PET) using 18F labeled 2-fluorodeoxyglucose, which is most often used to delineate sites of metastases in cancer patients.

History of Regulation of Radiopharmaceuticals In Usa1

1997, Congress passed the Food and Drug Administration Modernization Act (the Modernization Act). Section 121 of the Modernization Act directed Food and Drug Administration to

a. establish appropriate approval procedures and Current Good Manufacturing Practices (CGMPs) for PET drugs.(21 CFR 212)
b. Under the necessities of section 121 of the Modernization Act,, a new drug application (NDA) or abbreviated new drug application (ANDA) must be submitted for any PET drug marketed for clinical use in the United States.

FDA conducted several public meetings with various representatives of an industry trade association, the Academy for Molecular Imaging (formerly the Institute for Clinical PET (ICP)), and other interested persons to discuss FDA proposals for PET drug approval procedures and CGMP requirements. Because certain PET drugs have been used clinically for a number of years, FDA conducted its own review of the published literature to evaluate the safety and effectiveness of the PET drugs in widespread use for certain indications to facilitate the process of submitting applications for these products. The Agency discussed its preliminary findings on the safety and effectiveness of fludeoxyglucose F 18 injection (for the assessment of malignancy as well as left ventricular myocardial viability) and ammonia N 13 injection (for assessing myocardial perfusion) with the ICP at public meetings on February 1999.

In a notice in the Federal Register in March 2000 (the PET Safety and Effectiveness Notice),FDA presented its findings of safety and effectiveness for the PET drugs studied for certain indications and described the types of applications that can be submitted for fludeoxyglucose F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection used in PET imaging .

In April 2002, FDA issued a preliminary draft proposed CGMP regulation and a draft guidance on CGMP requirements for public comment; a proposed rule and revised draft guidance were issued in September 2005, to solicit additional public input. In December 2009, after carefully considering all public input, FDA published a final CGMP regulation, triggering the two-year time period for applicants to submit an NDA or ANDA for any PET drug used clinically. 2. GLOBAL MARKET SCENARIO OF RADIOPHARMACEUTICALS

Over the last few decades, global average life expectancy has increased which lead to increase in geriatric population globally. As the geriatric population is more prone to cardiovascular, neurological, oncological disorders and radiopharmaceuticals being a non-invasive technology, there is increased demand for radiopharmaceuticals around the world. Moreover, with a shift from Acute to Chronic diseases and raising awareness of radiopharmaceuticals among healthcare providers there is increased demand for radiopharmaceuticals in emerging economies.

Some of the key issues associated with the use radiopharmaceuticals are their inherent hazardous nature which mandates the availability of trained qualified technician for radiopharmaceuticals, who has the expertise to handle these drugs but there is a shortage of these qualified technicians also.

Other key issues are their shorter half-life, storage, transportation, waste disposal issues, and higher cost & supply shortage of radioisotopes

Table 1 Major companies and their radiopharmaceutical products.

c	Company	Diagnostic radiopharmaceuticals	Therapeutic radiopharmaceuticals
1	CARDINAL HEALTH	Gallium Ga 67 citrate Indium In 111 pentetate Indium In 111 pentetreotide Iodine I 123 iobenguane Iodine I 123 sodium iodide capsules Iodine I 131 human serum albumin Iodine I 131 sodium iodide Technetium Tc 99m bicisate Technetium Tc 99m disofenin Metastron ™ Fluorine F 18 flutemetamol Fluorine F 18 fludeoxyglucose Fluorine F 18 sodium fluoride	Iodine I 131 iobenguane (Azedra) Iodine I 131 sodium iodide Radium Ra 223 dichloride injection (XOFIGO®) Samarium Sm 153 lexidronam Strontium Sr 89 chloride Yttrium Y 90 ibritumomab tiuxetan
2	G E HEALTHCARE	Myoview ™ Ceretec ™ Drytec ™ Metaiodobenzylguanidine I ^{131} Injection	Metastron ™
3.	JUBILANT DRAXIMAGE	DRAXIMAGE® MAA DRAXIMAGE® MDP-25 DRAXIMAGE® DTPA DRAXIMAGE® I-131 Diagnostic Capsules DRAXIMAGE® I-131 Diagnostic Solution DRAXIMAGE® MDP DRAXIMAGE® Sestamibi DRAXIMAGE® Gluceptate	DRAXIMAGE® I-131 Diagnostic Solution DRAXIMAGE® I-131 Therapeutic Capsule

Market Share

The global market for radiopharmaceuticals is expected to grow at a CAGR of 5.4% over the period between 2017 and 2024, finds Transparency Market Research[2]

North America alone recorded more than 40% market share in the global radiopharmaceuticals domain in 2016 and is all estimated to cross US$ 4,000 by the end of 2026 growing at 6.2% CAGR

According to report by Transparency Market Research entitled "Radiopharmaceutical Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast 2016 – 2024" North America is all set to register 60 % share in the global radiopharmaceuticals market by 2024 while the Asia Pacific region is expected to emerge as the fastest expanding regional market in terms of revenue growing at 6.3% CAGR from 2016 to 2024

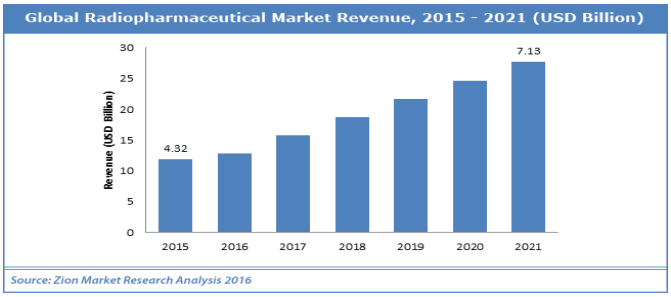

Figure 1 Global Radiopharmaceutical Market Revenue,2015-2021

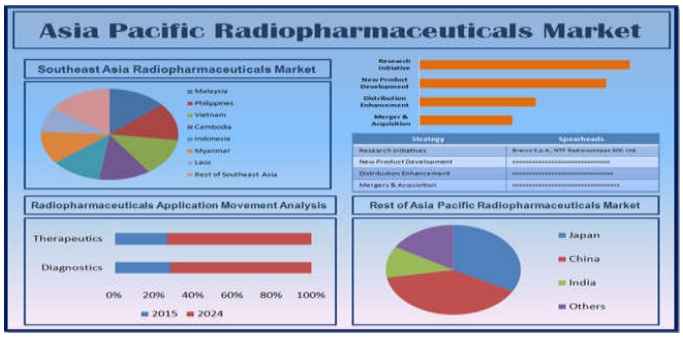

Figure 2 Asia Pacific Radiopharmaceuticals Market

Figure 3 Radiopharmaceuticals Market Value by Radioisotopes

Regulatory Framework of Radiopharmaceuticals In Usa

In US radiopharmaceuticals are mainly regulated by Center for Drug Evaluation and Research (CDER) which is a division of U.S. Food and Drug Administration (FDA). Another agency is Nuclear Regulatory Commission (NRC)[3] which is an independent U.S. government agency regulates the medical use of radioactive materials including regulations concerning radiation exposure. To assist the agency with being responsive to the needs of the medical community, the NRC has established an Advisory Committee on the Medical Uses of Isotopes (ACMUI).

Advisory Committee on the Medical Uses of Isotopes (ACMUI)advises the U.S. Nuclear regulatory Commission (NRC) on policy and technical problems that arise within the regulation of the medical use of radiopharmaceuticals used in diagnosis and therapy. The ACMUI membership includes health care professionals from various disciplines, who comment on changes to NRC regulations and guidance; evaluate certain non-routine uses of radioactive material; provide technical assistance in licensing, inspection, and produce key problems in front of the Commission for appropriate action.

The Department of Transportation (DOT), regulates transportation of radiopharmaceuticals in vehicle on public roads, on trains, or on airplanes.

Use of Positron Emission Tomography Drugs in US[4]

Clinical Use

Clinical use refers to administration of the PET drug to patients in order to treat them with no intent to determine the safety or effectiveness of the drug.

Clinical use of PET drug in US is allowed only if that drug has an approved new drug application (NDA) or abbreviated NDA (ANDA) .

Investigational use

Investigational use refers to the administration of PET drugs to human subjects under an IND in order to determine its safety and/or efficacy. The goal of IND study is to determine the safety/or effectiveness of IND use of the drug .

Research Use

Research use refers to administration of PET medicine to human subjects under the supervision of Radioactive Drug Research Committee (RDRC) with the objective to get basic information regarding the metabolism, physiology, pathophysiology or biochemistry of the PET drug. Such administration is neither intended for immediate therapeutic or diagnostic purposes, nor to determine the safety and effectiveness of the drug.

Regulatory Status of Radiopharmaceuticals In India

Atomic energy regulatory board (AERB) and Central Drugs Standard Control Organisation (CDSCO) are two main authorities which regulates radiopharmaceuticals in India. Radiopharmaceuticals are enlisted in Schedule K of Drug and Cosmetic Act and according to Rule 123 are exempted from the provisions of rules of its Chapter IV which concerns the manufacture, sale and distribution of drugs and cosmetics.[5]

Radiopharmaceuticals (diagnostic radiopharmaceuticals) fall under Medical Device category as per Indian Medical Device rules 2017 because they cannot be used stand-alone without any device/scan. Till date many radiopharmaceuticals are approved as drugs and many are approved as medical device because there is no clear cut understanding related to this topic. Transition phase from drugs to medical device is going on for radiopharmaceuticals.

Regulatory Authorities for Radiopharmaceuticals in India

Atomic Energy Regulatory Board (AERB)[6]

Atomic Energy Regulatory Board under Department of energy (DAE), Government of India (GoI) is the primary

Regulatory and safety monitoring authority for radiopharmaceuticals in India. AERB derives its regulatory functions from various rules and notifications propagated under the Atomic Energy Act, 1962 and the Environment (Protection) Act, 1986.

It is involved in site inspection and licensing of all the radiation facilities in India, and for authorization/approval of use of radiopharmaceuticals. The board has developed safety standards, guidelines and manual for the purpose i.e Safe transport of radioactive material, security of radioactive

material during transport, safety code and guides on radioactive waste management. Objective of safety standards is to ensure safety of members of the public and occupational workers as well as protection of environment.

AERB has initiated a web based application called eLORA (e-licensing of radiation applications) for facilitating automation in the regulatory process for various radiation facilities in India, wherein all the products are listed in its portal.

Central Drugs Standard Control Organisation (CDSCO)

CDSCO under board of Directors General of Health Services, Ministry of Health & Family Welfare, Government of India. CDSCO is responsible for approval of import and registration of radiopharmaceuticals in India

Board of Radiation and Isotopic Studies (BRIT)

The Board of Radiation and Isotopic Studies (BRIT) is an independent unit of the Department of Atomic Energy (DAE), GoI, which caters to the requirements of products based on radiation and radiopharmaceuticals in India.

In conjunction with Radiopharmaceuticals Division of the Bhabha Atomic Research Center (BARC), Mumbai it carries out development, production and supply of radiopharmaceuticals to many nuclear medicine centres throughout the country. BRIT manufactured radiopharmaceuticals are supplied according to a set dispatch schedules after Radiopharmaceutical committee (RPC) approval of BARC

Bhabha Atomic Research Centre (BARC)

BARC supplies reactor-produced radioisotopes to BRIT, where they are processed leading to production of radiopharmaceuticals for their multifarious applications in healthcare. These radiopharmaceuticals are produced by BRIT in strict compliance with regulations according to the Radiopharmaceutical Committee (RPC) guidelines of BARC.

Import of Radiopharmaceuticals in India [7]

Rule 23 to 27(A) of Drugs & Cosmetics Rules 1945 specify the provisions for grant of Registration Certificate and Import Licence for import of drugs including Radiopharmaceuticals.

Before importing these radiopharmaceuticals, the importer have to obtain no objection certificate from BARC for end user and same shall be submitted to Customs Authorities at the time of Import.

No consignment of such products shall be released without Import Licence. Transition period of 45 days has been given to importers to submit application for grant of import licence.

For those IN VIVO Radiopharmaceuticals products, which do not have indigenous manufacturing facility, Form 10 licence may be granted after the approval of central government, without Registration Certificate under Rule 24(2).

For those IN VIVO Radiopharmaceuticals for which indigenous manufacturing facilities are available, Import Registration and Licence in form 10 will have to be obtained as per the provisions of Drugs & Cosmetics rules 1945 and such products shall be tested for their quality at the time of import.

Importer should voluntarily make the sample available for test & analysis by Radiation Medicine Centre of BARC or Institute of Nuclear Medicine & Allied Sciences(INMAS) from out of samples imported within 10 working days of his order.

Necessary permission should be taken by importer from AERB to transport the sample to testing centre.

In case, where samples fail in test/analysis, no import from the manufacturer shall be permitted and stocks already imported or in transit shall be disposed off or re exported in prescribed manner.

In case of non submission of sample for testing /manufacturing within 10 working days by the importer, then no further import will be allowed.

Registration Certificate means a certificate issued under Rule 27A by the licensing authority in Form 41 for registration of the premises and the drugs manufactured by the manufacturer meant for import into and use in India.

Import licence means either a licence in Form 10 to import drugs; excluding those specified in Schedule X, or a licence in Form 10-A to import drugs specified in Schedule X;

Table 2 Various Guidelines for Radiopharmaceuticals In Us & India

S .No	Country	Regulatory Agency	Guidelines
1.	USA	USFDA	1. Nuclear Pharmacy Compounding Guidelines – 2001 . 2. Procedure Guidelines For Use of Radiopharmaceuticals – June 2001 3. The Transport of Radiopharmaceuticals in the United States - September 2004. 4. CGMP for Phase 1 Investigational Drugs – July 2008. 5. PET Drugs - Current Good Manufacturing Practice (CGMP) – December 2009. 6. Pediatric Radiopharmaceutical Administered Doses: 2010 North American Consensus Guidelines 7. PET Drugs - Current Good Manufacturing Practice (CGMP) : Small Entity Compliance Guide - August 2011 8. Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals - November 2011 9. Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs - December 2012 10. Clinical Trial Imaging Endpoint Process Standards Guidance For Industry - March 2015 11. Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities - December 2016 12. Compounding And Repackaging of Radiopharmaceuticals by State Licensed Nuclear Pharmacies and Federal Facilities - December 2016 13. Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations - September 2017
2.	INDIA	AERB CDSCO	1. Regulatory Inspection and Enforcement in Nuclear and Radiation Facilities - September 2002 2. Security of Radioactive Material During Transport - January 2008 3. Nuclear Medicine Facility - March 2011 4. Radioisotope Handling Facilities - August 2015

CONCLUSION

Radiopharmaceuticals have become important because of their twin application as diagnostic and therapeutic agent. The recent trend in increase of cancer cases, their detection and treatment has been a major factor drawing the attention of researchers towards radiopharmaceuticals which can be suitably exploited for such purposes.

Insufficiency of harmonized guideline is evident for radiopharmaceuticals. Therefore it's become pertinent to deal with all the problems associated with development, producing, dispensing, ADR reportage, transport, disposal, and labeling needs regarding radiopharmaceuticals. The implementation of strict restrictive guidelines to assess quality, safety, and efficacy of radiopharmaceuticals is need of the hour.

In India, with the advent and implementation of New Medical Device Rules 2017 there is an ambiguity prevailing whether certain category of radiopharmaceuticals should follow drug regulatory pathway or Medical Device. According to Indian Medical Device Rules 2017, these diagnostic radiopharmaceuticals are Medical Devices because as such they cannot be used stand alone, they require PET /SPECT scan for their functioning.

References

1. https://www.federalregister.gov/documents/2011/02/03/2011-2313/positron-emission-tomography-notice-of-public-meeting-request-for-comments
2. https://www.transparencymarketresearch.com/pressrelease/radiopharmaceuticals-market.htm
3. http://www.cdsco.nic.in/writereaddata/notice20_2_2017.pdf
4. https://www.fda.gov/downloads/drugs/%E2%80%A6/ucm291573.pdf
5. https://www.nrc.gov
6. https://www.aerb.gov.in
7. http://www.cdsco.nic.in/writereaddata/Drugs&CosmeticAct.pdf

How to cite this article:

Ritika Pal, Harvinder Popli and Sumati Randeo (2019) ' Radiopharmaceuticals - Regulatory Framework and Market Authorization Process in us and India', *International Journal of Current Advanced Research,* 08(04), pp. 18407-18411. DOI: http://dx.doi.org/10.24327/ijcar.2019.18411.3518

****