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REGULATORY FRAMEWORK OF RADIOPHARMACEUTICALS: CURRENT STATUS AND FUTURE RECOMMENDATIONS

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ABSTRACT: Radiopharmaceuticals are the new buzzword in the pharmaceutical industry and are truly an index of the modern medicine and a high-tech industry. The exponential rise in radiopharmaceutical domain can be attributed to their dual application as diagnostic as well as therapeutic agent. They are special group of pharmaceuticals containing a short lived radionuclides in their final form and are general used intravenously. This mandates utmost care during their manufacturing, dispensing, storage and disposal 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. Their production should conform to latest principles of Good Manufacturing Practice at each stage as majority of them cannot be reprocessed. Therefore radiopharmaceuticals needs to cater to the regulatory requirement of pharmaceutical regulator as well as nuclear regulator. Major regulatory bodies across the globe have their different perspective on radiopharmaceutical manufacturing, subsequent dispensing, their transport, storage and disposal etc. However regulatory framework of radiopharmaceuticals is still in its infancy stage in many developing countries. The present article aims at providing insight into current regulatory framework surrounding radiopharmaceuticals in major countries across the globe and attempts to provide recommendations so that high quality radio pharmaceutical are delivered in the most cost effective manner.

KEYWORDS: Radiopharmaceuticals, Guidelines, Good Manufacturing Practices, Good Radiopharmacy Practices, Radiation safety, Radiation facility

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1. INTRODUCTION

Radiopharmaceuticals are the agents which are used for diagnostic and therapeutic purposes. They are classified differently by various organizations around the world. According to WHO, they are classified as Ready-for-use radioactive products, Radionuclide generators, Non-radioactive components ("kits") for the preparation of labelled compounds with a radioactive component and Precursors used for radiolabelling other substances before administration [1]. According to Australia New Zealand Society for Nuclear Medicine (ANZSNM) they are classified into three groups: Preparations which are supplied as a radioactively-labelled product in a ready-to-inject form, Inactive products which are made radioactive immediately prior to patient injection and Radionuclide preparations that are combined with an inactive preparation to produce the final product for injection [2]. They are characterized by their chemical and physicochemical properties and by the radiation properties of the radionuclide which they contain. Radiopharmaceuticals consist of pharmaceutical component as well as radioactive component as shown in Figure 1 and strict requirement exists to fulfil the quality specifications for both of them.

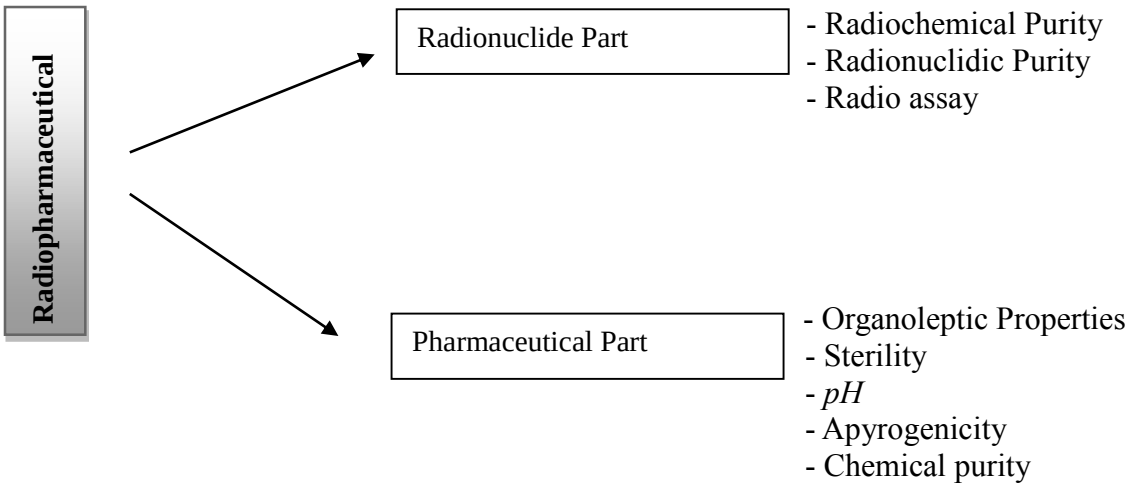

Fig.1. Depiction of Requirements for Quality Parameters for Radiopharmaceuticals.

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The development of nuclear medicine over the past several decades is intrinsically correlated to the advances in chemistry and the development of radionuclides and radiolabeled compounds [3]. Henri Becquerel originally discovered naturally occurring radioactivity. However it was Captain Bill Briner who paved the way for foundation of Practice of Radio pharmacy and is rightly said to be the "Father of Radio Pharmacy". The discovery of Technetium-99^m in the late 1930s by C. Perrier and E. Segre was a significant milestone in the path of radiopharmaceutical development. Historians also believe the discovery of artificially produced radionuclides by Frédéric Joliot-Curie and Irène Joliot-Curie in 1934 as the most significant milestone in nuclear medicine [4]. The development of a generator system to produce Technetium-99^m in the 1960s became a practical method for medical use. Radiotracers had been in use for various therapeutic purposes after discovery of radioactivity. However significant milestones for its advanced applications in diagnostic and therapeutic domain came with the availability of cyclotrons which could produce an array of radioisotopes. Subsequently nuclear reactors has now made it possible to produce even larger quantities of radioisotopes [5]. In 1971 American Medical Association officially recognized nuclear medicine as a medical specialty. The 1980s saw use of radiopharmaceuticals for diagnosing heart disease. The emergence of single photon emission computed tomography (SPECT), around the same time, led to three-dimensional reconstruction of the heart and establishment of the field of nuclear cardiology. More recent developments in nuclear medicine include the invention of first positron emission tomography scanner (PET) which is used in regular diagnostic imaging using Fluorine-18 in the form of fluorodeoxy glucose (^{18}F-FDG) [6].

2. CURRENT MARKET OF RADIOPHARMACEUTICALS

Radiopharmaceuticals have traditionally been used for various diagnostic procedures. However recent research has led to their use as therapeutic agent also. The global radiopharmaceuticals market is driven mostly by an aging population and cardiovascular, oncological and neurological disorders. Moreover radiopharmaceuticals use for pediatric population has now also been regulated leading to their widespread application [7]. The regular supply of radioisotope and its local production has paved the way for ample research on new radiopharmaceuticals and rush of products into the market. Most of the radiopharmaceuticals are used in nuclear imaging as it offers a non-invasive, stationary and dynamic image of the body's organ. Some of the major players in the global radiopharmaceuticals market include Bayer Healthcare AG, Cardinal Health, Inc., GE Healthcare, Eczacibasi-Monrol Nuclear Products, IBA Molecular Imaging, Mallinckrodt PLC,

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Medtronic PLC, Nordion, Inc., Siemens Healthcare and Jubilant Pharma. Market research report released by Transparency Market Research estimates the global radiopharmaceuticals market to witness rapid expansion at a CAGR of 18.30% during the period between 2012 and 2018. North America alone recorded more than 40% market share in the global radiopharmaceuticals domain in 2016 and is all poised to cross US$ 4,000 Mn by the end of 2026 growing at 6.2% CAGR. This has been attributed to the widespread availability of various SPECT and PET scanning machines and continued technological advances leading to launch of newer radiopharmaceuticals coupled with high level of accessibility to these modalities. 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 60.3% 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. According to Research and Markets the European nuclear medicine/radiopharmaceuticals market is expected to reach $1.62 billion by 2020 from $1.09 billion in 2015, growing at a CAGR of 8.2% from 2015 to 2020. Similar results exist for the Asia pacific region. It is estimated that Tc-99^{m} diagnostic procedures are expected to increase by more than 30% in the developing markets of the Asia-Pacific region including Australia, India and South Korea between 2010 and 2030. Japan is the most dominant market for diagnostic radioisotopes with almost 40% share and has around 1,600 gamma cameras installed in about 1120 institutions. PET diagnosis has increased dramatically after 2002. The total number of PET institutes in Japan has increased around 6-7 times in the last 10 year [8]. Thus it can be seen that stage is all set for boom of radiopharmaceuticals and that regulatory bodies need to relook into their current regulatory framework in order to facilitate their quick and easy entry into the market. Table I below compares the major drivers and inhibitors for radiopharmaceuticals.

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DRIVERS		INHIBITORS
Easy detection of metastatic sites and targeted treatment with lower side effects Expanding molecular imaging applications	Therapeutic application of radiopharmaceuticals in cardiology prognosis Rising incidence of cancer detection and treatment	Well established use of radioisotopes in diagnostic imaging Growing demands for PET and SPECT radioisotopes
Lack of harmonized guideline	Inherent hazardous nature	Lack of dosage standards

3. REGULATORY FRAMEWORK OF RADIOPHARMACEUTICALS - CURRENT STATUS

USA: In USA the radiopharmaceuticals are mainly regulated by Center for Drug Evaluation and Research (CDER) which is a division of U.S. Food and Drug Administration (FDA). Extensive research in field of radiopharmaceuticals has led to a comparatively strong regulatory framework for radiopharmaceuticals in USA. Radiopharmaceuticals are regulated presently in USA starting from developmental part and extend throughout its lifecycle to the ADR reporting. The FDA Modernization Act (Public Law 105-115) of 1997 was the major regulatory breakthrough giving special attention for PET drugs which were previously exempted from some of the FDA requirement. Section 121 of the Modernization Act directed FDA to establish Current Good Manufacturing Practices (CGMPs) and appropriate approval procedures for PET drugs [9]. The procedures were finalized and an implementation timeline was instituted on December 10 2009, when FDA finally published regulations that described the minimum CGMP standards that each PET drug manufacturer is to follow during the production of a PET drug (21 CFR part 212) and the guidance on PET Drugs – Current Good Manufacturing Practice (CGMP) in 2009. Similarly a number of important regulatory guidelines followed addressing concerns about NDAs and ANDAs and their contents and formats. More recently USFDA has come up with latest guidelines addressing compounding and repacking of radiopharmaceuticals by outsourcing agency as well as and State Licensed Nuclear Pharmacy. European Union: The European Union (EU) has its own regulatory framework for radiopharmaceuticals and represents the understanding of all member states across the Europe. The foremost agency overseeing medicines across Europe is European

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Medicine agency (EMA) which is a decentralized agency of the European Union (EU) and is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. The Committee for Medicinal Products for Human Use (CHMP) at EMA established the radiopharmaceuticals drafting group having the prime focus of drafting guidelines relating to radiopharmaceuticals [10]. Various guidelines ranging from Good Manufacturing Practices and Good Radio Pharmacy Practice to Early Phase Clinical Trials, Clinical Evaluation and Regulations on Market Authorization exists for Radiopharmaceuticals. Guideline on core SmPC and Package Leaflet for radiopharmaceuticals exists that explains applicants and regulators with harmonized guidance on the information which should be included in the Summary of product characteristics (SmPC) for radiopharmaceuticals. Guidelines on Investigational Medicinal Product Dossier (IMPD) has addressed concerns about radiopharmaceuticals during developmental part. Australia: The Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) is an Australian body that monitors and identifies solar radiation and nuclear radiation risks to the population of Australia including radiation protection guidelines. ARPANSA is also involved in various regulatory activities which include licensing, compliance, inspection and enforcement. ARPANSA support the Nuclear Safety Committee and the Radiation Health Committee and lead the development of standards, codes of practice, guidelines and other relevant material to support radiation protection and nuclear safety throughout Australia. The branch maintains the Australian Radiation Incident Register to which all radiation regulatory authorities report. Australia New Zealand Society of Nuclear Medicine (ANZSNM) is other major professional society representing nuclear medicine professionals in Australia and New Zealand. Together these societies functions to promote and protect interest of public and government in concerns relating to radiopharmaceuticals. Radio Pharmacy special interest group of Australian and New Zealand Society of Nuclear Medicine (ANZSNM) and Radio Pharmacy Specialist Practice Committee of Society of Hospital Pharmacist of Australia (SHPA) are also involved in developing guidance to various Good Radio Pharmacy aspects. Canada: Health Canada (HC) is the main regulatory agency of Canada with responsibility for national public health. Health Canada consists of various branches, sub branches and agencies each assigned different functions. The main branch dealing with radiopharmaceutical regulation is the Health Product and Food Branch (HPFB) whose activities are carried out through offices in national capital region and five regional offices. HPFB further consists of different directorates and offices amongst which Biologic and Genetic Therapy

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Directorate (BGTD) is most important and is Canadian federal agency that regulates Biologics and Radiopharmaceuticals for human use in Canada whether manufactured in Canada or elsewhere. BGTD further has three centers and six offices. Centre for Evaluation of Radiopharmaceuticals and Bio therapeutics is the main center among the three centers of BGTD which regulates radiopharmaceutical throughout Canada. Various guidance of Health Canada ranging from clinical trials and basic research in humans to market authorization and Good Manufacturing Practices strives to promote and protect the health of Canadians. Elaborated text guidance on adverse drug reaction reporting and Good Pharmacovigilance Practice (GPV) shows the intent of Health Canada in maintaining high standards for radiopharmaceuticals even after they have been used. India: Radiopharmaceuticals are mainly governed in India by Atomic Energy Regulatory Board (AERB) which is an important board of Department of Atomic Energy, Government of India. AERB was constituted in November 1983 by the President of India by exercising the powers conferred by Section 27 of the Atomic Energy Act, 1962 [11] and carries out various regulatory and safety functions of Atomic Energy Act, 1962. The regulatory functions of AERB are derived from rules and notifications promulgated under Atomic Energy Act, 1962 and Environment (Protection) Act, 1986. Bhabha Atomic Research Centre (BARC) is one of the important research centre of Department of Atomic Energy which monitors usage of radioactive material and promotes its applications in medicine. AERB publications consists of Codes and Guides, Annuals Reports, Newsletter, Booklet and AERB Bulletin. Central Drug Standard Control organization (CDSCO) under Ministry of Health and Family Welfare, Government of India with its Drug and Cosmetic Act 1940 and rules framed thereunder is also a key players overseeing radiopharmaceuticals in India. A less elaborate regulatory documents on radiopharmaceuticals in India highlights a strong and urgent need of adequate regulatory setup concerning radiopharmaceuticals. Moreover radiopharmaceuticals have been exempted from certain provisions of Drug and Cosmetic Act 1940 and rules framed thereunder. A detailed comparison of various countries and their guidelines is presented in Table II below to better understand the current status of radiopharmaceuticals across major regulatory agencies.

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Sr. No	COUNTRY	REGULATORY AGENCY	GUIDELINE	REF.
1	USA	USFDA	1. Nuclear Pharmacy Compounding Guidelines – 2001	[12]
			2. Procedure Guidelines For Use of Radiopharmaceuticals – June 2001	[13]
			3. Developing Medical Imaging Drug and Biological Products	
			Part 1: Conducting Safety Assessments - June 2004	[14]
			Part 2: Clinical Indications – June 2004	[15]
			Part 3: Design, Analysis, and Interpretation of Clinical Studies - June 2004	[16]
			4. The Transport of Radiopharmaceuticals in the United States - September 2004	[17]
			5. CGMP for Phase 1 Investigational Drugs – July 2008	[18]
			6. PET Drugs - Current Good Manufacturing Practice (CGMP) – December 2009	[19]
			7. Pediatric Radiopharmaceutical Administered Doses: 2010 North American Consensus Guidelines	[20]
			8. PET Drugs - Current Good Manufacturing Practice (CGMP) : Small Entity Compliance Guide - August 2011	[21]
			9. PET Drug Applications - Content And Format For NDAs and ANDAs – August 2011	[22]
			10. Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals - November 2011	[23]
			11. Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs - December 2012	[24]
			12. Clinical Trial Imaging Endpoint Process Standards Guidance For Industry - March 2015	[25]
			13. Compounding and Repackaging of Radiopharmaceuticals by Outsourcing	[26]

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			Facilities - December 2016 14. Compounding And Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities - December 2016 15. Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations - September 2017	[27] [28]
2	European Union	EMA	1. Guidelines on Current Good Radiopharmacy Practice (cGRPP) in the Preparation of Radiopharmaceuticals - March 2007 2. Eudralex - Volume 4: EU Guidelines to Good Manufacturing Practice, Annex 3: Manufacture of Radiopharmaceuticals – Sept. 2008 3. Guideline on Radiopharmaceuticals – November 2008 (For Marketing Authorization) 4. Guideline to Regulations for Radiopharmaceuticals in Early Phase Clinical Trials in the EU - November 2008 5. Guideline on Clinical Evaluation of Diagnostic Agents: Committee for Medicinal Producs for Human Use - July 2009 6. Guidance on Current Good Radiopharmacy Practice (cGRPP) for the small-scale Preparation of Radiopharmaceuticals - March 2010 7. Guideline on core SmPC and Package Leaflet for Radiopharmaceuticals – September 2011 8. Paediatric Radiopharmaceutical Administration : Harmonization of the 2007 EANM Paediatric dosage card (version 1.5.2008) and the 2010 North American Consensus Guidelines – February 2013 9. Guideline on the Acceptability of Names for Human Medicinal Products Processed through the Centralized Procedure - May 2014 10. EANM Guideline for the Preparation of an Investigational Medicinal	[29] [30] [31] [32] [33] [34] [35] [7] [36] [37]

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			Product Dossier (IMPD) - August 2014	
			11. Concept Paper on the Development of Guidance on the Non-clinical Evaluation of Radiopharmaceuticals - July 2017	[38]
			12. Guideline on the Requirements for the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials - September 2017	[39]
			13. European Medicines Agency pre-authorisation Procedural Advice for users of the Centralized Procedure – December 2017	[40]
3	Australia	ANZSNM, ARPANSA	1. Guidelines for the Administration of Diagnostic and Therapeutic Radiopharmaceuticals - 2000	[41]
			2. Guidelines for Good Radiopharmacy Practice - September 2001	[2]
			3. Australian Code of Good Manufacturing Practice For Medicinal Products; Annexure 3 - Manufacture of Radiopharmaceuticals - August 2002	[42]
			4. Radiation Protection in Nuclear Medicine - August 2008	[43]
			5. Australian Regulation to Prescription Medicine, Guidance 20: Radiopharmaceuticals - July 2013	[44]
4	Canada	Health Canada	1. Good Manufacturing Practices (GMP) for Positron Emitting Radiopharmaceuticals (PERS) - March 2006	[45]
			2. Cleaning Validation Guidelines - January 2008	[46]
			3. Design Guide for Nuclear Substance Laboratories and Nuclear Medicine Rooms - November 2008	[47]
			4. Guidance Document For Clinical Trial Sponsors: Clinical Trial Applications - May 2013	[48]
			5. Good Pharmacovigilance Practices (GVP) Guidelines - August 2013	[49]
			6. A Guide for the Preparation of Applications for Authorization of	[50]

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			Positron -emitting Radiopharmaceuticals for Use in Basic Clinical Research Studies - October 2014 7. Post-Notice of Compliance (NOC) Changes: Quality Document - October 2016	[51]
5	India	AERB	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	[52] [53] [54] [55]

4. PROBLEM ARISING DUE TO CURRENT STATUS AND FUTURE RECOMMENDATIONS

It is clearly evident from the table above that different regulatory agency has different approach to radiopharmaceuticals. Some countries stress more on developmental part of lifecycle while thrust area of others are post manufacturing aspect once radiopharmaceutical leave the manufacturing site. For e.g. USA stress most on developmental part and includes guidance on conducting safety assessment, clinical indications, design, analyses and interpretation of clinical studies in addition to guidance on PET drugs for INDA, format and content of NDA and ANDA, CMC issues for radiopharmaceuticals and CGMP for phase 1 Investigational Drugs. A unique aspect of regulation of European Union includes guidance on Summary of Product Characteristics (SmPC). This core SmPC and package leaflet covers all the radiopharmaceuticals including kits for radiopharmaceutical preparation. Health Canada in its forward regulatory plan 2016-2018 is trying to amend its Food and Drug Regulation in which it is recommended to include Drug Identification Number (DIN) number which was not previously required in Canada. DIN number is issued at time of market authorization and gives information about its market authorization status. As previously no DIN number existed for radiopharmaceuticals, it posed great problem when product recall was to be initiated. Guidelines also exist for Good Pharmacovigilance Practice and adverse drug reporting mechanism for radiopharmaceuticals. Australia presents useful guidance with regards to radiation protection and safety which is available as radiation protection series. It also includes useful information for radioactive waste disposal.

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5. CONCLUSION

Radiopharmaceuticals have become important because of their use 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. Scientific fraternity worldwide is continuously working in search of newer radiopharmaceutical of increased efficacy and minimum hazard. Recent market trend have shown their exponential rise and excellent market potential. However a single regulatory framework covering all aspects starting from developmental part to Good Manufacturing Aspects and the point where radiopharmaceutical leave from manufacturing area covering Good Radiopharmacy Practice, aspects of radioactive waste disposal, radiation safety, packing and transport, and ADR reporting is not presented by any single regulatory body for radiopharmaceuticals. ICH guidelines are amongst the best followed guidelines across the globe. However ICH framework still lacks guidance on various aspects of radiopharmaceutical manufacturing and subsequent stages. Schedule M of Drug and Cosmetic Act, 1940 and rules framed thereunder covers only quality control laboratory requirement and provide recommendations that separate air handling unit be provided for radiopharmaceutical laboratory. Radiopharmaceuticals are regulated differently in different countries and the time it takes for radiopharmaceutical to shift from bench side to bedside of suffering humanity is lengthy and cumbersome. Lack of harmonized guideline is clearly evident for radiopharmaceuticals. Therefore it has become pertinent to address all the issues related to development, manufacturing, dispensing, ADR reporting, transport, disposal, and labeling requirements concerning radiopharmaceuticals. The implementation of strict regulatory guidelines to assess quality, safety, and efficacy of radiopharmaceuticals is need of the hour. This will lead to public trust and insight into the safety of the radiopharmaceutical use. A comparative study of different regulatory bodies can help develop harmonized guidelines which could enable free exchange of radiopharmaceuticals across the globe in the most cost efficient manner.

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