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Review Article

Assessments of Regulatory managements of Radiopharmaceuticals Systematic Literature Review

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Abstract

Introduction: Radiopharmaceuticals are special class of pharmaceuticals and utmost care should be taken for their handling, storage, dispensing and use. The characteristic which sets them apart from pharmaceuticals includes their short half-life, inherent hazardous nature of radioisotope, issue of maintaining sterility with radiation safety simultaneously, storage, transport and waste disposal issues and the fact that minute change in dose may cause faulty diagnosis or even over exposure. Therefore the guidelines applicable to pharmaceuticals are not relevant for radiopharmaceutical and calls for separate regulatory setup for radiopharmaceuticals. ***Objectives:*** To review regulatory managements of radiopharmaceuticals. ***Methods:*** Systematic literature review in methodology was used. The review was conducted using reliable healthcare internet database namely; Google scholar, hinari and PubMed central. Ten scientific articles were scrutinized to obtain results for the review. ***Result:*** The results of this review showed that a total of ten articles were reviewed which talks about the regulatory management of radiopharmaceuticals of different guidelines and different regulatory bodies of different countries and causes and consequences of poor regulatory control. ***Conclusion:*** For good quality of radiopharmaceuticals there should be quality management system should be implemented, documented, and duly maintained; effectiveness should be continuously improved in accordance with the requirements of professional, regulatory, and accrediting bodies.

Keywords: Radiopharmaceuticals, Regulation, Management.

INTRODUCTION

Radiopharmaceuticals are the agents which are used for diagnostic and therapeutic purposes. They consist of two functional components, one of which is radioactive and another which is non-radioactive in nature. In diagnosis, the radioactive component which is nothing but a radio-nuclide with appropriate physical properties enables the detection of the product and is the active agent of the radiopharmaceutical during treatment. The non-radioactive component is a molecule or biological tracer with appropriate pharmacokinetics and shows organ specificity and metabolism. As radiopharmaceuticals consist of two components-pharmaceutical part and radioactive part, strict requirement exists to fulfill the quality specifications for both pharmaceutical part (pH, organoleptic properties, sterility, apyrogenicity, chemical purity, and dosage related properties) and the radioactive part (radionuclide purity, radiochemical purity, radio assay, etc.) [1].

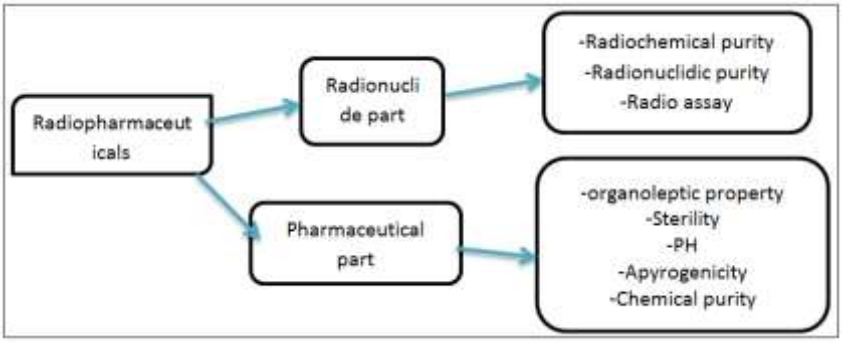

Fig-1: Requirements for quality parameters for radiopharmaceuticals

These quality control tests are necessary for finished radiopharmaceutical products before the licensing of the finished product can be obtained. Radiopharmaceuticals are now a crucial part of the healthcare industry due to their ability to identify various disease processes much earlier than other diagnostic tests [2]. The increasing acceptance of disease targeted treatment and rise in cancer patients coupled with high demand specifically from emerging countries due to its noninvasive nature and presence of potential radioisotopes in the pipeline have opened new frontiers for the ever increasing radiopharmaceutical use [2].

Radiopharmaceuticals are special class of pharmaceuticals and utmost care should be taken for their handling, storage, dispensing and use. The characteristic which sets them apart from pharmaceuticals includes their short half-life, inherent hazardous nature of radioisotope, issue of maintaining sterility with radiation safety simultaneously, storage, transport and waste disposal issues and the fact that minute change in dose may cause faulty diagnosis or even over exposure. Therefore the guidelines applicable to pharmaceuticals are not relevant for radiopharmaceutical and calls for separate regulatory setup for radiopharmaceuticals [2].

Those who regularly practice Nuclear Medicine are usually quite familiar with regulatory compliance. One such compliance requirement is the need to create and maintain written directives (WDs) for every therapy given in Nuclear Medicine. The introduction of the requirements for a WD can be traced back to a proposed quality assurance (QA) rulemaking by the United States Nuclear Regulatory Commission in 1987 that would impact ordering, prescribing, the administration of radiopharmaceuticals, and record keeping[4]. The Society of Nuclear Medicine (now known as the Society of Nuclear Medicine and Molecular Imaging) and the American College of Nuclear Physicians were not initially included in this rulemaking process [5]. Public statements from the Nuclear Medicine community and comments from the Society of Nuclear Medicine and American College of Nuclear Physicians explained that these regulations would adversely impact patient care, limit patient care flexibility, significantly increase the paperwork, and place users at undue risk for regulatory violations for little if any benefit. Subsequently the QA rule was reissued in the 1990 Federal Register which detailed the requirements of the WD [6]. Nuclear Medicine, medical specialty that uses radioactive substances, or radiopharmaceuticals, combined with imaging techniques to diagnose and treat injury or disease, such as sports injuries, heart disease, cancer, and Alzheimer's disease. When used for diagnosis, nuclear imaging lets doctors study bodily functions as they are occurring. In treatment applications, which are less common, substantially larger doses of radiation are used to destroy diseased tissues. Although some doctors practice nuclear medicine as a full-time specialty, many more physicians in such fields as radiology, pathology, and internal medicine use aspects of nuclear medicine in their work.

Despite attempts made by the Society of Nuclear Medicine and the American College of Nuclear Physicians to void the QA rule and the disapproval of the rule by the US Office of Management and Budget (which sided with the physician professional communities) the United States Nuclear Regulatory Commission rulemaking stood [7]. Today, the scope and requirements for the use of WDs can be found in title of the Code of Federal Regulations (CFR) part 35 sections 40 and 41 while the recordkeeping requirements are in part 35 sections 2040 and 2041 [8]. Agreement states are also required to implement and enforce these regulations [9].

A radiopharmaceutical is “any medicinal product which, when is ready for use, contains one or more incorporated radionuclides, for medical purposes” [10]. From the regulatory point of view, the radiopharmaceutical must be sterile, pyrogen-free, safe and effective. Therefore, quality assurance and radiochemical purity testing (RCP) are considered mandatory steps in the process of radiopharmaceutical synthesis, as well as radio-labeling according to national laws and guidelines in compliance with European directives [11]. In the case of radiopharmaceuticals prepared by industrial kits, through radioactive labeling within the unit where they are used, the responsibility for their quality at the time of administration to patients falls under the responsibility of the nuclear medicine specialist and an “on-site labeling process”. In short, using commercial kits and generators requires an “on-site control of the labeling process” [12].

The International Atomic Energy Agency (IAEA) [13] set up in 1957 as the world’s center for cooperation in the nuclear field, works with its Member States and multiple partners worldwide to promote the safe, secure, and peaceful use of nuclear technologies in various fields, including human health. For this purpose, among other initiatives, the Division of Human Health of the IAEA has developed quality management programs, which cover the medical fields where the Division of Human Health [14] supports its Member States, namely radiation oncology, nuclear medicine, and radiology. With regard to nuclear medicine, the Nuclear Medicine and Diagnostic Imaging Section, aiming to raise the quality of nuclear medicine practices in low-middle income countries up to internationally recognized minimum standards, has developed a program on Quality Management Audits in Nuclear Medicine (QUANUM) [15], based on a

combination of both internal and external audits. The internal audit processes are felt as essential to instill a culture of quality in the practice, followed when requested, by external auditing missions of multidisciplinary teams fielded by the IAEA through its Technical Cooperation Program and technically supported by the Nuclear Medicine and Diagnostic Imaging Section [16].

Table-1: Shows some examples of Radiopharmaceuticals and their various uses

Sr no.	Radiopharmaceutical	Trade Name	Primary Uses
1	Cobalt-57 cyanocobalamin	Rubratope	Schilling test
2	Cobalt -58 cyanocobalamin	Dicopac	Schilling test
3	Chromium-51sodium chromate	Chromotope	For labeling RBCs
4	Gallium-67	Neoscan	Soft-tissue tumor and inflammatory process imaging
5	Indium-111 chloride	Indiclor	For labeling monoclonal antibodies and peptides
6	Indium-111 Capromab pendetide	ProstaScint	Monoclonal antibody for imaging prostate cancer
7	Indium-111 Imciromab pentetate	Myoscint	Monoclonal antibody for diagnosis of myocardial necrosis
8	Indium-111 satumomab pendetide	OncoScint CR/ OV	Imaging of metastatic disease associated with colorectal and ovarian cancer
9	I-131 iodohippurate	Hippuran	Renal imaging and function studies
10	I-125 human serum albumin (RISA)	Isojex	Plasma volume determinations
11	Indium-111 pentetreotide	Octreoscan	Imaging of neuroendocrine tumors
12	I-125 iothalamate	Glofil	Measurement of glomerular filtration
13	Strontium-89	Metastron	Palliative treatment of bone pain of skeletal metastases
14	Tc-99m Sestamibi	Cardiolite	Myocardial perfusion imaging [3]

Nuclear medicine, a maladministration refers to the wrong patient being injected or the administration of an incorrect radiopharmaceutical type or dosage [17, 18]. Although debated, the unintended exposure to ionizing radiation from a maladministration may increase the long-term risk of cancer [19, 20]. Further, irreversible organ damage has been reported [21]. Hence, nuclear medicine can be hazardous. Australian data suggest that not only is the demand for nuclear medicine increasing but also that it attracts a significant amount of government expenditure,6 thus highlighting its importance to the community. Despite the widespread use of nuclear medicine and the potential for harm resulting from maladministrations, there are few publications about the incidence, causes and consequences of maladministrations. Research from other countries [23, 24] suggests that maladministration's occur infrequently. However, dissimilar notification criteria and regulatory environments limit their applicability to Australia.

A solitary Australian study reported an incidence of [24, 25] maladministration's per 100 000 procedures, as well as describing one case in which unintended organ damage occurred [21]. However, data from this study are now [25-29] years old and were sourced only from one state [21] Alternative statutory and non-statutory data sources are constrained by ambiguous notification criteria [25], are not truly national in scope [26], or lack a nuclear medicine focus [27, 28]. Thus, there is a paucity of contemporary information about maladministrations,which undermines risk management in nuclear medicine.

In contrast, the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) have been operating the Australian Radiation Incident Register (ARIR) for several decades as a national repository of data on maladministration in nuclear medicine [29]. The national scope, explicit notification criteria and mandatory obligation on regulatory bodies to report are unique features and suggest that the ARIR could be the best source of information about maladministration in Australia. Despite this, an analysis of the ARIR has never been conducted [30].

The use of both ionizing and non-ionizing radiations for medical imaging and treatment is rapidly increasing. The use of these medical tools has led to several breakthroughs in both diagnosis and treatment. The rapid development of imaging technology has contributed largely to progress of simple and complex diagnostic procedures as well as interventional radiology [31]. Hysterosalpingography (HSG) is a diagnostic procedure performed to determine if the fallopian tubes are patent (open), and to see if the structure and size of the uterine cavity are normal. This is a noninvasive procedure usually performed after the menstrual period has ended to prevent interference with an early pregnancy. It is performed by positioning a woman under a fluoroscope (real-time imager) on a table. The gynecologist or radiologist examines the patient and fills the uterus with contrast medium in order to visualize the outline of the inner size and shape of the uterus and fallopian tubes clearly. X-ray images are obtained during the introduction of the contrast medium using a tube. During the filling of the uterus

with the contrast medium, the fingers and the lower extremities of the gynecologist or radiologist is exposed to radiation [32, 33].

The HSG is a common procedure carried out in Nigeria essentially in infertile women. This is because of the cultural practice of disparaging women with infertility problems. The HSG procedure is also used a few months after a tubal sterilization procedure to make sure that the fallopian tube has not been completely blocked. The common indication for the use of HSG in Nigeria is infertility. Other indications Include, but are not limited to, the evaluation of: pelvic pain, irregular vaginal bleeding, congenital abnormalities or anatomic variants [34]. Other alternative procedures to HSG are laparoscopy, sonohysterosalpingogram and hysteroscopy. Nevertheless, HSG remains the most commonly performed procedure to evaluate tubal patency [32].

HSG procedure requires the radiologist or gynecologist (who is not trained to handle ionizing radiation) to hold the cannula and inject the contrast medium into the cervix of the patient while she is being irradiated. The supporting personnel also remain close to the patient. Though, a lead apron is worn, the hands of the radiologist are covered in latex gloves, making their hands vulnerable to x-rays. The exposure of the radiologists' hands to x-rays during this procedure is a continuous and inevitable experience during HSG procedures, hence the need to evaluate the dose exposed to the hands. The use of 99mTc has gained wide acceptance in nuclear medicine practice due to its advantages related to its specific characteristics. The physical half-life of 99mTc used in radionuclide bone scan is 6.02 hours [35, 36], thus it exposes a fairly low dose per unit intake due to its short half-life and radiation spectrum [37]. It has energy of 140 keV that is sufficient enough to be detected by the gamma camera through the body. The reason for the choice of 99mTc in bone scintigraphy arose because of its characteristic qualities. Bone scintigraphy/scan is one of the most common applications of ionizing radiation in nuclear medicine. Radionuclide bone scan is a diagnostic procedure used to evaluate the distribution of active bone formation in the body. The radiopharmaceutical is injected intravenously with and without cannula to the patient by a radiologic technologist and is distributed via blood flow throughout the body. It therefore passively diffuses into the extravascular and extracellular spaces, and bind to hydration shell around the bone crystal [38]. The use of 99mTc in patients undergoing bone scan procedure presents special concerns for the assessment of radiation dose and the attendant risk to the administering staff. As a result of the need for radiation protection of the administering staff, doses exposed to the hands of the radiologic technologist were measured [39].

The practice of radio pharmacy combines the expertise of pharmaceutical Preparation and the skills needed to handle radioactive substances. Diagnostic Radiopharmaceuticals do not normally have any pharmacological effect and their administration is not associated with major clinical side effects. Their clinical use, however, is associated with a risk deriving from radiation exposure and possible contamination during radiopharmaceutical formulation by chemical, biological and microbiological impurities. This is particularly important since the majority of radiopharmaceuticals are administered intravenously. A thorough quality assurance (QA) programm should, therefore, be in place before administration to the patient. [40].

Radiopharmaceuticals tend to differ from normal medicines in that they have a short half-life. Because of their rapid decay, they must be prepared shortly before their clinical use and comprehensive quality control (QC) of the final product is not possible: sterility testing, for instance, cannot be performed due to time limits. Safe and effective preparation and use of radiopharmaceuticals is, therefore, vital for the protection of the operator and the final user the patient [40].

Applications of Ionizing radiation in Ethiopia began in 1970 when the Institute of Pathobiology (IPB) of the Addis Ababa University acquired the first and only cobal WO radiation source together with other basic equipment. Since then around fifteen pathobiological and related research projects that employ ionizing radiation have been conducted. A nuclear medicine service was started in 1978 in the Tikur Ambessa (Black Lion) Hospital of Addis Ababa University. The Nuclear Medicine Unit (NMU) of this hospital is the only one of its kind in the country and serves as a referral centre for patients from all over Ethiopia. It also serves as a teaching unit and undertakes research in nuclear medicine [41]

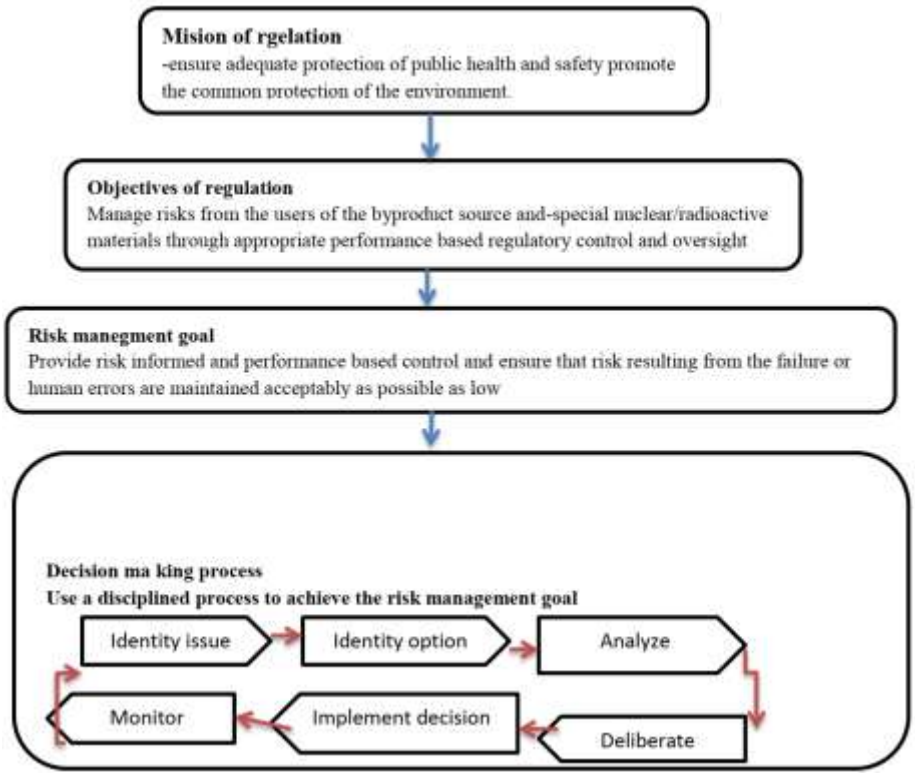

Fig-2: Radiopharmaceuticals risk management regulatory frame work

METHODOLOGY

Study Design

This review was conducted by reviewing the different available materials i.e. electronically like hinari, PubMed, Google scholar, which were conducted in various parts of the world.

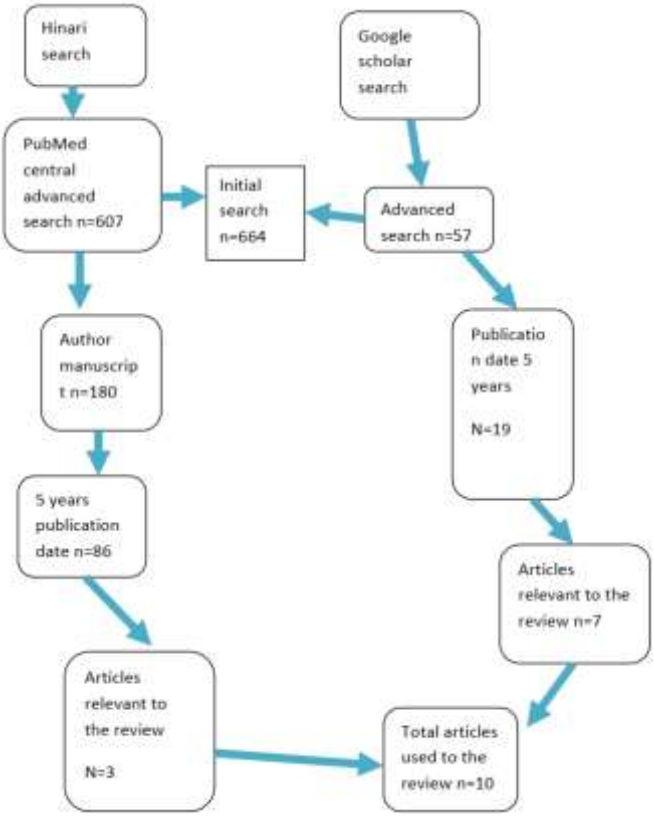

Fig-3: Review Selection Process

Inclusion Criteria

- Publications relevant to the review topic
- Literature available in The English Language
- Articles published from 2013-2018
- Articles have free access and contain full text

Exclusion Criteria

- Publications that are not in the English Language
- Publications before the year 2013
- Repeated articles in different database
- Publications not available online as free full text
- Literature not relevant to the review

RESULT AND DISCUSSION

The results of this review showed that a total of 10 articles were reviewed which talks about regulatory management of radiopharmaceuticals which are showed in (Table-2).

Table-2: Results of the articles/reviews for Results of the articles/reviews for regulatory management and radiopharmaceuticals

S.no	Titles/study	Author	Publication date	Country	Regulation guide line	Responsible regulator/agency
1	REGULATORY FRAMEWORK OF RADIOPHARMACEUTICALS: CURRENT STATUS AND FUTURE.RECOMMENDATIONS	Sandeep Sharma, Ashish Baldi, Rajesh K. Singh Rakesh Kumar Sharma [42]	2018 May	INDIA	Nuclear Medicine Facility - March 2011 And Radioisotope Handling Facilities - August 2015	AERB
2	Radiopharmaceuticals Regulations on Bioavailability and Bioequivalence: Present Status and Future Requirements	Sandeep Sharma, Ashish Baldi and Rakesh Kumar Sharma [3]	June 27, 2017	INDIA	Nuclear Medicine Facility - March 2011 And Radioisotope Handling Facilities - August 2015	AERB
3	Bringing New PET Drugs to Clinical Practice – A Regulatory Perspective	Joseph C. Hung [43]	013.11.01	USA	Clinical Trial Imaging Endpoint Process Standards Guidance For Industry - March 2015	USFDA
4	Maladministrations in nuclear medicine: revelations from the Australian Radiation Incident Register	george.larcos [30]	20 January 2014	Australia	Australian Regulation to Prescription Medicine, Guidance 20: Radiopharmaceuticals - July 2013	ANZSNM, ARPANSA
5	Quality control on radiochemical purity in Technetium-99m radiopharmaceuticals labelling: three years of experience on 2280 procedures	Claudio Maioli, Giovanni Lucignani1, 2, Aldo Strinchini, Luca Tagliabue, Angelo Del Sol [12]	2017	ITALIA	national laws and guidelines in compliance with European directives 2011	EMA
6	Managing Written Directives: A Software Solution to Streamline Workflow	Robert H. Wagner, Bital Savir-Baruch, Medhat S.	March 9, 2017	USA/CHICAGO	Clinical Trial Imaging Endpoint Process Standards Guidance For	USFDA

		Gabriel, James R. Halama, and Davide Bova [9]			Industry - March 2015	
7	Approval Status and Regulatory Actions for Radiopharmaceuticals in the United States and Japan	Nobuyuki Hanamura, MS, MBA1, and Atsushi Aruga, MD, PhD [44]	September 16, 2016	JAPN/USA	' JAPANGuideline on Clinical Evaluation for Diagnostic Radiopharmaceuticals'' (2012)	USAFDA/JSNM
8	Comprehensive Auditing in Nuclear Medicine Through the International Atomic Energy Agency Quality Management Audits in Nuclear Medicine Program. Part 2: Analysis of Results	Maurizio Dondi, MD,* Leonel Torres, PhD,† Mario Marengo, PhD [16]	2017.07.004	IAEA	radionuclidesGuidelines for setting up a facility. Vienna, International Atomic Energy Agency, 2009	Quality Management Audits in Nuclear Medicine (QUANUM)
9	Occupational Radiation Exposure to the Extremities of Medical Staff during Hysterosalpingography and Radionuclide Bone Scan Procedures in Several Nigerian Hospitals	Nnamdi Norbert Jibiri1, Tawakalitu Oluwatoyin Akintunde1, Musa Yusuf Dambele [39]	22.05.2016	NIGERIA		Nigerian Nuclear Regulatory Authority
10	Pharmaceutical Regulatory Framework in Ethiopia: A Critical Evaluation of Its Legal Basis and Implementation	Sultan Suleman,, Abdulkadir Woliyi3, Kifle Woldemichael4, Kora [45]	May 2016	ETHIOPIA	Current medicine law of the country proclamation No.661/2009	EFMHACA

The research done in INDIA which reviews the regulatory and management of different countries most of the countries have their own regulation guideline and regulatory agencies for example 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 [42].

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 parts 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 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. 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. A guideline on Investigational Medicinal Product Dossier (IMPD) has addressed concerns about radiopharmaceuticals during developmental part [42].

The other research done in Australia to describe the causes and consequences of the maladministration of radiopharmaceuticals/nuclear medicines in different Australian Hospitals as reported from the paper total, 149 maladministration's were reported: 16 in 2007, 40 in 2008, 23 in 2009, 33 in 2010 and 37 in 2011. All but two were diagnostic in nature. There were 2 552 513 nuclear medicine procedures recorded by Medicare over this period: 337 999 diagnostic non-imaging, 194 063 diagnostic imaging and 20 451 therapeutic nuclear medicine procedures. The incidence of maladministration for the years was 5.8 per 100 000 procedures about half of all maladministration arose from an incorrectly prepared and/or dispensed radiopharmaceutical. Of these, a little over half originated from a commercial laboratory. In descending order, other maladministration derived from an incorrect syringe, an inability to obtain diagnostic images because of technical failures and extravasations, and either an incorrect patient or incorrect test. In 10 of 13 cases in which an incorrect patient was examined, as well as in all maladministration involving the wrong procedure, we inferred from the ARIR narratives that, with two exceptions, there had been no review of the patient by a nuclear medicine specialist before radiopharmaceutical administration [30].

The other research done on approval and regulatory status of on PET drugs in JAPAN and United states on 36 types Radiopharmaceuticals listed in the drug product package insert database accessible on the PMDA website and 49 types of radiopharmaceuticals listed in the database accessible on the FDA website and compared the approval statuses of radiopharmaceuticals in Japan and the US. The guidance on PET drugs in the US and Japan.In Japan, there are types of regulatory review processes for PET drugs: the drug approval process and the medical device approval process. In the US, there is no medical device approval process for PET drugs, but the FDA regulates the manufacturing of PET drugs in each facility and each PET drug under current good manufacturing practice (cGMP). In 2009, the FDA published regulations16 describing the cGMP standards that each manufacturer is to follow during the production of a PET drug, as well as guidance on PET drug cGMP.17 Under the requirements of section 121 of the Modernization Act, a new drug application or abbreviated new drug application must be submitted for any PET drug marketed for clinical use in the US. In Japan, since 1985, the JRIA has certified the PET drug as ''established techniques'' when its manufacturing technology was mature.18 Fifteen PET drugs have been certified under this system. However, the JRIA has decided to end the certification system for mature technology and has proposed that some other system is needed to reflect the current efforts at globalization and standardization.18 for clinical evaluation, the FDA issued guidance on developing medical imaging drugs and draft guidance on standards for clinical trial imaging endpoints. In Japan, guidelines on clinical evaluation were issued in 2012.These guidelines on clinical evaluation in the US and Japan stress that the effectiveness of diagnostic radiopharmaceuticals should be demonstrated by accurate imaging information obtained from images and by clinical benefit of the information [44].

The other research done on Comprehensive Auditing in Nuclear Medicine Through the International Atomic Energy Agency Quality Management Audits in Nuclear Medicine Program to audit the regulatory and managements of radiopharmaceuticals by diveloping different auditing checklist and collecting data collection they check with checklist meet or not. After data from QUANUM v1 checklists were reorganized to be comparable with QUANUM v2 data, combined overall results were assessed. LoCs and level of NC per checklist, expressed as percentages, are reported in Average percentage of conformances and non-conformances per checklist. Checklist 1: Strategies and policies; Checklist 2: Administration and management; Checklist 3: Human resources

development; Checklist 4: Radiation regulations and safety compliance; Checklist 5: Radiation protection of patients; Checklist 6: evaluation of the quality management system; Checklist 7: Quality control for imaging equipment; Checklist 8: Computer systems and data handling; Checklist 9: General diagnostic clinical services; Checklist 12: General radionuclide therapy; Checklist 14: Radio pharmacy operational level 1; Checklist 15:Radiopharmacy operational level 2; Checklist 16: Radio pharmacy operational level 3; Checklist 17: Hormone and tumor markers The QUANUM v2 checklist allows collecting detailed information on specific imaging and therapeutic procedures from each audited nuclear medicine service This is done analyzing up to five cases and their reports, randomly selected, and assesses them against clinical information collected at referral; technical procedure; patient preparation; quality assurance/quality control (QA/QC) of both

radiopharmaceutical and instrumentation; and reporting and follow-up. The analysis of QUANUM audit reports has shown interesting aspects related to quality management in nuclear medicine practices in IAEA Member States. It appears that the QUANUM program can be applied in a wide variety of nuclear medicine practices, irrespective of geographical area and of socioeconomic conditions [16].

The other research done in Nigeria Occupational Radiation Exposure to the Extremities of Medical Staff during Hysterosalpingography and Radionuclide Bone Scan Procedures in Several Nigerian Hospitals and to show Regular monitoring of radiation doses received by the extremities of radiologists, physicians and technologists involved in HSG is very important in order to ascertain the level of exposure of the unprotected part of the hands of the personnel who carry out the procedure. The regular dose assessment of hands, eyes, gonads, and legs is essential to ensure that occupational doses received by radiologists are within the recommended annual dose limit. The results of this study demonstrated that each radiologist performed an average of 2 HSG procedures per week. For any nuclear medicine service, the adoption of a QMS should be a strategic decision taken with the aim of improving the standard of care provided. The design and implementation of a QMS is influenced by various needs and constraints, particular objectives, the nature of services provided, the processes employed, and the size and structure of the nuclear medicine facility. QMSs should be implemented, documented, and duly maintained; effectiveness should be continuously improved in accordance with the requirements of professional, regulatory, and accrediting bodies [39].

CONCLUSION

There are high hopes for the use of radiopharmaceutical molecular imaging in the field of personalized medicine, and standard methods for the clinical evaluation of radiopharmaceuticals are being established throughout the world. So quality management system should be implemented, documented, and duly maintained; effectiveness should be continuously improved in accordance with the requirements of professional, regulatory, and accrediting bodies and the management of radiopharmaceuticals must get concern throughout the world because radiopharmaceuticals are special and sensitive products.

RECOMMENDATION

Based on the review I want to give the following recommendations are forwarded

To The colleges of pharmacy: To incorporate to start nuclear pharmacy programs for future to get nuclear pharmacist.

To EFMHACA: To prepare brief guide line for regulation of radiopharmaceuticals.

To researchers: There is no research on this area especially in our country so it needs further research about Regulatory and managements of radiopharmaceuticals.

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