A SYSTEMATIC EVALUATION OF REGULATIONS FOR RADIOPHARMACY PRACTICE IN KENYA IN COMPARISON TO INTERNATIONAL GUIDELINES

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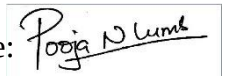
DECLARATION

Investigator

I, Pooja Neil Lumb, hereby declare that this is my original work and to the best of my knowledge, has not been presented elsewhere for a degree in any other university.

Signature: 

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DEDICATION

Oh God! Thou art the Giver of Life,

Remover of pain and sorrow,

The Bestower of happiness,

Oh! Creator of the Universe,

May we receive thy supreme sin-destroying light,

May Thou guide our intellect in the right direction.

- A translation of the Gayatri Mantra, a Hindu prayer

I would like to dedicate this work to my parents.

To my mother, Renu Lumb, I am proud to be your daughter. To my late father Neil Lumb, I hope I have grown into the person you envisioned me to be.

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Contents

ABBREVIATIONS AND ACRONYMS

ALARA – As low as reasonably achievable

BCP – Business Continuity Plan

CDSCO – Central Drugs Standard Control Organisation

CME – Continuous Medical Education

cGDP – Current Good Distribution Practices

cGMP – Current Good Manufacturing Practices

cGRPP – Current Good Radiopharmacy Practice

EMA – European Medicines Agency

FDA – Food and Drug Administration

GLP – Good Laboratory Practices

GXP – Good Practice Guidelines

HCG CCK – HealthCare Global Enterprise Limited and Cancer Care Kenya

IAEA – International Atomic Energy Agency

KNH-UON – Kenyatta National Hospital – University of Nairobi

KNRA – Kenya Nuclear Regulatory Authority

KUTTRH – Kenyatta University Teaching, Referral and Research Hospital

MHRA – Medicines and Healthcare products Regulatory Agency

NHIF – National Health Insurance Fund

PET – Positron Emission Tomography

PPB – Pharmacy and Poisons Board

SAHPRA – South African Health Products Regulatory Authority

SPECT – Single Photon Emission Computed Tomography

WHO – World Health Organization

KEY DEFINITIONS

Positron Emission Tomography (PET): A form of imaging that detects photons released by annihilation process of positrons and electrons. The positrons are produced during the decay of radiotracers administered to a patient (1).

Radiolabelling: This is the process of radiopharmaceutical formation where a radioactive molecule is introduced into a carrier substance (2).

Radiopharmaceutical: Radioactive pharmaceutical/medicinal product for clinical use (diagnostic or therapeutic) (2).

Radiopharmaceutical reagent kit: Sterile and pyrogen-free reaction vial(s) containing non-radioactive start material that is required to compound or produce a specific radiopharmaceutical (3).

Radiopharmacist (nuclear pharmacist): A professional with a state licence as a pharmacist or nuclear pharmacist (as applicable), who meets local/international training requirements related to radiopharmacy practice (1).

Radiopharmacy (nuclear pharmacy): A clinical service that procures, prepares or compounds, dispenses radiopharmaceuticals, and assures quality for diagnostic or therapeutic use in patients. It may be referred to as the nuclear medicine service of a hospital (1).

Radiopharmacy Laboratory: A facility found in a Healthcare Institution providing nuclear medicine services that is used for the preparation, dispensing, radiolabelling, compounding, and quality control of radiopharmaceuticals. It is also known as a “Hot Lab.” (3)

Single Photon Emission Computed Tomography (SPECT): A form of imaging that detects gamma rays produced by the decay of administered radiotracers (1).

ABSTRACT

Introduction: Radiopharmacy is a branch of nuclear medicine that involves the preparation and dispensing of radiopharmaceuticals for diagnostic, therapeutic or research applications. It combines the skills involved in pharmaceutical preparation and handling of radioactive substances. Radiopharmaceuticals find importance in the identification of a disease in its most basic stages and can precisely locate diseased tissue in a patient often before the disease becomes symptomatic or leads to abnormalities that can be detected with other diagnostic tests. Radiopharmacy is well established and practiced in several sites in the country such as at the Aga Khan University Hospital Nairobi, and with new sites emerging such as at the Kenyatta University Teaching, Referral and Research Hospital, however growth of the sector has been slow. One of the reasons for the slow growth is the lack of local regulations for the field.

As medicinal products, the production and handling of radiopharmaceuticals should comply with the rules for manufacturing sterile products intended for human medicinal use, however their radioactivity poses challenges in their management and requires further guidance. The local drug regulatory authority, Pharmacy and Poisons Board has published several guidelines for good practices in the pharmaceutical industry, referred to as GXP guidelines, on the manufacture, storage, distribution, dispensing and waste disposal of pharmaceutical products. However, these do not consider the unique requirements of radiopharmaceuticals. This study aimed to explore the creation of GXP guidelines specific to radiopharmacy practice in Kenya by comparing current local guidelines with international ones, to assess the alignment of these to the emerging radiopharmacy practice in the country, and to understand the challenges faced by stakeholders involved in the sector.

Study objectives: To analyse local and international drug regulatory authorities' guidelines on radiopharmaceuticals to identify gaps in local regulations, and explore how these could be addressed by adapting international regulations as guidance materials for regulation for radiopharmaceuticals in Kenya.

Methods: A desktop review of reference regulations and guidelines was performed using the regulatory or guidance bodies' official websites. In addition, a local radiopharmacy practicing site was audited for evaluation of adherence of IAEA requirements, and challenges in current practice were captured using key informant interviews.

Results: Differences in local guidelines and international radiopharmacy practice guidelines were noted that affect various aspects of the field by analysing local GXP guidelines against international radiopharmacy practice guidelines. These covered facets related to production, handling, distribution, and recall of the radiopharmaceuticals. The radiopharmacy unit at selected site of the Aga Khan University Hospital largely complied to the IAEA requirements, however the unit at the Kenyatta National Hospital could not be audited as it was inactive at the time of data collection. Key informant interviews shed light on the challenges faced in the sector and emphasized the need for local guidelines.

Study significance: The purpose of the study being to propose GXP guidelines specific to radiopharmacy practice in Kenya with the hope to create informed policies which lead to improvement and enhancement of the sector in Kenya thus ultimately benefit local and regional patients.

CHAPTER ONE - INTRODUCTION

1.1 Background

Radiopharmacy is a field that combines pharmaceutical preparations with the handling of radioactive compounds to use radioisotopes for diagnostic, therapeutic or research applications. It is a practice with growing popularity worldwide, and while there are several practicing sites in the country, it has been slow to grow in Kenya leading to medical tourisms by patients to Asian countries to receive these services. One of the reasons for this delay is the lack of local regulations for the field.

There are good practice (GXP) guidelines issued by local and international drug regulatory bodies to assure that quality of pharmaceutical products is maintained throughout the lifecycle of the products. However, these may not consider the different requirements of radiopharmaceuticals. Regulatory authorities Pharmacy and Poisons Board and Kenya Nuclear Regulatory Authority provide guidance on pharmaceutical and radioactive products respectively, however neither provide guidance on radiopharmacy practice in the country. Therefore, guidelines specific to this field are necessary and these should be suitable for the local sector.

1.2 Purpose of the study

This study sought to compare the differences between international radiopharmacy practice specific guidelines and local GXP guidelines for possible gaps and to explore the need for local GXP guidelines for radiopharmaceuticals in Kenya by assessing alignment of at least two local sites practicing radiopharmacy to existing international guidelines and gain insights on experiences from the key stakeholders in the country.

1.3 Significance and anticipated output

Radiopharmacy has been embraced in developed countries for its advantages over conventional therapies and diagnostics. This study sought to build on a pool of knowledge necessary in preparing a regulatory framework to enhance growth of radiopharmacy in Kenya. Such knowledge will cover appropriate and acceptable guidance on various aspects of radiopharmacy such as production, compounding, distribution, and dispensing. The study findings have been presented to the local drug regulatory authority Pharmacy and Poisons Board for consideration in supplementing current guidelines.

Ultimately this research aimed to improve and enhance the practice of radiopharmacy in the country with a view to benefitting the end users, patients.

1.4 Limitations

Reference materials such as current guidelines and laws, although valid, may not be recently updated. There is extensive information on standard pharmaceutical products, however not as much published information on radiopharmaceuticals is available and therefore there is a limited pool of information on the subject. This research did not directly address challenges in availability of radiopharmaceuticals but it indirectly addressed the matter by providing guidance on production, distribution and dispensing of radiopharmaceuticals.

1.5 Delimitations

Source materials considered only included guidelines that were current and valid during the data collection period between November 2021 and August 2022 from local and international regulatory and advisory bodies.

1.6 Theoretical Framework

To ensure that patients are receiving quality medicines, the pharmaceutical industry is tightly regulated using GXP guidelines as part of Quality Assurance. Radiopharmaceuticals are considered as medicines as they are used in the diagnosis and treatment of ailments. However, radiopharmaceuticals have unique handling requirements during production, distribution, dispensing and disposal.

It is therefore critical that guidelines specific to radiopharmaceuticals be established to develop and expand the growth of radiopharmacy in Kenya. By defining the good practices involved in production and distribution of radiopharmaceuticals, the procurement of radiopharmaceuticals may be improved or that production would be encouraged and thus improve the outcome and quality of services. A well-regulated practice of radiopharmacy will ultimately contribute towards attainment of optimum benefit by patients who are the end users.

CHAPTER TWO - LITERATURE REVIEW

Introduction

Radiopharmacy is a branch of nuclear medicine that uses radioisotopes for diagnostic, therapeutic or research applications (4–7). Radiopharmacy practice combines the skills involved in the preparation of pharmaceutical products with those required to handle radioactive substances (3,7). Radiopharmacy is a growing field internationally with over 37 million nuclear medicine procedures performed annually worldwide (8).

Radioactive isotopes, also known as radionuclides, may be manufactured in a nuclear reactor, cyclotron, and linear accelerator or from a radionuclide generator using particle bombardment techniques. A radiopharmaceutical is obtained by labelling a medicinal substance with the desired radionuclide (9).

Radiopharmaceuticals are used to interact with tissues or organs in the body and to detect and visualise physiological and disease conditions in the body by acting as a tracer that has a preferential uptake by a particular tissue (4,10). The uptake is imaged using detectors mounted in gamma cameras or Positron Emission Tomography (PET) devices (4,5).

Diagnostics based on radiopharmaceuticals differ from other methods such as ultrasound, CT scans, and X-rays, in that they are used to determine a medical condition based on the function of the organ, tissue or bone rather than structural appearance (11). Radiopharmaceuticals produce radioactivity using open or unsealed sources of radiation that are introduced into a patient's body through routes of administration such as oral, intravenous, percutaneous, intradermally, inhalation, intracapsular and become the source of radiation from within the patient (4).

As such, nuclear medicine techniques differ from other detection methods in that radiation is emanated from within a patient's body and the imaging cameras are external to the patient, whereas as other methods send external radiation through the body to perform imaging (1).

When used as a therapeutic agent, the radiation may be used to kill unwanted cells such as cancerous cells, reduce the size of a tumour, or reduce pain (4,12). The radiation levels used in therapeutics are higher than those used in diagnostics, which tend to be comparable to the radiation from a diagnostic X-ray procedure (11). This is due to diagnostic procedures requiring a lower energy isotope to visualise a target site during a scan, whereas therapeutic procedures utilize a higher energy isotope to kill targeted cells (1).

Other imaging procedures that use radiation but do not involve radioactive material include X-ray and mammograms. As such, they are considered radiological procedures and not radiopharmacy procedures (12).

Uses and benefits of radiopharmacy

Radiopharmacy is used in diagnosis or treatment of a range of pathological conditions for different age groups. It largely contributes to the fields of oncology, cardiology, nephrology, urology, musculoskeletal disease management, rheumatology and neuropsychiatry (10,13,14). Common diagnostic and therapeutic radiopharmaceutical procedures are summarized in Tables 1 and 2 respectively.

Table 1 – Common Diagnostic Radiopharmaceutical Procedures (13,15)

Description	**Uses**
Positron Emission Tomography (PET)	Stage, assess response to treatment, detect metastases, and evaluate recurrence of cancer
Single Photon Emission Computed Tomography (SPECT)	Diagnose and track heart disease progression, bone disorders, neurological disorders, gall bladder disease and intestinal blood loss.
Bone scan	Assess bone metabolism and stage cancers and bone diseases
Lung imaging	Diagnose pulmonary embolus
Myocardial perfusion imaging	Provide information about the blood supply to the heart by imaging blood flow differences in rested and stressed states
Kidney imaging	Assess kidney functions
Sentinel node imaging	Image a tumour's lymphatic involvement and to guide surgery in cancer patients

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) scans are the more commonly diagnostic procedures. PET imaging an external camera detects photons released by annihilation process of positrons and electrons. The positrons are produced during the decay of radiotracers administered to a patient. In SPECT

imaging, an external camera detects gamma rays produced by the decay of administered radiotracers (15).

Table 2 – Common Therapeutic Radiopharmaceutical Procedures (13,16)

Description	**Uses**
Administering radio-iodine	Treatment of thyroid cancer and overactive thyroid glands
Bone metastasis treatment	Control metastatic (or secondary) cancer in the bones and palliation.
Treatment of metastatic neuroendocrine tumours	Deposit large doses of radiation to the cancer and damage local malignant growth.
Brachytherapy	A temporary or permanent radioactive implant in cancerous tissue such as in the treatment of mouth, breast, lung, prostate, ovaries, or uterus cancers

Radiopharmacy has significant benefits in both therapeutics and diagnostics. When used for diagnosis, radiopharmacy provides a safer and more cost-effective means of diagnosis compared to exploratory surgery, which is invasive, more costly, or be unavailable depending on the part of the body being examined (1).

Some types of radiopharmaceuticals, for example in PET, can also identify a disease in its most basic stages and precisely locate diseased tissue in a patient's body often before the disease becomes symptomatic or leads to abnormalities that can be detected with other diagnostic tests (17). This can therefore provide a lead time of over 3 months compared to conventional diagnostic methods. This may have a drastic effect on a patient's outcome as treatment can be initiated earlier (4,5).

Radiopharmaceuticals may also provide valuable information in pharmaceutical drug development. The information provided by these techniques can improve and quicken the development cycle as researchers also use radiopharmaceutical imaging to focus on the most promising strategies and enhance the ability to evaluate the drug product's effectiveness and efficaciousness (17).

Concerns related to radiation

The use of radiation often leads to concerns of safety as high radiation levels can impair tissues functioning and can produce acute undesirable side effects that include skin redness, hair loss, radiation burns. Long-term effects of radiation may include mutagenesis, carcinogenesis, cataracts, blood and bone cell destruction, and may lead to death (8).

However radiopharmaceutical procedures are deemed safe as a patient's exposure to radiation is minimal as the amount of radiotracer used is very small. Diagnostic radiopharmaceuticals are not associated with major or long-term clinical side effects as they tend not to have any pharmacological effect. Allergic reactions may occur, however they tend to be rare and usually mild (1,3,4).

Every effort must be undertaken when using radiopharmaceuticals so as to minimize untoward radiation exposure to patients. This is known as the ALARA (as low as reasonably achievable) principle where the lowest reasonable amount of radiopharmaceutical that may provide precise and accurate imaging or therapeutics is used (1,15).

Radiopharmaceuticals

Radiopharmaceuticals may consist of a radioactive isotope on its own or combined with a carrier molecule. These carrier molecule selection is based on the function of the compound and they can be a specific protein, sugar, monoclonal antibody or the patient's own cells like their red blood cells (9,15,17,18). The process of radiolabelling incorporates a radioactive isotope into the molecule's structure for the purpose of determining the presence or biodistribution of the molecule after administering it to a patient (9). The compounds' nature dictates their distribution and accumulation in target organs while maintaining a low systemic level of radiation exposure (1,15).

As rapidly growing cancer cells utilize more glucose than normal cells, radiolabelled glucose molecules are frequently used in PET scans as a tracer compound in the detection of cancer and its metastatic spread in the body. An example of such a compound is ^{18}F labelled deoxyglucose (15). After accumulating in the body's tissues, the compound emits positrons that react with electrons that result in an annihilation reaction. Energy from the reaction is produced in the form of a pair of photons which are detected by a PET scanner. During imaging, tumours and areas of inflammation appear more intense than surrounding tissue as they accumulate larger amounts of glucose due to their higher level of metabolism. The areas are

referred to as ‘hot spots.’ Areas that appear less intense are referred to as ‘cold spots’ and have lower metabolic activity. Such information is useful in assessing and detecting abnormal conditions in patients (17).

Radiolabelled blood cells may be reinjected into a patient to identify the source of bleeding using a SPECT scan by detecting accumulation of radioactivity in the respective tissue. SPECT differs from PET in that SPECT imagers can detect the gamma ray emissions from the administered radiopharmaceutical compounds and not photon energy (15).

Radioimmunotherapy is another application of radiopharmaceuticals that involves monoclonal antibodies acting as carrier molecules for radionuclides. The monoclonal antibodies recognize and interact with cell specific features such as receptors and antigens. As such, they are more specific than conventional carrier molecules. Once administered to the patient, the compound attaches to the targeted cells delivering a high dose of radiation to the intended tissue (17).

As the monoclonal antibodies are highly specific, there is limited radiation exposed to normal, healthy cells therefore having fewer adverse effects than chemotherapy and radiotherapy which tends to be non-targeted. A combination of ^{90}Yttrium (^{90}Y) and the monoclonal antibody ibritumomab tiuxetan (Zevalin^{TM}), and a combination of ^{131}Iodine (^{131}I) and tositumomab (Bexxar^{TM}) are currently approved by FDA to treat patients with lymphoma that is nonresponsive to chemotherapy (17).

Radiopharmacy practice in Kenya

Radiopharmacy is not practiced widely in Kenya as few healthcare facilities provide services in the country (4,10,19), with less than 20 radiotherapy equipment across the country (20). As at 2018, there were less than 10 specialists in the country including radiopharmacists, nuclear medicine physicians, medical physicists, and radiopharmacy technologists, (4,10).

Notable facilities that provide radiopharmacy services include Kenyatta National Hospital (7), Aga Khan University Hospital (14), Health Care Global Enterprise Limited and Cancer Care Kenya (HCG CCK) Cancer Centre (21), Texas Cancer Centre (22) and the newly commissioned facilities in Kenyatta University Teaching, Referral & Research Hospital (23). Services provided locally include PET and SPECT scans, radioiodine administration and brachytherapy. The listed centres have “hot lab” facilities (7,14,21,22).

Guidelines from International Atomic Energy Agency (IAEA), the international regulatory body on nuclear technologies, define three levels of radiopharmacy practice. In level 1, there is no manipulation of the product at the healthcare facility level as the final radiopharmaceutical dose form is purchased and delivered ready for use. Operational level 1a involves dispensing of radiopharmaceuticals supplied in their final form from authorized manufacturers or centralized radiopharmacies. These are usually unit doses of prepared radiopharmaceuticals which do not require compounding. Operational level 1b involves the dispensing radioiodine and other ready to use radiopharmaceuticals for palliation care or therapy.

Level 2 practice involves minimal manipulation from prepared and approved reagents (kits). This is performed in a radiopharmacy/hot lab. Operational level 2a involves the preparation of radiopharmaceuticals using reagent kits, and generators radionuclides which use technetium generators or cold kits. Operational level 2b involves the radiolabelling of the patients' blood cells.

Level 3 production involves compounding from parent ingredients to create diagnostic radiopharmaceuticals, therapeutic radiopharmaceuticals, or synthesis and radiolabelling (3,5). Operational level 3a is the compounding of radiopharmaceuticals from ingredients for diagnostics use, modification to existing commercial kits; in-house production of reagent kits from ingredients.

Operational level 3b is the compounding of radiopharmaceuticals from ingredients and radionuclides for therapeutic application. Operational level 3c is the synthesis of positron emission tomography (PET) radiopharmaceuticals.

Radiopharmaceutical production in Kenya focusses on Level 1 and Level 2 (24), however, Level 3 production for PET radiopharmaceuticals are performed at the Aga Khan University Hospital and KUTRRH and includes the synthesis of ^{18}F-fluorodeoxyglucose (14).

Regulation of radiopharmacy practice

Pharmacy and Poisons Act (CAP 244) provides guidance for medicinal products in Kenya. Medicinal products are defined as "those that are used in treating, preventing or alleviating disease or symptoms of disease; diagnosing disease or ascertaining the existence, degree or extent of a physiological condition; or preventing or interfering with the normal operation of a physiological function." As radiopharmaceuticals are used to diagnose and treat illnesses, they

should be considered as medicinal products. However, the act does not specify special provisions for safety and time needs of radiopharmaceuticals (5,25).

As medicinal products, the production, characterization and quality control testing of radiopharmaceuticals should comply with the rules for manufacturing/compounding sterile products intended for human medicinal use (26).

In USA, the regulatory body Food and Drug Administration (FDA) provides approvals for radiopharmaceuticals after they are investigated for safety, preparation, and performance standards (1,15). In the UK and EU, radiopharmaceuticals are also regulated by the drug regulatory agencies Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA) respectively (2,27). However, locally there is a lack of clear regulations for radiopharmaceuticals (5).

Guidance for regulation of pharmaceutical products is provided by guidelines from the regulatory authorities for the regions (28). Collectively, guidelines for good practices in the pharmaceutical field are referred to as GXP and they focus on personnel, procedures, products, premises and equipment, documentation and processes involved in the different stages of a pharmaceutical product's life cycle (29). These are described in Table 3.

Table 3: Local guidelines used to regulate pharmaceuticals (29,30)

Name of guideline	**Abbreviation**	**Areas of focus**
Good Manufacturing Practices	cGMP	Products of good quality are consistently produced.
Good Distribution Practices	GDP	Medicine's quality is maintained throughout all stages of the supply chain.
Good Laboratory Practices	GLP	Reproducibility, accuracy, and consistency of laboratory procedures.
Good Clinical Practices	GCP	Clinical research is performed with established ethical and scientific quality standards
Good Storage/Warehousing Practices	GSP/GWP	Quality storage of medicals in warehouses and distribution centres.
Good Pharmacovigilance Practices	GVP	Performance of pharmacovigilance - detecting, assessing, understanding and preventing medicine related problems such as adverse events, misuse, abuse, or any other.

There are local guidelines issued by the regulatory board covering the production, distribution, pharmacovigilance, transportation, clinical trials, market recall and withdrawal waste management, however none focus on or consider the special requirements of radiopharmaceuticals (24,31).

GXP guidelines are a critical part of quality assurance whose purpose is to ensure that patients receive safe and effective medicines of an acceptable quality. Poor quality medicines may lead to adverse effects in patients, tarnish the reputation of healthcare systems and lead to economic losses (32).

Radiopharmaceuticals significantly differ from regular pharmaceuticals as they may have shorter half-lives. Due to time limits brought about by their rapid decay, they must be prepared shortly before their administration to a patient and cannot be prepared in mass quantities in advance. This may limit a comprehensive quality control analysis of the final product. Additionally, handling of radiopharmaceuticals brings on a health hazard due to possible exposure to radiations. It is therefore vital to safely and effectively prepare and use radiopharmaceuticals for the protection of the operator and patients (3,9).

They also have specific requirements during their production and dispensing that vary from the requirements of traditional pharmaceutical products such as the pressure differentials in production areas. Pharmaceutical products are required by GMP guidelines to be manufactured under a positive room pressure to protect them from external contamination. However, for radioactive compounds, IAEA guidelines require that their production be performed under negative pressure to contain possible radioactive contamination within a controlled environment and avoid uncontrolled spreading externally (9,33).

A study in South Africa in 2016 evaluated the appropriateness of applying the current regulatory guidelines on the manufacture of medicinal products within the radiopharmaceutical industry and noted that if the regulations were applied without industry specific considerations, it could result in an inappropriately regulated industry. The researcher determined that, "in order for the radiopharmaceutical manufacturing industry to be as appropriately regulated as the orthodox pharmaceutical industry, industry-specific guidelines are required to be developed by the regulatory authorities and adopted by the manufacturing industry" (9).

In 2019, the South African Health Products Regulatory Authority (SAHPRA) issued guidelines on Radiopharmaceutical Manufacturing to be read in conjunction with the South African Guidelines for Good Manufacturing Practices (34).

Locally, several radiopharmaceuticals are listed under the Kenya Essential Medicines list (35), however none are registered or currently approved by the local drug regulatory authority, Pharmacy and Poison's Board (PPB) (36). Radiopharmaceuticals listed in Kenya's essential medicines list for 2019 are listed in Table 4.

Table 4: Radiopharmaceuticals listed in Kenya's essential medicines list for 2019 and their common uses (35)

Description	**Use**
Dimercaptosuccinic acid (DMSA)	In SPECT assessment of renal morphology, structure and function
Hepatobiliary iminodiacetic acid (HIDA)	In SPECT imaging of bile ducts, gall bladder and liver
Iminodiacetic acid	In SPECT imaging of the liver and biliary tree
Hexamethylpropyleneamineoxime (HMPAO)	SPECT detection of eosinophilic infiltration in eosinophilic gastroenteritis; altered cerebral perfusion in stroke and other cerebrovascular diseases
^{123}Iodine	SPECT imaging and treating medullary thyroid cancer
^{131}Iodine	SPECT for treatment of hyperthyroidism and thyroid cancer
Mercaptoacetyltriglycine (MAG)	SPECT for evaluating functioning of the kidneys
Methylene diphosphonate (MDP)	SPECT for skeletal imaging
Sesta methoxyisobutylisonitrile (sestamibi)	SPECT for myocardial perfusion scintigraphy; identification of parathyroid adenomas; radioguided surgery of the parathyroid; scintimammography
Technetium-99m generator	Commonly used in SPECT imaging
^{18}F-Fluorodeoxyglucose (FDG)	PET imaging for the diagnosis and treatment monitoring for many cancers
^{177}Lutetium dotatate, ^{68}Gallium dotatate	PET and the treatment of neuroendocrine tumours
^{64}Copper	PET for diagnosis and targeted treatment of prostate cancer

Guidelines from IAEA are used by some of the local facilities to guide practice as well as enable auditing of facilities (7), however there is need for national regulations to augment the IAEA regulations (5).

The Radiation Protection Board also provided guidance for radiopharmaceuticals as it regulated nuclear energy in the country. The applicable legislation, CAP 243 Radiation Protection Act which dated from 1982, was superseded by the Nuclear Regulatory Act in 2019 (8,37,38). Under the new act, Kenya Nuclear Regulatory Authority (KNRA), become the successor to the Radiation Protection Board and has the power to "grant, amend and revoke authorisations, and to impose such conditions upon authorisation holders as it deems necessary" (39).

The mission of KNRA is "to regulate the peaceful use of atomic energy through the promotion of a radiation safety culture for the protection of persons, society and the environment against the hazards of radiation" (39). However, guidelines available for download from their official website are currently limited to those in the setting up on medical cyclotron facilities and requirements for practice licenses but do not cover GMP, GLP or GRPP – Good Radiopharmacy Practices (40).

Challenges facing radiopharmacy practice

In addition to a lack of local guidelines, others challenges facing radiopharmacy in the country include difficulty in distribution of radiopharmaceuticals (4), lack of specialist personnel (4,10,19), lack of local availability of radiopharmaceuticals (10,19), a general lack of awareness of radiopharmacy (4,10), waste management concerns (9,10), and high cost of procedures (10).

Radiopharmacy is taught as a unit in undergraduate pharmacy degrees locally and as a unit for Masters in Pharmacy in Industrial Pharmacy, however complete training for radiopharmacy is not available in the country and must be sought abroad (4,41). IAEA provides short trainings for African countries through the AFRA IAEA project (4,19), however these may not cater to knowledge gaps due to the difference in levels of technology and production between different countries (19).

A study to assess the levels of training in radiopharmacy staff in Africa showed that most BPharm graduates involved in radiopharmacy did not have any additional hands-on training. The short IAEA courses provided to them in radiopharmacy built competencies in the areas of

quality control, SPECT and PET preparations, radiation safety, radiation risk management, and radiation dose calculation. Skills gaps that were identified in the research included blood cell labelling, radiation dose calculations, PET radiopharmaceutical preparation, radiation protection, safe handling of ^{131}Iodine, GMP in radiopharmacy, quality control and quality assurance for radiopharmaceuticals (19).

Awareness of radiopharmaceuticals is also low amongst patients and within the healthcare sector (4,10). Kenyans have for long been travelling as part of medical tourism to Asian countries for PET imaging services due to the cost, lack of awareness of local facilities or due to frequent downtime of equipment of local sector (4,5). However, introduction of a cyclotron machine at the Aga Khan University Hospital in 2018 has improved the situation as it is the first cyclotron in East and Central Africa and is now offering PET scan for the region. This have been promoted by the national insurer National Health Insurance Fund (NHIF) covering part of the imaging procedures' cost (42). In addition, KUTRRH is coming up with a nuclear molecular imaging facility including a cyclotron and PET scan facilities for the country (43).

Kenya does not produce raw materials or kits for radiopharmacy and relies on imports (4,5,10). This is due to a lack of facilities (5) and supporting infrastructure, such as reliable and affordable power supply and radioactive waste management facilities (5,10). To tackle this, a waste management facility was recently inaugurated by the Ministry of Health in Ngong, the Central Radioactive Waste Processing Facility, Oloolua Forest, to handle radioactive waste, (4).

Reliance on imports also has its disadvantages. the global supply chain of radiopharmaceuticals has unreliable as the reactors in exporting countries are ageing and may experience longer maintenance periods and unscheduled shutdowns (44).

Success story and the way forward

A success story from Spain involves developing centralized radiopharmacies. Traditionally the doses to be administered to patients are prepared by hospital personnel in hot labs. Currently, 45% of the units doses are prepared and supplied from 6 centralized radiopharmacies while the remainder are prepared at the individual hospitals or by private contractors (45).

The key elements for the centralized radiopharmacies include a well-designed radiopharmaceutical unit, a computer-based management system and a quality management system. These ensure safe and efficient operation both for the product and the personnel,

fulfilling both radioactive and pharmaceuticals criteria, provide records and traceability. The benefits are summarized as: fulfilment of all regulatory requirements without hospital investments; improvements in flexibility and cost reduction; traceability; improvements in pharmacovigilance; and improvements in quality of services (45). The facility at KUTTRH proposes to work on this model (23).

2.1 Problem Statement and Study Justification

As medicinal products, the production, characterization, and quality control testing of radiopharmaceuticals should comply with the rules for manufacturing/compounding sterile products intended for human medicinal use. However, there has been slow growth of this technology in Kenya, leading to local patients seeking nuclear medicine services abroad as part of medical tourism. The local drug regulatory authority, Pharmacy and Poisons Board, has published several guidelines for good practices in the conventional pharmaceutical industry, referred to as GXP guidelines, on the manufacturing, storage, distribution, dispensing and waste disposal of pharmaceutical products. There is a lack of elaborate local guidelines and regulations specific for radiopharmaceuticals in Kenya.

This study aimed to explore the creation of GXP guidelines specific to radiopharmacy practice in Kenya by comparing current guidelines with international ones, and assessed the alignment of these to the emerging radiopharmacy practice in the country.

2.2 Research Questions

The research was guided by following questions:

Which guidelines are used in foreign regions for regulating radiopharmaceuticals?

- Regions or regulatory authorities considered include Food and Drug Administration (FDA), Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency (EMA), South African Health Products Regulatory Authority (SAHPRA), World Health Organization (WHO) and International Atomic Energy Agency (IAEA).

Do the current local guidelines fall within specifications of the international guidelines related to radiopharmaceuticals?

Do currently practicing radiopharmacy units in Nairobi perform appropriately in relation to an IAEA-based audit?

2.3 Objectives

2.3.1. General objective

To systematically analyse local and international drug regulatory authorities' guidelines on radiopharmaceuticals to identify gaps in local regulations, and explore how these can be addressed by adapting international regulations as guidance materials for regulation for radiopharmaceuticals in Kenya.

2.3.2. Specific objectives

i. To review international guidelines for practice of radiopharmacy practice regarding personnel, handling procedures, products, premises and equipment, documentation

ii. Determine regulatory gaps in practice of radiopharmacy in Kenya as compared to international guidelines.

iii. Evaluate the adherence to guidelines from IAEA by chosen local sites regarding personnel, handling procedures, products, premises and equipment, documentation and key processes in radiopharmacy practice, by auditing and scoring the sites.

iv. To determine factors and challenges affecting the practice of radiopharmacy in Kenya through interviews with key informants in the sector.

CHAPTER THREE - METHODOLOGY

3.1 Introduction

This research focused on the review of international guidelines required for radiopharmacy practice globally, with case for adaption for use in Kenya, and an audit of local radiopharmacy units' adherence with the prevailing guidelines. Stakeholders including a practicing radiopharmacist, nuclear medicine technologist, regulatory pharmacist at PPB, radiation protection specialist, were interviewed as key informants to understand the operations and challenges facing radiopharmacy in Kenya.

3.2 Research design

A qualitative research design was used comprising of qualitative comparative and descriptive studies. The qualitative comparative study consisted of two parts; a desktop document review and site audits. A desktop document review was performed comparing current local guidelines on good practices related to pharmaceuticals against international guidelines on current good radiopharmacy practice to assess gaps in the local guidance regarding radiopharmacy practice and assessing possible solutions. Site audits of local practicing sites comparing their functioning and quality management system to standards set by the international regulatory body, IAEA, and was used to give an indication of guidelines adherence.

The key informant interviews formed the qualitative descriptive arm of the study where semi-structured interviews of key informants in the sector were performed to understand challenges they faced in the sector and gauge their opinion on regulation of the industry.

3.3 Location of the study

A desktop review of reference regulations and guidelines was performed using the publicly available documents on the regulatory or guidance bodies' official websites listed in Table 5.

Two local radiopharmacy practicing sites were visited for evaluation of adherence of prevailing international guidance and to capture challenges in current practice through key informant interviews.

All data was collected between November 2021 and August 2022.

Table 5: List of websites of Regulatory Bodies

Name of body	Region	Website
Pharmacy and Poison's Board	Kenya	https://pharmacyboardkenya.org/downloads
International Atomic Energy Agency	International	https://www.iaea.org/publications
World Health Organization	International	https://www.who.int/publications/i
European Medicines Agency	Europe	https://www.ema.europa.eu/en
U.S. Food and Drug Administration	USA	https://www.fda.gov/regulatory-information/search-fda-guidance-documents
Medicines & Healthcare products Regulatory Agency	UK	https://www.gov.uk/search/guidance-and-regulation
South African Health Products Regulatory Authority	South Africa	https://www.sahpra.org.za/guidelines/

3.4 Target population and study population

For Radiopharmacy GXP guidelines, the target population was regulatory guidelines on pharmaceuticals; the study population were GXP guidelines from PPB and radiopharmacy specific guidelines from relevant international regulatory authorities. Regarding the

radiopharmacy practice site visits, two sites were purposively chosen as they had the most advanced facilities and were most actively involved in radiopharmacy practice in Kenya.

The target population for the key personnel interviews healthcare workers of different cadres practicing radiopharmacy at the selected practicing sites and regulatory affairs specialists at the pharmaceutical and radiation regulatory authorities, PPB and KNRA. Six persons were targeted to be interviewed comprising of two members of staff from each of the visited sites and a representative selected by each regulatory authority.

3.5 Inclusion and exclusion criteria

When assessing the local regulatory requirements, guidelines from PPB for pharmaceuticals were assessed. For comparison, the corresponding international regulations for radiopharmaceutical regulation were the current and valid versions. The regulations were issued by recognised regulatory or advisory bodies and not opinion papers or third-party documentation. Draft versions of guidelines were not considered as they were not finalised and validated.

For site audits and key personnel interviews the inclusion criteria were:

- The sites were involved in practice of radiopharmacy with a functioning hot lab.
- Healthcare workers considered for interviews were team members of the radiopharmacy units in the selected sites for visiting, and members of the regulatory affairs departments of the drug or radiation regulatory authorities.

Exclusion criteria for sites and key personnel interviews were:

- Sites with radiology departments that do not involve nuclear medicine
- Staff at visited sites not directly involved in radio-pharmacy practice.

3.6 Research instruments and data collection techniques

For evaluation of regulations, the collection and assessment of current good practice guidelines was performed, in comparison to their suitability and applicability within the local radiopharmaceutical industry, using industry specific requirements as the basis for the evaluation. These were compared to current international guidelines on radiopharmaceutical practice.

Documents were sourced directly from the regulatory agencies' official websites. The search terms used in the search boxes of the websites were "radiopharmacy", "radiopharmaceuticals", "radiopharmacy practice" or "good radiopharmacy practices".

A table was prepared highlighting the areas of focus (such as equipment, personnel) and guidelines for pharmaceutical products to be analysed to identify the gaps for radiopharmaceuticals and sourcing the appropriate solution from current guidelines. The table is included as Appendix 1.

The IAEA-issued hospital radiopharmacy unit audit checklist was used to assess local radio-pharmacy practicing study sites (46). Alignment of current practices with guidelines and challenges faced was noted, tabulated, and scored as per IAEA audit recommendation. Based on the observations, recommendations for the sites were shared with the respective teams. The checklist is included as Appendix 2.

Interviews of key informants working in radiopharmacy sites and regulatory authorities were conducted to assess their insight on the lack of local regulations, to understand challenges they are currently facing and their suggestions on the matter. The interviews were performed using an interview guide (Appendix 3) and was conducted in person or online as per the interviewee's request. After obtaining consent from the interviewee, in person interviews were recorded on the principal investigator's smartphone using a voice recorder application, while online interviews were recorded using the tele-networking application used for the interview.

The interview guide was arranged in several sections. Questions 1, 2, 3 and 4 provided information on the interviewees' profession and their roles/duties. Questions 5, 6, 7 and 8 had yes or no responses whose frequency was recorded. Responses to questions 5a, 8a, 9 and 10 were coded based on the category that the response corresponds to such as production, storage, distribution and dispensing of radiopharmaceutical products, training of personnel or others depending on the responses obtained. Key thematic points obtained from the responses and verbatim statements were presented in the final report.

3.7 Study results dissemination and utility

The audit reports of the site visits were shared with the respective sites within one month of the visit for their review. The results of this study shall be shared with PPB and KNRA as proposal for possible development of GXP guidelines specific to radiopharmacy practice in Kenya.

3.8 Ethical Considerations

Ethics approvals was obtained from KNH-UON ethics and research committee before carrying out study including site visit and interviews at Kenyatta National Hospital radiopharmacy department, referenced as P499/06/2021 and attached as Appendix 4. Similarly, approval was obtained from the Aga Khan University Hospital Institutional Research Ethics Committee, referenced as 2021/ISERC-171(v2) and included as Appendix 5. A study permit was then obtained from the National Commission Science Technology and Innovation (NACOSTI) reference number 915717 and attached as Appendix 6.

The audits were objective and non-biased and scored on the basis of implementation of practices. None of the audit and interview activities involved handling of radioactive material or visits to holding areas of such material.

All persons interviewed provided their written informed consent before the interview. Respondents were informed about the study purpose, objectives, benefits, risks and participants expectations. Participants were free to decline participation without suffering any dire consequences regarding their practice. Confidentiality was observed for obtained data by limiting access to data collected to the chief investigator by ensuring all hardcopy documents were kept under lock and key while all softcopy documents were secured by a password. Secure disposal of the data was performed after completion of data analysis. All responses were anonymised and coded so as to not reveal identifier details of the place of practice of the persons in the study.

CHAPTER 4 – RESULTS AND DISCUSSION

4.1. Comparison of local GXP guidelines and international radiopharmacy practice guidelines.

The guidelines referred to include a joint publication from WHO and IAEA, MHRA, SAHPRA, EMA. Guidelines from FDA regarding radiopharmacy were in their draft version during the data collection period and were not considered. The findings from the review indicating similarities and differences in international regulation of radiopharmaceuticals compared to local GXP guidelines for regular pharmaceuticals in Kenya are here presented.

4.1.1 General considerations

The presence of radioactivity is the key difference between orthodox medicines and radiopharmaceuticals and hence the difference in guidelines. This desired feature is essential in the use of the radiopharmaceuticals as either diagnostic or therapeutic products, however it also presents several challenges to the production, distribution, use and disposal of the products.

If used as a diagnostic, the quantity of the active radiopharmaceutical administered to a patient is minute and the product may have little to no pharmacological effects. When used as a therapeutic agent, radiation is desired and these may be administered in higher doses (2).

As radiopharmaceuticals are essentially medicines, they must comply with stringent requirements of current good practices throughout the products' lifecycle, however customisation of some processes is necessary to accommodate their unique features.

A feature that affects many facets of a radiopharmaceutical is rapid radioactive decay meaning that the products have decreasing content of radioactivity over time. Therefore, the shelf life of the products tends to be short, ranging between minutes to days, leading to their final preparation shortly before administration.

Due to the short shelf life of radiopharmaceuticals, unlike traditional medicines which are manufactured in large, predetermined batches, these tend to be produced in lesser quantities and according to orders received. Therefore, it should be noted during registration of the products by the regulatory authority that radiopharmaceuticals tend to have small batch sizes and that the batch size may vary on different occasions owing to demand at that time. A solution would be to define and justify by process validation, the minimum and maximum batch size of the product during production (2,47).

Prior to release of batched of orthodox medicines, thorough physical and chemical quality control tests are performed. However, due to the rapid radioactive decay of the products, radiopharmaceuticals are often released and administered to patients before completion of quality control testing (2).

As the products are usually administered parenterally, they are required to be sterile and free of endotoxins. Radionuclidic and radiochemical purity of the products are also essential for patient safety and efficacy of the products. These tests are necessary post-release and must be justified after thorough risk assessment (41,47).

As radiopharmaceuticals are radioactive, unlike traditional medicines, risk assessment should include exposure of staff and surroundings to radiation, ALARA principles should be included in risk assessment performed for all processes involved in preparation and control of the products (47).

The distribution chain of orthodox pharmaceuticals tends to involve many parties from distributor hubs, wholesalers and retailers or clinics. Owing to the earlier described reasons of short shelf and specialised handling, the distribution chain for radiopharmaceuticals tends to be much simpler, often involving the direct delivery of the product from the manufacturing or compounding unit to the administration unit (47).

4.1.2 Premises

Premises intended for the production operations of pharmaceuticals are designed, located, constructed, adapted, and maintained appropriately to assure the quality of the products. However, the activities performed usually do not involve radioactivity. As sterile products, the production or compounding of radiopharmaceuticals is performed in clean areas. Access to the technical areas must be controlled to avoid contamination such as to minimize the entrance of maintenance personnel to the production areas (48).

Premises in which radioactive products are handled must be licensed by the appropriate authorities. Radiation protection, ALARA compliance, and a high level of cleanliness with necessary controls to minimize microbial contamination are required (34).

The manufacture of any radiopharmaceutical product involving human blood or plasma should be performed in a dedicated area with the appropriate equipment to prevent any contamination of other products being produced in the area as well as protecting the personnel (2).

4.1.3. Personnel

To be able to appropriately handle radiopharmaceuticals due to their radioactive nature, personnel involved in handling the products in its different phases should receive additional training preparation and control of radiopharmaceuticals, the handling of radioactive materials and safety. Additionally, regular monitoring for radiation exposure and possible contamination must be performed for all personnel handling radioactive materials. A radiological sensor alarm system may also be included in the shipping unit so to create an alert and help protect both personnel and the surrounding environment (34,47).

4.1.4. Production and handling of preparations

In the production and quality control functions of traditional medicines, validated cleaning methods ensure some small equipment may be scrupulously cleaned and reused. However, when dealing with radiopharmaceuticals, the equipment may become irradiated and therefore not suitable for prolonged use by the personnel as per the ALARA principle. Therefore, it shall be advisable to regularly monitor equipment and safely dispose of those that exceed predefined safe levels of radioactive contamination. Staff should have dedicated facilities for changing before entering and after exiting active areas to prevent or contain any contamination (27,34,47).

Although radiopharmaceuticals are radioactive, the dose of radioactivity possessed may not be sufficient to sterilise the product itself. Therefore, all sterile products should be terminally sterilised before release by either autoclave or filtration (34).

To minimize the risk of product contamination in general pharmaceutical production, HVAC system and pressure cascade systems are used. Here, production takes place under positive pressure and filtered air is let into the technical space. While this is also important in the production of radiopharmaceuticals, the premises which handle these products must also account for radiation safety (34).

Production under positive pressure would lead to exposure of the surroundings of the facility to radioactive gases, therefore a negative pressure differential would be a safer choice. A pressure cascade system would be a compromise, where production is performed under positive pressure, thereby preventing contamination of the products, while being surrounded by a zone of negative pressure, preventing escape of radioactive gases to the external environment (34).

The pressure differentials should be controlled, monitored, and recorded. Radioactive gas emissions should also be effectively controlled and monitored with alarm systems in place. These should be exhausted through separate air-handling units fitted with the appropriate filters which should be regularly checked for their performance. The radioactive contaminated air should also not be recirculated (34).

4.1.5 Product distribution and recall

Regarding distribution of the radioactive products, the manner in which they are transported should be such that the to assure the safety of the personnel and the environment. Packaging should ensure adequate shielding and containment and may consist of multiple layers of packaging based on a "Russian-dolls" concept (49).

Like traditional medicines, the material used in the packaging should not react or alter the products being transported and it should be sturdy and reliable for long haul transportation. This may be performed using drop tests and fire tests (49,50).

After release and distribution of the products, batches of traditional medicines may be recalled from the market by the manufacturers or the regulators due to various deficiencies related to the safety, quality of efficacy of the products. Batch movement is traced and the products are removed from the market as they are returned to the manufacturers or their distributors (48).

In the case of radiopharmaceuticals, the return of the products may not be practical as they are used shortly after production. However, it is important that detailed distribution records be maintained with the aim to prevent the use of affected batches them. These modified recall procedures should be proven to be operable in a very short time and where the return of the products is expected, radioactivity safety must be considered (34,47).

The comparison of the guidelines is summarized in Appendix 7.

The details of the guidelines reviewed are listed in Table 6.

Table 6: List of reviewed guidelines

Regulatory body	Title	Version	Year of issue	Bibliography reference number
PPB	Guidelines for GMP Inspection for Manufacturers of Health Products and Technologies	HPT/ISE/GUD/071 Rev. no 0	2022	(48)

Regulatory body	Title	Version	Year of issue	Bibliography reference number
PPB	Guidelines for Good Distribution Practices for Medical Products and Health Technologies in Kenya	HPT/ISE/EFS/GUD/019 Rev. no 1	2022	(50)
WHO/IAEA	International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products	WHO Technical Report Series, No. 1025, 2020	2020	(47)
MHRA	Guidance for Specials Manufacturers	Revision 2	2021	(27)
SAHPRA	Radiopharmaceutical Manufacturing	4.07 Radiopharmaceutical manufacture Jun03 v1.doc	2019	(34)
IAEA	Regulations for the Safe Transport of Radioactive Material	No. SSR-6 (Rev. 1)	2018	(49)
EMA	Guideline on Radiopharmaceuticals	EMEA/CHMP/QWP/306970/2007	2008	(2)

4.2. Site Audits

4.2.1 Overview

Site audits of active radiopharmacy units was planned to be carried out using a validated audit checklist based on the IAEA guidance on Hospital Radiopharmacy (Appendix 2). The selected sites for the audits were the Kenyatta National Hospital and the Aga Khan University Hospital Nairobi. These sites have the longest history of nuclear medicine practice in the country.

The checklist consists of 7 sections. The first section of the audit was related to staffing. This looked into the qualification of staff, their training, performance reviews. The second section related to facilities and equipment, where the licensure of the facility, finishings of the premises, appropriateness of shielding, regular inspection of the site were considered.

The third section related to the purchase of materials, looking into the protocols in place for purchase, receipt, and acceptance process of products. The fourth section focused on dispensing protocols, looking into the availability of procedures involved in dispensing operations and batch traceability.

The fifth section investigated preparation protocols, confirming the presence of written procedures relating to the preparation of radiopharmaceuticals. The sixth section focused on quality assurance and quality control. Here, records were checked for regular quality control checks, product rejection protocols, complaint handling, release process and recalls.

The seventh and final section related to waste, focusing on the availability of written procedures related to the unit's waste management.

4.2.2 Kenyatta National Hospital Site Visit

From the previously recorded audits of Kenyatta National Hospital, the available radiopharmacy equipment included a dual-head gamma camera, a gamma probe, dose calibrators, rectilinear scanner, a hot lab, radioiodine fume hood and radioiodine uptake probe. Skilled staff at the unit included a nuclear medicine physician, nuclear medicine technologists, medical physicists, a radiation protection officer, and nurses. Services offered included nuclear medicine imaging procedures such as SPECT, bone, thyroid, and whole-body scans, thyroid ablation, renal scan, and lung scan, treatment of thyrotoxicosis (7).

During the data collection period, that is between November 2021 and August 2022, the Kenyatta National Hospital radiopharmacy unit was not functional hence it was not be audited. The unit had not been functional for over 2 years due to downtime of key equipment and had

previously experienced difficulty in procurement of radionuclides as well as shortages of key personnel.

4.2.3 Aga Khan University Hospital, Nairobi

The radiopharmacy unit at the Aga Khan University Hospital Nairobi was visited on 10th May 2022, and the lead auditee was Dr. Zahid Sroya, a radiopharmacist. He responded to all questions from the audit checklist and provided a site tour. Pictures and samples of documents were not taken during the audit; however, observations were made and recorded. Discrepancies noted were classified as either minor, major or critical.

Key equipment available in the unit included a Positron Emission Tomography (PET) CT scanner, a cyclotron, a dual head SPECT gamma camera, a hot lab and brachytherapy equipment. Skilled personnel included a radiopharmacist, a nuclear medicine physician, a radiologist with specialization in nuclear medicine, nuclear medicine technologist, and nurses. Various diagnostic and therapeutic nuclear medicine procedures were offered at the facility.

In summary, the radiopharmacy unit at Aga Khan University Hospital Nairobi largely complied with requirements based by the IAEA guidance on hospital radiopharmacy. Two major observations were made; one was related to facilities and equipment, where currently monometer readings of pressure differentials across HEPA filters are recorded monthly instead of the recommended daily checks. The second observation was related to preparation protocols where currently individual patient doses cannot be traced to a specific generator and kit batch number which may impede a recall procedure.

For the section on staffing, the professional responsible for the unit was Dr. Zahid Sroya, a radiopharmacist. The staff had valid practice licences as a pharmacist from Pharmacy and Poisons Board and a nuclear medicine technologist from Kenya Nuclear Regulatory Authority.

To ensure that the curriculum vitaes of the unit's staff are up-to-date, these are reviewed after every two years. There are written training manuals for all grades of staff. Trainings are quizzed and graded.

The unit does not perform level 2 operations; however, records were available on key training including calibration of equipment, working practices in the radiopharmacy (samples records referred to training on GLP and aseptic techniques), dose preparation, quality control techniques, dose release, record keeping and cleaning. Some of the trainings were performed

in-house while others were organised by principal companies that supplied radiopharmaceuticals to the unit.

There is a system for formal approval of all documentation including product preparation and formal release process. Annual performance reviews for the competencies of staff are performed using tests. As part of continuous improvement, weekly CMEs are also performed within the unit.

Regarding the second section on facilities and equipment, the facility had valid licences from both PPB and KNRA. The licence from PPB was a licence to manufacture pharmaceuticals and a wholesale dealer's licence to engage in their trade. The unit also had a valid A and B licence from KNRA

During the site tour it was noted that the unit had appropriately finished rooms, with adequate lighting, smooth impervious walls, floors and ceilings. The dispensing station was also noted to be shielded. Logs were available for all equipment and their maintenance or calibration schedules. There was also support available in case of the breakdown through an engineering team trained by the aforementioned principal companies.

Monometer readings of pressure differentials across HEPA filters were recorded, however the frequency was monthly instead of daily. Air velocity determination for the laminar airflow cabinets was noted to be performed annually. Visual inspection and integrity tests were carried out and recorded before use of negative pressure isolators.

A system was in place for planned maintenance of all equipment of the radiopharmacy. Daily monitoring and recordings were done for the over-pressures when using the clean rooms.

Regarding purchase of material, suitable protocols were in place for purchase of approved radiopharmaceuticals. A procedure was in place to ensure and record that all goods were correctly received against the order. Records for batch numbers and quantities received were noted to be kept. Prior to acceptance, visual inspections and label checks were noted to be performed. All batches of products and reagents were received with accompanying certificates of analysis from the suppliers.

It was observed that all products imported were not registered by the regulatory authorities. However, a control in place was that each consignment required an import permit whose approval is provided by the regulators. Therefore, although not all products used at the facility

were registered by the drug regulator, their approval was sought for each importation and therefore no products were used at the facility without a form of approval from the Pharmacy and Poisons Board.

Under the section related to dispensing protocols, there were written procedures available for dispensing operations undertaken in the unit. A labelling procedure was in place for dispensed products. Written procedures were also in place for dispensing or radioiodine solutions or capsules.

For operational level 1b activities related to individual patient therapy, batch traceability was performed from the prescription to administration of individual doses. There were written procedures in place for the use of generators and reconstitution of each radiopharmaceutical kit used.

The SOPs were independently reviewed and approved at specified intervals of two years. The preparation of (^{99m}Tc) Technetium radiopharmaceuticals from kits and generators was noted to be carried out in a LAF cabinet. There were set criteria in place before release for patients use. This was undertaken by the same operator.

It was noted that individual patient doses could not be traced to a specific generator and kit batch number. Level 2b operations were not performed at the unit at the time of the audit.

Regarding quality control and quality assurance, daily quality control checks were noted to be performed on radionuclide calibrators. Prior to purchase, prequalification checks performed on suppliers included checks of validity of operational licences, certificate of good manufacturing practice, samples of certificates of analysis for products supplied. The prequalification was performed by the material management department of the Aga Khan University Hospital Nairobi. The department was also responsible for the purchase of materials and ingredients.

Monthly quality control checks were performed on the unit's radiopharmaceuticals. There was a procedure in place for dealing with products that fail to meet required standards. A record was kept of complaints and their associated investigation.

Written procedures and records were available for regular contamination surveys of the radiopharmacy unit. For operational level 2 functions, records were available for purchase of radioactive ingredients, generator elution, yield, molybdenum and aluminium ion breakthrough, product preparation, quality control and release, aseptic technique and trend

analysis, laboratory cleaning and maintenance, equipment and plant calibration and maintenance, radioactive contamination monitoring and waste disposal, and product defects and SOP non-conformance. Molybdenum and aluminium breakthrough measurement was noted to be performed on the first eluate from each technetium generator.

An annual independent internal audit was noted to be performed. There were also records of routine microbiological monitoring of the preparation area of the radiopharmacy. A yearly programme was in place for checking the quality of radiopharmaceuticals. Daily checks performed on prepared radiopharmaceuticals considering patient safety included sterility tests, thin layer chromatography, gas chromatography, presence of endotoxins.

There was no record of changes of the source of the kits or ingredients used at the unit as there had been no change in sourcing.

Radiochemical purity was noted to be performed on the first use of a new batch or delivery of a radiopharmaceutical kit. Regular testing of pH of radiopharmaceuticals was noted.

Prior to release of products to patients, records for checks performed for radioactivity dose were present. Records of formal approval of products before administration to patients were present. The authorized person for the approvals was Dr. Zahid Sroya.

Written procedures for the recall of defective products were present. Records of complaints and their follow up investigation were present. Reports of self-inspection evaluation were available. A system was in place for external audits.

Regarding their waste management system, written procedures were in place for the disposal of radioactive and non-active waste in the radiopharmacy unit. A weekly review was performed of the arrival, use and disposal of all radioactive materials. Written logs were available for each solid radioactive sources that indicated their usage, transfer and disposal.

Descriptions of the audit sites are listed in Table 7.

Table 7 – Description of Radiopharmacy Practicing Sites

Description	**Kenyatta National Hospital**	**Aga Khan University Hospital**
Address and contact details	Hospital Road Nairobi, Kenya Tel. +254 (0) 20 272 6300 Email: knhadmin@knh.or.ke	3rd Parklands Avenue, Limuru Road Nairobi, Kenya. Tel. +254 (0) 20 366 2000 Email: akuh.nairobi@aku.edu

Description	Kenyatta National Hospital	Aga Khan University Hospital
Operation status	Not operational	Active; Level 2 and 3
Available radiopharmacy equipment	• Dual-head gamma camera • Dose calibrators • Gamma probe • Rectilinear scanner • Hot lab • Radioiodine fume hood • Radioiodine uptake probe	• Positron Emission Tomography (PET) CT scanner • Cyclotron • Dual head SPECT Gamma Camera • Hot lab • Brachytherapy equipment
Present skilled staff	• Nuclear medicine physician • Technologists • Medical physicists • Radiation Protection officer • Nurses	• Radiopharmacist • Nuclear medicine physician • Radiologist with specialization in nuclear medicine. • Nuclear medicine technologists • Nurses
Services offered	• Nuclear medicine imaging procedures such as SPECT • Bone, thyroid, and whole-body scans, thyroid ablation, renal scan, and lung scan. • Treatment of thyrotoxicosis.	Various diagnostic and therapeutic nuclear medicine procedures.

Results from the audit of the radiopharmacy unit at the Aga Khan University Hospital Nairobi are summarized in Appendix 8.

4.3. Key informant interviews

To gain a better understanding of the Kenyan radiopharmacy practice environment, five key informant interviews were conducted guided by an interview guide (Appendix 3). These respondents were purposively selected by being qualified personnel in preselected practicing sites, that is the Kenyatta National Hospital and Aga Khan University Hospital Nairobi, and both the drug and the radiation regulatory boards, Pharmacy and Poisons Board and Kenya Nuclear Regulatory Authority.

Although the target was to interview two members of the radiopharmacy unit at the Kenyatta National hospital, as it was inactive during the data collection period, only one member of staff attached to the unit was available for the interview.

The designations and areas of practice of interviewees were as follows a radiopharmacist, and a nuclear medicine technologist, both from the Aga Khan University Hospital Nairobi, a clinical pharmacist (trained in radiopharmacy) working at Kenyatta National Hospital, a deputy director inspection at the Pharmacy and Poisons Board and a deputy chief radioprotection officer at the Kenya Nuclear Regulatory Authority.

The work experience of the interviewees ranged from between 6 months to over 15 years, where one respondent had been working in his current workstation for 6 months, two had 3 years of experience while the two remaining had 4 years and over 15 years of experience in the field. Two of the five key informants represented a regulatory authority.

Regarding their work-related activities, four of the five responded that their daily work involves radiopharmacy related practices. These related to the preparation and dispensing of radiopharmaceuticals, administration to patients, quality assurance, quality control, radiopharmacy unit management, guiding establishment of radiopharmaceutical manufacturing units in the country, distribution of radiopharmaceuticals, and the oversight of importation of radioisotopes. Key details noted during importation of the radionuclides included the type of product, quantity imported, purpose of use of the product, and which industry they are intended for.

The single negative response from the respondent from the Kenyatta National Hospital was the inactive status of the radiopharmacy unit due to key equipment being unavailable at the time of the interview. Before closure, procurement challenges had also been experienced, as importation of radiopharmaceuticals through the current stringent government procurement procedures and requirements became a hindrance to provision of services at

the unit. Delays in receipt of the radiopharmaceuticals at the facility led to them lesser available shelf-life to work within. The smaller quantities of radiopharmaceuticals ordered when compared to regular medicines also meant that there was a smaller margin of error that could be afforded.

When asked about challenges face in their job related to radiopharmacy, four of the five responded positively that they have experienced challenges. These were related to personnel, equipment, facilities, distribution or regulations.

Two of the interviewees mentioned personnel, elaborating that there is limited manpower and few training opportunities in the local industry. One respondent explained that "we have very few radiopharmacists in the country; we have limited capacity", and the second went on to explain that "manpower is a challenge; work may not continue when the radiopharmacist is not available". "Training new staff" was also cited as a challenge related to personnel as they may not have been exposed to radiopharmacy prior to joining the unit. It was noted that the baseline understanding of radiopharmacy practice was not as robust as that of regular pharmaceutical products in the new graduates or interns at the practicing facilities.

Availability of certain key equipment or facilities were another challenge described by the frequent and long downtime of some machinery, such as a technetium generator or gamma camera may halt functioning of the entire radiopharmacy unit.

Another challenge described in the interviews was related to the distribution of radiopharmaceuticals. Specifically, delays in customs clearance of imports at ports of entry in the country was seen to reduce the effectiveness of the radionuclides due to their short half-life, that is, the products experience significant radioactive decay during the customs clearance delay.

Regarding regulation of the field, one respondent explained that it is "a green area for the regulators as well", that is, the field is relatively newer when compared to other established areas of pharmaceutical practice. This was later reiterated by another respondent as an additional comment towards the end of his interview.

All five of the interviewees were aware of GXP guidelines in pharmaceutical industry such as GMP and GDP. They were all also aware of the impact of quality assurance in the production, storage, distribution and dispensing of pharmaceutical products. During the

interview, one respondent exclaimed "of course it is important! Quality assurance is key at ensuring the products are effective".

All five respondents also mentioned that in their opinion industry-specific GXP guidelines for radiopharmacy were important. The areas of radiopharmacy practice that require further guidance material in their opinion were production, training of personnel such as in production of radiopharmaceuticals, procurement, dispensing, administering radiopharmaceuticals to patients, and distribution of radiopharmaceuticals. Four of the respondents added that "all areas of radiopharmacy practices" would require local guidance. The responses are summarized in Figure 1 below:

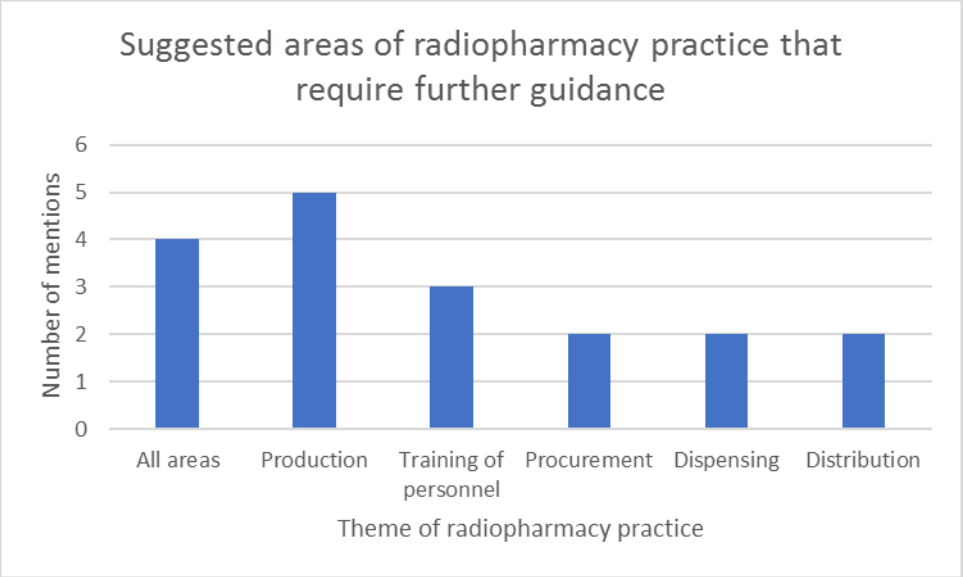

Figure 1: Suggested areas of radiopharmacy practice that require further guidance

A suggestion was also shared by one of the respondents to encourage the local universities to consider a master's program specialising in radiopharmacy involving at least one year of theory and 6 months in practice to build capacity of manpower in the field.

When asked which international guidelines they referred to for current radiopharmacy related practices, four of the five responded "IAEA", while one responded "none".

All five responded with "yes" when asked on their opinion on whether some of the challenges in practicing radiopharmacy may be addressed by establishing local radiopharmacy GXP guidelines. Responses from the informants explaining their opinion included that "different regions face different challenges and therefore application (of guidelines) should be localised" and "local guidelines are needed; a subcommittee from the

(regulatory) boards is required to discuss the guidelines before implementation. The subcommittee could involve stakeholders in public and private sector to come up with guidelines to help the situation".

The responses to the different questions are summarised in Appendix 9 while the written consent forms of the interviewees included as Appendix 10.

CHAPTER 5 – GENERAL DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

Local guidelines on good practices consider how the quality of orthodox medicines may be affected during production, distribution, storage and ultimately disposal. However, they do not consider the specific requirements of radiopharmaceuticals, especially their need to be sterile and sufficiently radioactive.

When considering the radioactivity of the products, protection of personnel and the environment are key hence appropriate shielding is necessary in each stage of the product's lifecycle. A guideline on how this is affected is therefore necessary.

Due to rapid radioactive decay, the radiopharmaceuticals must be processed, distributed, and administered much quicker than traditional medicines. This means that some steps followed in the production and quality control processing of orthodox products may be omitted for radiopharmaceuticals to save on time and ensuring that the product has not decayed to below optimum radioactivity levels. However, as the products are still medicines, their quality should not be compromised. Post-release quality control tests and process validation are necessary.

The status of radiopharmacy practice in the country is still wanting. It is unfortunate that the oldest radiopharmacy unit in the country, at the Kenyatta National Hospital, was inactive during the period of data collection and hence could not be assessed. The Aga Khan University Hospital was however functional and was assessed against the IAEA guidance on hospital radiopharmacy and was found largely complying in several spheres.

The distribution chain for radiopharmaceuticals tends to be much simpler, often involving the direct delivery of the product from the manufacturing or compounding unit to the administration unit – care during importation. However, the government procurement procedures can be a hindrance to service delivery if the concerned stakeholders are not well versed with the nature of products radiopharmaceuticals are.

5.2 Conclusion

International guidelines on radiopharmacy practice from WHO/IAEA, SAHPRA, EMA and MHRA were reviewed against local PPB issued guidelines on Good Manufacturing Practices, Good Distribution Practices. Gaps were noted in the local guidance in relation to personnel,

premises and equipment and procedures involved in the production and distribution of radiopharmaceuticals.

The Aga Khan University Hospital radiopharmacy unit was visited and noted to be compliant with guidance issued by IEAE. Challenges noted to be affecting radiopharmacy practice in the country through interviews with key informants in the sector related to all areas of practice, ranging from production to distribution, shortage of man power in the field and the lack of local guidelines.

Radiopharmacy practice in Kenya is a growing field with new practicing sites being established and current sites attempting to stay on par with global standards. However local radiopharmacy guidelines are not in place and this may lead to disparity within practicing sites. Some sites align to different international guidelines or in-house policies from the multinational companies that supply their products or equipment.

To ensure that there is uniformity in the services provided and key functions performed by the local practicing sites, local guidelines are necessary. The adoption of international guidelines without consideration for unique challenges in the local sector may not be beneficial as the local stakeholders may not be able to comply with all the requirements.

Therefore, it is imperative to establish local radiopharmacy practice guidelines for the improvement and enhancement of the sector in Kenya thus ultimately benefiting local and regional patients.

5.3 Recommendations

Recommendations for Policy and Practice

- Local guidelines on radiopharmacy practice should be established after consultation with key stakeholders in the field. Those include, the Pharmacy and Poisons Board (PPB), Kenya Nuclear Regulatory Authority (KNRA), and representatives from practicing sites.
- More local opportunities for training personnel for radiopharmacy practice to build the capacity of manpower in the local sector.
- Ensure business continuity planning for practicing sites in the country considering the field requires large investments in terms of premises, equipment and trained professionals.

Recommendations for Further Research

Site audits for the Kenyatta National Hospital radiopharmacy unit when it is active, and recently inaugurated Kenyatta University Teaching, Research and Referral Hospital are also recommended.

Follow up on feedback from key informants in the field after establishment of local guidelines is important to understand upcoming concerns and areas for improvement in the local sector as improvement should be a continual process. Focus areas may include improvement of radiopharmaceutical distribution and personnel capacity building.

As radiopharmaceuticals may be released and dispensed prior to complete quality control testing, research into the quality assurance programme of practicing units is also advised. Validation of quality control procedures should be confirmed.

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APPENDICES

Appendix 1: Summary of proposed regulations

S. NO.	AREA OF CONCERN	CONFLICT IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	RADIOPHARMACEUTICALS		

Appendix 2: Radiopharmacy Site Visit Criteria

This checklist is based on IAEA Guidance on Hospital Radiopharmacy - A safe and Effective Approach.

Staffing

No.	Component	Y/N	Verifiable – Manual, Reference documents, SOP, QC data, file record etc.	Comments/ Planned Action	Date achieved.
1	Is there a professional responsible for the radiopharmacy? Provide details.				
2	Is the radiopharmacy unit operated under the direction of a person with appropriate training as defined by local or national regulations?				
3	Do the staff have valid practice licence?				
4	Are regularly updated CV's of staff maintained that include their qualifications?				
5	Are there written staff training manuals for all grades of staff?				
6	Have all staff working at operational level 2 received specific staff training on the following:				
7	Calibration of equipment- please provide details and training records				
8	Working practices in the radiopharmacy - please provide details and training records				
9	Preparation of individual doses - please provide details and training records				

10	Quality control and analytical techniques - please provide details and training records				
11	Dose release - please provide details and training details				
12	Record keeping - please provide details and training records				
13	Cleaning - please provide details and training records				
14	Is there a system for formal approvals of all documentations including radiopharmaceutical (RP) preparation, QC and formal release to patient?				
15	What training is provided to staff performing final checks on all products prepared before release for patient use?				
16	Are there training records for all staff performing cell labelling, e.g. RBC, WBC?				
17	Is there an annual performance review to check the competencies of radiopharmacy staff?				

Facilities and Equipment

	Component	**Y/N**	**Verifiable – Manual, Reference documents, SOP, QC data, file record etc.**	**Comments/ Planned Action**	**Date achieved.**
18	Is the facility licensed by PPB/KNRA?				
19	Does the unit have appropriately finished rooms (including adequate lighting, appropriate finishes to walls, floors, ceilings and ventilation) and a shielded dispensing station?				

20	Is there a shielded dispensing station available?				
21	For operational level 1b is there a shielded dispensing station and/or a fume hood available? [Is there a fume cupboard with suitable filters for volatile radioactive materials such as ^{131}I solutions?]				
22	Is there a validated (annual check on air-flow, safety and challenge testing) fume hood with suitable filters for handling radioiodine solutions?				
23	Are there records and logs kept for all equipment irrespective of whether maintenance and calibration are performed 'in-house' or by external contractors?				
24	Is a list of all equipment maintained that includes the classification of and age of each equipment?				
25	Is there availability of support in case of a breakdown?				
26	For operational level 2: Are there regular checks on validated Class II type B microbiological safety cabinets located in a dedicated room?				
27	Are monometer readings of pressure differentials across HEPA filters recorded daily?				
28	Are there periodic records of air velocities determination for LAF cabinets or isolators?				
29	Is challenge testing of the HEPA filters in LAFs and isolators carried out annually?				
30	For negative pressure isolators: Before preparation takes place, are gloves or gauntlets visually inspected and integrity tests carried out and recorded?				

31	Is there a system and record of planned preventative maintenance for all equipment in the radiopharmacy including the refrigerator?				
32	When clean rooms are used, are the over-pressures gauges monitored and recorded daily?				

Purchase of materials

	Component	**Y/N**	**Verifiable – Manual, Reference documents, SOP, QC data, file record etc.**	**Comments/ Planned Action**	**Date achieved.**
33	Are there suitable protocols and trained staff for the purchase of approved or Marketing Authorized radiopharmaceuticals?				
34	Are all goods received checked and recorded against the order for correctness of delivery?				
35	Are records kept for batch numbers and quantities received?				
36	Are visual inspections and label checks carried out prior to acceptance?				
37	Do all products, kits and generators have product approval, marketing authorisation, or bear a product licence number?				
38	How many unlicensed or unapproved products are used each year and is there a record of them?				
39	For all unlicensed kits, radiopharmaceuticals or radio-chemicals are the prescribers or responsible medical doctors made aware of his/her responsibilities?				

40	Do the suppliers or reagents and unapproved products provide a "Certificate of Analysis"?				

Dispensing protocols

	Component	**Y/N**	**Verifiable – Manual, Reference documents, SOP, QC data, file record etc.**	**Comments/ Planned Action**	**Date achieved.**
41	Are there specific written radiopharmacy procedures for dispensing operations undertaken in the radiopharmacy?				
42	Under operational level 1a: Are there written procedures for the aseptic dispensing and labelling of unit doses of ready-to-use radiopharmaceuticals?				
43	Is there a system for labels which assesses quality, number produced and number applied to dispensed doses?				
44	For operational level 1b: Do the written procedures contain clear safety and monitoring instruction for dispensing radioiodine solutions or capsules?				
45	Under operational level 1b are there written procedures for calibration assay, preparation and dispensing of individual patient radionuclide therapy?				
46	Can the audit and documentation for each RP batch be traced from the prescription to the actual administration of individual patient doses?				

Preparation Protocols

	Component	Y/N	Verifiable – Manual, Reference documents, SOP, QC data, file record etc.	Comments/ Planned Action	Date achieved.
47	Are there written and approved procedures for the use of generators and reconstitution of each radiopharmaceutical kit used?				
48	Are SOPs independently reviewed and approved at specified intervals?				
49	Is the preparation of 99mTc radiopharmaceuticals from kits and generators carried out in a LAF cabinet?				
50	Are there set criteria before release for preparation for patients use? Is this undertaken by the same operator or a different individual?				
51	Can each individual patient dose be traced to a specific generator and kit batch number?				
52	Under operational level 2b: Do the written procedures for any autologous preparation, e.g. red and white blood cells, include a clear instructions on safety, cleaning and decontamination?				
53	Are there written procedures for the preparation and dispensing of approved kit formulations of radio-labelled biological e.g. monoclonal antibodies, peptides?				

Quality Assurance & Quality Control

	Component	Y/N	Verifiable – Manual, Reference documents, SOP, QC data, file record etc.	Comments/ Planned Action	Date achieved.
54	Are daily QC checks performed on radionuclide calibrators?				
55	What quality checks are undertaken on a supplier before purchase?				
56	Are periodic quality checks on radiopharmaceuticals (RP) performed?				
57	Is there a written procedure for dealing with product/s failing to meet the required standard?				
58	Is there a record of complaint/s and any associated follow-up and investigation?				
59	Are there written procedures and records for regular contamination surveys of the radiopharmacy unit?				
60	For operational level 2 are there records for the following:				
61	Purchase of radioactive products and ingredients				
62	Generator elution, yield, [^{99}Mo] molybdenum breakthrough and aluminium ion breakthrough				
63	Product preparation, QC and release				
64	Environmental and microbiological monitoring				
65	Aseptic process, aseptic operator validation and trend analysis				
66	Laboratory cleaning and maintenance				
67	Equipment and plant calibration and maintenance				

68	Radioactive contamination monitoring and radioactive waste disposal				
69	Product defects and SOPs non- conformance, i.e. when a procedure is performed in a manner other than that described in the relevant SOP				
70	Independent inspection and audit				
71	In line with the IAEA “Operational guidance on Hospital Radiopharmacy” document, are there records of routine microbiological monitoring of the preparation area in the radiopharmacy?				
72	Are there calibration and linearity checks of the dose calibrator response over the complete range of activities measured at least annually?				
73	Is there set programme for checking the quality of radiopharmaceuticals (RP)?				
74	Considering patient safety, are certain simple checks performed on prepared radiopharmaceutical, e.g. mini-chromatography?				
75	For operational level 2 is a [^{99}Mo] Molybdenum breakthrough measurement performed on the first eluate from each [^{99m}Tc] Technetium generator and repeated when the generator is moved?				
76	Is aluminium ion breakthrough checked on the first eluate from a [^{99m}Tc] Technetium generator?				
77	Are changes in the source of any kits, diluents or vehicle used, needles, syringes, swabs and sterile containers used within radiopharmacy recorded?				
78	On first use of a new batch or first new delivery of RP kits is radiochemical purity performed?				

79	Are rapid alternative methods employed for swift prospective QC for critical RP e.g. the determination of RCP for [^{99m}Tc] HMPAO)?				
80	Is there regular pH testing of RP carried out?				
81	Prior to release for patients is each individual radioactivity dose checked?				
82	Is there a record of the formal approval/release by an authorized person before a product is administered to a patient?				
83	Are there written procedures for the recall of defective products?				
84	Is there a record of complaints and any associated follow-up and investigation?				
85	Is there a system of recorded self-inspection and reports evaluation?				
86	Is there a system for external audit or peer review process?				

Waste

	Component	**Y/N**	**Verifiable – Manual, Reference documents, SOP, QC data, file record etc.**	**Comments/ Planned Action**	**Date achieved.**
87	Are there written procedures for the disposal of radioactive and non-active waste specific to the radiopharmacy?				
88	Is there a periodic review/audit of arrival, use and disposal of all radioactive materials?				

89	Are there written logs for each solid sources that indicate usage, transfer, disposal of solid sources?				

Audit Summary

The audit summary below should be completed by all units in order to prioritise needs.
Critical priorities have the highest importance.
Major priorities are second to critical priorities however they should still be addressed in a timely manner
Minor priorities are areas which need addressing but do not require such urgent attention as the above two categories.

Critical priority

	Class	Comment/action	Time frame	Date achieved

Major priority

	Class	Comment/action	Time frame	Date achieved

Minor priority

	Class	Comment/action	Time frame	Date achieved

Appendix 3: Key informant interview questionnaire and interview guide

This interview aims to identify the challenges facing radiopharmacy practice in Kenya, particularly the lack of local regulations. It will focus on thematic areas that are critical to radiopharmacy practices.

1. What is your current position?
2. What is your current place of work or institution?
    a. How long have you been at the current position?
3. Do you represent a regulatory body?
4. Does your work involve radiopharmacy practices?
    a. If so, kindly elaborate on functions related to radiopharmacy
5. Have you encountered challenges in your job related to radiopharmacy?
    a. If so, kindly elaborate on the challenges faced.
6. Are you aware of GXP guidelines in pharmaceutical industry such as GMP, GDP etc?
7. Are you aware of the impact of Quality Assurance in the production, storage, distribution and dispensing of pharmaceutical products?
8. Are industry-specific GXP guidelines important for radiopharmacy in your opinion?
    a. If so, which area(s) of radiopharmacy practice require further guidance material in your opinion?
9. Which international guidelines do you refer to for current radiopharmacy related practices?
10. In your opinion, may some of the challenges in radiopharmacy practice described earlier by addressed by establishing local radiopharmacy GXP guidelines?

Appendix 4: KNH-UoN ERC Approval

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
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KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/427

11th November 2021

Dr. Pooja Neil Lumb
Reg. No.U53/6810/2017
Dept.of Pharmaceutics and Pharmacy Practice
Faculty of Health Sciences
University of Nairobi

Dear Dr. Pooja

RESEARCH PROPOSAL: A SYSTEMATIC EVALUATION OF REGULATIONS FOR RADIOPHARMACY PRACTICE IN KENYA IN COMPARISON TO INTERNATIONAL GUIDELINES (P499/06/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P499/06/2021.** The approval period is 11th November 2021 – 10th November 2022.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely

PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Dean-Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. Lucy Tirop, Dept.of Pharmaceutics and Pharmacy Practice, UoN
Dr. Shital Maru, Dept.of Pharmaceutics and Pharmacy Practice, UoN
Dr. Beatrice Amugune, Dept.of Pharmaceutical Chemistry, UoN

Appendix 5: AKUH ERC Approval

THE AGA KHAN UNIVERSITY

Faculty of Health Sciences
Medical College

Ref: 2021/ISERC-171(v2)
March 28, 2022

Dr. Dr. Zahid Sroya - Aga Khan University
SupervisorDr. Lucy Tirop - University of Nairobi
Supervisor Pooja Neil Lumb – Masters in Industrial Pharmacy University of Nairobi

Dear Dr. Zahid Sroya / Pooja Neil Lumb and team

RE: A SYSTEMATIC EVALUATION OF REGULATIONS FOR RADIOPHARMACY PRACTICE IN KENYA IN COMPARISON TO INTERNATIONAL GUIDELINES

The Aga Khan University, Nairobi Institutional Scientific and Ethics Review Committee (ISERC), is in receipt of your protocol resubmitted to the Research Office (RO) on 19th March, 2022. The ISERC has reviewed and approvedthis project *{as per attached official stamped protocol and attachments - version Ref: 2021/ISERC-171(v2*). You are authorized to conduct this study from **March 28, 2022**. This approval is valid until **March 27, 2023** and is subject to compliance with the following requirements;

1. The conduct of the study shall be governed at all times by all applicable national and international laws, rules and regulations. ISERC guidelines and Aga Khan University Hospital policies shall also apply, and you shouldnotify the committee of any changes that may affect your research project (amendments, deviations and violations)
2. Researchers desiring to initiate research activities during COVID-19 pandemic must comply with the COVID-19 SOPs for Research as well as submit to the Research Office a Request Form to Initiate, Reinstate or ContinueResearch During COVID-19 Pandemic.
3. **Prior** to human subjects enrolment you must obtain a research license from the National Commission for Science, Technology and Innovation (NACOSTI), *where applicable*, site approvals from the targeted externalsite(s) and file the copies with the RO.
4. *As applicable*, **prior** to export of biological specimens/data, ensure a Material Transfer Agreement (MTA)/Data Transfer Agreement (DTA), is in place as well as seek shipment authority/permit from the relevant government ministry. Copies of these approvals, should be submitted to the RO for records purpose.
5. All Serious Adverse Events and the interventions undertaken must be reported to the ISERC as soon as they occur but not later than 48 hours. The SAE shall also be reported through the AKUHN quality monitoring mechanism(s) at Client Relations Department of the Chief of Staff's Office.
6. All consent forms must be filed in the study binder and where applicable, patient hospital record.
7. Further, you must provide an interim Progress Report Form **60 days before expiration** of the validity of this approval and request extension if additional time is required for study completion; as well as submit the completed Self-Assessment Tool -Monitoring Ethical Compliance in Research. You must advise the ISERC when this study is complete or discontinued and a final report submitted to the Research Office for record purposes.
8. The Aga Khan University Hospital management should be notified of manuscripts emanating from this work.

If you have any questions, please contact Research Office at AKUKenya.ResearchOffice@aku.edu or 020-366 2148/1136.

With best wishes

Dr. Christopher Opio,
Chair – Institutional Scientific and Ethics Review Committee (ISERC)
Aga Khan University, (Kenya)

Copy: Co-Investigators

Appendix 6: NACOSTI Research Licence

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: 915717

Date of Issue: 26/November/2021

RESEARCH LICENSE

This is to Certify that Dr., POOJA NEIL LUMB of University of Nairobi, has been licensed to conduct research in Nairobi on the topic: A SYSTEMATIC EVALUATION OF REGULATIONS FOR RADIOPHARMACY PRACTICE IN KENYA IN COMPARISON TO INTERNATIONAL GUIDELINES for the period ending : 26/November/2022.

License No: NACOSTI/P/21/14561

915717

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

NOTE: This is a computer generated License. To verify the authenticity of this document, Scan the QR Code using QR scanner application.

THE SCIENCE, TECHNOLOGY AND INNOVATION ACT, 2013
The Grant of Research Licenses is Guided by the Science, Technology and Innovation (Research Licensing) Regulations, 2014
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2. The License any rights thereunder are non-transferable
3. The Licensee shall inform the relevant County Director of Education, County Commissioner and County Governor before commencement of the research
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7. The Licensee shall submit one hard copy and upload a soft copy of their final report (thesis) within one year of completion of the
research
8. NACOSTI reserves the right to modify the conditions of the License including cancellation without prior notice

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Appendix 7: Summary of comparison of guidelines

S. NO.	AREA OF CONCERN	DIFFERENCES IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	RADIOPHARMACEUTICALS		
1	General	Batch sizes are often large (in the tens of thousands) and should be defined in the product registration dossier.	They are created in small and varying batch sizes.	Compliance with national regulations concerning production, supply, storage, use and disposal of radioactive products is necessary. Risk assessment and risk controls in the production and distribution of radiopharmaceuticals should include consideration of the unique qualities of the products and differences from pharmaceuticals. The process should be tailored to suit the individual products created. To accommodate the varying batch sizes, the minimum and maximum batch sizes should	PPB; EMA, IAEA/WHO, SAHPRA
		Shelf-life of products ranges in months to years.	They tend to have a short shelf-life that may range between minutes to days.		
		Thorough quality control testing is performed before release of the products.	Radiopharmaceutical administration to patients is often performed before completion of quality control testing. Therefore, tests such as endotoxin content determination, sterility, radionuclidic purity may be performed after release of the products.		
		Distribution chain may vary and can be quite long with many parties involved.	They often have a simple distribution chain, involving the direct delivery of the finished		

S. NO.	AREA OF CONCERN	DIFFERENCES IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	**RADIOPHARMACEUTICALS**		
			product from the manufacturing/compounding unit to the administration unit.	be defined and appropriately justified. The process of preparation and control of these products should comply with the principles of ALARA and local regulations on radiation safety.	
		Products are usually intended to exert a pharmacological activity.	Radiopharmaceuticals are used for diagnosis in small doses and therefore have a low potential to exert toxic or pharmacological effects.		
		The products and production process do not usually involve exposure to radioactivity.	The products are radioactive.		
2	Product Recall	Recall procedures are necessary to ensure specific batch(es) of a product are removed from the market due to deficiencies in its safety, quality, or efficacy.	The return of radiopharmaceuticals may not be practical as the products are used shortly after production.	The main purpose of the recall procedure may be to prevent the use of radiopharmaceuticals rather than physically returning the products as in the case of pharmaceuticals therefore detailed distribution records should be maintained.	PPB; EMA, IAEA/WHO, SAHPRA, MHRA

S. NO.	AREA OF CONCERN	DIFFERENCES IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	RADIOPHARMACEUTICALS		
				Recall procedures should be shown to be operable within a very short time. Radioactivity safety must be considered where return of the products is required.	
3	Personnel	The production process does not usually involve exposure to radioactivity.	Personnel must be well equipped to safely handle radioactive products.	Personnel require additional training on the preparation and control of radiopharmaceuticals, the handling of radioactive materials and safety. Monitoring for radiation exposure and possible contamination must be performed for all personnel handling radioactive materials.	PPB; EMA, IAEA/WHO, SAHPRA

S. NO.	AREA OF CONCERN	DIFFERENCES IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	RADIOPHARMACEUTICALS		
4	Premises	In order to suitably carry out operations intended, facilities should be designed, located, constructed, adapted and maintained appropriately. However, the activities do not normally involve radioactivity.	Processes shall involve the use of radioactive products. Products shall also require to be sterile. Access to technical and production areas must be controlled to avoid contamination. To minimize the risk of product contamination and to protect personnel from the risks of radiation exposure, the HVAC system and pressure cascade design for the different areas should be appropriately designed and maintained. Radioactive gases and vapours also need to be appropriately contained.	Premises in which radioactive products are handled must be licensed. Radiation protection, ALARA compliance, and a high level of cleanliness with necessary controls to minimize microbial contamination are required. Technical area access points should be configured to minimize the entrance of maintenance personnel to the production (clean) areas. The pressure differentials should be controlled, monitored and recorded. Radioactive gas emissions should also be effectively controlled and monitored with alarm systems in place.	PPB; EMA, IAEA/WHO, SAHPRA, MHRA

S. NO.	AREA OF CONCERN	DIFFERENCES IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	RADIOPHARMACEUTICALS		
				Radioactive gas should be exhausted through separate air-handling units fitted with the appropriate filters. These should be regularly checked for performance. Radioactive contaminated air should not be recirculated. Manufacture of any radiopharmaceutical product involving human blood or plasma should be performed in a dedicated area with the appropriate equipment. All sterile products should be terminally sterilised before release by either autoclave or filtration.	

S. NO.	AREA OF CONCERN	DIFFERENCES IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	RADIOPHARMACEUTICALS		
5	Production and Handling of Radioactive Preparations	Traditional medicines do not involve use of radioactivity.	Dedicated facilities required for changing, preparation and manipulation to minimise the risks of contamination.	Regularly monitor equipment and safely dispose of those that exceed predefined safe levels of radioactive contamination. Staff should have dedicated facilities for changing before entering and after exiting active areas to prevent or contain any contamination. The pressure differentials in working areas should be controlled, monitored and recorded. Radioactive gas emissions should also be effectively controlled and monitored with alarm systems in place. These should be exhausted through separate air-handling units fitted with the	PPB; EMA, IAEA/WHO, SAHPRA, MHRA

S. NO.	AREA OF CONCERN	DIFFERENCES IN REGULATIONS		POSSIBLE SOLUTIONS	SOURCE REFERENCE
		PHARMACEUTICALS	RADIOPHARMACEUTICALS		
				appropriate filters which should be regularly checked for their performance. The radioactive contaminated air should also not be recirculated.	
6	Distribution	Traditional medicines are not radioactivity.	Personnel and the environment need to be protected against radiation contamination.	Packaging should ensure adequate shielding and containment and may consist of multiple layers of packaging based on a "Russian-dolls" concept.	PPB; EMA, IAEA

Appendix 8: Summary of Findings of Aga Khan University Hospital Radiopharmacy Practice Unit Site Visit

No.	Component	Y/N	Verifiable – Manual, Reference documents, SOP, QC data, file record etc.	Comments/ Planned Action
1	Is there a professional responsible for the radiopharmacy? Provide details.	Y	Radiopharmacist on site is Dr. Zahid Sroya.	
2	Is the radiopharmacy unit operated under the direction of a person with appropriate training as defined by local or national regulations?	Y	Training certificates present	The radiopharmacist has been extensively trained on radiopharmacy practices e.g. from GE Healthcare.
3	Do the staff have valid practice licence?	Y	Pharmacist and Nuclear Medicine Technologist	Active pharmacist practice licence confirmed using Pharmacy and Poisons Bord portal.
4	Are regularly updated CV's of staff maintained that include their qualifications?	Y		Updated every 2 years
5	Are there written staff training manuals for all grades of staff?	Y		
6	Have all staff working at operational level 2 received specific staff training on the following:			Trainings are graded with a pass mark of 60%
7	Calibration of equipment- please provide details and training records	Y	Calibration schedule maintained	
8	Working practices in the radiopharmacy - please provide details and training records	Y	Sampled certified for trainings on Good Laboratory Practices, Aseptic Technique	
9	Preparation of individual doses - please provide details and training records	Y		
10	Quality control and analytical techniques - please provide details and training records	Y	GE Healthcare training provided	

11	Dose release - please provide details and training details	Y	Rayes Training	
12	Record keeping - please provide details and training records	Y		
13	Cleaning - please provide details and training records	Y		
14	Is there a system for formal approvals of all documentations including radiopharmaceutical (RP) preparation, QC and formal release to patient?	Y		Approvals from Quality Assurance manager upon liaising with quality control team
15	What training is provided to staff performing final checks on all products prepared before release for patient use?		Quality control testing training performed	
16	Are there training records for all staff performing cell labelling, e.g. RBC, WBC?	Not Applicable		
17	Is there an annual performance review to check the competencies of radiopharmacy staff?	Y	Annual training performed	Additionally weekly CMEs are conducted

	Component	**Y/N**	**Verifiable – Manual, Reference documents, SOP, QC data, file record etc.**	**Comments/ Planned Action**
18	Is the facility licensed by PPB/KNRA?	Y	KNRA Licences A and B, PPB licence to manufacture, wholesale dealers licence	Licences were issued in January 2022
19	Does the unit have appropriately finished rooms (including adequate lighting, appropriate finishes to walls, floors, ceilings and ventilation) and a shielded dispensing station?	Y	Observed	
20	Is there a shielded dispensing station available?	Y		

21	For operational level 1b is there a shielded dispensing station and/or a fume hood available? [Is there a fume cupboard with suitable filters for volatile radioactive materials such as ^{131}I solutions?]	Y		
22	Is there a validated (annual check on air-flow, safety and challenge testing) fume hood with suitable filters for handling radioiodine solutions?	Y		
23	Are there records and logs kept for all equipment irrespective of whether maintenance and calibration are performed 'in-house' or by external contractors?	Y		
24	Is a list of all equipment maintained that includes the classification of and age of each equipment?	Y		List is maintained; however, the age of the equipment is not included.
25	Is there availability of support in case of a breakdown?	Y	Engineering team supported by GE Healthcare, BCP	
26	For operational level 2: Are there regular checks on validated Class II type B microbiological safety cabinets located in a dedicated room?	Y		Annual check performed
27	Are monometer readings of pressure differentials across HEPA filters recorded daily?	N		Currently monthly recordings performed.
28	Are there periodic records of air velocities determination for LAF cabinets or isolators?	Y		Annual checks
29	Is challenge testing of the HEPA filters in LAFs and isolators carried out annually?	Y		
30	For negative pressure isolators: Before preparation takes place, are gloves or gauntlets visually inspected and integrity tests carried out and recorded?	Y	Observed	

31	Is there a system and record of planned preventative maintenance for all equipment in the radiopharmacy including the refrigerator?	Y	Observed	
32	When clean rooms are used, are the over-pressures gauges monitored and recorded daily?	Y		Realtime monitoring in place

	Component	**Y/N**	**Verifiable – Manual, Reference documents, SOP, QC data, file record etc.**	**Comments/ Planned Action**
33	Are there suitable protocols and trained staff for the purchase of approved or Marketing Authorized radiopharmaceuticals?	Y		
34	Are all goods received checked and recorded against the order for correctness of delivery?	Y		
35	Are records kept for batch numbers and quantities received?	Y		
36	Are visual inspections and label checks carried out prior to acceptance?	Y		
37	Do all products, kits and generators have product approval, marketing authorisation, or bear a product licence number?	N		Not all products are licensed by the authorities, however all imports are approved by them using import permits
38	How many unlicensed or unapproved products are used each year and is there a record of them?	Not available		
39	For all unlicensed kits, radiopharmaceuticals or radio-chemicals are the prescribers or responsible medical doctors made aware of his/her responsibilities?	Y		
40	Do the suppliers or reagents and unapproved products provide a "Certificate of Analysis"?	Y	Sample observed	

	Component	Y/N	Verifiable – Manual, Reference documents, SOP, QC data, file record etc.	Comments/ Planned Action
41	Are there specific written radiopharmacy procedures for dispensing operations undertaken in the radiopharmacy?	Y	Various SOPs observed	
42	Under operational level 1a: Are there written procedures for the aseptic dispensing and labelling of unit doses of ready-to-use radiopharmaceuticals?	Not Applicable		Ready-to-use products are already labelled
43	Is there a system for labels which assesses quality, number produced and number applied to dispensed doses?	Y		
44	For operational level 1b: Do the written procedures contain clear safety and monitoring instruction for dispensing radioiodine solutions or capsules?	Y		
45	Under operational level 1b are there written procedures for calibration assay, preparation and dispensing of individual patient radionuclide therapy?	N		The unit doses are received as prepared from suppliers. Their activity is confirmed.
46	Can the audit and documentation for each RP batch be traced from the prescription to the actual administration of individual patient doses?	Y		

	Component	Y/N	Verifiable – Manual, Reference documents, SOP,	Comments/ Planned Action

			QC data, file record etc.	
47	Are there written and approved procedures for the use of generators and reconstitution of each radiopharmaceutical kit used?	Y		
48	Are SOPs independently reviewed and approved at specified intervals?	Y		SOPs are reviewed every 2 years
49	Is the preparation of 99mTc radiopharmaceuticals from kits and generators carried out in a LAF cabinet?	Y		
50	Are there set criteria before release for preparation for patients use? Is this undertaken by the same operator or a different individual?	Y		
51	Can each individual patient dose be traced to a specific generator and kit batch number?	N		
52	Under operational level 2b: Do the written procedures for any autologous preparation, e.g. red and white blood cells, include a clear instructions on safety, cleaning and decontamination?	Not applicable		
53	Are there written procedures for the preparation and dispensing of approved kit formulations of radio-labelled biological e.g. monoclonal antibodies, peptides?	Not applicable		

	Component	Y/N	Verifiable – Manual, Reference documents, SOP, QC data, file record etc.	Comments/ Planned Action
54	Are daily QC checks performed on radionuclide calibrators?	Y		
55	What quality checks are undertaken on a supplier before purchase?		Prequalification, licences, sample certificate of analysis, GMP certificate	
56	Are periodic quality checks on radiopharmaceuticals (RP) performed?	Y		Monthly
57	Is there a written procedure for dealing with product/s failing to meet the required standard?	Y	Document reference QAPR0003	
58	Is there a record of complaint/s and any associated follow-up and investigation?	Y		General Aga Khan University hospital procedure
59	Are there written procedures and records for regular contamination surveys of the radiopharmacy unit?	Y		
60	For operational level 2 are there records for the following:			
61	Purchase of radioactive products and ingredients	Y		
62	Generator elution, yield, [99Mo] molybdenum breakthrough and aluminium ion breakthrough	Y		
63	Product preparation, QC and release	Y		
64	Environmental and microbiological monitoring	Y		
65	Aseptic process, aseptic operator validation and trend analysis	Y		
66	Laboratory cleaning and maintenance	Y		
67	Equipment and plant calibration and maintenance	Y		

68	Radioactive contamination monitoring and radioactive waste disposal	Y		
69	Product defects and SOPs non- conformance, i.e. when a procedure is performed in a manner other than that described in the relevant SOP	Y		
70	Independent inspection and audit	Y		Annual internal audit performed
71	In line with the IAEA "Operational guidance on Hospital Radiopharmacy" document, are there records of routine microbiological monitoring of the preparation area in the radiopharmacy?	Y		Performed quarterly
72	Are there calibration and linearity checks of the dose calibrator response over the complete range of activities measured at least annually?	Y		
73	Is there set programme for checking the quality of radiopharmaceuticals (RP)?	Y	Yearly programme in place	
74	Considering patient safety, are certain simple checks performed on prepared radiopharmaceutical, e.g. mini-chromatography?	Y		Sterility test, chromatographic tests, endotoxin presence tests are performed daily
75	For operational level 2 is a [99Mo] Molybdenum breakthrough measurement performed on the first eluate from each [99mTc] Technetium generator and repeated when the generator is moved?	Y		
76	Is aluminium ion breakthrough checked on the first eluate from a [99mTc] Technetium generator?	Y		
77	Are changes in the source of any kits, diluents or vehicle used, needles, syringes, swabs and sterile containers used within radiopharmacy recorded?	No		Sources have never been changed
78	On first use of a new batch or first new delivery of RP kits is radiochemical purity performed?	Y		
79	Are rapid alternative methods employed for swift prospective QC for critical RP e.g. the determination of RCP for [99mTc] HMPAO)?	Not applicable		
80	Is there regular pH testing of RP carried out?	Y		

81	Prior to release for patients is each individual radioactivity dose checked?	Y		
82	Is there a record of the formal approval/release by an authorized person before a product is administered to a patient?	Y		Approval of products is authorized by Dr. Sroya
83	Are there written procedures for the recall of defective products?	Y		
84	Is there a record of complaints and any associated follow-up and investigation?	Y	Document reviewed: QAGEN005	
85	Is there a system of recorded self-inspection and reports evaluation?	Y	Document reviewed: QAGEN010	
86	Is there a system for external audit or peer review process?	Y		
	Component	Y/N	Verifiable – Manual, Reference documents, SOP, QC data, file record etc.	Comments/ Planned Action
87	Are there written procedures for the disposal of radioactive and non-active waste specific to the radiopharmacy?	Y	Document reviewed: QAGEN001	
88	Is there a periodic review/audit of arrival, use and disposal of all radioactive materials?	Y		Weekly trending performed
89	Are there written logs for each solid sources that indicate usage, transfer, disposal of solid sources?	Y		

Audit Summary

The audit summary below should be completed by all units in order to prioritise needs.
Critical priorities have the highest importance.

Major priorities are second to critical priorities however they should still be addressed in a timely manner
Minor priorities are areas which need addressing but do not require such urgent attention as the above two categories.

Critical priority

	Class	**Comment/action**	**Time frame**	**Date achieved**
	None			

Major priority

	Class	**Comment/action**	**Time frame**	**Date achieved**
27	Facilities and Equipment – Currently monometer readings of pressure differentials across HEPA filters are recorded monthly instead of daily.	To consider increasing frequency of pressure differential checks or justify monthly checks.		
51	Preparation protocols – currently individual patient doses cannot be traced to a specific generator and kit batch number which may impede a recall procedure.	To consider product traceability process		

Minor priority

	Class	**Comment/action**	**Time frame**	**Date achieved**
	None			

Appendix 9: Summary of Key Informant Interview Responses

QUESTION	RESPONSE	FREQUENCY/DETAILS
1. What is your current position?	Radiopharmacist	1
	Nuclear medicine technologist	1
	Clinical pharmacist	1
	Deputy chief radioprotection officer	1
	Deputy director inspection	1
2. What is your current place of work or institution?	Aga khan university hospital Nairobi	2
	Kenyatta national hospital	1
	Kenya nuclear regulatory authority	1
	Pharmacy and Poisons Board	1
2a. How long have you been at the current position?	6 months	1
	3 years	2
	15+ years	1
	4 years	1
3. Do you represent a regulatory body?	Yes	2
	No	3
4. Does your work involve radiopharmacy practices?	Yes	4
	No	1
4a. If so, kindly elaborate on functions related to radiopharmacy	Preparation and dispensing of radiopharmaceuticals, administration to patients	1
	Quality assurance, quality control, radiopharmacy unit management	1
	None (as radiopharmacy unit is inactive)	1

QUESTION	RESPONSE	FREQUENCY/DETAILS
	Oversight of importation of radioisotopes	1
	Guiding establishment of radiopharmaceutical manufacturing units and distribution of radiopharmaceuticals in the country	1
5. Have you encountered challenges in your job related to radiopharmacy?	Yes	4 – GREEN AREA OF SPECIALIZATION
	No	1
5a. If so, kindly elaborate on the challenges faced.	Personnel	2, few manpower and training opportunities in the industry
	Regulation	2, green area for regulators
	Distribution	1, Delays in customs clearance of imports affects effectiveness of the radionuclides due to their short half-life
	Equipment/Facilities	1, Downtime of machines
6. Are you aware of GXP guidelines in pharmaceutical industry such as GMP, GDP etc?	Yes	5
	No	0
7. Are you aware of the impact of Quality Assurance in the production, storage, distribution and dispensing of	Yes	5
	No	0

QUESTION	RESPONSE	FREQUENCY/DETAILS
pharmaceutical products?		
8. Are industry-specific GXP guidelines important for radiopharmacy in your opinion?	Yes	5
	No	0
8a. If so, which area(s) of radiopharmacy practice require further guidance material in your opinion?	Production	5
	All	4
	Training of personnel	3
	Procurement	2
	Dispensing	2
	Distribution	2
9. Which international guidelines do you refer to for current radiopharmacy related practices?	IAEA/WHO	4
	None	1
10. In your opinion, may some of the challenges in radiopharmacy practice described earlier by addressed by establishing local radiopharmacy GXP guidelines?	Yes	5
	No	0

Appendix 10: KNH-UoN ERC Written Consent Information Forms

KNH-UoN/ERC/FORM/IC04

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Website: http://www.erc.uonbi.ac.ke
Facebook: ttps://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC ttps://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Written Consent Information Form

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INVESTIGATOR DECLARATION

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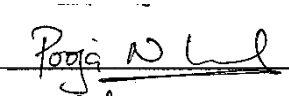
Signature: 

Date: 10/05/2022

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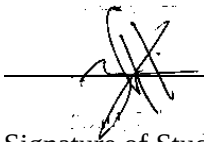

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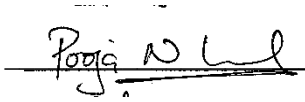

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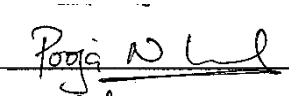
Signature: 

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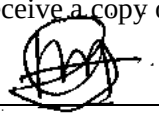

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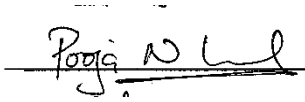

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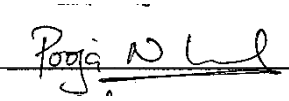
Signature: 

Date: 02/06/2022

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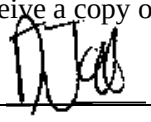

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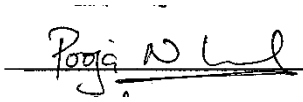

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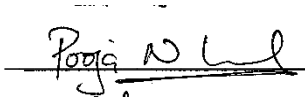

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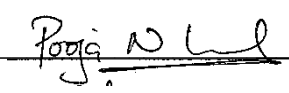
Signature: 

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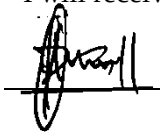

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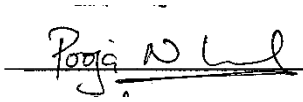

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