ASSESSMENT OF THE QUALITY AND SUITABILITY OF RADIOPHARMACEUTICAL COLD KITS AND $^{99}Mo/^{99m}Tc$ GENERATOR USED AT THE NUCLEAR MEDICINE UNIT, KORLE-BU TEACHING HOSPITAL, ACCRA

By

ASIMENG ADU SARKODIE

(10705506)

B. Tech (ATU, Accra) 2016

Thesis submitted to the School of Nuclear and Allied Sciences (SNAS), College of Basic and Applied Sciences (CBAS), University of Ghana, in Partial fulfilment of the requirement for the award of the degree:

Master of Philosophy (MPhil) in Nuclear and Radiochemistry

July 2020

THESIS DECLARATION

Student's Declaration

I, Asimeng Adu Sarkodie, hereby declare that the thesis resulted from a research I undertook, except where due references have been made to other people's work. This research work was jointly carried out at the Korle-Bu Teaching Hospital (KBTH), specifically the National Radiotherapy, Oncology and Nuclear Medicine Centre (NRONMC); and the University of Ghana's School of Nuclear and Allied Sciences (SNAS); with supervision from Dr. Dennis Kpakpo Adotey, Dr. Nii Boye Hammond and Dr. Godfred Odame. This research work has never been written before nor submitted by any other person for the award of a degree in any educational institution.

..... Date 23/03/2021

Asimeng Adu Sarkodie

(Student)

Declaration by Thesis Supervisors

The Supervisors hereby declare that the research, thesis preparation and presentation, were done according to the University of Ghana's Guidelines for Thesis Supervision.

..... Date 23/03/2021

Dr. Dennis Kpakpo Adotey

(Supervisor)

..... Date 23/03/2021

Dr. Nii Boye Hammond

(Supervisor)

..... Date 23/03/2021

Dr. Godfred Odame

(Supervisor)

ABSTRACT

The study investigated the quality and suitability of ^{99m}Tc radionuclide labelled cold kits used at the Nuclear Medicine Unit of Ghana's Premier Korle Bu Teaching Hospital (KBTH) for diagnosis of diseases. The quality evaluation involved: **(a)** appraisal of four (4) imported ^{99}Mo/^{99m}Tc generator packages to ensure compliance with United States Nuclear Regulatory Commission (USNRC) and International Atomic Energy Commission (IAEA) recommended acceptance criteria; **(b)** assessment of radionuclide purity (^{99}Mo breakthrough [MoBT] or ^{99}Mo contamination); **(c)** evaluation of the chemical purity (Al^{3+} content) of ^{99m}Tc eluate using colorimetric method; **(d)** suitability of fusing ^{99m}Tc eluate with human blood; (**e)** the radiochemical purity (RCP) of three (3) formulated radiopharmaceuticals: methylenediphosphonic acid (^{99m}Tc-MDP); diethylene triamine penta acetic acid (^{99m}Tc-DTPA); 2-methoxy isobutyl isonitrile (^{99m}Tc-MIBI); and, **(f)** the accuracy of the well type γ-counter and the Capintec dose calibrator, as well as the geometry dependence of the dose calibrator. The Wipe Test for radioactive material contamination showed no radiation leakage. The respective 1-meter radiation exposure measurements of 525, 415, 225 and 305 (µR/h) for the four generators used were all below the USNRC recommended value of 719.9×10^6 µR/h (200 mrem). Sodium pertechnetate ($Na^{99m}TcO_4$) eluate quality from the ^{99}Mo/^{99m}Tc generators were high as a result of low MoBT (0.0001-0.039 µCi ^{99}Mo/mCi ^{99m}Tc) for all elutions. The MoBT range is lower than the IAEA and US Pharmacopeia recommended MoBT of ≤ 0.15 µCi ^{99}Mo/mCi ^{99m}Tc. Low MoBT signifies high γ-camera image quality (resolution); and absence of excess radiation from formulated radiopharmaceutical (RP). Chemical purity (Al^{3+} breakthrough) of < 10 ppm were obtained for each of the 38 elutions from the four generators. This observation satisfies

the ≤ 10 ppm recommended Al^{3+} leakage from the generator into the $Na^{99m}TcO_4$ eluate; signifying eluate of good quality and safe for formulation of radiopharmaceuticals. Interestingly, ^{99m}Tc eluates from all four generators gave a measured respective pH of 7; which is within the European Pharmacopeia recommended pH of 4-8 for ^{99m}Tc eluates, and appropriate and safe for fusing into human blood (pH 7.35-7.45). The assessed RCP for ^{99m}Tc-MDP and ^{99m}Tc-DTPA ranged 94.2-99.8% and 96.8-99.8% respectively. The estimated RCP for ^{99m}Tc-MIBI range from 92.6 to 96.8%. The RCP ranges obtained revealed the absence of unacceptable radiation in the three formulated radiopharmaceuticals.. The estimated RCPs for ^{99m}Tc-MIBI and, ^{99m}Tc-MDP in addition to ^{99m}Tc-DTPA were comparable to respective recommended RCP ≥ 94% (^{99m}Tc-MIBI) plus ≥ 95% (^{99m} Tc-MDP and ^{99m} Tc-DTPA) set by the IAEA, and the United States and European Pharmacopeiae. Quality testing of the Well-type γ-counter and Capintec Dose Calibrator gave reliable results. The accuracy test for both instruments revealed that calculated percentage (%) errors were within the IAEA recommended ±5% error margin. For geometry, the Capintec dose calibrator response of the ^{99m}Tc radioactive source established that 10 mL, 5 mL and 2 mL syringe volumes had Volume Correction Factors (VCF's) within the IAEA recommended range of 0.95<VCF<1.05; and additionally, the plot of VCF for 15 consecutive days showed good regression coefficients [R^2 =0.8492 (10 mL syringe), R^2 = 0.962 (5 mL syringe) and R^2=1 (2 mL syringe)]. The ^{99m}Tc radiopharmaceuticals and cold kits were suitable for use in nuclear medicine diagnostics because all the quality assessments complied with globally accepted/recommended criteria.

DEDICATION OF THESIS

‘For the Great Things He has Done, Glory be to God.’ Through all the changing scenes of life, He has brought me this far. This research work is dedicated to my charmingly beautiful and lovely wife, Mrs Christine Mawusi Sarkodie, for the Love, Moral, Financial and Spiritual support. It is also dedicated to my children, Master Mawuli K. Adu-Sarkodie and Ms Nana Afia M. Adu-Sarkodie for their Love and Endurance during the period of this work. I further dedicate this work to my late mother, Madam Dora Afia Aboagye for bringing me to this earth and for nurturing me. This work is also dedicated to all loved ones and well-wishers for their immense support, love and encouragement.

ACKNOWLEDGEMENTS

First and foremost, I thank God for His Grace and Strength during the research and preparation of Thesis.

My profound indebtedness/appreciation to Dr. Dennis K. Adotey, Dr. Nii Boye Hammond and Dr. Godfred Odame and for the guidance and support rendered to me in seeing this research work to completion.

I would also like to acknowledge Dr. Joel Yarney [Director, National Radiotherapy, Oncology and Nuclear Medicine Centre (NRONMC) of Korle Bu Teaching Hospital (KBTH)], for granting me the opportunity to use the Centre (NRONMC) for this research work.

Very special thanks to Dr. Alfred Ankrah [Head, Nuclear Medicine Unit of NRONMC], and the staff of NRONMC for the co-operation throughout the research work.

My sincere appreciation goes to Dr. Francis Hasford for his immersed contribution throughout this research work.

My sincere thanks to all Lecturers and auxiliary staff of SNAS for the knowledge and support received from them throughout my stay at SNAS. Last but not the least, to all my mates and friends at SNAS.

CONTENTS

FIGURES

TABLES

SYMBOLS /ABBREVIATIONS

ATU	Accra Technical University
BDH	British Drug House
B. TECH.	Bachelor of Technology
DTPA	Diethylene triamine penta acetic acid
HR-Tc	Reduced hydrolyzed Technetium
IAEA	International Atomic Energy Agency
ITLC	Instant Thin-Layer Chromatograpy
KBTH	Korle-Bu Teaching Hospital
m	Metastable
MDP	Methylenediphosphonic acid
MIBI	2-methoxy isobutyl isonitrile
Mo	Molybdenum
NRONMC	National Radiotherapy, Oncology and Nuclear Medicine Centre
PET	Positron Emission Tomograpy
ppm	Parts per Million
SPECT	Single-Photon Emission Computed Tomograpy
Tc	Technetium

CHAPTER ONE

INTRODUCTION

1.1 Background of the Research Study

Radiopharmacy (Nuclear Pharmacy), a nuclear medicine branch relies on radiopharmaceuticals in the diagnostic and therapeutic of human diseases; and for research purposes. The World Health Organization (WHO) describes radiopharmaceuticals (radiotracer or tracer) as a distinctive medicinal formulations containing radioisotopes used in major clinical divisions/areas for diagnosis and/or therapy (Molavipordanjani & Hosseinimehr, 2018). Radioactive tracer is a biochemical compound with a radioisotope replacing one or more atoms. Minimal amounts are applied during diagnosis and/or therapy , for that reason, it has no pharmacologic effect *in-vivo*. Besides, its used for exploring the mechanism of biochemical reactions through tracing the path of the radioisotope from reactant to product (EAFP, 2014).

Also, radiopharmaceuticals are radioactive drugs when used for diagnostic/therapeutic purposes, frequently exhibit no physiological reaction from patients (Amin et al., 2012). These radiopharmaceuticals are integrated into the human body either by intravenous injection, oral ingestion (capsules, solutions), or inhalation (gases, Aerosol) (Maria, 2011).

The diseases include:

(i) Cancers, **osteomyelitis** (bone diseases, skeletal pain, bone infection or injury), **fractures** (through bone scan ^{99m}Tc-MDP). MDP is methylenediphosphonic acid.

(ii) Renal impairment (through renal scan ^{99m}Tc-DTPA, ^{99m}Tc-DMSA). Diethylene triamine penta acetic acid and dimercaptosuccinic acid are DTPA and DMSA respectively.

(iii) Heart and parathyroid diseases (through 2-methoxy isobutyl isonitrile (MIBI) myocardial perfusion and parathyroid imaging)**.**

(iv) Hepatobiliary (liver, gall bladder, collective duct) diseases (through HIDA [iminodiacetic acid] scan)**.**

Radiopharmaceuticals labelled with ^{99m}Tc are commonly used in diagnostic nuclear medical imaging services throughout the world. This is as a result of its favourable characteristics (half life [$t_{1/2=}$ 6.02 hours] and gamma energy [$E\gamma$= 140 keV]) for gamma camera diagnostic-imaging, low cost besides ready obtainability (Shah et al., 2009).

Generally, ^{99m}Tc radiopharmaceuticals are prepared using existing cold kits from accredited manufacturers. Cold kit consist of ligand (e.g. MDP, DTPA, DMSA, MIBI and HIDA) to be complexed with ^{99m}Tc, suitable amount of reducing agent (Sn^{2+}, ferric acid, ascorbic acid), pH adjustment buffer (citrate buffer) convenient for labeling conditions, ascorbic and gentisic acid (for stabilization) and inactive substance (Amin et al., 2012).The cold kits are prepared in lyophized form with a long shelf-life (months to years) by manufacturing companies; and released for sale after all prescribed quality control tests are completed. The cold kits (lyophilized) may be transported at room temperature; stored/refrigerated at 2-8 ^{o}C which ensures long shelf life in most cases. Therefore the composition, chemical purity, apyrogenecity, sterility and particle size of the cold kit are guaranteed by the manufacturer. The ^{99m}Tc used in these formulations is obtained from ^{99}Mo/^{99m}Tc generators sold by various manufacturer (Shah et al., 2009).

The ^{99}Mo/^{99m}Tc generator (Fig. 1.1) containing ^{99}Mo adsorbed on alumina is the most common source of ^{99m}Tc for labeling radiopharmaceuticals in nuclear medicine globally. The

radionuclide quality of eluates from these generators is essential for the subsequent quality imaging outcome and appropriate diagnosis by nuclear medicine physicians.

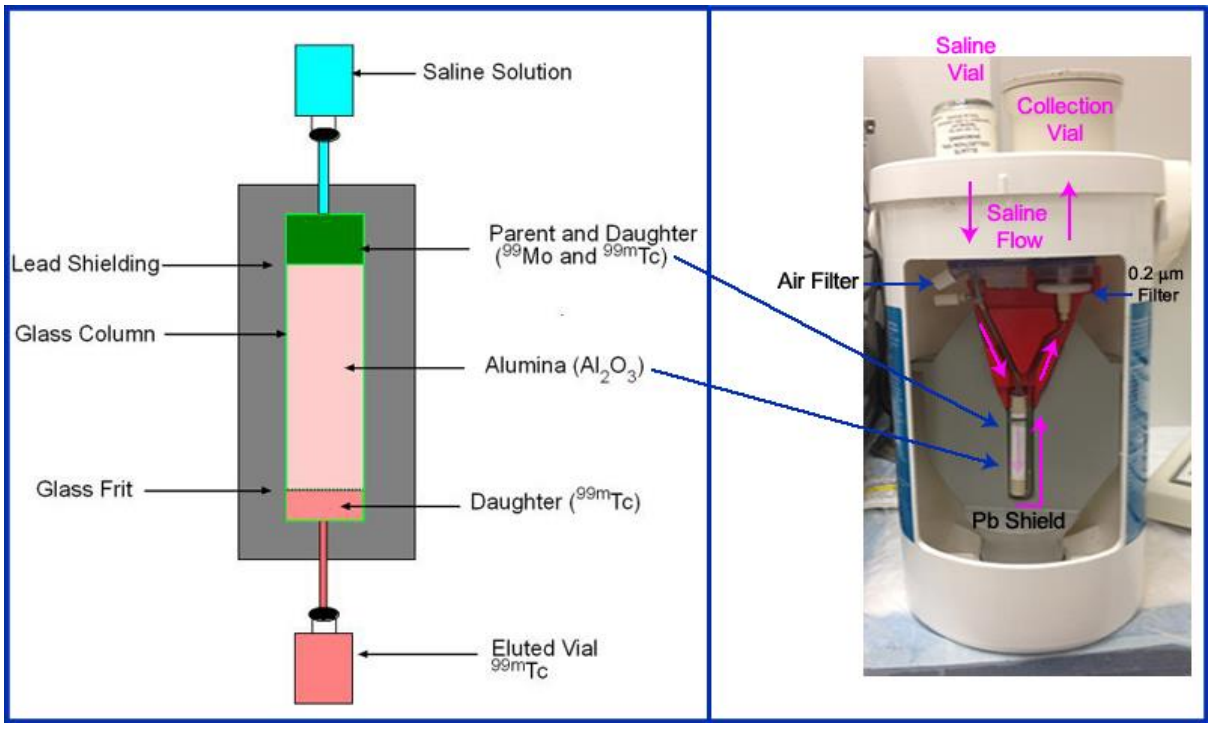

Fig. 1.1: ^{99}Mo/^{99m}Tc Generator Elution diagram

Radionuclide selection for radio-diagnostic/radio-therapeutic purposes need to cogitate the following: **(i)** For quality acquisition of scintigraphy, radionuclide need a particular gamma radiation energy characteristics; **(ii)** The radiation dose (internal) a patient receives after radiopharmaceutical administration requires a radionuclide of suitable radiation energy as well as half-life; such that the patient will receive as low as imaginable radiation throughout the procedure; **(iii)** The radionuclide must possess definite chemical features that are specific to the targeted organ only when administed; **(iv)** Biological half-life of radionuclide need to be

reasonably short; **(v)** The radionuclide must exhibit no physiological effect as well as be non-toxic to specific organs/groups of organs, to be metabolized in some cases.

Categorization of radionuclides can be achieve through its preparation procedures besides its characteristics:

a. Target irradiation must result in products, with higher/lower degree of chemical processing;

b. Radionuclides produced from generators; daughter-radionuclide with short half-life attained from radionuclide-parent with longer half-life by means of elution from solvent extraction/ chromatographic column;

c. Radioactive isotopes labelled with organic compounds, (mostly radiopharmaceutical compounds), are tested for radiochemical and radionuclide purity control after preparation and prior to usage. These checks are imperative, for all labelled compound (most especially organic radiopharmaceutical labelled compounds undergo a decay process over time).

The purity concept of radiopharmaceutical compounds entails three-stage consideration: (i) radionuclide purity, (ii) radiochemical purity, (iii) chemical purity (Neacsu et al., 2013). Radionuclide purity is an indispensable parameter for radiopharmaceuticals quality control (Maria, 2011). Contaminants from ^{99}Mo/^{99m}Tc radionuclide generator are; ^{60}Co, ^{86}Rb, ^{92}Nb, ^{103}Ru, ^{105}Rh , ^{110}Rg, ^{131}I, ^{134}Cs , ^{198}Au and ^{99}Mo (Shah et al., 2009).

The most common radionuclide impurity in the ^{99m}Tc eluate is ^{99}Mo. The ^{99}Mo ($t_{1/2}$ = 66.7h) emits gamma rays of 740 and 780 keV energies. These ^{99}Mo gamma emissions cause a significant unwanted radiation dose to the patients during investigations besides image degradations (leading to wrong diagnosis by nuclear medicine physicians) (Shah et al., 2009). The current international regulations pose a limit of 0.15kBq ^{99}Mo/mBq of ^{99m}Tc at the time

of administration of labelled radiopharmaceutical to the Patient (Memon et al., 2014). Another possible contaminant is aluminum ion (Al^{3+}) content in the ^{99m}Tc eluate due to ^{99}Mo adsorbed on alumina column in the generator (it may wash off into the eluate). This may happen as a result of transportation and handling; as well as the possibilities of damages within the alumina column of the generator. The ^{99m}Tc and cold kits used in radiopharmaceutical formulation at the Korle-Bu Teaching Hospital, Accra, is obtained from $^{99}Mo/^{99m}Tc$ generator imported from Eczacibasi Monrol, Turkey.

1.2 Statement of Research Problem

Technetium-99m based radiopharmaceuticals (^{99m}Tc RPs) are widely used in nuclear medicine, often in tandem with cold kits (Ullah et al., 2019). The authoritative requirement of quality control (QC) tests of the cold kits towards the evaluation of composition, purity, apyrogenecity, sterility and particle size are usually guaranteed by the producer (Haleem et al., 2015; Shah et al., 2009). Notwithstanding, the appraisal of the labeling process of the Technetium-99m with the cold kits, which may be affected by multiple factors, is generally the responsibility of the end-user (Ullah et al., 2019) . While various radiopharmaceuticals kits for diagnosis of diseases have been developed, reliable outcome for these kits depends upon the quality, purity, radiolabeling techniques and safety of the radiopharmaceuticals product (Maioli et al., 2017; Ullah et al., 2019). The preparation steps throughout the reconstitution procedure must be carefully done to produce a quality radiopharmaceutical. Radiopharmaceuticals for diagnostics require suitable quality parameters acceptable in nuclear medicine investigation. This ensures effective and non-delivery of needless radiation to the patient. Notwithstanding, for therapeutic radiopharmaceuticals it is compulsory to satisfy all ‘in-house’ preparations sanctioned for quality control (with deadly consequences to patients if done otherwise) [UNM, 2003]. In ideal situation, the quality of radiopharmaceutical kits must be check before injecting it to patient

but due to some challenges and financial constraint, it is often difficult to evaluate the quality on each radiopharmaceuticals imported. As a result, it is the post diagnostic image often used to ascertain the quality of radiopharmaceuticals through bio-distribution into organs and tissues. Therefore, there is scarce data/ information on imported radiopharmaceutical quality used at the Nuclear Medicine Unit, KBTH (an important medical care center in the country).

The literature data on quality of formulated radiopharmaceuticals in Ghana is also limited. Accordingly, since the radionuclide, Technetium-99m forms the basis for most in–house preparation of radiopharmaceuticals in the Nuclear Medicine Unit of KBTH, there is the need to establish its quality and suitability before injection, in order not to give needless radiation exposure to the patients as well as poor image outcome. This may result in inappropriate diagnosis by the nuclear medicine physician. The radionuclide Molybdenum-99/Technetium-99m generator used at Nuclear Medicine Unit of KBTH is imported from Turkey; during transportation and handling there may be damages within the alumina column (manufacturing material) of the generator and aluminum may wash off into the ^{99m}Tc eluate. There is therefore, the need to ensure that the radionuclide is safe for humans. As a result it is imperative to assess the radionuclide purity, chemical purity, the pH of the eluate in order to evaluate its suitability fusing with the human blood, before reconstituting it with the cold kits. Radiochemical purity assessment is also undertaken. This study is to appraise the quality (conformance to internationally accepted standard) of radionuclide Molybdenum-99/Technetium-99m generator and the cold kits imported by the nuclear medicine unit of KBTH from Turkey.

1.3 Objectives of Research

1.3.1 Overall Objective of Research

To investigate the radiopharmaceutical quality and suitability of Technetium-99m (^{99m}Tc) radionuclide labelled cold kits used at the Korle Bu Teaching Hospital (KBTH) for diagnosis of diseases.

1.3.2 Specific Objectives of Research

(a) To appraise the imported ^{99}Mo/^{99m}Tc generator package to ensure compliance with the United States Nuclear Regulatory Commission (USNRC) and IAEA recommended initially acceptance criteria (wipe test and 1-meter mandatory radiation exposure test);

(b) To assess the radionuclide purity (^{99}Mo breakthrough or ^{99}Mo contamination) of eluted ^{99m}Tc radionuclide using the attenuation method; and in addition, evaluate the chemical purity (Al^{3+} content) in ^{99m}Tc eluate by the colorimetric method;

(c) To evaluate the radiochemical purity of formulated radiopharmaceuticals using ITLC-SG (Instant Thin-layer Chromatography-Silica Gel) and Gamma Scintillation Spectrometry; and, estimate the suitability of fusing ^{99m}Tc eluate with human blood through measurement of pH; and,

(d) To assess the accuracy of the well-type γ-counter and the Capintec dose calibrator, and the geometry dependence of the dose calibrator.

1.4 Scope of Research Study

This study involved selected ^{99m}Tc-radiopharmaceuticals for nuclear medicine diagnostic imaging at KBTH. A total of Thirty-seven (37) ^{99m}Tc-radiopharmaceuticals will be employed in this study. This is made up of: (i) methylenediphosphonic acid (^{99m}Tc-MDP) [25]; (ii) diethylene triamine penta acetic acid; (^{99m}Tc-DTPA) **[9]**; (iii) 2-methoxy isobutyl isonitrile (^{99m}Tc-MIBI) **[3].** In addition, four (4) ^{99}Mo/^{99m}Tc generators would be assessed.

CHAPTER TWO

LITERATURE REVIEW

This chapter is a review of pertinent works related to nuclear medicine; types of nuclear medicine units; previous work done in Ghana, Africa and other parts of the world; production of ^{99m}Tc from ^{99}Mo; radiopharmaceuticals cold kits/ radionuclide generators; application of ^{99m}Tc radionuclide in diagnosis/treatment as well as quality of ^{99m}Tc radiopharmaceuticals.

2.1 The Role of Nuclear Medicine in Health Care

Nuclear Medicine is prominent/essential in contemporary healthcare. It relies on biomolecules tagged with radioisotopes; which identifies varied molecular targets in the human body or seek hallmarks of benign and malignant conditions. The distribution of trace amounts of radioactive-labelled molecule, radiotracer, can be traced non-invasively throughout the human body using a dedicated imaging system, specifically single photon emission computed tomography (SPECT) or positron emission tomography (PET). This trace approach delivers longitudinal sets of volumetric and quantitative images used for diagnosis of a number of diseases and assess response to disease-specific treatments (Hacker et al., 2014).

Imaging in nuclear medicine, comprises SPECT and PET; and provides essential quantitative and functional information about normal tissues or disease condition. This is contrary to conventional, anatomical imaging techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). For the period of treatment, tumor-targeting agents, conjugated with therapeutic radionuclides, may be used to transfer lethal radiation at tumor sites (Kramer-marek & Capala, 2012).

Nuclear medicine is a medical field that employs trace amounts of radioactive materials (radiopharmaceuticals) to diagnose, as well as direct the management and treat diseases. Most nuclear medicine procedures are based on molecular imaging techniques that uses radioactive substances. Molecular imaging procedures are highly effective, safe and painless diagnostic imaging; treatment tools present physicians with a detailed view of what's going on inside/*in - vivo* a person's cellularly.

Molecular imaging/nuclear medicine specialists carefully, effectively and painlessly determine if organs like the heart, lungs, brain, thyroid, liver and kidneys are working properly. Molecular imaging/nuclear medicine techniques commonly used diagnosis and treatment of cancer patients are SPECT/CT and PET/CT scanning.

Injection, swallowing or inhalation, of trace amounts of radioactive materials into the body, targets a specific body organ. The trace radiopharmaceutical is detected using special cameras attached to computers that provides pictures of the affected area of the body, as well as offer information on an organ's physiology or function. The presence of a disease is predicted based on biological or molecular changes, rather than variations in anatomy. Radiopharmaceuticals heads directly to the target organ; and used for treatment of hyperthyroidism, thyroid and lymphoma cancers, blood imbalances and pain relief for some bone cancer types (Paez et al., 2016).

2.1.1 Improvement in Patient Care

Molecular imaging and nuclear medicine offer techniques that are indispensable in several medical specialties (pediatrics, cardiology, neurology and oncology). Molecular imaging and nuclear medicine techniques are unique ways to collect medical information that would otherwise be unreachable, require surgery or expensive diagnostic tests. The commonly

performed biological imaging techniques are a fundamental part of patient care, early abnormalities identification before development of a disease (normally before medical problems are obvious with other diagnostic tests). Early detection allows a disease to be treated when there may be a more effective prognosis (PET PROS, 2009).

2.1.2 Diagnosis and Treatment

In year 2007, about 16 million patients were estimated to have been diagnosed and treated with nuclear medicine procedures in over seven thousand three hundred (7,300) hospitals and non-hospital sites in the United States of America (that is about 68,000 patients/day). In 2014, an estimated 11.7 million patients received nuclear medicine scans in the USA over fourteen thousand (14,000) SPECT and SPECT/CT scanner; representing a mean yearly decline of 9.6% in procedures per year [since year 2012 when 14.5 million patient studies were performed] (IMV, 2019). Almost all hospitals, in addition to several clinics and private medical facilities carry out nuclear medicine tests and scans. Nuclear medicine diagnose and monitor treatment of cancer, cardiac stress (heart function), bone scans (orthopeadic injuries) and lung scans (for blood clots).

Nuclear medicine imaging techniques aids physicians to visualize the structure and function of an organ, tissue, bone or other organ. In adults, nuclear medicine is utilized in the following areas:

i) Heart

(a) Visualize blood flow and function of the heart (myocardial perfusion scan);

(b) Identify coronary artery diseases as well as extent of coronary stenosis;

(c) Assessment of heart damage following a heart attack;

(d) Appraise treatment options (eg. whether to bypass heart surgery and angioplasty);

(e) Evaluation of revascularization (blood flow restoration) results;

(f) Detection of heart transplant rejection; and,

(g) Evaluation of heart function prior to and after chemotherapy (MUGA).

ii) Lungs

(a) Scanning of lungs for blood flow and respiratory problems;

(b) Assessment of differential lung function for lung reduction or transplant surgery;

(c) Detection of lung transplant rejection;

iii) Bones

(a) Bone evaluation for fractures, infection and arthritis;

(b) Metastatic bone disease assessment;

(c) Evaluation of excruciating prosthetic joints;

(d) Bone tumors evaluation and identification of sites for biopsy;

iv) Brain

(a) Brain abnormality investigation in patients with symptoms or disorders (memory loss, seizures, and suspected blood flow abnormality);

(b) Detection of onset of neurological disorders (eg. Alzheimer's disease);

(c) Support for surgical planning and identification of areas of the brain responsible for particular seizure;

(d) Evaluation of abnormalities in certain chemicals found in the brain and responsible controlling movement in patients with suspected Parkinson's disease, as well as related movement disorders; and,

(e) Evaluation of surgical or radiation planning, suspected brain tumor recurrence, or localization for biopsy.

v) Other

(a) Identification of inflammation or abnormal gallbladder function;

(b) Identification of bleeding into bowel;

(c) Assessment of post-operation complications in gallbladder surgery;

(d) Lymphedema assessment;

(e) Appraisal of origin of unknown fevers;

(f) Infection location;

(g) Measurement of thyroid function for detection of overactive or underactive thyroid;

(h) Support the diagnosis of blood cell disorders and hyperthyroidism;

(I) Hyperparathyroidism evaluation (overactive parathyroid gland);

(j) Evaluation of stomach emptying; and,

(k) Spinal fluid flow and potential spinal fluid leaks evaluation.

Nuclear medicine is applied for the diagnosis and treatment of the following diseases in adults and children:

vi) Cancer

(a) Cancer staging through assessing the presence or spread of cancer in various parts of the body;

(b) Localization of sentinel lymph nodes prior to surgery in patients (with breast cancer or skin and soft tissue tumors);

(c) Treatment plan;

(d) Response to therapy evaluation;

(e) Cancer recurrence detection; and,

(f) Detection of rare tumors of pancreas and adrenal glands.

vii) Renal

(a) Analysis of natural and transplant kidney blood flow and function;

(b) Urinary tract obstruction detection;

(c) Hypertension (high blood pressure) related to the kidney arteries evaluation;

(d) Evaluation for kidneys infection/scar; and,

(e) Detection of urinary reflux.

Additionally, Nuclear Medicine in children's health care has seen application in:

(a) Access disorders/abnormalities in the esophagus. (esophageal reflux or motility disorders)

(b) Investigate the openness of the tear ducts and the openness of the ventricular shunts in the brain; and,

(c) Evaluate congenital heart disease for shunts as well as pulmonary blood flow (Radiological Society, 2020).

Furthermore, Nuclear medicine is crucial in modern trends to cancer treatment through:

(a) Assessment of the extent or severity of a disease, metastases inclusive;

(b) Effective therapy selection based on patients unique biologic characteristics and the tumor molecular properties;

(c) Accurate assessment of the effectiveness of a treatment regimen;

(d) Quick treatment plan adoption in response to variation in biochemical and molecular characteristics of tumor;

(e) Disease progression assessment; and,

(f) Disease recurrence identification and management of ongoing care (Kramer-marek & Capala, 2012).

2.2 Previous Work Done in Ghana, Africa and Other Parts of the World

Significant number of radiopharmaceuticals studies have been reported for early detection of myocardial infarction. Notable is the preference for ^{201}Th for diagnosis and evaluation of coronary artery disease as well as determination of position and degree of ischemia along with infarction. Thallium-201 is not readily available, accordingly ^{99m}Tc based radiopharmaceuticals have been developed. The radiopharmaceuticals, ^{99m}Tc-pyrophosphate

and ^{99m}Tc-antimyocin antibodies have shown to accumulate irreversibly injured myocardial tissue (Babbar & Sharma, 2003).

^{99m}Tc-pyrophosphate, accumulates in ribs (due to its affinity for sequestered calcium) with consequent inferior image quality. There are limitations in the use of antimyocin antibody imaging and this includes high liver uptake besides slow blood clearance, preluding imaging for close to 24 hrs after injection in addition to its high cost. Methoxy-isobutyl-isonitrile-6 (MIBI), teboroxime7 plus tetrofosmin-8 have been declared as clinically beneficial in myocardial perfusion investigations (Babbar & Sharma, 2003).

According to Babbar and Sharma (2003), optimum labelling yield and stability are obtained with when 500 µg ($SnCl_2$) is used for complexation with 12 mg glucaric acid plus 50-500 MBq ^{99m}Tc-pertechnetate (pH 5).

Shah et al. (2009) observed that about five percent manufactured (indigenous) ^{99}Mo/^{99m}Tc generator had high Molybdenum Breakthrough (MoBT) levels. Concerning elutions, twenty-four percent elutions recorded high MoBT levels (1.43-1.63 kBq ^{99}Mo/MBq ^{99m}Tc). Whereas imported radionuclide-generators had Molybdenum Breakthrough within permissible levels. The ^{99m}Tc eluate showing higher levels of ^{99}Mo were purified before using it for routine radiolabelling. The purification process was observed that average 26% of initial ^{99m}Tc radioactivity was lost.

A wide variety of RPs has been used for evaluation of various pathological or physiological processes of body organs at Institute of Radiotherapy and Nuclear Medicine (IRNUM), Peshawar, Pakistan. The total number of cold kits used at the IRNUM during a 3-year period. Precisely, out of all 518 kits, only 14 (2.70%) preparations were found with RCP less than the acceptable limit in the cold kits. In terms of the number of individual kits, 180(34.75%) were

MDP, 144 (27.80%) DTPA, 36 (6.95%) renal DMSA, 8 (1.54%) MAG-3, 12 (2.32%) MIBI. The rest are: 36 (6.95%) Phytate, 7(1.35%) Octreotide, 6(1.16%) Nanocolloid, 12(2.32%) MAA, 36 (6.95%) HIDA/BrIDA, 13 (2.51%) Pentavalent DMSA (V) and 28 (5.40%) were Miscellaneous kits used during this period (Ullah et al., 2019)

Vincenti (2016) indicated that radionuclide mostly agreed with required standards, particularly the European Pharmacopeia. Radionuclide purity met standards because ^{99}Mo did not exceed 0.1% of Tc-99m total activity. Chemical purity test showed that none of the samples contained aluminium ion (Al^{3+}) and measured pH within accepted range (4-8). However, the results revealed sub-standard radiopharmaceuticals were frequently prepared, (radiochemical purity of most samples [~ 60.6%] were below the acceptable lower limit. During the data collection period, QC to assess radiochemical purity of MIBI and HDP was conducted on all reconstituted kits. A total of 33 samples was obtained, with 17 samples being MIBI radiopharmaceuticals and 16 samples being HDP radiopharmaceuticals. Sub-standard radiochemical purities constituted 60.6% while 39.4% were within acceptable levels for radiochemical purities. The results demonstrated more than half of the samples were below the requisite standards. Results also showed that majority (51.5%) of samples that were below standards were mostly MIBI radiopharmaceuticals. MIBI radiopharmaceuticals have a mandatory radiochemical purity of ≥ 94%. Not a single MIBI radiopharmaceuticals was >94%; indicating all MIBI sub-standard radiopharmaceuticals.

HDP radiopharmaceuticals have a recommended radiochemical purity of ≥90%. About 81.3% HDP radiopharmaceutical had radiochemical purity of >90%. For the sixteen (16) tested samples, three (3) constituting 18.7% had radiochemical purity below the recommended limit.

2.3 Production of ^{99m}Tc from ^{99}Mo

^{99}Mo a radioactive isotope undergoes β-decay with half-life of 66-hours (Fig. 2.1). Approximately 88% of the decays leads to the production of ^{99m}Tc (metastable isotope of Technetium) [Fig. 2.1], subsequently decaying to ^{99g}Tc with a half-life of about 6-hrs. The standard process for producing ^{99}Mo for medical use involves neutron fission of ^{235}U [^{235}U(n, f)^{99}Mo] with regards to multi-purpose for research reactors (Fig. 2.2). Approximately 6.1% of ^{235}U fissions produced ^{99}Mo. Neutron cross-section for the reaction is large (~584 barns for thermal neutrons); in comparison with other production routes (Fig. 2.2). Multi-purpose research reactors are well suited for ^{99}Mo production due to availability of space for irradiating multiple targets at high neutron fluence rates 10^{13}–10^{14} n·cm^{-2}·s $^{-1}$. ^{99}Mo can be produced through other schemes (Fig. 2.2).

(a) Fission of ^{235}U with neutrons produced in accelerators (deuteron and proton) using (D, n) and (p, n) heavy target reactions.

(b) Neutron activation of ^{98}Mo [^{98}Mo (n, γ) ^{99}Mo]. Production through this reaction is nuclear reactor-based due to the small (0.13barns) activation cross-section for neutrons (thermal). In comparision to Molybdenum-99 production through neutron fission, this route of producing Molybdenum-99 has low activity (specific).

(c) Photo-fission through ^{100}Mo(γ, n)^{99}Mo. Energetic photons used for the production scheme are through irradiation of heavy targets with linear accelerators-produced electron beams (IAEA, 2013).

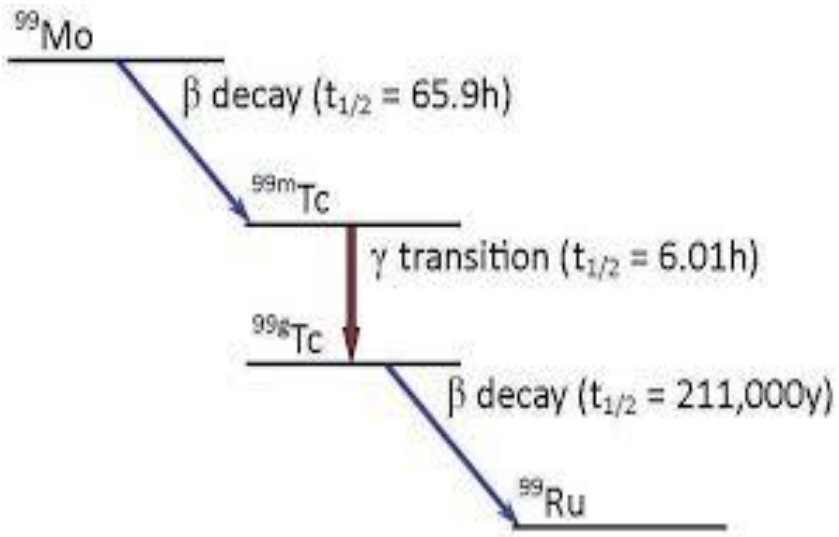

Fig. 2.1: Decay scheme for ^{99}Mo

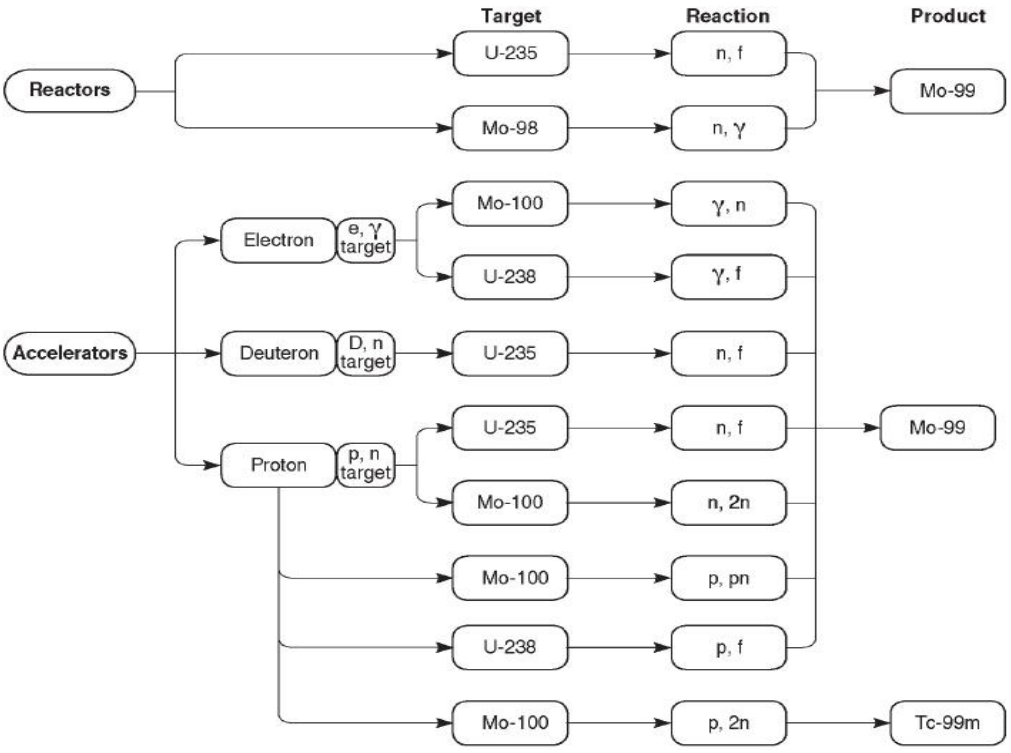

Fig. 2.2: Scheme for production of ^{99}Mo and ^{99m}Tc

There are two ways of ^{99}Mo production: (n, γ) and (n, fission) reactions. The cross-section of the ^{98}Mo(n, γ)^{99}Mo reaction for neutrons (thermal) is 0.13 barns, and the resonance energy integral cross section is 7.2 barns. With flux of 1.10^{13} neutrons/cm$^{2/}$s maximum achievable activity per quantity of ^{99}Mo (2.0 GBq.g^{-1}) of molybdenum target (assuming 98% enrichment in ^{98}Mo of the target). When the (n, fission) reaction is used the target material is ^{235}U. The fission macroscopic cross section for ^{235}U is 0.061 cm^2.g^{-1}. A specific activity of $4.4.10^6$ GBq.g$^{-.1}$ was obtained for ^{99}Mo with a thermal flux of 1.10^{13} neutron n.cm^{-2}.s^{-1}.

^{99m}Tc and ^{99}Mo produced by charged particle bombardment is also possible. The most suitable reactions for production of ^{99}Mo are ^{100}Mo(p,pn)^{99}Mo and ^{100}Mo(d,p2n)^{99}Mo while for production of ^{99m}Tc the ^{100}Mo(p,2n)^{99m}Tc and ^{100}Mo(d,3n)^{99m}Tc reactions are preferable (Takacs et al., 2003)**.** When bombarding ^{nat} Mo target with an energetic proton beam ^{99m}Tc is produced in direct reactions and as a result of the decay of ^{99}Mo nuclei. Two reactions contribute to the direct production of ^{99m}Tc [i.e., ^{100}Mo(p,2n)^{99m}Tc and ^{98}Mo(p, γ)^{99m}Tc]. Since it is known from systematics that the (p, γ) reaction has a significantly lower cross section (in the order of a few hundreds of μbarn only) than the (p,2n) reaction, the contribution of the (p, γ) process is very small and can be neglected in first approximation. The ^{99m}Tc radionuclide has only one gamma-line at 140.5 keV energy (Takacs et al., 2003).

2.3.1 Chemistry of ^{99m}Tc

Technetium was discovered by Perrier and Segrè (1937) in a molybdenum sample irradiated by deuterons. This newly discovered element received its name from the Greek word “technetos”, (meaning artificial). This is because technetium was the first previously unknown element to be made artificially. Seaborg and Segrè in 1939 observed that irradiation of ^{98}Mo with slow neutrons results in ^{99}Tc via the decay of (^{99m}Tc metastable isomer) . Twenty-one

isotopes of technetium were later discovered (^{90}Tc to ^{110}Tc); Tc-110 with $t_{1/2}$ = 0.86 sec (shortest half-life) and ^{97}Tc with $t_{1/2}$ = 2.6 x 10^6 y (longest half life). Technetium isotopes are radioactive. ^{99m}Tc has widespread application in diagnostic nuclear medicine. The metastable isomer decays with $t_{1/2}$ = 6.01 hours to ^{99}Tc. With half-life of 2.13 x 10^5 years, ^{99}Tc is basically stable. Technetium-99 has aided explanation of the chemistry of technetium with regards to its radiopharmaceutical compounds. ^{99m}Tc is 0.1427 MeV beyond ground state of ^{99}Tc. Gamma photons (γ1, γ2, and γ3), with respective energies of 0.0022, 0.1405, and 0.1427 MeV, are released during ^{99m}Tc decay; with γ2 the most abundant produced in all nuclear transitions (89.1 %). It is the main photon detected in nuclear medicine imaging studies/analysis.

Chemical forms of the earliest Tc compounds for clinical use were; ^{99m}Tc-$NaTcO_4$ (brain and thyroid imaging) and ^{99m}Tc-sulfur colloid (liver, spleen and bone marrow imaging). Varied compounds were developed for imaging of other organs. A key requirement for preparation of technetium-labeled compounds was varying the oxidation state of Tc. Achieved by using a reducing agent in radiolabeling procedures. Early Tc compounds were prepared extemporaneously through stepwise admixture of ligand, reducing agent, TcO_4^-, and adjuvants with requisite adjustment of pH or temperature. Labeling yields were mostly not quantitative with final purification to remove unbound pertechnetate required. The final product sterilized through membrane filtration or autoclaving. Sterile radiopharmaceutical kits were eventually developed simplifying the compounding procedure and yielding technetium compounds of high purity without the need to remove unreacted TcO_4^- . The methodology is still a standard practice till date (Professionals, 2012).

2.3.1.1 The Oxidation States of Tc

Technetium is positioned on the Periodic Table together with manganese and rhenium, with chemistry similar to rhenium. A transition metal (Group VII B), Tc has seven electrons more than krypton's noble gas configuration residing in the 4d and 5s subshells. Tc easily loses these 7 electrons to produce the +7 oxidation state, which exists in pertechnetate (TcO_4^-). With Pertechnetate the most stable state in aqueous solution, Tc compounds have been prepared with various oxidation states (ranging from -1 to +7). Radiochemical studies have proved that Tc is reduced to Tc(V) as $[TcOCl_4]^-$ in cold concentrated HCl; as well as to Tc(IV) as $(TcCl_6)^{2-}$ in HCl (hot). Under these conditions, hydrolysis to insoluble TcO_2 is prevented, but can occur in less concentrated solution than 2 M HCl unless a coordinating ligand is available. A significant number of Tc coordination complexes have been made by displacing halide ligands in the reduced chloro-complexes with coordinating ligands that confer chemical stability and favorable properties for diagnostic imaging (Professionals, 2012).

2.3.1.2 General Application of Technetium

^{99}Tc is an excellent superconductor at low temperatures. ^{99}Tc has anti-corrosive properties. At a concentration of 5 ppm, Tc will protect carbon steels from corrosion (at room temperature). Metastable Tc (^{99m}Tc) is used brain, bone, liver, spleen, kidney, and thyroid scanning; as well as blood flow studies; Widely used radiotracer for medical diagnosis (USEPA, 2002).

2.4 Radiopharmaceutical Cold kits/ Radionuclide Generators

2.4.1 Cold kits

Technetium-99m radiopharmaceuticals are formulated generally from kits prepared in certified manufacturing facility. Cold kit contains the ligand which ^{99m}Tc is complexed to appropriate quantity of reducing agent, a buffer solution for pH adjustment suitable labelling, stabilizing agents and excipients. Cold kits are prepared in freeze-dried form with a long shelf-life, (from several months to years). Cold kits can be transported at room temperature; notwithstanding, storage in a refrigerator (2-8 °C) is advantageous and ensuring a long shelf-life. Compounding of ^{99m}Tc- radiopharmaceuticals using kits is fairly easy, involving the addition of generator-eluted $^{99m}TcO_4^-$ at room temperature; but at times with warming. Chromatographic techniques: paper, thin layer (Instant) or HPL are recommended RP evaluation of ultimate product; prior to administration. Formulation of RP should be done according ISO 5 recommendation are (Amin et al., 2012). A description of the various cold kits are presented.

2.4.1.1 Diethylene triamine penta acetic acid (DTPA)

^{99m}Tc-DTPA is a hydrophilic radiopharmaceutical. About 10% of the ^{99m}Tc-DTPA is bound to plasma proteins; with complete glomerular excretion occurring through the kidneys. Over 90% of ^{99m}Tc-DTPA activity injected is washed out within 2 hrs. Additional applications of ^{99m}Tc-DTPA radiopharmaceutical include cerebrospinal fluid circulation investigation, blood flow studies/analysis (heart, extremities, and brain), transportation investigation in gastrointestinal tract using labeled foods besides drinks and inhalation studies/examination (Amin et al., 2012).

2.4.1.2 Methylenediphosphonic acid (MDP)

Most ^{99m}Tc-phosphonates with ligands such as MDP are characterized by the general formula H_2O_3P-X-PO_3H_2, for MDP X = -CH_2. Independent of the substituents, phosphonates show tendency to form oligomers, which can be prevented through addition of antioxidants like ascorbic acid before the product is freeze-dried. The chief field of MDP application is Bone Scintigraphy; where ^{99m}Tc-phosphonates are absorbed by normal bone and bone lesions by chemisorption, followed by exchange on the hydroxdyapatite, the inorganic matrix of the bone. Higher uptake is observed when regular blood flow is high owing to hydroxyapatite formation with an increased osteoplastic activity. The activity of technetium phosphonates may accumulate in bone lesions for 2–8 times with increased osteoblastic activity (rupture, tumor metastases) in relation with normal bone (Amin et al., 2012).

2.4.1.3 2-Methoxy isobutyl isonitrile (MIBI)

^{99m}Tc-MIBI, otherwise referred to as ^{99m}Tc-sestamibi, is a lipophilic complex mostly used clinically. To ensure the positive for the complex to acquire its positive charge, technetium atom with +1 oxidation state is reacted with the monodentate isonitrile ligand yielding [Tc(-C=NR)6]$^+$ with a hexacoordinated structure. Each carbon atom bound to technetium possesses non-paired electron (overlapping with the electron lone pair of adjacent nitrogen), So Tc-sestamibi molecules are paramagnetic. Due to the volatile nature of isonitriles, they are unstable. MIBI is available in stabilized form as copper tetrafluoroborate adduct, $[Cu(MIBI)_4]BF_4$, which must undergo decomposition during labelling. Process is achieved at an elevated temperature through immersion of vial in boiling water for about 10 minutes (Atkins, 1975). ^{99m}Tc-MIBI is taken up by cells of myocardium in passive diffusion and

appears in cytosol localized in mitochondria. The uptake is proportional to myocardial perfusion, with a rather slow washing.

At stress, the dose injected (3% of total) accumulates in the myocardium, with the exclusion/removal of non-bound portion through hepatobilliary. ^{99m}Tc-MIBI's uptake in addition in tumors as well as metastases, expanding its application clinically. Cationic Tc complexes are also obtained when technetium in +3 oxidation state or +5. tetrofosmin is currently available for clinical use. In the latter biscomplex, four trivalent phosphorus atoms and two oxo-oxygen atoms are coordinated to technetium (+5). Tetrofosmin can be labelled at ambient temperature, and its uptake in the myocardium and in tumors and metastases is similar to that of ^{99m}Tc-MIBI (passive diffusion, no redistribution) (Atkins, 1975).

2.5 Radionuclide Generators

A radionuclide generator (RNG) is a self-contained system housing an equilibrium mixture of a parent/daughter radionuclide pair and designed to provide the daughter radionuclide formed by the decay of the parent radionuclide (Dash & Chakravarty, 2019). The parent/daughter nuclear relationships offer the possibility of separating the daughter radionuclide at repeated time intervals. The inherent determinant for the success of RNGs resides with the selection of parent/daughter pairs and appropriate radiochemical separation strategies, which are based on a number of considerations (Dash & Chakravarty, 2019).

2.5.1 Types of Generators and Their Basic Uses

Short-lived radionuclides are often the agents of choice in nuclear medicine because they permit the use of ample radioactivity while keeping the absorbed dose to the patient within

acceptable limits. In general, however, the use of short-lived radionuclides entails many problems that stem from their fast decay. For example, the time available for processing, transportation, storage and dispensing is very limited and is often insufficient to assure quality in labeling and in radionuclidic purity. A generator solves some of the problems associated with the transportation of short-lived radionuclides. Radionuclide generators are devices that produce a useful short-lived medical radionuclide (known as "daughter") from the radioactive transformation of a non-medical long-lived radionuclide (called a "Parent"). By means of having a supply of 'Parent' on hand at a facility, the 'Daughter' is continually generated on site (John & Kathrine, 2014).

The generator allows ready separation of Daughter radionuclide from Parent. Immediately separation occurs, the generator starts producing the Daughter that can also be separated in adequate quantities later. For practical generator systems, the parent must have a relatively long half-life and the generator device ("Cow") must provide repeated separations of the daughter product. The separation process is called elution ("milking") .The example of outstanding importance is the $^{99}Mo/^{99m}Tc$ ("Moly") generator. ^{99}Mo ($t_{1/2=}$ 66 hrs) can be easily transported over long distances without remarkable loss of activity. The $^{99}Mo/^{99m}Tc$ generator has approximately Three-Parent half-lives, about 1-week. A ^{99m}Tc generator is a device used to extract metastable isotope, ^{99m}Tc from a decaying ^{99}Mo source (John & Kathrine, 2014).

^{99}Mo used in generators are produced by neutron irradiation of:

(i) $(^{98}Mo + {}^{1}n \rightarrow {}^{99}Mo + \gamma)$ (2.1)

(ii) fission of U-235 (Uranium-235) in a nuclear reactor. Column chromatography is applied in $^{99}Mo/^{99m}Tc$ generators available commercially. The alumina column (Al_2O_3) adsorbs ^{99}Mo. Pushing usual saline (NaCl) solution down the inactive ^{99}Mo soluble elute, ^{99m}Tc; leading to

^{99m}Tc-contained NaCl solution and significant amount of ^{99}Tc. ^{99}Tc is a carrier (i.e for all practical purposes, stable). Chemically, ^{99}Tc similarly to ^{99m}Tc. ^{99}Tc cannot be separated from ^{99m}Tc. (John & Kathrine, 2014).

The ceramic column at the heart of the generator absorbs ^{99}Mo onto its surface. An eluent passed through the column reacts with Tc available. Positive pressure system forces the eluent through the ceramic column. The ceramic column and collection vials are Pb shielded against γ-radiation. All components are maintained in a sterile condition because the collected solution are administered to patients undergoing diagnosis. As ^{99}Mo, decays, the concentration of its Daughter (^{99}Tc) increases in the ceramic column; reaches maximum after 24 hours (Fig. 2.3). Due to the chemical difference between the daughter and its parent, it is unbounded to the column, and while accumulating in the solvent. Anytime the column is flushed with NaCl (aq), it produces a solution containining $NaTcO_4$. After flushing, the concentration of ^{99m}Tc is mostly washed-out from the column however, it immediately starts increasing. The increase in daughter activity continues but begins slowing down ultimately (John & Kathrine, 2014).

Eventually the daughter activity is produced at a rate that equals the decay rate. The system attains equilibrium when the ratio of the rate of production of the daughter and rate of decay of the daughter is stabilized. Fig. 2.3 shows the ^{99}Mo/^{99m}Tc radionuclide generator with a much longer half-life of the parent compared with the daughter nuclide. Fifty percent (50%) of the equilibrium activity is attained within one daughter half-life; with 75% within two daughter half-lives. It takes close to four daughter half-lives to attain equilibrium. At equilibrium the parent and daughter radioactivities can only be disturbed through chemical separation (Fig. 2.4). Eluting the daughter from the generator ("milking") is done every 6 hours and at most, two times in the ^{99}Mo/^{99m}Tc generator. Because the half-life of ^{99}Mo is 66 hours the supply of

parent product diminishes to insufficient levels in approximately 1-week and replaced with a fresh system (John & Kathrine, 2014).

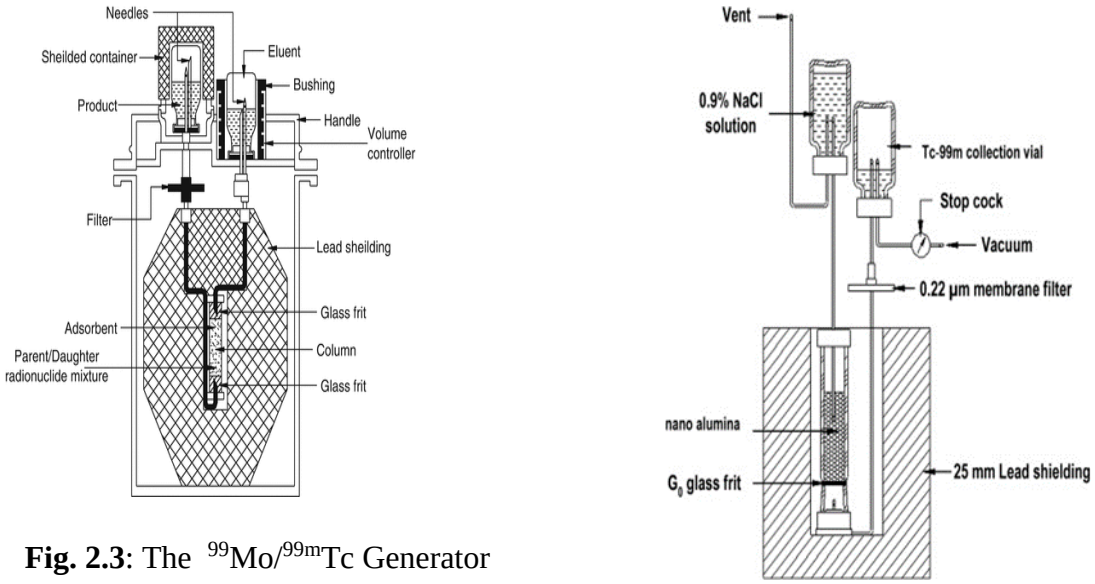

Fig. 2.3: The $^{99}Mo/^{99m}Tc$ Generator

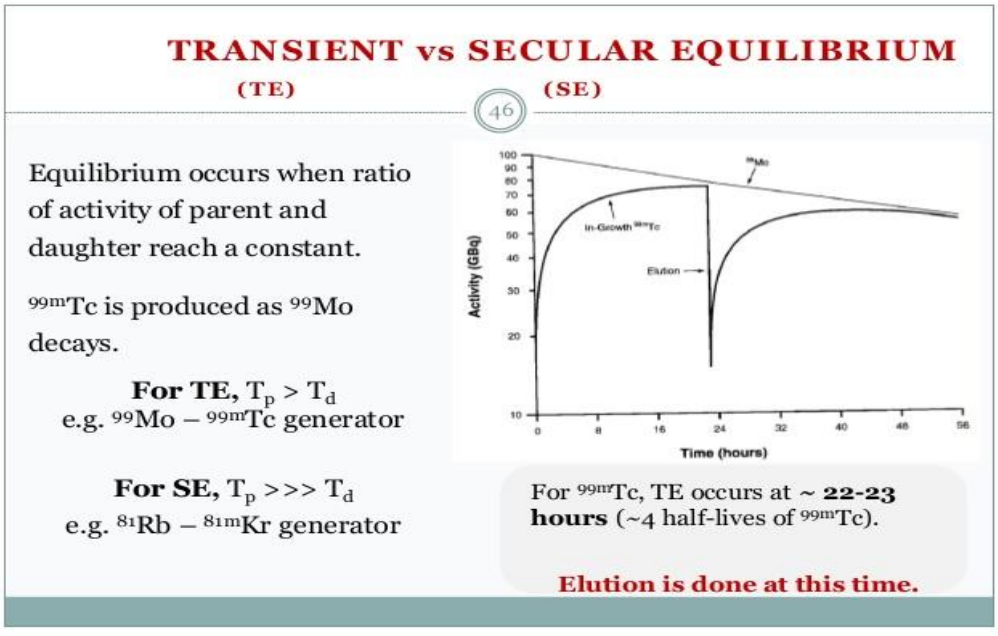

Fig. 2.4: Transient and Secular equilibrium of $^{99}Mo/^{99m}Tc$ generator

2.5.1.1 Generators for Diagnostics

(a) ^{99}Mo/^{99m}Tc Systems Generator

Generally the foundational radionuclide of diagnostic nuclear medicine is ^{99m}Tc to the numerous radiopharmaceuticals developed using the radiotracer. This position of preeminence in the radionuclide armamentarium is in large part due to the early and consistent availability of ^{99}Mo/^{99m}Tc generator. The generator was conceived in the late 1950s at Brookhaven National Laboratory (Phillips, 1996). Till 1966, the Brookhaven National Laboratory manufactured and distributed the generators, based on column chromatographic separation. Commercial generators have evolved over the years, initially based on ^{99}Mo produced through ^{98}Mo(n, γ) ^{99}Tc. Currently, ^{99}Mo produced via fission is used due to its relatively high specific activity making its application to small-column generator-systems suitable.

(b) ^{201}Pb /^{201}Tl Generator

^{201}TI is the most extensively used radionuclide in clinical diagnostics after ^{99m}Tc. It is applied in planar and SPECT perfusion imaging for non-invasive diagnosis of heart diseases. The radionuclide has been produced by direct irradiation of Hg-containing targets with deuterons/protons to yield a product with relatively poor radionuclidic purity, (unless highly enriched ^{201}Hg is applied). Alternatively, the approach to production of ^{201}TI with high specific activity and high radionuclidic purity is to produce ^{201}Pb; and allow it ($t_{1/2=}$ 9.4hrs) to decay to ^{201}TI ($t_{1/2}$ = 73.5 hrs), followed by chemical separation of Pb and TI. Interesting, this is not a classical generator in which a longer-lived parent decays to short-Iived daughter nuclide. The parent half-life is shorter than the daughter. Therefore, no generator system can be developed and shipped. Alternatively, the ^{201}Pb is produced regularly by commercial suppliers; the ^{201}TI separated and distributed for clinical use (Phillips, 1996).

(c) ^{81}Rb/^{81m}Kr

^{81m}Kr, a radionuclide of an inert gas has been used clinically in lung ventilation studies as well as pulmonary function scans. Due to its short half-life of 13s, and favorable dosimetry, the radionuclide is particularly effective for Pediatric Pulmonary Function Tests. It is also used in injectable form to remedy heart evaluation (Phillips, 1996).

(d) ^{82}Sr/^{82}Rb Generator

The sole generator with US FDA-approved application in PET scan. With its $t_{1/2}$ = 75 sec. and half-life and monovalent charge, ^{82}Rb is an exceptional tracer for myocardial perfusion PET studies; this resulted in the approval the generator received from the US FDA in 1990. Its additionally used to study blood-brain barrier leakage (Phillips, 1996) .

(e) ^{68}Ge/^{68}Ga Generator

Numerous systems for ^{68}Ge/^{68}Ga generator have been assessed. This generator is attractive because ^{68}Ge has a comparatively longer long half-life (270 days); With ^{68}Ga having a 68-min half-Iife; well suited for diverse prospective diagnostic techniques (Phillips, 1996).

2.5.1.2 Generators for Therapy

(a) ^{90}Sr/^{90}Y Generator

β-emitting radionuclides of suitable $t_{1/2}$ and chemistry have been recognized as prospective agents for in-vivo therapy of some diseases. The beta particles have high linear energy transfer over relatively short range in tissue. Accordingly, if the β-emitting nuclide can be delivered and localized in a diseased tissue like cancerous cells, cure may be induced by cell-kill. The technique has found effective application and accordingly referred to as radionuclide therapy (Phillips, 1996).

(b) $^{188}W/^{188}Re$ Generator

$^{188}W/^{188}Re$ generator is one of the promising system for therapeutic use. In addition ^{188}Re emits β-particles applied in RAIT as well as other therapeutic applications; ^{188}Re emits additionally imageable 155 keV γ-photon (16% abundance). The chemistry of rhenium is similar to that of technetium, therefore it is believed that radiopharmaceuticals developed for Technetium may have rhenium analogs (Phillips, 1996).

(c) $^{224}Ra/^{212}Bi$ Generator

α-emitting nuclides have been advocated as potential therapeutic agents due to their exceptional high LET for α-particles. ^{212}Bi from the $^{224}Ra/^{212}Bi$ generator has been used for treatment of cancer (Phillips, 1996).

2.5.2 Application of Tc-99m-Radiopharmaceuticals in Diagnosis of Diseases

The most commonly performed nuclear medicine procedure is bone scintigraphy. Introduction of ^{99m}Tc labeled diphosphonates in the1970s was responsible for the establishment of bone scanning as a key diagnostic technique. The ratio of ^{99m}Tc-methylene bone-to-soft tissue are ideal for bone imaging. Though ^{99m}Tc-MDP is used for evaluation of skeletal pathologic conditions, excellent clearance from the soft tissues enables detection of abnormal extra skeletal ^{99m}Tc-MDP accumulation (Peller et al., 1993).

2.5.3 Quality Control of ^{99m}Tc Radiopharmaceuticals

The European and US Pharmacopoeia recommends that injections should be sterile, apyrogenic, extraneous particles free, and suitable pH. Furthermore, radioactive injections should have appropriate radiochemical purity and radionuclide purity; and in addition possess correct radioactivity present at the time of injection. QC of Radiopharmaceuticals is crucial

and involves two aspects: **(a)** Radioactive parameters (RP) **(b)** Pharmaceutical parameters (PP). PP is designed to ensure that microbiological, pyrogenic or particulate contamination does not harm patients. Radioactive parameter is designed to facilitate the desired radiation exposure to patients through confirmation of assured radioactivity, radiochemical and radionuclide purity. Performance of QC procedures should always accompany radiopharmaceutical preparation; to ensure optimal radiopharmaceutical product administered to patients. These QC tests are performed by manufacturers, as well as by the compounding personnel (Molavipordanjani & Hosseinimehr, 2018). Radionuclide purity and radiochemical purity are in the determination of the quality of radiopharmaceuticals (Early and Sodee, 1985). Therefore, these parameters are basic in any QC programme (Vincenti, 2016).

2.5.3.1 Radionuclide Purity

The amount of radioactivity due to the radionuclide concerned in comparison with the measured activity of the prepared radiopharmaceutical, expressed as a percentage. Monographs in the European and US Pharmacopoeiae gives permitted limits to the radionuclide impurities in each radiopharmaceutical preparation. Presence of significant levels of other radionuclides may alter the biological distribution. Radionuclide impurities occur during the manufacturing process. Impurities may arise due to the presence of traces parent nuclide. Radionuclide purity may be determined by γ-spectrometry or by $t_{1/2}$ determination. The half-life technique is advantageous for extremely short-lived isotopes in the application of PET, (an example is Oxygen-15 with 2 min half-life).

The Attenuation method can be used in the determination of the amount of ^{99}Mo in a solution of ^{99m}Tc. These radionuclides emit γ-radiation different energies. Sample activity is determined in an ionization chamber on Tc setting. The measured activity would be due to ^{99m}Tc and ^{99}Mo

The sample is placed in Pb-canister (thickness; 6 mm) and measured on the ^{99}Mo setting. Radiation emitted by ^{99m}Tc (energy: 140 keV) is absorbed by Pb. Radiation emitted by ^{99}Mo (energy: 740 keV) is attenuated by a third. Measured activity is due to the presence of ^{99}Mo. Calculated of the proportion of ^{99}Mo in the sample is done. Allowable limit is 0.1%. The test should be performed during first elution of the ^{99}Mo/^{99m}Tc generator on a daily basis.

Due to differences in the half-lives of the radionuclides present in a preparation, radionuclide purity may vary with time. Radionuclide purity requirements must be satisfied throughout the validity period (EANM, 2019).

Radionuclide purity is the percentage radioactivity making up a specified radionuclide. It is based on the percentage of radionuclide present in desired radionuclide (contaminant-free) determine whether other radionuclides that are not of interest are present in the solution. Radionuclide other than those of interest are considered impure (Vincenti, 2016).

2.5.3.2 Chemical Purity

Chemical purity requires identification and quantification of discrete chemical constituents radiopharmaceutical in a formulation. Routine test for chemical purity is done on the ^{99m}Tc-$NaTcO_4$ solution eluted from a ^{99}Mo/^{99m}Tc generator. The $NaTcO_4$ solution may be contaminated with Al^{3+} originating from the generator's column alumina bed. The presence of Al^{3+} interferes with the preparation of certain ^{99m}Tc preparations (colloids) and labelling of red blood cells with ^{99m}Tc leading to their agglutination. The Al^{3+} in the eluate can be detected using chrome azurol S chromatographic cellulose paper. The chrome azurol paper has a complexing agent impregnated in it. A spot of the standard solution [Al^{3+} solution (10 µg/mL)] causes a colour change. The spot of elutate from generator is compared to the standard spot. If

the colour is more an intense colour in the eluate spot signifies the eluate contains greater than 10 µg/mL Al^{3+} ion. This implies lack of column stability, therefore eluate must be abandoned (EANM, 2019). The amount of desired chemical in a radiopharmaceutical formulation is required to as Chemical Purity. Identification of undesired chemicals in eluate is achieved by determination of Chemical Purity (Vincenti, 2016).

2.5.3.3 Eluate pH

The pH of the radiopharmaceutical formulation should be within the acceptable physiologically pH range (4- 8) or at optimum pH to ensure the stability of formulation. It is especially important to check The pH of PET radiopharmaceuticals needs constant check because the preparative procedure may lead to extreme pH conditions (EANM, 2019).

2.5.3.4 Radiochemical Purity

Radiochemical purity is the fraction of radionuclide found in the desired form; that is, the percentage of radionuclide bound to the ligand in the kit. It can also befined as the fraction of radionuclide that did not bind to the ligand (EANM, 2016; Vincenti, 2016).

Majority of the radioactive isotopes are attached to the ligand and not free or attached to another chemical entity to avoid different bio-distribution (EANM, 2019). During diagnostic scanning, bio-distribution of contaminating radioactive chemicals interfere with clinical diagnosis through obscuring the region of interest and making interpretation of the scan difficult. Abnormal biodistribution may also be as a result of patient medication. Determination of RCP helps clarify abnormal scan. In therapeutic radiopharmaceuticals, a low RCP could mean unacceptable radiation to healthy tissues and organs (EANM, 2019).

In most radiopharmaceuticals, minimum limit of RCP is 95%, (at least 95% radioactive isotope must be attached to ligand). RCP determinations are carried out by variety of chromatographic techniques:

2.5.3.4.1 Paper (PC) and Thin Layer (TLC) Chromatography

In PC and TLC, a drop of the radiopharmaceutical is placed on the bottom of a strip paper or silica gel coated sheets. The strip is then placed into a tank containing small amount of organic solvent. Components of the radiopharmaceutical formulation are separated based to the solubility of the solvent and adsorption to supporting medium. Radioactivity detection in the strip is carried out in various ways:

i) The simplest method is to cut the strip and count the activity in the sections using the Well-type Scintillation Counter. The percentage activity in each section is then determined. If a strip is cut in two sections 'A' and 'B,' the percentage activity in 'A' (EANM, 2019):

$$\%Activity = \frac{A}{A+B} \times 100 \, . \qquad (2.2)$$

The methods do not have lots of limitations. Radionuclide calibrators are not accurate for samples with low activity because of the low level detectability and accuracy of calibrator at lower range setting. Well-type scintillation counters should not be used for samples with high activity, because they can exceed the count rate capabilities due to detection system's resolving time.

ii) Imaging of strip under gamma camera. The region of interest is drawn around the radioactivity areas and the percentage counts in each region determined. The method has the advantage of imaging the entire chromatography strip for visible artefact, nonetheless, it is not

practical for medical facilities as the gamma camera may be needed for other patient imaging procedures.

iii) Use of radiochromatogram scanner for strip imaging. A radiochromatogram scanner uses a NaI for detection of radioactive emission. This equipment is not suitable for detecting emissions from isotopes like ^{51}Cr and ^{125}I as a result of statistics associated with low activities detection.

iv) Use of storage phosphor imaging. A phosphor screen accumulates latent image of the radioactivity distribution on the strip. Laser scanner screen enables the radioactivity location and intensity to be analyzed and stored. Results are shown as in image of the strip. Regions of interest can be drawn and integration carried out to determine activity in each region. Variation of strip exposure time to the phosphor screen, makes it possible to analyse radiopharmaceuticals containing different isotopes, or activities (EANM, 2019).

2.5.3.4.2 Solid Phase Extraction (SPE)

Variety of bonded silica sorbents are available in packed disposable cartridges or columns. Sorbents selectively retain specific chemical compounds from column-loaded sample. Components in loaded sample are selectively eluted through carefully selected solvents. Eluates collected have sufficient activity are counted in radionuclide calibrator (EANM, 2019).

2.5.3.4.3 High Performance Liquid Chromatography (HPLC)

Radiochemical purity (RCP) using thin layer chromatographic (TLC) methods may not be good for identification of product components. The high sensitivity and resolving power of HPLC makes it the method of choice. HPLC separation operates on the hydrophilic/lipophilic

properties of the components of a sample, γ-emitters are detected with a well-type scintillation counter connected to a rate meter. Detectors such as UV or refractive index can be connected in series to allow simultaneous compounds identification (EANM, 2019).

2.5.3.4.4 Electrophoresis

Electrophoresis separates components according to charge and size of molecules. Frequently used electrophoresic method in radiopharmacy is in RCP determination of radiolabelled albumin in which the sample is run on a barbitone buffer filter paper support (EANM, 2019).

2.5.3.5 Biological Control

Sterility Testing is performed to ascertain that radiopharmaceuticals are free of viable microorganisms (fungi and bacteria). Tests must be performed aseptically to ensure non-interference from external contaminations during test sample experimentation. Preferably, a sterile laminar-flow hood and trained professional are required. States Pharmacopeia (USP 32) states that "sterility tests are performed by incubation of radiopharmaceutical in two ways in order to detect bacterial and fungal contaminations" (Molavipordanjani & Hosseinimehr, 2018):

a) Bacterial contaminations: radiopharmaceutical sample is incubated for 14 days in fluid thioglycollate medium (30–35 ^{o}C).

b) Fungal contaminations: radiopharmaceutical sample is be incubated for 14 days in soybean casein digest medium (20–25 ^{o}C). Test sample volume must be at least same as that for human dosage. Observed bacterial growth in either test, signifies non-sterility of radiopharmaceutical.

Prominent drawback for radiopharmaceutical sterility test is that assessment takes longer than the half-lives of common short-lived radionuclides like ^{99m}Tc. The product of interest is released for human use provided manufacturer has established its sterility and apyrogenicity (Molavipordanjani & Hosseinimehr, 2018).

2.5.3.6 Pyrogenicity tests

Radiopharmaceuticals for human administration should be pyrogen-free as a requirement. Pyrogens are polysaccharides or proteins produced through the metabolism of microorganisms. Though the bold examples of pyrogens are bacterial endotoxins (BE), various chemicals may add pyrogens to radiopharmaceutical solutions. Sterility of a solution does not guarantee apyrogenicity; and sterilization process does not destroy pyrogens in radiopharmaceuticals. No specific method is recommended for making a sample apyrogenic, accordingly, appropriate precautions are required from onset. Pyrogens originates from bacteria metabolism; hence, to prevent pyrogenic contamination, sterile glassware, solutions, equipment under aseptic conditions are used (Molavipordanjani & Hosseinimehr, 2018).

2.6 Detection Devices

Two principal diagnosis imaging devices used in Nuclear Medicine are Gamma Camera and Positron Camera. Generally, both cameras uses scintillation counters (primary radiation detector) due to the fact that in high scintillation crystals, X-rays and γ-rays have a good density stopping power (Bailey et al., 2014).

2.6.1 The Gamma Camera

The gamma camera was invented by an America Engineer and Physicist Hal Anger in the 1950s. The principle of operation is based on the application of a single large area NaI(Tl) phosphor connected to Photomultiplier tubes. Gamma camera (SPECT) is applied in the detection of emitted γ-rays by radiopharmaceuticals within the human (Fig. 2.3). Pb-Collimator in front of the scintillation counter selects the device entering γ-rays path; additionally, enables the tracer image to biodistribution.

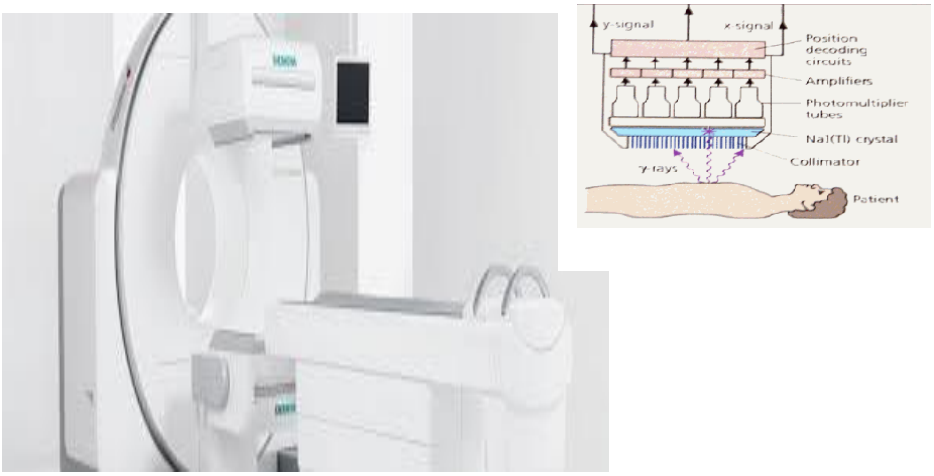

Fig. 2.5 Schematic diagram of a γ-camera being used for γ-rays detection emitted by a radiotracer distributed in a patient

Photomultiplier tubes (PMT) produce signals that are directly proportional to the light generated in crystal. Positional information is obtained by comparing the size of signals from different PMTs, whilst energy information is related to the sum of PMT signals. Accuracy of both energy and positional information depends on stability of signal production and electronics applied. The amplitude of analogue signals from PMTs depends on PMT and electronic stability, and noise generated in signal amplification. The noise is kept low by amplification close to each PMT. Amplified/ summed signal from photomultiplier can be converted to digital pulse train using analogue-to- digital converter (ADC), [number of pulses

is directly proportional to the pulse height or signal charge]. This signal is used to select events in which most of the γ-ray energy is detected using a camera (useful tool to reduce effect on image production by γ rays scattered in the body before detection). It is important at this stage to include signals from PMTs that provides information above intrinsic noise levels of the electronics; this is achieved using signal thresholding, like a comparator. The individual PMT pulses are digitized close to PMTs with these signals are analysed using capacitor or resistor circuits to determine positional information sent to computer system for image formation. The centroid energy/pulse height information provides a position closely related to the point at which γ-ray enters the crystal. Current trends for calculating this position is based on digital outputs from PMTs that uses nearest neighbour calculations (on stored reference map of positional information). The methods provide accurate estimates of incident radiation entry point. Therefore, accuracy of image production process is determined by initial signal sizes and subsequent amplification as well as digitization (Bailey et al., 2014).

2.6.1.2 β^+ Camera

β^+ camera is used to simultaneously detect two annihilation photons produced by β^+ emitting tracers distributed in the human body. Detectors are made of housands of small scintillating crystals coupled to about a thousand PMTs. Meaning there are many amplifiers which may have to function at higher count rates than those used in gamma camera. Detection of these two γ-rays requires the addition of coincidence circuits used to select pulses from single annihilation. The format of a positron camera Fig. 2.4 based on multiple scintillating counters in which signals can be read to form a 3-D image. Difference in electronics between positron camera and gamma camera is the large number of PMT channels involved and the count rates achieved in both cases. Additionally, the pulses from a β^+ camera should be carefully shaped to allow for accurate timing information to be gathered from coincidence circuits to ensure that

both annihilation photons from a single event are detected. The time jitter in pulses will affect this process, allowing the inclusion of random photons from multiple nucleic decays in data acquisition. Also recent introduction of so-called ‘time of flight’ cameras requires accurate (sub-nanosecond) timing to be made between two annihilation photons.

Fig. 2.6 Positron Camera

2.7 Radiation Counting Devices

2.7.1 Dose Calibrator

Applied in assaying activities present in radiopharmaceutical syringes and vials; and brachytherapy source. It consists of pressurized gas filled ionization chamber with a sealed sensitive volume configured in a ‘well’ geometry. The intrinsic sensitivity of the dose calibrator, is relatively low. The well-type configuration of its sensitive volume provides high geometry efficiency, making the general sensitivity entirely adequate for relatively high radiopharmaceutical activities (10–100 MBq) typically encountered in clinical nuclear medicine. The dose calibrators are equipped with isotope-specific push-buttons and potentiometer (with isotope-specific settings) to adjust differences in energy-dependent

response; and thereby yield accurate read-outs activity (kBq or MBq) for radioisotopes (Bailey et al., 2014).

Fig. 2.7 Radionuclide Dose Calibrator

2.7.2 Well-type Gamma Counter

Well counters are gamma radioactvie counting devices used for high sensitivity counting of radioactive specimens like blood or urine or 'wipes' from surveys of removable contamination. Such counting results are expressed in terms of activity (MBq) using isotope specific calibration factor (cpm/MBq) for measured isotope. Devices generally comprises of a cylindrical scintillation crystal [commonly, NaI(TI)] with a circular bore (well) for sample drilled path-way into the crystal and backed by PMT and associated electronics. Alternative design for well counters is the 'through-hole' detection system; in which the hole is drilled through the entire crystal. Through-hole design facilitates sample exchange; because samples are centred lengthwise in the detector and yields a constant response for different sample volumes and slightly higher sensitivity than well counters. Both well and through-hole designs

have crystals surrounded by thick Pb shielding to minimize background as a result of ambient radiation (Bailey et al., 2014).

Well-type counters are used for high-sensitivity counting of radioactive specimens such as blood, urine or "wipes" from Wipe Test. Counting results are expressed in activity (μCi), using appropriate isotope-specific calibration factor (μCi/cpm). The devices comprise of a cylindrical scintillation crystal (mostly TI-doped NaI) with circular bore (Well) for sample and backed by a photomultiplier tube (PMT) with associated electronics. Latest scintillation well-counters are equipped with multichannel analyzer (MCA) for energy (isotope-selective counting), and automatic sample changer for counting of multiple samples. Due to the high intrinsic and geometric efficiencies (resulting from the use of thick crystal and well-type counting geometry respectively). The well-counters are extremely sensitive and reliably used for counting activities up to about 37 kBq. Dead-time counting losses become prohibitive and measured counts inaccurate at high activities (Bailey et al., 2014).

Fig.2.8 well-type Gamma Counter

CHAPTER THREE

MATERIALS AND METHODS

This chapter outlines in details the materials and experimental methods employed in the study. The experimental work was largely undertaken at Korle Bu Teaching Hospital Centre for Radiotherapy, Oncology and Nuclear Medicine, Accra.

3.1 The National Centre for Radiotherapy, Oncology and Nuclear Medicine (NCRONM), KBTH

The Centre has been in existence for twenty-one (21) years; and recognized by Ghana's Health Ministry as a 'Centre of Excellence'. The establishment was facilitated by a collaboration between the Government of Ghana (through Ministry of Health) and Ghana Atomic Energy Commission) and the International Atomic Energy Agency (IAEA). Officially commissioned on 26th May 1998. Reasons that necessitated the establishment of NCRONM were:

(a) To meet the needs of Ghanaian Cancer patients who could not afford treatment outside Ghana; and,

(b) The realization that 40% of all cancer cures was as a result of radiation treatment, whilst 60% of cancer patients require treatment with radiation at certain stages in the course of treatment (cure or palliation).

NCRONM manages tumors (benign and solid) through ionizing radiation application, use of chemotherapy and offer supportive care. Besides the main pre-occupation NCRONM is also mandated to:

(i) Create increased awareness and understanding (management) of cancer;

(ii) Safely and efficiently support/ensure affordable treatment of cancer with the ultimate aim of enhancing the quality of patients life; and,

(iii) To extend survival and lessen suffering.

There are currently two (2) public centers and one private centers: Kumas-based Komfo Anokye Teaching Hospital, Accra-based Korle-Bu Teaching Hospital and Sweden-Ghana Medical Centre, also base in Accra. The building housing NCRONM is shown in Fig. 3.1.

Fig. 3.1 The NCRONM building at KBTH

3.1.1 The Nuclear Medicine Unit of NCRONM

The Unit responsible for Nuclear Medicine at the centre is engaged in:

(a) the application of Iodine-131 (^{131}I) for the treatment of hyperthyroidism and thyroid cancers; and

(b) the formulation of ^{99m}Tc radiopharmaceuticals for investigation of human diseases (through the use of ^{99}Mo/^{99m}Tc generator eluate which forms the main radionuclide for all 'in-house' radiopharmaceuticals preparations). The generator is imported from Turkey.

3.2 Importation of ^{99}Mo/^{99m}Tc Generator/Cold Kits

The Nuclear Medicine Unit imports the Molybdenum-99/Technetium-99m generator (15GBq) and cold kits from Turkey. The importation usually takes one-week to arrive in Ghana. Before the importation, authorization is sought from the Ghana Nuclear Regulatory Authority to aid the process. On arrival at the Kotoka International Airport in Accra, the importation is cleared by the Ghana Supply Company Limited on behalf of KBTH; and transported to the Nuclear Medicine Unit of KBTH.

Supplied in a variety of ^{99}Mo activities, generators are as 30.7GBq to 614.2 GBq (that is 0.83-16 Ci) at calibration; generators from Nordion are as 6.5 to 70 GBq (0.17-1.89 Ci); and those from Monrol Turkey as 5- 50 GBq (that is 0.135-1.35 Ci). Variety of supplies and accessories employed during elution process are also imported.

3.3 Receipt of ^{99}Mo/^{99m}Tc Generator/Cold Kits at Nuclear Medicine Unit of KBTH

On receipt of the generator/cold kits at the Nuclear Medicine Unit of KBTH, they were immediately subjected to: **(i)** wipe test for radioactive material contamination, **(ii)** 1-metre radiation exposure test. This is to ascertain compliance with globally accepted criteria for imported ^{99}Mo/^{99m}Tc generator packages. When these two conditions are satisfied, the package is then removed from its packaging case.

Subsequently, the 'activity' purchased and other relevant initial information are checked and data obtained recorded appropriately. Afterward, the generator is placed in a laminar flow hood to minimize personnel exposure to emitted radiation; followed by generation of the ^{99m}Tc eluate from the generator.

3.3.1 Assessment of Compliance with Globally Accepted Criteria for Imported $^{99}Mo/^{99m}Tc$ Generator Packages

3.3.1.1 Wipe Test for Radioactive Material Contamination

The wipe test conducted upon receipt of the imported radioative material package is to ensure that there was no radiation leakages or contamination emanating from the imported package. This confirms optimum protection of nuclear medicine personnel, patients undergoing radionuclide scintigraphy, and the public from possible radiation within the building housing the package (UT Health, 2008).

Materials Used

The following materials were used for the Wipe Test for radioactive material contamination; Ethanolic cotton wool (Swab), Test tube, Forceps and Well-type γ-counter.

Radioactive material package was streaked in an 'S-like' motion with ethanolic cotton wool mops/swabs/wipes (the cotton wool swabs prepared by immersion of cotton wool into ethanol) while rotating the ethanolic cotton wool wipes in different surface of the package with the aid of a pair of forceps.

The resultant ethanolic cotton wool swabs transferred into γ-ray counting vials, covered with a lid, and the vials inserted into Capintec dose calibrator for radioactivity measurement.

3.3.1.2 1-Meter External Radiation Exposure

The mandatory 1-meter external radiation exposure test conducted with a contamination survey meter is one of the recommended test on receipt of the package containing the radioactive material. The test is a measure of the radiation exposure level to personnel at a 1-meter distance from the package. External exposure is from radioactive materials existing on the ground,

suspended in the air, or attached to clothes or the surface of the body. The exposure occurs when the radiation from these sources interacts with the human body; and dose occurs when the radiation leaves some of the energy in the body. The amount of external radiation exposure a body receives is related to the distance from the source, the energy of the emitted radiation, the total amount of radioactive material present or the machine setting, and the time of exposure (Radiation Answers, 2020).

Material Used and Assessment Procedure

Contamination survey meter was used to measure the 1 m external radiation exposure.

The detailed procedure for the assessment of the external radiation exposure test is described:

(i) The radioactive package was placed on a flat surface;

(ii) A contamination survey meter was used to measure one-meter external radiation exposure from the package; and the measurement readings were recorded.

3.4 Generation of ^{99m}Tc Eluate from the ^{99}Mo/^{99m}Tc Generator; and ^{99m}Tc Radiopharmaceutical Formulation

Apparatus

Capintec CRC-15R dose calibrator; pH Indicator; well-type scintillation counter (gamma counter); Survey meter; Lead canister; Insertion holder; Lead tongs; ‘Lead pot’; Forceps; A pair of scissors; ruler; pencil; Counting tubes; Two small (10mL) vials with cover; 27 G needle or syringe; and strips used for thin-layer chromatography (1cm×6cm).

Chemicals/Reagents

^{99}Mo/^{99m}Tc generator; Cold kits (MDP; DTPA; and MIBI); and Acetone.

Standards

Aluminum 'breakthrough' kit (Aluminum standard solution and filter paper), ^{137}Cs source, 0.9% NaCl (sterile isotonic saline solution) as eluent and sterile vials of various sizes (mL).

Mandatory Laboratory Working Conditons

Aseptic conditions was maintained during generator use to ensure sterile/pyrogen-free environment. Gloved-hand were used throughout elution and formulations. The generator's sealed column besides the fluid path were left intact on the radiation shield system till elution. Cold kits were kept refrigerated (2-8 $^{\circ}$C).

3.4.1 Elution of ^{99}Mo/^{99m}Tc Generator to generate ^{99m}Tc

To generate ^{99m}Tc radionuclide for radiopharmaceutical formulation, the ^{99}Mo/^{99m}Tc generator positioned in the laminar flow hood was eluted by passing 0.9% NaCl through the column and the Sodium Pertechnetate ($NaTcO_4$) generated ('milked') was collected in an evacuated vial; and subsequently, assayed for molybdenum 'breakthrough', pH and Al^{3+} ion content concentration. The first eluate was not used on patients because there would be a build-up of molybdenum-99 in the column which will deposit in the ^{99m}Tc eluate and affects the labeling of the cold kits. Accordingly, the elution was repeated and the eluates obtained used for the radiopharmaceutical formulations. The elutions were done for two weeks consecutively.

Materials Used

The following materials were used in the elution process: $^{99}Mo/^{99m}Tc$ generator, laminar flow hood, evacuated vial, Pb "Pot" tongs, sterile NaCl solution and ethanolic cotton swab.

The step-by-step elution of $^{99}Mo/^{99m}Tc$ generator to generate the ^{99m}Tc eluate is described below:

(a) The generator was removed from its shipping container and placed in a laminar flow hood (positioned in an appropriate area in the laboratory). This ensured that during dispensing procedures, operator radiation exposure was minimal.

(b) The sterile 0.9% NaCl (isotonic saline) solution was placed on one of the inlets of the generator (Fig 3.2A and Fig. 3.2B).

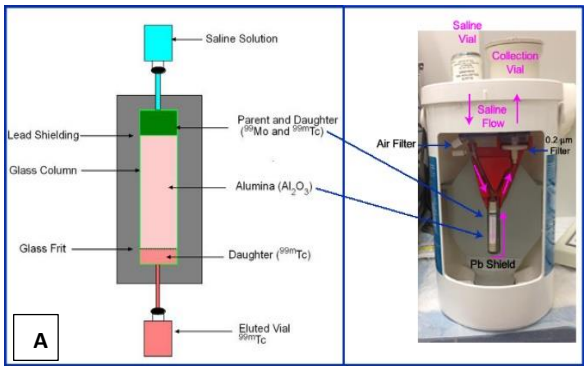

Fig 3.2A Schematic diagram of the $^{99}Mo/^{99m}Tc$ Generator during ^{99m}Tc eluate production

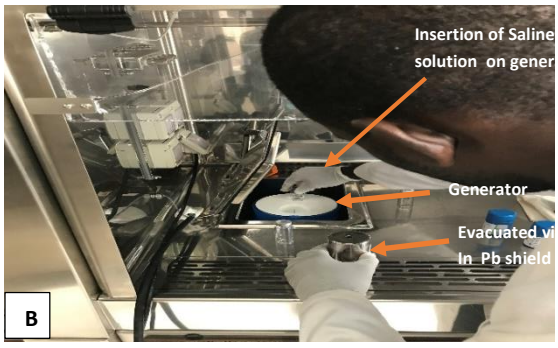

Fig 3.2B Experimental procedure of the $^{99}Mo/^{99m}Tc$ Generator during ^{99m}Tc eluate production

(c) Appropriate volume of elution vial to hold generator-drawn eluate by ethanolic swabbing of the vial followed by drying.

(d) Pb shielded container for absorption of radiation emitted by ^{99m}Tc (contained in the elution vial).

(e) Removal of elution vial (in Pb shielded container) from generator followed by capping of elution needle. At this juncture, the elution vial was placed on the generator inlet needle till succeding elution- (elution vial equipped with shielded cover to prevent radiation through exposed septum end of vial). The eluted ^{99m}Tc was taken for activity assay and quality test (quality control) prior to dispensing/formulation ^{99m}Tc radiopharmaceuticals.

3.4.2 Formulation of ^{99m}Tc Radiopharmaceuticals (^{99m}Tc-MDP; ^{99m}Tc-DTPA and ^{99m}Tc MIBI)

Materials Used

^{99m}Tc eluate, cold kits (MDP, DTPA, MIBI), Pb "Pot", syringes, gloves, ethanolic cotton swab, and water bath were the materials used in the formulation of ^{99m}Tc radiopharmaceuticals.

The experimental procedure is described:

(i) The rubber septa of each radiopharmaceutical cold kit and elution vial was swabbed with an ethanol (C_2H_5OH) wipe in preparation for needle penetration.

(ii) The eluted $Na^{99m}TcO_4$ (Sodium Technetium Pertechnetate solution) was added to the cold kit with the aid of a syringe and an equal volume of air (drawn from vial) to establish stability.

(iii) A new needle was used each time the eluate vial was sampled.

(iv) Septal penetration of the eluate vial with 21-G needles was done repeatedly for 30–50 times per day for radiopharmaceutical kit preparation and for drawing of ^{99m}Tc for direct injection.

All the preparations (formulations) follows the procedure described above with the exception of ^{99m}Tc-MIBI; in which case the formulation was heated on water at 100 ^{o}C for 10 minutes followed by cooling (15 minutes) at room temperature.

3.5 Assessment of Quality of ^{99m}Tc Eluate and Formulated Radiopharmaceutical

The radionuclide purity, chemical purity, the pH and radiochemical purity of the ^{99m}Tc eluate of the ^{99}Mo/^{99m}Tc radionuclide generators were studied. The measurements were accomplished over an eight-month period (a generator per month) and performed at the times each generator was eluated.

The general overview of laboratory determinations for this research work is presented in Fig.3.3

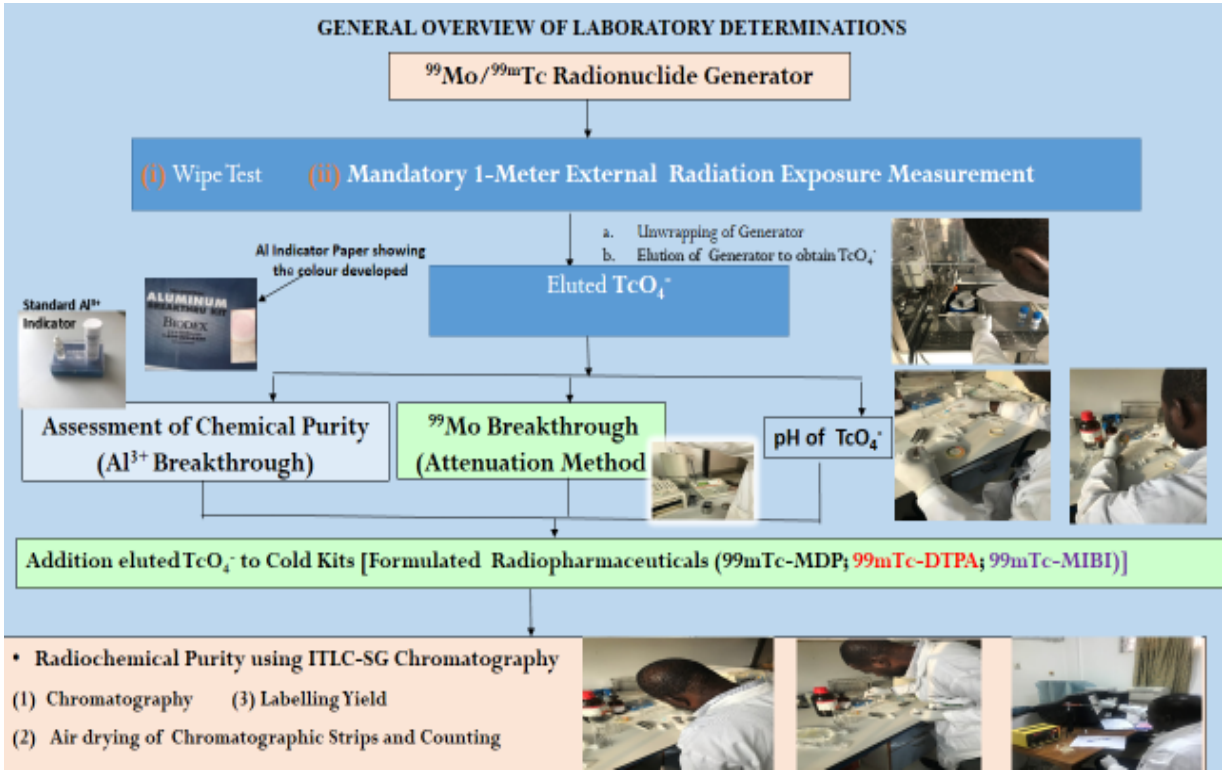

Fig. 3.3: Overview of laboratory determinations of ^{99m}Tc and formulated radiophrmaceutical purities

3.5.1 Quality of ^{99m}Tc Eluate

3.5.1.1 Radionuclide Purity

Radionuclide purity is the activity in a radiopharmaceutical due to the desired radionuclide. ^{99}Mo in the $^{99m}TcO_4$ eluate is a radionuclide purity. Accordingly ^{99}Mo breakthrough test is performed to access the level of ^{99}Mo. Presence of ^{99}Mo in the eluate leads to increased radiation due to its high energy and longer half-life (WHO, 2014).

The flow chart for the evaluation of ^{99}Mo 'breakthrough' (^{99}Mo Contamination) is presented in Fig 3.4 (Radionuclide purity).

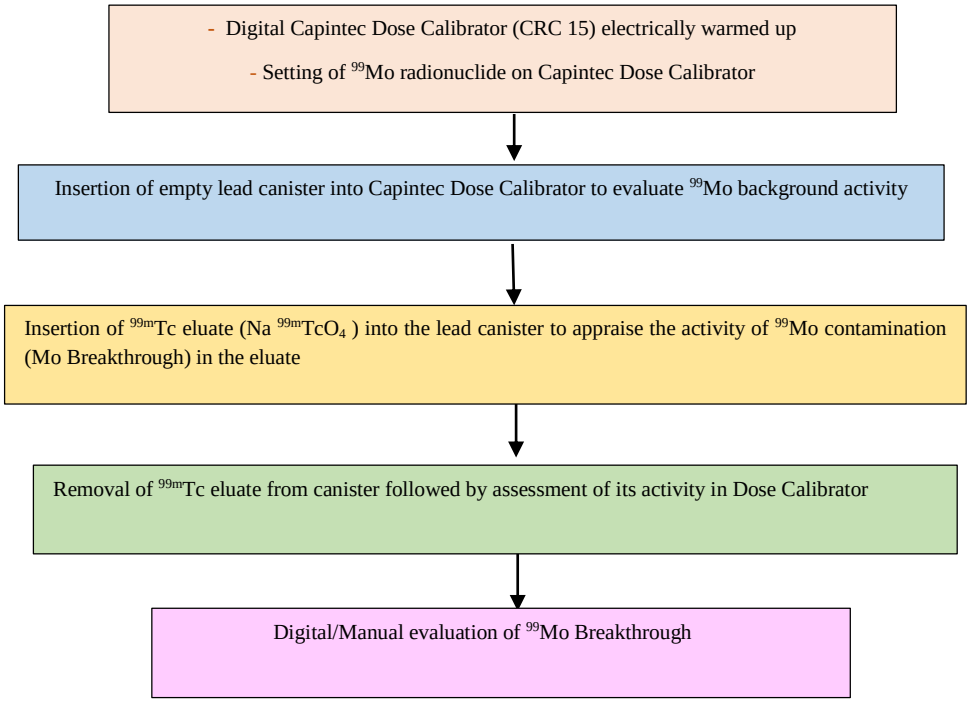

Fig. 3.4: Flow chart for ^{99}Mo 'breakthrough' evaluation

Materials Used

The materials used for the evaluation of ^{99}Mo "breakthrough" were: Capintec CRC-15R calibrator , ^{99m}Tc eluate, Pb canister, insertion holder and tongs.

In vitro measurements (to evaluate the amount of ^{99}Mo contamination in the ^{99m}Tc eluate) were made using the following: a calibrated Capintec CRC-15R (Capintec Inc. NJ, USA), a standard lead canister and an insertion holder.

The experimental procedure is enumerated:

(a) The empty lead canister of 6 mm thickness was measured at the ^{99}Mo assay window to determine the background activity.

(b) The lead thickness is sufficient to offset almost 100% of ^{99m}Tc radiation and around 50% of ^{99}Mo radiation. From these measurements, the purity of the solution was assessed and Mo-99 'breakthrough' (MoBT) determined, using equation (Andrade & Lima, 2009):

$$MoBT = \frac{A_{99_{Mo}} \cdot 2}{A_{99m_{Tc}}} \qquad (3.1)$$

Where; - **MoBT** is the Molybdenum 'breakthrough'.

- $\mathbf{A^{99}Mo}$ is the measured activity of ^{99}Mo
- The constant **2** represents double shielding
- $\boldsymbol{A_{99m_{Tc}}}$ is the measured activity of ^{99m}Tc without shielding.

(c) The β-activity of the sodium pertechnetate ($NaTcO_4$) eluate was measured inside the Pb canister with the same window at 740-780 keV. The activity obtained was a combination of the total amount of molybdenum and the background.

(i) The net amount of ^{99}Mo activity was determined after subtraction of background activity (Mo-BG).

(ii) The activity of ^{99m}Tc eluate was determined without the canister at the appropriate window (^{99m}Tc).

(iii) The ratio of the ^{99}Mo contamination was calculated by dividing the net ^{99}Mo activity in (µCi) by the activity of ^{99m}Tc eluate (mCi)

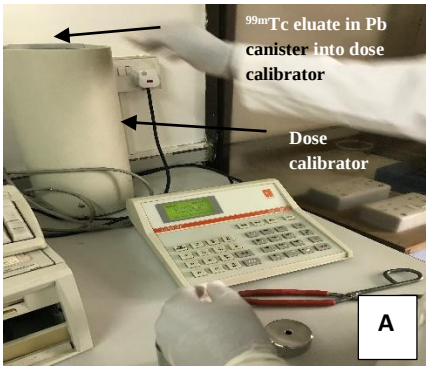

Fig. 3.5A: Measured activity of the ^{99}Mo of the ^{99m}Tc in Pb canister.

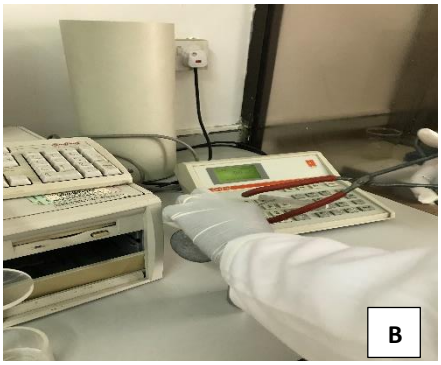

Fig. 3.5B: Removal of ^{99m}Tc eluate from the Pb canister to assay ^{99m}Tc activity

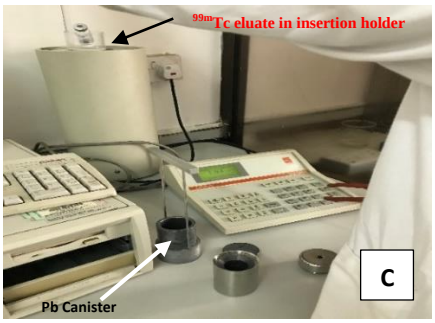

Fig. 3.5C: Measurement of ^{99m}Tc eluate activity

3.5.1.2 Chemical Purity

Chemical purity is the amount of $^{99m}TcO_4^-$ in the correct chemical form. Alumina is a possible chemical contaminant. Excess alumina may cause flocculation in sulphate radiopharmaceuticals and clumping in particulates (WHO, 2014).

Fig. 3.6 is a schematic flow chart for the determination of chemical purity.

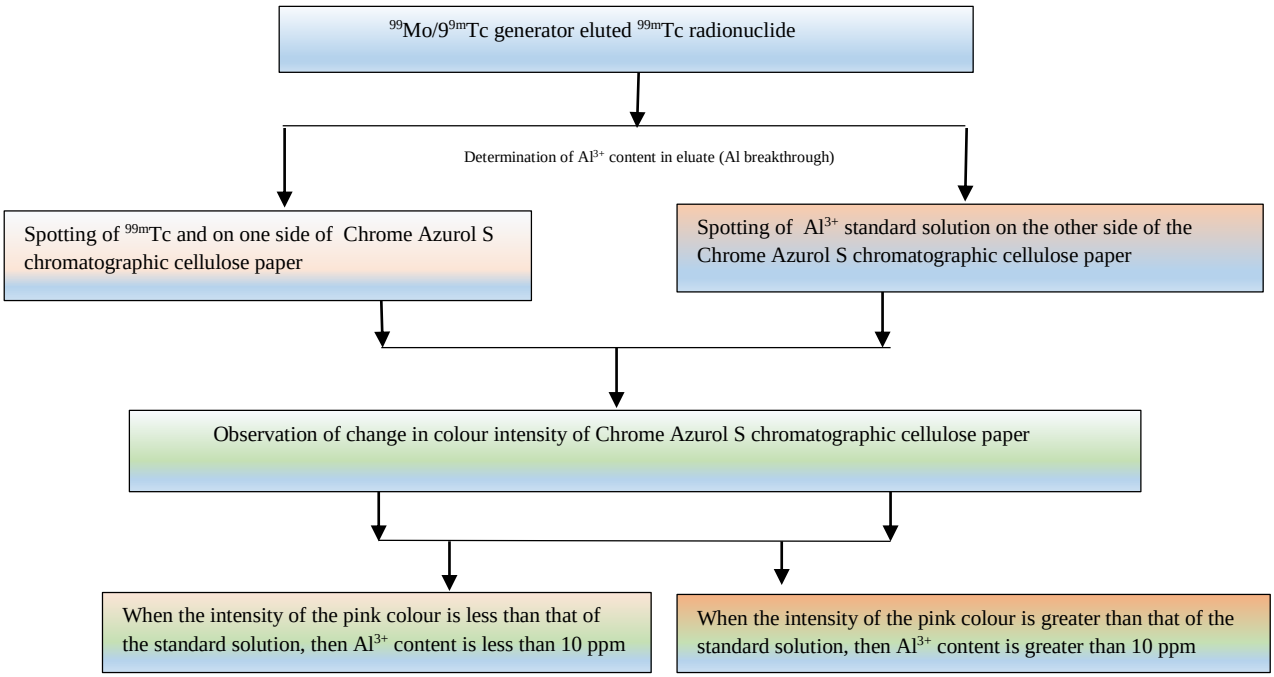

Fig. 3.6 Flow chart for the evaluation of chemical purity (Al^{3+}content)

Materials Used

Al^{3+} standard solution (10 µg/mL), Chrome Asurol S chromatographic cellulose paper, ^{99m}Tc eluate, syringes were used to determine the chemical purity.

The experimental details is as follows:

(i) A spot of the Al^{3+} standard solution (10 µg/mL) was spotted on one side of the Chrome Asurol S chromatographic cellulose paper. This result in a change of the colour of the paper from creamish white to pink.

(ii) A spot of the generator eluate (^{99m}Tc eluate) was also spotted on the other side of the same Chrome Asurol S chromatographic cellulose paper.

(iii) The colour change and the colour intensity at the ends of the paper (Al^{3+} Standard spot and that of ^{99m}Tc eluate spot) were observed and compared.

(iv) If the colour less intense in the ^{99m}Tc eluate spot as compared to the Al^{3+} standard then the eluate contains less than 10 µg/mL Al^{3+}; conversely, if the intensity of the ^{99m}Tc eluate spot more intense than the standard Al^{3+}, then the eluate contains more than 10 µg/mL Al^{3+}. The observation indicates lack of stability in the generator column, consequently, the eluate should be discarded.

3.5.1.3 pH Measurement

pH is the quantitative measure of the acidity or basicity of aqueous or other liquid solutions.

The flow chart for the determination of pH is presented in Fig. 3.7

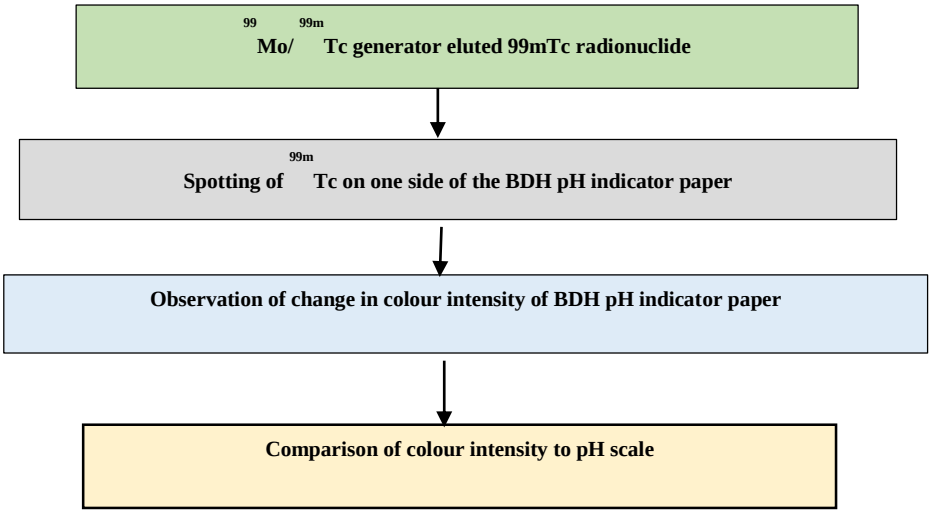

Fig. 3.7: Flow chart of quantitative measurement of acidity/basicity (pH) of eluted ^{99m}Tc.

Materials Used

^{99m}Tc eluate, British Drug House (BDH) pH indicator paper, and syringe were used for pH measurement. The experimental details are described:

(a) A small aliquot of the Technetium-99m eluate was spotted on the British Drug House (BDH) pH indicator paper.

(b) The change in colour intensity of the BDH pH indicator paper was observed for 30 sec.

(c) The intensity of the colour developed was compared to pH scale on the BDH pH indicator.

Fig. 3.7A and Fig 3.7B represented the experimental procedure to determine the pH of ^{99m}Tc eluate.

Fig.3.7A: ^{99m}Tc on the BDH pH indicator paper to determine the pH.

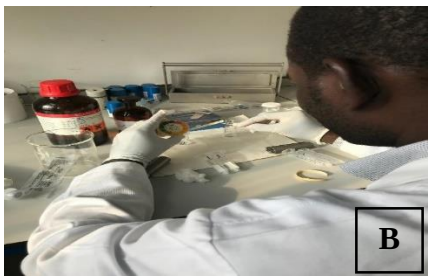

Fig. 3.7B: Comparison of colour intensity on BDH pH indicator

3.5.1.4 Evaluation of Radiochemical Purity

Radiochemical purity is the fraction of the activity due to radiopharmaceutical in the correct chemical form. The free pertechnetate (TcO_4^-) and hydrolyzed reduced technetium (HTc) are possible radiochemical contaminants (WHO, 2014).

Fig. 3.8 is the flow chart for the determination of Radiochemical Purity

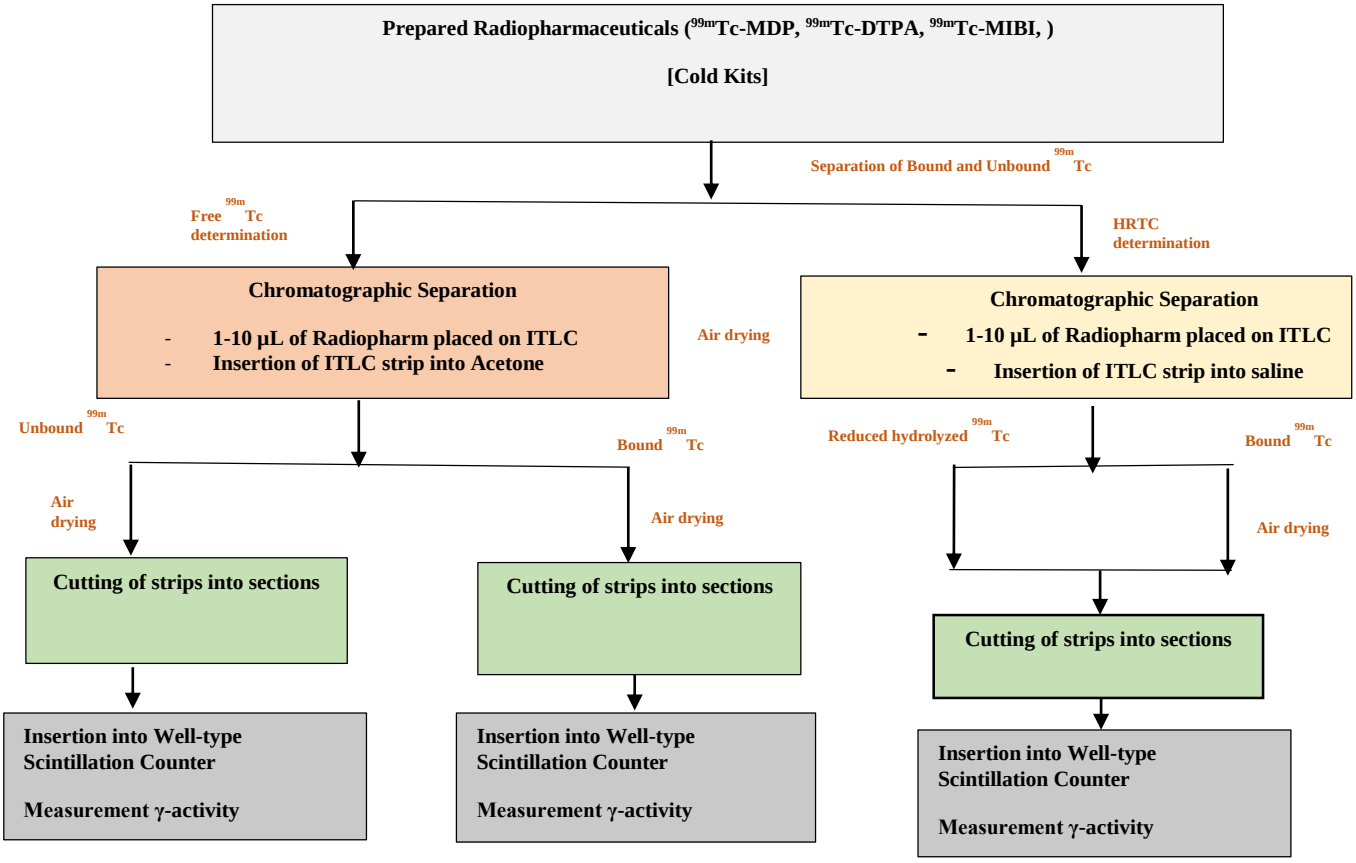

Fig. 3.8: Flow chart for the evaluation of radiochemical (radiopharmaceutical) Purity

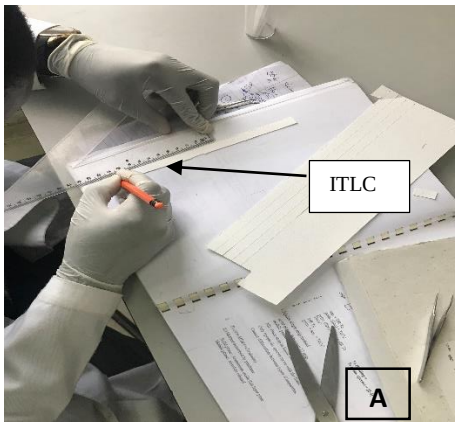

Fig.3.9A. Measurement of ITLC

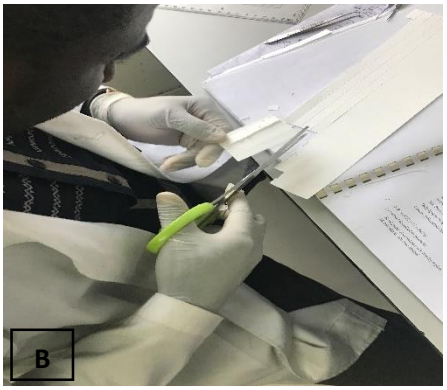

Fig.3.9B. Cutting of ITLC strips into actual measurement (1×6 cm)

Fig.3.10. Reconstitution of radiopharmaceutical

Fig.3.11. Spotted radiopharmaceutical on ITLC paper

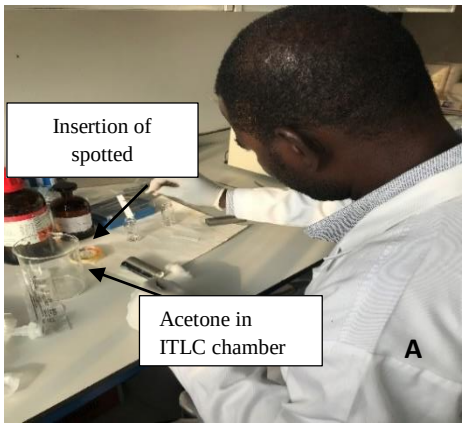

Fig.3.12A. Insertion of spotted radiopharmaceutical into acetone

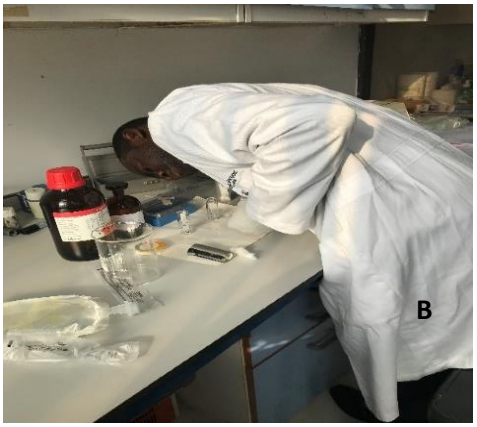

Fig 3.12B Observation of ITLC development

Fig.3.12C. Removal of ITLC strip from acetone chamber

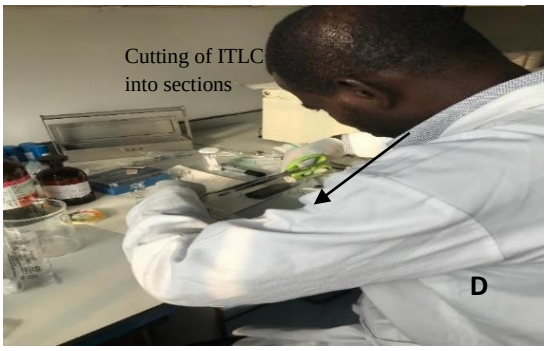

Fig.3.12D. Cutting of ITLC strip into sections to count

Fig.3.12E. Insertion of ITLC sections into γ-ray counting glass vials

Materials Used

The following materials were used in the determination of radiochemical purity; formulated ^{99m}Tc radiopharmaceuticals (^{99m}Tc-MDP, ^{99m}Tc-DTPA, ^{99m}Tc-MIBI,), instant thin layer chromatographic strip-silica gel (ITLC-SG), ruler, pencil, forceps, acetone, saline, a pair of scissors, well-type γ-counter, chromatographic glass chamber, and γ-ray counting glass vials. The experimental procedure is described:

(i) The prepared radiopharmaceutical (1-10 µL) was spotted at the origin of two separate prepared (1×6 cm) Instant Thin Layer Chromatographic Strip-Silica Gel (ITLC-SG).

(ii) One of the spotted ITLC-SG was instantly inserted into a Thin Layer Chromatographic glass chamber (10 cm) containing approximately 1 mL acetone [$(CH_3)_2CO$] to avoid the sample getting dry in order prevent oxidation. This was used to evaluate free perchnetate ($^{99m}TcO_4^-$).

(iii) The other prepared (1×6 cm) Instant Thin Layer Chromatographic Strip-Silica Gel (ITLC-SG) was also immediately inserted in a thin layer chromatographic glass chamber containing approximately 1 mL of normal saline.

It was ensured that radiopharmaceutical spots were above the solvent level and the glass chamber was closed with a cap. It was also ensured that the strip did not touch the wall of the glass chamber.

(iv) The two systems were allowed to run till the ‘solvent front line’ was reached.

(v) The ITLC-SG strips were removed from their respective glass chambers using forceps.

(vi) They were air-dried for about 2 to 3 min and divided at the cut line (middle line) into sections using a clean laboratory scissors.

The ITLC-SG strips from the acetone chamber was labelled into sections 1and 2; representing bottom and top respectively. The free pertechnetate (TcO_4^-) migrated to the top leaving for example MDP and HRTC at the bottom. The ITLC-SG strips from the normal saline chamber was labeled into sections 3 and 4; which determines the hydrolyzed reduced Technetium. In this strip the MDP and TcO_4^- migrated to the top of the strip, leaving HRTC at the bottom.

(vii) Each section of the strip was placed into separate γ-ray counting glass vials.

(viii) Individual γ-ray counting vials were placed into a well-type scintillation counter (Gamma counter) for radioactivity distribution counting in each section.

(viiii) The percentage of the free pertechnetate was calculated from the equation (Molavipordanjani & Hosseinimehr, 2018):

$$\% \text{ Free } NaTcO_4 = \frac{\gamma_1 \, Counts \, in \, Section \, 2}{\gamma_2 Counts \, (Section \, 2 + Section \, 1)} \times 100 \qquad (3.2)$$

Where;

$\% \, NaTcO_4$ is the percentage free pertechnetate

γ_1 is the gamma radioactivity counts in section 2 (upper piece)

γ_2 is the gamma radioactivity counts in section 2 +1(lower piece)

The hydrolyzed reduced Technetium was calculated from the equation (Molavipordanjani & Hosseinimehr, 2018). :

$$\%HR\text{–}^{99m}Tc = \frac{\gamma 1 \, counts \, in \, Section \, 3}{\gamma 2 \, counts \, in \, Section \, 3 + Section \, 4} \times 100 \qquad (3.3)$$

Where;

%HR-^{99m}Tc is the hydrolyzed reduced Technetium-99m.

γ_1 is the gamma radioactivity counts in section 3 (lower piece) of the ITLC strip

γ_2 is the total gamma radioactivity counts in Sections 3 + 4 (upper piece) of the ITLC strips.

The percentage of labelling yield of the Technetium-99m with the cold kit was also calculated;

$$\%RCP = [100\% - (\% NaTcO_4 + \% HR\text{-}^{99m}Tc)] \quad (3.4)$$

Where; **%RCP** (% Radiochemical purity) is the labelling yield of ^{99m}Tc-radiopharmaceutical;

% $NaTcO_4$ is the percentage of free pertechnetate; and

%HR-^{99m}Tc is the hydrolyzed reduced Technetium-99m.

Fig.3.13 Radioactivity distribution counting in the ITLC sections.

3.6 Quality Assurance/Control

3.6.1. Calibration, Quality and Consistency Checks of Equipment used

(i) Capintec CRC-15R dose Calibrator:

For accuracy and constancy tests/checks, long-lived ^{137}Cs standard radionuclide sealed source in vial form (Code No.: CDR562) of activity 9.21 MBq (248.92 µCi) calibrated for 13th October 2005 and manufactured by AEA Technology QSA GmbH (USA) was used. About 1 mL of ^{99m}Tc (10 mL syringe) was used for geometry.

3.6.2 Accuracy Test

Designed to demonstrated that the calibrator readings are correct throughout the energy scale encountered. Using recommended settings, high, medium and Low calibrants; ^{57}Co, ^{133}Ba or ^{137}Cs and ^{60}Co are respectively measured on the dose Calibrator. Followed by comparison of standards and measured values (Karesh, 1996). The procedure for accuracy of dose calibrator is as follows:

Materials Used

Capintec CRC-15R dose calibrator, ^{137}Cs source, forceps, and insertion holder.

(a) The background of ^{137}Cs window on the calibrator was recorded;

(b) The radioactive source was lowered with the aid of forceps into the well chamber of the calibrator;

(c) The reading was taken after 10 s of insertion of the Source into the calibrator. The time was chosen due to the optimum value of the response time for the Capintec CRC-15R dose calibrator;

(d) The mean measured activity was compared to the decay-corrected activity of the standard source after three replicate measurements;

(e) Accuracy was calculated using the formula (Biodex Medical Systems, 2010);

$$\%Error = \frac{Mean\ activity - Expected\ activity}{Expected\ activity} \times 100 \qquad (3.5)$$

3.6.3 Geometry Test

Geometry test is the most significant source of assay errors, specifically, the difference between the container used to obtain the initial calibration settings and the containers used to assay dosages in clinical practice (AAPM, 2012). Ideally, the geometry of the standard source should be identical to the geometry of the source being assayed (AAPM, 2012).

Used to assess the possibility of the radioactive source causing errors in assay using the dose calibrator due geometrical differences between the standard source and the measured source (Biodex Medical System, 2010).

Materials Used

The following materials were used in the geometry testing: ^{99m}Tc eluate, sample holder, forceps, syringes (10 mL, 5 mL, 2mL), water, and Capintec CRC-15R dose calibrator. The detailed experimental procedure is described:

(a) The 1 mL ^{99m}Tc (19.9 mC) contained in 10 mL polyethylene-syringe was placed into a sample holder with the aid of forceps;

(b) The syringe was lowered into the chamber well of the calibrator and the activity obtained was recorded post 10 s of insertion;

(c) The syringe was removed and extra 0.5 mL H_2O added to same syringe, diluted to volume (1.5 m Litre).

(d) The syringe was then assayed in the calibrator. The measured activity, time and volume of water added were recorded;

(e) The procedure was repeated for each points of dilution of water till it reached 8 mL of the 10 mL syringe;

(f) The process was repeated for 2 mL and 5 mL syringes;

(g) The mean of the measured activity was compared with the decay-corrected activity for each volume and time elapsed. Volume correction factors (VCF) were calculated using the equation (Biodex Medical Systems, 2010):

$$VCF = \frac{Average\ of\ Expected\ Activity}{Activity\ of\ sample\ volume\ (V1)} \qquad (3.6)$$

(h) The data was evaluated to appraise the effect of geometry (sample) on dose calibrator readings.

(ii) Well-Type Scintillation Counter

Accuracy Test:

Accuracy Test is an examination of the system stability. The test involves measuring one to three traceable long-lived standards (typically, ^{57}Co, ^{133}Ba, and ^{137}Cs) whose energies ranged over the linear portion of the response-energy curve (AAPM, 2012).

Materials Used

^{125}I-radioactive source, source holder, well-type γ-counter, and forceps.

The experimental details is as follows:

(a) The background γ-activity of the well-type scintillation counter (Gamma counter) was recorded;

(b) The ^{125}I-radioactive source contained in the source-holder was lowered into the counter by the aid of forceps;

(c) The γ-activity was taken after 10s of insertion of the source into the counter. The time was chosen due to the optimum value of the response time for the counter;

(d) Three-replicate measurements were undertaken and mean measured γ-activity was compared to the decay-corrected activity of the standard source; and,

(e) Accuracy was calculated using the formula (Biodex Medical Systems, 2010):

$$\%Error = \frac{Mean\ activity - Expected\ activity}{Expected\ activity} \times 100 \qquad (3.7)$$

CHAPTER FOUR

RESULTS AND DISCUSSION

Results obtained are presented. The results are presented in the form of tables and figures, followed by detailed discussion and interpretation based on theory.

4.1 QUALITY OF ^{99}MO/^{99M}TC RADIONUCLIDE GENERATOR ON RECEIPT

4.1.1 Acceptance Criteria for Imported ^{99}Mo/^{99m}Tc Generator Packages

4.1.1.1 Wipe Test

The wipe test conducted on the imported ^{99}Mo/^{99m}Tc generator packages indicated no radiation leakage or broken package. This is because there were no activity recorded (0.00 µCi) after γ-ray spectrometric measurement.The results obtained were below the U.S. NRC (United States Nuclear Regulatory Commission) recommended limit 0.01 µCi (22,000 disintegrations per minute) per 100 cm^2 of the package surface area monitored (NRC, U.S., 1975). Accordingly, there was no radiation contamination of the packages; hence the generators were deemed to meet the acceptable criteria (US NRC, 2018). This was followed by the U.S. NRC recommended mandatory 1-meter external radiation exposure measurement.

4.1.1.2 External Radiation Exposure Measurement

U.S. NRC recommended exposure limit for one meter (1 m) external exposure is 719.9×10^6 µR/h (200 mrem) (U.S. NRC 2018). The measured 1-m external exposure are presented on Table 4.1. The measured 1-meter exposure measurements of 525,415,225 and 305 (µR/h) for generators 1, 2, 3 and 4 were all below the U.S. NRC recommended value of 719.9×10^6 µR/h

(200 mrem). External exposure is from; (a) radioactive materials existing on the ground; (b) suspended in the air; or (c) attached to cloth surface body. Exposure happens when radiation from sources interacts with human body. Dose occurs when radiation leaves some energy in the body. The quantity of external radiation a body is exposed to relates to distance from source, energy of emitted radiation, total amount of radioactive material present machine setting, and exposure time (Radiation Answers, 2020). On satisfying the criteria, elution of the generator followed by the recommended QA/QC analytical procedures on the eluate were undertaken.

Table 4.1 One-meter external radiation exposure measurements

Generator	Exposure (µR/h)
1	525
2	415
3	225
4	305

4.2 ^{99}Mo Breakthrough (MoBT)

In the commercial ^{99}Mo/^{99m}Tc generator, ^{99}Mo (parent) is chemically bound to the Al_2O_3 column. The binding is strong to prevent ^{99}Mo from being easily washed from the column by the isotonic saline solution (applied in the elution of ^{99m}Tc). Nevertheless, traces of ^{99}Mo that appears in the ^{99m}Tc product eluted. This is referred to as "molybdenum breakthrough" or radionuclidic impurity. Varying regulations concerning permissible levels of ^{99}Mo in eluted product exist in radiopharmaceuticals prepared for human administration. The risks posed by ^{99}Mo relates to its adverse decay characteristics (β^- decay and long $t_{1/2}$), causing needless radiation dose to patients. Generally accepted condition (United States Pharmacopoeia) is that the formulated radiopharmaceutical at the time of administration should not contain greater than 0.15 kBq of ^{99}Mo per MBq of ^{99m}Tc (0.15 µCi of ^{99}Mo per mCi of ^{99m}Tc). Also, total

activity of ^{99}Mo acceptable in a single administration may be controlled, usually the order of 185 kBq (5 µCi). The rules vary based on the country; in Europe it's 0.1 kBq per MBq, and 0.03 kBq/MBq for Canada. The decay half-life of ^{99}Mo longer than that of ^{99m}Tc; therefore, the ratio of ^{99}Mo activity to ^{99m}Tc activity will increase with time, (doubling every 6 hours). Measurements made at the time of elution must consider latest time at which the product might be injected. ^{99}Mo 'breakthrough' and expiration time for ^{99m}Tc must be determined for all elutions. The expiration time should not exceed 12 hours from time of elution (IAEA, 2016).

The results for ^{99}Mo 'breakthrough' is presented in Fig. 4.1 (Raw data presented in Appendix A). From Fig. 4.1 it is clear that the ^{99}Mo 'breakthrough' values (G1:0.0001-0.035 ; G2:0.004 -0.039 ; G3:0.001- 0.006 ; G4:0.001-0.011 µCi ^{99}Mo/mCi ^{99m}Tc) obtained were far below the US Pharmacopea recommended value of 0.15 µCi ^{99}Mo/mCi ^{99m}Tc.

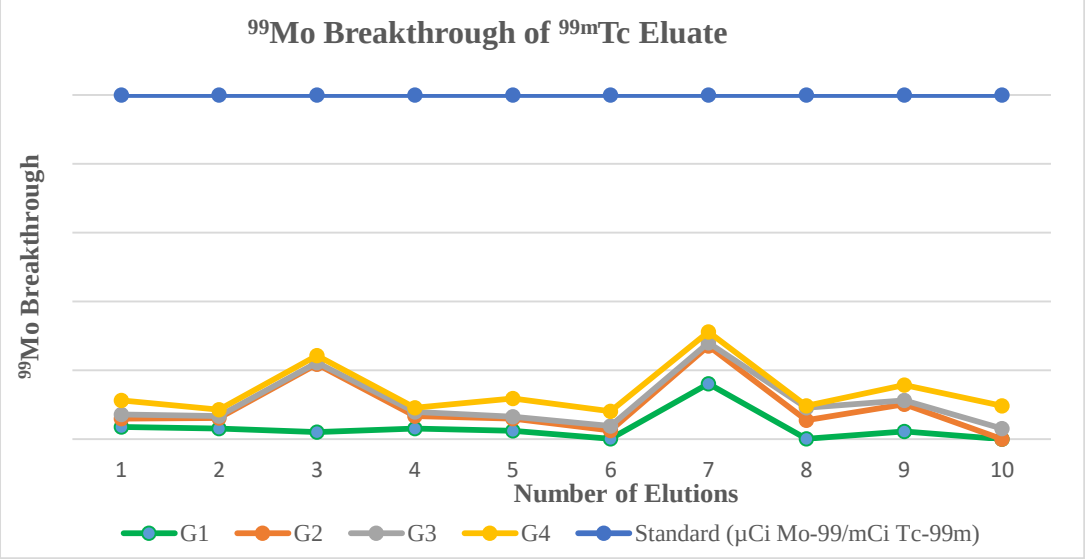

Fig. 4.1: Comparison of ^{99}Mo Breakthrough for Generators (1 to 4) with recommended value.

Table 4.2: MoBT with literature data

Reference	Country	Measured MoBT (µCi/mCi)				Measurement Technique	Recommended MoBT
		G1	G2	G3	G4		
This Study (2020)	Ghana	0.0001-0.035	0.004 -0.039	0.001- 0.006	0.001-0.011	Attenuation Method	≤ 0.15µCi/mCi
Demeter et al. (2018)	Canada	0.00	0.00	0.00	0.00		
Memon et al. (2014)	Pakistan	0.00-0.09				Attenuation Method	
Khan et al. (2012)	Pakistan	0.00 -0.06				Attenuation Method	
Momennezhad et al.(2010)	Iran	0.00932± 0.0043	0.0170±0.0127			Attenuation Method	
Shah et al. (2009)	Pakistan	0.01-0.14				Attenuation Method	
Zulkifli et al. (2010)	Malaysia	0.0295- 0.1076				Attenuation Method	
Uccelli et al. (2013)	Italy	$(2.1 \pm 0.2)\times 10^{-2} - (2.7 \pm 0.3) \times 10^{-2}$				Attenuation Method	

MoBT (Molybdenum breakthrough) **G** (^{99}Mo/^{99m}Tc Generator)

Molybdenum breakthrough (MoBT) values obtained in this study was compared with literature data for similar studies conducted in other parts of the world (Table 4.2). Data obtained in this study compares favourably with data obtained for studies in Canada, Pakistan, Iran, Malaysia and Italy. The entire studies (including this study) obtained MoBT values less than the recommended value of ≤ 0.15 µCi ^{99}Mo/mCi ^{99m}Tc by the IAEA, EU Pharmacopeia and US Pharmacopeia.

4.3 pH

Eluted pertechnetate ($Na^{99m}TcO_4$) can be directly injected into patients after it numerous quality control checks (including pH). pH is a critical parameter in radiopharmaceutical injection. Accordingly, there is a need to ensure that the pH of the $Na^{99m}TcO_4$ fall within internationally accepted/recommended pH range for human administration (ie it must fall within the human blood pH range). During the study, the pH of $Na^{99m}TcO_4$ for every radiopharmaceutical formulation was assessed. The results obtained is presented graphically in Fig. 4.2 (The data is presented in Appendix F). pH 7 was obtained for all 38 elutions carried out on four (4) different generators (G1-G4). The results obtained were within the US Pharmacopea recommended pH range of 4 to 8; and also agrees perfectly with the near-neutral pH (7.35-7.45) of human blood (Schwalfenberg, 2012).

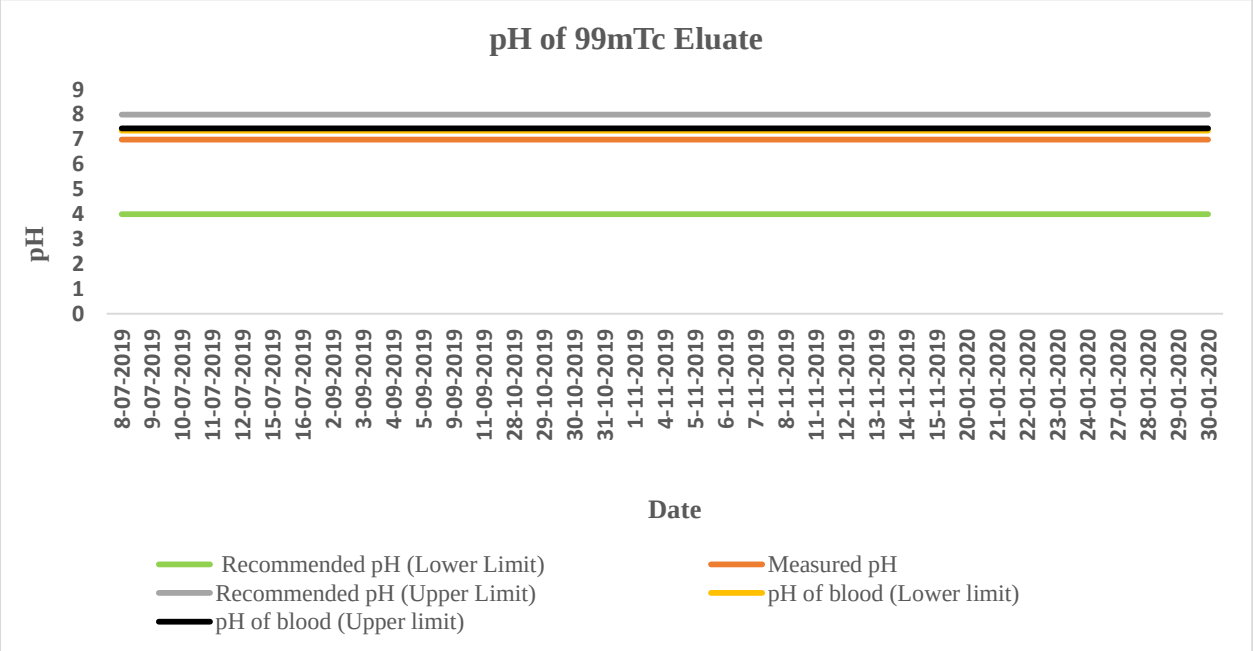

Fig. 4.2: Measurement of pH of ^{99m}Tc Eluate of different generators compared with recommended limit as well as the blood**.**

Table 4.3: Comparison of eluate pH obtained in this study with literature data

Country [Institute]	Measured pH	Measurement Technique	Reference
Ghana [KBTH]	7	pH paper	This Study
Canada [WHSC]	5.39-6.34		Demeter et al., 2018
Malta [MDH]	5-7	pH paper	Vincenti et al., 2016
Germany	5-5.5		Hammermaier et al., 1986
Hungary	5-6		Tasdelen, 2011
Malaysia	6.5		Zulkifli et al., 2010
Italy	(6.0 ± 0.3) – (6.2 ± 0.1)	pH paper	Uccelli et al., 2013

Recommended pH Range **4-8** (European Pharmacopeia) **4.5-7.5** (USA Pharmacopeia)

KBTH (Korle Bu Teaching Hospital) **WHSC** (Winnepeg Health Sciences Centre) **MDH** (Mater Dei Hospital)

Table. 4.3 is a comparison of $NaTcO_4$ eluate pH obtained (in ranges) in the present study and the pH of $Na^{99m}TcO_4$ eluate from published data. The pH were measured using largely the same technique (Universal BDH pH paper) in this study and the studies conducted in other parts of the world. The pH for Canada (5.39-6.34); Malta (5-7); Germany (5-5.5); Hungary (5-6); Malaysia (6.5); and, Italy (6.0 ± 0.3) – (6.2 ± 0.1) were comparable to the mean pH of 7 obtained in this study. The pH values obtained were within the recommended pH range of 4-8 (European Pharmacopeia) and 4.5-7.5 (USA Pharmacopeia).

4.4 Chemical Purity (Aluminium Breakthrough)

Aluminium ions, may be washed from the Al_2O_3 column during elution (though this is rare in practice). Excess Al^{3+} in eluate is indicates breakdown of Al_2O_3 column and may harmfully affect radiopharmaceutical formulations causing undesirable uptake of activity (lung uptake bone imaging formulations). Therefore, Al^{3+} concentration in eluates should be assessed; otherwise known as aluminum breakthrough or chemical purity of the radiopharmaceutical. It is however difficult to totally eliminate aluminium ions, as a result there are recommended levels that is accepted internationally. According to the United States Pharmacopoeia (USP), the recommended limits for Al^{3+} concentrations in the eluate should be $\leq$ 10 µg/mL, (for column prepared from fission ^{99}Mo and 20 µg/mL (thermal neutron activation used to prepare ^{99}Mo) [IAEA, 2016].

The results of the evaluation of Al^{3+} concentrations in the eluates (column prepared from fission molybdenum) are presented in Table 4.4 (Comprehensive data is presented in Appendix E). All thirty-eight (38) elutions from the four different generators, indicated Al^{3+} concentration of

less than ten parts per million (< 10 ppm). An indication that the eluates in all the formulations contained acceptable concentrations of Al^{3+} according to USP.

Table 4.4: Results of Al^{3+} breakthrough evaluation of four generators (G1-G4)

Elution No.	Generator, G (ppm)				
	G1	G2	G3	G4	Standard
1	<10	<10	<10	<10	≤10
3	<10	<10	<10	<10	≤10
4	<10	<10	<10	<10	≤10
5	<10	<10	<10	<10	≤10
6	<10	<10	<10	<10	≤10
7	<10	<10	<10	<10	≤10
8	<10	<10	<10	<10	≤10
9	<10	<10	<10	<10	≤10
10			<10	<10	≤10

Table 4.5: Al^{3+} breakthrough from this study and studies in other parts of the world

Reference	Country	Measured Al^{3+} (ppm)	Measurement Technique	Globally Accepted Recommended Al^{3+} Value (ppm)
This Study	Ghana	<10	Colorimetric Method	≤ 10
Hammermaier et al. (1986)	Germany	< 1	Colorimetric Method	
Uccelli et al. (2013)	Italy	< 5	Colorimetric Method	

Aluminum breakthrough or chemical purity of $Na^{99m}TcO_4$ eluate should be ≤ 10 ppm. Comparison of the aluminium breakthrough values obtained for studies by Hammermaier et al. (1986) and Uccelli et al. (2013) conducted in Germany and Italy respectively gave values < 10 ppm (the recommended aluminum breakthrough or chemical purity of $Na^{99m}TcO_4$ eluate). Also, the values (<1 and <5) obtained in the studies conducted in Germany and Italy respectively were less than the chemical purity of <10 obtained in this study.

4.5 Radiochemical Purity

Radiochemical purity considered a critical parameter due to the radiochemical form determines the radiopharmaceutical bio-distribution. Radiochemical impurities (if present) have different patterns of bio-distribution which obscures diagnostic image and render the investgation fruitless (IAEA, 2016).

Results obtained for the radiochemical purity assessment for the various cold kits are presented and discussed.

4.5.1 Radiochemical Purity for ^{99m}Tc-MDP

Technetium-99m-methyl diphosphonate (^{99m}Tc-MDP), is a radiotracer applied in nuclear medicine for bone scans. A disease process which results in extracellular fluid expansion leads to accumulation of the tracer.

The radiochemical purity of percentage purity of ^{99m}Tc-MDP after twenty-five (N= 25) formulations with four different generators is presented in Fig. 4.3 (Detailed data presented in Appendix B). Among the formulations from Fig. 4.3 six preparations (94.2; 94.3; 94.3; 94.4; 94.7; and 94.7) were below the US Pharmacopea recommended value of $\geq$ 95% which represented 24% and nineteen formulations (76%) were either equal or greater than the recommended value.

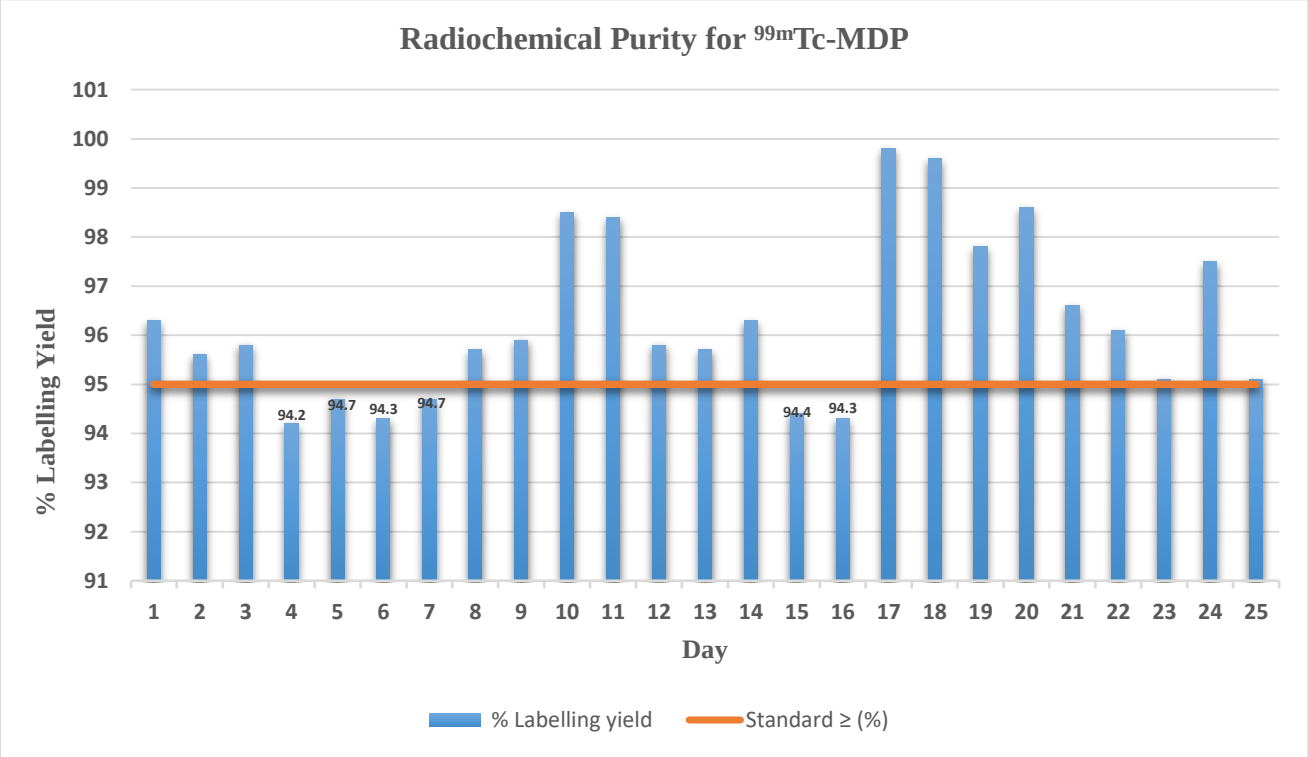

Fig.4.3 Radiochemical purity for ^{99m}Tc-MDP formulations for four different generators.

Table 4.6: Radiochemical purity for ^{99m}Tc-MDP compared to data obtained in other studies.

Country	RCP (%)	Measurement Technique/Conditions						Reference
		System I St. Ph	Mob. Ph	Loc. of Bou. Ag.	System II St. Ph	Mob. Ph	Loc. of Bou. Ag.	
Ghana	94.2-99.8	ITLC-SG	Acetone	Bottom	ITLC-SG	0.9% NaCl	Top	This Study
Italy	(99.01± 0.24; 99.11 ± 0.33)	TLC-RP-18	Methanol	Bottom	Whatman No.1	0.9% NaCl	Top	Uccelli et al.(2013)
Iran	(90.20 ± 5.87; 95.9 ± 3.87)	Whatman No.1	Acetone	Bottom	ITLC-SG	0.9% NaCl	Top	Sadeghpour et al. (2015)
Bangladesh	77.24	Whatman No.1	MEK	Bottom	Whatman no.1	0.9% NaCl	Top	Amin et al. (2012)

ITLC-SG (Instant Thin- Layer Chromatograpy) **St. Ph** (Stational phase) **Mob. Ph** (Mobile phase) **Loc. of Bou. Ag** (Location of bound agent)

MEK (Methyl Ethyle Ketone) Recommended Labelling yield (%) ≥ 95

Comparison of RCP values, measurement techniques and conditions used, for this study and studies conducted by Uccelli et al. (2013), Sadeghpour et al. (2015), Amin et al. (2012) in Italy, Iran and Bangladesh respectively shows significant differences (Table 4.6). To begin with, the RCP value of 77.24% reported in the study for Bangladesh by Amin et al. (2012), indicates remarkable difference to the values (in ranges [%]) 94.2-99.8 (Ghana); 99.01± 0.24, and 99.11 ± 0.33 (Italy); and, 90.20 ± 5.87 and 95.9 ± 3.87 (Iran). With the exception of the 77.24% reported for Bangladesh, which was largely different, all the other RCP valus were comparable/above the recommended labelling yield of ≥ 95% by the IAEA, EU Pharmacopeia and US Pharmacopeia.

4.5.2 Radiochemcal Purity for ^{99m}Tc-DTPA

^{99m}Tc-DTPA is used to measure the relative renal function (ie. the performance of the kidneys), renal scan/scintigraphy is mostly used. Radiopharmaceuticals often used are Technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA), Technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), Technetium-99m mercaptoacetyltriglycine (^{99m}Tc-MAG3), ^{131}I orthoiodohippurate (OIH); and Technetium-99m ethylenedicysteine (^{99m}Tc-EC) were used (Yalçın et al., 2011).

The results of percentage labelling yield for ^{99m}Tc-DTPA of nine formulations were shown in Fig. 4.4 (The detailed data is presented in Appendix C). From Fig. 4.4, it is clear that the percentage labelling yield for ^{99m}Tc-DTPA of nine formulations were all above the US Pharmacopoeia recommended value of ≥ 95%. Accordingly, ^{99m}Tc-DTPA of all nine formulations are suitable for use in renal scan/scintigraphy.

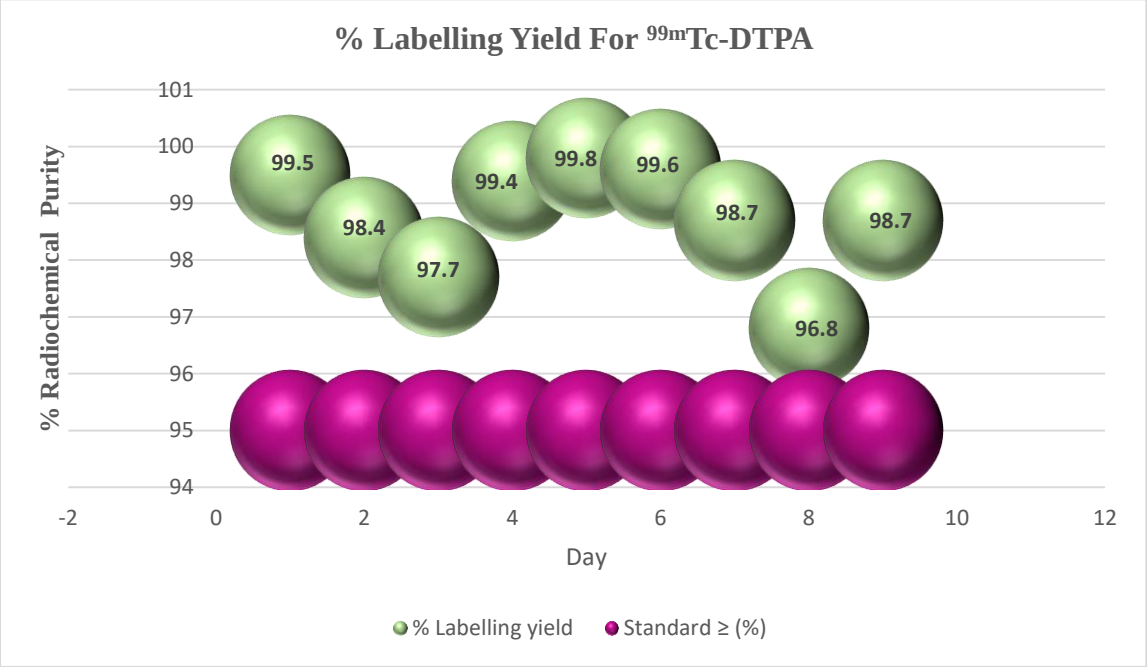

Fig.4.4 Radiochemical purity for ^{99m}Tc-DTPA for nine different formulations.

Table 4.7: Comparison of radiochemical purity obtained for ^{99m}Tc-DTPA with published data

Country	RCP (%)	Measurement Technique/Conditions						Reference
		System I			System II			
		St. Ph	Mob. Ph	Loc. of Bou. Ag.	St. Ph	Mob. Ph	Loc. of Bou. Ag.	
Ghana	96.8- 99.8	ITLC-SG	Acetone	Bottom	ITLC-SG	0.9% NaCl	Top	This Study
U.S.A	98.0- 99.1	Whatman 31ET	Acetone	Bottom	ITLC-SG	distilled water	Top	Ahmed et al. (2015)
Sudan	98.40- 98.48	ITLC-paper	Acetone	Bottom	ITLC-Paper	0.9% NaCl	Top	Abdallah et al. (2016)
Italy	98.84 ± 1.01; 99.14 ± 0.12	TLC-RP-18	Methanol	Bottom	Whatman No.1	0.9% NaCl	Top	Uccelli et al. (2013)
Brazil	96.36 ± 2.70; 96.78 ± 0.51; 98.89 ± 0.31	W3MM paper	Acetone	Bottom	W3MM Paper	0.9% NaCl	Top	Miranda et al. (2019)
Iran	94.88 ± 4.10; 98.21 ± 2.20)	Whatman no.1	Acetone	Bottom	ITLC-SG	0.9% NaCl	Top	Sadeghpour et al. (2015)
Bangladesh	82.81	Whatman no.1	MEK	Bottom	Whatman No.1	0.9% NaCl	Top	Amin et al. (2012)

ITLC-SG (Instant Thin- Layer Chromatograpy- Silica Gel) **St. Ph** (Stational phase) W3MM (Whatman 3MM) **Mob. Ph** (Mobile phase) **Loc. of Bou. Ag** (Location of bound agent)

MEK (Methyl Ethyle Ketone) Recommended Labelling yield (%) ≥ 95

Table 4.7 is a comparison of radiochemical purity obtained for ^{99m}Tc-DTPA in this study and published data. Table 4.7 also compares the measurement techniques/conditions (System 1 and System II). The published data (%): U.S.A **[**98.0- 99.1]; Sudan [98.40- 98.48]; Italy [98.84 ± 1.01; 99.14 ± 0.12] Brazil [96.36 ± 2.70; 96.78 ± 0.51; 98.89 ± 0.31];Iran [94.88 ± 4.10; 98.21 ± 2.20] were higher than the recommended labelling yield (%) of ≥ 95 and, comparable to the range of values (96.8- 99.8%) reported for this study. Though the measurement techniques and measurement conditions used by Amin et al. (2012) in the Bangladesh study were relatively similar to the other studies reported; the % RCP of 82.81 was low compared to the recommended labelling yield (%) of ≥ 95 and the % RCP reported for the other studies (Table 4.7**).**

4.5.3 Radiochemical Purity for ^{99m}Tc-MIBI

^{99m}Tc hexakis-2-methoxyisobutyl isonitrile (^{99m}Tc-MIBI) is a radiopharmaceutical used broadly for in-vivo imaging of myocardial perfusion. Myocardial perfusion imaging/scanning is a nuclear medicine technique used for assessment of abnormalities in the function of human heart muscle. Also it evaluates lot of heart conditions, (coronary artery disease, hypertrophic cardiomyopathy, as well as heart wall motion abnormalities). Besides, suitability suitable in identifying several types of tumors, such as breast, lung and thyroid cancers (Taşdelen, 2011). ^{99m}Tc-MIBI is a lipophilic cation that behaves like Na^+; using the Na^+/H^+ antiport system to enter human heart cell (Arias et al., 2010).

The evaluated percentage labelling yield (purity) of ^{99m}Tc-MIBI is presented together with the USP/EU recommended percentage labelling yield of ^{99m}Tc-MIBI radiopharmacetical formulations (Fig. 4.5). The raw data is presented in Appendix D.

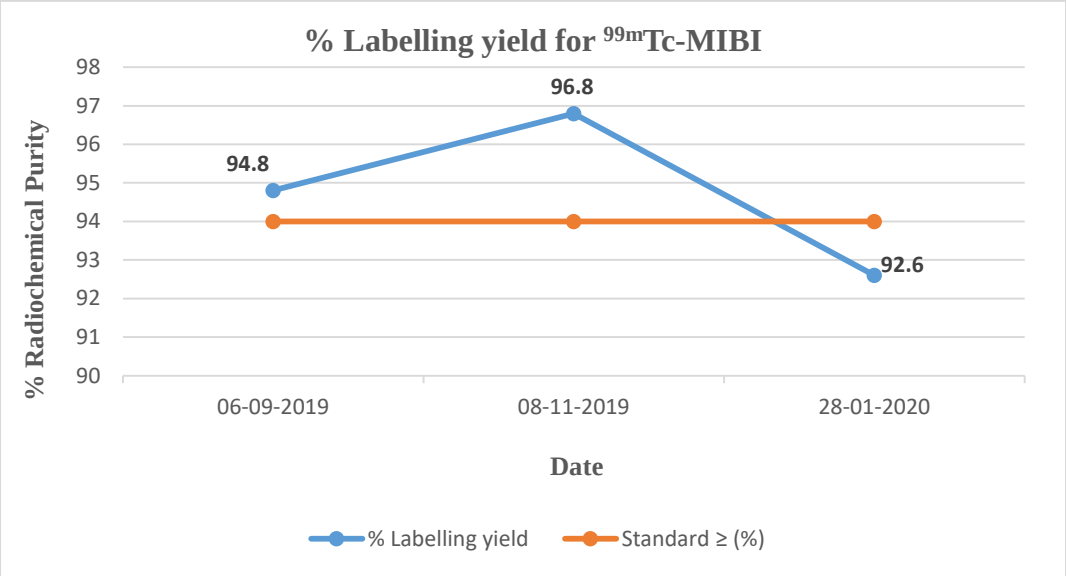

Fig. 4.5 Radiochmeical purity for ^{99m}Tc-MIBI formulations.

From Fig. 4.5, the percentage labelling yield (purity) of ^{99m}Tc-MIBI obtained were above the recommended percentage (≥ 94%). However, one percentage labelling yield (92.6%) was below the recommended ≥ 94%. This may be attributed to factors that potentially affect the radiochemical purity of ^{99m}Tc-MIBI. The factors are: eluate age (radioactive concentration of $^{99m}TcO_4^-$), the amount of $^{99m}TcO_4^-$ (eluate) activity added to the MIBI reagent kits (Cold kits), age of formulated radiolabelled product (^{99m}Tc-MIBI), and, heating temperature and time of ^{99m}Tc-MIBI (Taşdelen, 2011).

Published data for Italy [Uccelli et al. (2013)], Iran [Doroudi et al. (2016); Taşdelen (2011)] and Turkey [Sadeghpour et al. (2015)] were compared to data obtained this study (Table 4.8). The reported data: 98.1± 0.23 and 98.45± 0.09 (Italy); (93.97± 1.35), (95.45± 2.19) and 96.60

± 4.44; 97.46 ± 2.64 (Iran); and, 99.10- 99.35 (Turkey); 92.6- 96.8 (This study), were comparable and also favourably compares with the recommended labelling yield (≥ 94%).

Table 4.8: Radiochemical Purity for ^{99m}Tc-MIBI compared with data available in scientific literature

Reference	RCP (%)	Measurement Technique						Country
		System I			System II			
		St. Ph	Mob. Ph	Loc. of Bou. Ag.	St. Ph	Mob. Ph	Loc. of Bou. Ag.	
This Study	92.6- 96.8	TLC-SG	Acetone	Bottom	ITLC-SG	0.9% NaCl	Top	Ghana
Uccelli et al.(2013)	(98.1± 0.23); (98.45± 0.09)	TLC-RP 18	Methanol	Bottom	Whatman no.1	0.9% NaCl	Top	Italy
Doroudi et al. (2016)	(93.97± 1.35);- (95.45± 2.19)	Whatman No.3	Methanol	Bottom	Whatman no.3	0.9% NaCl	Top	Iran
Taşdelen (2011)	99.10- 99.35	ITLC-SG	Acetone	Bottom	ITLC-SG	0.9% NaCl	Top	Turkey
Sadeghpour et al. (2015)	[96.60 ± 4.44];- [97.46 ± 2.64]	ITLC-SG	Ethanol	Top	ITLC-SG	0.9% NaCl	Top	Iran

ITLC-SG (Instant Thin- Layer Chromatograpy) **St. Ph** (Stational phase) **Mob. Ph** (Mobile phase) **Loc. of Bou. Ag** (Location of bound agent)

Recommended Labelling yield (%) ≥ 94

4.6 Quality Assurance and Control (QAC) Testing of Capintec Dose Calibrator and Well-type γ-ray Counter

Testing the quality quality control (QC) of the Capintec dose calibrator and the well-type γ-ray counter is a regular approach for ensuring high standard efficiency and reliability through aiding the reduction of uncertainties and errors in the equipment performance (Mwape, 2018).

Parameters considered to affirm the quality of the Capintec dose calibrator and the well-type γ-ray counter are: accuracy, geometry, constancy, and linearity. Due to cost, time and availability of radioactive sources, two parameters (accuracy and geometry) were tested for the Capintec dose calibrator and well-type γ-ray counter.

4.6.1 Capintec Dose Capintec

4.6.1.1 Geometry

Used to assess the possibility of the radioactive source causing errors in assay using the dose calibrator. Due to geometrical differences between the standard source and the measured source (Biodex Medical System, 2010).

Table 4.9: Calibrator dependence on geometry

Equipment	**Syringes Geometry (Volume mL)**		
Capintec Dose Calibrator	**10**	**5**	**2**
Mean Measured Activity (mCi)	19.64± 0.95%	5.32± 0.37%	2.51± 0%
Expected Activity (mCi)	19.83	5.34	2.51

Table 4.9 gives the geometry measurements/data obtained during the QC testing of the dose calibrator (ie. the deviation of measured activity from expected activities of ^{99m}Tc activity using different syringe geometry). The errors introduced by the 10 mL, 5mL and 2 mL syringes geometry were found to be 0.95%, 0.37% and 0% respectively. The calculated errors were within the IAEA recommended tolerance levels ±5% (IAEA TRS 454, 2006) for geometry testing of dose calibrators. Accordingly, the Capintec dose calibrator used for the study passed the IAEA recommended geometry test. Additional data for 10 mL, 5 mL, and 2 mL syringes are presented in Appendices G, H and I respectively.

Fig. 4.6A; 4.6B and 4.6C shows the respective Volume Correction Factor (VCF) for 10 mL, 5 mL and 2 mL syringes. The VCF for all three syringe volumes were within the standard recommended value of [0.95<VCF<1.05], with good regression coefficients [R^2 =0.8492 (10 mL syringe), R^2 = 0.962 (5 mL syringe) and R^2=1 (2 mL syringe)]. Biodex Medical System 2010; IAEA TRS 454, 2006). Since all the VCF were within the recommended limits, there was no need to construct a correction table that will facilitate the conversion from indicated activity to true activity (Biodex Medical System 2010). The volume correction factors was calculated using the equation:

$$VCF = \frac{Average\ of\ Expected\ Activity}{Activity\ of\ Sample\ Volume} \qquad (4.1)$$

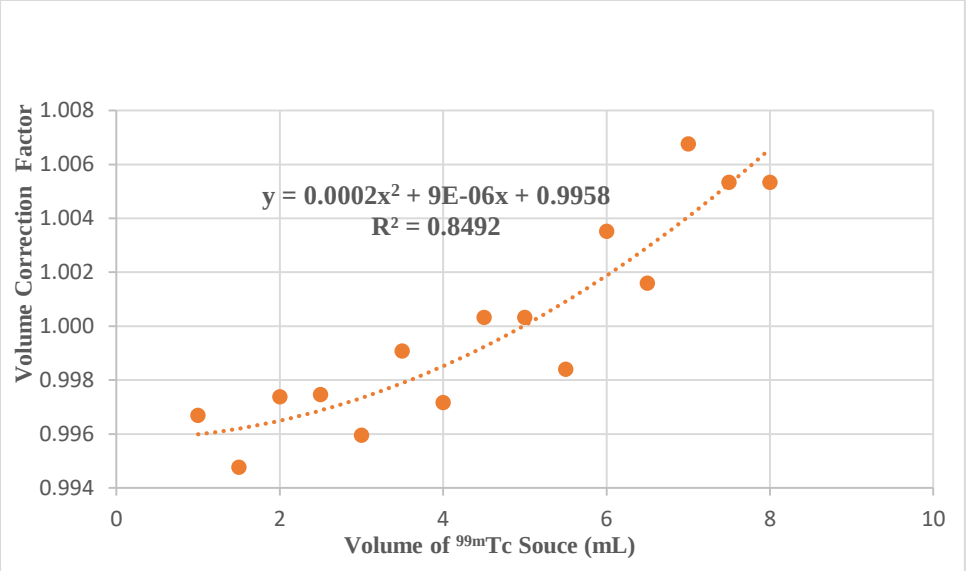

Fig. 4.6A Calibrator dependence on Geometry (10 mL Syringe) of ^{99m}Tc Source

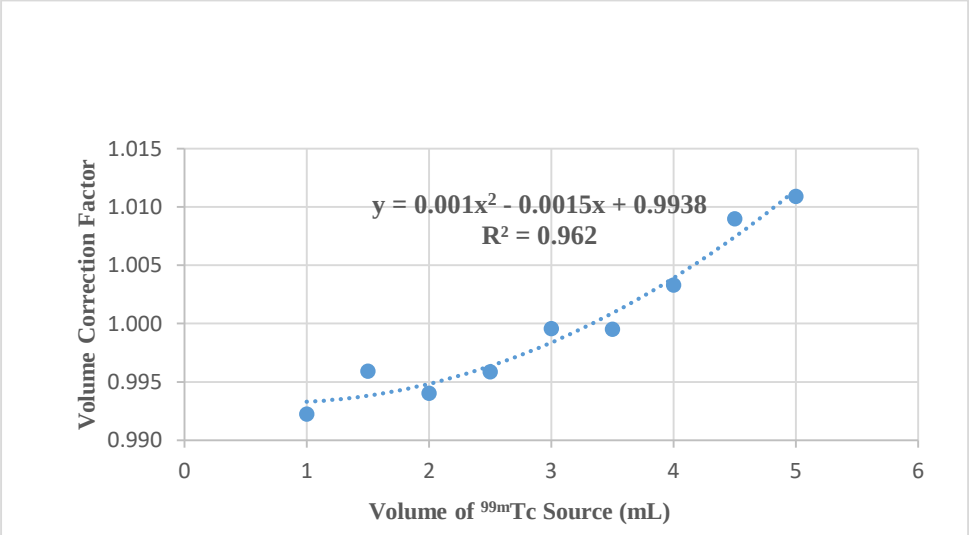

Fig. 4.6B Calibrator dependence on Geometry (5 mL Syringe) of ^{99m}Tc Source

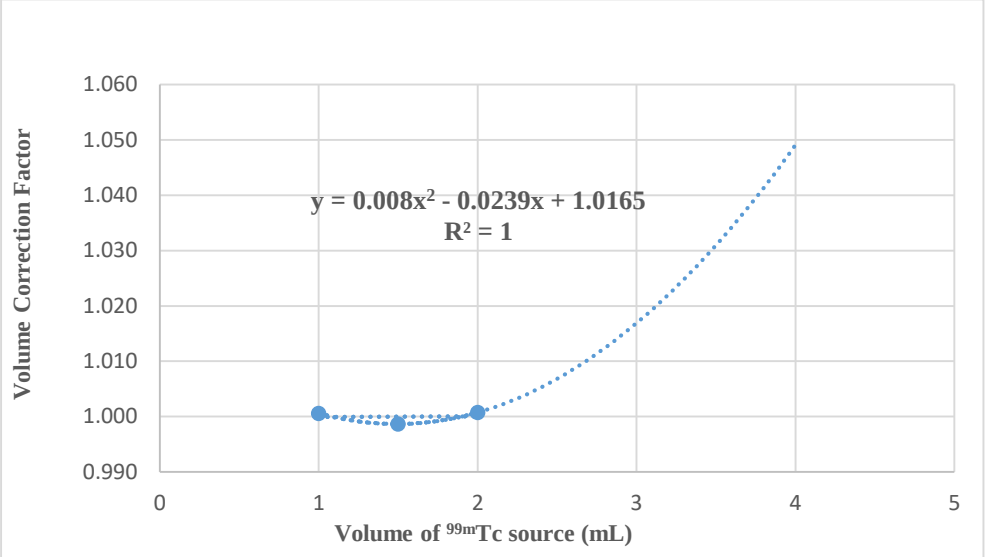

Fig. 4.6C Calibrator dependence on Geometry (2 mL Syringe) of ^{99m}Tc Source

4.6.1.2 Accuracy

Accuracy test on the dose calibrator gives correct readings/measurement throughout the entire energy scale;(using recommended settings, high, medium and low calibrants; ^{57}Co, ^{133}Ba/^{137}Cs and ^{60}Co are respectively measured on the dose calibrator). The label value showing the activity at specific calibration time and date is mathematically decay-corrected to the date of testing (www.nucmedtutorials.com).

Table 4.10: Accuracy of Capintec Dose Calibrator

Equipment	**Radioactive source**	**Percentage**
Capintec dose calibrator	**^{137}Cs activity (µCi)**	**deviation (%)**
Mean Measured Activity (µCi)	183.1	
		0.66%
Expected/Calculated Activity (µCi)	181.9	

Table 4.10 shows the accuracy in the measurement of ^{137}Cs Standard Radionuclide Source Activity of 181.9 µCi for the period of 15 days; the measured mean activitiy with the related uncerntainty for the Capintec Dose Calibrator was found to be 183.1 µCi ±0.66%. This indicates that the accuracy test was within the ±5% standard recommended tolerance level (Biodex Medical Systems 2010; IAEA TRS 454, 2006). Supplementary data is presented in Appendix J.

4.6.2 Well-type γ-ray Counter

Well-type γ-ray counters are gamma radioactvie counting devices for high sensitivity counting of radioactive specimens (blood or urine or 'wipes' from surveys). Counting results may be expressed in terms of activity (e.g. MBq) and applying the measured isotope-specific calibration factor [cpm/Mbq] (Bailey et al., 2014).

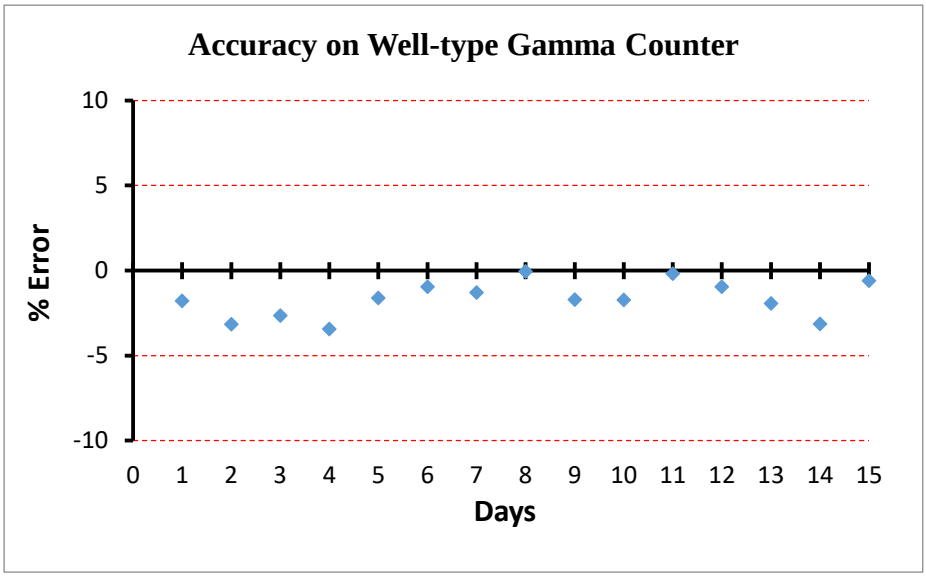

Fig. 4.7 Accuracy on Well-type γ- Counter

Fig. 4.7 is a plot of calculated %error over a fifteen day period for the data/results obtained on testing of the accuracy of the well-type γ- counter. It is evident from Fig. 4.7 that the calculated %errors obtained were within the recommended ±5% error margin. (Biodex Medical Systems 2010; IAEA TRS 454, 2006). Based on the plot obtained (Fig. 4.7) for the accuracy test of the well-type γ- counter it can confidently be concluded that the instrument was in good working condition during the period of the study.

Overall, the various quality tests performed on the ^{99m}Tc eluates from ^{99}Mo/^{99m}Tc generator and the cold kits showed comformity/compliance with IAEA, EU pharmacopeia and US pharmacopeia globally accepted recommendations. Consequently, the formulated radiopharmceuticals would be suitable for diagnosis; and will have minimal/insignificant or no adverse effects when administered to/injected into patients.

Due to the compliance of the Capintec dose calibrator with the IAEA recommended geometry test; additionally, both the Capintec dose calibrator and the well-type γ-ray counter passed the IAEA recommended accuracy test (±5 tolerance level). The results obtained using both instruments are highly reliable; making them suitable for analysis.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

Overall the study investigated the radiopharmaceutical quality and suitability of Technetium-99m (^{99m}Tc) radionuclide labelled cold kits used at the Korle Bu Teaching Hospital (KBTH) for diagnosis of diseases. The conclusions drawn were based on data generated from the study.

The quality of $Na^{99m}TcO_4$ eluate produced by the ^{99}Mo/^{99m}Tc generator was high due to low MBT (0.0001-0.039 µCi ^{99}Mo/mCi ^{99m}Tc) for all elutions for the four generators assessed. The IAEA, and US Pharmacopeia recommended MoBT is ≤ 0.15 µCi ^{99}Mo/mCi ^{99m}Tc. Due to the low MoBT obtained the γ-camera image quality (resolution) will be high, and secondly patients would not receive excessive radiation.

Due to the poisonous nature of Al^{3+} to the human body, it must be ensured that Al^{3+} leakage from the generator into the $NaT^{99m}cO_4$ eluate is ≤ 10 ppm (IAEA, 2016). The study gave an Al^{3+} breakthrough of < 10 ppm for elutions carried out on the four generators. This indicated that the eluate was of good quality and safe for use in the formulation of the radiopharmaceuticals.

The measured eluate pH of 7 for the entire ^{99m}Tc eluates (all four generators) were highly suitable and safe for fusing into human blood (pH 7.35-7.45). The measured pH of 7 is also in within the recommended pH of 4-8 (European Pharmacopeia) for ^{99m}Tc eluates.

During diagnostic scanning, varied bio-distribution of radioactive chemical contaminants interference may obscure the region of interest during clinical diagnosis; and further interfere with scan interpretation. Abnormalous/irregular biodistribution may also be due to patient

medication. Consequently, determining RCP could help clarify abnormal scan through ruling out defective products (Cold kits). The estimated RCP for ^{99m}Tc-MDP and ^{99m}Tc-DTPA ranged 94.2-99.8% and 96.8-99.8% respectively; for ^{99m}Tc-MIBI, the estimated RCP ranges from 92.6 to 96.8%. The estimated RCPs obtained gave an indication that all three formulated radiopharmaceuticals were no unacceptable radiation to healthy organs and tissues which could have possibly led to misinterpretation of the images. The estimated RCPs for ^{99m}Tc-MIBI and, ^{99m}Tc-MDP and ^{99m}Tc-DTPA were highly comparable with respect to respective recommended RCP $\geq$ 94% (^{99m}Tc-MIBI); and $\geq$ 95% (^{99m}Tc-MDP and ^{99m}Tc-DTPA) [IAEA, US and European Pharmacopeiae].

In radiopharmaceuticals therapy, low RCP may mean patient going back to the Medical facility to undertake another scan with it's attendant cost implications as well as a repeat patient radiation exposure.

Furthermore, tests (wipe test for radioactive material contamination and the 1-metre mandatory exposure) performed to check whether the imported ^{99}Mo/^{99m}Tc generator packages meets the acceptance criteria set by U.S. NRC (United States Nuclear Regulatory Commission) revealed that:

(i) Wipe test conducted on the imported ^{99}Mo/^{99m}Tc generator packages showed no radiation leakage or broken package (that is there were no activity recorded (0.00 μCi) after γ-ray spectrometric measurement); hence the generators were deemed to meet the acceptable criteria. The U.S. NRC (United States Nuclear Regulatory Commission) recommended a 0.01 μCi limit (22,000 disintegrations per minute) per 100 cm^2 of the package surface area monitored.

(ii) The measured 1-meter radiation exposure measurements of 525, 415, 225 and 305 µR/h for all four generators were below the U.S. NRC recommended value of 719.9×10^6 µR/h (200 mrem).

Fulfilling the acceptance criteria (wipe test for radioactive material contamination and the 1-metre radiation exposure test) paved way for the elution of the generator, which allowed the recommended QA/QC assessment procedures on the eluate to be carried out.

both well-type γ-counter and Capintec dose calibrator gave reliable results during the study because accuracy test for both revealed that calculated %errors were within the IAEA recommended ±5% error margin. The geometry, the Capintec dose calibrator response of the ^{99m}Tc radioactive source established that 10 mL, 5 mL and 2 mL syringe volume had VCF's within the IAEA recommended range of $0.95<VCF<1.05$ with good regression coefficients [R^2 =0.8492 (10 mL syringe), R^2 = 0.962 (5 mL syringe) and R^2=1 (2 mL syringe)].

Overall, the various quality tests performed on the ^{99m}Tc eluates from ^{99}Mo/^{99m}Tc generator and the cold kits showed comformity/compliance with IAEA, EU pharmacopeia and US pharmacopeia globally accepted recommendations. Consequently, the formulated radiopharmceuticals would be suitable for diagnosis; and will have minimal/insignificant or no adverse effects when administered to/injected into patients.

Due to compliance of the Capintec dose calibrator with the IAEA recommended geometry test; additionally, both the Capintec dose calibrator and the well-type γ-ray counter passed the IAEA recommended accuracy test (±5 tolerance level). The results obtained using both instruments are highly reliable; making them suitable for analysis.

5.2 RECOMMENDATIONS

Based on the study results and conclusions drawn, the under-listed recommendations are proffered:

(a) There should be further studies to extend the quality-assessed formulated radiopharmaceuticals to diagnose patients in order to assess the link between the formulated RP and the quality image obtained.

(b) The baseline data obtained should serve as guide for studies involving quality assessment of radiopharmaceutical formulations, and the use of the formulations in the diagnosis of diseases.

(c) The Nuclear Medicine Department of KBTH should institute an appropriate protocol for regular assessment of the quality and suitability of radiopharmaceutical cold kits and $^{99}Mo/^{99m}Tc$ generators.

REFERENCES

AAPM [American Association of Physicists in Medicine] (2012). The Selection, use, Calibration, and Quality Assurance of Radionuclide Calibrators used in Nuclear Medicine. Report of AAPM Task Group 181.

Abdallah, Y., Gar-elnabi, M. E., Ahmed, S., & Abdelmajed, N. (2016). Evaluation of Radiochemical Purity of Receikaresved ^{99}Mo/^{99m}Tc Generator using Paper Chromatography Test. *Asian Journal of Medical Radiological Research*, *5*(1), 4-10.

Ahmed, H., Zimmer, M., Cutrera, P., McKay, B., Riehle, L., & Spies, S. (2015). Radichemical Purity and Stability of Generic ^{99m}Tc-DTPA. *Journal of Nuclear Medicine*, *56*(supplement 3), 2740–2740.

Amin M, R., Haque, A., Biswas, A., & Mozumder, T. H. (2012). Preparation and Labeling of Technitium-99M Kit in Pharmaceutical Grade Clean Room. *Journal of Chemical Engineering, IEB*, *27*(2), 31–35.

Andrade, W. G., & Lima, F. F. (2009). Evaluation of the Eluate Quality of ^{99}Mo/^{99m}Tc Generators in Recife, Brazil.

Arias J. A., Garcia S., Cuadrado M. L., Pardo C., Lapena G., & Jose L. (2010). ^{99m}Tc-MIBI muscle imaging and approach to assess functional anatomy of lower limb muscles. Available at www.semanticscholar.org . Accessed on June, 26 2020.

Atkins, H. L. (1975). EANM Tc-99m Pharmaceuticals. *Physics Reports*, *21*(6), 315–367. https://doi.org/10.1016/0370-1573(75)90013-7

Babbar, A. K., & Sharma, R. K. (2003). Formulation of lyophilized Cold Kit for instant preparation of ^{99m}Tc-glucarate and its scintigraphic evaluation in experimental models of infarction, 13–20.

Bailey, D. L., Humm, J. L., & Aswegen, A. Van. (2014). *Nuclear Medicine Physics: a Handbook for Teachers and Students. Vienna: International Energy Agency (IAEA).*

Biodex Medical Systems, Inc. (2015). The Geometry Test. Nuclear Medicine, Biodex Medical Systems. Available at http://www.biodex.com/nuclear-medicine. Accessed on March 13, 2020.

Biodex Medical Systems, (2010). Quality Assurance Testing of AtomLab Dose Calibrators (Manufacturer's Instructions). Available at http://www.biodex.com-quality assurance testing. Accessed on March 13, 2020.

Dash, A., & Chakravarty, R. (2019). Radionuclide generators: the prospect of availing PET radiotracers to meet current clinical needs and future research demands. *American Journal of Nuclear Medicine and Molecular Imaging*, *9*(1), 30–66.

Doroudi, A., Saraji, F., Erfani, M., Saadati, S. M., Kisast, A., Ahmadi, F., & Etesami, B. (2016). The stability of 99mTc-MIBI (Sestamibi) complex samples which prepared under ultrasound irradiation technique versus boiling water bath method. *Journal of Applied Pharmaceutical Science*, *6*(11), 126–134. https://doi.org/10.7324/JAPS.2016.601120

EANM. (2016). The Radiopharmacy A Technologist ' s Guide, 22–23. Available at http://www.eanm.org. Accessed on November 18, 2019.

EANM, (2019). Radiopharmacy Quality Control. European Association of Nuclear Medicine. Available at http://www.yumpu.com. Accessed on November 18, 2019.

Early, P. J. & Sodee, D. B. (1985). Principles and Practice of Nuclear Medicine St. Louis Mosby.

European Association of Faculties of Pharmacy (EAFP), (2014). Wider Horizons for Pharmacists. Radiopharmacy. Available at http://www.eafponline.eu. Accessed on June 29, 2020.

Hacker, M., Beyer, T., Baum, R. P., Kalemis, A., Lammertsma, A. A., Lewington, V., … Verzijlbergen, F. (2014). Nuclear medicine innovations help (drive) healthcare (benefits). *European Journal of Nuclear Medicine and Molecular Imaging*, *42*(2), 173–175. https://doi.org/10.1007/s00259-014-2957-6

IAEA (2013). IAEA Nuclear Energy Series Non-HEU Production Technologies for Molybdenum-99 and. *IAEA Nuclear Energy Series*, 1–75.

IAEA (2006). Internationl Atomic Energy Agency, Quality Assurance for Radioactivity Measurement in Nuclear Medicine. IAEA Technical Report Series. No. 454, IAEA, Vienna.

John, P., & Kathrine, G. (2014). Nuclear Laboratory 1: Radionuclide Generator. *Nuclear Laboratory*, *98*, 1–12.

Karesh, S. (1996). Quality Control of Radioisotope Dose Calibrators. Available at http://www.meddean.luc.edu. Accessed on : March 13, 2020.

Kramer-marek, G., & Capala, J. (2012). The role of nuclear medicine in modern therapy of cancer, *Tumor Bio* 33 (3): 629-640, (March). https://doi.org/10.1007/s13277-012-0373-8

Maioli, C., Lucignani, G., Strinchini, A., Tagliabue, L., & Del Sole, A. (2017). Quality control on radiochemical purity in technetium-99m radiopharmaceuticals labelling: Three years of experience on 2280 procedures. *Acta Biomedica*, *88*(1), 49–56. https://doi.org/10.23750/abm.v88i1.5285

Maria, S. (2011). Role of the Radionuclide Metrology in Nuclear Medicine. In *Role of the Radionuclide Metrology in Nuclear Medicine*. https://doi.org/10.5772/26305

Memon, S. A., Laghari, N. A., Qureshi, S. T., & Mehdi, F. (2014). Assessment of molybdenum breakthrough levels in molybdenum-99 / technetium-99m generators : One year experience at NIMRA Jamshoro Pakistan. *International Journal of Radiation Research*, *12*(4), 6–9.

Miranda, A. C. C., Durante, A. C. R., Fuscaldi, L. L., & de Barboza, M. F. (2019). Current approach in radiochemical quality control of the 99mTc-radiopharmaceuticals: A mini-review. *Brazilian Archives of Biology and Technology*, *62*, 1–7. https://doi.org/10.1590/1678-4324-2019180545

Molavipordanjani, S., & Hosseinimehr, S. J. (2018). Fundamental concepts of radiopharmaceuticals quality controls. *Pharmaceutical and Biomedical Research*, *4*(3), 1–8.

Mwape, E. (2018). Performance Evaluation and Cross-Calibration of Capintec Crc 15r and Comecer Dose Calibrators. Available at http://ugspace.ug.edu.gh/handle/123456789/25818. Accessed on June 18, 2020.

Neacsu, B., Cimpeanu, C., & Barna, C. (2013). Radionuclidic purity - An essential parameter in quality control of radiopharmaceuticals. *Romanian Reports in Physics*, *65*(1), 155–167.

NRC, U.S. (1975). Regulatory guide. Procedures for Picking Up and Receiving Packages of Radioactive Material. Available at http://www.nrc.gov. Accessed on March 16, 2020.

Paez, D., Becic, T., Bhonsle, U., Jalilian, A. R., Nuñez-Miller, R., & Osso, J. A. (2016). Current status of nuclear medicine practice in the middle east. *Seminars in Nuclear Medicine*, *46*(4), 265–272.

Peller, P. J., Ho, V. B., & Kransdorf, M. J. (1993). Extraosseous Tc-99m MDP uptake: a pathophysiologic approach. *Radiographics : A Review Publication of the Radiological Society of North America, Inc*, *13*(4), 715–734.

Phillips, D. R. (1996). Radionuclide Generator Systems for Nuclear Medicine. Correspondence Continuing Education Courses for Nuclear Pharmacists and Nuclear Medicine Professionals. The University of New Mexico College of Pharmacy Alabuquerque, New Mexico., *1*(039).

Professionals, N. M. (2012). Book Review: Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine, 3rd Edition. *Annals of Pharmacotherapy*, *46*(9), 1272–1272.

Radiation Answers, (2020). External Exposure. Available at https://www.radiationanswers.org. Accessed on January 12, 2020.

Schwalfenberg, G. K. (2012). The alkaline diet: Is there evidence that an alkaline pH diet benefits health? *Journal of Environmental and Public Health*, 727630. doi:10.1155/2012/727630

Shah, A. S., Hameedullah, Khan, A., Khan, S. U., & Shahid, S. (2009). Comparisons of 99 Mo Break Through levels in 99 Mo/ 99m Tc generator eluates from two manufacturers and its purification for Nuclear Medicine Imaging. *PJR*, *19*(2), 46–49.

Takacs, S., Szucs, Z., & Hermanne, A. (2003). Evaluation of proton induced reactions on 100Mo: New cross sections for production of ^{99m}Tc and ^{99}Mo. *Radioanalytical and Nuclear Chemistry*, *257*(1), 195–201. https://doi.org/10.1023/A

Taşdelen, B. (2011). ITLC-SG (Instant Thin- Layer Chromatograpy) St. Ph (Stational phase) Mob. Ph (Mobile phase) Loc. of Bou. Ag (Location of bound agent). *Journal of Radioanalytical and Nuclear Chemistry*, *290*(2), 283–287.

Uccelli, L., Boschi, A., Pasquali, M., Duatti, A., Di Domenico, G., Pupillo, G., … Gambaccini, M. (2013). Influence of the generator in-growth time on the final radiochemical purity and stability of 99mTc radiopharmaceuticals. *Science and Technology of Nuclear Installations*. https://doi.org/10.1155/2013/379283

Ullah, H., Ahmad, I., Rauf Khattak, M., Shah, S., Ahmad, S., Khan, K., & Zeeshan Ahmad, S. (2019). Evaluation of radiochemical purities of routinely used radiopharmaceuticals: Three years' experience of a single institute. *Iranian Journal of Nuclear Medicine*, *27*(1), 19–25.

United States Environmental Protection Agency (2002). EPA facts about Technetium-99. Available at http://www.epa.gov/radiation/radionuclide-basic-technetium-99. Accessed on June 29, 2020.

UNM, (2003). Quality Control of Compounded Radiopharmaceuticals. Available at http://www.pharmacyce.unm.edu. Accessed on July 25, 2019.

UTHealth, (2008). Radiation Safety Program. Environmental Health and Safety 713-500-5840. The University of Texas. Available at https://www.uth.edu. Accessed on July 16, 2020.

Vincenti, L. P. (2016). Establishing Radiopharmaceutical Standards at a Nuclear Medicine Unit in Malta. *International Journal of Radiology and Imaging Technology*, *2*(1), 2–5. https://doi.org/10.23937/2572-3235.1510012

WHO, (2014). Radiopharmaceuticals: General monograh. WHO Drug Information Vol. 28, No 2. pp162-164.

Yalçın, H., Özen, A., Günay, E. C., Aliç Özaslan, İ., & Özer, C. (2011). Can ^{99m}Tc- DTPA be Used in Adult Patients in Evaluation of Relative Renal Function Measurement as the Reference ^{99m}Tc-DMSA Method? *Molecular Imaging and Radionuclide Therapy*, *20*(1), 14–18. https://doi.org/10.4274/mirt.20.03

Zulkifli, H., Bohari Y., Zakaria I., & Wan Hamirul B.W.K. (2010). Minimizing Molybdenum- 99 Contamibation in Technetium-99m Pertechnetate from the Elution of ^{99}Mo/^{99m}Tc Generator. Available at https://inis.iaea.org. Accessed on June 30, 2020.

APPENDICES

APPENDIX A: EVALUATION OF ^{99}Mo BREAKTHROUGH

Elution No.	Generator Lot No.	Date	Elution Time (AM)	Reading time (AM)	^{99m}Tc (mCi)	^{99}Mo (µCi)	Background (BG)[µCi]	^{99}Mo-BG	^{99}Mo/^{99m}Tc	Standard (µCi Mo-99/mCi Tc-99m)
1	**A1**	08/07/2019	4:40	4:50	689.77	13.76	9.62	4.14	0.006	0.15
2		09/07/2019	4:40	4:45	503.75	11.81	9.29	2.52	0.005	0.15
3		10/07/2019	4:45	4:48	388.49	10.84	9.29	1.55	0.004	0.15
4		11/07/2019	4:04	4:08	306.83	11.21	9.68	1.53	0.005	0.15
5		12/07/2019	4:16	4:20	239.28	10.64	9.68	0.96	0.004	0.15
6		15/07/2019	4:45	4:50	121.30	9.90	9.89	0.01	0.0001	0.15
7		16/07/2019	8:00	8:05	81.66	12.48	9.62	2.86	0.035	0.15
8		02/09/2019	8:05	8:10	62.63	9.63	9.62	0.01	0.0001	0.15
9		03/09/2019	7:59	8:04	49.55	9.82	9.62	0.20	0.004	0.15
10	**A2**	04/09/2019	5:00	5:03	685.80	12.42	9.68	2.74	0.004	0.15
11		05/09/2019	5:12	5:15	499.49	12.12	9.62	2.50	0.005	0.15
12		09/09/2019	5:20	5:22	388.49	24.44	9.29	15.15	0.039	0.15
13		11/09/2019	5:30	5:33	304.80	11.70	9.87	1.83	0.006	0.15
14		28/10/2019	5:25	5:27	236.20	11.04	9.62	1.42	0.006	0.15
15		29/10/2019	5:31	5:34	120.91	9.77	9.29	0.48	0.004	0.15
16		30/10/2019	8:27	8:29	86.02	11.73	9.67	2.06	0.024	0.15
17		31/10/2019	8:15	8:17	65.00	10.28	9.69	0.59	0.009	0.15
18		01/11/2019	8:15	8:17	49.55	9.98	9.29	0.69	0.014	0.15
19	**A3**	04/11/2019	5:10	5:14	677.87	10.65	9.29	1.36	0.002	0.15

20		05/11/2019	5:12	5:15	507.42	10.18	9.67	0.51	0.001	0.15
21		06/11/2019	4:54	4:57	392.45	9.65	9.26	0.39	0.001	0.15
22		07/11/2019	4:50	4:53	313.17	10.32	9.69	0.63	0.002	0.15
23		08/11/2019	4:40	4:43	246.18	9.54	9.29	0.25	0.001	0.15
24		11/11/2019	5:40	5:43	124.08	9.54	9.29	0.25	0.002	0.15
25		12/11/2019	5:30	5:34	68.00	9.83	9.69	0.14	0.002	0.15
26		13/11/2019	8:37	8:41	64.22	10.25	9.86	0.39	0.006	0.15
27		14/11/2019	8:10	8:14	51.14	9.96	9.86	0.10	0.002	0.15
28		15/11/2019	8:11	8:14	37.90	9.81	9.62	0.19	0.005	0.15
29	**A4**	20/01/2020	4:00	4:02	436.00	12.83	9.78	3.05	0.007	0.15
30		21/01/2020	4:11	4:15	527.00	11.47	9.89	1.58	0.003	0.15
31		22/01/2020	4:47	4:53	408.31	11.66	10.03	1.63	0.004	0.15
32		23/01/2020	4:54	4:55	319.12	10.56	9.92	0.64	0.002	0.15
33		24/01/2020	4:51	4:55	248.16	12.02	9.79	2.23	0.009	0.15
34		27/01/2020	5:06	5:10	124.08	10.69	9.82	0.87	0.007	0.15
35		28/01/2020	7:57	8:00	89.19	10.40	9.78	0.62	0.007	0.15
36		29/01/2020	8:08	8:10	63.03	10.02	9.68	0.06	0.001	0.15
37		30/01/2020	7:58	8:00	51.90	10.30	9.88	0.42	0.008	0.15
38		31/01/2020	8:08	8:10	40.40	10.00	9.56	0.44	0.011	0.15

APPENDIX B: RADIOCHEMICAL PURITY FOR MDP

			Acetone System				Saline System			
No. of Elution/ formulations	Date	BKG counts (cpm)	Origin counts (cpm)	Solvent fronts counts (cpm)	% of $NaTcO_4$	% of HRTC	Origin Counts (cpm)	Solvent front Counts (cpm)	% Labelling yield	Standard ≥ (%)
1	08/07/2019	528	34160	658	0.38	3.3	3343	81748	96.3	95
2	09/07/2019	242	80411	482	0.3	4.1	3438	74131	95.6	95
3	10/07/2019	1157	75471	2385	1.6	2.6	2917	66766	95.8	95
4	11/07/2019	167	84897	333	0.19	5.6	2313	36628	94.2	95
5	12/07/2019	118	26820	614	1.8	3.5	2825	75826	94.7	95
6	03/09/2019	186	57741	1461	2.2	3.5	2414	61403	94.3	95
7	04/09/2019	137	91739	1692	1.7	3.6	2498	62764	94.7	95
8	05/09/2019	204	32929	548	1	3.3	1642	42265	95.7	95
9	09/09/2019	149	98768	911	0.7	3.4	1942	51706	95.9	95
10	11/09/2019	133	6479	201	1.1	0.4	140	1777	98.5	95
11	28/10/2019	366	73730	970	0.8	0.8	964	75493	98.4	95
12	29/10/2019	175	85508	1313	1.3	2.9	3002	93643	95.8	95
13	30/10/2019	152	55170	1258	1.9	2.4	1960	75002	95.7	95
14	01/11/2019	129	76643	935	1	2.7	2196	74661	96.3	95
15	04/11/2019	175	55356	238	0.1	5.5	2456	41443	94.4	95
16	05/11/2019	172	48051	229	0.1	5.6	5289	86478	94.3	95
17	06/11/2019	175	59551	196	0.03	0.2	355	98022	99.8	95
18	07/11/2019	184	63782	462	0.4	0.05	208	45814	99.6	95
19	20/01/2020	175	75886	1289	1.5	0.7	380	29270	97.8	95
20	21/01/2020	118	85036	359	0.3	1.1	725	56928	98.6	95
21	22/01/2020	121	43670	451	0.7	2.7	2041	70003	96.6	95

22	23/01/2020	134	44080	651	1.2	2.7	1261	39931	96.1	95
23	24/01/2020	355	62308	1423	1.7	3.2	3008	78200	95.1	95
24	25/01/2020	221	76430	373	0.2	2.3	2262	85825	97.5	95
25	27/01/2020	190	85668	577	0.5	4.4	3798	78110	95.1	95

APPENDIX C: RADIOCHEMICAL PURITY FOR DTPA

		Acetone System				Saline System			
Date	BKG Counts :pm)	Origin Count (cpm)	Solvent fronts Count (cmp)	%$NaTcO_4$	%HRTc	Origin Count (cpm)	Solvent Count (cpm)	% Labelling yield	Standard ≥ (%)
17/07/2019	169	35429	262	0.3	0.2	301	55364	99.5	95
18/07/2019	1146	16117	1343	1.3	0.3	1204	19740	98.4	95
10/09/2019	395	59012	980	1	1.3	773	29697	97.7	95
12/09/2019	191	42011	323	0.3	0.3	355	54980	99.4	95
06/11/2019	175	59551	196	0.03	0.2	355	98022	99.8	95
07/11/2019	184	63782	462	0.4	0.05	208	45814	99.6	95
29/01/2020	113	38487	561	1.2	0.1	137	39390	98.7	95
30/01/2020	578	26884	1441	3.1	0.1	590	14095	96.8	95
31/01/2020	444	14519	571	0.9	0.4	507	16774	98.7	95

APPENDIX D: RADIOCHEMICAL PURITY FOR MIBI

		Acetone System			Saline System				
Date	**BGK (cpm)**	**Origin Count (cpm)**	**Solvent front Count (cpm)**	**%$NaTcO_4$**	**%HRTc**	**Origin Count (cpm)**	**Solvent front Count (cpm)**	**% Labelling yield**	**Standard ≥ (%)**
06/09/2019	164	46141	1138	2.1	3.1	3145	92713	94.8	94
08/11/2019	174	84243	1016	0.99	2.2	658	21288	96.8	94
28/01/2020	162	13123	1097	6.7	0.7	415	11983	92.6	94

APPENDIX E: CHEMICAL PURITY (Al^{3+} BREAKTHROUGH)

Generator lot no.	Date	Elution no.	Colour Intensity	Colour Intensity	Standard Al^{3+}
A1	08/07/2019	1	Less intense than standard	< 10	10
	09/07/2019	2	Less intense than standard	<10	10
	10/07/2019	3	Less intense than standard	<10	10
	11/07/2019	4	Less intense than standard	<10	10
	12/07/2019	5	Less intense than standard	<10	10
	15/07/2019	6	Less intense than standard	<10	10
	16/07/2019	7	Less intense than standard	<10	10
	02/09/2019	8	Less intense than standard	<10	10
	03/09/2019	9	Less intense than standard	<10	10
A2	04/09/2019	10	Less intense than standard	<10	10
	05/09/2019	11	Less intense than standard	<10	10
	09/09/2019	12	Less intense than standard	<10	10
	11/09/2019	13	Less intense than standard	<10	10
	28/10/2019	14	Less intense than standard	<10	10
	29/10/2019	15	Less intense than standard	<10	10
	30/10/2019	16	Less intense than standard	<10	10
	31/10/2019	17	Less intense than standard	<10	10
	01/11/2019	18	Less intense than standard	<10	10
A3	04/11/2019	19	Less intense than standard	<10	10
	05/11/2019	20	Less intense than standard	<10	10
	06/11/2019	21	Less intense than standard	<10	10
	07/11/2019	22	Less intense than standard	<10	10

	08/11/2019	23	Less intense than standard	<10	10
	11/11/2019	24	Less intense than standard	<10	10
	12/11/2019	25	Less intense than standard	<10	10
	13/11/2019	26	Less intense than standard	<10	10
	14/11/2019	27	Less intense than standard	<10	10
	15/11/2019	28	Less intense than standard	<10	10
A4	20/01/2020	29	Less intense than standard	<10	10
	21/01/2020	30	Less intense than standard	<10	10
	22/01/2020	31	Less intense than standard	<10	10
	23/01/2020	32	Less intense than standard	<10	10
	24/01/2020	33	Less intense than standard	<10	10
	27/01/2020	34	Less intense than standard	<10	10
	28/01/2020	35	Less intense than standard	<10	10
	29/01/2020	36	Less intense than standard	<10	10
	30/01/2020	37	Less intense than standard	<10	10
	31/01/2020	38	Less intense than standard	<10	10

APPENDIX F: pH ASSESSMENT

Generator lot. No	Date	Elution no.	pH Value	pH Standard
A1	08/07/2019	1	7	4-8
	09/07/2019	2	7	4-8
	10/07/2019	3	7	4-8
	11/07/2019	4	7	4-8
	12/07/2019	5	7	4-8
	15/07/2019	6	7	4-8
	16/07/2019	7	7	4-8
	02/09/2019	8	7	4-8
	03/09/2019	9	7	4-8
A2	04/09/2019	10	7	4-8
	05/09/2019	11	7	4-8
	09/09/2019	12	7	4-8
	11/09/2019	13	7	4-8
	28/10/2019	14	7	4-8
	29/10/2019	15	7	4-8
	30/10/2019	16	7	4-8
	31/10/2019	17	7	4-8
	01/11/2019	18	7	4-8
A3	04/11/2019	19	7	4-8

	05/11/2019	20	7	4-8
	06/11/2019	21	7	4-8
	07/11/2019	22	7	4-8
	08/11/2019	23	7	4-8
	11/11/2019	24	7	4-8
	12/11/2019	25	7	4-8
	13/11/2019	26	7	4-8
	14/11/2019	27	7	4-8
	15/11/2019	28	7	4-8
A4	20/01/2020	29	7	4-8
	21/01/2020	30	7	4-8
	22/01/2020	31	7	4-8
	23/01/2020	32	7	4-8
	24/01/2020	33	7	4-8
	27/01/2020	34	7	4-8
	28/01/2020	35	7	4-8
	29/01/2020	36	7	4-8
	30/01/2020	37	7	4-8
	31/01/2020	38	7	4-8

APPENDIX G: 10 mL SYRINGE RANGE GEOMETRY DEPENDENCE ON CAPINTEC

Volume (mL)	Time	Measured Activity (mCi)	Time elapsed/ hours	Expected Activity	VCF
1	10:01	19.90	0.0000	19.90	0.997
1.5	10:02	19.90	0.0167	19.94	0.995
2	10:03	19.81	0.0333	19.89	0.997
2.5	10:04	19.77	0.0500	19.88	0.997
3	10:04	19.80	0.0500	19.91	0.996
3.5	10:05	19.70	0.0667	19.85	0.999
4	10:06	19.70	0.0833	19.89	0.997
4.5	10:07	19.60	0.1000	19.83	1.000
5	10:07	19.60	0.1000	19.83	1.000
5.5	10:08	19.60	0.1167	19.87	0.998
6	10:08	19.50	0.1167	19.76	1.004
6.5	10:09	19.50	0.1333	19.80	1.002
7	10:09	19.40	0.1333	19.70	1.007
7.5	10:10	19.39	0.1500	19.73	1.005
8	10:10	19.39	0.1500	19.73	1.005
		Average Expected Activity		19.83	
		19.64			

APPENDIX H: 5 mL SYRINGE RANGE GEOMETRY DEPENDENCE ON CAPINTEC

Volume (mL)	Time	Measured Activity (mCi)	Time elapsed/ hours	Expected Activity	VCF
1	10:26	5.38	0.0000	5.38	0.992
1.5	10:26	5.36	0.0000	5.36	0.996
2	10:27	5.36	0.0167	5.37	0.994
2.5	10:27	5.35	0.0167	5.36	0.996
3	10:28	5.32	0.0333	5.34	1.000
3.5	10:29	5.31	0.0500	5.34	1.000
4	10:29	5.29	0.0500	5.32	1.003
4.5	10:30	5.25	0.0667	5.29	1.009
5	10:31	5.23	0.0833	5.28	1.011
		Average Expected Activity		5.34	
		5.32			

APPENDIX I: 2 mL SYRINGE RANGE GEOMETRY DEPENDENCE ON CAPINTEC

Volume (mL)	Time	Measured Activity (mCi)	Time elapsed/ hours	Expected Activity	VCF
1	10:33	2.51	0.0000	2.51	1.001
1.5	10:34	2.51	0.0167	2.51	0.999
2	10:35	2.50	0.0333	2.51	1.001
		Average Expected Activity		2.51	
		2.51			

APPENDIX J: ACCURACY TEST FOR DOSE CALIBRATOR

Activity: Cs 137 @ 9.21MBq ; 13/ 10/2005) $t_{1/2}$= 30.17yrs

Date	Measurement	Run 1 Activity (µCi)	Run 2 Activity (µCi)	Run3 Activity (µCi)	Average Activity (µCi)	t (year)	Calculated Activity (µCi)	% error
03/06/2019	1	182	186	182	183.3	13.6408	181.96	0.747552
04/06/2019	2	182	182	180	181.3	13.6435	181.95	-0.34092
05/06/2019	3	186	186	184	185.3	13.6463	181.94	1.831025
06/06/2019	4	186	182	182	183.3	13.649	181.93	0.766245
07/06/2019	5	184	186	184	184.7	13.6518	181.92	1.48907
10/06/2019	6	186	184	182	184.0	13.66	181.88	1.150767
11/06/2019	7	185	185	185	185.0	13.6628	181.87	1.69141
12/06/2019	8	180	182	180	180.7	13.6655	181.86	-0.6603
13/06/2019	9	177	182	180	179.7	13.6682	181.85	-1.21429
14/06/2019	10	180	180	184	181.3	13.6709	181.84	-0.27779
17/06/2019	11	180	180	180	180.0	13.6791	181.80	-1.00156
18/06/2019	12	184	184	186	184.7	13.6819	181.79	1.557157
19/06/2019	13	186	182	182	183.3	13.6846	181.78	0.847359
20/06/2019	14	184	188	184	185.3	13.6873	181.77	1.923434
21/06/2019	15	186	184	184	184.7	13.6801	181.80	1.553087
				mean	**183.1**		**181.9**	
				Stand. Dev	**1.990719207**			

APPENDIX K: ACCURACY TEST FOR WELL-TYPE γ- COUNTER

Accuracy for Well-type Counter: I-125; @ 2018-04-07

Initial counts 170434782.6 c/s Activity =0.392mCi

Initial time 07/04/2018 Half life 60 days

Date	Run1 count (c/s)	Run 2 count (c/s)	Run 3 count (c/s)	Run 4 count (c/s)	Run 5 count (c/s)	BKG (c/s)	Average count (Measured)	Time (Days) elapse	Counts (Theoretical)	% Error
10/02/2020	71030	70400	70287	70450	70437	74	70446.8	673	71733.5	-1.793735635
11/02/2020	68838	68506	68670	68852	68891	80	68671.4	674	70909.8	-3.156623332
13/02/2020	67622	67501	67537	67306	67628	63	67455.8	676	69290.5	-2.647855652
14/02/2020	66467	66307	65844	66528	65808	61	66129.8	677	68494.8	-3.452832865
18/02/2020	64540	64491	64528	64121	64349	63	64342.8	681	65402.3	-1.620029661
20/02/2020	63332	63455	63119	63510	63385	63	63297.2	683	63908.9	-0.957080691
24/02/2020	60257	60241	59907	60262	60751	57	60226.6	687	61023.4	-1.305787702
25/02/2020	59899	60345	60587	60651	60288	70	60284	688	60322.7	-0.064106166
26/02/2020	58340	58828	58577	58989	58718	81	58609.4	689	59630.0	-1.711475234
27/02/2020	57703	58195	57939	58253	57825	58	57925	690	58945.2	-1.730740153
28/02/2020	58701	57743	58598	58013	58057	66	58156.4	691	58268.3	-0.192021671
03/03/2020	55440	56194	55824	55956	55641	63	55748	694	56283.9	-0.952084751
04/03/2020	54945	54272	54492	54692	54562	71	54562	695	55637.5	-1.933103812
05/03/2020	53061	53586	53264	53378	53385	62	53272.8	696	54998.6	-3.137923765
09/03/2020	52482	52443	52248	52255	51959	73	52204.4	700	52515.5	-0.592359916