Chapter One
Introduction

1.1. Introduction:

Nuclear medicine procedures use many different radioactive isotopes for radiation diagnostics and for therapy. The amount of radioactivity has to be determined exactly before it is applied to a patient. The isotope calibrators have to measure the radioactivity of gamma and beta emitting isotopes with different energies precisely for high quality imaging and for applying the right amount of radiation to treat disease. They must be able to measure low isotope activities for patient application and high activities during isotope production. The isotope calibrators should allow easy and fast operation in routine work as well as quick and effective cleaning in case of contamination. Continuous quality control of isotope calibrators is mandatory according to international standards and guidelines such as international electrotechnical committee, IEC 61303 “Medical electrical equipment – Radionuclide calibrators – Particular methods for describing performance”. Those methods include background measurement, accuracy, reproducibility and linearity checks as well as contamination tests. All these parameters influence the quality of activity measurements and consequently the radiation load for the patients. The high quality isotope calibrators assist responsible staffs in nuclear medicine laboratories to perform precise activity measurements and to fulfill the ICRP 60 requirement to keep the radiation load as low as achievable for patients. The radionuclide activity dose calibrators are routinely used in nuclear medicine practices to quantify the radioactivity dose of the radiopharmaceuticals to be administered to the patients. According to the current standards and regulations for NM worldwide practices, including those adopted by the international atomic energy agency (IAEA), and national regulations such as those promulgated by the United States Nuclear Regulatory

Commission (U.S.NRC), the radioactivity of any radiopharmaceutical that contains a photon-emitting radionuclide must be measured by a dose calibrator prior to administration to patients or for human research purposes. Obviously, the administration of the prescribed amount of activity to the patient requires proper operation of the dose calibrator, which shall be verified by implementing the required quality control tests on the instrument. Several quality control tests are necessary to ensure the proper operation of the dose calibrators, among which the tests for the linearity of the response, accuracy, precision, and physical functioning of the instrument are of more importance. The linearity of the response test confirms the ability of the instrument to measure a range of low to high activity doses with a required degree of accuracy. It is important that the linearity of the response of the dose calibrator to be ascertained over the range of its use between the maximum activity administered and 1 MBq. It has been recommended that the test to be carried out upon acceptance, repair, and then annually. This test is mostly carried out by measuring a high activity, short-lived radionuclide for a given period of time by the instrument. Typically, Tc-99m is used for this purpose. Accuracy is a quality control measure performed upon acceptance, repair, and then annually, to ensure that the activity values determined by the dose calibrator are traceable to national or international standards of radioactivity within the indicated uncertainties. Precision test is to confirm that the random uncertainty of a single measurement is primarily determined by the random nature of radioactive decay. A larger than expected value indicates the possible presence of another random source of uncertainty that had not been anticipated. The recommended values for the above QC measures are within +/- 5 to 10 %, depending on the radionuclide of interest and measurement conditions (Zeinali*et al*, 2008).

1.2. Problem of the Study:

There are many problems due to absence of quality control of dose calibrator which are used for dose measurements in Elneelain Medical Diagnostic Center; therefore many patients may take incorrect dose due to uncertainties in dose. Routine quality control use to check the performance of dose calibrator according to international standards and guidelines using unique protocols which must be in the different hospitals.

1.3. Objectives:

The main objective of this study is to assess the performance of the dose calibrator that is being used in Al Nelein Diagnostic Center Nuclear Medicine Department

1.3.1. Specific Objectives:

- To insure the accuracy of calibrators
- To measure the deviation percent of calibrators from standard level

1.4. *Area of study*

This study was conducted in Al Nelein Medical Diagnostic Center – Khartoum

1.5. Study Duration

The study period will be form July 2014 to February 2015

1.6. Ethic issues

The confidentiality of the equipment and staff members of department was maintained throughout the study . Permission of nuclear medicine department was taken .

1.7. Thesis out line

The research skeleton consists of five chapters. Chapter one will deal with introduction, problem of the study, objectives and methodology. Chapter two consists the literature review related to the current study. Chapter three shows the methodology upon which the thesis carried out, chapter four will shows the results

and discussion and chapter five shows the conclusion, recommendation, some limitations faced the researcher and references.

Chapter Two

Literature Review

2.1. Theoretical Background

2.1. 1. Radionuclide Generators

A radionuclide generator consists of a parent daughter radionuclide pair contained in an apparatus that permits separation and extraction of the daughter from the parent. The daughter product activity is replenished continuously by decay of the parent and may be extracted repeatedly. The most important generator in nuclear medicine is the $^{99}Mo^{99m}Tc$ system, because of the widespread use of ^{99m}Tc for radionuclide imaging. Technetium-99m emits γ-rays (140 keV) that are very favorable for use with a gamma camera. It has a reasonable half-life (6 hours), delivers a relatively low radiation dose per emitted **γ** ray, and can be used to label a wide variety of imaging agents. More than 1850 TBq (50,000 Ci) of ^{99}Mo per week are required to meet the worldwide requirements for nuclear medicine procedures. The parent ^{99}Mo activity in the form of molybdate ion, (Mo) is bound to an alumina ($^{3+}A1$) column. The daughter ^{99m}Tc activity, produced in the form of $^{99m}TcO_4$ (pertechnetate), is not as strongly bound to alumina and is eluted from the column with 5 to 25 mL of normal saline. Typically, 75% to 85% of the available ^{99m}Tc activity is extracted in a single elution. Technetium-99m activity builds up again after an elution, and maximum activity is available about 24 hours later; however, usable quantities of ^{99m}Tc are available 3 to 6 hours later. Commercially prepared generators are sterilized, well shielded, and largely automated in operation. Typically they are used for about 1 week and then discarded because of natural decay of the ^{99}Mo parent (Alberto et al.1998).

Table 2-1. Characteristics of most common used Generators

Generator (Parent–Daughter)	Clinical Uses of Daughter Nuclide	Half-Life of Parent ($T_{1/2p}$)	Half-Life of Daughter ($T_{1/2d}$)	$T_{1/2p}/T_{1/2d}$
^{99}Mo–^{99m}Tc (molybdenum-99–technetium-99m)	Used in most radiopharmaceuticals for nuclear medicine studies	67 h	6 h	11.2
^{82}Sr–^{82}Rb (strontium-82–rubidium-82)	Cardiac perfusion imaging	600 h	0.021 h (75 s)	28 571
^{81}Rb–^{81m}Kr (rubidium-81–krypton-81m)	Lung ventilation scans	4.7 h	0.004 h (13 s)	1175

Molybdenum-99 activity is obtained by separation from reactor fission fragments or by (n, γ) activation of stable molybdenum (23.8% ^{98}Mo). The former, sometimes called “fission moly,” has significantly higher specific activity and is currently the production method of choice. The volume of alumina required in a ^{99}Mo-^{99m}Tc generator is determined essentially by the amount of stable ^{99}Mo carrier. That is present. Therefore, “fission moly” generators require much smaller volumes of alumina per unit of ^{99}Mo activity. They can be eluted with very small volumes of normal saline (5 mL), which is useful in some dynamic imaging studies requiring bolus injections of very small volumes of high activity (740 MBq, 20 mCi) of ^{99m}Tc. One problem with ^{99}Tc generators ^{99}Mo “breakthrough,” that is, partial elution of the ^{99}Mo parent along with ^{99m}TC from the generator. From the standpoint of patient radiation safety, the amount of ^{99}Mo should be kept to a minimum. Maximum amounts, according to Nuclear Regulatory Commission regulations, are 0.15 Bq^{99}Mo per kBq ^{99m}Tc (0.15 mCi ^{99}Mo per mCi ^{99m}Tc) (Alberto et al.1998)

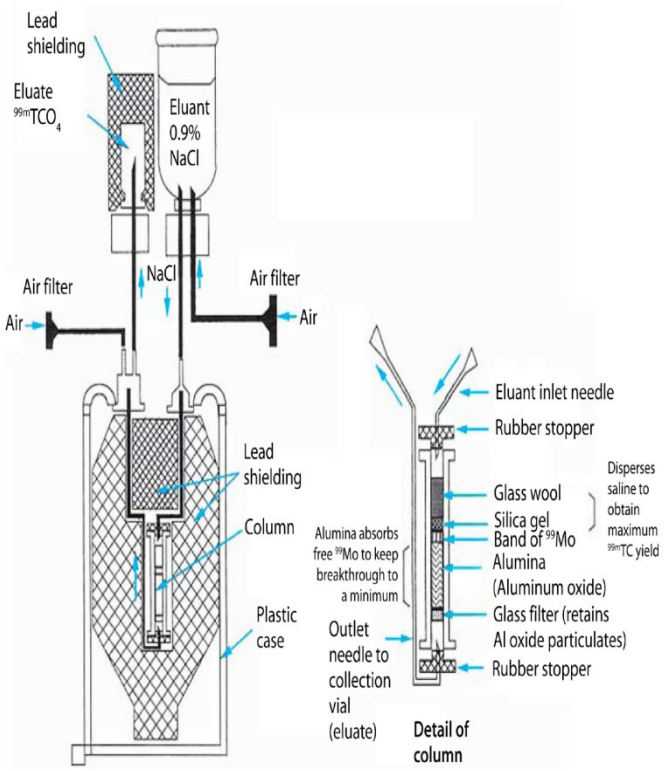

Figure 2-1. Aluminum targets for EBCO Cyclotron. An ^{18}O water target (top) for the production of ^{18}F as Fluoride and ^{14}N gas target (bottom) for the production of ^{11}C as carbon dioxide

It is possible to assay ^{99}Mo activity in the presence of much larger ^{99m}Tc activity using NaI (Tl) counting systems by, surrounding the sample with about 3 mm of lead, which is an efficient absorber of the 140 keV rays of ^{99m}Tc but relatively transparent to the 740-780 keV γ rays of ^{99}Mo. Thus small quantities of ^{99}Mo can be detected in the presence of much larger amounts of ^{99m}Tc. Some dose calibrators are provided with a lead-lined container called a “moly shield” specifically for this purpose. Other radioactive contaminants also are occasionally found in $^{99}Mo^{99m}Tc$ generator eluate. A second major concern is breakthrough of aluminum ion, which interferes with labeling processes and also can cause clumping of red blood cells and possible micro emboli. Maximum permissible levels are 10 μg/mL of ^{99m}Tc solution. Chemical test

kits are available from generator manufacturers to test for the presence of aluminum ion (Zanzonico, 1995).

The type and energy of emissions from the radionuclide determine the availability of useful photons or γ-rays for counting or imaging. For external detection of a radio-nuclide inside the body, photons or γ rays in the 50-600 keV energy range are suitable. Very low energy photons and γ-rays (< 50 keV), or particulate radiation, have a high likelihood of interacting in the body and will not in general escape for external detection. The presence of such low energy or particulate emissions increases the radiation dose to the patient. An example of this would be 1311, which decays by (n, γ) emit-ting a 3, followed by y rays at 364 (82%), 637 (8.5%), 284 (5.8%), or 80 keV (2.6%). The ‘y rays are in an appropriate range for external detection; however, the 3 contributes additional dose as compared with radionuclides that decay by (EC, γ). The physical half-life of the radionuclide be within the range of seconds to days (preferably minutes to hours) for clinical applications. If the half-life is too short, there is insufficient time for preparation of the radiopharmaceutical and injection into the patient. If the half-life is longer, a much wider range of compounds could be labeled. Other radionuclides have half-lives that are too long for practical purposes. Most of the radiation is emitted of the examination time, which can result in a high radiation dose to the patient in relation to the number of decays detected during the study. Long-lived radionuclides also can cause problems in terms of storage and disposal. An example of a very long-lived radionuclide that is not used in human studies due to half-life considerations is ^{22}Na ($T_{1/2}$ = 2.6 yr). The specific activity of the radionuclide largely determines the mass of a compound that is introduced for a given radiation dose. Since nuclear the medicine relies on the use of sub-pharmacologic tracer doses that do not perturb the biologic system under study,

the mass should be low and the specific activity high. At low specific active should only a small fraction of the molecules in the sample are radioactive and therefore signal-producing, whereas the rest of the molecules add to the mass of the compound being introduced, without producing signal. Theoretically, the attainable specific activity of a radionuclide is inversely proportional to its half-life, although in practice, many other factors (e.g., the abundance of stable isotopes in air and glassware) can determine the actual specific activity of the injected labeled compound. The radionuclides purity is defined as the fraction of the total radioactivity in a sample that is in the form of the desired radionuclide. Radionuclides contaminants arise in the production of radionuclides and can be significant in some situations. The effect of these contaminants is to increase the radiation dose to the patient. They may also increase detector dead time, and if the enter of the emissions falls within the acceptance window of the detector system; contaminants may result in incorrect counting rate or pixel intensities in images. Of concern in radionuclide generator systems is contamination with the long-lived parent radionuclide. In the case of the $^{99}Mo^{99m}Tc$ generator, the radionuclides purity of the ^{99m}Tc must be higher than 99.985%. The chemical properties of the radionuclide also are an important factor. Radionuclides of elements that can easily produce useful precursors (chemical forms that are readily reacted to form a wide range of labeled products) and that can undergo a wide range of chemical syntheses are preferred (e.g., ^{123}I ^{18}F, and ^{11}C). Radionuclides of elements that are easily incorporated into bimolecular, without significantly changing their biochemical properties, also are attractive. Examples are ^{11}C, ^{13}N, ^{15}O, elements that are found naturally in many bimolecular. Metals such as ^{99m}Tc and ^{67}Ga also are widely used as labels in nuclear medicine, because of the desirable imaging properties of the radionuclide. To incorporate such elements into biologically relevant

molecules is challenging but can be achieved by chelating and other techniques that seek to “hide” or shield the metal atom from the biologically active sites of the molecule (Zanzonico,1995).

Finally, the cost and/or complexity of preparing a radionuclide must be considered. Sufficient quantities of radionuclide for radiopharmaceutical labeling and subsequent patient injection must be produced at a cost (both materials and labor) consistent with today’s health care market (Anderson et al. (2001).

As noted earlier, radionuclides almost always are attached as labels to compounds of biomedical interest for nuclear medicine applications. Because of the practical considerations discussed in the preceding section, the number of different radionuclides routinely used in nuclear medicine is relatively small; perhaps fewer than a dozen even in large hospitals. On the other hand, the number of labeled compounds is much larger and continuously growing, owing to very active research in radiochemistry and radiopharmaceutical preparation (Anderson et al. (2001).

2.1.2. Technetium 99m-Labeled Radiopharmaceuticals

The $^{99}Mo^{99m}Tc$ generator produces technetium in the form of $^{99m}TcO_4$. A number of “cold kits” are available that allow different ^{99m}Tc complexes to be produced by simply mixing the $^{99m}TcO_4$ and the contents of the cold kit together. The cold kit generally contains a reducing agent, usually stannous chloride, which reduces the ^{99m}Tc to lower oxidation states, allowing it to bind to a complexion agent (also known as the legend) to form the radiopharmaceutical. Using these kits, a range of ^{99m}Tc labe1ed radiopharmaceuticals that are targeted to different organ systems and different biologic processes can be prepared quickly and conveniently in the hospital setting.

Figure 2-2 lists a few examples of ^{99m}Tc radiopharmaceuticals that are prepared from kits (Antoni and Langstrom, 2005).

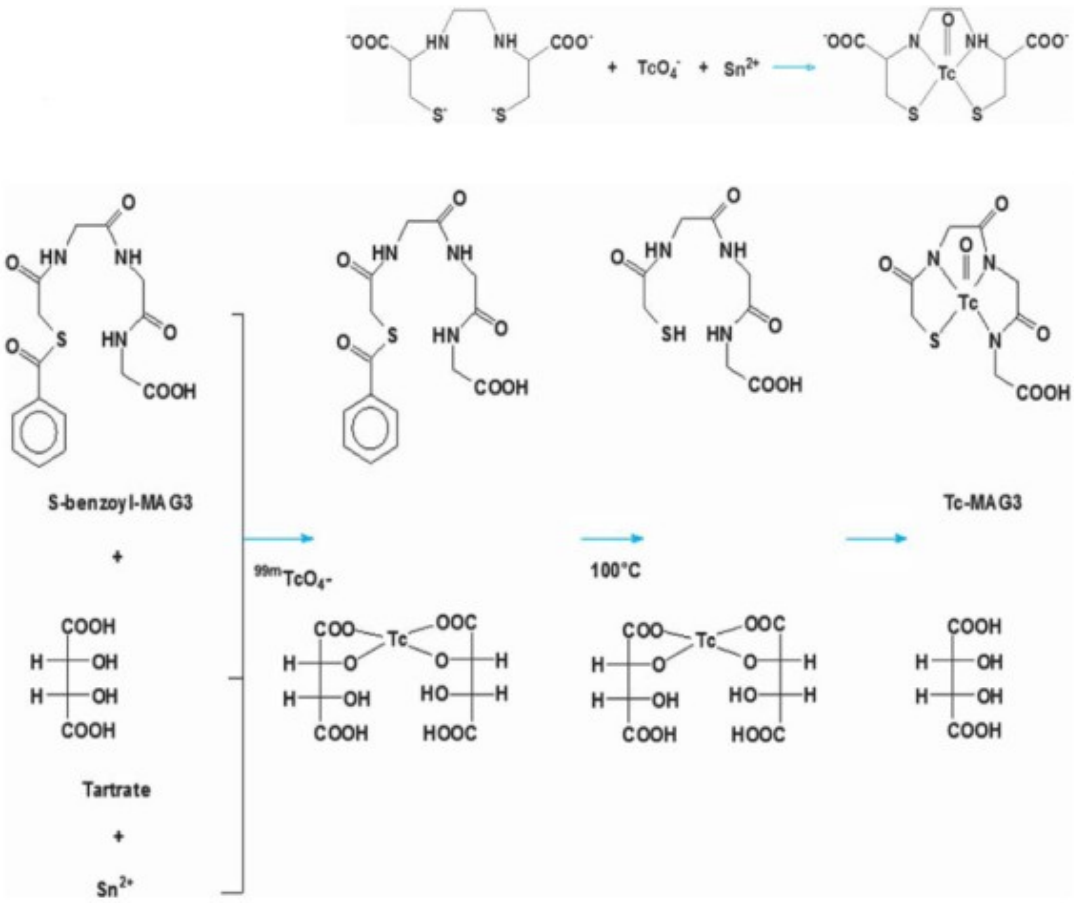

Figure 2.2. Direct labeling can be performed if ligand is present in metal binding form (Antoni and Langstrom, 2005)

Positron emitters such as ^{11}C, ^{18}N, and ^{15}O can be substituted for stable atoms of the same elements in compounds of biologic importance. This results in radiolabeled compounds with exactly the same biochemical properties as the original compound. Alternatively, ^{18}F, another positron-emitting radionuclide, can be substituted for hydrogen to produce labeled analogs. Several hundreds of compounds have been synthesized with ^{11}C, ^{18}N, ^{18}O, or ^{18}F labels for imaging with positron emission

tomography (PET). The short half-life of ^{11}C, ^{18}N, ^{18}O, or ^{18}F, and requires in-house radionuclide production in a biomedical cyclotron and rapid synthesis techniques to incorporate them with radiopharmaceuticals. On the other hand, the relatively longer half-life of ^{18}F permits its distribution within a radius of a few hundred miles from the site of production, thus obviating the need of a cyclotron in the nuclear medicine imaging facility (Bailey et al. 2005).

The most widely used positron-labeled radiopharmaceutical is the glucose analog FDG. Glucose is used by cells to produce adenosine triphosphate, the energy "currency" of the body, and accumulation of FDG in cells is proportional to the metabolic rate for glucose. Because the energy demands of cells are altered in many disease states, FDG has been shown to be a sensitive marker for a range of clinically important conditions, including neurodegenerative diseases, epilepsy, coronary artery disease, and most cancers and their metastasis (Banati et al. (1999).

Other radiopharmaceuticals are designed for therapy applications. These are normally labeled with a 3 emitter, and the radio- pharmaceutical is targeted against abnormal cells, commonly cancer cells. The 3 emitter deposits radiation only within a small radius (typically 0.1 to 1 mm) and selectively kills cells in this region through radiation damage. If the radiopharmaceutical is more readily accumulated by cancer cells than normal cells, a therapeutic effect can be obtained. Many different radiopharmaceuticals have been approved for use in clinical nuclear medicine studies. Each of these radiopharmaceuticals is targeted to measuring a specific biologic process, and therefore what is measured depends directly on which radiopharmaceutical is administered to the patient. Some of the more common radiopharmaceuticals (Barrio et al.1997).

Most radiopharmaceuticals are used in conjunction with imaging systems that can determine the location of the radiopharmaceutical within the body. Often, the rate of change of radiopharmaceutical localization within a specific tissue (the rate of uptake or clearance) is also important and is measured by acquiring multiple images as a function of time (Cho et al.2000).

2.1.3 ^{99m}Tc-^{99}Mo Generator:

The dry column generator was developed to alleviate poor elution yields of $^{99m}TcO_4$ by removing saline after elution. This decreases the amount of radiolysis products formed. The dry column generator employs a 5-20 ml saline charge, which is applied to au exterior part of the generator. An evacuated vial draws saline through the generator to remove $^{99m}TcO_4$, followed by air to dry the column caving the air on the column promotes oxidation of any reduced ^{99m}Tc species back to + 7 valence state of $^{99m}TcO_4$ which can then be eluted (Antoni and Langstrom, 2005).

2.1.3.1 Parent - daughter relationships

There are two types of parent-daughter relationships. Firstly, transient equilibrium is where the parent's half-life is a factor 10-100 times greater than that of the daughter (e.g.: Mo/^{99m}Tc generator, where the parent, ^{99m}Mo, has a half-Life of 67 hours, compared to 6 hours for the daughter, ^{99m}Tc). The second equilibrium state is known as secular. This is where the half—life of the parent is many times greater (100-N) times) that of the daughter's half-life,

$$^{90}Sr \rightarrow \beta^{-} {}^{90}\gamma \text{ (29.1 yrs) - 2.67 days)}$$

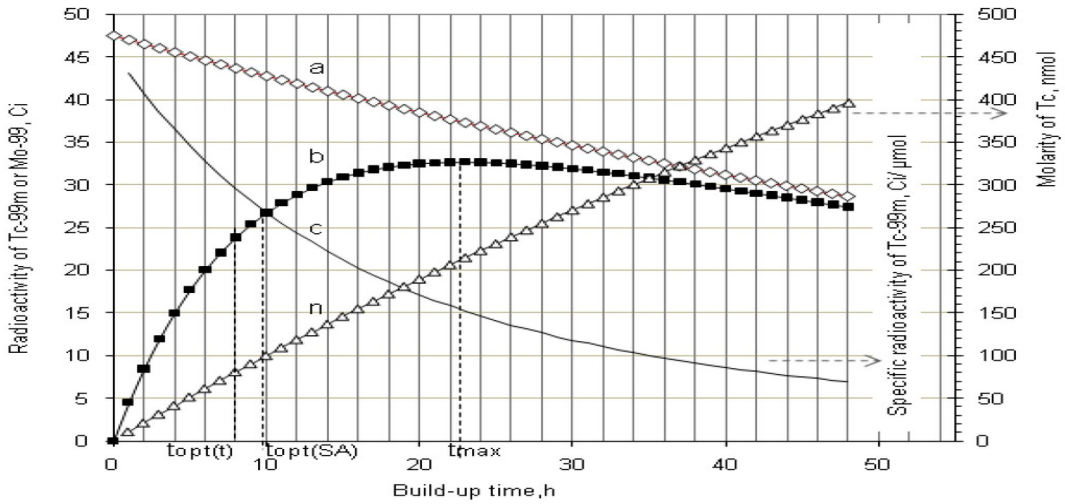

Figure 2.3. shows the radioactive decay and decay growth relationship between^{99}Mo/^{99m}Tc

The three curves of figure 2.3 are demonstrating what happens with the growth and decay of a daughter radionuclide in a transient equilibrium situation Curve A indicates the radioactivity of the parent radionuclide at subsequent lime intervals, showing its radioactive, decay. Curve B indicates the radioactivity of the ^{99m}Tc daughter. Curve C is the radioactivity of ^{99}Tc present in ^{99}Mo/^{99m}Tc generator, i.e. it demonstrates how the radioactivity of ^{99m}Tc grows to a maximum value and then gradually decays away. Before this maximum value, ^{99m}Tc is growing into the system faster than it is decaying, which leads to a progressive build-up of the level of ^{99m}Tc. After the maximum value, the ^{99m}Tc growth rate equals its decay rate. However from this point on, the growth rate of ^{99m}Tc gets progressively smaller as the parent ^{99}Mo decays away but the system is self - compensating by reducing the rate of decay of ^{99m}Tc. The overall net effect is the establishment of transient equilibrium in which the ratio of ^{99m}Mo radioactivity ^{99m}Tc radioactivity remains at a constant value. The daughter radionuclide can he separated from the parent by chemical means. In the case of the ^{99}Mo/^{99m}Tc generator, ^{99m}Tc is separated from ^{99}Mo by passing saline through the column. The ^{99m}Tc is eluted

off the generator column as sodium pertechnetate ($NaCl^{99m}TcO_4$). The ^{99}Mo remains immobilized on the column. Alternative separation techniques include solvent extraction and sublimation. (Zanzonico et.al 2000)

2.1.3.2Elution profile

The columns contain a small alumina bed allowing elution of $^{99m}TcO_4^-$ in small volumes (high specific activities). The elution profile indicates the volume of elute which removes all the ^{99m}Tc activity out of the column. The bulk of ^{99m}Tc activity is eluted in the first half of the elution volume. The first 1 mL contains no activity (dead space of the tubing). An elution volume of 6 mL will remove approximately 90% of available ^{99m}Tc, so the larger volumes serve only to dilute the bulk of activity already eluted. Thus high specific activity solutions can be obtained by collecting only over the peak of the elution profile (2-6 mL) (Zanzonico, 2004).

2.1.3.3 Elution of generator

The process of elution can be repeated as many times as is thought necessary; however, the percent yield will vary. After the daughter has been eluted, the daughter activity remaining on the column is low but begins to increase (regenerate) until it eventually approximates the activity of the parent again. If the column has completely regenerated, the usual yield is approximately 70% of the parent activity. In the case of $^{99}Mo/^{99m}Tc$ generator, regeneration requires 24 hours. Any elutions that are performed before that time will result in lower yields per elution; however a large net yield can be realized if several premature elutions are performed over any period of time. This is caused by the exponential buildup of the daughter product after elution but concentration is reduced. (Alrabiah et al. 1996)

Table 2-2: the % of maximum radioactivity per time $^{99}Mo/^{99m}Tc$ generator:

Time (hr)	*% of maximum radioactivity*
4.5	50.1
8.0	72.9
12.0	88.2
24.0	99.9

The plot of $^{99}Mo/^{99m}Tc$ decay (*Figure* 2.3) shown as a dotted line and ^{99m}Tc shown as a solid line. The generator is eluted on days 1, 3 and 5, changing in no way the course of decay of ^{99}Mo. Following each elution, it requires approximately four physical half-lives [25 hours] to return to equilibrium. Regeneration is an exponential function with approximately 50% regeneration during the first half-life, 25% during the second half-life and So on. (Zanzonico et.al 1995)

2.1.3.4 Laboratory techniques

Correct handling of radiopharmaceuticals ensures good aseptic techniques. All procedures in the hot laboratory are designed to optimize patient care and minimize radiation exposure to all personnel in the department. The patient must receive the correct radiopharmaceiitica1 at the correct dose with high radiochemical purity. This requires that accurate and sterile doses are prepared for patient administration by well trained and qualified personnel. Aseptic techniques and sterile and pyrogen - free ingredients are used at all times to minimize bacterial and pyrogen contamination. Appropriate records must he maintained to document the receipt, patient use, and ultimate disposition of all radioactive materials. To minimize the chance of errors, be sure the work area is clear. Work with only one radiopharmaceutical agent at a time.

In addition, check the dose calibrator setting when assaying the patient's dose (Alrabiah et al. 1996).

Urbano et al. (2005) mentioned in their study of evaluation of fresh and old eluate of ^{99}Mo-^{99m}Tc generators used for labeling of different pharmaceutical kit that these "risky" elutions might be appropriately used, in "emergency" conditions, for labeling radiopharmaceuticals although their radiochemical purity control is recommended prior to patient administration. Sixty ^{99}Mo-^{99m}Tc wet column generators, loaded with two different ^{99}Mo activities, were analyzed in order to assess the quality of their eluates. Each elution was used for labeling of different radiopharmaceuticals, in order to evaluate whether "risky" elutions, namely those performed just after generator delivery and at 72 hours or more from the last elution, could be conveniently employed when fresh available radioactivity is not enough for the planned labeling or when shipping problems arise, or delay in delivery of a new generator occurs. Radiochemical quality control of all radiopharmaceuticals labeled with these elutions was performed. The elutions differed mainly in ^{99}Tc ground state (^{99g}Tc) and amounts of oxidizing impurities. Radiolabeling procedures, however, were not affected, suggesting that these "risky" elutions might be appropriately used, in "emergency" conditions, for labeling radiopharmaceuticals although their radiochemical purity control is recommended prior to patient administration.

2.1.3.5 Quality Assurance in Nuclear Medicine

One important aspect of any QA programme is continuous quality improvement. This implies a commitment by the staff to continuously strive to improve the use of unsealed sources in diagnosis and therapy based on new information learned from the QA programme and new techniques developed by the nuclear medicine community at large. Feedback from operating experience and lessons learned from accidents or

averted accidents can help to identify potential problems and correct deficiencies, and therefore their systematic use as part of the continuous quality improvement process is to be encouraged.

With regard to radioactivity measurements in nuclear medicine, it is important that QA covers at least the following:

a) Acceptance, commissioning and QC of equipment and software.
b) QC of radiopharmaceuticals, radionuclide generators and other unsealed radionuclide.
c) Measurements of the physical parameters of all equipment at the time of commissioning and periodically thereafter.
d) Verification of the appropriate chemical and physical factors (e.g. amount of radioactivity, radiopharmaceutical composition) used in patient diagnosis or treatment.
e) Review of the procedures, taking into account the clinical factors that may influence the results.
f) Written records of relevant procedures and results.
g) Verification of the appropriate calibration and conditions of operation of the radionuclide activity calibrator.
h) Verification of the quality of the prepared radiopharmaceutical.
i) Reporting.
j) Training and continuing education of staff.
k) Clinical audit and interlaboratory comparison.
l) General outcome of nuclear medicine service.

The maintenance of management documents and records is an important part of the QA programme, and the management system’s documentation needs to be communicated to, understood by, available to and implemented by the appropriate personnel. The organization must establish and maintain procedures to control all documents that form part of its management system. This includes those generated internally and those from external sources, such as regulations, standards, other normative documents, and test and/or calibration methods, as well as drawings, software, specifications, instructions and manuals. Ideally, the person responsible for

the overall operation of the QA programme, the quality manager (QM), will identify and provide to the QAC a list of tasks related to QA that need written procedures. The QAC will then establish the person(s) responsible for drafting and signing each procedure and for teaching the procedure to the users, where appropriate. The QAC and the QM will maintain a file with copies of all procedures. All changes are to be reviewed and approved by the group that performed the original review, unless other personnel are specifically designated. The designated personnel must have access to pertinent background information upon which to base their review and approval. The procedure(s) adopted must ensure that:

a) Authorized editions of appropriate documents are available at all locations where operations essential to the effective functioning of the nuclear medicine facility are performed.
b) Documents are periodically reviewed and, where necessary, revised to ensure continuing suitability and compliance with applicable requirements.
c) Invalid or obsolete documents are promptly removed from all points of issue or use, or otherwise assured against unintended use.
d) Obsolete documents retained for either legal or knowledge preservation purposes are suitably marked (Urbano et al, 2005).

2.1.4 Review of requests, tenders and contracts

2.1.4.1 Providers of calibrated radioactive sources

The use of calibrated radioactivity standards is a necessary part of the management system. Ensuring that the sources are prepared correctly and according to the user's specifications can help to minimize unnecessary radiation exposure. Because the capabilities of each laboratory are likely to be different, it is important that each facility decide upon the products and services that it will provide based on a review of its capabilities. In turn, clients need to be made aware of the laboratory's capabilities

and any limitations on the services that can be provided. In requesting a measurement service (calibration, standardized sources, etc.), the customer needs to specify as completely as possible the requirements for and intended use of the service. Ideally, the formal request will include the following information (where relevant):

a) Identity of requestor, including name of authorized individual responsible for the request.
b) Name(s) of radionuclide(s).
c) Amount of radioactivity, including units.
d) Reference time for measurement.
e) Chemical form and physical configuration of source.
f) Type of instrument, and model and serial numbers (if the request is for calibration).
g) Physical quantities to be calibrated and range of variables over which calibration is required (e.g. calibration of radionuclide activity calibrator for activity over the range from 100 kBq to 1 GBq for energies over the range from 141 to 1000 keV) (Cherry et. al, 2003).

2.1.4.2 End users of radiopharmaceuticals and radioactive devices

This report assumes that medical radiation exposures from unsealed radionuclides are justified by weighing the diagnostic or therapeutic benefits they produce against the radiation detriment they might cause, taking into account the benefits and risks of available alternative diagnostic techniques that may or may not involve medical exposure (e.g. X ray, computed tomography (CT), ultrasound or magnetic resonance imaging (MRI)), or the benefits and risks of available alternative therapeutic techniques that may or may not involve ionizing radiation exposure (e.g. external beam radiotherapy, drug therapy or surgery). Such a decision is generally made by the attending nuclear medicine (or similarly qualified) physician, based on experience and training, and is governed by acceptable medical practice and safety guidelines such as the BSS. Each request for administration of radionuclides needs to include at least the following information:

a) Name of patient.
b) Name of procedure.
c) Indication for procedure.
d) Date and time of procedure if different from date and time of calibration.
e) Name of prescribing physician or authorized user.

The following information must be also supplied in the patient record if it is not included in the administration request:

a) Name of radionuclide.
b) Name of radiopharmaceutical or chemical form.
c) If applicable (particularly for receptor ligands, chiral molecules, colloids and macro-aggregated albumin).
d) Required mass or specific activity.
e) Conformal isomer.
f) Number of particles.
g) Size of particles.

When reporting an activity measurement value, the BSS [1] specify that “unsealed sources for nuclear medicine procedures [shall] be calibrated in terms of activity of the radiopharmaceutical to be administered, the activity being determined and recorded at the time of administration” (BSS, para. II.19 (d)) and that “the calibration of sources used for medical exposure be traceable to a Standards dosimetry laboratory” (BSS, para II.19 (a)) (Blower et al, 2000).

2.1.4.3 Subtracting of tests and Calibrations:

When a laboratory subcontracts work, whether for unforeseen reasons (e.g. workload, need for further expertise or temporary incapacity) or on a continuing basis (e.g. through permanent subcontracting, agency or franchising arrangements), competent subcontractors must be selected. A competent subcontractor is one that, for example, complies with the principles included in this report or a similar accepted standard, as well as with the regulatory requirements of the country. The laboratory needs to advise the client of the subcontractor arrangement in writing and, where appropriate, gain the approval of the client, preferably in writing. The laboratory is responsible to

the client for the subcontractor's work, except in the case where the client or a regulatory authority specifies which subcontractor is to be used. It is advisable for the laboratory to maintain a register of all subcontractors that it uses for tests and/or calibrations and a record of compliance with the principles included here for the work in question. It is highly desirable for the laboratory to have a policy and procedure(s) for the selection and purchase of the services and supplies it uses that affect the quality of the test(s) and/or calibration. Procedures need to be in place for the purchase, receipt (particularly with regard to safety inspection) and storage of radionuclides and consumable materials relevant for the tests and calibrations. It is important to note that some consumable supplies are critical to the accuracy of the measurements of radioactivity. For example, the geometry, chemical composition and dimensions (especially wall thickness) of the container (vial, syringe, etc.) may have a significant effect on the radioactivity measurement. It is important, therefore, to completely specify such equipment and verify that it meets the requirements upon delivery. For suppliers of radiopharmaceuticals, it is important that the end user be notified of any changes in the container, such as a change in the type of vial in which the drug is delivered. Such a change may affect calibrations derived from previous shipments of the drug in other types of container. The laboratory must ensure that the purchased supplies and radionuclides are not used until they have been inspected or otherwise verified as complying with the standard specifications or requirements defined in methods for the tests and/or calibrations concerned. It is important that records of actions taken to check compliance be maintained (Bjurling et al, 1989).

2.1.5 **Equipment and services used in Quality assurance:**

The following principles apply to all equipment and instrumentation used in the delivery of radioactivity measurement services at both the SSRL and end user levels.

The design of the facility and consequent purchase of equipment must take into consideration the type of work intended to be done and the types and activities of the radionuclides intended to be used. Ideally, written methods will be developed, with the involvement of the responsible staff (e.g. the medical physicist) and possibly the QAC, for the purchase, installation, acceptance, commissioning, and use, maintenance and QC of equipment and radiopharmaceuticals and other unsealed sources. The manufacturer's operating manual must be available in a language understood by the operators. Before submission to management, all purchase proposals need to be discussed in the QAC, which will: supervise the specification of the equipment; identify possible increases in staff needed to properly handle the new equipment; establish all necessary additional education and training, and new procedures; and review the maintenance programme from the point of view of safety. The set of tests to be used for acceptance of the equipment is to be specified in the purchase conditions (Bass et. al, 2000).

2.1.6 Radioactive sources

Radioactive sources must be tracked from receipt to transfer or disposal to ensure accountability; to identify when licensed material could be lost, stolen or misplaced; and to ensure that source activity limits authorized in the license are not exceeded. The activities listed below are to be carried out following approved procedures only:

(a) **Opening of package.**

Procedures must include visual inspection of the package, monitoring of external radiation levels and possible removable contamination, verification that contents agree with packing slip and order record, and monitoring of the packing material and the empty package;

(b) **Check of sources.**

Procedures must include means of safely handling sources and verifying their activity.

2.1.7 Service to the client:

Where laboratories are not the end users of their products (i.e. if they provide calibration services for other entities), they must cooperate with the client to clarify the request and follow up to ensure that the needs were met.

2.1.8 Complaints:

The laboratory must have a policy and procedure for the resolution of complaints received from clients or other parties. Records need to be maintained of all complaints and of the investigations and corrective actions taken by the laboratory.

2.1.9 Control of non-conforming tests:

It is advisable that the laboratory, in consultation with workers through their representatives (if appropriate), include in the local rules and procedures the values of all relevant warning or action levels and the procedure to be followed in the event that any such value is exceeded. These procedures will include those situations where measurement assays are to be halted until the problem is resolved. Warning and action levels serve as a tool for determining the integrity of existing procedures and performance. An exceedance of either of these levels signals the need to review the situation to determine the cause. The QM must conduct formal investigations whenever:

a) At the end user level, any of the operational parameters related to administered patient dosage are out of the normal range established for operational conditions.
b) At the SSRL level, any abnormal condition leading to erroneous measurement results is present.

The investigation must be initiated as soon as possible following the event, and a written report must be prepared concerning the cause, corrective actions and instructions or recommendations to avoid recurrence. Incidents involving patient exposure e must be investigated in accordance with the requirements set out in appendix II of the BSS [1]. For events related to clinical use, an investigation must be carried out that includes determination or verification of any doses received, and the results must be included in the report. The report is to be submitted to the QAC and other concerned bodies, as required, as soon as possible after the investigation, or as otherwise specified, and kept for at least three years (or other period, as appropriate) (Bangard et. al, 2000)

2.1.10 Corrective Action:

It is advisable for the laboratory to establish a policy and procedure, and to designate appropriate authorities for implementing corrective action when non-conforming work or departures from policies and procedures in the quality system or technical operation have been identified. Identification of non-conforming work or problems with the quality system or with measurement activities can occur at various places within the quality system and technical operations. Examples are customer complaints, QC, instrument calibration, checking of consumable materials, staff observations or supervision, measurement report checking, management reviews and internal or external audits. The procedure for corrective action starts with an investigation to determine the root cause(s) of the problem. When corrective action is needed, the laboratory must identify potential corrective actions and select and implement those most likely to eliminate the problem and to prevent recurrence. The degree of corrective action must be appropriate for the magnitude and risk of the problem. Any required changes resulting from corrective action investigations need to

be implemented and documented. It is advisable that the results be monitored to ensure that the corrective actions taken have been effective (Bailey et al, 2005).

2.1.11 Preventive Action:

Needed improvements and potential sources of non-conformance, either technical or concerning the quality system, must be identified. If preventive action is required, action plans are to be developed, implemented and monitored to reduce the likelihood of the occurrence of such non-conformance and to take advantage of the opportunities for improvement. Procedures for preventive actions are to include the initiation of such actions and application of controls to ensure that they are effective.

2.1.12 Control of quality assurance records

The laboratory must establish and maintain procedures for identification, collection, indexing, accessibility, filing, storage, maintenance and disposal of quality and technical records. Quality records ideally will include reports from internal audits and management reviews, as well as records of corrective and preventive actions. All records must be legible and must be stored and retained in such a way that they are readily retrievable in facilities that provide a suitable environment for preventing damage or deterioration and loss. It is advisable that the laboratory have procedures to protect and back up records stored electronically and to prevent unauthorized access to or amendment of these records. The laboratory needs to retain, for a defined period (typically five years), records of original observations, derived data and sufficient information to establish an audit trail, calibration records and a copy of each test report or calibration certificate issued. The records for each test or calibration must contain sufficient information to facilitate, if possible, identification of factors affecting the uncertainty of measurements and to enable the test or calibration to be repeated under conditions as close as possible to the original conditions. The records

must include the identities of the personnel responsible for the sampling, performance of each test and/or calibration, and checking of the results. Observations, data and calculations must be recorded at the time they are made and must be assignable to a specific task. When mistakes occur in records, each mistake is to be crossed out not erased, made illegible or deleted and the correct value entered alongside it. All such alterations to records are to be signed or initialed by the person making the correction. In the case of records stored electronically, equivalent measures are to be taken to avoid the loss or alteration of original data, as well as to identify when and by whom a required change is made (Bailey et al, 2005).

2.1.13 Internal Assessment in nuclear medicine:

Internal assessments of activities must be carried out according to a predetermined schedule (typically yearly) to verify that operations continue to comply with the requirements of the quality system and the principles included here. Ideally, the internal assessment programme will address all elements of the management system, including the availability of written records of relevant procedures and results from testing and/or calibration activities. It is the responsibility of the QM to plan and organize audits as required by the schedule and requested by management. Such assessments must be carried out by trained and qualified personnel who are, wherever resources permit, independent of the activity to be audited. When findings cast doubt on the effectiveness of the operations or on the correctness or validity of the nuclear medicine facility's test or calibration results, the laboratory must take timely corrective action and must notify clients in writing if investigations show that the nuclear medicine facility results may have been affected. The area of the activity audited, the audit findings and corrective actions that arise from them must be

recorded. Follow-up activities need to verify and record the implementation and effectiveness of the corrective actions taken (Anderson et. al, 2005).

2.1.14 General Procedures in Quality Control:

QC measures are necessary to ensure that a product complies with all the requirements and specifications laid out for it. The QC unit should have well documented procedures for QC, which is to be undertaken for each starting material used for production as well as for finished products. It is suggested that the manufacturers refer to national pharmacopoeias, the USP, the EP or any other international pharmacopoeia when designing appropriate QC specifications and methods.

2.1.15 Quality Control of starting materials:

All starting materials, including active pharmaceutical ingredients (active substances), excipients and primary packaging materials used for kit production; need to be approved before use. Generally, the starting materials such as buffer salts and reducing agents are used in many types of kit and are to be analyzed when a new bottle is opened. The specifications for such substances are described in various pharmacopoeias. However, it should be borne in mind that 99mTc radiopharmaceuticals are a special class of products in which ‘no carrier added’ grade 99mTc is used to form a complex with ligands, most often in the presence of a reducing agent such as Sn+2 salts. The presence of even small quantities of competing metal ions or oxidants could cause problems in the formation of the desired radiopharmaceutical. Thus it is difficult to provide complete specifications for all the starting materials with respect to the components that should not be present. Often, the use of high quality materials from reputed manufacturers is adequate to ensure good quality products. QA for the material that forms the radiopharmaceutical (along

with the ligand and other materials, which are pretested) is advisable. A QC certificate from the manufacturer should be procured. Although the compliance certificate from the manufacturer may appear to be adequate, compliance with the rules laid out by the local regulatory authorities is desirable. Throughout the world, the laws governing the manufacture and sale of medical and pharmaceutical products are modified from time to time, becoming progressively more stringent and specific. In most countries, when a new product is manufactured for use in humans, all the starting materials are to be tested for their quality. This can be done by having the starting materials analyzed at an approved laboratory; alternatively, the QC analysis can be done in the manufacturer's own laboratory. The quality of all the materials should comply with the specifications in the pharmacopoeias or recommended by the regulatory body of the country. The vials and rubber closures should be purchased from approved manufacturers, and a certificate of quality compliance should be obtained and archived (Anderson et. al, 2005).

2.1.16 Quality Control of active substances used in the kit:

Many of the active substances used for kit manufacture can be purchased from commercial sources. However, certain active ingredients are synthesized in the manufacturing facility. Regardless of the source, they must undergo QC analysis before being used to produce kits. Chemical identity, purity and amount (or assay) of the ligand are the three most important criteria, and these need to be ascertained by identification of the ligand, estimation of the purity of the preparation and assay of the amount of the ligand in the starting material.

2.1.16.1 Identification:

To identify the ligand in the starting material, one or a combination of several analytical methods such as melting point determination, elemental analysis, IR

spectroscopy, UV/VIS spectroscopy, NMR spectroscopy, mass spectroscopy and HPLC analysis should be used. If the ligand is synthesized in-house, the progress and completion of the reaction need to be monitored, which again is done with the aid of the above techniques. Often, a few independent analytical techniques need to be used to prove the identity of the product unequivocally. It is desirable to keep a set of typical analysis results in the monograph file for each product. The specific absorption pattern (IR, UV/ VIS or NMR spectroscopy) of each molecule could act as a 'fingerprint' for identifying the molecule and ensuring the absence of impurities in the preparation. A brief description of the information available from different analytical methods is given below:

- Melting point determination is a simple method often used to confirm the identity of the substance, although not for establishing it unequivocally.
- Elemental analysis is a tool for ascertaining the identity of the product. Although the values for elemental composition vary to some extent, it is a useful technique for proving the identity when other techniques fail to provide sufficient information.
- IR spectroscopy is based on the selective absorption of energy in the IR region by asymmetric bonds such as C=O (vibrational transitions). Thus, the presence of such asymmetric IR active groups is identified and quantified using IR spectroscopy. IR spectroscopy is also an important technique for monitoring the progress of synthesis and ensuring the absence of impurities, when such groups are involved.
- UV/VIS spectroscopy is based on the absorption of light in the UV/VIS region by the molecule as a result of electronic transitions. In the presence of conjugated double bonds, metal complexes where d-d transitions occur in the UV/VIS region are often identified and quantified by the UV/VIS spectrum.

- NMR spectroscopy is based on the absorption of energy by the nucleus of atoms that have net nuclear magnetic moment. Some of the most widely used NMR active atoms are ^{1}H, ^{13}C and ^{31}P. The pattern of the energy absorption (chemical shift) is indicative of the chemical environment of the atom, and hence of the groups present. NMR patterns are very useful in determining structures, confirming reactions and determining the purity of the preparation. Proton NMR is the most widely used, as nearly all the molecules contain a large proportion of ^{1}H, and a quick NMR can indicate the distribution of various kinds of hydrogen atoms in the molecule. On the other hand, ^{13}C and ^{31}P NMR give information on the number and distribution of carbon and phosphorus atoms, respectively. Most of the time, a 'fingerprint' ^{1}H NMR spectrum is adequate to prove the identity and purity of a ligand. However, the presence of very similar compounds or precursors cannot be completely ruled out by perusing the
- ^{1}H NMR alone. Also useful for establishing the identity of the compound/ ligand are ^{13}C NMR and ^{31}P NMR (when phosphorus is present in the ligand, which is not always the case).
- Mass spectrometry is a well-established technique based on the principle that when a charged particle passes through a magnetic field, it is deflected along a circular path of a radius that is proportional to the mass to charge ratio. Mass spectrometry is a powerful tool that can distinguish a difference of just one mass number in the molecules.

Typically, a small amount of the substance is injected into the sample port, where it is vaporized and ionized. The deflection/path of the ions is used to calculate the mass. Since under ionization conditions many cleavages take place, mass spectra are invariably a set of lines corresponding to a series of ions, the highest giving a clue as

to the mass of the molecule and the others corresponding to the various ions formed by cleavages of labile groups in succession. Thus, it is possible to logically prove the identity of the compound. Although mass spectroscopy is a useful tool for identifying and testing the purity of a compound, difficulties associated with purchasing and maintaining such an expensive instrument limit its use. More often, laboratories have the samples analyzed at an institute with a mass spectrometer (Adam and Wilbur, 2005).

2.1.16.2 **Purity:**

The ligand can be contaminated with trace amounts of un-reacted starting materials used for synthesis and with degradation products formed during storage. Thus the estimation of impurities in the substance is important. The tests used to prove the identity of the substance can also give valuable information about the purity of the product. HPLC is the most commonly used technique for estimating such impurities. It is a very sensitive tool for separation based on different physicochemical characteristics (e.g. residual charge on the various groups in the molecule, lipophilicity/hydrophilicity, and molecular weight). The compounds are separated from the chromatographic columns by elution at different retention times. The separation is facilitated by the use of a variety of columns such as C-18, PRP and silica gel, as well as by the choice of an appropriate solvent system. The use of a combination of solvents of different polarities and of gradient elution is often required to obtain complete separation of the ligand from closely related substances (Adam and Wilbur, 2005).

2.1.16.3 **Assay**

Assaying the exact amount of the ligand is vital for preparation of the kit vials. A quantitative estimate of the ligand can be done by simple gravimetry, if the ligand is

of high purity. In the preparation of kits for technetium radiopharmaceuticals, the ligands are used in the range of milligrams per vial, which translates into handling gram quantities per batch. With the availability of weighing balances that can weigh a tenth of a milligram with high accuracy, gravimetry is the simplest, most ideal mode of quantification. However, if the ligand is present with salts, it must be assayed. Ideally, any of the methods used for testing the purity can also be used for the assay. Standards of known concentration/amount are used for calibration/comparison. Spectrophotometry (UV/VIS or IR) is an easy method frequently used for assaying the ligands.

2.1.17 Quality Control of finished Kits:

QC analysis of the finished kit starts with sampling from the lot, followed by different types of analysis including visual inspection of the kit vials and analytical tests of kit content dissolved in saline or water for injection and of the ^{99m}Tc labeled product.

2.1.18 Sampling

Sampling of the finished product for QC is an important step to ensure that the samples collected are representative of the batch. QC personnel should randomly pick 2% of the total number of vials or a minimum of 20 vials, whichever is greater, for testing. Pharmacopoeias give guidelines for the number of samples needed for sterility testing. USP 30 requires 10 vials for sterility testing when the batch size is 100-500 and 2% or 20 vials for larger batches, whichever is less.

2.1.19 Control of pharmaceutical form:

The physical appearance of each of the reagents, the solubility of the ligand and other reagents in the defined medium, and the pH of the dissolved product are tested to ascertain the product’s compliance with requirements. At this stage, a failure of any of

the parameters to comply with requirements, such as non-dissolution of the contents or presence of suspended particles in the vial, indicates that the ligand has undergone some degradation either during storage or during the freeze-drying cycle. Similarly, a pH value far outside the expected range indicates erroneous reagent preparation at the production end. Whenever the values are not within the expected range, the tests are to be repeated and the quality of the reagents used for testing, as well as the glassware, needs to be checked. Whenever multiple components from different vials are used for kit formulation, the test should be done in each component vial and then in the final product (Adam and Wilbur, 2005).

2.1.20 Sn(II) content assay

Almost all kits for technetium radiopharmaceuticals employ stannous ions to reduce the technetium from +7 to the desired oxidation state. In most cases, the amount of Sn(II) is not critical. However, in certain cases it is crucial to maintain a minimum Sn(II) level, as very low amounts of Sn(II) will result in inadequate oxidation of technetium, while high amounts will damage the compound formed. One such example is the kit for ^{99m}Tc-HMPAO. It is necessary to measure the Sn(II) content in the kit vial. Estimation of the Sn(II) content could be carried out by simple methods such as titration with iodine or N-bromosuccinimide. However, interference owing to the presence of other reducing agents is possible, and it is necessary to ensure that such interference does not occur. Alternatively, polarography could be used. Iodometry is very sensitive (up to 1.5 ppm levels) and is often used for Sn(II) estimation. Certain laboratories employ spot test methods (such as the one based on ammonium phosphomolybdate color correlated to stannous content) for semi-quantitative estimation of Sn(II) in order to ensure that the levels are within

prescribed limits. A limit for Sn(II) contamination is often fixed by the manufacturer, for example, not less than 50% of the quoted value at the expiry of the kit.

2.1.21 Microbiological safety

Tests for sterility and the absence of pyrogens are used to ensure the microbiological safety of a product. However, since 99mTc radiopharmaceuticals are constituted using the reagents provided in the kit, any breach of sterility or apyrogenicity can in turn be due to the presence of microbial organisms in one or more of the reagents. Hence, in the case of kits, each reagent needs to be certified for microbiological safety. The microbiological safety of the product is established by conducting sterility tests and tests for bacterial endotoxins. These tests are conducted on each component of the kit when a fresh batch is made. Sterility testing Conventional tests for sterility is well established. The tests can be carried out by membrane filtration of the product or by direct inoculation of the culture medium with the product to be examined. Direct inoculation involves aseptic transfer of the contents of the vial into two kinds of growth medium soybean casein digest medium (SCDM) and Fluid Thioglycollate Medium (FTM) to determine if the product is free of viable bacterial and fungal contamination. These broths are incubated for 14 d, as required by the USP (or for the period required by the regulatory requirements of the country), and inspected for evidence of bacterial and fungal growth. Briefly, the contents of the vial to be tested are reconstituted with tested sterile solvent (water or saline, as necessary), and an aliquot (typically 100 µL) is taken with a syringe and inoculated into the media, taking care to use sterile glassware and carrying out the work in a clean work area, such as a laminar flow bench/hood. The agar plates and the tubes are covered, placed in an incubator at 37ºC and monitored daily for any growth for 14 d. The absence of growth indicates adequate sterility of the product. The membrane filtration technique

is recommended for filterable aqueous preparation, as is the case with kits. Conventionally, the absence of pyrogens was tested by injecting an aliquot of the preparation into rabbits and watching for any increase in their body temperature. If gram-negative bacteria are present in a product, they are destroyed during sterilization, and the endotoxins are released from their cell walls. A bacterial endotoxin test (BET) using Limulus Amebocyte Lysate (LAL) is now used to determine the presence of endotoxins much faster and with far greater sensitivity than the rabbit based pyrogen test. Briefly, the BET is based on the principle that the bacterial endotoxins react with LAL and form a gel-like precipitate. The pyrogenicity is expressed in BET units; the limits for BET are well established for various products and depend on the volumes generally injected into patients. For example, vehicles such as saline and water for injection have a very low limit of 0.25 BET units, whereas a finished radiopharmaceutical units. This test needs to be carried out in a clean environment in a laminar flow hood. Appropriate amounts of the product to be tested (depending on the limits set) are allowed to react with the LAL reagents, along with positive and negative controls, and are monitored for the formation of gel at the end of the incubation period (typically 30 min). The absence of gel formation indicates the absence of bacterial endotoxins. Annex VII discusses sterility testing; environmental monitoring is discussed in Annex VIII; and Annex IX discusses the bacterial endotoxin test (Saha, 2004).

2.1.22 Radiochemical purity

The radiochemical purity of the labeled product is generally estimated with a chromatographic technique such as paper chromatography, thin layer chromatography, HPLC or column chromatography. Other techniques such as paper electrophoresis are

also used to estimate the radiochemical purity of ^{99m}Tc radiopharmaceuticals (Cherry et al 2003).

2.1.23 Biodistribution

The biodistribution of the radiopharmaceutical is an important criterion for product utility. It is ascertained by biological QC, where the radiolabelled product is administered to an appropriate small animal (rat or mouse) and the biodistribution is examined at the end of a prescribed time interval. Such biological control is essential when a product is first introduced on the market until consistent results are obtained for several consecutive batches. After approval, the tests may be performed at a frequency required by the regulatory authority. However, in a few cases, such as with mebrofenin or MDP, biodistribution control studies are carried out on every batch.

2.2 Previous studies

Many considerable studies were carried out in the scope of survey and assessment of the dose calibrator's performance through quality control tests.

By H. Zamani Zeinali1, N. Alirezazadeh2*, F. Atabi3 An investigation on the performance of dose calibrators in nuclear medicine centers in Iran was done

To investigate the status of the nuclear medicine (NM) centers in Iran for the performance of dose calibrators, 18 out of 54 centers providing NM services in Iran were randomly selected and inspected in1997. In the first phaseof the study the selected centers were inspected for performing of quality control (QC) tests of dose calibrators. The linearity of the activity response,precision, accuracy, and the physical functions of the instruments, were studied. In the second phaseof the study, carried out in 2006, 28 out of 75 NM centers were investigated for QC tests performance.

According to the obtained results in the first phase of the study, 10 centers were foundto be in unacceptable situation. Following this study,all the concerned NM centers were informed aboutthe results, and at the same time the repair andadjustment of the dose calibrators were requested.In addition, the appropriate training courses alongwith the QC testing manuals were provided to the centers. Based on the data of the second phase of the study, only 6 NM centers were in unacceptable situation. The

results indicated the effectiveness of the improvements carried out in the working procedures of the centers during interval between the two phases of investigation. Iran. J. Radiat. Res., 2008; 6 (2): 6469

Considering the results and findings of this investigation the NRPD of Iran, has first prepared and formulated the QC system applicable in nuclear medicine practice in Iran, and then, by providing the relevant documentation to the centers, has forced them to implement a comprehensive QC program properly. Hopefully, this promising trend will be further strengthened and extended in future with the full assistance of the relevant bodies, as well as with the close cooperation of the centers.

Another study by Ana Carolina Moreira de Bessa1, Alessandro Martins da Costa2, Linda V. E. Caldas3. Survey on quality control of radiopharmaceutical dose calibrators in nuclear medicine units in the city of São Paulo, SP, Brazil*

To perform a survey on routine quality control tests of dose calibrators at nuclear medicine units in the city of São Paulo, SP, Brazil. To evaluate the accuracy of measurements of seven dose calibrators activities, utilizing sources of clinically significant radionuclides at the calibration laboratory of Instituto de Pesquisas Energéticas e Nucleares.

The survey results on the quality control tests of the dose calibrators showed some inappropriateness, for example, the absence of daily reproducibility tests in all of the units. The accuracy tests for the seven dose calibrators showed results within the acceptable limit in compliance with the national regulations (±5%).

According to the few nuclear medicine units participating in the survey,the dose calibrators quality control is unsatisfactory. The accuracy study of seven dose calibrators has not demonstrated any performance faults, and has established the calibration of these instruments for the utilized sources.

Then By Zhenya Krasteva11SBALNP “Sv . Naum” , Sofia , Bulgaria The purpose of this study is to carry out quality control (QC) of dose calibrators in some nuclear medicine departments in Bulgaria .

The methods used for QC are based on established international and national recommendations . For each typeof dose calibrator requirements of the producer are taken into account . Depending on the type of dose calibrator there might be a need to modify QC procedures . The following sources of photon radiation were used for the measurements Tc-99m , Cs-137 and Ba-133 . To ensure the proper

operation of a dose calibrator , four QC parameters must be tested : accuracy , precision , constancy and linearity.

The results from the measurements showed that the parameters that were traced for dose calibrators are within the Bulgarian and International standards . It is essential to perform daily testing for background activity and constancy . Deviations from normal values of these two parameters is the first sign of degradation of the dose calibrator . Regular QC should cover precision , accuracy and linearity of the instrument . according to IAEA s tandards and Ordinance **NO 30** (31October 2005) of Ministry of Health . That will guarantee accuracy of the used patients radioactive doses and therefore proper practice of nuclear medicine diagnosis .

Chapter Three
Materials and Methods

The following study is an experimental study designed and conducted in Elnilien Medical Diagnostic Center which is located in Khartoum. The QC tests in this work were conducted in accordance with the internationally accepted standards for dose calibrators. The tests included constancy (reproducibility), accuracy, precision, background, linearity, clock accuracy and geometry

3.1. Materials of the study:-

3.1.1. Dose Calibrator

The nuclear medicine department of Elnilein medical diagnostic center, uses dose calibrator model CAPINTEC CII CRC®-25R, manufactured on July 2008. The ionization chamber is a thin wall, deep well, high pressure type 13.6 Kg weight, with dimensions of 25 cm high×6 cm diameter and interconnecting cable of 3.7m. The resolution of 0.01 MBq (0.01 μCi) maximum. Response time is within 2 seconds, for very low activity sample 4-16 seconds.

Table (3.1) shows the CRC-25R dose calibrator

Specification	*CRC_25R dose Caliber*
1. Interconnection cable length.	3.7 meters
2. Nuclear sitting keys	8 preset keys
3. Power requirements	100-240 VAC (50/60 Hz) 90 mA
4. Chamber weight	13.6 KG
5. Display unit weight	1.8Kg

The display unit of the system consists of display screen which is dot matrix liquid crystal type with direct reading in Bq or Ci. It contains 8 pre-set nuclear keys which include, ^{57} Co, ^{67}Ga, ^{99m}Tc, ^{18}F, ^{111}In, ^{123}I, ^{131}I and ^{133}Xe . (Fig 3.1).

The system memory contains 4 standard sources, ^{60}Co, ^{57}Co, ^{133}Ba, and ^{137}Cs.It also contains over 80 nuclides with calibration number and half-life (see Fig 3.1) .

Fig 3.1 shows the dose calibrator model CAPINTEC-CRC®-25R, manufactured on July 2008-Elnilein Medical diagnostic Center-Khartoum.

3.1.2. Standard Radionuclide sources:-

Quality control tests are easily achieved and maintained by the use of long-lived reference sources.

The one standard radionuclide source was used in this study to perform quality control tests (accuracy and constancy) **^{137}Cs** .The standard source is only available in Elnilein Medical diagnostic Center (see Fig 3.2).

Fig 3.2 show standard radionuclide source^{137}Cs

Table (3.2) shows specifications of standard source

Radionuclide	Half-life	Decay constant (λ)	Energy, Eγ (frequency), of principal x or γ-ray (keV)	Specific γ -ray constant, (mR/h/cm^2/MBq)	Geometry and activity	QC application
^{137}Cs	30 years	0.00254/y	662 (86%)	25.1	Vial/small bottle, 187 µCi	Dose calibrator accuracy and constancy

3.2. Methods

3.2.1 Methods of Data collection

The tests include constancy (Reproducibility), accuracy, Precision, Background, linearity, Clock accuracy and geometry on the dose calibrator using ^{137}**Cs**, and ^{99m}**Tc.**

The dose calibrator was tested in place without any movement, and with some modifications to the quality control procedures according to the dose calibrator type and manufacturers recommendations. The methods of data collection included observation, tests and reference form IAEA.

3.2.2 Methods of data analysis

The data were analyzed using Microsoft office 2007 – Excel Program under windows –xp, in addition to equation and statistical methods.

Chapter Four
Results

The following chapter will show the general results dealing with the performance of dose calibrator used in nuclear medicine department as evaluated by four quality control tests.

4.1 Physical Inspection test :

Table 4-1. Shows physical inspection test

MANUFACTURE PTW	PTW
Model	CURIEMENTOR4
Power	50 TO 60Hz
Volt	(100 TO 230) ±15%
Current	0.05A
Manuals	Available
Radioactive Check source	Available
Condition	Ok
Log-book	Initiated

4.2 Background test:

The background measurement determine the basic ionizing radiation in the vicinity of the measuring system (before inserting the sample).

Table 4-2. Shows background test

S . NO	Reading in mci

First reading	0.91
Second Reading	0.84
Mean	0.875
SD	0.035
Cv%	4

4.3 Reproducibility (constancy) test:

The test has been carried out to check the day reproducibility of performance of radionuclide calibrator in measurements on commonly used radionuclide in N.M department for Q.C test.

Table 4-3. Shows reproducibility test of radionuclide calibrator using Cs-137

S. No	**Reading in mCi**
1	152.1
2	152.4
3	152.7
4	152.7
5	152.4
6	152.6
7	152.3
8	152.8
9	152.7
10	152.4
Mean	**152.5**
SD	***0.22***
Cv%	***0.144***

4.4 Clock accuracy:

It is the stabilization of time between two measurements (time required for any measurement should be the same).

Table 4-4. Shows clock accuracy test of radionuclide calibrator

No	Reading (seconds)
1	1.59
2	1.30
3	1.11
4	1.19
5	1.12
6	1.09
7	1.13
8	1.23
9	1.28
10	1.20
Mean	1.22
SD	0.15

4.5 Accuracy:

The accuracy of a measurement is determined by how close it is to the true value (reference condition).

Table 4-5. Shows accuracy test of radionuclide calibrator using Cs-137

S. No	***Reading (mci)***
1	152.32

2	152.35
3	152.39
4	152.31
5	152.33
6	152.38
7	152.32
8	152.37
9	152.35
10	152.34
Mean	***152.35***
SD	***0.27***
Cv%	***1.77***

Calculation

C at 12 / 10 /2014 for Cs-137 is equal:

$T_{1/2}$ = 30 year

C_0 (certified activity) = 187mci at 1/4/2007

$C = C_0 e^{-\lambda t}$

$\lambda = \underline{\ln 2} / T_{1/2}$

t = (7.5) years

A = Mean (Form the reading)

Accuracy % = A - C /C× 100

Accuracy % = 152.35-157.37/157.37 ×100 = 0.032%

4.6 Precision test:

Precision is a measure of the spread of values obtained from a sequence of measurements. It is usually defined in terms of the standard deviation of a set of 10 consecutive measurements.

Table 4-6. Shows precision test of radionuclide calibrator

S. No	***Reading in mCi***
1	2.769
2	2.767
3	2.773
4	2.778
5	2.774
6	2.779
7	2.776
8	2.778
9	2.779
10	2.781
Mean	***2.7754***
SD	***0.0046***
Cv%	***0.166***

4.7 Linearity test:

The purpose of this test is to chick the linearity of the activity response of a radionuclide calibrator over the range of activities for which it is to be used.

Table 4-7. Shows Linearity test of radionuclide calibrator, using Tc-99m

S. No	**Elapsed time*(min)***	**Expected reading*(mCi)***	***Calibrator Reading in mCi***
1	0	145	146.2
2	30	136.97	137.3
3	60	129.2	130.4
4	90	122.2	123.5
5	120	115.1	113.4
6	150	109.04	109.1
7	180	102.5	102.9
8	210	97.3	97.8
9	240	91.9	91.5
10	270	86.8	86.1

Figure 4.1 shows that the relation between Time and Activity is Exponential

4.8 Geometry Test:-

Testing for geometry independence ensures that the indicated activity does not change with volume or configuration

Table 4-8. Shows the effect of calibrator Geometry on the activity according to volume

No	**Sample Volume*(ml)***	**Activity (mCi)**
1	0.5	19.7
2	1.0	19.6
3	2.0	19.4
4	3.0	19.3
5	4.0	19.2
6	5.0	18.8
7	6.0	18.6

Chapter Five

Discussion, Conclusion and Recommendations

5.1. Discussion:

Concerning the physical inspection test (table 4-1) the calibrator looks in a good condition .

it was clear that these features help in providing good outcomes in terms of imaging capacity of the department. It was found that imaging procedures are so organized that every particular study is usually done on a known separate day during the week, and this minimizes errors during a radiopharmaceuticals preparation.

Table (4-2) shows background test, the result of test was good and in normal exposure range (0.875 ±.049 mCi). The implementation of radiation protection rules was good in some aspects of the work. No in-house preset standards that were available in

printed manuals and also no check listed and no permanent records. The involvement of technologists directly in management may inhance the implementation of the rules concerning quality control of radiopharmaceuticals (IAEA-TECDOC-602).

Table (4-3) results concerning the reproducibility test of radionuclide calibrator, the day reproducibility of performance of radionuclide calibrator was good with very error (152.5 $\pm$ 0.22).

Concerning clock accuracy (table 4-4), the stabilization of time between two measurements showed no significant difference (1.22$\pm$ 0.15)

In table (4-5) the results obtained concerning accuracy showed that the dose calibrator has accurate reading and the percentage of error was 0.32% which is accepted (IAEA-TECDOC-602 and 1599). The percentage of accuracy of dose calibrator was easily detected by using accuracy equation (see table 4.5).

The precision test (table 4-6), is a measure of the spread of values obtained from a sequence of measurements. These results showed high precision in dose calibrator.

Table (4-7) showed linearity test of the radionuclide calibrator. After time elapse in order to compare between the expected reading (according to equations) and measured (true) reading of the calibrator.

Table (4-8) showed geometry test to show if there is any change in the activity reading according to the increase of the activity volume. The test showed no change and the activity result was within the accepted rang.

5.2. Conclusion:

The Al Nelein Diagnostic Center has an acceptable situation in terms of the QC measures for dose calibrator.

From the results of the study, the dose calibrator under study is valid for use.

5.3. Recommendations:

Considering the results and findings of this evaluation of the performance of dose calibrator that were included in this study, the following recommendations could be proposed;

- Preparation and formulation of quality control system should be applied in nuclear medicine practice in Sudan for all nuclear medicine equipment.
- Providing the relevant documentation to the nuclear medicine centers to implement a comprehensive QC program properly.
- Encouraging the cooperation between the relevant regulatory bodies and nuclear medicine centers in Sudan.
- Encouraging the cooperation between the relevant regulatory bodies in Sudan and International Atomic Energy Agency, to provide technical support, training courses and quality control tools for nuclear medicine centers through regional and national projects.

Limitations:

Researcher faced some problems that concerning the implementation of the quality control tests to dose calibrator in Elneelain Medical Center - Nuclear Medicine Department, Including the absence of modern tests facilities, multiple radioactive sources (only Cs137 is available) and lack of cooperation showed by some people.

In the future, the researcher advises to carry out more research on other aspects which were not included in this study due to the limitations mentioned above and other factors.

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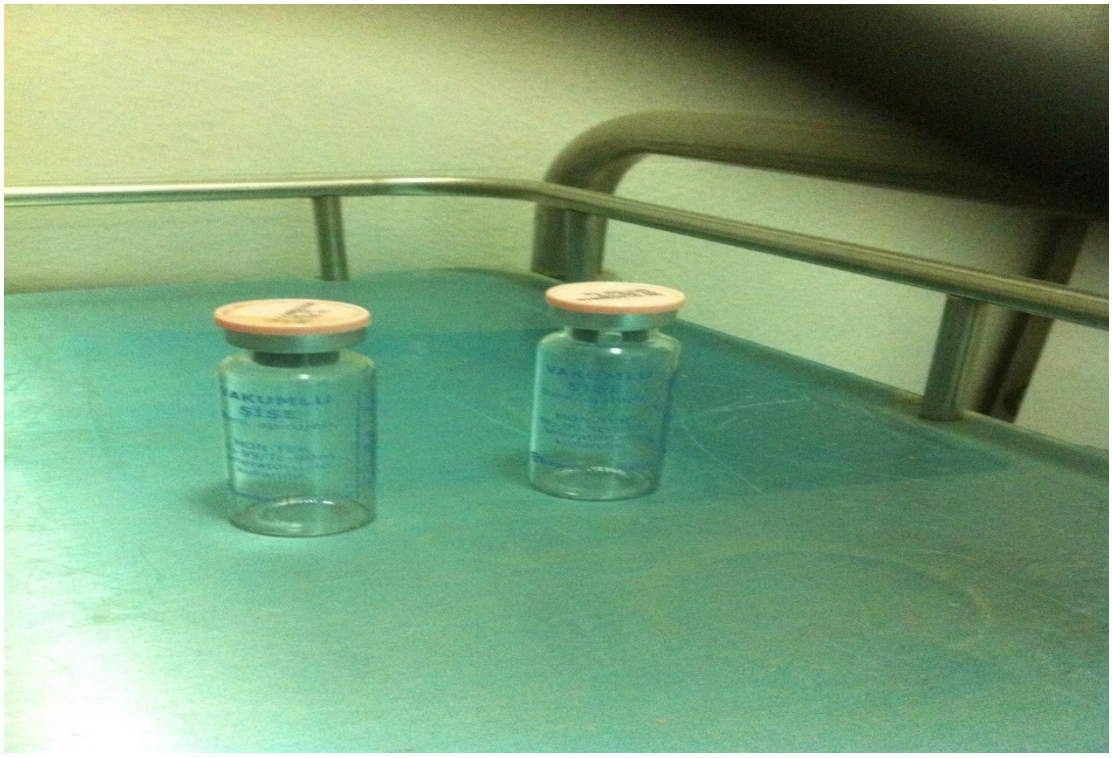
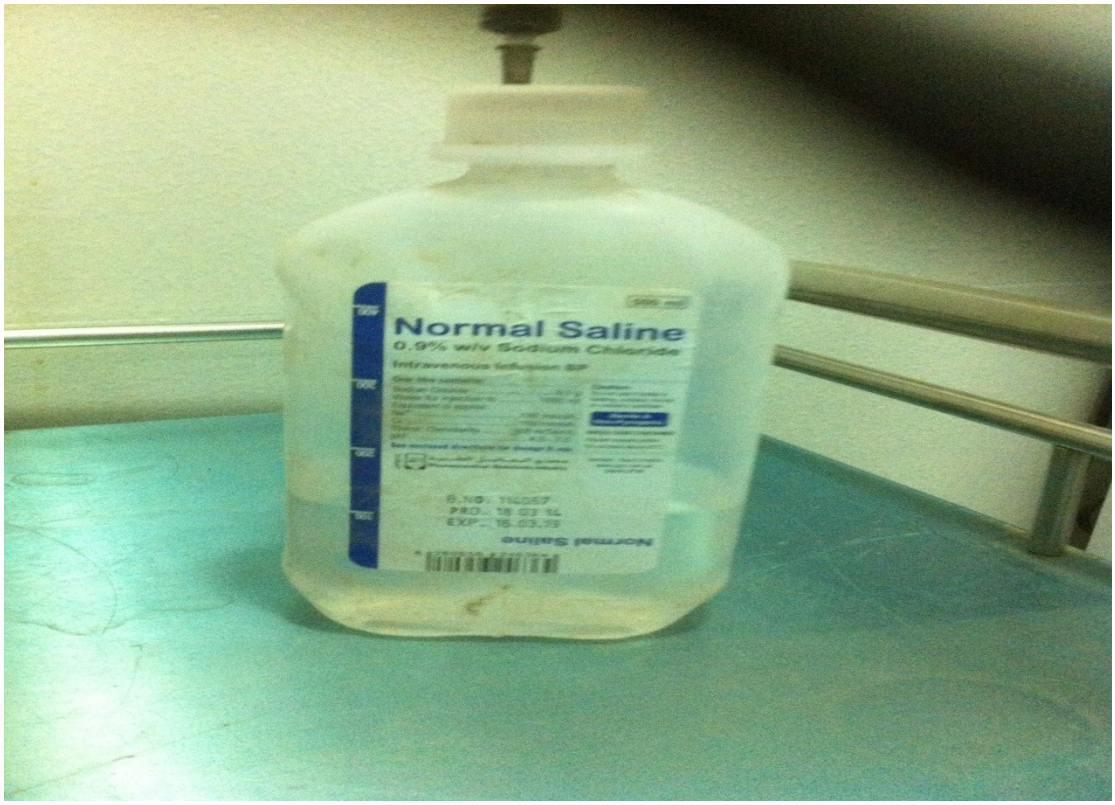
Appendix A



Appendix B


RADIOACTIVE
CONTENTS Mo 99
ACTIVITY 15 GBq
0.9
TRANSPORT INDEX
7

Appendix C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0.9% w/v Sodium Chloride
Intravenous Infusion BP