Quality assurance and quality control at dose calibrator to support nuclear medicine services

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Abstract. One of the most important factors in health services is the quality and speed of service. However, the speed of service must be supported by the quality of service. Quality is often used as a benchmark and differentiator for a health service. Therefore, all producers and providers of health services must look for ways to maintain and improve their quality. In this paper quality assurance (QA) and quality control (QC) will be presented at the dose calibrator (DC) to support nuclear medicine services. DC is a very useful tool for measuring radiopharmaceutical activity / dose (which will be given to patients) for diagnostic or therapeutic purposes. For accurate measurements, DC must be calibrated routinely, must pay attention to electronic factors, statistical considerations, ion recombination, background radiation, the source and volume container effects, source position, source adsorption, pure beta transmitter measurements and the presence of contaminants. One of the successes of patient care in nuclear medicine (NM) is by giving accurate doses, according to the type of cancer, the volume and severity of cancer cells. Accurate doses can be achieved by implementing QA and QC at DC, which starts from the calibration stage, checks stability, linearity, and pays attention to parameters that can affect measurement. The aim is to ensure that the measurement results meet the requirements and quality standards set. There are 5 parameters that can support QC implementation, namely PC3M: Person, Chain, Machine, Material and Method. If one of these 5 parameters is missing then QC cannot be implemented.

1. Introduction
The use of ionizing radiation in medical physics, nuclear medicine, and research brings great benefits to people when used in a safe manner, meaning that it meets the applicable rules [1,2]. However, the potential for radiation risk must be assessed and controlled, one of which is by conducting QA and QC.

QC is an activity of researching, developing, designing to provide good service and meet customer / customer satisfaction where the implementation involves all personnel in the company / agency, starting from the top leadership to executive employees (Dr. K. Ishikawa) [3].

One of the most important factors in competing health services is service quality. Quality is often used as a benchmark and differentiator for a service. Therefore, service providers must find ways to improve the quality of services. Quality can be interpreted as the level of good or bad of a service product produced, and whether the product produced is in accordance with specifications that have been determined or according to needs.
To maintain and improve quality, QC and QA can be used as Inspecting, Testing and Grading functions. By using statistics, good and bad results can be obtained (grading), so that it can be determined which are acceptable and which are rejected [5].

The aim of QA and QC is to ensure that service products have met the requirements and quality standards set means that the products or services to be provided to customers are free from defects. If a defective service is found that is not in accordance with what is offered, corrective action is needed. Therefore, every organization that applies QC must have a Quality Manual, which is distributed to customers, so that customers can find out the quality of services offered.

2. Literature review

Nuclear medicine (NM) is a branch of medical science that uses radionuclides to diagnose, staging diseases, therapy and monitoring the response of disease processes. Nuclear medicine is a powerful translation tool in basic sciences such as biology, and the discovery of drugs and pre-clinical medicine. Development at NM was facilitated by sophistication in multi-disciplinary science, which included: physics, chemistry, computers, mathematics, pharmacology and biology.

The tool used in NM to measure radioactivity is Calibrated Ionization Chamber, known as Well Ionization Chamber or Dose Calibrator (DC) (Figure 1a, 1b, 1c) [16,17]. DC consist of cylindrical chamber, connected with an electrometer controlled by a microprocessor, calibrated with a radionuclide range commonly used in NM.

The chamber is made of aluminum which is filled with argon gas, pressurized (1-2) MPa, or (10-20) atmosphere. DC with lower gas pressure are usually used in the Positron Emmission Tomography (PET) production facility, where the measured activity is very large.

For quality assurance (QA), DC must be calibrated annually, based on the PERKA BAPETEN No. 1/2006 [2]. For appropriate evaluation and maintenance, DC is routinely tested for performance, especially the linearity test. This test aims to evaluate whether the device is still capable of measuring radiopharmaceutical activity in a number of different activities according to activities used in both diagnostic and therapeutic [6,19, 20].

Many DC types and designs are present at Figure 2, but generally a typical IC consists of a gas-filled tube and electrode present at Figure 1. The type of gas used varies, so does the volume, pressure and stress of the work, so it has a different response. Radiation entering the ionizing chamber, will ionize the gas in the ionizing chamber tube into positive ions and electrons. Because of the influence of the electric field of the detector work voltage, the ions will be swept in the opposite direction. The collection of charged particles will produce ionization currents that are in accordance with the measured radionuclide activity

Each radionuclide has different energies, as well as its gamma probability. For the same activity of a radionuclide it will produce different ionization levels in the ionizing chamber gas cylinders. Ionizing room wall material, wall thickness, filled gas type, pressure and volume, radionuclide type, holder thickness, measurement position, radionuclide shape / volume will affect the level of ionization, and therefore will affect the calibration figure. Each radionuclide has a unique calibration figure (CF), with units of pA / MBq or pA / photon.

Dose Calibrator are usually equipped with Well-liners, which are made of materials with a low atomic number (Z) (such as Perspex or Lucite), which can be replaced if contamination occurs. The sample holder is provided by the manufacturer to place a vial or syring so that its position is at the maximum position of measurement. Dose Calibrator is equipped with a printer, to print measurable activity documents or RS-232 serial communication ports or USB ports for Calibrator interfaces to Computerized Radiopharmacy Management Systems.

DC is usually given a shield by the manufacturer with a 6 mm Pb shield to reduce background reading. Depending on the DC location, the user may add shields, whether to reduce the background inside the chamber or to protect the operator when measuring radionuclides with high energy and activity. This will cause a change in calibration factor due to backscattering and X-ray emission from
Pb shield. If used for shielding, DC must be recalibrated to ensure that activity readings remain correct.

Dose Calibrator is calibrated in terms of activity, that is by comparing DC readings with standard activities, which are directly traceable to national primary standards. National primary standards are maintained by NMI (National Metrology Institute), such as National Physical Laboratory (NPL) in the UK (United Kingdom), ANSTO in Australia or SSDL-Jakarta (Secondary Standard Dosimetry Laboratory) in Indonesia.

3. Method

By using standard activity, the efficiency of the Ionization Chamber (IC) can be determined for each radionuclide (RN), by using equation (1)

\[ \frac{I_x}{I_{Ra}} = \varepsilon_N(x) A_x \]

Where:

\[ I_x \]: Current produced by radionuclides inside of IC (pA)
\[ I_{Ra} \]: The current produced by 226Ra
\[ \varepsilon_N(x) \]: IC efficiency with RN-X.
\[ p_i (E_i) \]: Probability of emission per decay photon on Ei energy
\[ \varepsilon_i (E_i) \]: IC efficiency against energy

4. Equipment and materials

- Dose Calibrator (Figure 1a, 1b, 1c.)
- Standard sources: 137Cs, 60Co, 54Mn, 65Zn (Table 1)

Figure 1a. Dose Calibrator Capintec CRC-7BT [16].
Figure 1b. Dose Calibrator CRC25R [17].
Figure 1c. Atomlab 500 Dose Calibrator [17].

Ionization Chamber or DC is placed in a conditioned room, in accordance with the manual instruction of the equipment. For stability reading, follow the instructions from the manual. For testing readability and stability, sources of 137Cs (half life 30 years) or other radionuclides can be used that
have a long half-life such as $^{226}$Ra (1600 years). For linearity test, it can be used $^{99m}$Tc with adequate activity (example: 5 mCi).

![Figure 2](image_url)

**Figure 2.** Dose calibrator / ionization chamber system.

5. Results and discussion

In figure 3 and table 1 was presented the efficiency of the Ionization Chamber, Merlin Gerin against standard radionuclides, the calculation of efficiency was used equation (2).

![Figure 3](image_url)

**Figure 3.** IC efficiency curve against radionuclides with photon energy, $E_i$ [6].

The thin-walled aluminum chamber shows the peak power efficiency at about 50 keV photon energy. This IC efficiency curve depends on gamma energy because the IC must be calibrated for each nuclide.

The uncertainty of standard sources and the uncertainty of the efficiency of IC or DC will contribute to the uncertainty in measuring the radiopharmaceutical activity to be given to patients.

**Table 1.** IC merlin gerin efficiency.

| RN      | $E$(keV)         | Activity (MBq) | Efficiency pA/MBq |
|---------|------------------|----------------|------------------|
| Co-60 PTB | 1173 (99.9%)     | 1,86607        | 0.160995         |
|         | 1332 (100%)      |                |                  |
| Mn-54 ETL | 834 (100)        | 0.12823        | 0.227130         |
| Cs-137 NPL | 641.6 (89.8%)  | 1.40384        | 0.1009           |
| Co-57 ETL | 118.9            | 4.4203         | 0.0486           |
| RN    | E(keV)                  | Activity (MBq) | Efficiency pA/MBq |
|-------|-------------------------|----------------|------------------|
| Cd-109 PTB | 14 (9,19%)             | 17,685         | 0.06366          |
|        | 122 (85.6%)             |                |                  |
|        | 136,5 (10.6%)           |                |                  |
|        | 692 (0.16%)             |                |                  |
| Zn-65 ETL | 511 (2.92%)            | 147,78         | 0.33158          |
|        | 1116 (50.7%)            |                |                  |

5.1 Uncertainty of dose calibrator (DC)

5.1.1 Calibration / efficiency factor. For medical radionuclides, such as $^{99m}$Tc, and $^{131}$I, typical uncertainties of national standards are usually around (1-3)%. When a standard is used to calibrate a medical DC, the uncertainty will be greater because of the inherent limit on instrument repetition. In addition, calibration factors for the size and thickness of certain vials and the volume of solutions are used for national standards. Calibration factors for different containers (example: syring), and or different volumes will vary / differ from the specified calibration.

5.1.2 Electronic. The electrometer measures the output current of a DC with a range of 10 fA to $\mu$A, according to the level of activity from kBq to hundreds of GBq. Modern DC automatically adjusts the range when measuring, while old DC, the range must be chosen by the operator. The potential for different linear characteristics for each range will produce discontinuities when the range is changed. The influence of inherent accuracy, linearity and range changes, is shown in figure 4.

![Figure 4](image-url)

**Figure 4.** Inaccuracy of electrometer [6].

5.1.3 Statistical considerations. Repetition of measurements on a single sample will not be identical because the nature of radioactive decay is random. If the measurement period is constant, the precision of the measured activity will increase if the activity increases, otherwise the precision will decrease for sources with low activity.

5.1.4 Ion recombination. If the activity of the radioactive source increases, the recombination probability of positive and electron ions increases (Figure 5). In high activity, the effect of recombination will be significant, and lead to a reduction in current measurements. For most modern DCs, the recombination effect is less than 1% when measuring $^{99m}$Tc with 100 GBq of activity.
5.1.5 Radiation background. When the source holder is empty, DC will still record a reading that is not zero, because of background radiation. This measurement will include natural background and from contaminants in the holder or well-liner. Therefore it is important to do a regular check on the background radiation level.

5.1.6 The source and volume container effects. Variations in the composition and thickness of the source of containers increase according to the variation of activity measured. The effect will be evident for transmitting low energy photons and pure beta transmitters. Examples of measurements carried out in the NPL, UK (Table 2), showed that variations in the thickness of the glass wall caused errors of up to 7% for $^{125}$I.

When the activity is moved to syringe, the source geometry will be different from the Vial. Not only is the composition and thickness of the syringe wall different, but also the distribution of sources will differ depending on the size of the syringe used. This evidence is clearly presented in Figure 6, measurement in NPL for $^{111}$In source in 3 syringe volume sizes from two different manufacturers for standard P6 vial. Effect of volume changes without changes in activity. Self-absorption of the emitted radiation will change if the volume changes. This is important for low energy radionuclides such as $^{123}$I. For a $^{99m}$Tc correction it is usually less than 1% but it must be confirmed for a new Dose Calibrator or if the supplier is changing.

5.1.7 Source position. The source holder from manufacturing is designed to keep the source in the maximum response area on the vertical axis of the chamber. Variation in response because changes in vertical height or horizontal position of several mm are usually not significant.

| Radionuclide | Decreased response with increasing vial wall thickness |
|--------------|-------------------------------------------------------|
| $^{125}$I    | 0.08 mm | 0.2 mm |
| $^{123}$I    | 3%      | 7%     |
| $^{111}$In   | 0.6%    | 1.5%   |
| $^{131}$I    | 0.2%    | 0.4%   |
|              | 0.1%    | 0.25%  |

Table 2. Decreasing DC response due to increased thickness of glass vial walls.

Geometry variations and sample size can affect measurements. For example, in figure 6. the results of measurements of sample activity are presented with variations in the geometry of sample $^{111}$I and different vial materials, even though the activity should be the same.
5.1.8 Source adsorption. Certain radiopharmaceuticals have been observed, absorbed by the surface of the container. Example: ²⁰¹Tl activity is absorbed by P6 Vial glasses by up to 30%. ⁹⁹mTc - Tetrofosmin is absorbed by syring by 19% while ⁹⁹mTc-Macro Aggregate Albumin (MAA) is absorbed by up to 15%. It should be considered if the syringes are used from other manufacturers.

5.1.9 Measurement of pure beta transmitter. The efficiency of DC for beta radiation is mostly low. Beta particles are absorbed in the source solution (self absorption), inside the walls of the container, or by the walls of the IC. The DC response of beta particles is almost entirely from bremsstrahlung radiation. For energy ROI for DC measurements, the spectrum of bremsstrahlung photons is the same as beta energy distribution.

Measurements of pure beta transmitters for therapies such as: ³²P, ⁹⁰Sr, and ⁹⁰Y must consider geometry factors and the system must be calibrated for specific containers, the volume of samples used clinically.

Manufacturing now produces specific DC for measuring beta transmitters. The use of the NaI (Tl) detector instead of DC results in increased detection efficiency, but the manufacturer states in its product literature, measurements still require attention to the sample container, sample volume and activity concentration to achieve accurate results.

Most commercially available IC are equipped with calibration factors for beta transmitters which are commonly used in vial containers. The type of vial used for calibration is not specific, so the user must verify himself for the vial used in practice. Calibration of activities in syringe size used in the clinic must be established.

The results of the comparison of efficiency of intrinsic DC from 5 different manufacturers found that all systems have good calibration for ³²P, decreased efficiency (10-20)% for ⁹⁰Sr, and wide divergence for ⁹⁰Sr. For these radionuclides, the results obtained use a manufacturing supply calibration factor, ranging from 64% to 144% of the true value. It needs to be confirmed in the nuclear medicine section, so that it can be re-calibrated.

Some pure beta transmitters used for therapy contain gamma rays. These radionuclides include ¹³¹I (364 keV, 81.5%); ¹⁸⁶Re (137keV, 9.5%). For such radionuclides, the efficiency of the IC, primarily determined by the contribution of gamma, and calibration supplied by the manufacturer are usually accurate in ±10% [5].
5.2 Contaminant problems

Radionuclide solutions are not 100% pure, the proportion of total radioactivity present as specific radionuclides is defined as radionuclide purity. National and international pharmacopoeia provide specifications for radiopharmaceutical radionuclide purity. For example, European Pharmacopoeia, requires injection of $^{67}\text{Ga-citrate}$, no more containing $^{66}\text{Ga}$ (0.2%), while Pharmacopoeia US, requires injection of $^{67}\text{Ga}$ citrate (99%).

The presence of contaminants although less than 1% can increase the effect on the current of the Ionization Chamber (IC) and on the activity measured. British Pharmacopoeia provides specifications for $^{201}\text{Tl}$ Thallous-Cloride, no more than 2% ($^{202}\text{Tl}$), not less than 97% ($^{201}\text{Tl}$). $T_{1/2}$ ($^{202}\text{Tl}$): 12.2 days and the main photon energy is 440 keV. Another possible contaminant is $^{200}\text{Tl}$, which has a half-life of 1.09 days, and energy: 368 keV and 1.2 MeV.

The contaminants of the two radionuclides will have high efficiency in a DC. If the half-time of $^{201}\text{Tl}$ is longer than $^{201}\text{Tl}$, the relative proportion of $^{202}\text{Tl}$ to $^{201}\text{Tl}$ will increase with time. If the DC accuracy is checked with a $^{201}\text{Tl}$ source, false accuracy can change depending on when the measurements are made, relative to those stated on the calibration date.

Other possible contaminants are $^{200}\text{Tl}$, which has a half-life of 1.09 days, and energy: 368 keV and 1.2 MeV. These two radionuclide contaminants will have high efficiency in a DC. If the half-life of $^{202}\text{Tl}$ is longer than $^{201}\text{Tl}$, the relative proportion of $^{202}\text{Tl}$ to $^{201}\text{Tl}$ will increase with time. If DC accuracy is checked with a $^{201}\text{Tl}$ source, pseudo accuracy can change depending on when the measurement was made, relative to what was stated on the calibration date. The presence of high energy contaminants will have a detrimental effect on image quality because septal penetration increases and will also increase the radiation dose to the patient.

5.3 Quality control dose calibrator acceptance test

DC acceptability tests include: measurements of accuracy, repeatability, linearity, and geometry response. The aim is to ensure the unit meets manufacturer's specifications and provides basic figures for quality control [8,9,10,11].

5.3.1 Accuracy and repeatability. Accuracy is determined by comparing measurements of activities using a calibrated or traceable standard with the activities stated by the Lab. Primary or Secondary, corrected by radioactive decay. Accuracy is expressed in percent deviations from the actual activity and should be measured for all radionuclides to be used routinely. It is recommended that source measurements with a long half-life, such as: $^{137}\text{Cs}$, be corrected at the start of the test, for each radionuclide setting, which is used clinically for quality control.

Repeatability or constancy or stability can be tested by repeated measurements from the same source. Examples of measurements of repeatability are presented in figures 7, the repeatability of measurement should be in between $\bar{X} \pm 2\sigma$ (standard deviation).

![Figure 7. Repeatability of capintec CRC7BT using $^{137}\text{Cs}$ [12, 14].](image-url)
The stability of DC can be checked by $^{137}$Cs (Half life 30 years), see Figure 8 and 9. The stability of instrument should be In linear regression.

![Figure 8](image1.png)

**Figure 8.** Stability check of merlin gerin IC using $^{137}$Cs [12,14].

![Figure 9](image2.png)

**Figure 9.** Stability check of CAPINTEC using $^{137}$Cs [12,14].

To check the stability of Ionization Chamber or Dose Calibrators can be used $^{226}$Ra or $^{137}$Cs or other radionuclides that emit gamma, with a long half-life.

5.3.2. Linearity. There are several approaches to measurement of a DC linearity response. Typically, a vial containing $^{99m}$Tc of high activity is measured repeatedly in a period of at least 5 days. During this time, the 100 GBq source will decay to 0.1 MBq. It is important that the initial activity represents the highest activity that might be used in clinical practice, which is usually the initial elution of the new Mo / Tc generator. The semi-log plot of the measurement corrected background, must follow the expected decay of radionuclides [7].

Each deviation from the expected line in high activity shows the saturation of the IC response, accurate background measurements at the time of each test. It is important if the background will be a component that increases reading such as source decay. The deviation from linearity at low activity may be due to the impurity of radionuclides, such as Mo in a vial containing $^{99m}$Tc.

Another approach that can be used to examine linearity requires a series of radioactive sources that cover the range of activities to be measured. The source must be prepared from the same solution stock and the volume distributed (dispensed volume) is measured accurately by weighing the vials before and after dispensing. The volume of solution in each vial must be arranged with non-radioactive solution, so the volume is identical in each vial, to eliminate any geometric dependence on the measurement. Measured activity was corrected for decay to the measurement time from the first vial and plotted against volume dispensing to test DC linearity. The error in this method will increase
if there are small variations in the vial wall thickness, otherwise all the vials are the same for all measurements [20].

Finally, linearity can be tested by repeated measurements in a single vial using a series of multilevel attenuators suitable for specific test sources. This is a typical series of concentric cylinders, which correspond to the vial. Attenuation through each cylinder must be known accurately to use this method.

5.3.3. Geometry response. Measured activity may vary with the position of the source in the IC, with the composition of vials or syringes or the volume of fluid in vials or syringes. Correction factors must be established for the containers and radionuclides to be used clinically, especially if radionuclides having low energy, such as $^{123}$I, are to be used.

For each vial or syringe to be used, a series of measurements must be taken so that the activity remains constant but the volume increases from 10 to 90% of the maximum volume with the addition of water or saline. Correction of decay, the activity plot against volume must be a straight horizontal line. Each deviation from this, can be used to calculate the appropriate correction factor.

The correction factor for vials to syringes can be determined by measuring the activity that is transferred from vials to syringes. (original vial activity minus residual activity) and compare this to the measured activity in the syringe. The geometry dependence should not change with time, but if the practitioner changes the fabric manufacturing of the syringe or obtains radiopharmaceuticals in different vial sizes, then it must be determined.

There are 5 parameters that can support the implementation of QC, namely PC3M: Person, Chain, Machine, Material and Method. These five parameters must run together in order to implement QC. If one of these 5 parameters does not exist, the QC cannot run properly.

6. Conclusion
A very important factor in market competition is service quality. The service provider must be able to maintain and improve the quality of the service provided for the customer.

The success of nuclear medicine patient care is by giving accurate doses, according to the type of cancer, volume and severity of cancer cells. An accurate dose can be achieved by implementing QA and QC on the dose calibrator, which starts from the stage of calibration, determination of efficiency, checks stability, and considers sources that can affect the measurement.

There are 5 parameters that can support the implementation of QA and QC, namely PC3M: Person, Chain, Machine, Material and Method. These five parameters must run together in order to implement QA and QC. If one of these 5 parameters does not exist, the QC cannot run properly.

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