The Science of Measurement:
A Primer on Radioactivity Dose Calibrators

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

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SCIENCE OF MEASUREMENT:
A PRIMER ON RADIOACTIVITY DOSE CALIBRATORS

STATEMENT OF LEARNING OBJECTIVES:

The first section will provide an overview of the use of gas-filled ionization chambers or radioactivity calibrators, more commonly termed dose calibrators, as measuring instruments. Instrument-related variance/variables that may impact dose assays will also be addressed. The second section will address the issue of measuring different radionuclides. External variables that impact the accuracy of measuring patient dosage will be discussed as well as methods to increase assay accuracy.

Upon successful completion of this lesson, the reader should be able to:

1. Explain how a dose calibrator is used to measure radioactivity
2. Discuss the NRC required tests and their application to daily use of the dose calibrator.
3. Define the terms precision, accuracy, reliability, traceability and percent variance as pertain to dose calibrators. Give an example of each.
4. Discuss the contribution of container type and material to assay variance.
5. Describe the effects of volume [geometry], decay mode, emissions and energy on assays.
6. Explain Standard Reference Material and methods for use that contribute to calibrator accuracy and reliability in patient doses.
7. Determine a calibration factor for an isotope in a specific configuration.
8. Explain apparent variance between calibrators as a function of any of the above.
9. Discuss how one knows that the patient dose is "correct".

COURSE OUTLINE

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Science of Measurement: A Primer on Activity Calibrators

Gabriel Candelaria and Daniel Irwin

ACTIVITY CALIBRATOR

Introduction

The dose calibrator is a gas-filled ionization chamber used to measure the ionizing radiation exposure of a given radioisotope. It is most commonly employed during the compounding of radiopharmaceuticals and in verifying patient dose radioactivities prior to administration. Calibrators are generally gas-filled cylinders with a well in the center of the ionization chamber into which the radioactivity is placed. One example, the Capintec CRC-15R dose calibrator has a well depth and diameter of 25.4cm and 6.1cm, respectively.[1] The geometric goal is to have the measured radiation source placed within the well to simulate the ideal 4π geometry, that of a point source in the center of a spherical detector (Figure 1). The reproducibility of the placement within the well is critical, as it is well known that the response for most chambers drops off at the top and bottom of the chambers due to combination of geometry and electronic effects.

Figure 1. Well Design Simulating 4π Geometry

These ionization chamber radiation detectors are typically filled with highly pressurized Argon [^{18}Ar] gas, compressed to around 20 atmospheres[2], and are theoretically able to measure activities anywhere from 1μCi-20Ci (3.7kBq – 740MBq). The highly compressed gas creates an ionic environment that favors the possibility of ionizing events. There is a direct correlation between the increased gas pressure and detector efficiency.

Radioactive decay can produce high-energy photons or charged particles that can interact with and deposit their energy into the surrounding gas medium. High-energy photons interact in three direct ways: photoelectric effect, Compton scattering and pair production. In all of these interactions between photons and matter (the argon gas), energy is transferred, leaving a trail of ion pairs behind. The primary mode by which photons interact with the gas medium is through Compton scattering. Compton scattering is the dominant interaction at 100keV-10MeV, including those energies most commonly found in nuclear medicine procedures, namely 100- 511keV.[1]

Compton scattering can be thought of as a collision between the photon and an outer shell electron. This collision transfers a portion of the photon's energy to the electron, knocking it free, while sending the photon off at some angle θ. The freed electron creates its own path of ionization in addition to the ionization of the scattered photon.

$$E_{Sc} = \frac{E_0}{1+\left(\frac{E_0}{0.511}\right)(1-cos\theta)} \quad \text{Eqn. 1} \ ^{(3)}$$

Where E_{Sc} = Energy of the scattered photon, in MeV
E_0 = Energy of the incoming photon, in MeV
θ = angle of deflection between the photon and the scattered electron

This interaction transfers its energy to the gas molecules within the detector space creating ion pairs. At lower energies, the photon maintains the majority of its initial energy. However at higher energies, for example 10MeV, the majority of the energy is transferred to the electron.

The photoelectric effect is a process involving the total absorption of the incident photon energy into the atom causing an electron to be ejected from the K-shell orbital:

$$E_{PE} = E_0 - K_B \quad \text{Eqn. 2} \ ^{(3)}$$

where E_0 is the initial energy of the incoming photon and K_B is the binding energy of the K-shell of the atom. In order for this interaction to occur the photon must have energy equal to or greater than the binding energy holding the electron in the orbital shell within the atom. The photoelectric effect dominates at lower energy and higher atomic numbers due to the following relationship:

$$PE \sim \frac{Z^3}{E^3} \quad \text{Eqn. 3} \ ^{(11)}$$

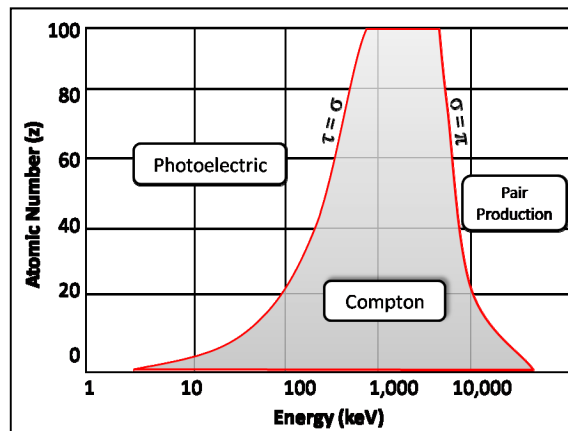The photoelectric effect decreases rapidly with increasing photon energy (Figure 2).

Figure 2. Region of Dominant Interaction

Pair production is a more exotic interaction and dominates at very high-energy, greater than 10MeV. Because of the high-energy requirement, pair production interactions are not common in nuclear medicine. Pair production requires a **minimum** energy that is twice the rest mass of an electron or 1.022MeV.

An indirect interaction which poses problems in measurement for certain radionuclides is Bremsstrahlung radiation. Bremsstrahlung is the German word for "braking". Bremsstrahlung occurs when an electron interacts with the positively charge atomic nucleus and its path is deflected (or bent). This deflection causes the electron to emit x-rays in a continuous spectrum with the average energy of the emission being one third that of the maximum energy. This poses a problem when measuring pure beta emitting sources such as ^{90}Y. The emitted beta particle undergoes numerous interactions from within the source itself, the vial and the outside wall of the detector before it even reaches the detector volume.

How It Works

To collect the ion pairs created from these interactions, the detector has an applied voltage with the negative cathode as the chamber wall and a positive anode within the ionization chamber. After ionization, positively charged ions (cations) drift toward the cathode and the negatively charged ions (anions) drift toward the anode. The dose calibrator is very effective at measuring radiation since the number of ion pairs is directly related to the amount of energy deposited within the detector.[1]

The positive and negative charge is supplied by a high-voltage supply, or a battery acting as a capacitor, within the dose calibrator (Figure 3). This battery keeps the voltage on the cathode and anode constant and functions as a backup if there is ever a power outage to keep the calibration factors stored in memory.

The dose calibrator operates in the "ionization chamber" region of the voltage response curve shown in figure 4, where the ion pairs created by the radiation are collected. An increase in the
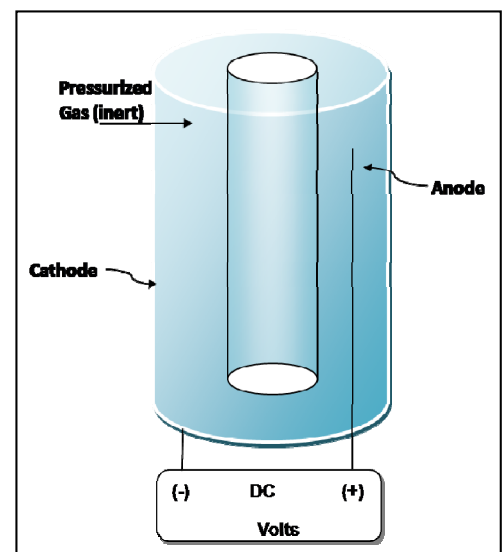

Figure 3. Basic Structure of Activity calibrator Chamber

voltage does not significantly increase the number of ion pairs collected. Since the number of collected ion pairs is essentially constant, the current that is generated and measured is also essentially constant. This is called the *ionization chamber plateau*: there is no increase in measured current because all ion pairs are collected and there is no recombination of pairs taking place (Figure 4).[3] This results in the collection of a steady current that is an accurate measurement of the ion pairs being created within the chamber. If a volume of gas is irradiated at a constant rate, a constant amount of ion pairs are formed, and a constant current is generated. [4]

The advantage of measuring the charge generated within the volume is that the current generated can be directly correlated to the radiation exposure. The activity of the source correlates with the characteristic radiation exposure of each radionuclide. A major disadvantage with the dose calibrator is a lack of information about individual ionization events or the energy(s) generating the current. This makes it impossible for the dose calibrator to identify or distinguish radionuclides in mixed or contaminated samples.
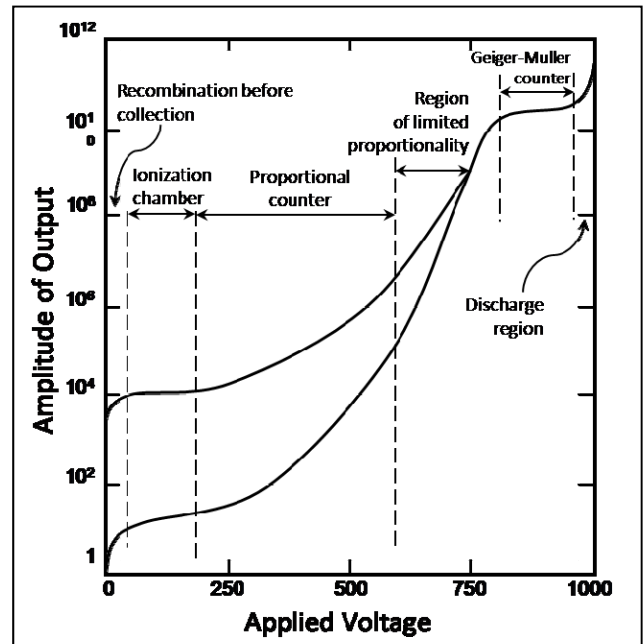
Figure 4. Voltage Response Curve

The dose calibrator differs from solid-crystal well counter in that a gas-filled detector measures ionizations created by photons (radiation), while a solid sodium iodide (NaI(Tl)) crystal directly detects discrete decay events (radioactivity). The ionization plateau collects all ionization events avoiding dead time effects seen with well counters. The well counter is used for counting swipes from around the work area to detect small traces of contamination. The well counter also allows for energy discrimination and presentation of energy spectra of samples.

As stated before the dose calibrator measures the ionization created by a radioactive source placed within the detector. The measured exposure is then converted into activity by the equation below:

$$A = \frac{E \times d^2}{\Gamma} \quad \text{Eqn. 4 }^{(4)}$$

Where A is the calculated activity, E is the measured exposure rate, d is the distance between the source and the detector and Γ is the specific gamma constant. Each radionuclide has different gamma energies emitted with specific probabilities. As a result, each radionuclide will generate different currents within the dose calibrator per decay.[5] This unique ionization, and consequently unique current being measured, is proportional to the amount of radioactivity placed within the detector.[2]

From Eqn. 4 above one can see the impact of the distance (d) in determining the activity. The Inverse Square Law states that the calculated activity is proportional to the square of the distance between the source and detector (i.e., the ionization chamber gas). Small variations in source placement can result in significantly different measurements of activity even for the same source. The dipper that comes with the dose calibrator is designed to minimize discrepancies of the physical placement of the dose. Consistency of the dose location during assay is critical in achieving accurate dose measurements.

The dose calibrator is able to measure high levels of activity because it operates in current mode, which avoids dead-time effects. Dead time effects occur when operating in pulse mode. A sodium iodide crystal, used in well counters, operates in pulse mode to capture ionization events. Each energy event creates a voltage pulse. If the pulses are too frequent as from a high activity source, the detector is unable to count the pulses quickly enough and they begin to blend into one another. This is problematic because information is lost and the resultant measurement isn't a true representation of the activity of the source. The dose calibrator does not directly measure the energy of a radionuclide only the current generated from ionization events, and the measurement is not affected by this problem. To accurately convert the respondent current to a specific radionuclide, a calibration factor must be determined.

Converting current to activity

The unique current produced by a radioactive source is dependent on the specific gamma constant; in other words, the amount of radiation (related to radioactivity) and the energy of the photons. Higher activities generate more photons which, in turn generate more current. The chamber's response is different for 1Bq of ^{99m}Tc (140 keV) and for 1Bq of ^{131}I (364 keV). For the dose calibrator display to read one millicurie (mCi) for both isotopes, a conversion factor must be applied. This is accomplished by using adjustable resistors to regulate the amplifier gain (analog method) or by multiplying the digital output with an isotope specific calibration factor (digital method).[6]

The ion chamber is maintained at a constant voltage in the absence of ionizing radiation from the capacitor. Maintaining a constant voltage is critical when trying to measure the current being detected. Direct current (DC) circuits tend to not be as stable as an alternating current (AC) circuit and so a way to convert the DC output to AC is using a vibrating reed electrometer.[4] Ohm's law allows us to relate the voltage (V) to the current (I) and resistance (R).

$$V = IR \text{ Eqn. 7}$$

The voltage can then be related to the capacitance held within the capacitor attached to the detector volume from the following equation:

$$Q = CV \text{ Eqn. 8}$$

Where Q is the charge held within the capacitor, C is the capacitance of the capacitor and V is the voltage. The reason for relating the voltage to charge stored within the capacitor is because when a charged particle interacts with the anode attached to the capacitor a corresponding change in the capacitance occurs that is proportional to the charge detected. This in turn induces a change in amplitude of the voltage across a resistor within the circuit.[4]

$$\Delta V = \frac{Q}{C^2} \Delta C \text{ Eqn. 9 [4]}$$

By substituting CV for Q and then substituting IR for V the change in voltage can be related to the current.

$$\Delta V = I \frac{R}{C} \Delta C \text{ Eqn. 10 [4]}$$

The amplitude of the voltage measured is then proportional to the amount of current being generated by the ionizing source within the detector space.[4] This shows how critical it is for the voltage to remain constant across the circuit. Any deviation will affect the measurement of the current and give rise to errors.

The calibration factor is determined by measuring the amount of current generated from a specific source with a known activity. These sources can be obtained from the National Institute of Standards and Technology (NIST) and are usually accurate to within 1%. The response of the detector is measured against a source with a known activity, usually ^{60}Co.

$$R_A = \frac{\dfrac{\text{Detector Output Due to Sample A}}{\text{Activity of Sample A}}}{\dfrac{\text{Detector Output Due to Co}^{60}}{\text{Certified Activity of Co}^{60}}} \qquad \text{Eqn.11}^{(1)}$$

Capintec calibrates and certifies each of its units with ^{60}Co and ^{57}Co[1]. Using calibration settings and the chamber response for ^{60}Co and ^{57}Co, the calibration number for isotope R_A can be determined by calculating the average energy per decay for the radionuclide of interest and interpolating along the response curve. This requires that all nuclear and atomic data are correct, and that all radiation (including bremsstrahlung) is properly accounted for in this method.

$$N_A = \left\{ R_A - \left(1 - \frac{(R_{Co_{60}} - R_{Co_{57}})}{(N_{Co_{60}} - N_{Co_{57}})} \times N_{Co_{60}} \right) \right\} \times \frac{(N_{Co_{60}} - N_{Co_{57}})}{(R_{Co_{60}} - R_{Co_{57}})} \quad \text{Eqn.12}^{(1)}$$

In Eqn. 6 above N_A represents the calibration setting number. The difference between the calculated and measured responses lies within $\pm 3\%$ error. [1] Typically the detectors come pre-calibrated for a number of nuclides. For more exotic radionuclides, such as pure beta emitters (^{90}Y) and positron emitters (^{18}F), it is recommended that each institution determine calibration factors specific to the dose calibrator that is being used.

The manufacturer has developed a chamber response curve using a series of long-lived radionuclide sources with activity traceable to NIST (Figure 5). Activity calibrators have a separate resistor or (digital) setting for each nuclide to be calibrated, based on the curve determined for the calibrator. The settings for selected nuclides are normalized to this curve. Where traceable standards are not available, settings are determined by
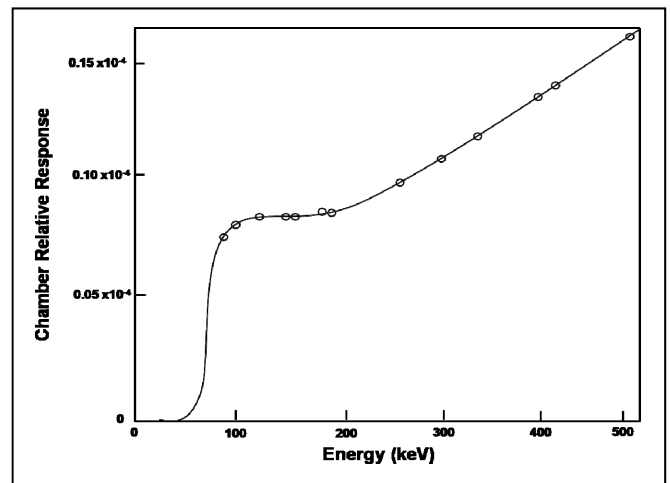

Figure 5. Relative response (current) in ionization chamber by gamma emission[8]

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[1] It should be stressed that this procedure applies to Capintec and that other manufacturers do it differently.

interpolation. In older dose calibrators, pressing the nuclide selector button changes the resistance to match the nuclide. Newer units use digital conversion factors. A manual mode allows the user to "dial in" conversion factors not available on the preset buttons. The conversion factor is applied to the current measured when a source is placed into the well.

Quality Assurance (QA)

The Nuclear Regulatory Commission (NRC) requires that regular quality control be performed on dose calibrators and that the records be retained for at least 3 years. A regular schedule should be in place in order to ensure the accuracy of all measurements made on the dose calibrator. Routine checks include daily constancy tests and periodic accuracy and linearity tests. The geometrical dependency needs to be checked upon installation, after service and anytime the detector has been moved. [7] The NRC (or Agreement State) regulations must be met by the institution's Radioactive Materials License. It is this license that should be referenced when making a determination as to whether or not the machine meets the requirements set by the local institution.

Constancy involves zeroing the dose calibrator and then subtracting the background within the room. Constancy is defined by the NRC as the ability to reproduce the measurement of a NIST source of a long period of time. [8] A long-lived source such as ^{137}Cs or ^{57}Co, is used so that direct comparisons measurements can be made over a long period of time. Day-to-day readings should agree to within $\pm$10%, percent error, or better [2] and should be recorded daily. If there is greater than the $\pm$10% error the unit must either be repaired or replaced.[8]

Accuracy is defined by the NRC as the ability to make an accurate reading of a NIST calibrated source. [12] NIST traceable sources such as ^{57}Co, ^{137}Cs and ^{133}Ba and ^{22}Na are often used. Three measurements of each isotope are made and then averaged together. The decay corrected value should once again fall within the $\pm$5% error.[8]

Linearity determines the response of the dose calibrator over a wide range of activities and time with ^{99m}Tc, ^{18}F, or some other short lived and readily available radionuclide. This is necessary to establish the operating limits of the instrument across the dynamic range of radioactivity. The NRC specifies that linearity must be confirmed from an activity of 30μCi to whatever the maximum activity that is used at the clinic. [8] The measurements can be plotted versus time on a semi-log graph.[9] Each point

should be within ±10% of the measured value and that same point on a best-fit curve.[8] An alternative method used to measure linearity is with different thicknesses of lead sleeves that slide into the dose calibrator. These sleeves are designed to attenuate radiation from the source and mimic the actual physical decay of the nuclide. The advantage of this method is that it saves time and energy and does not consume the nuclide being used. The manufacturer's product directions should be followed, including an initial physical decay calibration to be sure the sleeves are accurately estimating decay. [9] Great care should be used when handling the lead sleeves since they are soft and easily bent. Any change in the geometry of the sleeves causes errors in measurement wasting time and money. If the linearity at certain points is greater than 10%, a correction factor should be applied in the range where the error occurred. [9] Calculating correction factors can be done as follows:

$$correction\ factor = \frac{expected\ value}{measured\ activity} \text{Eqn.13 [2]}$$

Alternatively one may use a decay method in which an initial activity of Tc-99m is measured at various time intervals after the assigned reference time (ART), decay correcting the observed activity to the ART using equation 14 (the decay equation), and comparing the decay-corrected observed activity to the initial reference activity. This method maybe further simplified by selecting ART +6, 12, 24, 30 and 48 hours, respectively and applying the decay factors calculated in table 1.

$$A = A_0 e^{-kt} \text{ where } k = 0.693/t1/2 \quad \text{Eqn. 14}$$

Table 1.

Decay correction factors					
Day-time	**Reading**	**Elapsed time**	**Factor**	**Calc Act**	**% Difference**
1-0600	500 mCi	-32 hours	40.2	498.12	0.04%
1-1400	201 mCi	-24 hours	15.9	197.9	1.56%
2-0700	27.3 mCi	-7 hours	2.24	27.8 mCi	1.8%
2-1400	12.4 mCi	** 0	1	12.4 mCi	0
3-0600	2.0 mCi	+16 hours	0.158	1.96	2.0%
3-1500	71 uCi	-25 hours	0.056	0.69	2.48%

The dose calibrator works most efficiently when the activity is placed as low as possible, but still within the region of maximum (constant) response. This is ensured by using only the "dipper" supplied by the instrument manufacturer, rather than after-market equipment which may not place the sample in

the optimum position within the well chamber. More detector surface area is exposed to the activity which will give a more accurate representation of the activity being assayed. Geometrical variability depends on where the source is placed within the detector and the volume assayed. To test for geometrical affects a ^{99m}Tc source should be placed inside the dose calibrator in the same position and fashion as it when assaying patient doses. [9] Replicating the geometry is important because there will be variability depending on its placement within the detector. These effects can be minimized through a conscious effort on the part of the operator making these measurements. By adding saline incrementally to the dose, it is possible to see how the response of the detector changes. The difference in measurement should never be greater than $\pm$10% of the original assay of the dose.[8] The calibration settings are only valid for a specific geometry. If there is a change in how the dose is assayed, i.e. without the dipper, the dial setting should be recalibrated with the new geometrical setup. [9]

Conclusion on Activity calibrator

The dose calibrator is a highly pressurized gas filled ionization chamber which measures the amount of ionization generated by a radioactive source via the Compton scattering interaction. Individual nuclides will cause a different amount of ionization within the chamber due to the gamma constant associated with each particular nuclide. The differing amount of ionization necessitates normalizing the response of the detector to a known source with known activity, for the CRC-15R ^{60}Co.

A properly calibrated dose calibrator is critical to good patient care. The stochastic nature of radioactivity gives rise to some intrinsic error and it is critical that work be done to mitigate error in measurement. Following the standard QA protocol, as discussed above, will help yield more accurate dose measurements and also alert the facility to any malfunctions that could potentially result in administration errors.

ACTIVITY CALIBRATOR PRACTICAL CONSIDERATIONS

Introduction

Activity calibrators are used clinically to measure the amount of radioactivity in a radiopharmaceutical prior to patient administration. The amount of radioactivity is determined by measuring the current produced as radiation ionizes a volume of pressurized gas that fills the dose calibrator chamber.

Measurement of radioactive materials using a dose calibrator is dependent on the characteristic emissions from the particular radionuclide. Differences in emissions between the various radionuclides are accounted for by using different dial settings (calibration factor) to accurately relate the response of the dose calibrator to units of radioactivity (Figure 6). In addition to calibrating the instrument for the particular radionuclide being measured, it might also be necessary to correct for the different types of containers used (Figure 7) and their ranges of filling volumes (Figure 8).
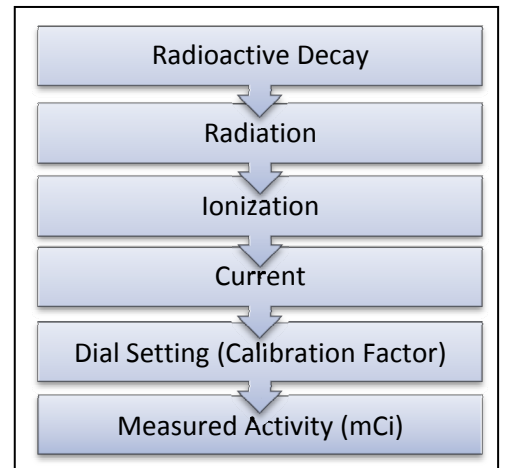

Figure 6. Measurement of radioactive materials.
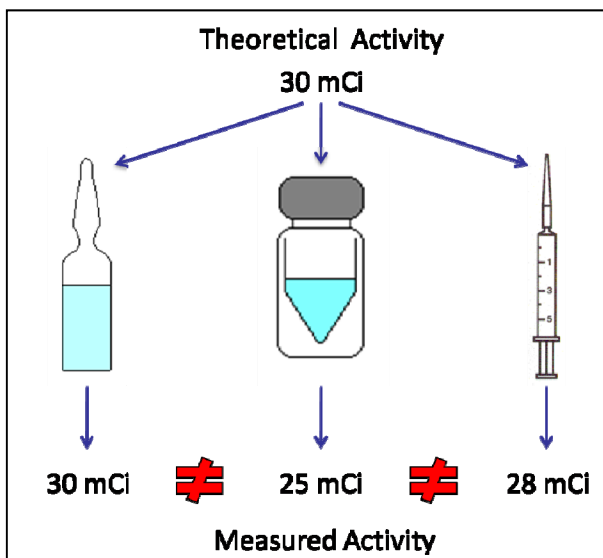
Figure 7. Correction may be necessary for the different containers used in the measurement of radioactive materials.
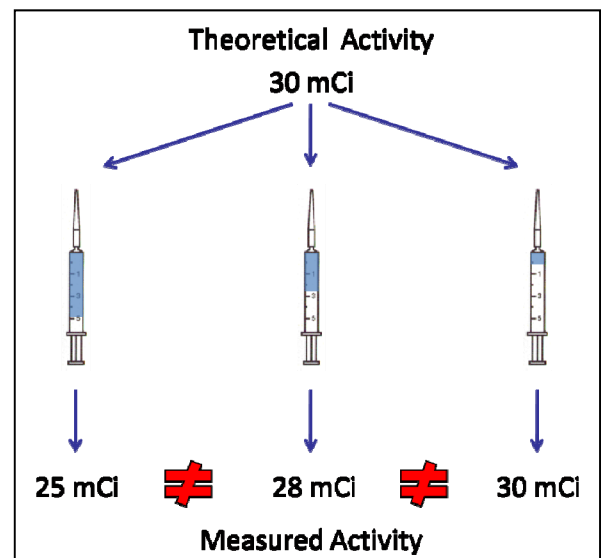
Figure 8. Correction may be necessary when measuring radioactive materials in the same container with different volumes.

The dose calibrator dial settings recommended by most manufacturers are established through interpolation from measurements of primary reference standard radioactive sources produced by the National Institute of Standards and Technology (NIST). The typical NIST source used in the determination of activity calibrator dial settings is a 5-mL flame-sealed, thin-walled glass ampoule.[10]

Radiopharmacies and nuclear medicine departments typically assay patient doses in glass vials or single-dose plastic syringes. Both containers have different photon absorption characteristics from the 5-mL ampoule geometry used for determining the manufacturer's calibration factor. Unless the activity calibrator is recalibrated for the exact geometry being used, significant differences in measured activity <u>might</u> be obtained (Figure 9).[11] In order to perform accurate assays of a radioactive source in a container other than the 5-mL ampoule, it is necessary to understand the causes of variations in activity readings and to be able to experimentally determine the dial setting for the particular geometry being used.[12]
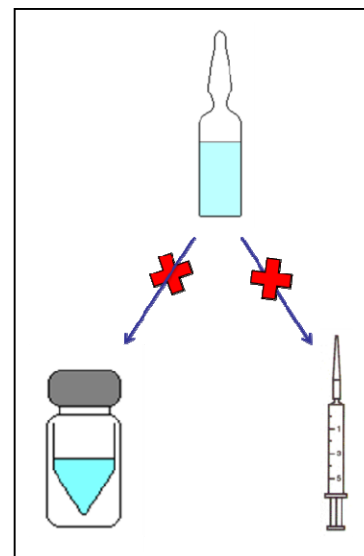

Figure 9. Assay of radioactive materials in containers other than the standard NIST geometry might produce significant differences in measured activity.

Accuracy and Uncertainty of Measurements

A certain level of random error (uncertainty) is always associated with activity calibrator measurements due to the physical limitations of the measurement system and the random variations in radioactive decay and emissions (Figure 10). Understanding sources of error and utilizing proper techniques can minimize inaccurate measurements (Figure 11). Additionally, regulatory agencies require a certain level of accuracy in the measurement of radiopharmaceuticals. The US Pharmacopeia (USP) <u>requires</u> injectable radiopharmaceuticals to be calibrated within ±10% of the prescribed dosage, and the US Nuclear Regulatory Commission (NRC) conformance limits for defining therapeutic misadministration are ±20%.[13]

Random Errors	Systematic Errors
• Precision / Uncertainty	• Accuracy
• Instrument Limitations	• Can be Reproducible
• Radioactive Decay	• Mistaken Confidence
• Always Present	• Correctable

Figure 10. Sources of error in the measurement of radioactive materials. Random errors (precision/uncertainty)are always present to a certain extent, while systematic errors (accuracy) are correctable.

Figure 11. Accuracy and precision of measurements. Measurements made in the radiopharmacy setting will always be relatively imprecise compared to the measurements carried out at NIST. It may be possible to improve the accuracy of measurements made in the radiopharmacy.

Efficiency

Many errors associated with activity calibrator measurements can be explained in terms of efficiency. Assuming that ionization chamber response is approximately constant for beta-emitters in the medium-energy range (0.7–1.3 MeV), the chamber response may differ significantly for low-energy beta-
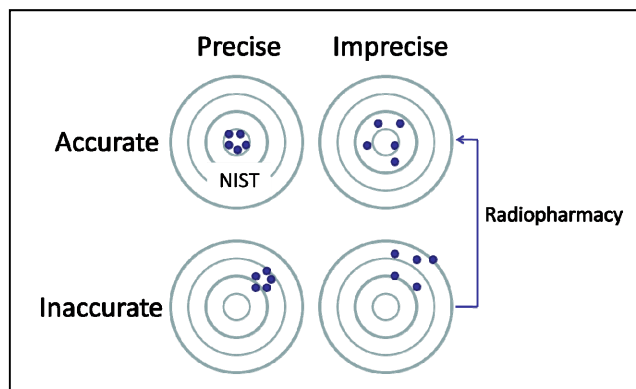
emitters because of wall attenuation and for high-energy beta-emitters (2 MeV) in which beta-radiation contributes directly to ionization in the gas-filled chamber's sensitive volume. (Figure 12). Efficiency is composed of several components related to the radioactive source such as the energy of emissions, abundance of emissions, and absorption of these emissions within the source

$$Efficiency \ = \ \frac{Response\ of\ Dose\ Calibrator}{Rate\ of\ Radioactive\ Decay}$$

$$E = e_1 \times e_2 \times e_3 \ldots e_n$$

Figure 12. Efficiency of measurements. Efficiency is the relationship between the rate of radioactive decay and the response of the activity calibrator. There are many individual factors which together determine the overall efficiency of the activity calibrator.

itself. Efficiency is also affected by the geometry of the source, positioning within the activity calibrator, and attenuation of emission within the container material. Finally, the activity calibrator itself has an intrinsic efficiency, which is its ability to detect a response to radiation passing through its volume of pressurized gas. Certain types of radioactive decay result in low detection efficiency. Any change in the individual components of efficiency will produce an effect on the measured response (Figure 12).

Geometric Effects

The geometric differences between the various containers used in the assay of radiopharmaceuticals include the container material, dimensions and shape, as well as the filling volume within the container (Figure 13). Radionuclides particularly susceptible to geometric effects are beta-emitters and low-energy gamma-emitters.
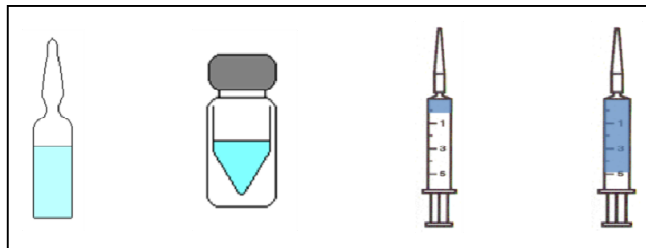
Figure 13. Geometric differences can include different types of containers and different filling volumes within the same container.

Beta-Emitters

For beta-emitters, activity calibrator activity measurement is mainly based on indirect detection of Bremsstrahlung radiation produced by the slowing of the beta particles as they interact with the solution volume and container material (Figure 14). Beta particle range and the detection of resultant Bremsstrahlung radiation are highly dependent on the energy of the beta particle and the composition and amount of stopping material (Figure 15). Measurement of these radionuclides is likely to be

effected by such factors as container type and possibly solution density and filling volume.[14] Activity calibrator response can differ significantly for low-energy beta-emitters (<0.7 MeV) because of wall attenuation and for high-energy beta-emitters (>2 MeV) whose beta-radiation contributes directly to ionization in the gas chamber of the activity calibrator (Figure 16).[15] The accurate assay of beta-emitters is of particular concern considering their use in therapeutic applications where inaccurate measurements could result in a therapeutic misadministration.
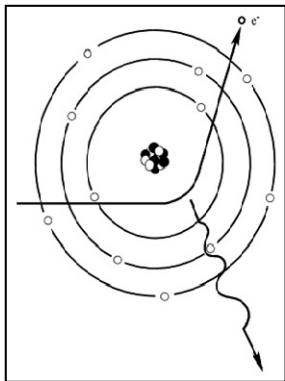

Figure 14. Bremsstrahlung radiation is produced by the slowing of the beta particles as they pass near the nucleus of another atom.

Radionuclide	E β$_{Max}$ (MeV)	Water Range (cm)	Air Range(cm)
F-18	0.635	0.23	176.0
N-13	1.190	0.51	395.0
Y-90	2.280	1.08	839.4

Figure 15. The range of beta particles is energy dependent. Beta particle range is relatively short in water, but significantly greater in air.
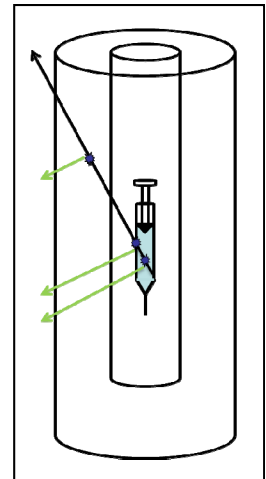

Figure 16. Beta particles can interact with the solution volume, container material and gas chamber. The frequency of these interactions is dependent on the energy of the beta particles.

Low-Energy Gamma-Emitters

Radionuclides with significant low-energy gamma emissions, such as In-111, are also prone to errors in measurement due to geometric effects. When measuring In-111, the difference from true activity ranged from 18 to 35% based on the geometry of different glass vials. [16] Activity readings in plastic syringes showed a general overestimation when compared to readings in the glass vials, with a maximum deviation of 33% when measured in a 1-mL plastic syringe. [16] This large discrepancy is attributed to the significant amount of low-energy x-ray emissions in the decay of In-111(Figure 17).

γ-ray energy (KeV)	Emission probability (%)	X-ray energy (KeV)	Emission probability (%)
245.35	94.09	23.17	44.50
171.28	90.66	22.98	23.60
		26.15	12.40
		26.67	2.30

Figure 17. In-111 emissions. Significant low-energy x-ray emissions are more easily attenuated leading to lower detection efficiency.

Need for Volume Correction Factors

Activity calibrator activity measurements are also sensitive to volumetric effects, the filling volume of the container, as the apparent activity tends to decrease as the filling volume is increased (Figure 18). This is most likely due to photon absorption by the source liquid leading to a lower response in the activity calibrator. [10] As might be expected from their geometric dependence, pure beta-emitters and low-energy gamma-emitters have been shown to have significant volumetric effects. It has also been shown that the measurement of the positron-emitter F-18 is affected by volume.
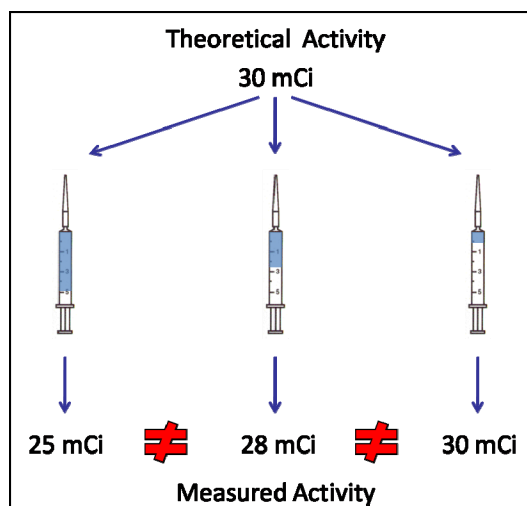

Figure 18. Volumetric effects. Measured activity tends to decrease as filling volume if increased.

Volume correction factors should be considered if the measured activity differs from the theoretical activity by more than 2%. Volume correction factors (CF) can be determined by calculating the ratio of measured activities (A_m) for each volume to a reference volume activity (A_R) $CF = A_R / A_m$. The true activity (A_T) can then be calculated by multiplying the measured activity (A_m) by the volume correction factor (CF), which is specific to each radionuclide and source container $A_T = A_m \times CF$ (Figure 19).

$$CF = A_R / A_m$$

$$A_T = A_m \times CF$$

Volume (mL)	A_m (mCi)	CF
4	2.85	0.70
8	2.30	0.87
10 (A_R)	2.00	1.00

Figure 19. Volume correction factors. Calculated correction factors using 10 mL as the reference volume.

Y-90

In the assay of Y-90, there appears to be a detectable trend toward lower chamber response as the filling volume increases, particularly above 6 mL. (Figure 20) [14] Volume also had significant effects on measurements of Y-90 in a 30-mL glass vial (Figure 21). These measurement errors were in excess of 10% and were seen until the solution was diluted to 10 mL.[17]
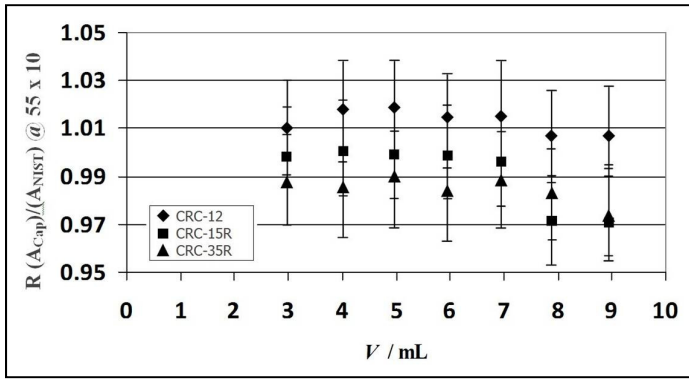
Figure 20. Ratio of measured activity to NIST calibrated activity for solutions of Y-90 in a 10-mL plastic syringe as a function of volume.

Glass vial (30-ml)		
Sample (ml)	Dial 775 x 70	Dial 48 x 10
0.05	148	137
2.5	133	122
5.0	122	115
10.0	118	115
15.0	118	118
17.5	118	111
22.5	118	111
27.5	118	111
32.5	118	111
35.0	118	111

Figure 21. Activity calibrator measurements of Y-90 in increasing solution volumes in a 30mL glass vial.

In-111

In-111 is also dependent on filling volume when assayed in plastic syringes. The deviation has been shown to be in the range of 2-4%, increasing with filling volume (Figure 22).[16]

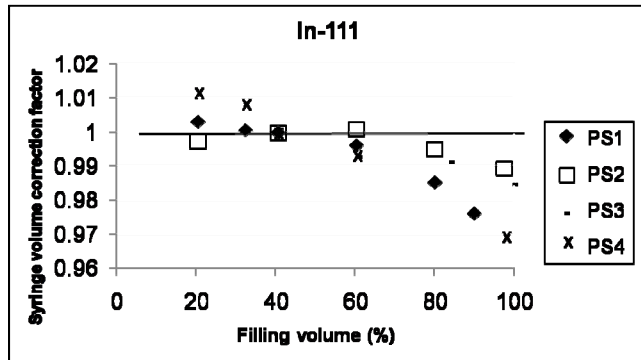**Figure 22.** Volume correction factors for In-111 measure in plastic syringes sized 10, 5, 2.5 and 1 mL.

F-18

An error of 6.2% in the activity was seen when measuring F-18 in a glass vial over the volume range of 0.1-9 mL. [18] This uncertainty is corrected for by adjusting the dial setting (Figure 23).
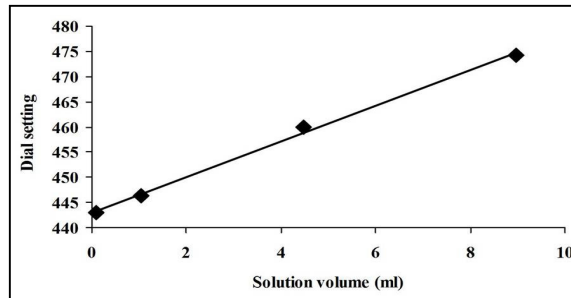

Figure 23. Plot of dial setting as a function of volume for the assay of F-18.

Practical Dial Settings for a Volume Range

While there is evidence for the effects of filling volume on the accuracy of measurements, there are some circumstances where volume effects result in no significant difference in activity readings. Recent studies have brought to light specific geometries where a single calibration factor can be used for the assay of Y-90 without volume correction factors.

Siegel et al. [19] found no correction factor necessary for a activity calibrator dial setting when measuring Y-90 in plastic syringes over the volume range of 3-9 mL. The maximum observed variation in the activity reading was 1.7%. Similarly, Zimmerman et al. [14] found that a single calibration factor for measuring Y-90 in 10-mL plastic syringes can be used for a volume range of 3-9 mL for Capintec and AtomLab activity calibrators, with an uncertainty of approximately 1%. Because the observed effect filling volume has on the chamber response is less than the magnitude of uncertainty in the activity determination, it is possible to use a single calibration factor over the entire range of 3-9 mL in 10-mL plastic syringes.

Establishing Volume Correction Factors

1
- Volumetric
- Constant Specific Activity

2
- Gravimetric
- Constant Specific Activity

3
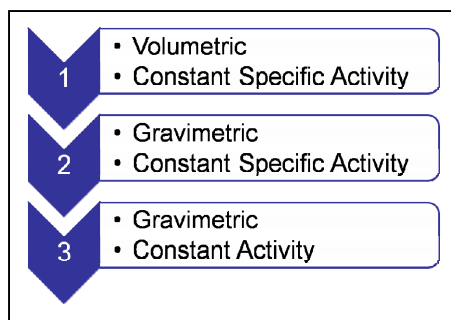- Gravimetric
- Constant Activity

Figure 24. Methods of determining volumetric effects in the assay of radioactive materials.

While volume correction factors might not be necessary for all radionuclides and geometries, it is important to understand appropriate techniques for evaluating volume effects and establishing volume correction factors if necessary. Strigari et al. [20] reviewed three common methods of determining volume effects, which are presented below (Figure 24). Each method compares the filling volume to the measured activity and uses regression to quantify the uncertainty in the activity reading.

Volumetric, Constant Specific Activity Method

This method (Figure 25) is based on the addition of volumetrically determined quantities of radioactive solution withdrawn from the same master solution. Syringes are assayed after each successive aliquot is withdrawn from a stock radioactive solution; volume is determined by graduation markings on the syringe barrel. This is the least desirable method, as the uncertainty on the volume reading can be as

great as 25%. The high uncertainty observed with this method is largely the result of error in volume reading.

Figure 25. Volumetric, constant specific activity method of determining volumetric effects.

Gravimetric, Constant Specific Activity Method

This method (Figure 26)is based on the addition of gravimetrically determined quantities of radioactive solution withdrawn from the same master solution. Syringes are assayed after each successive aliquot is withdrawn from a stock radioactive solution, and volume is determined based on the weight of solution added to the syringe. This method is relatively accurate, resulting in a maximum uncertainty of 0.5%.

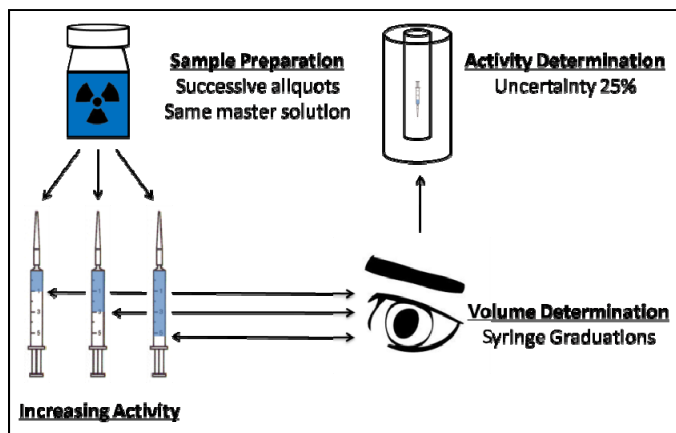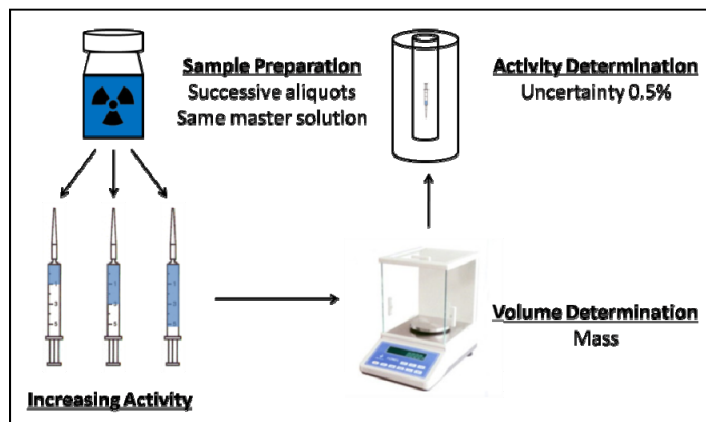**Figure 26.** Gravimetric, constant specific activity method of determining volumetric effects.

Gravimetric, Constant Activity Method

This method (Figure 27) is based on the addition of gravimetrically determined increasing quantities of non-radioactive solution. An initial volume of radioactive solution is drawn into the syringe, and

successive aliquots of a non-radioactive liquid are added. Volume is determined based on the weight of solution added to the syringe. This is the preferred method for the determination of volume correction factors as overall uncertainty is generally on the order of 0.1 % or less.
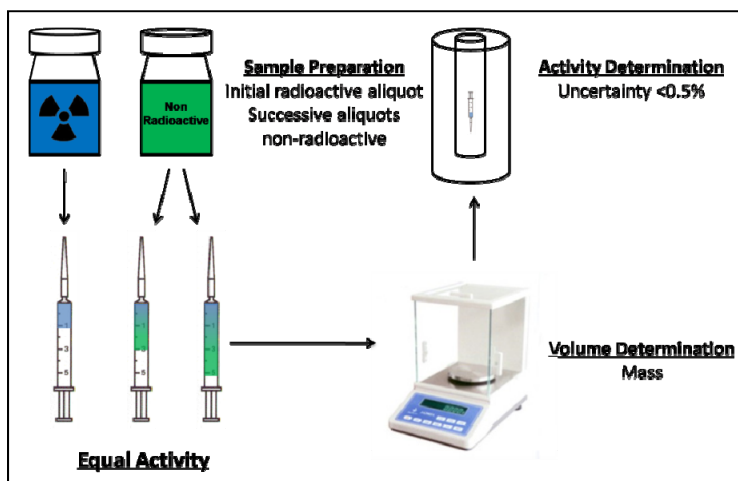
Figure 27. Gravimetric, constant activity method of determining volumetric effects.

Optimization

Santos et al.[21] investigated the effect of syringe shape and positioning on the efficiency of the activity calibrator. In general, as the source volume is increased the relative efficiency of the activity calibrator measurement will decrease, with more pronounced volume effects seen with syringes of smaller volume (Figure 28). The effect of increasing syringe volume is best characterized according to the liquid column height formed inside the syringe. When normalizing syringe volumes based on the liquid column height, a more predictable decrease in efficiency is observed across all syringe sizes (Figure 29).

Activity efficiency curves were developed based on the vertical position of a source inside the activity calibrator. From this curve, efficiency cutoffs of 5% and 10% can be established based on the vertical position of the source (Figure 30). These measures of efficiency can be useful in optimizing the assay of radioactive solutions in the syringe geometry. The ideal position for measurements would require placement of the syringe such that the entire liquid column would rest inside the region of >95% efficiency.

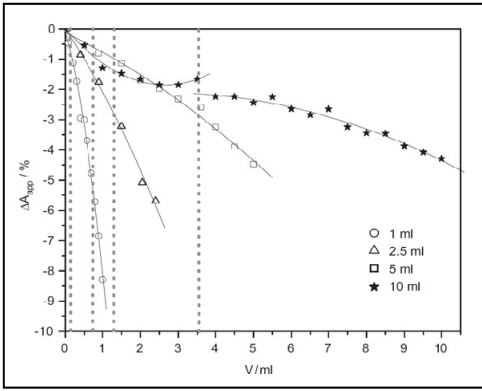**Figure 28.** Curves of apparent activity deviation for several syringes measured with the same activity inside each syringe but different volume. [21]
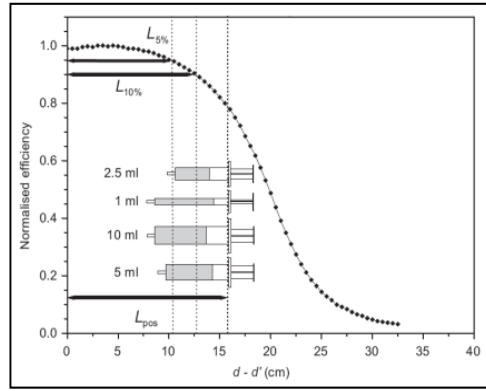

Figure 29. Experimental measurements of apparent activity deviation as function of the liquid column height inside each syringe. [21]
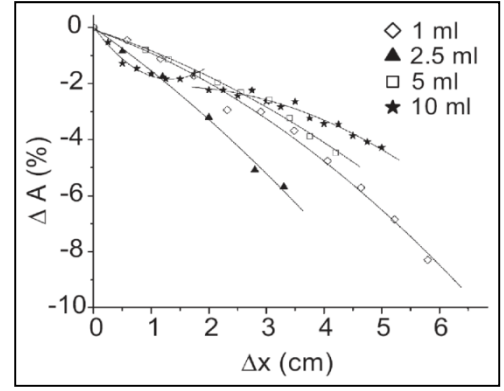

Figure 30. Normalized activity efficiency curve compared with the position of the studied syringes inside the activity calibrator. $L_{5\%}$ and $L_{10\%}$ represent efficiency cutoffs based on the vertical position of the source within the activity calibrator. [21]

Dial Setting Determination

Activity calibrator manufacturers typically determine dial settings using calibration curves. Calibration curves are generated by measuring the response of two radionuclides of different energies, typically Co-57 and Co-60, across the entire range of dial settings. The calibration curve can then be used to determine the dial setting for any additional radionuclide by comparing its detector output to that of Co-60. It is important to note that the initial calibration curve must be made using sources of the same geometry, and any subsequent dial settings are only valid for the geometry in which the original standards were measured.[22]

For greatest accuracy, it is recommended that radiopharmacies individually verify and, if necessary, determine their own activity calibrator dial settings based on NIST-traceable activity sources. [19] The establishment of dial setting with NIST-traceable activity sources allows each source supplied to a medical facility to be used as a secondary reference standard. Additionally, this allows each medical facility to determine its own calibrated dial setting based on the initial activity received from a commercial radiopharmacy.[19]

Dial-In Method

The procedure (Figure 31) is most appropriate for relatively long-lived radionuclides and consists of measuring the activity of a master solution (A1) with an established method such as $4\pi\beta$ liquid scintillation counting. Once the activity and the associated uncertainty have been determined, a portion

of the master solution is dispensed by mass into the container in which the dose calibrator measurements will be made. The true activity of the secondary container (A_2) can be calculated based on the mass of the solution in the secondary container (M_2) relative to the mass of the master solution (M_1). The correct dial setting is found by placing the source in the activity calibrator and turning the dial until the correct activity is displayed on the readout.[22]
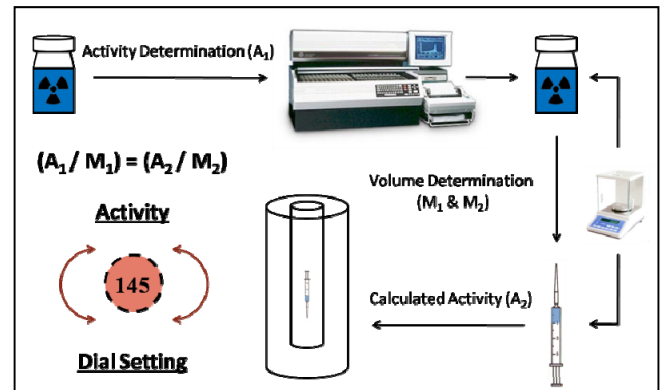
Figure 31. Dial-in method of determining activity calibrator dial settings.

Calibration Curve Method

When using radionuclides of high specific activity or short half-life it could be impractical to make the activity measurement before performing the activity calibrator measurements. In these situations, a dial setting can be determined by plotting a calibration curve of "apparent activity" versus dial setting for a source that will eventually be used to make the activity measurements.
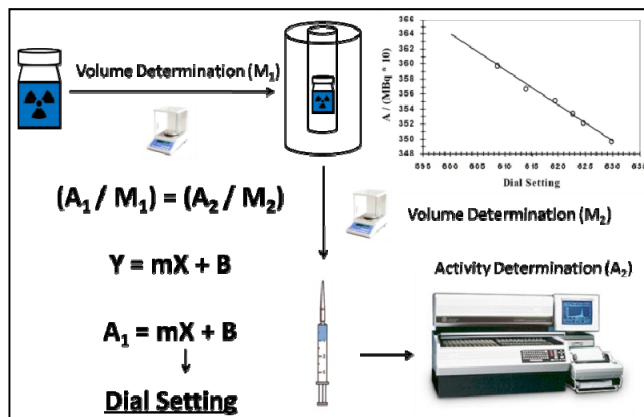
Figure 32. Calibration curve method of dial setting determination.

This procedure (Figure 32) involves placing the radioactive source of known mass (M_1) into the activity calibrator and recording the displayed activity while the dial setting is varied. An aliquot from the source is then set aside for definitive activity determination (A_2). The true activity of the original container (A_1) can be calculated based on the mass of the solution in the secondary container (M_2) relative to the mass of the master solution (M_1). Once the true activity of the original container is known, the dial setting for this geometry can be determined according to the equation of the line formed from the plot of apparent activity versus dial setting.[22]

Activity Difference Method

Many commercial radiopharmacies or nuclear medicine departments do not have the capability of performing their own activity determinations via liquid scintillation counting. In these cases, facilities can establish their own calibrated dial setting for a particular geometry using a NIST-traceable source and an activity difference method (Figure 33). An aliquot of radioactive solution

Figure 33. Activity difference method of dial setting determination.

can be transferred from the NIST-traceable source (A) to a secondary container with a different geometry. Activity of a NIST-traceable source is measured before and after removal of source material, with the initial volume in the vial being restored prior to remeasurement (B). The difference between these two vial measurements is the activity of the secondary container, which is still NIST traceable.[19]

CONCLUSION

Activity calibrators can be valuable tools for the assay of radioactive materials, but it is important to understand their limitations. Radionuclides with significant low-energy x-ray emissions and beta-emissions are especially susceptible to errors in measurement. For these radionuclides, particular attention must be paid to source geometry and filling volume to ensure that activity measurements are as accurate as possible. In many cases, the radionuclide dial setting provided by the manufacturer might not be applicable to the particular geometries used in practice. In these cases, it is important for facilities to accurately determine their own calibrated dial settings.
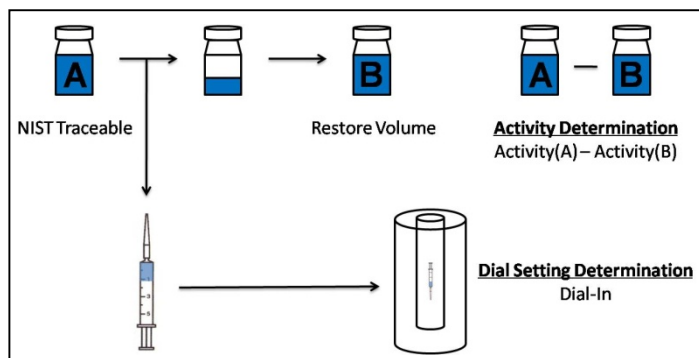
REFERENCES

1. Chandra, R. *Nuclear Medicine Physics: The Basics 5th Ed*. Philadelphia: Lippincott Williams & Wilkins; 1998.

2. Radioisotope Dose Calibrator Owner's Manual. CRC - 15R s.l. Ramsey, NJ: Capintec, Inc.

3. Bushberg, JT, Siebert, JA, Leidholt, EM, Boone, JM. *The Essential Physics of Medical Imaging 2nd Ed.* Philadelphia: Lippincott Williams and Wilkins, 2002.

4. Hendee, WR, Ritenour, ER. *Medical Imaging Physics 4th Ed.* New York: Wiley-Liss, Inc., 2002.

5. Knoll, GF. *Radiation Detection and Measurement 3rd Ed.* Hoboken, NJ: John Wiley and Sons, Inc., 2000.

6. Christian,PE., Waterstram-Rich, KM. *Nuclear Medicine and PET/CT: Technology and Techniques.* Philadelphia: Mosby, 2007.

7. Calhoun, JM. *Radioactive Calibration with the 4pi Gamma Ionization Chamber and other radioactivity calibration capabilities.* NBS special publication 250-10. Gaithersburg, MD: US Dept of Commerce, National Bureau of Standards, 1987.

8. Zanzonico, P. Routine Quality Control of Clinical Nuclear Medicine Instrumentation: A Brief Review. *Journal of Nuclear Medicine*. 2008; 49(7); 1114-1131.

9. Steves, AM, Wells, PC. *Review of Nuclear Medicine Technology Preparation for Certification Examinations.* 3rd ed. Reston, VA: Society of Nuclear Medicine; 2004.

10. Zimmerman BE, Coursey BM, Cessna JT Correct use of dose calibrator values. *Journal of Nuclear Medicine*. 1998; 39: 575-576.

11. Tyler DK, Woods MJ. Syringe calibration factors for the NPL Secondary Standard Radionuclide Calibrator for selected medical radionuclides. *Applied Radiation and Isotopes*. 2003; 59: 367-372.

12. Zimmerman BE, Kubicek GJ, Cessna JT, Plascjak PS, Eckelman WC. Radioassays and experimental evaluation of dose calibrator settings for 18F. *Applied Radiation and Isotopes*.2001; 54: 113-122.

13. Code of Federal Regulation. *Medical Use of Byproduct Material 10CFR (Part 35) US Nuclear Reglatory Commission,.* Washington, DC: NRC; 2005, pp. 562-609.

14. Zimmerman BE, Cessna JT, Milligan MA. Experimental determination of calibration settings for plastic syringes containing solutions of Y-90 using commercial radionuclide calibrators. *Applied Radiation and Isotopes*. 2004; 60: 511-517.

15. Valley JF, Bulling S, Leresche M, Wastiel C. Determination of the Efficiency of Comercially Available Dose Calibrators for Beta-Emitters. *Journal of Nuclear Medicine Technology*. 2003; 3:27-32.

16. Ceccatelli A, Benassi M**,** D'Andrea M, De Felice P, Fazio A, Nocentini S, Strigari L. Experimental determination of calibration settings of a commercially available radionuclide calibrator for various clinical measurement geometries and radionuclides. *Applied Radiation and Isotopes*. 2007; 65:120-125.

17. Salako QA, DeNardo SJ. Radioassay of Yttrium-90 Radiation Using the Radionuclide Dose Calibrator. *Journal of Nuclear Medicine*,1997; 38: 723-726.

18. Mo L, Reinhard MI, Davies JB, Alexiev D, Baldock C. Calibration of the Capintec CRC-712M dose calibrator for F-18. *Applied Radiation and Isotopes*. 2006; 64: 485-489.

19. Siegel JA, Zimmerman BE, Kodimer K, Dell MA, Simon WE. Accurate Dose Calibrator Activity Measurement of Y-90-Ibritumomab Tiuxetan. *Journal of Nuclear Medicine.* 2004; 45:450-454.

20. Strigari L, Benassi M, De Felice P, D'Andrea M, Fazio A, Nocentini S, d'Angelo A, Ceccatelli A. Comparison of methods to determine accurate dose calibrator. *Journal of Experimental & Clinical Cancer Research.* 2008; 27(14).

21. Santos JAM, Carrasco MF, Lencart J, Bastos AL. Syringe shape and positioning relative to efficiency volume in side dose calibrators and its role in nuclear medicine quality assurance programs. *Applied Radiation and Isotopes*. 2009; 67:1104-1109.

22. Zimmerman BE, Cessna JT. Experimental determinations of commercial 'dose calibrator' settings for nuclides used in nuclear medicine. *Applied Radiation and Isotopes*, 2000; 52: 615-619.

23. Cherry, Sorenson, Phelps. *Physics in Nuclear Medicine 3rd Edition.* Philadelphia: Saunders, 2003.

24. Prekeges, J. *Nuclear Medicine Instrumentation.* Sudbury: Jones and Bartlett; 2009.

25. D.B. Howe, M. Beardsley, S.R. Bakhsh. *Consolidated Guidance About Materials Licenses: Program - Specific Guidance About Medical use Licenses (NUREG-1556).* Washington, D.C. : s.l., 2008. p. Vol. 9.

ASSESSMENT QUESTIONS

1.   The primary interaction of radiation with matter used in imaging is _____?

        a. Bremsstrahlung.
        b. Photoelectric effect.
        c. Rayleigh scattering.
        d. Compton scattering.

2.   The constancy test performed on the dose calibrator determines _____?

        a. response over a range of activities.
        b. response over a range of volumes.
        c. response from day to day.
        d. response from geometrical variance.

3.   The response of the assayed isotope is relative to which standard nuclide for the CRC-15R?

        a. ^{133}Ba.
        b. ^{57}Co.
        c. ^{60}Co.
        d. ^{99m}Tc.

4.   The photoelectric effect _____?

        a. is heavily dependent upon the energy of the photon.
        b. involves the scattering of a photon off an outer shell electron.
        c. is the dominant interaction in the clinical setting.
        d. is the interaction of a photon and the electric field of the nucleus of the atom.

5.   If a photon of 140keV interacts with an argon atom with a binding energy of 32keV via the photoelectric effect what is the energy of the free electron?

        a. 172eV.
        b. 108eV.
        c. 108keV.
        d. 172keV.

6.   Bremsstrahlung radiation is _____?

        a. emitted in a continuous spectrum with the average energy 1/3 that of the maximum energy.
        b. emitted at an energy 1/3 that of the maximum energy.
        c. emitted in a continuous spectrum.

7.   A constant voltage is needed across the digital circuit because _____?

      a. the ions generated need to be pulled towards the anode at a constant rate.
      b. a constant voltage collects the most ions.
      c. minor fluctuations in voltage will change the measured value of the current.
      d. the amount of current generated within the detector depends on the voltage.

8.   The radionuclide selectors on an analog calibrator worked by adjusting the calibrator _____?

      a. voltage.
      b. resistance.
      c. gain.
      d. current.

9.   When doing QA on the instrument the _____?

      a. NRC regulations must be followed.
      b. site license requirements must be followed.
      c. manufacturer's requirements must be met.

10.   The change in the charge within a capacitor _____?

      a. induces a current within the digital circuit.
      b. is proportional to the activity of the source.
      c. induces a voltage within the digital circuit.
      d. keeps the voltage constant within the detector space.

11.   The reed electrometer is used to _____?

      a. maintain a constant voltage in the digital circuit.
      b. display the activity of the source.
      c. collect the ions generated in the detector space.
      d. change direct current to alternating current.

12.   The linearity measurement should be made over activities ranging from _____?

      a. 30µCi to the maximum activity used at the clinic.
      b. whatever the site license specifies.
      c. 30µCi to 20Ci.
      d. the minimal detectable activity of the dose calibrator to the maximum activity used at the clinic.

13.   Volumetric effects will change the _____?

      a. activity of the source.
      b. amount of activity within the vial/syringe.
      c. response of the detector.

14. Dose calibrators have varying levels of uncertainty. Several factors contribute to the overall efficiency of radionuclide measurements in a dose calibrator. Which of the following factors does NOT contribute to the calibrator efficiency?

   a. Energy of emissions
   b. Physical half life
   c. Abundance of emissions
   d. Container material

15. Two nuclides have comparable emission energies. Nuclide A is a pure beta emitter while nuclide B is a gamma emitter. Assuming all other factors are equal which of the configurations listed below is **most** likely to register the lowest activity in a dose calibrator?

   a. Beta in plastic syringe
   b. Gamma in plastic syringe
   c. Beta in glass vial
   d. Gamma in glass vial

16. A 1 mL sample of radionuclide is sequentially diluted with normal saline within the original container. Assuming all other factors remain constant, which volume would you expect to register the least amount of activity?

   a. 1 mL
   b. 3 mL
   c. 5 mL
   d. 10 mL

17. Two studies found **NO** need for correction factors when measuring solution volumes of 3 – 9 mL in a plastic syringe. This radionuclide is _____?

   a. F-18
   b. Y-90
   c. In-111
   d. Xe-133

18. National Institute of Standards and Technology provides calibrated reference sources for determining dose calibrator settings. One of the drawbacks in using these sources is that they are _____?

   a. Calibrated to ± 5% labeled activity
   b. Packaged in glass ampoules
   c. Only applicable to long-lived radioisotopes
   d. Subject to geometrical errors

19. Which of the following is the correct sequence of events in the measurement of radioactive materials?

    a. Radiation→Radioactivity→ Ionization→Current→Calibration Factor→Measured Activity
    b. Radiation→Radioactivity→ Calibration Factor→Ionization→Current→ Measured Activity
    c. Radioactivity→Radiation→Calibration Factor→Ionization→Current→ Measured Activity
    d. Radioactivity→Radiation→Ionization→Current→Calibration Factor→Measured Activity

20. Changes in which of the following can produce error in measure activity?

    I.   Container material (glass vs. plastic)
    II.   Filling volume
    III.   Efficiency

    a. I Only
    b. III Only
    c. I and II
    d. II and III
    e. I, II and III

21. The following geometries are more likely to produce inaccurate measurements.

    I. 5 mL NIST ampoule
    II. 5 mL plastic syringe
    III. 30 mL glass vial

    a. I only
    b. III only
    c. I and II
    d. II and III
    e. I, II and III

22. Which of the following statements are FALSE

    I. Inaccurate measurements are a result of instrument limitations
    II. Radiopharmacy measurements are generally more imprecise than NIST measurements
    III. Inaccurate measurements can be corrected

    a. I only
    b. III only
    c. I and II
    d. II and III
    e. I, II and III

23. A radionuclide measured in a dose calibrator has the following efficiency characteristics: intrinsic efficiency 80%, radionuclide efficiency 50% and geometric efficiency 50%. Assuming there are no efficiency limitations, the overall efficiency of the system is most likely

    a. > 90%
    b. > 50 %
    c. < 30%
    d. < 5%

24. Which of the following beta particles would have the greatest range

    a. 1.00 MeV beta particle in air
    b. 2.00 MeV beta particle in water
    c. 2.00 MeV beta particle in air
    d. 2.50 MeV beta particle in water

25. Which of the following directly contribute to ionization when assaying beta particles

    I. Low energy beta particles
    II. Low energy Bremsstrahlung radiation
    III. High-energy beta particles

    a. I only
    b. III only
    c. I and II
    d. II and III
    e. I, II and III

26. Which of the following are possible sites of Bremsstrahlung production when assaying high-energy beta emitters?

    I. Solution volume
    II. Wall of the syringe
    III. Gas volume of the dose calibrator

    a. I only
    b. III only
    c. I and II
    d. II and III
    e. I, II and III

27. Measurements of In-111 are of particular concern due to

    a. Bremsstrahlung radiation
    b. Beta particle range
    c. Low energy x-ray emissions
    d. High-energy gamma-ray emissions

28. Which of the following best describes the need for a volume correction factor

    a. ↑ volume = ↓ efficiency
    b. ↓ volume = ↑ attenuation
    c. ↑ volume = ↑ efficiency
    d. ↓ volume = ↓ efficiency

29. Which of the following methods of volumetric determinations was shown to have the lowest uncertainty.

    a. Volumetric, Constant Specific Activity
    b. Volumetric, Constant Activity
    c. Gravimetric, Constant Specific Activity
    d. Gravimetric, Constant Activity

30. Using the following table, what is the volume correction factor for a syringe filled to 4 mL when the reference volume is 10 mL.

Volume (mL)	A_m (mCi)
4	2.85
8	2.30
10 (A_R)	2.00

    a. 0.70
    b. 0.87
    c. 1.12
    d. 1.35

31. Change in measured activity is best characterized according to

    a. Syringe volume
    b. Liquid column height
    c. Solution density
    d. Syringe wall thickness

32. Which of the following is an important step in the dial-in method of dial setting determination?

    a. Restore NIST traceable source to original volume
    b. Assay each container three times to determine uncertainty
    c. Determine mass of solution in secondary container
    d. Dilute secondary container with non-radioactive solution

33. Which of the following is an important step in the activity difference method of dial setting determination?

    a. Restore NIST traceable source to original volume
    b. Assay each container three times to determine uncertainty
    c. Determine mass of solution in secondary container
    d. Dilute secondary container with non-radioactive solution