INSTRUMENT REVIEW AND BEST PRACTICES FOR NUCLEAR PHARMACY

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OBJECTIVES

1. Describe radioactivity measurements using activity calibrators
2. Review radiologic properties and their impact on measurement
3. Describe National Institute of Standards and Technology primary and secondary sources
4. Explain the error rate in measuring activity from various radiopharmaceuticals
5. Describe how to change or add a new calibration setting on the dose calibrators

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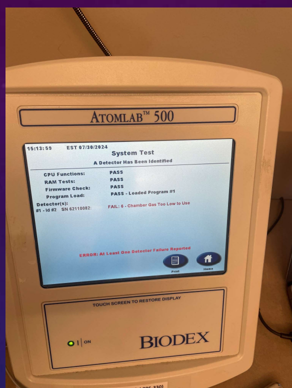
ATOMLAB™ 500
15:13:59 EST 07/30/2024
System Test
A Detector Has Been Identified
CPU Functions: PASS
RAM Tests: PASS
Firmware Check: PASS
Program Load: PASS - Loaded Program #1
Detector(s):
#1 - Id #2 SN 62110082: FAIL: 6 - Chamber Gas Too Low to Use
ERROR: At Least One Detector Failure Reported
Print
Home
TOUCH SCREEN TO RESTORE DISPLAY
ON
BIODEX


036-336-M311
1190507

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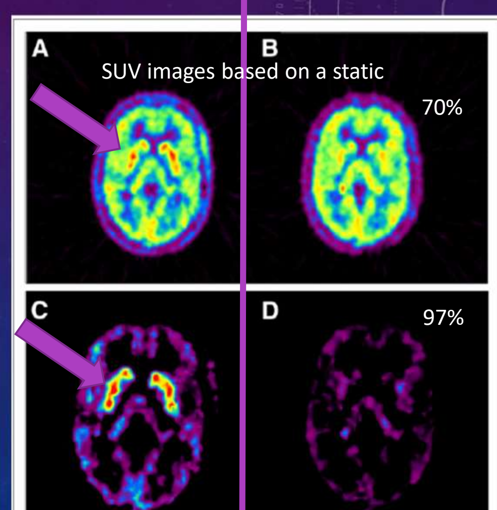
Adriaan A. Lammertsma J Nucl Med 2017; 58:1019–1024

WHY ±20% IS NOT GOOD ENOUGH

- **The case for quantitation**
- **NK1 antagonists: Aprepitant (Emend)**

is approved for preventing chemotherapy-induced nausea and vomiting

Baseline | **After 125-mg Emend**



Dynamic calculation of nondisplaceable binding potential, or BP_{ND} (the ratio at equilibrium of specifically bound tracer to nondisplaceable tracer in tissue), on a voxel-by-voxel basis = 97% saturation

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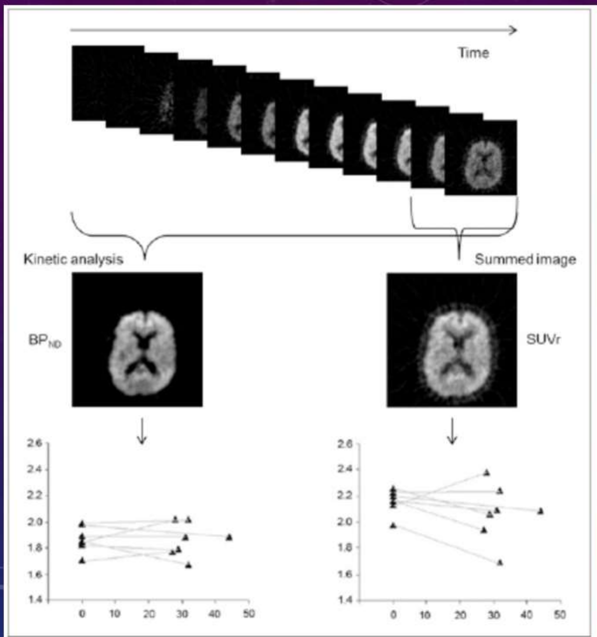

No antiamyloid treatment was given and patients were followed for 2–4 y. Yet, SUVr showed a small but significant counterintuitive decrease in amyloid load, whereas BP_{ND} remained unchanged.

In an attempt to explain these findings, simulation studies were performed. These simulations showed that the reduction in SUVr most likely was due to a decrease in CBF, a known phenomenon in Alzheimer disease

Adriaan A. Lammertsma J Nucl Med 2017; 58:1019–1024

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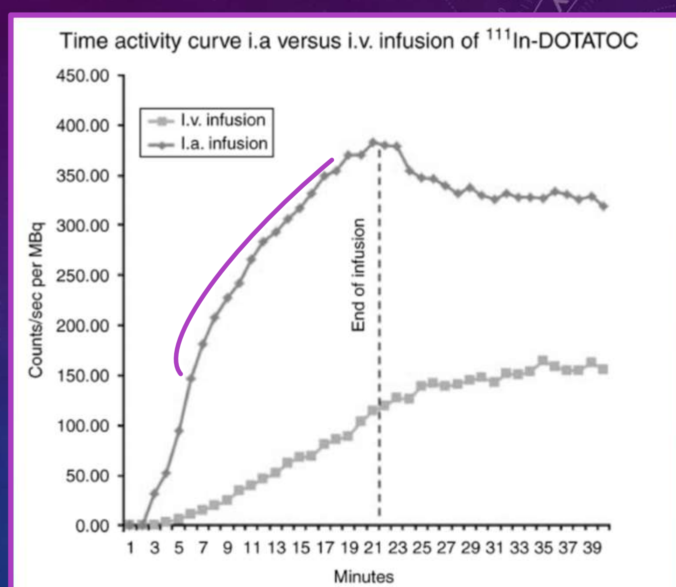
- SPECT will be quantitative for therapies
- Purple indicates shoulder of saturation with

Arterial infusion vs venous infusion

- Planning for Lu177 and Y-90 therapy



C Kratochwil. Endocr Relat Cancer. 2011 October ; 18(5): 595–602.

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QUANTITATIVE AND DOSIMETRIC EVALUATION OF LU-177 SPECT IMAGING ON STARGUIDE CZT-BASED SPECT CAMERA: A PHANTOM STUDY

- **Patient-specific dosimetry has the potential to significantly increase the therapeutic benefit of targeted radionuclides by delivering the maximum administered activity without exceeding normal tissue toxicity limits. Voxel-based dosimetry has the potential to provide patient-specific dose volume information**
- **Energy deposition (absorbed dose) is a function of how much activity is in a gram of tissue**
- **The quantitation begins with the Dose Calibrator**

Yazdan Salimi JNM June 2024, 65 (supplement 2) 241763

Stephen Graves, Ashok Tiwari, Yusuf Menda, Mark Madsen and John Sunderland. JNM 2019;S1

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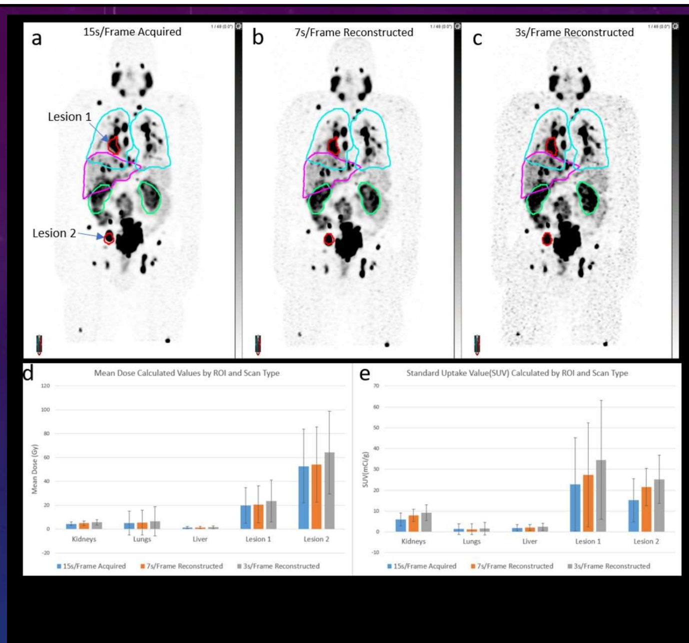

The Journal of NUCLEAR MEDICINE

Celeste Winters et al. J Nucl Med 2024;65:242413

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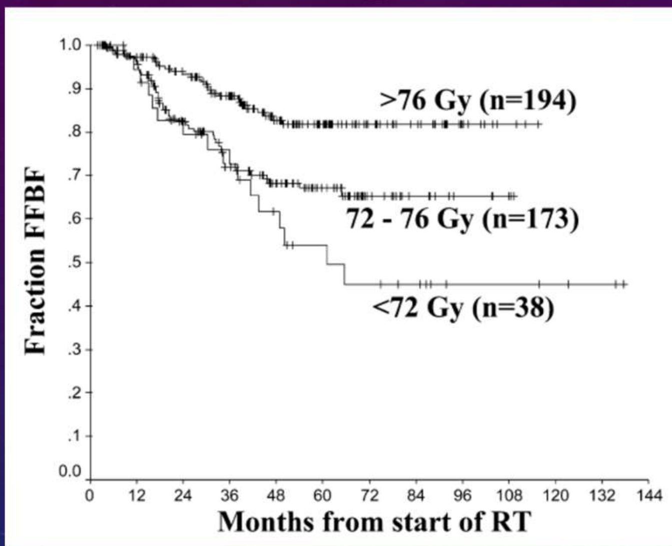

Intermediate Risk of Prostate External Beam Radio Therapy

Freedom from biochemical failure at 5 years following therapy

5.2% big difference in care

Radiation therapy dose escalation for prostate cancer: a rationale for IMRT. World J Urol (2003) 21: 200–208

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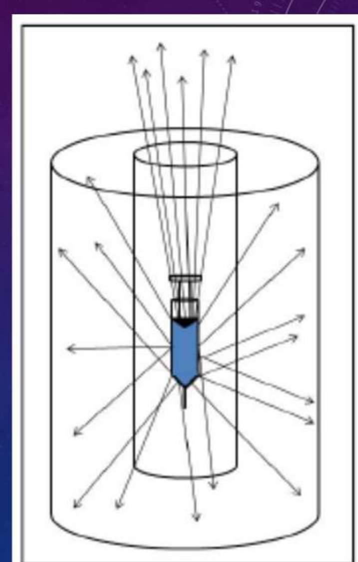
BECQUEREL IS THE FIRST STEP

Bq/cm^3
Bq/mL
Bq/gram



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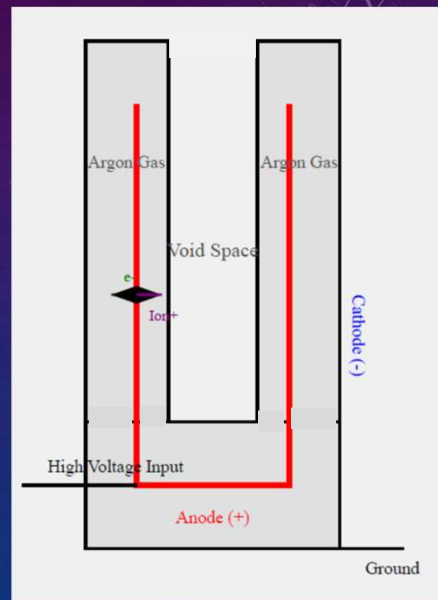
DOSE CALIBRATOR

^{40}AR ARGON MASS 40 G ATOMIC NUMBER 18
IONIZATION ENERGY 15.760 EV
0.0017837 GRAMS PER CUBIC CENTIMETER

CAPINTEC CRC-15R DOSE CALIBRATOR HAS
A WELL DEPTH AND DIAMETER OF 25.4 CM AND 6.1 CM



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TYPES OF RADIOACTIVITY

- Alpha decay: Emission of a He nucleus
- Beta decay: Emission of electron (β-) or positron (β+)
- Electron Capture: 'Capture' of orbital electron into nucleus
- Gamma/conversion electron-emission: De-excitation of daughter nucleus

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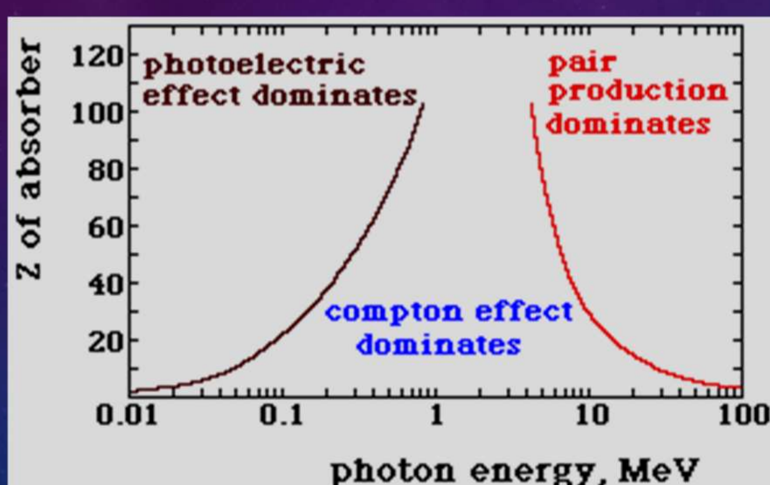
CONTRIBUTIONS TO TOTAL PHOTON ABSORPTION



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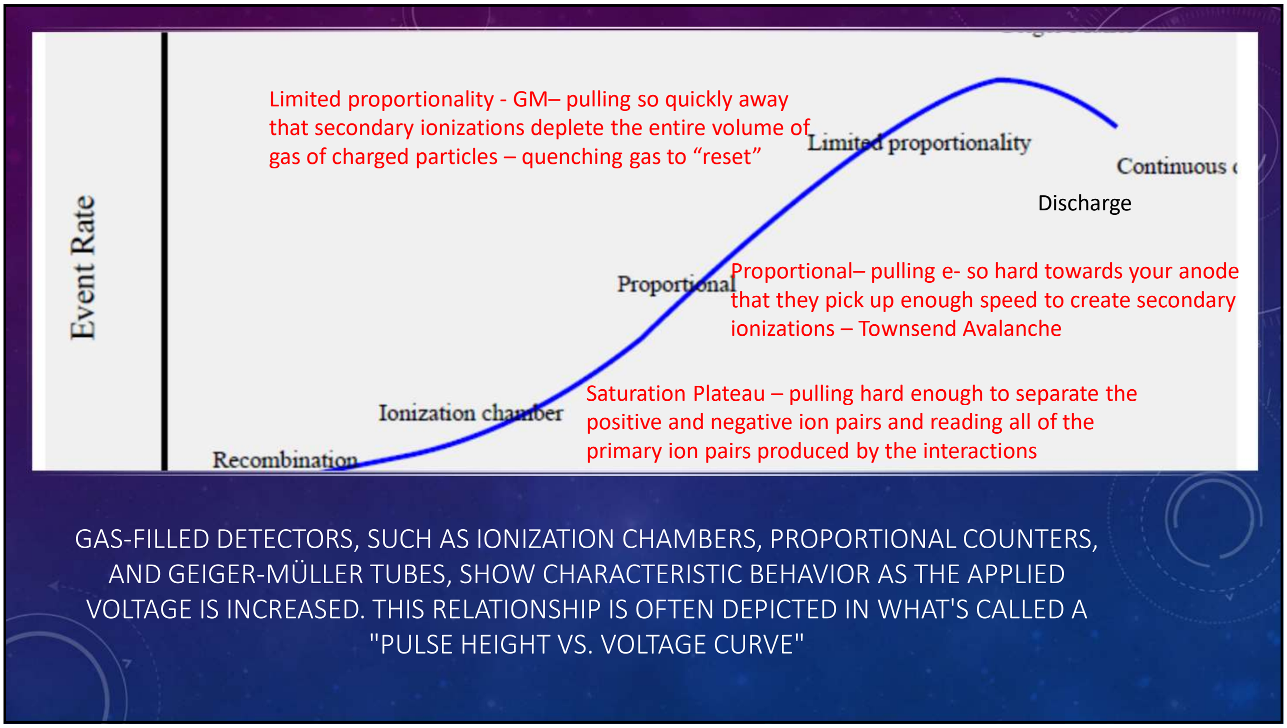
Event Rate
Limited proportionality - GM– pulling so quickly away that secondary ionizations deplete the entire volume of gas of charged particles – quenching gas to “reset”
Limited proportionality
Continuous
Discharge
Proportional
Proportional– pulling e- so hard towards your anode that they pick up enough speed to create secondary ionizations – Townsend Avalanche
Saturation Plateau – pulling hard enough to separate the positive and negative ion pairs and reading all of the primary ion pairs produced by the interactions
Ionization chamber
Recombination
GAS-FILLED DETECTORS, SUCH AS IONIZATION CHAMBERS, PROPORTIONAL COUNTERS, AND GEIGER-MÜLLER TUBES, SHOW CHARACTERISTIC BEHAVIOR AS THE APPLIED VOLTAGE IS INCREASED. THIS RELATIONSHIP IS OFTEN DEPICTED IN WHAT'S CALLED A "PULSE HEIGHT VS. VOLTAGE CURVE"

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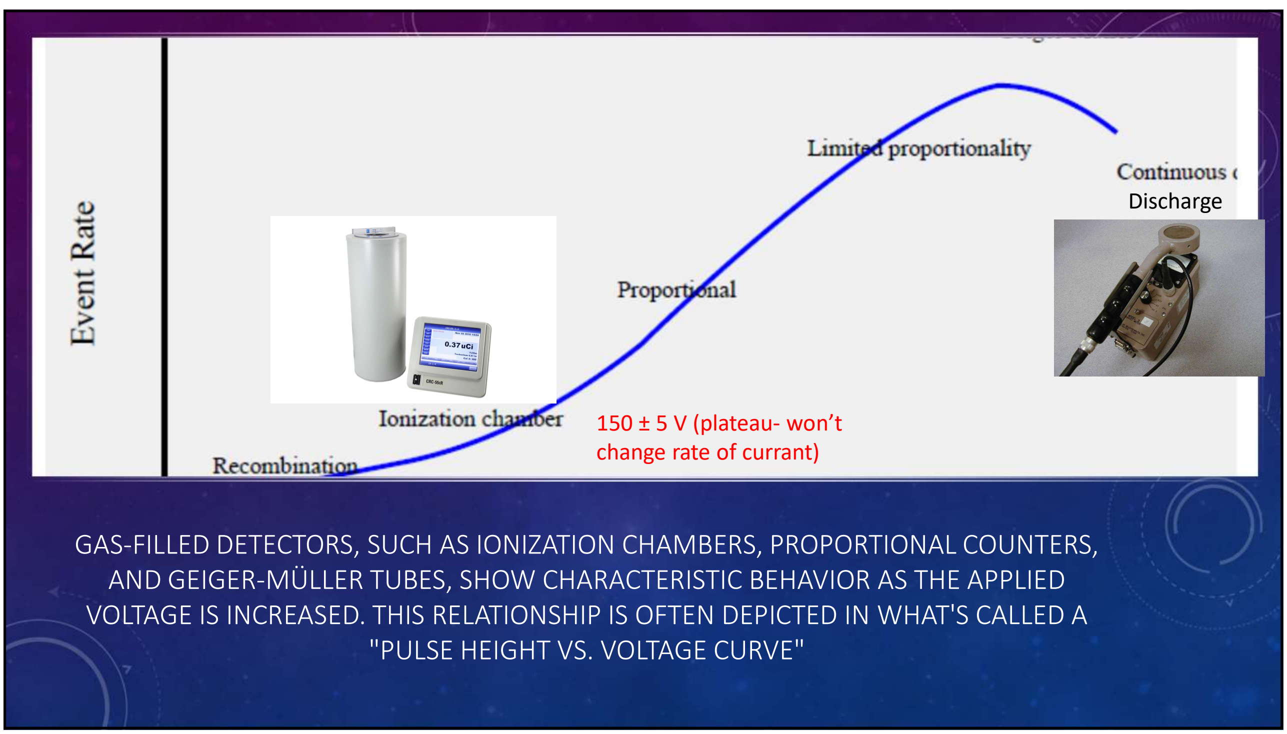
Event Rate
Limited proportionality
Continuous
Discharge
Proportional
Ionization chamber
150 ± 5 V (plateau- won’t change rate of currant)
Recombination
GAS-FILLED DETECTORS, SUCH AS IONIZATION CHAMBERS, PROPORTIONAL COUNTERS, AND GEIGER-MÜLLER TUBES, SHOW CHARACTERISTIC BEHAVIOR AS THE APPLIED VOLTAGE IS INCREASED. THIS RELATIONSHIP IS OFTEN DEPICTED IN WHAT'S CALLED A "PULSE HEIGHT VS. VOLTAGE CURVE"

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$$A = \frac{E \times d^2}{\Gamma}$$

$$V = IR$$

$$Q = CV$$

$$\Delta V = \frac{Q}{C^2}\Delta C$$

$$\Delta V = I\frac{R}{C}\Delta C$$

A= CALCULATED ACTIVITY; E= EXPOSURE RATE; D= DISTANCE BETWEEN THE SOURCE AND THE DETECTOR; Γ = SPECIFIC GAMMA CONSTANT FOR RN; V=VOLTAGE; I= CURRENT; R= RESISTANCE; Q=CHARGE HELD IN THE CAPACITOR; C=CAPACITANCE OF THE CAPACITOR;

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. The amplitude of the voltage measured is then proportional to the amount of current being generated by the ionizing source within the detector space.

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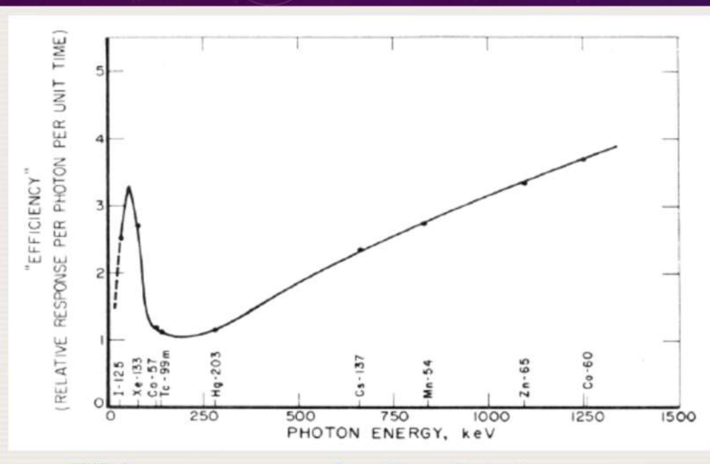

Efficiency curve as a function of photon energy.

$$R_A = \frac{\frac{\text{Detector Output Due to Sample A}}{\text{Activity of Sample A}}}{\frac{\text{Detector Output Due to Co}^{60}}{\text{Certified Activity of Co}^{60}}}$$

RESPONSE-ENERGY CURVE RELATIVE TO CO-60

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HOW DO THE MANUFACTURERS CONVERT CURRENT TO ACTIVITY

Radioactive Decay (DPS)
↓
Radiation emission (photons)
↓
Ionization (Argon Ion Pairs)
↓
Current (uA)
↓
Dial Setting (Calibration Factor)
↓
Measured Activity (mCi)

Dr. Wayne The University of Iowa Hospitals and Clinics – Everything you need to know about the dose calibrator for quantitative data – 2023 SNMMI Annual Meeting

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- Radionuclide calibrator manufacturers typically calibrate their instruments using a national standard vial (e.g., the NIST SRM borosilicate-glass ampoule) or a specific multi-dose vial.
- Ampoule dimensions shall be: o Height: (75 ± 1) mm o Straight length of body: (37 ± 1) mm o Diameter of body: (16.5 ± 0.1) mm o Wall thickness of body: (0.60 ± 0.05) mm o Neck diameters (as group), not critical at about 7 mm to 8 mm and 9 mm to 11.5 mm o Stem wall diameter at opening: (6.2 ± 0.5) mm, some minor flare can be present, o Stem wall thickness: (0.40 ± 0.05) mm

205.5 - Radiopharmaceuticals (solution and gaseous forms)

These SRMs are intended for the calibration of radioactivity-measuring instruments. They are calibrated in terms of activity per gram of solution (except SRM 4415, which is calibrated in terms of activity). Each SRM is contained in a 5 mL flame-sealed glass ampoule and, except for SRM 4415, consists of the radionuclide dissolved in an aqueous solution (usually acidic).These SRMs are produced in collaboration with the NRMAP, Inc. and, because of the short half lives, are available only at specific times.

When an import permit for radioactive material is required of a customer outside the U.S., NIST must have a copy to complete an order and facilitate shipment.

"Radionuclide Calibration Services"

"Radioactive SRM Purchasing Instructions & License Certification Form"

"Radioactive SRMs-General Info"

PLEASE NOTE: The tables are presented to facilitate comparisons among a family of materials to help customers select the best SRM for their needs. For specific values and uncertainties, the certificate is the only official source.

SRM	Description	Unit of Issue	Half Life (days)	Month Produced **	NRC License or Equivalent Required*
4401L	Iodine-131 Radioactivity Standard	5 mL	8.0	February	X
4404L	Thallium-201 Radioactivity Standard	5 mL	3.0	June	X
4407L	Iodine-125 Radioactivity Standard	5 mL	59.4	December	X
4410H	Technetium-99m Radioactivity Standard	5 mL	0.3	September	X
4412L	Molybdenum-99 Radioactivity Standard	5 mL	2.74	April	X
4415L	Xenon-133 Radioactivity Standard	5 mL	5.243	Sept	X
4416L	Gallium-67 Radioactivity Standard	5 mL	3.3	May	X
4417L	Indium-111 Radioactivity Standard	5 mL	2.8	August	X
4427L	Yttrium-90 Radioactivity Standard	5 mL	64.0 hrs	October	X

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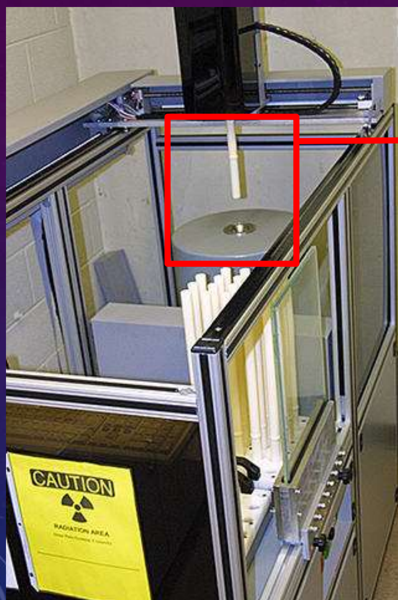

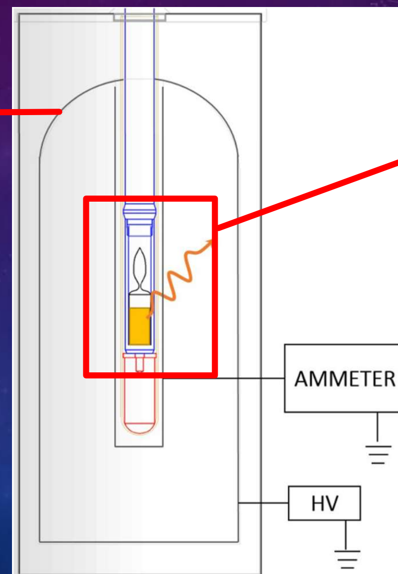

glass ampoule sitting in a sample holder (blue)

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CALIBRATOR MANUFACTURER

- Manufacturers are required to obtain an FDA (510K) approval for their calibrators
- The 510K requirements are satisfied differently by different calibrator manufacturers
- Manufacturers should provide traceable calibrations for common source geometries and qualify when the calibrations may or may not be used for other geometries
- This is not the case and the user should be aware of the qualifications placed on the use of the calibrations provided by the manufacturers
- The manufacturer suggests an acceptable error of ±10%
- The manufacturer provides a table with estimates of the errors associated with syringe assays. The errors range from 2% to 15% for common clinically used radionuclides.
- For high-energy pure beta emitters (e.g., Y-90), the manufacturer notes that the supplied calibration coefficients are for estimation only

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PRIMARY AND SECONDARY STANDARDS

Primary standard: uncertainties that range typically from 0.5% to 1%

- Highest metrological quality
- Not calibrated by or subordinate to other standards
- Linked to fundamental physical units

Secondary Reference Standard (SRS) uncertainty 1-2%:

- Linked to a primary standard through comparisons or calibrations
- Larger uncertainty than primary standards

-Both require complete, documented uncertainty assessment

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NIST Standard Reference Materials (SRMs) and Calibrations for Radionuclides Used in Nuclear Medicine and Biology

Nuclide	SRM/Calibration or Calibration only	Nuclide	SRM/Calibration or Calibration only	Nuclide	SRM/Calibration or Calibration only
^{18}F	C	^{90}Y	S	^{169}Yb	S
^{32}P	S	^{99}Mo	S	^{177}Lu	C
^{35}S	S	^{99m}Tc	S	^{186}Re	C
^{36}Cl	S	^{103}Pd	C	^{188}Re	C
^{51}Cr	S	^{111}In	S	$^{188}W/^{188}Re$	C
^{57}Co	S	$^{113}Sn/^{113m}In$	S	^{195}Au	S
^{59}Fe	S	^{117m}Sn	C	^{197}Hg	S
^{62}Cu	C	^{123}I	S	^{198}Au	S
^{64}Cu	C	^{124}I	C	^{210}Po	C
^{67}Ga	S	^{125}I	S	^{201}Tl	S
$^{68}Ge/^{68}Ga$	C	^{131}I	S	^{203}Hg	S
^{75}Se	S	^{133}Xe	S	^{203}Pb	C
^{85}Sr	S	^{133}Ba	S	(^{212}Pb)	C
^{88}Y	C	^{153}Sm	S	^{223}Ra	C
^{89}Sr	S	^{153}Gd	S	^{224}Ra	C
^{90}Sr	S	^{166}Ho	C		

Brian E. Zimmerman, PhD
Radiation Physics Division, Physical Measurement Laboratory
National Institute of Standards and Technology
APhA 2022

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IMPORTANCE OF RADIOACTIVITY STANDARDS

- Ensure correct dosage administration
- Ensure measurement equivalence across clinics and instruments
- Maintain consistency over time
- Enable comparability of data in multi-clinic trials
- Provide 'Gold Standard' for new method development
- Assure correct activity delivery to customers

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TRACEABILITY

- Ensures measurements can be referenced to a common standard
- Important for clinical trials and international approval of radiopharmaceuticals
- Ensures long-term consistency and accuracy
- Refers to a measurement result, not an instrument or laboratory
- Requires unbroken measurement chain

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AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE (AAPM) REPORT 181 (2012)

- AAPM Report 181 (5.1) Individuals in medical facilities or in commercial nuclear pharmacies who use radionuclide calibrators on a daily basis may not fully understand the calibrator's operating characteristics and may not have read and/or understood the operating manual.
- They are initially measured or calculated for a manufacturer's master or typical production system. The calibrations are then transferred to each field instrument using limited source measurements and an algorithm that relates dial settings to calibration factors.
- It is up to the user to either demonstrate that the change is not significant It is up to the user to either demonstrate that the change is not significant (<5%) or, if significant, new calibration settings, calibration coefficients, or correction factors need to be derived and applied.

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AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE (AAPM) REPORT 181 (2012)

Table 2. Common Sources of Uncertainty in the Assay of Radionuclides with Ionization Chambers

1. Errors in calibration of standard reference sources
2. Errors in calibration by interpolation using "master" chamber response-energy curve and published decay schemes as extrapolated to "field" instruments
3. Variation in "field" instrument wall thickness and chamber gas pressure
4. Backscatter from chamber shielding
5. Inherent accuracy and linearity of electronics, including range changing errors (with and without with auto-ranging electrometers) and rounding or truncation errors
6. Ion pair recombination with high-activity sources
7. Variations in radiation background with low-activity sources
8. Differences between calibration containers and sample containers
9. Variation in attenuation due to variations in sample containers' wall thickness or material and sample volume
10. Sample position in the chamber (including changes in sample volume)
11. Solution density and homogeneity are potential problems but typically not significant. Non-homogeneity due to settling can be a problem with microsphere dosages

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PRACTICAL TIPS FOR ACTIVITY CALIBRATORS IN NUCLEAR MEDICINE

- Setting Up New Radiopharmaceuticals: Use of Activity Calibrators for Radioactivity Measurement

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HISTORY- GEOMETRICAL VARIATION

- 2001 61 medical events – Sm-153 28 percent less activity over 4-years
- 2015 Ra223 dichloride (Xofigo) Change in NIST Standard Reference Material – 10% numerical increase in Bq/mL in the vial- new dial setting
- 1994 14 medical events – Sr-89 less activity
- 2007-2023 Y-90 Spheres 523 medical events - Pure beta Y-90 has a little spike of 511; but majority are x-ray breaking radiation – depending on geometry especially careful – draw out activity and then re-assay vial, but use a correction factor based on the volume displaced that you calculate from carefully doing the trial volume testing, you don't have to replace the volume after you have a correction factor

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NIST F-18 SYRINGE STANDARD (GE-68/GA68)

Accuracy of F-18 calibration settings in commercial dose calibrators using a new traceable Ge-68 standard (2010) From 439 to 472 on some Capintec models

- Clinical site establishing syringe F-18 dial setting with Ge68/Ga68 syringe geometry source
- Clinical site is filling F-18 phantom to perform PET normalization
- PET scanner converts F-18 normalization into calibration for OTHER ISOTOPES (Bq/mL)
- Dose Calibrator assay of all ISOTOPES injected activity- input the absolute activity given to patient
- Quantitative PET SUV

Natasia O'Brien, Mike Zimmer, Nancy McDonald and Stewart Spies
Journal of Nuclear Medicine April 2010, 51 (supplement 2) 2112;

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GRAVES ET AL, 2021-SIR SPHERES 23% HIGHER GNESIN ET AL, 2022-THERASPHERES 20% LOWER

- These articles measured the true activity of the Y-90 spheres and the manufacturer was 20% wrong in the activity on the vial, and hence prescribed by the AUs and hence the DOSE (Gy) delivered to the patients.
- This was consistent with SIR Spheres all the way back to the trials
  - Resin microspheres are known to have a lower liver toxicity dose threshold – 52 Gy = 50% NTCP; implies 40 Gy = 15% NTCP
- It was inconsistent with Theraspheres
  - Glass spheres are known to have a higher liver toxicity – 70 Gy = 15% NTCP (normal tissue complication prob)

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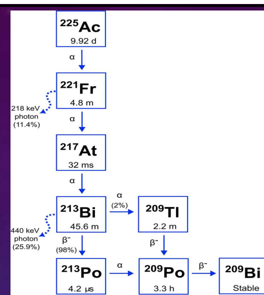
ALPHA EMITTERS



- For an alpha emitter – decay chains can lead to measurements being made before equilibrium is reached – must rely on the MCA for timing
- Low energy x-rays can lead to significant geometry effects
- Administered activities are low, on the order of 50 to 200 microcuries - Measurement of the residual can be a larger fraction of the administered activity.
- A series of decays means you need to know when the RN was produced and when it's in equilibrium

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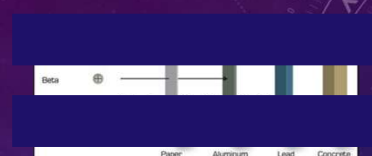
5.4.2 BETA EMITTERS



- Beta emitters can be accurately measured in a radionuclide calibrator using the bremsstrahlung produced as the beta particles interact with surrounding materials
- most of the first bremsstrahlung interactions occur in the source (solution and container) followed by interactions with the chamber's aluminum wall
- Higher energy Beta's have direct ionization of the chamber volume and may significantly distort assay results. A beta emitter with an Emax greater than 2 MeV is considered a high-energy beta emitter
- The authors recommend that commercial nuclear pharmacies establish a Y-90–calibrated setting based on the NIST standard reference source so that each source supplied to a medical facility could be used as a secondary reference standard and each medical facility determine its own calibration setting based on the initial Y-90 activity received from the pharmacy

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GRAVES, SNMMI 2023

- **Based on UAB and IOWA the Lu177 Lutathera and Pluvicto are approximately -3.3% and +3.2% compared to Novartis activity specifications.**
- **This indicates that different dial settings should be used 20 cc in a glass vial and 10 cc in a glass vial is not the difference your seeing with only volume difference in the vial**

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5.4.3 BETA-GAMMA EMITTERS

- Sm-153 is a beta-gamma emitter with medium-energy betas of
  - 640 keV (32%), 710 keV (30%), and 810 keV (18%) and a gamma of 103 keV (30%)
- Measurement efficiency is mainly determined by the gamma emission
- Due to the low energy of the gamma, assaying Sm-153 in a syringe geometry using a calibration factor obtained for glass-vial geometry may significantly overestimate (potentially >20%) the sample activity

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5.4 PROBLEM RADIONUCLIDES
5.4.1 LOW-ENERGY PHOTON EMITTERS (<100 KEV)

- A number of commonly used radionuclides emit relatively abundant characteristic x-rays in addition to their principal photons
- The characteristic x-rays from these radionuclides have energies that fall within the peak and potentially contribute a large component to the ionization current
- If the source container is glass, the x-rays may be highly absorbed in the glass wall
- If the container is a capsule or plastic syringe, a significant number of the x-rays will penetrate to the sensitive volume of the chamber

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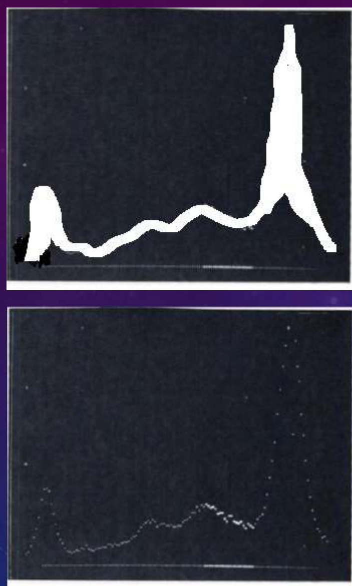
Comecer data for container type

ISOTOPE	CONTAINER CORRECTION	
	GLASS VIAL	PLASTIC SYRINGE
^{241} Am	+5%	-5%
^{123} I	+15%	-15%
^{125} I	+25%	-25%
^{111} In	+10%	-10%
^{133} Xe	+10%	-10%

Ionization current was 100% at 5-7 cm from the bottom of the chamber.

40

A



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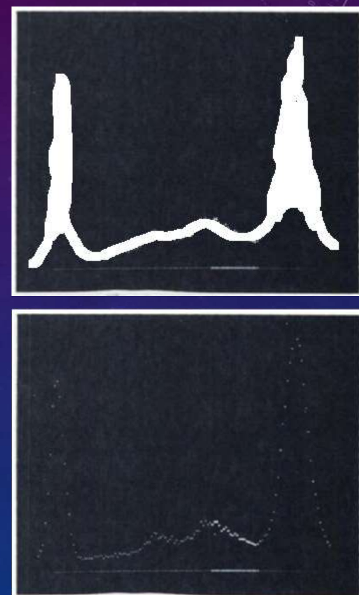

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Use of a Copper Filter for Dose-Calibrator Measurements of Nuclides Emitting K X-Rays, K. S. Wiarda, Journal of Nuclear Medicine May 1984, 25 (5) 633-634

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Professional Services Department
900 Hornet Drive
P.O. Box 5840
St. Louis, MO 63134
Telephone (800) 325-3688

****** TECHNICAL BULLETIN ******

Dose Calibrator Correction Factors for Assaying ^{111}In in Various Geometries and Volumes

^{111}In is a clinically useful isotope with a half-life of 2.805 days and has 2 major photoelectric peaks (171.28 and 245.30 keV) that are used for imaging. In addition, ^{111}In has 3 significantly abundant x-ray peaks between 20 and 26 keV which can contribute to assay errors depending on the container's geometry and material.

TABLE I - NUCLEAR DECAY DATA FOR ^{111}In [1]

Radiation Type	Energy (keV)	Intensity (%)
X-ray L	3.13	7.00
X-ray $K_{\alpha 2}$	22.98	23.50
X-ray $K_{\alpha 1}$	23.17	44.40
X-ray K_{β}	26.00	14.50
γ 1	171.28	90.93
γ 2	245.39	94.00

A study performed in Mallinckrodt Medical's radioisotope testing laboratories demonstrated significant differences between assay values depending on the solution volume and material composition of the container. Correction factors were determined for various geometries, volumes and dose calibrators.

RadCal 4050, Atom Lab 100, and Capintec CRC 12 dose calibrators were used in the study. A known activity of ^{111}In (NIST traceable), in duplicate, was added to 10 cc molded glass vials, a 1 cc syringe, a 3 cc syringe, and a 10 cc syringe. All syringes were made of plastic. Saline was added to make a final volume of 1.0, 3.0, and 6.0 mL in each configuration. All syringes were assayed with the needle and needle guard attached to the syringe. Each sample was assayed in each dose calibrator using the manufacturers' recommended calibration factors.

Volume effects were observed in assaying ^{111}In in plastic syringes. The correction factors are presented in Table II on the reverse side of this page.

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TABLE II - ^{111}In CORRECTION FACTORS FOR VARIOUS GEOMETRIES

DOSE CALIBRATOR MODEL #		RAD CAL 4050	ATOM LAB 100	CAPINTEC CRC 12
MANUFACTURER'S CALIBRATION FACTOR		1141	12.7	303
	Volume in VIAL or SYRINGE	Correction Factor	Correction Factor	Correction Factor
10 CC Molded Glass Vial	1.0 to 6.0 mL	1.154	1.213	1.136
1 CC SYRINGE	1.0 mL	0.770	0.812	0.797
3 to 10 CC SYRINGE	1.0 mL	0.786	0.828	0.812
3 to 10 CC SYRINGE	3.0 mL	0.798	0.843	0.821
6 to 10 CC SYRINGE	6.0 mL	0.815	0.859	0.835

Example 1: A Capintec Model CRC 12 is used to assay a 10 cc molded glass vial containing 1.1 mL of $^{111}InCl_3$. The obtained value is 5.28 mCi. The correction factor from Table II is 1.136. The actual activity contained in the vial is:

5.28 mCi x 1.136 = 6.00 mCi

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5.6 OPERATOR ERRORS

- Operators need to understand that calibration coefficients are radionuclide and geometry dependent.
- Source holders must be used as instructed by the manufacturers and should be placed in the chamber properly, not physically altered, and replaced when broken.
- Source holders from different calibrator manufacturers should not be interchanged without verifying the accuracy of the calibration coefficients for the holder/calibrator combination.

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DIPPER AND SOURCE POSITION 1-3% DIFFERENCE DEPENDING ON WHERE THE SAMPLE IS PLACED IN THE DIPPER- EVEN WITH CORRECT DIAL SETTING AND GEOMETRY

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6. POST-ASSAY ERRORS

Table 3. Stages and Typical Uncertainties in Radiopharmaceutical Dosage Delivery

	Source of Uncertainty	Uncertainty
Prescribed Dosage		
↓		
Dosage Prepared	Technique/Human Error	Unknown
↓		
Assayed Dosage	Calibrator Accuracy	±5%–10%*
	% of Prescribed Dosage	±5%–10%*
↓		
Time to Administration	E.g., Tc-99m	0.2%/min
	E.g., F-18	0.6%/min
↓		
Residual Activity	E.g., Syringe-Needle Dead Volume	(–) ~6%
↓		
	E.g., Adsorption to Vessel Wall	(–) ~1%–30%
Administered Dosage	% of Prescribed Dosage	±10%*

*Recommended Maximum

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NRC REGS 15 YEARS AGO

- Geometry-at time of installation, repair, recalibration, or relocation ± 5%
- Accuracy-annually-two radionuclides ± 5%
- Constancy-Daily –reference source ± 5%
- Linearity-Quarterly –shielding or decay method ± 5%

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10CFR35

- **§ 35.60 Possession, use, and calibration of instruments used to measure the activity of unsealed byproduct material**
- (a) For direct measurements performed in accordance with § 35.63, a licensee shall possess and use instrumentation to measure the activity of unsealed byproduct material before it is administered to each patient or human research subject.
- (b) A licensee shall calibrate the instrumentation required in paragraph (a) of this section in accordance with nationally recognized standards or the manufacturer's instructions.
- (c) A licensee shall retain a record of each instrument calibration required by this section in accordance with § 35.2060.
- § 35.63 Determination of dosages of unsealed byproduct material for medical use. (d) Unless otherwise directed by the authorized user, a licensee may not use a dosage if the dosage does not fall within the prescribed dosage range or if the dosage differs from the prescribed dosage by more than 20 percent.

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AAPM REPORT NO. 181

10.4 Recommended Quality Control Programs

10.4.1 Test Frequencies

	Acceptance[a]	Daily[b]	Annually
Physical Inspection	X	X	X
System Electronic	X	X	X
Clock Accuracy	X	X	X
High Voltage	X	X	X
Zero Adjustment	X	X	X
Background	X	X	X
Check Source	X	X	X
Accuracy Test	X		X
Reproducibility	X		X
System Linearity	X		X
Supplier Equivalence	X		X

[a] And after repair.
[b] At the beginning of each day-of-use. **Note:** The term "day-of-use" may lead to some confusion for facilities that offer after-hour services. For purposes of radionuclide calibrator quality control, "day-of-use" means a normal 24-hour day starting at 12:00 a.m.

The IAEA, IEC, and European Association for Nuclear Medicine (EANM) recommend routine linearity testing on an annual basis.

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COMMERCIAL NUCLEAR PHARMACY & RADIOPHARMACEUTICAL MANUFACTURER (10CFR32)

Professional Guidelines:

- AAPM TG-181 ± 2% FOR ANY ABSOLUTE ACTIVITY QUANTIFICATION
- NUREG 1556 VOLUME 13 REV 2 APPENDIX L ± 10%
- NUREG 1556 VOLUME 9 REV 3 APPENDIX G ± 10%

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ROLE OF STANDARDS IN QA/QC

- Regular checks should utilize traceable standards
- Sources should be traceable to NIST
- Acceptance criteria for various tests (e.g., accuracy, precision, linearity)
- Perform tests at different frequencies: daily, monthly, annually
- New calibration factors needed when geometry effect > 5%

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TRUE OR FALSE

- The amount of activity in a diagnostic unit dose from a radiopharmacy does not need to be measured in a dose calibrator if the dose at the time of administration is calculated from the labeled activity and decay time.

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10.4.2 COMMERCIAL NUCLEAR PHARMACIES (INCLUDING MANUFACTURERS)

- **10.5 Personnel Requirements**

Facility management should establish (in writing) the qualifications and training requirements (including continuing education) necessary for those personnel who operate a radionuclide calibrator.

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. 2018 Jun;39(6):500-504

An update on 'dose calibrator' settings for nuclides used in nuclear medicine

- Most clinical radioactivity measurements rely on commercial re-entrant ionization chambers ('dose calibrators')
- The National Institute of Standards and Technology (NIST) maintains calibrators and links settings to primary radioactivity standards
- This study provides updated dial settings for 22 radionuclides

Denis E. Bergeron and Jeffrey T. Cessna Nucl Med Commun. 2018 Jun;39(6):500-504

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METHODS

- Collected previously published dial settings
- Determined new settings using:
- - Calibration curve method
- - Dialing-in approach

Based on presentation by Brian E. Zimmerman, PhD, National Institute of Standards and Technology

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RESULTS

- Comprehensive table of dial settings with uncertainties for 22 radionuclides
- Multiple geometries considered for some nuclides
- Settings provided for various calibrator models:
- - Vinten 671
- - Capintec CRC series (no support for older models)
- - Biodex AtomLab series (discontinued-no longer supported)

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KEY FINDINGS

- Most manufacturer-provided settings now agree with NIST standards within a few percent
- Significant improvement from 2000 study, where some settings overestimated activities by >20%
- Reflects positive impact of emphasis on traceability to common measurement standards

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7.4.2 SUBSIDIARY CALIBRATION

- The ANSI standard requires that calibrators be calibrated with identified radionuclide sources of known activity and established purity. ANSI nomenclature and definitions for radioactive standard sources from are used in this document, as follows:

  1. **National radioactivity standard source.** A calibrated radioactive source prepared and distributed as a standard reference material by the U.S. National Institute of Standards and Technology.

  2. **Certified radioactivity standard source.** A calibrated radioactive source, with stated accuracy whose calibration is certified by the source supplier as traceable to the National Radioactivity Measurements System.

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HOW ACCURATE ARE OUR ACTIVITY MEASUREMENTS

- Generally we obtain a NIST-traceable source in a clinically relevant geometry to establish a clinical dial setting
- In practice, it's much more common to establish a "supplier equivalence" rather than NIST traceability
- It is NOT guaranteed that the manufacturer/supplier has established traceability - especially for phase I and II
- In the past there was a measurement assurance program-NIST eliminated 2018

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SPECT QUANTITATION REQUIRES A NIST CALIBRATED VIAL OF ACTIVITY TO ESTABLISH A TRIAL ACCURATE ACTIVITY FOR EACH TRIAL

- I-131 has a wide therapeutic window
- Y-90 23 Gy to kidneys depends on renal absorbed dose – narrow therapeutic window

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CALIBRATING ACTIVITY CALIBRATORS

Two main methods:

1. 'Dialing-in' (when activity is known):
- - Use traceable standard in correct geometry
- - Adjust dial setting until correct activity is displayed

2. Response curve (when activity is initially unknown):
- - Measure response curve for specific geometry
- - Calculate dial setting from fit of response curve

Based on presentation by Brian E. Zimmerman, PhD, National Institute of Standards and Technology

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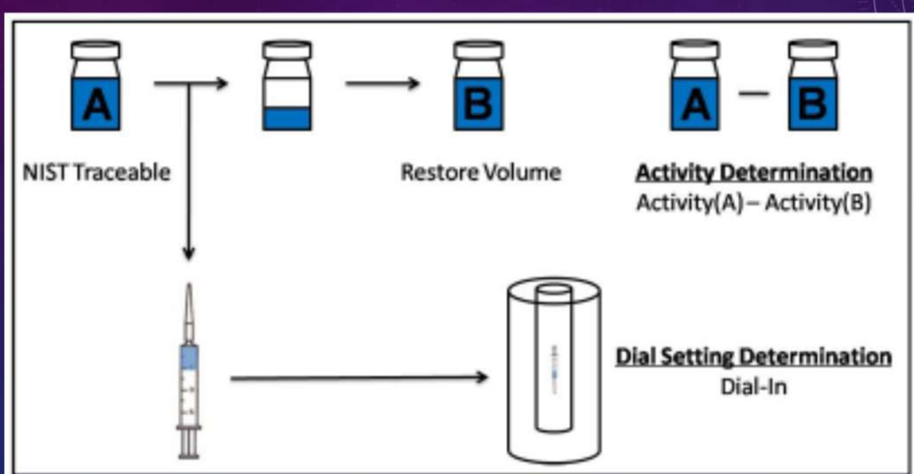
ACTIVITY DIFFERENCE METHOD



Gabriel Candelaria and Daniel Irwin. UNM CE 2010. Vol 15. Science of Measurement: A Primer on Radioactivity Dose Calibrators

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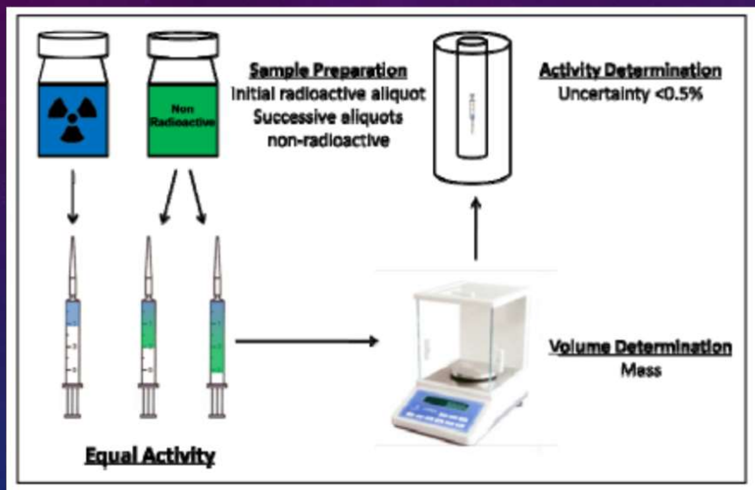
GRAVIMETRIC, CONSTANT ACTIVITY METHOD



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$$CF = A_R / A_m$$

$$A_T = A_m \times CF$$

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

Gabriel Candelaria and Daniel Irwin. UNM CE 2010. Vol 15. Science of Measurement: A Primer on Radioactivity Dose Calibrators

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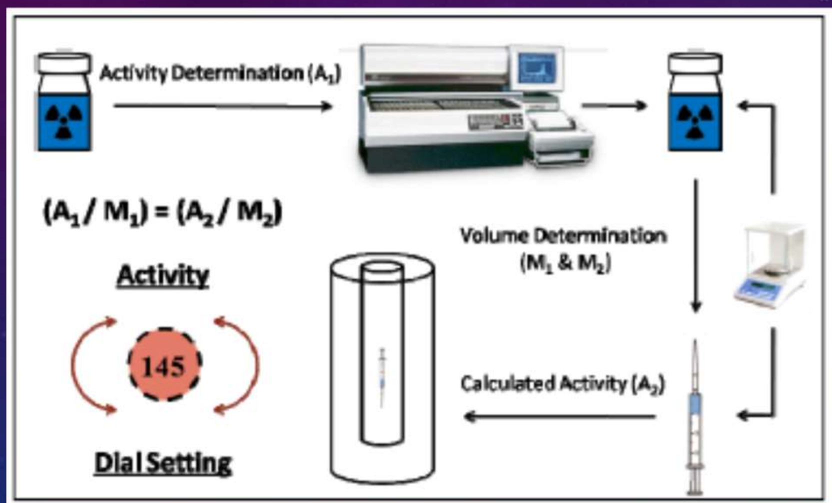
DIAL IN METHOD



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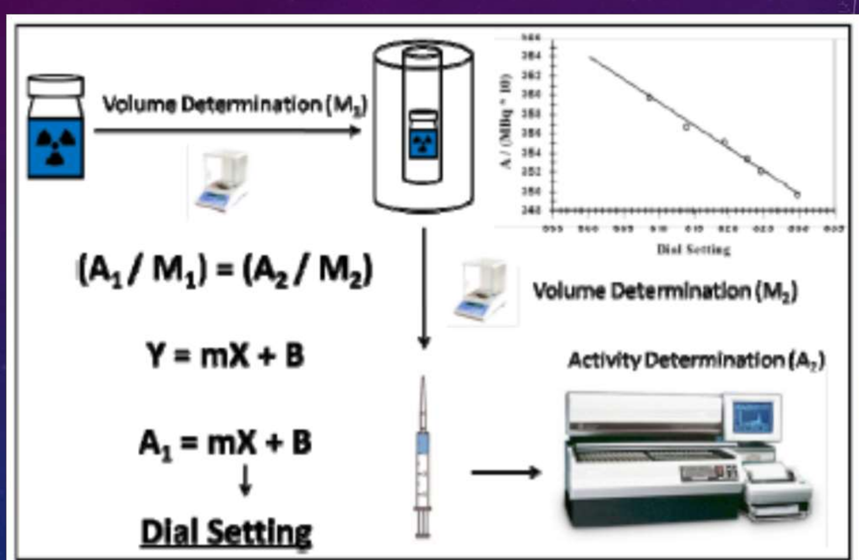
CALIBRATION CURVE METHOD



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CONCLUSION

- 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 geometry with known activity.
- Quantification in any capacity necessitates a better understanding of errors to assaying and matching the manufacturers or NIST standard source or secondary reference standard to a maximum of 2% error.

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