Radiopharmaceuticals for Nuclear Cardiac Imaging: Generator Systems for Tc-99m and Rb-82

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Objectives

- List common SPECT MPI agents
- Describe preparation problems associated with using Tc-99m generator eluates
- Describe common Tc-99m radiochemical impurities
- Describe other common problems encountered when radiolabeling Tc-99m kits
- List available PET MPI agents
- Describe Rb-82 generator

Summary of Commonly Used Commercially Available Radiopharmaceutical Agents for SPECT MPI

	Thallium 201	Sestamibi Tc-99m	Tetrofosmin Tc-99m
Brand name	N/A	Cardiolite	Myoview
Half-life, h	73.1	6.0	6.0
Photon energy	67-83	140	140
Radionuclide Availability	Cyclotron produced	Generator produced	Generator produced
Whole-body radiation after typical MPI dose, rad	0.68	0.50	0.50

Radionuclide Generator Systems

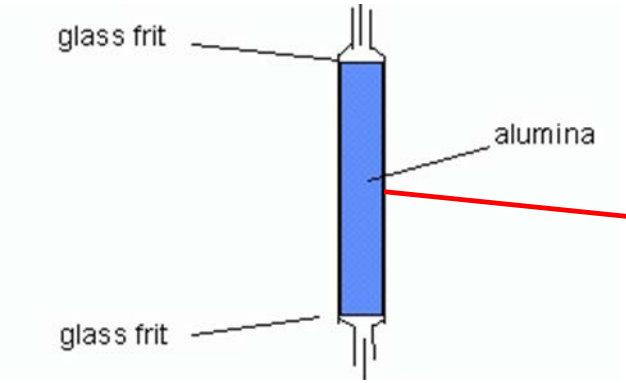
- Alternative to reactors or cyclotron is to use a 'mother' isotope that has a **long half-life** that **decays to a short half-life** 'daughter' that can be used for imaging.
- The mother isotope is produced in a nuclear reactor and then shipped in a 'generator'.
- The daughter radionuclide is a **different element** than the parent and will therefore often be in a quite **different chemical** form than the parent.
- As needed, the daughter isotope is 'eluted' and combined into a radiopharmaceutical.

Molybdenum-99/Technetium-99m Generator Systems

- Most common radionuclide generator for nuclear cardiology imaging is the ^{99}Mo-^{99m}Tc generator in which a stored quantity of ^{99}Mo decays with half life of 66 hours into the 6 hour half life ^{99m}Tc.
- These generators are produced and delivered on weekly and provide all of the ^{99m}Tc used daily.

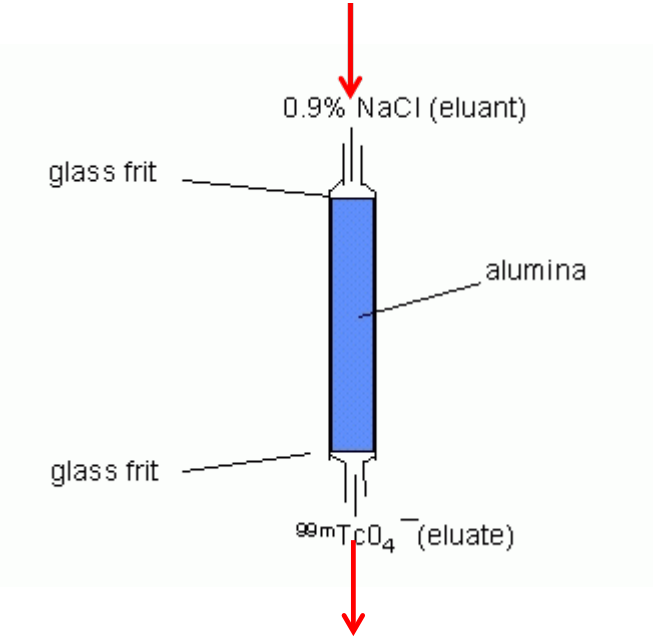
Molybdenum-99/Technetium-99m Generator Systems

- Prior to shipping the generator, Mo-99 sodium molybdate is immobilized on a column of alumina (Al_2O_3; aluminum oxide) due to its very high affinity for alumina.



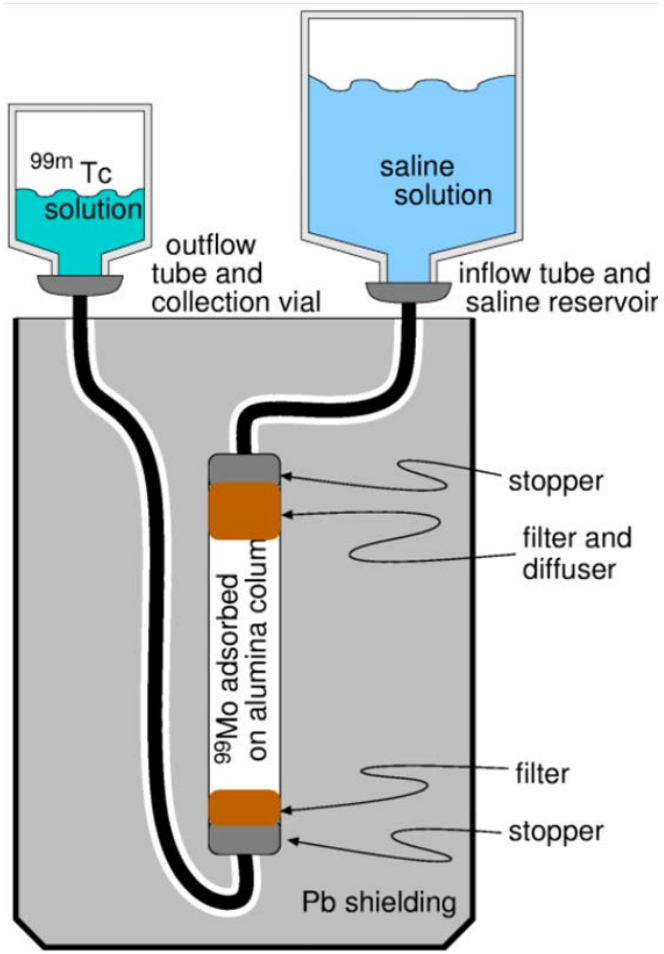
Molybdenum-99/Technetium-99m Generator Systems

- 0.9% saline solution (the **eluant**) is passed through the column and sodium pertechnetate, the daughter of Mo-99 decay, is eluted from the column due to its almost total lack of affinity for alumina.

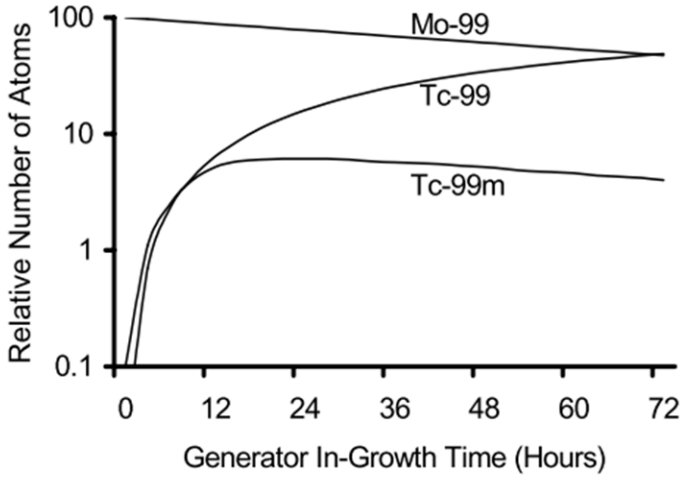


Molybdenum-99/Technetium-99m Generator Systems

- The pertechnetate is collected in a shielded, evacuated sterile vial and calibrated prior to use. It is referred to as the **eluate**.
- Quantitative removal of pertechnetate is attributed to the lack of affinity of pertechnetate for alumina, whereas molybdate is essentially completely and irreversibly bound to the alumina.



Relative Number of Atoms in Mo-99/Tc-99m Generator



- Tc-99 is a decay product of Mo-99 (approximately 12% of Mo-99 decay bypasses the metastable state and goes directly to ground state.
- Tc-99 is always present in Tc-99m samples.
- Product remaining after Tc99m decay.
- Tc-99 rate of decay is negligible.

Generator Quality Control

- Safety concern is breakthrough of the parent nuclide into the eluent.
- If parent introduced into the patient it will decay and produce extra radiation dose and degrade image.
- Alumina contamination of eluent may interfere with pharmaceutical synthesis.
- Allowable levels of parent radionuclide(s) and alumina are set by federal and state regulations.

Radionuclide Purity Test

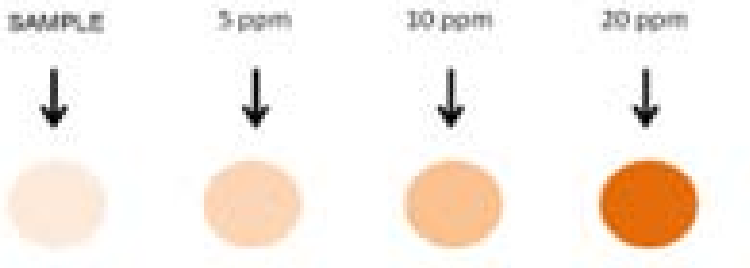
- Tc-99m solution is placed inside a special Pb shield with 7 mm Pb thickness.
- Shielded solution placed in dose calibrator.
- Any presence of measured activity from shielded solution must be Mo-99 due to high energy emission.
- Max allowed breakthrough is 0.15 uCi per mCi of Tc-99m.

Chemical Purity Check

- Aluminum is an impurity which can potentially arise from the alumina columns present in the $^{99}Mo/^{99m}Tc$ generator.
- Although rare, breakdown of the column structure can occasionally occur resulting in significant levels of Al^{+3} ions in the generator eluates.
- Levels of Al^{+3} ions greater than 10µg per ml can cause problems with some radiopharmaceuticals.
- Levels of Al^{+3} ions greater than 10µg per ml can be measured using a colorimetric test or using special indicator paper.

“Aluminum breakthrough”

- Alumina assessment test uses a semi-quantitative colorimetrical test with standard solutions of Al^{+3}
- The eluate sample color is compared with that of standard reference solution of aluminum



Molybdenum-99/Technetium-99m Generator Systems

Problem	Issue	Standard
Excess Mo-99 in eluant	Additional radiation exposure to the patient	<0.15 uCi Mo-99/mCi Tc-99m *at time of dosage administration*
Al_2O_3 from generator ion exchange column in eluant	Interferes with the normal distribution of some radiopharmaceuticals	<10 ug/ml
Reduced oxidation states of Tc-99m (+4, +5, or +6)	Preparation of commercial pharmaceutical kits are predicated on the +7 oxidation state	95% of Tc-99m activity should be in +7 oxidation state

MPI Kit Problems Associated with Tc-99m Generator Eluates

- Excessive Tc-99m
- Excessive Tc-99
- Oxidation of stannous ion
- Inadequate stannous ion

Reductive Capacity of the Preparation of Tc-99m Radiopharmaceuticals

Kit	$SnCl_2 \cdot 2H_2O$ (µg)	Maximum Recommended Activity (mCi Tc-99m	Molar Ratio Sn:Tc (24-hr Generator Buildup, Fresh Eluate)	Molar Ratio Sn:Tc (24-hr Generator Build-up, 12 Hour Aged Eluate; or 72hr Generator Buildup, Fresh Eluate)
Sestamibi	75	150	325	81
Tetrofosmin	30	240	81	20

Recommendations

- In order to minimize problems associated with Tc-99m generator eluates used for the preparation of Tc-99m radiopharmaceuticals:
- Use eluates from generators which have in-growth times of no more than 24 hours whenever possible.
- Avoid the use of aged Tc-99m eluates, especially those more than 12 hours old.
- Avoid adding excessive Tc-99m activity to kits.
- Avoid maintaining excessive concentrations of radioactive solutions; i.e., dilute solutions to lower radioactive concentrations

Radiochemical Purity

- Predominant radiochemical impurity associated with most Tc-99m radiopharmaceuticals is **free, unlabeled** Tc-99m in the chemical form of pertechnetate ion (i.e., TcO4-).
- Pertechnetate distributes throughout the vasculature and interstitial fluid, and concentrates primarily in the stomach, intestinal tract, urinary tract, thyroid gland, and salivary glands.
- Second radiochemical impurity associated with some Tc-99m radiopharmaceuticals is insoluble Tc-99m in the chemical form of technetium hydroxides or technetium labeled stannous hydroxide (also referred to as **hydrolyzed-reduced technetium**).
- These species are in the physical form of colloid particles which are phagocytized by cells of the reticuloendothelial system located primarily in the liver, spleen, and marrow.

Conventional Drugs vs Tc-99m Radiopharmaceuticals

- Tc-99m labeled radiopharmaceuticals characteristics that are potentially problematic in their preparation and dispensing:
  - preparation involves chemical reactions that may produce undesired radiochemical impurities
  - emitted radiation may produce radiolytic effects that can result in undesired impurities
- May result in undesired adsorption to container components
- These problems may result in unexpected alterations in biodistribution and/or inadequate localization in organs of interest, and interfere with **diagnostic interpretation.**

Conventional Drugs vs Tc-99m Radiopharmaceuticals

- Reagent kit is approved for distribution to persons licensed by the U.S. Nuclear Regulatory Commission to use byproduct material or under an equivalent license issued by an Agreement State.
- Contents of the kit before preparation are not radioactive.
- After the Sodium Pertechnetate Tc 99m Injection is added, adequate shielding of the final preparation must be maintained.
- It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation.

Conventional Drugs vs Tc-99m Radiopharmaceuticals

- Technetium Tc 99m labeling reactions depend on maintaining the stannous ion in the reduced state.
- Technetium TC 99m Sestamibi should not be used more than six hours after preparation.
- Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

AUTHORIZED USER TRAINING AND EXPERIENCE AND PRECEPTOR ATTESTATION
(for uses defined under 35.100, 35.200, and 35.500)
[10 CFR 35.190, 35.290, and 35.590]

Name of Proposed Authorized User: PEDI KINAR, M.D.
State or Territory Where Licensed: PENNSYLVANIA

Requested Authorization(s) (check all that apply)
- [X] 35.100 Uptake, dilution, and excretion studies
- [X] 35.200 Imaging and localization studies
- [ ] 35.500 Sealed sources for diagnosis (specify device _____)

PART I – TRAINING AND EXPERIENCE
(Select one of the three methods below)

Training and Experience, including board certification, must have been obtained within the 7 years preceding the date of application or the individual must have obtained related continuing education and experience since the required training and experience was completed. Provide dates, duration, and description of continuing education and experience related to the uses checked above.

- [ ] 1. Board Certification
  - a. Provide a copy of the board certification.
  - b. If using only 35.500 materials, stop here. If using 35.100 and 35.200 materials, skip to and complete Part II Preceptor Attestation.
- [ ] 2. Current 35.290 Authorized User Seeking Additional 35.290 Authorization
  - a. Authorized user on Materials License _____ meeting 10 CFR 35.290 or equivalent Agreement State requirements seeking authorization for 35.290.
  - b. Supervised Work Experience. (If more than one supervising individual is necessary to document supervised work experience, provide multiple copies of this section.)

Description of Experience	Location of Experience/License or Permit Number of Facility	Clock Hours	Dates of Experience*
Using generator systems appropriate for the preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs.			
Total Hours of Experience:			

Supervising Individual: _____ License/Permit Number listing supervising individual as an authorized user: _____

Supervisor meets the requirements below, or equivalent Agreement State requirements (check all that apply).
- [ ] 35.290
- [ ] 35.200 + generator experience in 32.290(c)(1)(ii)(D)

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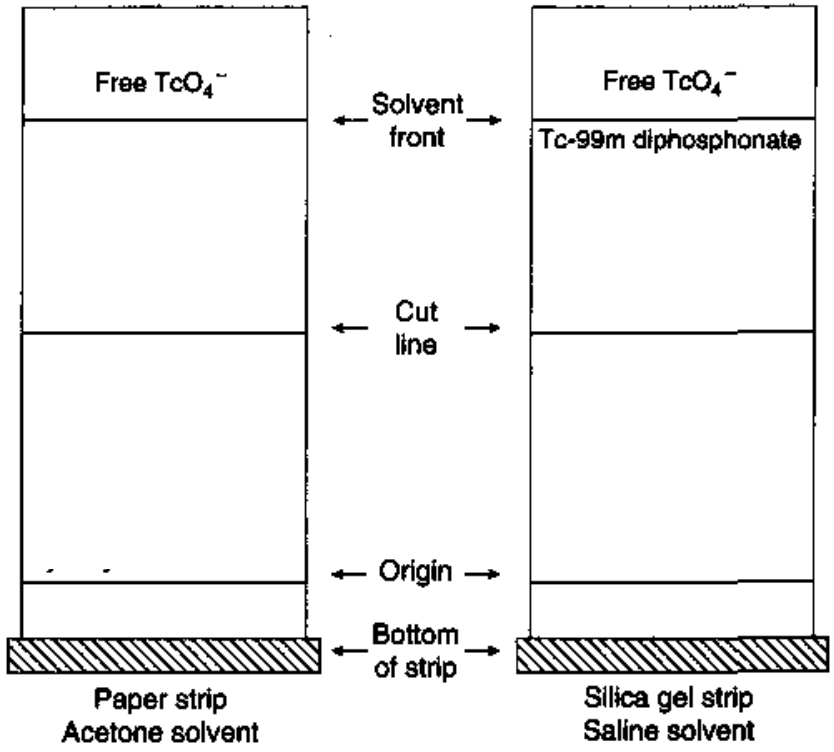
Quality Assurance of Tc-99m Labeled Radiopharmaceuticals

- Causes of radiochemical impurities include poor initial labeling, radiolysis, decomposition, pH changes, light exposure, or presence of oxidizing or reducing agents.
- For many agents the presence of a radiochemical impurity can be recognized by altered in vivo biodistribution.
- In vivo, radiochemical impurities contribute to background activity or other unwanted localization and degrade image quality.
- Intercepting the offending preparation before administration to a patient is obviously desirable.

Quality Assurance of Tc-99m Labeled Radiopharmaceuticals

- A number of systems have been developed to assay radiochemical purity.
- The basic approach developed to assay radiochemical purity is thin-layer chromatography.
- In brief, radiochromatography is accomplished in the same manner as conventional chromatography, by spotting a sample of the test material at one end of a strip.
- A solvent is then selected for which the desired radiochemical and the potential contaminants have known migration patterns.



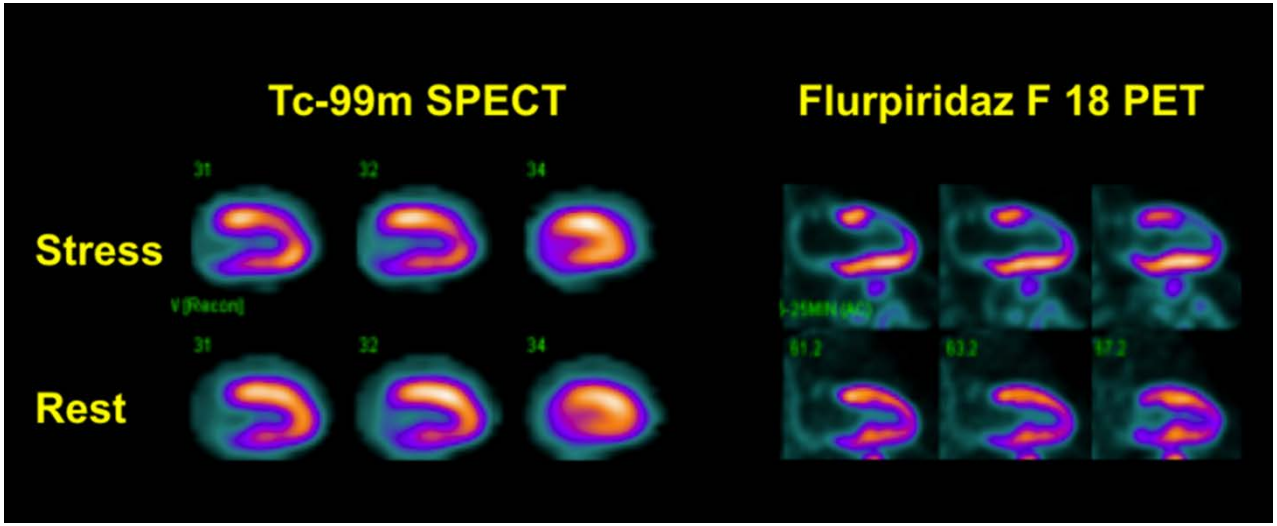
Recommendations

- Avoid adding air (i.e., oxygen) to vials unless otherwise directed.
- Avoid use of bacteriostatic normal saline for preparation or dilution of Tc-99m radiopharmaceuticals.
- Choose kit products that contain free radical scavengers or other stabilizing agents (e.g., antioxidants) whenever available.
- Consider storage at low temperatures (e.g., refrigeration) unless otherwise impractical.
- Avoid the practice of fractionating kits; if fractionation is necessary, employ appropriate strategies to inhibit oxidation of stannous ion.
- Do not use discolored eluates.

Other Common Problems Involved in Radiolabeling MPI Kits

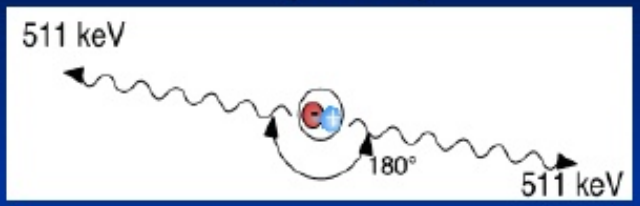
- Improper Heating
- Improper Mixing Order
- Reagent Concentration
- Incubation/Time Delays
- Decomposition During Storage
- Adsorption to Container Walls

PET MPI



- Myocardial perfusion imaging (MPI) with positron emission tomography (PET) has been shown to be superior to single photon emission computed tomography (SPECT).
- Nevertheless, widespread clinical use of PET MPI has been limited by the currently available PET myocardial perfusion tracers.

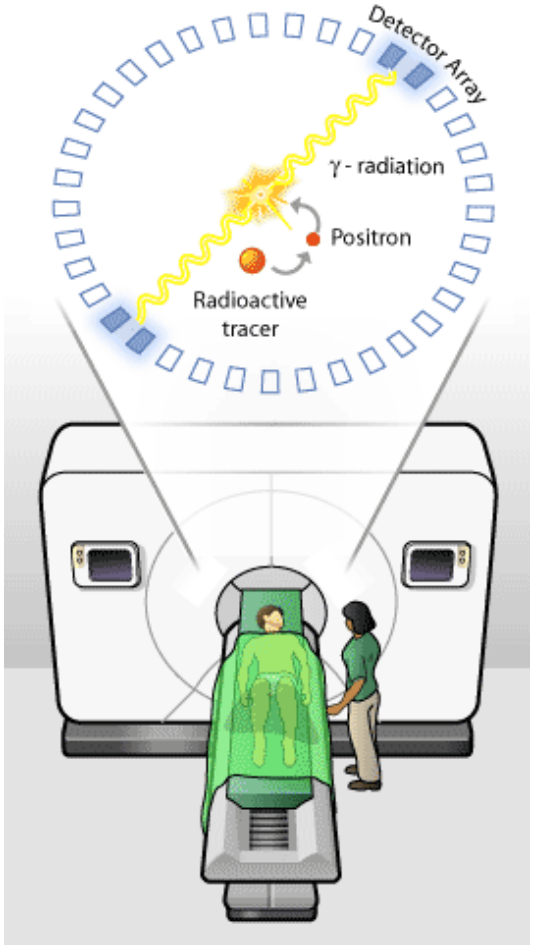
Physics of Rb-82 Positron Emission Tomography (PET)



- Rb-82 decay via a proton changing into a neutron, a positron and a neutrino (a positron has the same mass as electrons, but a positive charge)
- The positron is emitted into the patient where it comes to a stop (~3mm). The positron then annihilates with a near-by electron.
- Annihilation event – positron and electron collide, then convert into a pair of high energy (511 keV) photons
- Annihilation photons travel in opposite directions, conserving momentum and energy

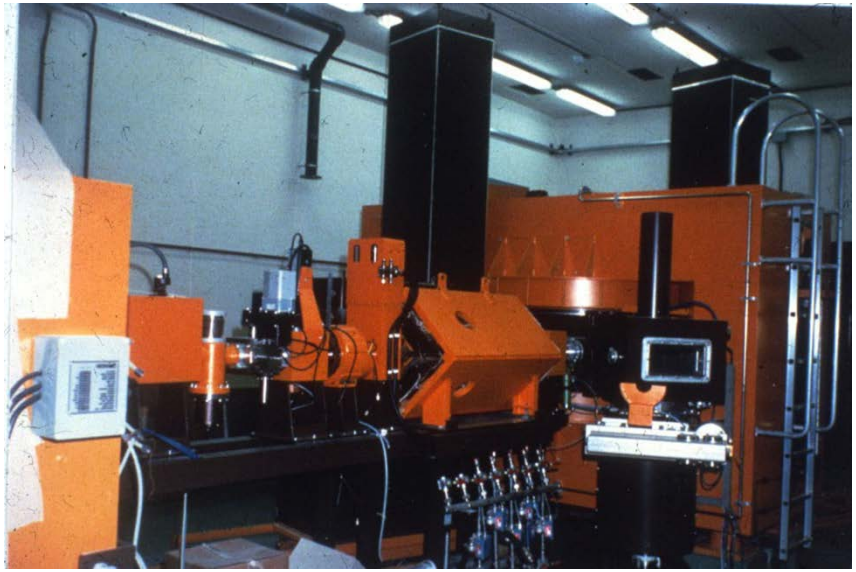
Process of Producing and Detecting Photons used in PET Scanners

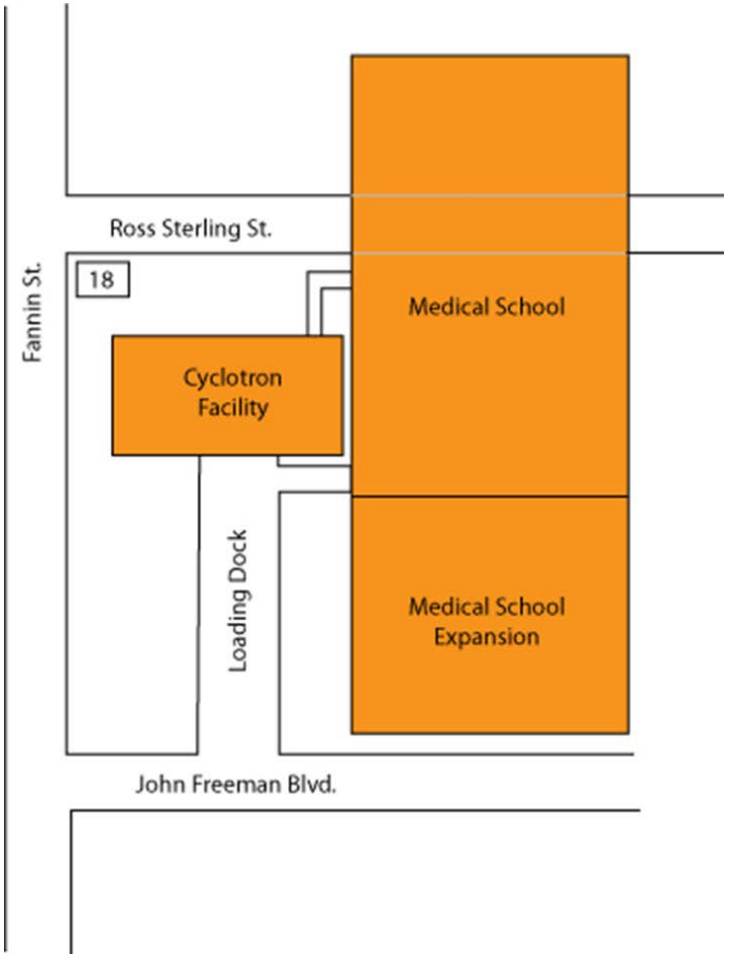
- Nucleus emits β^+ which travels a short distance before colliding with an electron (β^-) of a nearby atom.
- When β^+ comes in contact with an β^- , the two particles annihilate turning the mass of the two particles into two 511 keV gamma rays that are emitted almost 180 degree to each other.



Characteristic	Rb-82 Chloride	N-13 Ammonia	F-18 Flurpirdaz	O-15 Water
Production	Generator	Onsite cyclotron	Offsite cyclotron	Onsite cyclotron
Half-life	76 s	10 min	110 min	112 s
Positron range	2.6 mm	0.6 mm	0.2 mm	1 mm
Advantages	Commercially available generator Fast scan time Low radiation dose Short half-life permits quick repeated testing	Excellent contrast Low radiation dose	Excellent contrast and spatial resolution No investment in cyclotron or generator	Low radiation dose Short half-life permits quick repeated testing
Disadvantages	Lowest spatial resolution (better than SPECT)	Requires onsite cyclotron	Highest radiation dose (less than SPECT agents) Not FDA approved	Requires onsite cyclotron Low contrast and spatial resolution

McGovern Medical School UTHSC at Houston Cyclotron Building





The Weatherhead PET Imaging Center

- Rubidium Rb 82 chloride injection is indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.
- Closed system used to produce rubidium Rb 82 chloride injection for intravenous administration.

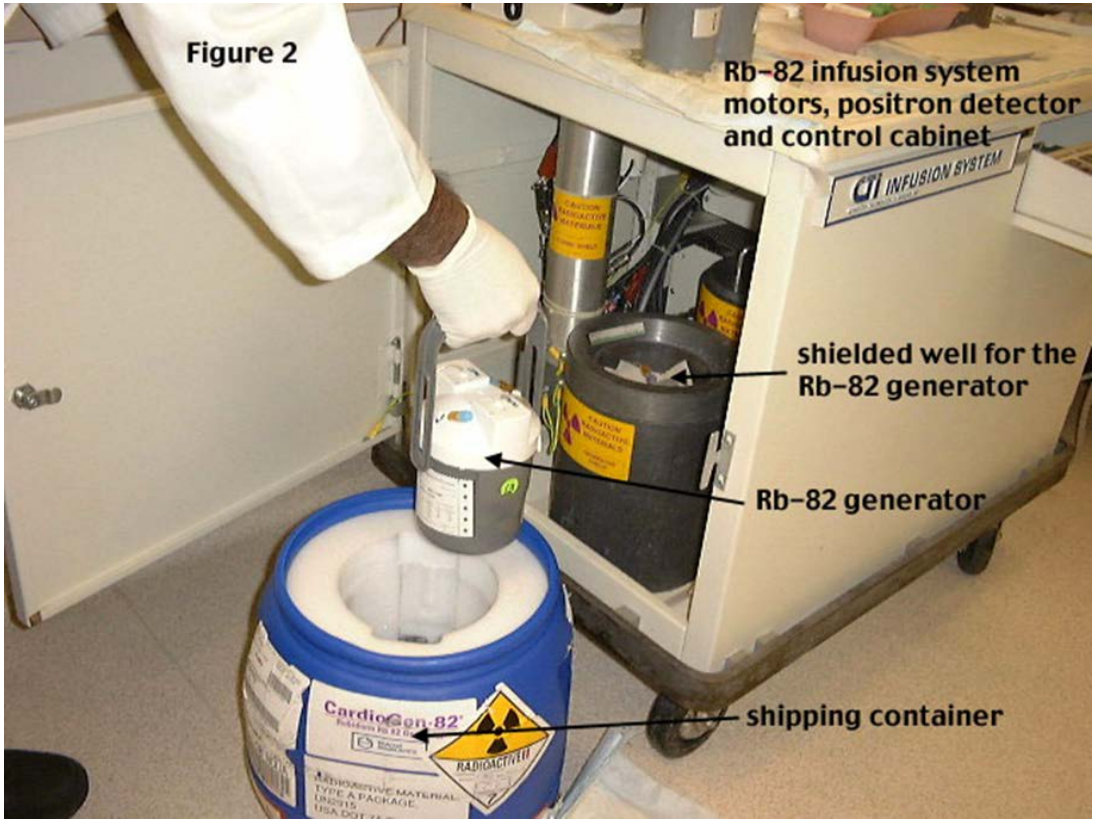
CardioGen-82® (Rubidium Rb 82 Generator)

- Rubidium-82 (Rb-82) is produced by decay of Strontium-82 (Sr-82)
- 75 second T½
- Kinetics:
  - Potassium analog
  - High extraction fraction at high flow rates
- Defects visualized 2-7 minutes after injection
- Same sized dose at stress & rest due to short T½
- New generator every 28 days
- Fixed price, not unit dose
- Dose available 24 hours per day, 7 days per week
- Pharmacologic stress studies

CardioGen-82®
(Rubidium Rb 82 Generator)

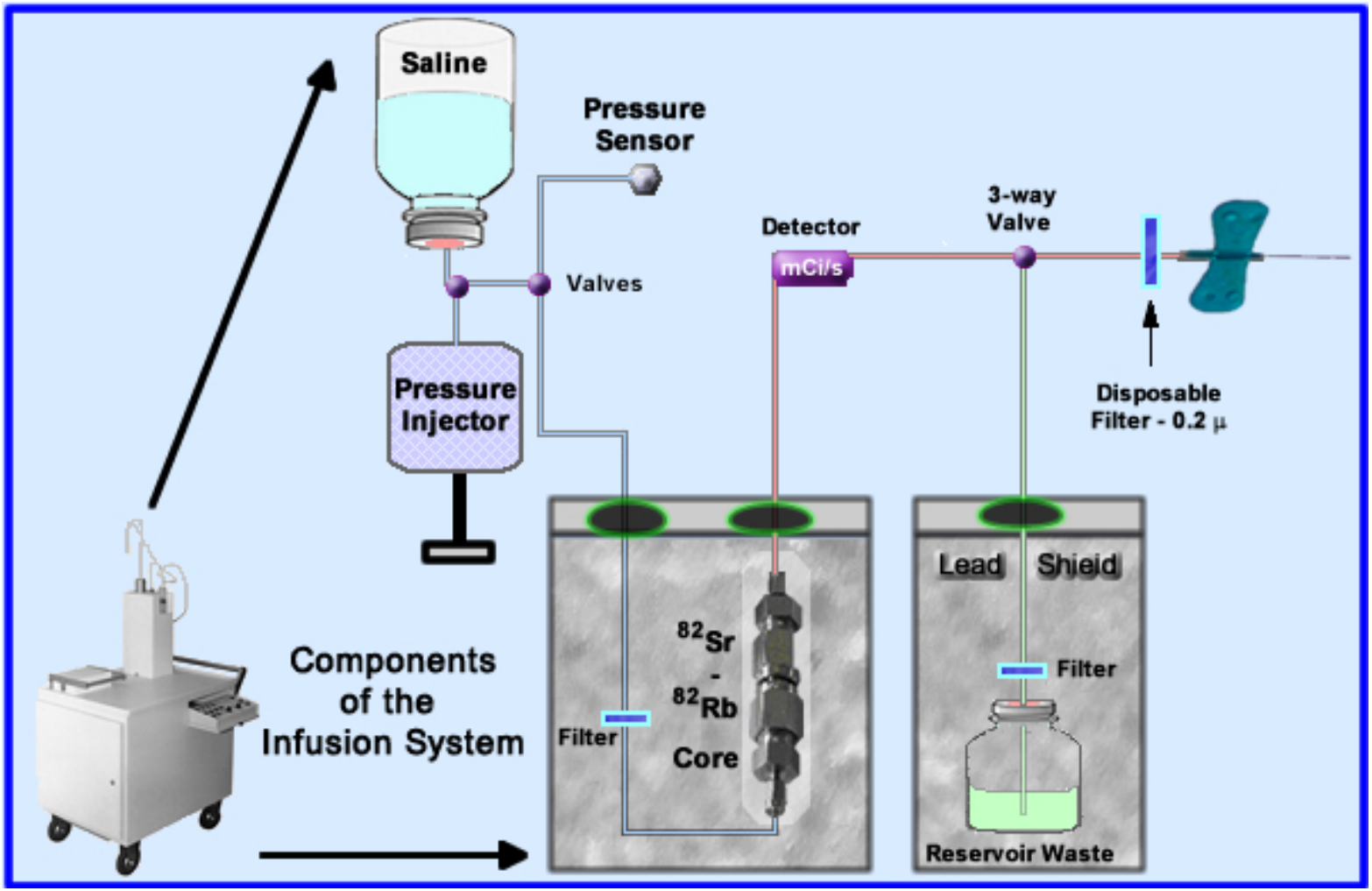
- Generator replaced every 28 days
- Rb-82 dose is provided within 10 minutes
- Infusion System is automated for the infusion and patient dose
- Permits accurate dosing with minimal operator interface, thus decreasing radiation exposure
- Contains shielding vault for CardioGen-82® Generator and waste container

Rb-82 Generator and Delivery System



The generator taken from shipping container and placed into an infusion system for patient administration.

Rb-82 Generator and Delivery System



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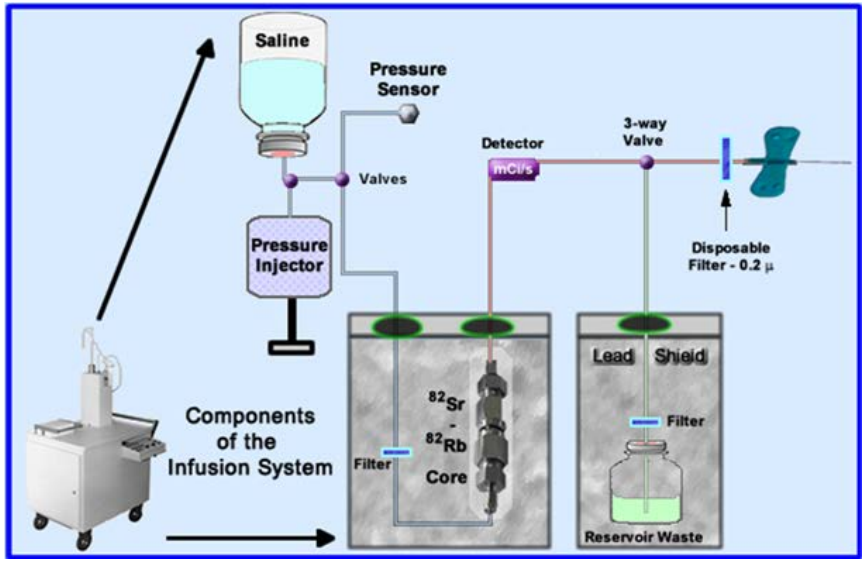
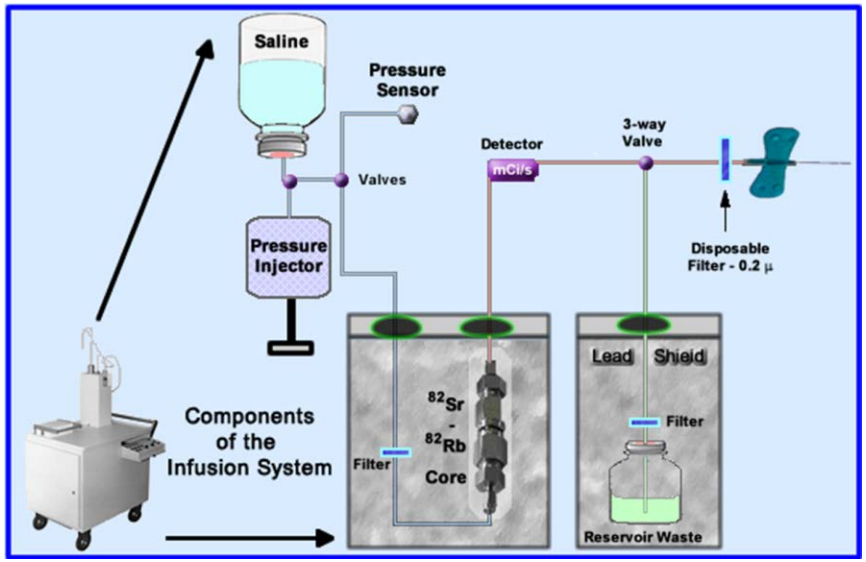


- Several filters are used to reduce the possibility of injecting particulate matter
- Some specifics regarding the elution and its delivery - First follow the flow of saline(blue = saline, red = tracer, and green = discard)!

Rb-82 Generator and Delivery System



- Saline (upper left) enters the system with the assistance of a pressure injector that is controlled by the technologist
- Saline is sent through the radioactive core and then out to the patient

Unintended Radiation Exposure from CardioGen

- Unintended radiation exposure occurs when the levels of Sr 82 or Sr 85 in the rubidium Rb 82 chloride injection exceed specified limits.
- To monitor for Strontium contaminates generator eluate tests are perform at specific frequencies.
- Unintended radiation exposure occurs when the Sr-82 and Sr-85 levels in rubidium Rb 82 chloride injections exceed the specified generator eluate limits.

Unintended Radiation Exposure from CardioGen

- Unintended exposure to strontium radiation has occurred in some patients who received rubidium Rb 82 injections at clinical sites where generator eluate testing appeared insufficient.
- The physical half lives of Sr-82 and Sr-85 are 25 days and 65 days, respectively, in contrast to Rb-82 which has a physical half-life of 75 seconds.
- Unintended exposure to strontium radiation contributes to a patient's overall cumulative radiation dose

CardioGen Quality Control Testing

- Determine Rb 82, Sr 82, Sr 85 in the generator eluate:
  - Once a day, prior to any drug administration, and
  - At additional daily tests after detection of an Alert Limit. Alert Limits are:
    - 20 L for the generator's cumulative eluate volume, or
    - An eluate Sr 82 level of 0.004 µCi/ mCi (kBq/MBq) Rb 82, or
    - An eluate Sr 85 level of 0.04 µCi/ mCi (kBq/MBq) Rb 82.
  - Perform additional daily tests every 4 patients after detection of an alert limit
- Stop use of a generator at any of the following Expiration Limits. Expiry Limits are:
  - 30 L for the generator's cumulative eluate volume, or
  - Expiration date of the generator (60 days post-manufacturing)
  - An eluate Sr 82 level of 0.01 µCi /mCi (kBq/MBq) Rb 82, or
  - An eluate Sr 85 level of 0.1 µCi /mCi (kBq/MBq)

Determination of Sr Breakthrough

- Relate this procedure to Mo-99 breakthrough (more involved)
- Must be done prior to any patient use
- Purge system with saline and discard it
- After 10 minutes send saline through the system and collect it in a glass elution vial
- Measure ^{82}Rb noting the time between measuring the activity and the time that the elution was started
- Decay correct activity back to time when the elution was started
- Let the vial decay for 1 hour post elution
- Measure the Sr activity and calculate breakthrough (This is a multiple step process)

Directions for Correct Eluting Rubidium Rb 82 Chloride Injection

- Allow at least 10 minutes between elutions for regeneration of Rb 82.
- Elute with additive-free 0.9% Sodium Chloride Injection USP only.
- Additives (particularly calcium ions, to which strontium ions are chemically analogous), may cause the release of substantial amounts of Sr 82 and/or Sr 85 into the eluate regardless of the age or prior use of the generator.

Radiation Safety

What are the ingredients?

- Shielding
- Controlling access (Time)
- Training (Dose Management Techniques)
- Monitoring
- Communication

Safety in Nuclear Medicine

- Two concerns in nuclear medicine
  - Radiation emitted from nearby sources including patients (external exposure)
  - Contamination (both external and internal exposure)

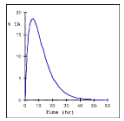
External Radiation Protection in Nuclear Medicine

- Sources of external exposure include:
  - Receiving and processing radioactive packages
  - Radiopharmaceutical preparation and assay
  - Administration of radiopharmaceutical
  - The injected patient
  - Radioactive waste

Exposure is Affected by Physiological Concentration of Radiopharmaceutical

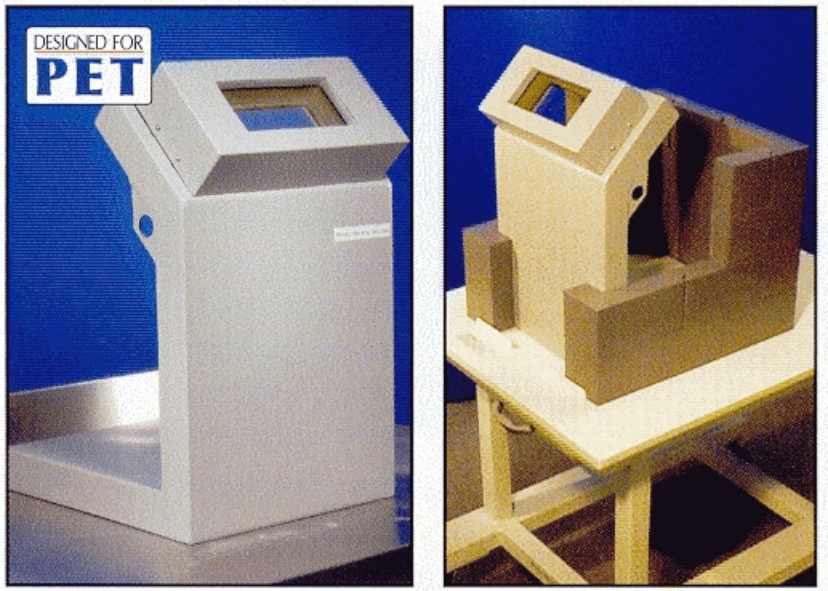
- Exposure at a fixed distance from injected patient changes over time.
- Starts about 2-3 mR/hr.
- For Tc-99m based cardiac pharmaceuticals the whole body clearance is 65% in 48 hours.

Summary

- Exposure is affected by Distance.
- Exposure is affected by Concentration of Radiopharmaceutical.
  - Quantity injected (10 or 30 mCi)
  - Time since injection (ie 1 hr 10% physical decay)
  - Physiological clearance of drug 
- Exposure is affected by length of time exposed. 

Bench Top Shield

- Bench shield should be 50 mm (2 in) lead and 65 mm (2.5 in) lead-glass.
- Weight of these shields require stronger bench supports.

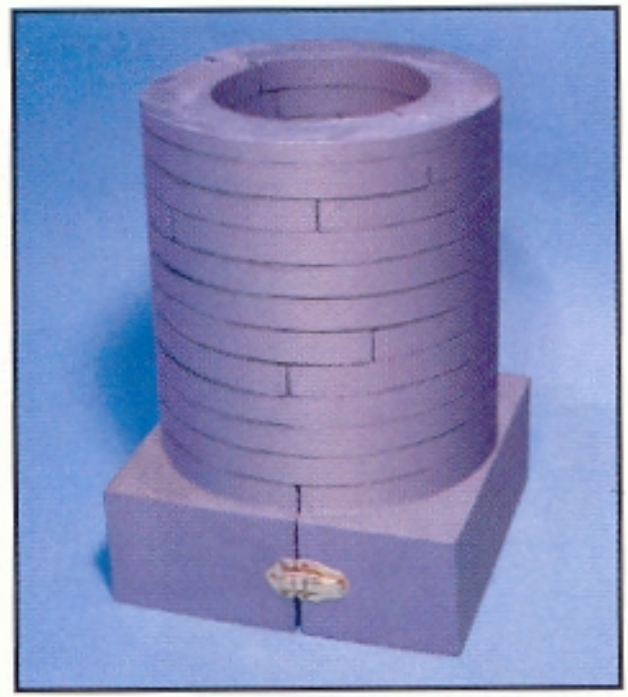


Protection Considerations

- Because 511 keV photons of F-18 are more penetrating than the 140 keV photons of ^{99m}Tc, more stringent protective measures are required for a PET facility compared to a conventional nuclear medicine facility
  - Staff doses
  - Doses in adjacent areas
  - Facility design
  - Protection equipment
  - Heavier shielding needed at hot lab

Dose Calibrator Shield

- Dose calibrators designed for traditional nuclear medicine applications generally provide 3-6 mm (3/16 in) of inherent lead shielding.
- PET Dose calibrator shield should be 50 mm (2 in) lead rings



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