syncor

The National Pharmaceutical Service Network

September 26, 1988

A. Bert Davis
Regional Administrator
U.S.N.R.C., Region III
799 Roosevelt Road
Glen Ellyn, IL 60137

RE: Syncor Facilities in Region III: License Numbers 34-16654-01MD (Toledo,OH), 21-17189-01MD (Ferndale, MI), 34-18309-01MD (Blue Ash, OH), 34-18484-01MD (Columbus,OH), 34-19008-01MD (Akron, OH), 13-19229-01MD (Indianapolis, IN), 21-19219-01MD (Grand Rapids, MI), 13-19451-01MD (Dyer, IN), 34-19007-01MD (Dayton, OH), 21-21141-01MD (Flint, MI), 34-16405-01MD (Cleveland, OH), 24-16617-01MD (Kansas City, MO), 24-19360-01MD (St. Louis, MO), 22-19174-01MD (St. Paul, MN), 22-24309-01MD (Moorhead, MN), 48-17466-01MD (Wauwatosa, WI).

Dear Mr. Davis:

Recently NRC staff members have expressed concerns over the quality control procedures being performed at Syncor facilities in Region III. In response to these concerns please amend all Syncor licenses in Region III (referenced above) to include a quality control commitment for Tc-99m labeled radiopharmaceuticals. The quality control procedure used will be either the enclosed Syncor procedure or that of a commercially available quality control kit. We confirm that any changes made to these procedures will be equivalent or superior to those submitted.

The amendment fee of $3680.00 for the 16 license amendments is enclosed. If there are questions about this amendment request, please contact me.

Sincerely,

Jack L. Coffey

Jack L. Coffey, M.S., C.H.P.
Corporate Radiation Safety Officer

cc: Syncor Region III Facilities
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CONTROL NO. 86147.

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11.0 RADIONUCLIDIC PURITY

11.1 PURPOSE

When Technetium-99m is eluted from a Molybdenum-99\Technetium-99m generator, Molybdenum-99 could be eluted along with the Technetium. This possible outcome is termed "Molybdenum breakthrough". The US Pharmacopeia XXI specifies that Technetium-99m radiopharmaceuticals contain no more than 0.15 microcurie of Molybdenum-99 per millicurie of Technetium-99m radiopharmaceutical at the time of patient administration. It is mandatory that every elution from a Molybdenum-99/Technetium-99m generator be tested for Molybdenum breakthrough and the expiration time for the Technetium-99m be determined. Under no circumstances will the expiration time exceed 12 hours from time of elution.

11.2 RATIONALE

Since Molybdenum-99 has a longer half life and produces higher energy beta emissions, the radiation dose to the patient would be significantly increased should the radiopharmaceutical contain more than the allowable amount of Molybdenum-99. Therefore, maximum levels for Molybdenum content are set by law.

11.3 EQUIPMENT

Dose Calibrator
Molybdenum Assay Shield (moly assay shield)

11.4 PROCEDURE

a. Using calibrated dose calibrator, select the "pre-set" Molybdenum-99 option or adjust the dose calibrator in order to assay Molybdenum-99 on the lowest or most sensitive radioactivity scale.

b. With the Molybdenum-99 assay shield in place, zero the dose calibrator, or record the displayed existing background radioactivity if applicable.

c. Working behind a lead shield and using a remote handling device, transfer the Technetium-99m pertechnetate eluate vial from the elution shield to the "Moly" assay shield.

d. Place the "Moly" assay shield containing the eluate vial into the dose calibrator's well and assay on the lowest or most sensitive scale.

e. Record and initial the total displayed activity in microcuries.

CONTROL NO 84147

f. Subtract the background activity (Step b) from the total displayed radioactivity reading, and record net Mo-99 activity as measured in microcuries.

g. Remove the "Moly" assay shield containing the eluate vial from the well and transfer the eluate to a suitable shielded container.

h. Calculate the Molybdenum-99 content as follows:

Total Molybdenum-99 content= net 99 Mo activity (Step F) multiplied by the "Moly" assay shield's attenuation factor.

Note: The "Moly" assay shield attenuation factor is supplied by the manufacturer and can be found in the operation manual for the dose calibrator.

i. Enter the total 99 Mo content and the time of assay in the appropriate records.

j. Divide the total 99 Mo content (microcuries) by the 99m Tc radioactivity (millicuries) to obtain the ratio of microcuries of 99 Mo per millicurie of 99m Tc at calibration time.

11.5 SHELF LIFE OF 99m TECHNETIUM PERTECHNETATE ELUATE

Limits: The USP XXI specifies a limit of 0.15 microcuries of 99 Molybdenum per millicurie of 99m Technetium at the time of patient administration.

Note: The 99 Molybdenum/99m Technetium ratio may be acceptable at the time of elution but may become unacceptable at the actual time of patient administration. This is due to the fact that 99m Technetium (physical half life = 6 hours) decays more rapidly than 99 Molybdenum (physical half life = 67 hours).

a. Determine the initial ratio of microcuries (uCi) 99 Mo to millicuries (mCi) 99m Tc. This initial uCi 99 Mo/mCi 99m Tc is described as the eluate's N value.

$$N = \frac{\text{uCi 99 Mo}}{\text{mCi 99m Tc}}$$

b. Locate the eluate's N value in the following table and corresponding hourly expiration time interval.

SHELF LIFE OF TECHNETIUM

uCi Mo-99/mCi Tc-99m (N)	(hours)
.0425	12.0
.0472	11.0
.0524	10.0
.0582	9.0
.0647	8.0
.0719	6.0
.0887	5.0

Note: The maximum expiration time for Technetium-99m eluate is 12 hours from time of elution.

12.0 CHEMICAL PURITY OF ELUATE

12.1 Purpose

When a Molybdenum-99\Technetium-99m generator is eluted, it is possible to elute aluminum ion along with the Technetium-99m. This procedure uses a semi-quantitative colorometric test method to test for breakthrough of aluminium in a generator elution.

12.2 RATIONALE

This procedure is performed to ensure that the aluminum ion concentration in Technetium-99m eluates is within allowable limits of the U.S. Pharmacopeia XXI.

12.3 EQUIPMENT

Colorimeter Test Kit for Aluminum Ion.

12.4 PROCEDURE

12.4.1 Aluminum Ion Breakthrough Test

(Follow any additional manufacturer's directions on kit use)

a) Place one drop of standard solution on an indicator strip provided in the kit. This solution contains 10 mcg per ml aluminum ion.

b) Working behind a shielded work station, aseptically withdraw a small amount of eluate and place a drop of same on the indicator strip next to the standard solution spot.

c) Compare the color intensity of the two spots.

d) If the eluate spot is more intense than the standard solution spot, the Al^{+3} ion is excessive and the eluate should not be used.

Note: The U.S. Pharmacopeia XXI allows 10 micrograms of Al^{+3} ion per milliliter of Technetium-99m eluate from fission produced Molybdenum-99 generators.

e) Record and initial the results.

Note: Saline used in product preparation and dose dispensing should contain no benzyl alcohol (used as a preservative). If present, benzyl alcohol will inhibit/compromise the product's binding efficiency.

13.0 RADIOCHEMICAL PURITY

13.1 PURPOSE

When a radiopharmaceutical kit is prepared using Tc99m as the tagging agent, the Tc-99m becomes attached to a substrate molecule designed to localize in a specific organ system. An efficient radiopharmaceutical has most of the Tc-99m tagged to the substrate, leaving very little untagged or free Technetium-99m. Hydrolyzed reduced Technetium-99m may also be present and it will locate in organ systems differently than the radiopharmaceutical.

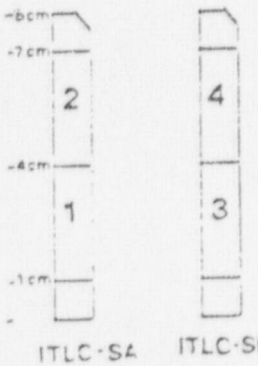
Both free Technetium-99m and hydrolyzed reduced Technetium-99m localizing in the organ systems of the patient can give artifacts on scanning that may mislead the clinician or make assessment of scans difficult. Unless the radiopharmaceutical is efficiently tagged, the accuracy of the resultant diagnosis can be compromised. Syncor has set minimum standards for tagging efficiency, and each vial of radiopharmaceutical prepared in a Syncor pharmacy must be tested for the parameters appropriate to the radiopharmaceutical. Procedures for each radiopharmaceutical can be found in Section 13.4.

13.2 RATIONALE

Radiochemical purity evaluations are essential because the agents tested are for human use in diagnostic evaluations. These agents are targeted to specific organ systems, and it is necessary to assure that the quality of the resulting diagnostic image is optimized, and that the radiation dose to nontarget organs is minimized.

13.3 EQUIPMENT AND SUPPLIES

Acetone
Saline (0.9%)
Saline (20%)
Pencil
ITLC-SG strips (see figure A)
ITLC-SA strips (see figure A)
Water (distilled)
Multichannel Analyzer/Scaler with scintillation well.



To identify top from bottom, cut a small corner off the top of the strip.

FIGURE A

13.4 PROCEDURES

13.4.1 General Guidelines

Quality Control for radiochemical purity must be performed on every vial of radiopharmaceutical tagged with Tc-99m and dispensed from a Syncor pharmacy for patient use. The table below lists radiopharmaceuticals, the appropriate test procedure as found in Section 13.4.2, the minimum acceptable purity, and the potential radiochemical contaminants.

Radiopharmaceuticals	Test Procedure	Minimum Acceptable Purity	Potential Radiochemical Contaminants
99m Tc-Pertechnetate	No. 1	*95%	99m TcO2-and other HR species
99m Tc-Sulfur Colloid	No. 2	*92%	99-m TcO4-
99m Tc-Albumin Colloid	No. 3	92%	99-m TcO4-
99m Tc-Macroaggregated Albumin	No. 2	*90%	99m TcO4-
99m Tc-Disofenin 99m Tc-Mebrofenin	No. 5 No. 5	90% 90%	99m TcO2-; 99m Tc-Sn Colloid; and 99m TcO4-
99m Tc-Medronate (MDP) 99m Tc-Oxidronate (HDP) 99m Tc-Pyrophosphate (PYP)	No. 3 No. 3 No. 3	*90% *90% *90%	99m TcO2-; 99m TcO4- and 99m Tc-Sn Colloid
99m Tc-Pentatate 99m Tc-Gluceptate	No. 3 No. 3	*90% *90%	99m TcO2-; 99m TcO4-; and 99m Tc-Sn Colloid

* Acceptable Purity Requirement as Established, USP XXI

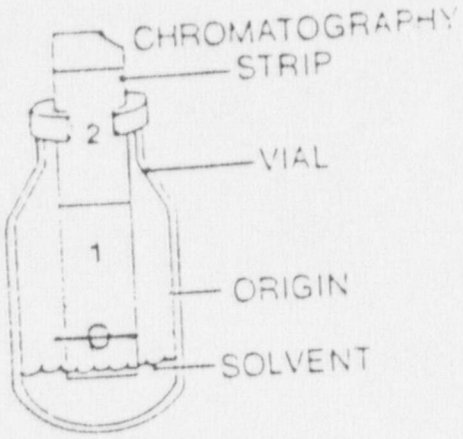


FIGURE B: Procedures 1,2,and 4

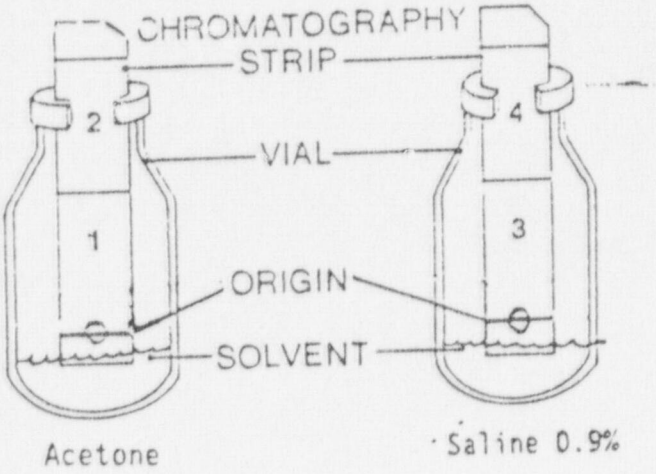


FIGURE C: Procedure 3

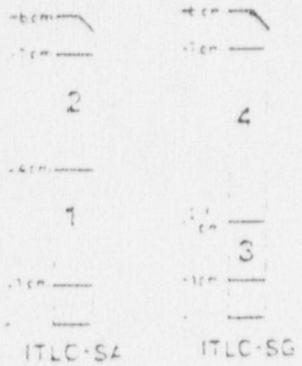


FIGURE D: Preparation of Chromatography strips for Procedure 5

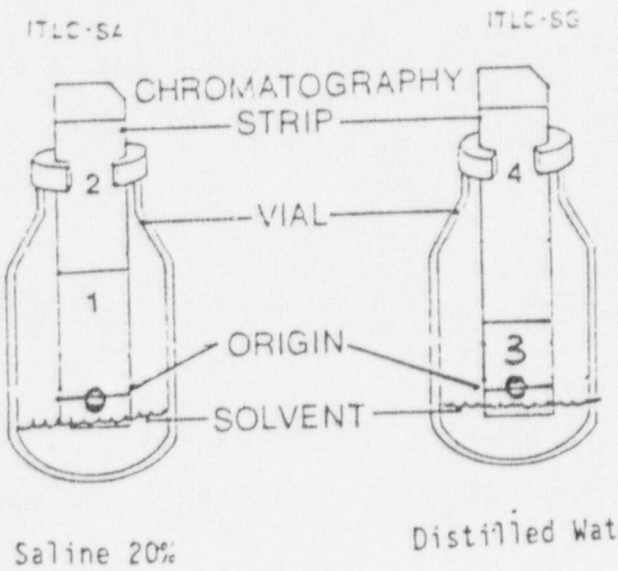


FIGURE E: Procedure 5

13.4.2 PROCEDURE 1

Detection of Tc-99m hydrolyzed reduced in sodium pertechnetate.

a. Place enough acetone in developing vial to just cover the bottom of the vial. (See figure B.)

b. Using a tuberculin syringe with a small needle, spot the sodium pertechnetate on the bottom pencil line of ITLC-SG Media strip.

c. Immediately develop the strip in acetone. Do not allow the solvent front to reach the end of the strip.

d. Cut strip at center pencil line producing sections 1 & 2 (See figure B).

e. Count each section in well counter on appropriate settings and record raw data results.

f. Using the following formula, calculate % free TcO_4

$$\frac{\text{(net activity of section 2)}}{\text{(net activity of sec. 1) + (net activity of sec. 2)}} \times 100$$

13.4.3 PROCEDURE 2

Detection of Free 99m Tc in Particulate Radiopharmaceuticals.

a. Place enough saline 0.9% in developing unit to just cover the bottom of the vial. (See figure B)

b. Using a tuberculin syringe with a small needle, spot the sodium pertechnetate on the bottom pencil line of ITLC-SG Media Strip.

c. Immediately place strip in vial and develop. Do not allow saline to reach the end of the strip.

d. Cut strip at center pencil line producing Sections 1 & 2. (See figure B)

e. Count each section in well counter on appropriate settings and record raw data results.

f. Using the following formula, calculate % of free TcO_4.

$$\frac{\text{(net counts in section 2)}}{\text{(net counts in section 1) + (net counts in section 2)}} \times 100$$

g. % of 99m-Tc bound = 100 - % Free TcO4.

13.4.4 PROCEDURE 3

Detection of free TcO4 and Tc-Hydrolyzed reduced in water-soluble Tc-radiopharmaceuticals.

a. Place acetone in one developing vial and normal saline in another. Use just enough solvent to cover the bottom of each vial. (See figure C)

b. Spot radiopharmaceutical on bottom pencil lines of ITLC-SG media strips.

c. Immediately develop one strip ITLC-SG in acetone and the second strip in normal saline.

d. Cut strips at center pencil lines producing section 1, 2, 3, and 4 (See figure C).

e. Count each section in a well counter on appropriate settings and record raw data results.

f. % free TcO4 equals:

$$\frac{\text{(net activity of section 2)}}{\text{(net activity section 1) + (net activity section 2)}} \times 100$$

g. % HR-Tc equals:

$$\frac{\text{(net activity of section 3)}}{\text{(net activity section 3) + (net activity section 4)}} \times 100$$

h. % bound = 100 - (% Free TcO4 + % HR-Tc).

13.4.5 PROCEDURE 4

Detection of free TcO4

a. Follow Procedure No. 2; however, acetone should be used as the developing solvent.

13.4.6 PROCEDURE 5

Detection of free TcO4 and Tc-Hydrolyzed reduced in Tc-labeled IDA agents.

a. Place saline 20% in one developing vial and 2-4 mm distilled water in another developing vial. Use just enough solvent to cover the bottom of each vial. (see figure E).

b. Spot radiopharmaceutical on bottom pencil line of ITLC-SA and ITLC-SG chromatography strips.

c. Immediately develop the SA strip in Saline 20% and the SG strip in distilled water until solvents migrate to top pencil line.

d. Cut the SA strip at the center pencil line and the SG strip at 2 cm from origin producing sections 1, 2, 3, and 4 (see figure D).

e. Count each section in a well counter on appropriate settings. Record raw data results.

f. Free % TcO4 equals:

$$\frac{\text{(net activity of section 2)}}{\text{(net activity section 1) + (net activity section 2)}} \times 100$$

g. % HR-Tc equals:

$$\frac{\text{(net activity of section 3)}}{\text{(net activity section 3) + (net activity section 4)}} \times 100$$

h. % bound = 100 - (% TcO4 + % HR-Tc).

14.0 PARTICLE SIZING

14.1 PURPOSE

Prepared kits of particulate Technetium - 99m radiopharmaceuticals will be checked for particle size. Particle sizes must meet the specifications of the U.S. Pharmacopeia XXI.

14.2 RATIONALE

Appropriate particle size in particulate radiopharmaceuticals permit the desired biodistribution during human administration while minimizing patient risk.

14.3 EQUIPMENT

Microscope
Hemocytometer (50 micrometers per grid square)
Cover Slides
Glass Slides

14.4 PROCEDURE

14.4.1 Technetium-99m Lung Imaging Agents

a. Using safe radiation handling practices, place a sample containing not less than 100 particles on the hemocytometer grid. Place a cover slide over the hemocytometer.

b. Place the hemocytometer under the microscope, focus on the appropriate power resolution and observe particle sizes.

c. 90% or greater of all lung imaging particles should be from 10 to 90 micrometers in diameter with no particles greater than 150 micrometers.

d. Prepared kits that meet the specifications above may be used for unit and multidose prescriptions. Those exceeding the specifications must be removed from use.

Samples of Quality Control Data Collection Forms Follow

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Quality Control Reminders

1. Always use fresh noncontaminated solvents.
2. Spot the strip on the origin line and assure the spot is not immersed in the solvent.
3. Secure the solvent vial in a rack or other configuration to prevent tipping over.
4. Frequently check tweezers, tongs, and scissors for contamination.
5. Use glass counting tubes so the identity of the strip can readily be determined.
6. Use a reproducible counting geometry which minimizes deadtime/coincidence counting losses.
7. Use a counting region of interest which is specific for Tc-99m.

CONTROL NO 86147

DATE: ____________________

LOCATION: ____________________

FORMULAS:
A + B = C
B / C × 100 = F
D + E = G
D / G × 100 = H
100 - (H + F) = T

PRODUCTS	TIME	ACETONE/ITLC-SG ORIGIN COUNTS A	TOP COUNTS B	TOTAL COUNTS C	% FREE F	SALINE ITLC-SG ORIGIN COUNTS D	TOP COUNTS E	TOTAL COUNTS G	% HYDROL H	% TAG T	INITIALS
MDP #1											
MDP #2											
MDP #3											
MDP #4											
MAA #1											
DTPA #1											
DTPA #2											
DTPA #3											
DTPA #4											
DTPA #5											
PYP #1											
PYP #2											
PYP #3											
GLUCO #1											
		SALINE 20%/ITLC-SA				DISTILLED WATER/ITLC-SG					
HEP #1											
HEP #2											

CONTRACT. 85147

QUALITY CONTROL DATA

DATE: _____

FORMULAS: A - B = C
B = C x 100 = F
100 - F = T

PRODUCT	TIME	SALINE/ITLC-SC PARTICLE SIZE	ORIGIN COUNTS A	TOP COUNTS B	TOTAL COUNTS C	% FREE F	% TAGGED T	INITIA
LL #1								
LL #2								
LL #3								
LC #1								
LC #2								
LC #3								
LC #4								

FORMULAS: A - B = C
B = C x 100 = H
100 - H = T

TC04	TIME	SALINE 0.9% ITLC-SC N/A	ORIGIN COUNTS A	TOP COUNTS B	TOTAL COUNTS C	% HYDROL H	% TC04 T	INITIA
ELU #1								
ELU #2								
ELU #3								
ELU #4								
ELU #5								
ELU #6								
ELU #7								

CONTROL NO 86147