Quality Control in the Radiopharmacy

Karen L. Ramberg-Laskaris

Tufts–New England Medical Center, Boston, Massachusetts

This is the first of a series of four continuing education articles on radiopharmaceuticals. (This topic was developed in response to the results of the Journal's 1983 reader survey.) The radiopharmaceutical series will discuss quality control in the radiopharmacy, development of new radiopharmaceuticals and their applications, including gold-195m and iodine-123 amphetamines, preparation and imaging of indium-III-labeled leukocytes, and radiopharmaceuticals for renal imaging. After reading and studying this article, the nuclear medicine technologist will be familiar with NRC and USP-NF regulations that apply to the radiopharmacy, and able to review the radiopharmacy quality control program at his or her institution to insure compliance.

As medicine relies more on advanced technology, regulatory requirements and quality assurance programs have become increasingly important to verify and maintain the accuracy of complex methodologies. This trend is very much in evidence in nuclear medicine, a relatively new field that must conform to both Nuclear Regulatory Commission (NRC) regulations and pharmaceutical standards of the United States Pharmacopeia and National Formulary (USP-NF). Preparation of diagnostic pharmaceuticals must meet the rules and regulations of the Food and Drug Administration and the standards as set forth in the official pharmaceutical compendium, the USP-NF. This article will review pertinent regulations and describe a quality assurance program to meet these requirements, as well as suggest alternate approaches to satisfy regulations.

Radiopharmaceuticals can be divided into two main categories: those purchased from a manufacturer and administered unchanged, and those prepared in-house. The quality control of radiopharmaceuticals administered unchanged is primarily the responsibility of the manufacturer. The nuclear medicine department is responsible for the quality control of radiopharmaceuticals prepared in-house, and this article will discuss quality control of the technetium-99m radiopharmaceuticals most frequently prepared in-house.

Quality Control of Tc-99m Pharmaceuticals

Radionuclidic Purity: Both NRC and USP-NF limit the amount of radionuclide contamination allowed in Tc-99m solutions for patient use. The major radionuclide contaminant of Tc-99m solutions is its parent, molybdenum-99. The NRC limits the amount of Mo-99 contamination to 1 μCi of Mo-99 per mCi of Tc-99m at the time of administration. The amount of Mo-99 is further limited to a maximum of 5 μCi per patient dose (*1*). The USP-NF has more stringent criteria; it limits the amount of Mo-99 to 0.15 μCi per mCi of Tc-99m at the time of administration (*2*).

The most common method for determining the amount of Mo-99 present in any given eluate is to use a Tc-99m/Mo-99 assay kit available through dose calibrator manufacturers. The kit consists of a calibrated lead canister and insertion holder. The canister reduces the Tc-99m reading to nearly zero while partially attenuating the high energy gamma-rays from Mo-99 (*3*). The Tc-99m/Mo-99 assay is performed by reading the amount of activity in the unshielded vial on the Tc-99m setting of the dose calibrator to determine the amount of Tc-99m. Then the vial is placed in the lead canister and again assayed in the dose calibrator on the Mo-99 setting. Next the Mo-99 assay reading is multiplied by a correction factor supplied by the manufacturer to correct for the canister attenuation (approximately 70%) of the Mo-99 activity.

The corrected Mo-99 activity expressed in μCi is divided by the unshielded Tc-99m activity expressed in mCi, and should be less than 0.15 μCi/mCi to meet requirements (Fig. 1) (*1,2*). Alternative methods for determining the amount of Mo-99 contamination include use of a multichannel analyzer or single channel analyzer with a shield and cesium-137 source (*4*). The result of these assays must be recorded and kept on file for at least three years to meet NRC requirements. For legal purposes many institutions maintain records for seven years.

Fission generators have specified limits for iodine-131, ruthenium-103, strontium-89, and strontium-90. Generators cannot contain more than 0.1 μCi of other beta- and gamma-emitting nuclides per mCi of Tc-99m or more than 0.001 nCi of alpha impurities per mCi of Tc-99m. Monitoring for these contaminants is the responsibility of the generator manufacturers. Large amounts of the contaminants specified above would be detected, but would appear as Mo-99 during the Tc-99m/Mo-99 assay because of the high energy gamma rays from these radionuclides.

Chemical Purity: One major chemical contaminant in the Tc-99m eluate is aluminum ion (Al^{3+}) from the generator column. High concentrations of Al^{3+} can interfere with the binding efficiency of Tc-99m and, in the case of Tc-99m sulfur colloid, can cause clumping of the colloid (*5*). The USP-NF establishes limits of 10 μg/ml of Al^{3+} in eluates from fission generators (*2*). Commercial kits are available for checking aluminum ion concentrations (*6*).

In addition to using aluminum ion indicator kits, some laboratories routinely check the pH of each eluate with litmus paper to validate that it is between 4.5 and 7.5 as specified in the USP-NF.

For reprints contact: Karen L. Ramberg-Laskaris, Dept. of Nuclear Medicine, Tufts–New England Medical Center, 171 Harrison Ave., Boston, MA 02111.

Determining Corrected Mo-99 Activity

Example 1:

Tc-99m reading = 586 mCi
Mo-99 assay reading = 2.0 μCi

Corrected Mo-99 assay reading = 2.0 μCi × 3.5* = 7.0 μCi

$$\frac{\text{Corrected Mo-99 assay reading in } \mu\text{Ci}}{\text{Tc-99m reading in mCi}} = \frac{7.0\ \mu\text{Ci}}{586\ \text{mCi}} = 0.01\ \mu\text{Ci/mCi}$$

0.01 μCi/mCi is below NRC and USP-NF limits.

Example 2:

Tc-99m reading = 325 mCi
Mo-99 assay reading = 15.2 μCi

Corrected Mo-99 assay reading = 15.2 μCi × 3.5* = 53.2 μCi

$$\frac{\text{Corrected Mo-99 assay reading in } \mu\text{Ci}}{\text{Tc-99m reading in mCi}} = \frac{53.2\ \mu\text{Ci}}{325\ \text{mCi}} = 0.16\ \mu\text{Ci/mCi}$$

0.16 μCi/mCi is below NRC limits, but above USP-NF limits.

(*3.5 is the correction factor for Capintec.)

FIG. 1. Calculations for extent of Mo-99 contamination in Tc-99m eluates.

Radiochemical Purity: The USP-NF establishes radiochemical purity standards for most Tc-99m radiopharmaceuticals. Radiochemical purity is the amount of the radioactivity in the correct chemical form, i.e., what percent of the Tc-99m is bound to DTPA, sulfur colloid, etc.

Large amounts of free Tc-99m or hydrolyzed reduced Tc-99m (Tc-99m HR) degrade the quality of the image and therefore the diagnostic potential of the procedure. The benefit-versus-risk ratio is altered by these contaminants because the radioactivity in these chemical forms does not add any diagnostic information.

The requirement for Tc-99m macroaggregated albumin, Tc-99m pentetate sodium (DTPA), and Tc-99m gluceptate (glucoheptonate) is 90% radiochemical purity. For Tc-99m sulfur colloid, it is 92%. For these agents a single-solvent chromatographic system is used to separate the bound from the free Tc-99m (i.e., pertechnetate). Most hospitals use a recognized technique employing instant thin layer chromatography (ITLC), which can be developed and counted in 5 to 10 min (*7*). This allows determination of radiochemical purity for each preparation prior to injection.

The required radiochemical purity for Tc-99m pyrophosphate and Tc-99m etidrenate is also 90%; however a two-solvent system must be used, one to separate the amount of free pertechnetate and another to separate the hydrolyzed reduced technetium. The percent of Tc-99m in these two forms cannot exceed 10%. Suggested chromatographic systems are given in Table 1. The chromatographic strips can be counted manually to determine percent bound (Fig. 2), or by automated systems marketed by various manufacturers.

To obtain valid results from ITLC radiochemical purity tests, proper techniques must be carefully followed (*8,9*). A currently accepted technique is to dry the spot with nitrogen to prevent any solvent-solvent interactions and any alteration in the chemical composition of the spot due to exposure to oxygen in the air (*9*).

Sterility and Pyrogenicity Testing: The USP-NF allows for the dispensing of Tc-99m radiopharmaceuticals prior to the completion of sterility testing. This exception is made because it takes at least seven days to complete sterility testing. Sterility testing should be started on the day of manufacture.

The official test requires the innoculation of two culture media: fluid thioglycollate incubated at 37 ° C for 7 to 14 days to test for bacterial contamination and soybean casien digest medium incubated at 25 ° C for 7 to 14 days to test for fungi (*10*).

The pyrogenicity test used for radiopharmaceuticals is the Limulus amebocyte lysate test, which is more sensitive than the standard rabbit test and requires only small volumes of samples (*11,12*).

Quality Control of Dose Calibrators

A quality assurance program for radiopharmaceuticals must include testing the instruments used in their preparation and dispensing.

Constancy and Accuracy: The NRC requires that dose calibrators be checked daily for constancy using at least one relatively long-lived isotope such as Cs-137, Co-57, or Ra-226. The readings must be recorded daily and may be plotted on semilog paper. In addition, the accuracy of the dose calibrator must be checked at least once a year with standards traceable to the National Bureau of Standards (NBS) (*13*). Many laboratories use a traceable standard daily. Two standards should be employed: Cs-137 to check the response of the dose calibrator to high energy gamma emitters and Co-57 to check the response to gamma energies in the range of Tc-99m. The Cs-137 can be read on the most commonly used clinical settings: Tl-201, Ga-67, Xe-133, and Mo-99, while Co-57 can be read on the Tc-99m setting. These secondary readings are of value only as a series to check for changes in the constancy

TABLE 1. ITLC Systems for Determining Radiochemical Purity

Radiopharmaceutical	ITLC	Solvent	Location of bound agent
Tc-99m DTPA	SG	acetone	bottom
Tc-99m glucoheptate	SG	acetone	bottom
Tc-99m microspheres	SG	saline	bottom
Tc-99m sulfur colloid	SG	saline	bottom
Tc-99m disofenin	SA	20% potassium or sodium chloride	bottom
Tc-99m pyrophosphate	SG	acetone*	bottom
Tc-99m pyrophosphate	SG	saline†	top
Tc-99m oxidronate	SG	acetone*	bottom
Tc-99m oxidronate	SG	saline†	top

SG = silica gel; SA = polysilicic acid gel.

*separates free Tc-99m from bound
†separates hydrolyzed reduced Tc-99m from bound

Determining Radiochemical Purity

Example 1:

Results from quality control of Tc-99m DTPA
Background = 18 cpm
ITLC-SG with acetone as solvent
top (free [^{99m}Tc] pertechnetate) = 365 cpm
bottom (bound Tc-99m) = 21,060 cpm

$$\% \text{ bound} = \frac{(\text{counts bound Tc-99m} - \text{bkg}) \times 100}{(\text{counts bound} - \text{bkg}) + (\text{counts free} - \text{bkg})}$$

$$= \frac{(21{,}060 - 18) \times 100}{(21{,}060 - 18) + (365 - 18)}$$

% bound = 98.4%.

Example 2:

Results from quality control of Tc-99m oxidronate
Background = 16 cpm
ITLC-SG with acetone as solvent
top (free Tc-99m) = 283 cpm
bottom (bound Tc-99m) = 23,156 cpm
ITLC-SG with saline as solvent
top (bound Tc-99m) = 31,842
bottom (hydrolyzed reduced) = 785

% bound = 100 − (% free) − (% hydrolyzed).

$$\% \text{ free} = \frac{(\text{counts free Tc-99m} - \text{bkg}) \times 100}{(\text{counts free Tc-99m} - \text{bkg}) + (\text{counts bound Tc-99m} - \text{bkg})}$$

$$= \frac{(283 - 16) \times 100}{(283 - 16) + (23{,}156 - 16)} = 1.1\% \text{ free Tc-99m.}$$

$$\% \text{ hydrolyzed} = \frac{(\text{counts hydrolyzed Tc-99m} - \text{bkg}) \times 100}{(\text{counts hydrolyzed Tc-99m} - \text{bkg}) + (\text{counts bound Tc-99m} - \text{bkg})}$$

$$= \frac{(785 - 16) \times 100}{(785 - 16) + (31{,}842 - 16)} = 2.4\% \text{ hydrolyzed.}$$

% bound
= 100 − 1.1% free − 2.4% hydrolyzed = 96.5% bound.

FIG. 2. Calculations for radiochemical purity.

of the dose calibrator. The accuracy readings for the standards should be within 5% of the labeled activity, corrected for decay if necessary. The secondary readings of the standards on the alternate settings should follow the decay pattern of the standard used.

Instrument Linearity: To verify the response of the dose calibrator to a range of activities, a dose calibrator's accuracy in reading varying quantities of activity must be documented. The NRC requires that a linearity test be performed quarterly. There are three methods for performing this test and there are advantages and disadvantages to each. For all three, the eluate used for the test should represent the largest amount of activity routinely measured in the dose calibrator.

Decay Method: The generator is eluted and the amount of Tc-99m is assayed and recorded. The vial is reassayed at time intervals of 6, 24, 30, and 48 hr. All readings are decay corrected to a selected time for comparison. The calculated values and measured activities should not vary by more than 5% (*14*).

The decay method requires no additional equipment; however, it increases personnel exposure, requires exact timing over a two-day period, and prevents use of the eluate for clinical purposes.

Dilution Method: The generator is eluted and the Tc-99m assayed and recorded. One-tenth of the volume of the eluate is accurately pipetted into an empty elution vial. Sufficient saline is added to the second vial so that the volume in the second equals that in the first to eliminate any geometric variation. The second vial is assayed and the measured activity should be equal to 10% of the original activity of the eluate. A 5% deviation is allowed (*14*).

This method requires minimal extra equipment. The major disadvantage is the potential for personnel exposure and contamination during the pipetting procedure.

Attenuation Method: This method requires the purchase of a series of lead tubes of increasing thickness (Calcorp, Inc., Cleveland, OH). These tubes fit into the dose calibrator around the eluate (*15*). The generator eluate is placed in a plastic tube and then both are placed in the dose calibrator and the reading recorded. Tubes of increasing thickness of lead are used to accurately increase the attenuation of the Tc-99m sample. The plastic tube ensures the eluate's central location during the test procedure. The attenuation of the lead shields approximates the values of 6, 12, 20, 30, 40, and 50 hr of radionuclide decay. The readings are then multiplied by the proper correction factors (which must be determined on an individual basis for each institution). The calculated activities should be within 5% of the mean activity.

This method has the advantage of reproducibility, low personnel exposure, no wasted radioactivity, and completion times of less than 5 min.

The negative aspects are: initial expense, time necessary for original calibration of the kit, and in most cases, an institution's NRC license must be amended.

Quality Assurance of Personnel Exposure

Proper handling of radiopharmaceuticals to decrease radiation exposure to patients and personnel is part of any quality assurance program. This discussion is focused on preparation procedures, in particular, those that detect and limit radioactive contamination in the radiopharmacy. Further information on shipment handling, patient procedures, etc. can be obtained from Federal guidelines (*16*).

Disposable gloves, absorbent materials on work surfaces, and constant monitoring are necessary to limit the spread of contamination. To help in the detection of contamination, NRC requires that a radiation detector that emits an audible signal be placed in the "hot lab" or radiopharmacy to ensure that personnel are aware of any changes in ambient levels of radioactivity (*16*). Additional regulations state that the area in which radiopharmaceuticals are prepared must be surveyed to detect any contamination of the work surfaces (*14*). The radiopharmacy's sinks, hoods, preparation and quality control areas, and waste sites should be surveyed on a daily basis. All personnel handling radioisotopes must monitor their hands and wrists prior to departure and record the results (*16*). If contamination is found on any surface, the area must be decontaminated and the count rate reduced to twice background or below.

The NRC requires that sealed sources be checked for contamination and leakage at least twice a year (*14*). The procedure requires wiping the surface of the sealed source with an alcohol wipe or gauze pad, then assaying the wipe or pad.

Summary

The practice of nuclear medicine and, in particular, nuclear pharmacy is regulated by several government agencies. The following is a brief summary of NRC requirements for radiopharmaceuticals, dose calibrators, and hot lab facilities.

Written records of the results of these tests and assays must be readily available:

- ☐ The level of Mo-99 contamination in each eluate
- ☐ Daily constancy and yearly accuracy tests on all dose calibrators
- ☐ Quarterly linearity tests on all dose calibrators
- ☐ Semiannual wipe tests on sealed sources
- ☐ The maintenance of survey equipment
- ☐ Survey results of the hot lab area.

The following tests and procedures are recommended:

- ☐ Radiochemical purity tests
- ☐ Aluminum ion test
- ☐ Sterility and apyrogenicity test
- ☐ Secondary readings of dose calibrator standards on all commonly used isotope settings
- ☐ Records of all personnel monitoring for contamination of hands and wrists.

In closing, it should be remembered that additional standards of practice and safety procedures are required by the Joint Commission on the Accreditation of Hospitals.

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