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Quality Control of Compounded Radiopharmaceuticals

Continuing Education for Nuclear Pharmacists
And
Nuclear Medicine Professionals

By

Vivian S. Loveless, Pharm.D., BCNP, FAPhA
Associate Professor
Department of Pharmaceutical Sciences
College of Pharmacy
The University of Tennessee Health Science Center

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QUALITY CONTROL OF COMPOUNDED RADIOPHARMACEUTICALS

STATEMENT OF LEARNING OBJECTIVES:

Upon successful completion of this CE lesson, the participant should be able to discuss the general concepts and processes associated with the quality control procedures of radiopharmaceuticals. Specifically, the participant should be able to:

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

1. Discuss the various types of quality control procedures involved in the compounding of radiopharmaceuticals and the importance of each.
2. Understand the principles of radiochemical purity testing.
3. Select the proper media and solvents for radiochemical analyses.
4. Determine the appropriate counting instruments to use for radiochemical analyses.
5. Define the steps necessary in developing and validating an alternate procedure to that prescribed in the manufacturer's package insert.
6. Identify potential pitfalls in radiochemical testing that could lead to false results.
7. Explain the principles of radionuclidic purity testing.
8. Discuss the potential pitfalls in performing radionuclidic purity testing.
9. Describe the procedures for performing quality control for a chemical contaminant.
10. Describe procedures for identifying pharmaceutical concerns.
11. List quality control procedures for Positron Emission Tomography radiopharmaceuticals.

COURSE OUTLINE

QUALITY CONTROL OF COMPOUNDED RADIOPHARMACEUTICALS

Vivian S. Loveless, Pharm.D, BCNP, FAPhA
Associate Professor
Department of Pharmaceutical Sciences
College of Pharmacy
The University of Tennessee Health Science Center

INTRODUCTION

A radiopharmaceutical is only as good as the care taken in each preparation step throughout the compounding process. With diagnostic radiopharmaceuticals it is important to have a product with acceptable quality control (QC) parameters in order for the nuclear medicine study to be effective yet deliver unnecessary radiation exposure to the patient. However, with therapeutic radiopharmaceuticals it is mandatory to satisfy the guidelines for quality control because otherwise, the results could be life-threatening to the patient.

QUALITY CONTROL PROCEDURES

These procedures include tests for radiochemical, radionuclidic, and chemical purity as well as checks for pharmaceutical concerns. Some of these tests are performed by the manufacturers, while others must be performed by the compounding personnel. The emphasis of this article will be on the quality control tests performed by the compounding personnel. Official requirements for the quality control standards can be found in the manufacturer's package inserts, the *United States Pharmacopeia* (USP), and Nuclear Regulatory Commission (NRC) regulations; however, a licensee must always adhere to standards established in the radioactive materials license under which they are working. Quality control procedures should always be performed following radiopharmaceutical preparation and prior to patient administration to ensure optimal radiopharmaceutical product.

PRINCIPLE OF RADIOCHEMICAL PURITY ANALYSIS

Radiochemical purity (RCP) of a radiopharmaceutical is defined as the percent of the total radioactivity present in the desired chemical form in a radioactive pharmaceutical.[1] Without acceptable RCP in a diagnostic radiopharmaceutical, image interpretation can be compromised which can result in a delay of an accurate diagnosis and unnecessary radiation exposure since the nuclear

medicine study must be repeated. With a therapeutic radiopharmaceutical, an unacceptable RCP can lead to the radiopharmaceutical localizing in an unintended target, which may result in organ damage. In clinical practice, the RCP analysis must be quick, accurate, and economical whereas in a research environment greater emphasis is placed upon accuracy, while the time and economical factors are sometimes less important. In the case of Positron Emission Tomography (PET) radiopharmaceuticals which are characterized by a short half-life, time is more critical. Keep in mind that the solvents used can be potentially hazardous and must be properly stored and handled in accordance with local, state, and federal regulations.

With regard to traditional technetium ^{99m}Tc radiopharmaceuticals, the three types of radiochemical impurities to be determined are as follows: free technetium ^{99m}Tc pertechnetate ($^{99m}TcO_4^-$), hydrolyzed-reduced ^{99m}Tc (insoluble ^{99m}Tc dioxide and/or ^{99m}Tc tin colloid), and bound ^{99m}Tc to the ligand of interest (desirable radiochemical form).[2] All of impurities can be determined using a chromatography system, consisting of a stationary phase and a mobile (solvent) phase. For certain newer technetium ^{99m}Tc radiopharmaceuticals, a fourth type of radiochemical impurity may be present as well: ^{99m}Tc labeled to other (secondary) chemical compounds (e.g., the hydrophilic species in ^{99m}Tc exametazime)[3] or transfer ligands (e.g., ^{99m}Tc tartrate in ^{99m}Tc-mertiatide,[4] and ^{99m}Tc gluconate in tetrofosmin)[5]. Also, the manufacturer's package insert for ^{99m}Tc-mertiatide refers to non-elutable impurities, other than the hydrolyzed-reduced impurity, remaining on the Sep-Pak® C18 column after elution.[4]

Chromatography is a procedure for separating the components of a mixture or solution, thus allowing the quantification of the desired compound and the impurities. The components of the mixture traveling the farthest are those that are most soluble in the solvent and least attracted to the stationary medium.[6] In traditional nuclear pharmacy, the most frequently encountered procedures involve solid-phase extraction or instant thin-layer and paper chromatography. Mobile phase (solvent) moves the solute through the stationary medium effecting a separation from other solutes that are eluted earlier or later.[7] Thus, the identification of a radiochemical species is due to its transfer through a stationary phase via a mobile phase until it finally emerges separated from the other radiochemical species that are eluted earlier or later. The movement of various radiochemical species is hindered by the stationary phase's electrostatic forces (adsorption) as the solvent phase moves them forward. The radiochemical species advance at different speeds due to the electrostatic forces of the stationary phase as well as the variations in solubility of the mobile phase.[2]

When performing paper or instant thin-layer chromatography, a microliter sample of the radiopharmaceutical is applied to the strip at the origin. The chromatography strip is then placed into a suitable solvent in a chromatography chamber (vials or test tubes). After permitting the solvent front (SF) to migrate up the strip to the desired distance, the strip is retrieved from the chromatography chamber and allowed to dry. Each radiochemical species travels a characteristic distance, and this is represented as the relative front (R_f) value. The definition of R_f is the ratio of the distance traveled on the medium (stationary phase) by a given radiochemical species to the distance traversed by the mobile phase's solvent front. The R_f values for the different radiochemical species have been determined for specified controlled conditions, and it is known that the values vary with different experimental conditions.[2] Once the R_f values are known, the strips are cut according to these values in order to determine the number of counts in each region representing specific radiochemical complex or complexes. These sections of the strip are then counted individually using the appropriate instrumentation. Alternatively, intact strips can be scanned with a radiochromatogram scanner. After determination of the number of counts, calculations can be performed to determine the percentage bound and the percentage of radiochemical impurities.

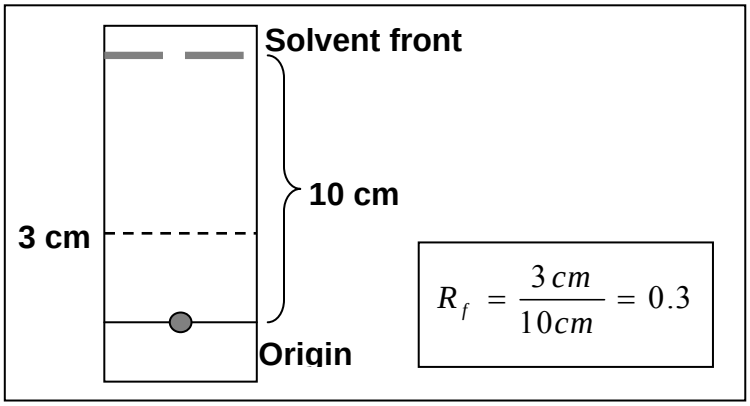

Figure 1. In this case the radiochemical species has been determined to migrate to 3 cm above the origin when the solvent front is allowed to migrate 10 cm from the origin. The R_f value is 0.3.

Choices for paper chromatography media include Whatman 3MM or 31ET paper and Gelman Solvent Saturation Pads. Paper media consists of cellulose fibers pressed together. As the mobile phase migrates over the fibers and through the pores, the paper simply behaves as a filter by separating the components of the mixture (radiopharmaceutical). Factors that determine the distance traveled on the paper are particle size, molecular mass, and charge of the various solute particles in the radiopharmaceutical.[6] Obviously, the components of the radiopharmaceutical most soluble in the mobile phase and the least attracted to the paper will migrate the farthest. Solvent (mobile phase) polarity influences the solubility of the radiochemical species present in a radiopharmaceutical. Solvent selection is based on the ability of the solvent to separate the radiopharmaceutical components on a medium.[2] For the mobile phase 0.9% saline, 20% saline, water, methyl ethyl ketone (MEK), acetone, and methanol are some of the solvents utilized. When thin-layer chromatography is used in

traditional nuclear pharmacy practice, a modified version is used in that instant thin-layer chromatography (ITLC) strips are utilized. ITLC is a glass fiber sheet impregnated with either an amorphous monosilic silica gel (ITLC-SG) which is slightly acidic or with a polysilicic gel (ITLC-SA). ITLC-SG provides superb resolution for nonpolar compounds while ITLC-SA is great for separating polar compounds.[8] Unfortunately, the manufacturer of ITLC-SG strips recently discontinued their production.

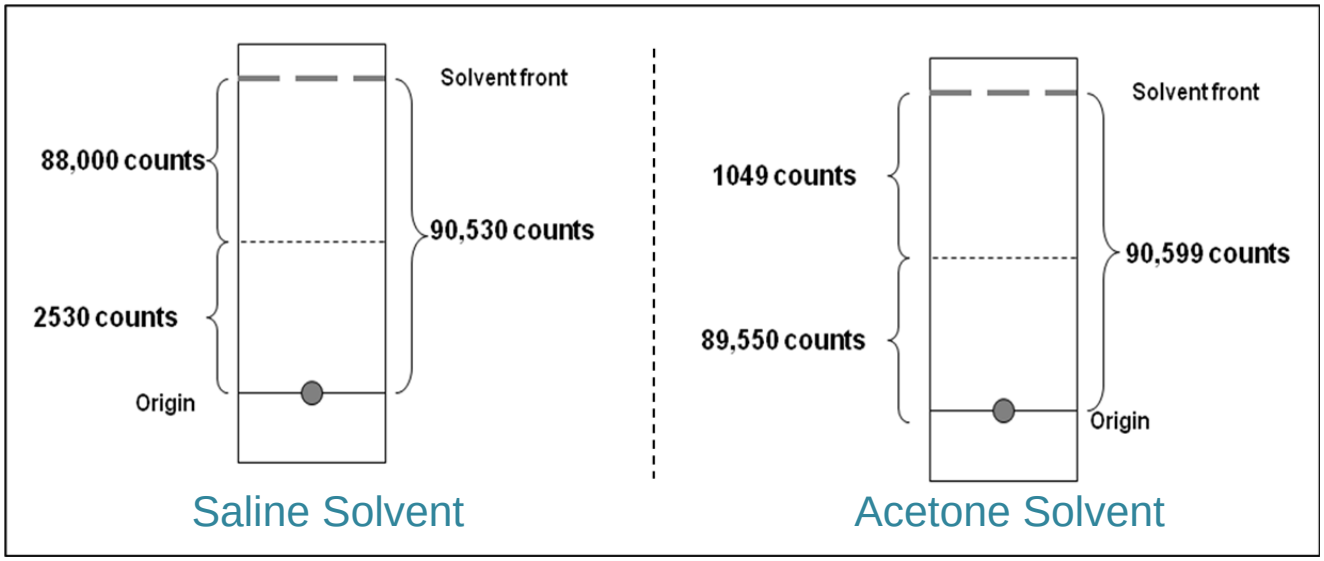

Figure 2. Chromatography strips representative of a soluble technetium ^{99m}Tc radiopharmaceutical, such as technetium ^{99m}Tc-MDP

Figure 2 is an example of a ^{99m}Tc-labeled compound soluble in saline. As can be seen from the R_f values given in Table 1, the chromatography system requires two strips in order to determine the percentage of radiochemical purity:

Table 1.

R_F VALUES FOR A SOLUBLE TECHNETIUM ^{99M}TC RADIOPHARMACEUTICAL		
	R_f values for Saline	**R_f values for Acetone**
^{99m}Tc-labeled complex	1.0	0.0
Hydrolyzed ^{99m}Tc	0.0	0.0
$^{99m}TcO_4^-$	1.0	1.0

The percentage of hydrolyzed ^{99m}Tc is determined using the counts from the strip developed in saline.

$$\%\ Hydrolyzed-reduced\ ^{99m}Tc = \frac{2530}{90,530} \times 100 = 2.8\%$$

The percentage of ^{99m}Tc pertechnetate is determined from counts on the strip developed in acetone.

$$\%\ ^{99m}TcO_4^- = \frac{1049}{90,599} \times 100 = 1.2\%$$

% ^{99m}Tc-labeled complex = 100% - (%Hydrolyzed-reduced ^{99m}Tc + %^{99m}TcO$_4^-$)

% ^{99m}Tc-labeled complex = 100% - (2.8% + 1.2%) = 96%

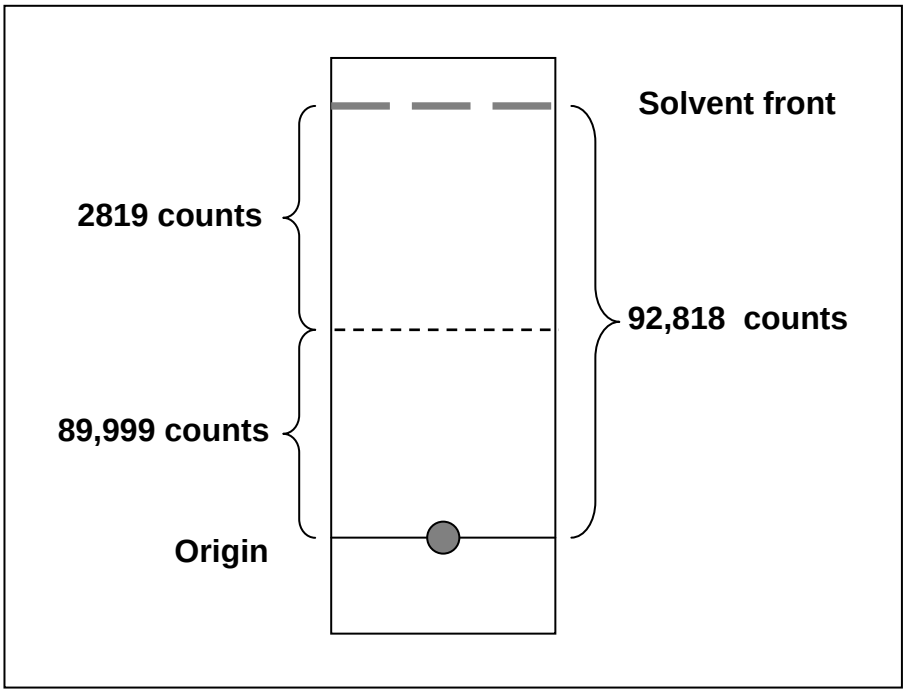

Figure 3. Chromatography strip representative of a technetium ^{9m}Tc particulate radiopharmaceutical, such as ^{99m}Tc-sulfur colloid

Figure 3 is an example of a chromatography strip for a particulate radiopharmaceutical. Both the particulate technetium ^{99m}Tc ligand and the hydrolyzed reduced species do not migrate with the solvent front so both remain at the origin, as shown in Table 2. Since the bound ligand cannot be separated from the hydrolyzed-reduced species of ^{99m}Tc, the only radiochemical impurity that can be separated is the free ^{99m}Tc pertechnetate. Routinely when reporting the per cent bound for particulate radiopharmaceuticals, the value actually includes both the bound technetium ^{99m}Tc ligand and the hydrolyzed reduced species of technetium ^{99m}Tc.

Table 2.

R_F VALUES FOR A PARTICULATE TECHNETIUM ^{99M}TC RADIOPHARMACEUTICAL	
	R_f values for Saline
^{99m}Tc-labeled complex	0.0
Hydrolyzed ^{99m}Tc	0.0
$^{99m}TcO_4^-$	1.0

Sep-Pak® cartridges are useful for chromatography since they operate on the principle of solid-phase extraction or column chromatography.[5,9] They are available with a variety of different packing materials.[9] The manufacturer's package inserts for ^{99m}Tc-mertiatide[4] and ^{111}In-pentetreotide[10] recommend the Sep-Pak® C18 chromatography cartridge for the determination of radiochemical purity. This cartridge is composed of a solid, nonpolar material (sorbent) that enables the separation of the various radiochemical species of interest.[11] When using Sep-Pak® chromatography cartridges for radiochemical analysis, there are multiple steps involved in the procedure.[4,10] The first step involves preconditioning the sorbent with an organic solvent.[9] The eluate is discarded.[4,10] If this step is not performed, a highly aqueous solvent would not be able to penetrate the hydrophobic surface and wet the sorbent resulting in only a small portion of the surface area of the sorbent being accessible for interaction with the radiopharmaceutical sample.[9] The next step in preconditioning involves an equilibration step which uses a flush of a low-strength solvent such as water.[9,10] The eluate from the equilibration step is also discarded.[4,10] The manufacturer's package insert for ^{99m}Tc-mertiatide[4] also instructs to drain the cartridge by pushing 5 mL of air through the cartridge while the package insert for ^{111}In pentetreotide[10] does not have this step.

The following is the manufacturer's package insert description of the procedure for using a Sep-Pak® C18 chromatography cartridge in determination of radiochemical purity of ^{111} In-pentetreotide. After the Sep-Pak® C18 cartridge is prepared (preconditioning and equilibration steps), the radiopharmaceutical sample is applied to the long end of the cartridge and is followed promptly by slowly washing the column with 5 mL of water by using a dropwise administration. This eluate, Fraction 1, is retained for counting. Next, slowly push 5 mL of methanol so the eluate appears in a dropwise manner. This eluate is collected and labeled as Fraction 2. Also still using the longer end of the cartridge, flush the device with two 5 mL portions of air and collect this in the tube labeled Fraction 2. Assay Fraction 1, Fraction 2, and the Sep-Pak® C18 cartridge in a dose calibrator. Fraction 1 contains the hydrophilic impurities, such as unbound indium ^{111}In while Fraction 2 contains the

indium ^{111}In pentetreotide, the desired radiochemical species. The cartridge retains the non-elutable ^{111}In impurities.[10]

$$\%\ indium\ ^{111}In\ pentetreotide = \frac{Activity\ in\ Fraction\ 2}{Ativity\ in\ Fractions\ 1\ \&\ 2\ \&\ Sep-Pak^{®}} \times 100$$

RADIATION DETECTION INSTRUMENTATION

The following radiation detection instruments can be used in the determination of RCP: scintillation well counters, dose calibrators, and radiochromatogram scanners. The determining factor for choosing the instrument is the amount of radioactivity used in the chromatography system.

Well Scintillation Counters

A sodium iodide [NaI(Tl)] crystal well detector is an excellent choice for determining radioactive counts from paper and ITLC strips; however, the scintillation well counter's count rate capabilities must be known in order not to exceed its maximum counting rate. The high detection efficiency of NaI (Tl) well counters limits the amount of activity that can be accurately counted, and this activity is characteristically in the range of 10^2 to 10^4 Bq.[12] If the sample has too much radioactivity, the resolving time of the detection system is exceeded and this may lead to dead-time, causing a decrease in count rate with increasing amounts of radioactivity. Thus, it is important to know the maximum amount of radioactivity the well counter can accurately count. Different procedures have been suggested to avoid exceeding the maximum counting capabilities of the scintillation well counter.[2] One involves increasing the distance between the radioactive sample and detector; this is based on the inverse square law. Another method calls for the use of an attenuator over the opening of the well counter. A third method recommends using a smaller sample size, and this is particularly important when the activity concentration of the radiopharmaceutical is high. A fourth method utilizes a dead-time correction device that is available on some well counters.[2] The basis for this is the correction device automatically corrects for the high radioactivity. Prior to relying on this device, it should be tested to verify its accuracy.[2] Whichever method is utilized, background counts should be determined and subtracted from the counts on the chromatography strips.

Dose Calibrators

When using a dose calibrator for assaying chromatography samples, one of the main concerns is the sensitivity and accuracy of the instrument in the microCurie range. Robbins states that in order to limit

percent error to 1% or less when using a radionuclide calibrator, one should apply a minimum of 0.1 mCi to the chromatography strip or Sep-Pak®. The radionuclide dose calibrator should not be used for to measure samples with less than 0.1mCi, as the per cent error maybe unacceptable.[2] As with dose calibrators, the background count rate should be determined and subtracted from the counts on the chromatography strips or the elutions from the Sep-Pak® cartridges.

Radiochromatogram Scanners

A radiochromatogram scanner is very useful in the identification and quantification of the radioactivity distribution on a radiochromatography strip. It has the advantage of being able to quantify relative amounts of radiochemical species over a broad range of radioactivity. The downside is that the scanner is expensive and the procedure requires more time than using a well scintillation counter.[13] It is probably used more in the determination of radiochemical purity of radiopharmaceuticals where greater resolution is needed or where multiple impurities are suspected, such as fludeoxyglucose ^{18}F and other fluorinated PET radiopharmaceuticals.

DEVELOPMENT OF ALTERNATE PROCEDURES FOR RADIOCHEMICAL TESTING

It is important that the determination of RCP be quick, accurate, and economical. It is sometimes desirable to develop alternate RCP testing procedures to those described in a manufacturer's package insert. The motivation to develop due alternate methods to the manufacturer's prescribed chromatography procedure maybe due to the time required, the cost of the components used, or the desire to use a less toxic solvent. A more recent problem encountered is the decrease in availability of certain chromatography media. According to the APhA Section on Nuclear Pharmacy's Alternative Radiochemical Purity Testing Procedures for the Compounded Radiopharmaceuticals Approved from 1988-1997, it is necessary an alternative procedure be quick, safe, accurate, economical, and/or founded on technical simplicity, while maintaining radiation exposures as low as reasonably achievable (ALARA).[1] The specific support media and solvent system must quantify the various components of the test sample is dictated by the radiopharmaceutical being evaluated as well as the potential radiochemical impurities.[14] Thus, knowledge of the chemical composition of the radiopharmaceutical will facilitate the choice of the stationary phase and mobile phase necessary to effect the desired separation. For example, it must be known whether the desired labeled compound is lipophilic or hydrophilic.

The alternate procedure must be validated against other methods described in the manufacturer's package insert or the product monograph in the USP. Validation requires that the alternate method be tested against the standard chromatography procedure with enough replicates to allow a valid statistical analysis to be performed. The percent RCP of the alternative procedure must agree with the standard chromatography procedure. Also, the alternative procedure must demonstrate the ability to detect radiochemical impurities. One method would be to apply technetium ^{99m}Tc pertechnetate to the system to verify it can be identified and distinguished from the technetium ^{99m}Tc labeled compound.[2] The procedure utilized as well as the results should be well documented. Many alternative radiochemical procedures are found in the literature. [1-3,5,11,15-27]

PITFALLS IN DETERMINATION OF RADIOCHEMICAL PURITY [2,13,28-30]

Errors in chromatographic analysis can occur which can yield technical artifacts. These errors can be categorized according to technique, instrumentation, incorrect selection of media, and incorrect selection of solvent. The more knowledge regarding the chemistry of the radiolabeling process of a particular radiopharmaceutical, the better prepared an individual is to obtain accurate results when analyzing radiochemical purity. When performing analysis of radiochemical purity, a precise procedure must be followed. Inter- and intra-operator variability may influence the final results when there are deviations from the standard protocol.

The following are examples of problems and pitfalls commonly encountered when performing end-product quality control testing:

(1) Insufficient Sample: Insufficient sample being applied to the stationary phase can result in insufficient number of counts. When you consider that radioactive material license require instruments used for counting wipes be able to detect 0.005 μCi, this is more of a problem with a dose calibrator than a well counter. When radioactivity limits approach the lower level of detection for a dose calibrator, then a well scintillation counter should be used. On the other hand, the radioactive test sample must be at a sufficient distance from the detector in well scintillation counter so that dead time is not exceeded.

(2) Chemical Decomposition: Because certain reduced states of ^{99m}Tc are easily oxidized, radiopharmaceutical samples should not be allowed to air dry on the ITLC or paper strip prior to placing the strip in the chromatography chamber. When the sample is allowed to dry, the oxidation may cause the formation of technetium ^{99m}Tc pertechnetate which was not originally present in the radiopharmaceutical sample; thus, this could result in a false failure of radiochemical purity.

(3) Insufficient Separation: Streaking (no separation or insufficient separation of technetium ^{99m}Tc pertechnetate and reduced technetium ^{99m}Tc impurity from the radiolabeled ^{99m}Tc compound) is frequently the result of technetium ^{99m}Tc binding with the stationary medium. Sometimes a substance will move along a TLC plate as a long streak, rather than as a single discrete spot. This is the result of spotting the plate with too large of a sample, in excess of what the moving solvent can handle. The solvent moves as much sample as it can, but a substantial amount is left behind. The sample is dragged along by the solvent leaving a trail of sample that may sometimes span the entire distance between the starting point and the solvent front. Streaking can be eliminated by systematically diluting the sample until development and visualization demonstrate the substances moving as single entities, rather than elongated streaks. The other possible reason for streaking is that the solvent does not contain or contains an insufficient quantity of a component with the same chemical property as the compound being separated.

(4) Sample Preparation: When applying the radiopharmaceutical sample to the strip, splattering or uneven spotting could result in incorrect results.

(5) Contamination of Media: The fingers should not ever touch the strips since natural oils from the skin could contaminate the strips and interfere with solvent migration. Of course anytime one is working with radioactivity, gloves should be worn to adhere to ALARA guidelines. Ink markers, used to denote movement of the solvent, may interact with a radiochemical species thus, yielding inaccurate results.

(6) Handling Errors: The strip should not be allowed to touch the side of a wet chromatography chamber since the results may not be valid.

(7) Radioactive Contamination: It is necessary to keep the chromatography area free of contamination because of ALARA concepts and in order to prevent cross contamination of strips from other technetium ^{99m}Tc radiopharmaceuticals. Transfer of radioactivity from contaminated tweezers and scissors to the stationary media can result in erroneous results. If the work surface is not level or if there is an excessive amount of solvent in the chamber, the radiopharmaceutical sample can be washed off the strip resulting in contamination of the solvent. This can also occur if the solvent is splashed on the spot or the sample spot is submerged in the solvent when the strip is placed in the chamber. The radiopharmaceutical sample should be placed at least 1 cm from the bottom of the chromatography strip so it will be above the solvent level. If the chromatography chamber is moved after the strip has been placed in the solvent, the solvent can wash off some of the radioactive sample. This can not only produce erroneous results with the current chromatography procedure, but also with subsequent chromatography analyses if the solvent is not changed.

(8) Inappropriate Media: It is imperative to select both an acceptable stationary phase and solvent phase for a particular radiopharmaceutical; otherwise, the results could be compromised.

(9) Contamination of Solvents: If solvents are not fresh, spurious results can be interpreted. When moisture is absorbed in an organic solvent, an altered R_f value can occur. When solvents are ordered in large quantities, it is a good idea to transfer some to a smaller container in order to minimize exposure of the stock bottle to room air from frequent openings of the container. This secondary container should be a tightly closed container and appropriately labeled. Radioactive contamination of the solvent, as described in 7 above, may also lead to erroneous results.

(10) Improper Storage of Media: To make certain reproducible results are obtained for radiochromatographic analysis, it is necessary to use fresh strips. Storage of strips should be stored under conditions of low humidity, such as using a desiccant. The length and cut line of these strips should be standardized to ensure accurate results.

(11) Inappropriate or Insufficient Solvent: Inadequate mixing and/or altered proportions of solvents in a mixture can lead to misleading test results. Another reason for an altered R_f value is when one solvent in a mixture evaporates due to excessive exposure to the atmosphere. If insufficient solvent is present in the chamber, the solvent does not flow up to the solvent front line. This is another cause of inaccurate results.

(12) Inappropriate Strip Development: It is necessary that the solvent not be allowed to go past the solvent front line because the cut line will then incorrect. If this occurs, the cut line on the strip must be modified in order to preserve an accurate R_f value.

(13) Radiation Measurement: If instruments settings are incorrect or if radioactive contamination is present on any part of the instrument, then false results can occur.

PRINCIPLE OF RADIONUCLIDIC PURITY QUALITY CONTROL

The definition of radionuclidic purity is the ratio of the stated radionuclide activity to the total radioactivity. This is given as a percentage.[13] Radionuclidic impurities can contribute significant effects on the patient's overall radiation dose as well as impact the image quality.[31] Radionuclidic impurities can originate from extraneous nuclear reactions as a result of isotopic impurities present in the target material or due to the fission process occurring in a reactor. These impurities may be a radioisotope of the desired radionuclide or may be an entirely different nuclide.[32]

A radionuclidic impurity of particular concern to nuclear pharmacies is molybdenum ^{99}Mo contamination in a ^{99m}Tc elution. This occurs when ^{99}Mo is eluted along with ^{99m}Tc pertechnetate during a generator elution.[33] The NRC limits for radionuclidic impurities in technetium ^{99m}Tc can be found in 10CFR 35.204.[34] The NRC[34] and USP[35] limit for ^{99}Mo is $\leq$0.15 μCi ^{99}Mo per mCi of ^{99m}Tc at the time of patient administration. The assay for ^{99}Mo breakthrough can be performed using a dose calibrator and a lead or tungsten shield of sufficient thickness to attenuate the 140 keV gamma emission of ^{99m}Tc while allowing the penetration of a portion of the higher energy gammas of ^{99}Mo.[14] Since only a portion of the higher energy gammas (740 – 780 keV) of ^{99}Mo will be attenuated, a correction factor is used to determine total ^{99}Mo contamination. Modern dose calibrators have this correction factor pre-programmed allowing immediate readout of the corrected ^{99}Mo.[14] Molybdenum ^{99}Mo ($T_{½}$ = 66 hours) and ^{99m}Tc ($T_{½}$ = 6 hours) have different physical half-lives therefore, the ratio of

^{99}Mo to ^{99m}Tc changes with time. For example, if the initial ratio is 0.09 μCi ^{99}Mo per mCi ^{99m}Tc, six hours later the ratio would exceed 0.15 μCi ^{99}Mo per mCi ^{99m}Tc. When the initial concentration is determined, one must determine the expiration time of the product such that the ratio will be within regulatory limits until. According to 10 CFR 35.204, the NRC requires measurement of the ^{99}Mo concentration of the first eluate following receipt of the generator.[34] On January 12, 2009, the NRC issued an information notice (IN) informing Agreement States, medical, generator manufacturer, and radiopharmacy licensees about elevated molybdenum ^{99}Mo breakthrough in generator elution. This IN discusses reports of ^{99}Mo breakthrough exceeding the limits at the first elution whereas others reported ^{99}Mo concentration within limits on the first elution but exceeded limits on subsequent elutions. In the IN, the NRC strongly recommends that all licensees using ^{99}Mo /^{99m}Tc generators assay each eluate for ^{99}Mo breakthrough prior to the administration of ^{99m}Tc to humans.[38]

Technetium-99 is the decay daughter of technetium ^{99m}Tc. This radioisotopic impurity is present in all ^{99}Mo /^{99m}Tc generator eluates along with the desired radionuclide ^{99m}Tc. Technetium-99 has a sufficiently long physical half-life (2.13×10^5 years) to assuage concerns regarding untoward dosimetry. However, excessive ^{99}Tc has been shown to compete with ^{99m}Tc in radiolabeling reactions resulting in decreased radiochemical purity.

In 10CFR35.204[34], the NRC provides the limits of radionuclide impurities in ^{82}Rb eluate to be $\leq$0.02 μCi ^{82}Sr/mCi ^{82}Rb chloride and $\leq$0.2 μCi ^{85}Sr/mCi ^{82}Rb chloride. In comply with these regulations, licensees must determine the amount of ^{82}Sr and ^{85}Sr present in the ^{82}Rb eluate prior to administration to the first patient each day. [34]

PRINCIPLE OF CHEMICAL PURITY

Chemical purity is the proportion of the total mass present in the stated chemical form.[32] With respect to radiopharmaceuticals, this refers to the amount of undesirable chemical species present.[13] In the compounding of short-lived radiopharmaceuticals, chemical impurities are considered all nonradioactive substances that can either affect radiolabling or directly produce adverse biological effects.[31]

In ^{99}Mo /^{99m}Tc generators, alumina oxide (Al_2O_3) is used as the column media to which the ^{99}Mo radioactivity in the form of molybdate ion (MoO_4) is bound. Alumina breakthrough resulting in significant quantities of aluminum ions present in ^{99m}Tc eluates have been reported to cause the agglomeration of ^{99m}Tc sulfur colloid to yield undesirably large particles, This, in turn, may cause lung uptake on a liver/spleen study.[14] The USP limits the amount of aluminum ion to 10 µg Al^{3+}/mL ^{99m}Tc eluate from a generator using fission produced ^{99}Mo.[35] In skeletal imaging using ^{99m}Tc diphosphonates, liver uptake has been observed when the aluminum ion concentration exceeded this limit.[13] The assay for aluminum ion is a colorimetric spot test of the generator eluate. It involves applying one drop of generator eluate and the same size drop of a standard solution containing 10 µg Al^{3+}/mL to test paper impregnated with the aluminum ion specific indicator (ammonium salt of aurin tricarboxylic acid) and comparing the two spots.[33,40] When the aluminum ion reacts with the indicator, a pink color is produced, and the intensity of the pink color is proportionate to the amount of aluminum ion present.[40] If the color of the eluate spot is not as intense as that of the aluminum standard solution, the test is interpreted as negative.[33]

Figure 4. This is an example of a negative test for Al^{3+} contamination. The spot on the bottom of the indicator strip is the standard solution, and the spot at the top represents the technetium ^{99m}Tc pertechnetate elution.

It has been noted that metal ions (such as iron, aluminum, zinc, copper, and cadmium) should be avoided when labeling with ^{111}In as they may interfere with the radiolabeling process.[41] Incorporation yields have been reported to be appreciably decreased when trace metals are present, particularly when labeling platelets with indium ^{111}In oxine.[13]

Another example of a chemical impurity is excess stannous ion present in commercially available radiopharmaceutical kits. Excess stannous ion is suspected of causing the formation of a ^{99m}Tc tin colloid in the preparation of a bone imaging radiopharmaceutical.[31] The presence of carrier iodide in radioiodide solutions may compete during radioiodinations resulting in decreased labeling efficiency. Iodine carrier is also known to compete with radioiodine for uptake in studies of the thyroid gland.[13]

PHARMACEUTICAL CONCERNS

Pharmaceutical concerns include the physical characteristics, biologic purity, particle size, particle number, and pH. Biologic purity includes tests for sterility and pyrogenicity. These tests for biologic purity are covered in greater detail in a previous CE lesson devoted to the topic.

Appearance

A radiopharmaceutical's physical appearance is important, both at the time of receipt and throughout its useful shelflife. The nuclear pharmacist should inspect the color and clarity of each radiopharmaceutical preparation. If a radiopharmaceutical is a true solution, no particulate matter should be present.[32] Particulate ^{99m}Tc radiopharmaceuticals have varying degrees of turbidity in appearance, ranging from white to milky.[13] All radiopharmaceuticals should be free of foreign particulates, such as black particles sometimes resulting from improper penetration of the stopper.

There are two phosphorus ^{32}P radiopharmaceuticals available. Phosphorus ^{32}P-sodium phosphate is a clear and colorless solution, approved for intravenously or oral administration. In contrast, ^{32}P-chromic phosphate is a blue-green colloidal suspension administered via intracavitary instillation. Freshly prepared ^{131}I-sodium iodide solution is clear and colorless. Over time, discoloration due to oxidation and/or radiolysis occurs resulting in a change of color ranging from light amber to brown. This color change does not indicate a change in quality.[13] Visual inspection should be conducted through leaded-glass which is neither fogged nor tinted in order to avoid interference with the observation.[13]

Particle Size and Number

In order to achieve the desired biodistribution of particulate radiopharmaceuticals, it is critical to have the proper size and number of particles for a particular indication. For performing liver/spleen studies, ^{99m}Tc sulfur colloid must have a particle range of 0.1-1um. To observe such small particles, one would need either an ultramicroscope or an electron microscope.[32] When this same radiopharmaceutical is used for lymphoscintigraphy, the product maybe filtered to remove larger particles, thus selecting smaller particles. At least two methods using 0.1um sterile membrane filtration yielding average particle sizes of 0.01-0.3 uM have been reported [Eshima CE references 52 and 53]. A modified preparation method combined with ultrafiltration using a 0.22um sterile filter is also reported to smaller, and more uniform particle sizes necessary for lymphoscintigraphy. [Eshima CE reference 54]

According to the USP monograph, 90% of ^{99m}Tc macroaggregated albumin (MAA) particles should have a diameter 10-90 μm, with none exceeding 150 μm.[42] This is necessary to target the pre-capillary arerioles in the lung. The upper limit of the particle size range for ^{99m}Tc MAA is aimed at preventing localization within the larger pulmonary vessels.[32] The lower limit of the size range helps to ensure the particles are trapped in the pre-capillary pulmonary arerioles rather than simply passing through the lungs and being trapped in other small spaces, such as those found in the reticuloendothelial system (liver, bone marrow).[43]

Adjusting the number of ^{99m}Tc-MAA particles administered is important in patients with conditions such as a right-to-left cardiac shunt [44] as well as in neonates and children. [43] The size of ^{99m}Tc-MAA particles can be determined using a light microscope and a hemacytometer. When the total number of particles in a kit preparation are known, the number of particles in one milliliter can be estimated using a hemacytometer and a light microscope. Figure 5 is a view of MAA particles on a hemacytometer slide. Each large block has dimensions of 200 μm^2 and is composed of 16 smaller blocks which are 50 μm^2.[45] Knowing the depth of the sample on the slide, the number of particles per volume can also be estimated. For example, if the hemacytometer slide is 100 μm (0.1 mm) deep and a total of 50 particles are observed in an area of 1000 μm^2 (1 mm^2), then there would be 50 particles/0.1 mm^3 which equals 500 particles/mm^3 (500 particles/μL) or 500,000 particles/mL.[13] Another method for estimating the number of particles in a dose is to first determine the number of particles per milliliter by dividing the total particles in a MAA kit by the total volume and then multiplying the particles per milliliter by the volume to be administered.[46]

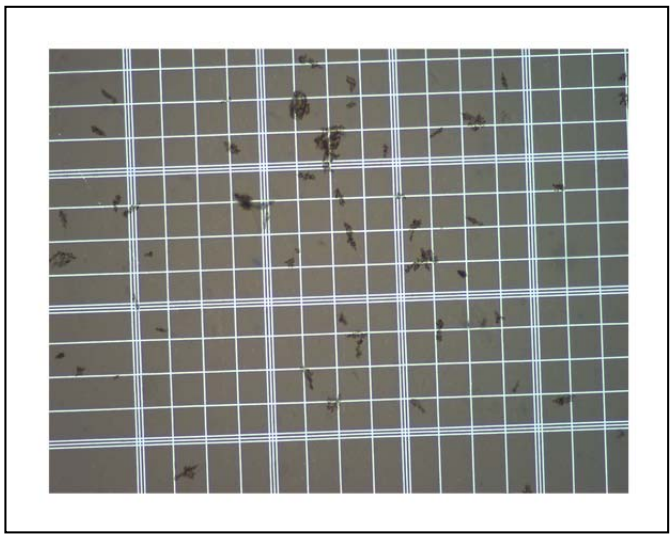

Figure 5. Hemacytomer slide

Example:

Given: If each MAA kit has 5,000,000 particles and the total volume in the prepared kit is 10 mL.

Volume necessary to deliver desired dosage of radioactivity is 0.5 mL

Problem: How many particles will be administered?

$$\frac{5,000,000\,particles}{10mL} = 500,000\,particles/mL$$

$$(500,000\,particles/mL)(0.5mL) = 250,000\,particles\,in\,patient\,dose$$

pH

In order to ensure stability and integrity, all radiopharmaceuticals must be formulated at, and maintain an appropriate pH. Ideally, the pH of a parenteral radiopharmaceutical should be that of blood, pH = 7.4; however due to the blood's high buffer capacity, it is acceptable for the pH to vary between 2 and 9.[32] Although there are some exceptions, the pH of most radiopharmaceuticals are within a range of 4 to 8. *Unstabilized* ^{99m}Tc exametazime has a pH ranging from 9.0 to 9.8. The pH of *stabilized* ^{99m}Tc exametazime ranges from 6.5 to 7.5.[13] In order to avoid volatilization of iodine, solutions of radioiodine should be maintained at an alkaline pH.[13]

Even though the colorimetric evaluation with pH paper is not as accurate as with a pH meter, a narrow-band pH paper can be used for pH determination. Initially, the pH paper should be validated against standard buffers. The accuracy of the pH paper has been reported to be $\geq\pm$ 0.25 units and should bear upon such measurements.[13]

Ionic Strength, Isotonicity, and Osmolality

In order to be acceptable for human administration, radiopharmaceuticals must also possess the proper ionic strength, isotonicity, and osmolality. When diluting a radiopharmaceutical, it is critical to utilize the proper diluent because pH and ionic strength are important aspects in providing both radiopharmaceutical stability and physiologic compatibility. If at all possible, the same solvent as used in the original preparation should be utilized.[32] Due to the blood's high dilution and buffering capacity the tolerances for pH and osmolality of intravenous injections are broad. However, the pH and osmolality tolerances are critical for intrathecal administrations.[13] The preparation and selection of radiopharmaceuticals, and diluents used for intrathecal administration requires special consideration.

QUALITY CONTROL FOR POSITRON EMISSION TOMOGRAPHY RADIOPHARMACEUTICALS

PET radiopharmaceuticals are compounded legend drugs, and as such, they are required to undergo quality control testing prior to release to ensure patient safety. USP Chapter <823> [47]describes the quality control tests that a PET radiopharmaceutical must undergo to make certain that the preparation satisfies the appropriate standards of purity, strength, and quality. These tests are to be completed only by individuals who are trained and qualified in performing these tasks.[47] In the following paragraphs, a brief overview of the tests performed on PET radiopharmaceuticals will be provided. Individual PET radiopharmaceuticals differ in the analytical tests required. The guidance offered here is provided as a general description of the quality control procedures. For more detailed descriptions of the product-specific requirements, the reader is advised to consult to USP Chapter <823> as well as the individual monographs for the various PET radiopharmaceuticals.

Radionuclidic Purity

Radionuclidic impurities can originate from two sources during the production process. They may arise from radionuclides produced during the target irradiation. They may also be the result of target material impurities. Before initial use of PET radionuclides in the synthesis of radiolabeled compounds, the radionuclidic impurities must be determined.[48]

The level of long-lived radionuclidic impurities do not vary considerably from one batch to another in routine preparations of these agents, it is advisable to validate the integrity of the production method.[48] Quantification of the level of long-lived impurities in a PET radiopharmaceutical sample maybe determined using a high-resolution multichannel analyzer, and this should be conducted on an established schedule and with regularity.[31] Half-life determinations for routine identity testing of PET radiopharmaceuticals such as fluorine F-18 fludeoxyglucose (^{18}F-FDG) are commonly performed using a dose calibrator and linear regression analysis. In the example of ^{18}F, the allowable physical half-life is 109.7 minutes, and the acceptable range is 105 to 155 minutes.[31]

Radiochemical Purity

Radiochemical impurities may originate from incomplete labeling, breakdown of radiolabeled preparations with time as a result of instability, or through the introduction of inappropriate ingredients during the synthesic processes. These radiochemical impurities can hinder clinical interpretation by decreasing the target to non-target ratio. They may also cause altered biodistribution resulting in

increased radiation absorbed dose to the patient.[48] The appropriate methods for characterization and the allowable limits of radiochemical impurities are found within the USP monographs for individual PET radiopharmaceuticals. Other useful information regarding formulation and quality assurance of PET radiopharmaceuticals is also available in text.[49]

Radiochemical purity analysis can be performed by gas chromatography, high-performance liquid chromatography (HPLC), or thin-layer chromatography (TLC).[49] When using HPLC, the fractions collected can be identified and quantified by UV detector to determine the level of absorbance or by assaying the radioactivity in a well counter.[48] TLC strips maybe analyzed using a radiochromatogram scanner[13,48] to demonstrate the distribution of the radioactivity along the intact strip in order to determine radiochemical purity. Radiochemical impurities are separated due to differing affinities to the TLC media. The separation of various radiochemical species with different retention times allows the determination of radiochemical purity. This method has the advantage of being useful over a wide range of radioactivity. However, the procedure is time consuming and the scanner is another piece of equipment with the associate costs of purchase, qualification, validation, and maintenance.[13] When using a NaI well counter, the TLC strips are cut into segments based upon the established patterns of retention of radiopharmaceuticals and the known radiochemical impurities. The counts from the each portion of the strip can be used to calculate the radiochemical purity.[48]

Chemical Purity

Since synthetic methods are utilized in the preparation of these PET compounds, analysis of chemical purity is also necessary.[49] To characterize and determine the quantity of potential chemical contaminants in the final product several methods maybe used, including gas chromatography, HPLC, spectrophotometry, ion exchange and solvent extractions.[48] Using the example of ^{18}F-FDG, a colorimetric test for the detection of Kryptofix 2.2.2 has been developed to streamline the clinical production of this product. With this test, one can interpret whether the level of Kryptofix 2.2.2 is within the acceptable regulatory limits in the USP monograph for ^{18}F-Fluorodeoxyglucose.

pH

Individual USP monographs provide the acceptable pH range for PET radiopharmaceuticals. The assessment of pH can be performed using pH paper since an approximate pH value is acceptable. However, standard buffers should be used to initially characterize the accuracy and thereby, "qualify" the pH paper.[13]

Sterility

Due to the short half-life of radiopharmaceuticals, PET drugs are exempt from pre-release sterility testing. Testing for microbial contamination is performed post-release as means of surveillance. Within 24 hours of sterile filtration of the PET radiopharmaceutical, an aliquot of the batch maybe inoculated for sterility testing.[47] The USP sterility test consists of 2 components: fluid thioglycollate medium (FTM) and soybean-casein digest medium. FTM is incubated at 30° to 35°C for 14 days while the soybean-casein digest medium is incubated at 20° to 25°C for 14 days. If microbiological growth occurs in either medium, the product is considered non-sterile or contaminated.[48]

Often, the final PET product is passed through a 0.22 μm membrane filter as a means of cold sterilization.[48] In order to verify the integrity of the filter, a membrane filter integrity test is performed using the bubble point measurement immediately after the product is filtered.[13,47]

Bacterial Endotoxin Test

Prior to the release of PET radiopharmaceuticals, the bacterial endotoxin test (BET) is performed to determine the presence of bacterial endotoxins from gram-negative organisms. This test uses limulus amebocyte lysate obtained from the common horseshoe crab (*Limulus polyphemus*) which reacts with bacterial endotoxins to form a gel-clot. This so called "gel-clot" methods is a very sensitive, rapid, cost-effective procedure.[31] The maximum allowable endotoxins in radiopharmaceutical injections, for all routes of administration except intrathecal, is 175 EU/V where V is the maximum volume (mL) of drug administered at the time of expiration. For radiopharmaceuticals intended for intrathecal administration, the endotoxin limit is 14 EU/V due to the greater risk for CNS toxicity from intrathecal administration.[13]

SUMMARY

Information on QC testing is also found in professional practice guidelines such as the APhA Nuclear Pharmacy Practice Guidelines[50] and SNM Procedure Guideline on the Use of Radiopharmaceuticals.[51] By dispensing a radiopharmaceutical of the highest quality, one can help to minimize the risk of having to repeat a nuclear medicine study due to poorly performing radiopharmaceuticals. Thus seeking to maximize patients' benefits from radiopharmaceuticals, while minimizing their risks from radiation exposure. This is particularly important when considering therapeutic applications of radiopharmaceuticals.

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ASSESSMENT QUESTIONS

1. Radiochemical analysis was performed on technetium ^{99m}Tc-DTPA using ITLC-SG strips. Calculate the percent free technetium ^{99m}Tc pertechentate using the following data:

   Saline: 28,000 counts at the solvent front
   389 counts at the origin

   Acetone: 2000 counts at the solvent front
   27,000 counts at the origin

   a. 1.4%
   b. 6.9%
   c. 93.1%
   d. 98.6%

2. According to the manufacturer's package insert, which radiopharmaceutical uses a Sep-Pak® C18 cartridge in the quality control analysis?

   a. 99mTc DTPA
   b. 99mTc MAG3
   c. 99mTc MDP
   d. 99mTc Sestamibi

3. The upper limit of the acceptable size range for technetium ^{99m}Tc MAA particles is:

   a. 1 μm
   b. 10 μm
   c. 90 μm
   d. 150 μm

4. Radiochemical purity of a techentium^{99m}Tc diphosphonate radiopharmaceutical is established by:

   a. Chromatography
   b. Colorimetric analysis
   c. ^{99}Mo breakthrough testing
   d. pH determination

5. Which of the following is a method to determine radionuclidic purity?

   a. Chromatography
   b. Colorimetric analysis
   c. ^{99}Mo breakthrough testing
   d. pH determination

6. Technetium ^{99m}Tc pertechnetate present in ^{99m}Tc MAA is a:

   a. Chemical impurity
   b. Physical impurity
   c. Radiochemical impurity
   d. Radionuclidic impurity

7. Calculate the percent hydrolyzed-reduced technetium ^{99m}Tc in a technetium ^{99m}Tc HDP preparation from the following data obtained using ITLC-SG strips:

   Acetone front: 6200 counts
   Origin: 884,000 counts
   Background: 120 counts

   Saline front: 900,000 counts
   Origin: 10,000 counts
   Background: 500 counts

   a. 0.68%
   b. 1.05%
   c. 11.1%
   d. 98.9%

8. Determine the percent bound ligand for technetium ^{99m}Tc sulfur colloid from the following data obtained using an ITLC-SG strip:

   Acetone front: 980 counts
   Acetone origin: 30,000 counts

   a. 0.32%
   b. 0.97%
   c. 3.2%
   d. 96.8%

9. Determine the percent bound from the following information for technetium ^{99m}Tc MDP obtained using ITLC-SG strips:

   Background for each strip: 60 counts
   Acetone front: 100 counts
   Acetone origin: 4811 counts

   Background for each strip: 60 counts
   Saline front: 5000 counts
   Saline origin: 79 counts

   a. 96.4%
   b. 98%
   c. 98.8%
   d. 99.2%

10. What type of contamination is technetium ^{99m}Tc pertechnetate found in a technetium ^{99m}Tc-DTPA preparation?

    a. Chemical
    b. Physical
    c. Radiochemical
    d. Radionuclidic

11. Which of the following is an example of a radionuclidic impurity?

    a. Aluminum ion in technetium ^{99m}Tc pertechnetate
    b. Hydrolyzed reduced technetium ^{99m}Tc in ^{99m}Tc mebrofenin
    c. Molybdenum ^{99}Mo in ^{99m}Tc tetrofosmin
    d. Technetium ^{99m}Tc pertechnetate in ^{99m}Tc bicisate

12. A ^{99}Mo/^{99m}Tc generator was eluted in 20 mL, and the eluate contained 1000 mCi of technetium ^{99m}Tc pertechnetate, 85 μCi of ^{99}Mo, and 20 mg of Al^{3+} as of 10:00 AM.

    Which of the following statements is correct?

    a. At noon, the ^{99}Mo concentration and the Al^{3+} level exceed acceptable limits
    b. At noon, the ^{99}Mo concentration exceeds acceptable limits but the Al^{3+} level is acceptable
    c. At 4:00 PM, the ^{99}Mo concentration exceeds acceptable limits and the Al^{3+} level is above acceptable limits
    d. At 4:00 PM, the ^{99}Mo concentration is still within acceptable limits but the Al^{3+} level is above acceptable limits

13. Radionuclidic testing is routinely performed in a nuclear pharmacy using:

    a. A dose calibrator
    b. A multi-channel analyzer
    c. Colorimetric analysis
    d. HPLC

14. At 8:00 AM a radiopharmaceutical kit was prepared using an eluate calibrated at 7:00 AM for 500 mCi of technetium ^{99m}Tc pertechnetate and 48 μCi of ^{99}Mo. Which of the following times is the last time that a dose can be used from this technetium ^{99m}Tc kit and still be within USP limits for ^{99}Mo breakthrough?

    a. 10:00 AM
    b. 12:00 Noon
    c. 1:2 0 PM
    d. 2:30 PM

15. Al^{+++} is an example of a:

    a. Chemical impurity
    b. Physical impurity
    c. Radiochemical impurity
    d. Radionuclidic impurity

16. Given: 1000 mCi of technetium ^{99m}Tc pertechnetate at 2:00 AM and 63μCi ^{99}Mo at 2:00 AM

    According to the NRC, which of the following times is the latest time this eluate can be used for patient administration based upon the ^{99}Mo content?

    a. 8:00 AM
    b. 10:00 AM
    c. 11:00 AM
    d. 12:00 Noon

17. Where would a radiolabeled complex be found on a chromatography strip if the R_f value is 1.0?

    a. At the origin
    b. At the solvent front
    c. Evenly distributed over the entire strip
    d. In the middle

18. Sep-Pak® C18 cartridges are composed of:

    a. A nonpolar solid material
    b. A nonpolar liquid
    c. A polar liquid
    d. A polar solid sorbent

19. Which instrument is ***NOT*** acceptable for measuring radioactive counts in chromatography samples?

    a. Dose calibrator
    b. G-M survey meter
    c. Multi-channel analyzer
    d. Single channel analyzer

20. Which of the following statements is ***TRUE***?

    a. Osmolatlity is more important for intrathecal administration versus intravenous administration.
    b. Osmolatlity is more important for intravenous administration versus intrathecal administration.
    c. pH and osmolality are equally important for both intravenous and intrathecal administration.
    d. pH is more important for intravenous administration than intrathecal administration.

21. When using a dose calibrator to count chromatography samples, what is the minimum amount of radioactivity that can be applied to the chromatography medium in order to limit the percent error to ≤1%?

    a. 1 μCi
    b. 10 μCi
    c. 100 μCi
    d. 1000 μCi

22. Which of the following statements is ***TRUE***?

    a. In order to avoid volatilization of iodine, a radioiodine solution should be maintained at an alkaline pH
    b. pH paper is less accurate than a pH meter
    c. The accuracy of pH paper is ± 1 unit.
    d. The pH of most radiopharmaceuticals is 9.0 to 9.8.

23. Which of the following does ***NOT*** meet the limit for ^{82}Sr contamination in ^{82}Rb chloride?

    a. 0.15 μCi/10 mCi
    b. 0.2 μCi/10 mCi
    c. 1.5 μCi/8 mCi
    d. 2.0 μCi/100 mCi

24. In order to avoid dead time issues when counting samples in a well counter, radioactivity should be limited to no greater than:

    a. 2.7×10^{-3} μCi
    b. 2.7×10^{-1} μCi
    c. 100 μCi
    d. 10 mCi

25. Which statement is true concerning radiochemical purity testing of radiopharmaceuticals?

    a. It is optional for a day to day procedure as long as it is performed at least once a week.
    b. If radionuclidic testing is performed, radiochemical analysis is not necessary.
    c. Radiochemical analysis should always be completed prior to patient administration of the radiopharmaceutical.
    d. Recommended practice only requires radiochemical testing to be conducted by the end of the business day.