The AAPM/RSNA Physics Tutorial for Residents

LEARNING OBJECTIVES

After reading this article and taking the test, the reader will be able to:

- Define and describe a radiopharmaceutical.

- List desirable characteristics of a diagnostic radiopharmaceutical.

- Describe various methods of isotope production.

- Describe the chemistry of technetium and the preparation of technetium-99m chelates.

- Define various purity standards and describe quality control testing procedures.

Radiopharmaceuticals[1]

James A. Ponto, MS, RPh

Radiopharmaceuticals are essential to the performance of nuclear medicine procedures. These radioactive drugs consist of two components: a drug component for localization in a specific tissue or organ and a radioactive component for diagnostic or therapeutic purposes. The majority of radiopharmaceuticals are used for diagnostic imaging procedures. The radioisotopes used for radiopharmaceuticals are produced in a number of ways: as by-products of fission, by means of neutron activation, by cyclotrons, and by generators. These methods produce isotopes with both desirable and undesirable properties. Approximately 80% of all nuclear medicine procedures performed in the United States use radiopharmaceuticals labeled with technetium-99m. The chemical properties of technetium allow relatively simple preparation of Tc-99m compounds by using reagent kits. Quality control testing of radiopharmaceuticals is routinely performed to ensure compliance with various purity standards such as assay for radioactivity, radionuclidic purity, chemical purity, radiochemical purity, pharmaceutical purity, and biologic purity.

■ INTRODUCTION

Radiopharmaceuticals are essential to the performance of nuclear medicine procedures. Radiologists, nuclear medicine physicians, and other physicians who perform nuclear medicine procedures must possess ample knowledge of radiopharmaceuticals to comply with Nuclear Regulatory Commission requirements for human use of radioactive materials as well as to provide optimal medical care to the patients they serve. Even radiologists who are not involved in nuclear medicine procedures should possess some basic knowledge of radiopharmaceuticals to appropriately interact with their colleagues in nuclear medicine.

In this article, the following topics are discussed: (*a*) definition and description of a radiopharmaceutical, (*b*) desirable characteristics of diagnostic radiopharmaceuticals, (*c*) production of radioisotopes for radiopharmaceuticals, (*d*) the chemistry of technetium and radiolabeling processes, and (*e*) purity standards and quality control testing.

Figure 1. One fission pathway for U-235 and the resulting by-products. The underlined isotopes are stable end products. I = iodine, Mo = molybdenum, n = neutron, Rh = rhodium, Ru = ruthenium, Sb = antimony, Sn = tin, Te = tellurium, Xe = xenon.

$$^{235}U + n \nearrow 2n + energy$$

$$^{103}Mo \rightarrow ^{103}Tc \rightarrow ^{103}Ru \rightarrow ^{103}\underline{Rh}$$

$$^{131}Sn \rightarrow ^{131}Sb \rightarrow ^{131}Te \rightarrow ^{131}I \rightarrow ^{131}\underline{Xe}$$
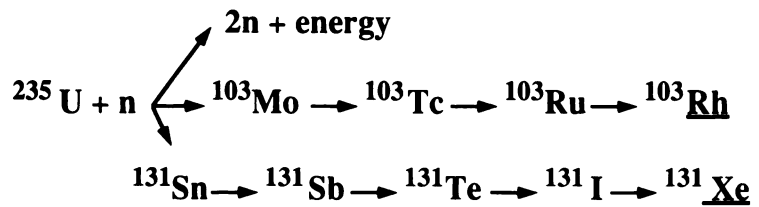
■ DEFINITION AND DESCRIPTION OF A RADIOPHARMACEUTICAL

The Food and Drug Administration (FDA) defines a radiopharmaceutical, which is also referred to as a radioactive drug, as "any substance defined as a drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons." From this definition, it is apparent that a radiopharmaceutical consists of both a drug component and a radioactive component. The drug component is responsible for localization in a specific tissue or organ. The radioactive component is responsible for the emission of gamma rays for external detection (ie, diagnostic imaging) or the emission of particulate radiation for radionuclide therapy. (The FDA classifies brachytherapy sources as devices rather than drugs.)

Some radiopharmaceuticals are simply elemental salts of radioisotopes (eg, sodium iodide I-131, thallous chloride Tl-201), but most radiopharmaceuticals incorporate radioactive atoms into chemical compounds that serve to carry the radioactive atoms to the intended tissue or organ. Some radiopharmaceuticals are manufactured and marketed by pharmaceutical companies in a final, ready-for-use dosage form; however, because of their short half-lives, most radiopharmaceuticals require preparation of the final product either on-site (ie, in-house) or locally (eg, a commercial nuclear pharmacy).

Radiopharmaceuticals can also be categorized as diagnostic or therapeutic. Diagnostic radiopharmaceuticals are intended for use in the diagnosis or monitoring of various disease states. Relatively small radiation doses are delivered, which are similar in magnitude to radiation doses from diagnostic x-ray procedures. Examples of diagnostic radiopharmaceuticals include technetium-99m diphosphonates for bone scans, Tc-99m macroaggregated albumin (MAA) for lung scans, and thallous chloride Tl-201 for myocardial perfusion scans. Conversely, therapeutic radiopharmaceuticals are intended for use in the treatment of various disease states. Relatively large radiation doses are purposely delivered to cause localized radiation damage; the radiation doses are similar in magnitude to those from teletherapy irradiation. A common therapeutic radiopharmaceutical is sodium iodide I-131, which is used to treat hyperthyroidism or thyroid cancer. The radiation dose given for the latter is sufficient to ablate the thyroid.

■ DESIRABLE CHARACTERISTICS OF DIAGNOSTIC RADIOPHARMACEUTICALS

Because more than 95% of the procedures in which radiopharmaceuticals are used are diagnostic, diagnostic radiopharmaceuticals will be emphasized throughout this article. Desirable characteristics of a diagnostic radiopharmaceutical are as follows: (a) gamma radiation suitable for imaging (in terms of both energy and abundance); (b) a half-life of appropriate length (long enough to allow optimal localization and imaging, but not unnecessarily long so that the radiation dose and interference with other procedures are limited); (c) absence of particulate emissions (so that the radiation dose is substantially low); (d) high specific activity (a high radioactivity-to-mass ratio provides an abundance of gamma radiation with negligible mass effects, ie, the radiopharmaceutical behaves as a tracer of physiologic function); (e) absence of pharmacologic and toxic effects (no adverse reactions); (f) a biodistribution suitable for the intended procedure (localization only in the tissue or organ of interest); and (g) availability at a reasonable cost.

■ PRODUCTION OF RADIOISOTOPES FOR RADIOPHARMACEUTICALS

The various radioisotopes found in nature (eg, potassium-40, radium-226, uranium-238) generally have undesirable properties, which include
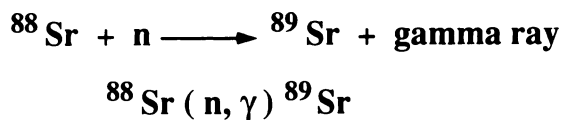
$$^{88}Sr + n \longrightarrow {}^{89}Sr + \text{gamma ray}$$

$$^{88}Sr\,(\,n,\gamma\,)\,{}^{89}Sr$$

Figure 2. Production of Sr-89 by neutron activation as represented with the traditional equation (top) and the standard nuclear shorthand (bottom). n = neutron.

$$^{124}Te + p \longrightarrow {}^{123}I + 2n$$

$$^{124}Te\,(\,p,\,2n\,)\,{}^{123}I$$

Figure 3. One scheme for cyclotron production of I-123 as represented with the traditional equation (top) and the standard nuclear shorthand (bottom). n = neutron, p = proton.

very long half-lives (thousands or millions of years); particulate emissions (alpha or beta decay); and low specific activity (ie, the radioisotope is mixed with stable isotopes of the same element). None of these naturally occurring radioisotopes are used for radiopharmaceuticals.

A limited class of radioisotopes is obtained as by-products of the fission of U-235 (the fuel in nuclear reactors). When an atom of U-235 undergoes fission, it splits into two pieces. These pieces are not of equal size; typically, one fragment has an atomic mass of approximately 100 and the other an atomic mass of approximately 130. Because each U-235 atom can split in a number of ways, a variety of radioisotopes will be directly produced as fission fragments. Even more radioisotopes will be produced as decay products of these fission fragments. Figure 1 shows one fission pathway for U-235. The two fission fragments, Mo-103 and Sn-131, each decay through a chain of radioisotopes and end up as stable isotopes. These radioisotopes, whether directly produced fission fragments or subsequent members in a decay chain, are referred to as fission by-products and can be chemically separated for use in radiopharmaceuticals. An example of a fission by-product used for radiopharmaceuticals is I-131.

Desirable properties of fission by-products are high specific activity and moderate cost. Undesirable properties of fission by-products are particulate emission (beta decay) and the limited variety of radioisotopes produced (ie, those with atomic masses near 100 or near 130). As a result, only a few fission by-products (eg, I-131, Xe-133) are commonly used for radiopharmaceuticals. Perhaps the most important fission by-product is Mo-99, which is used in Mo-99/Tc-99m generators.
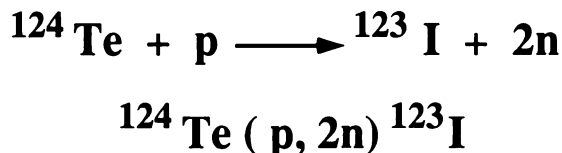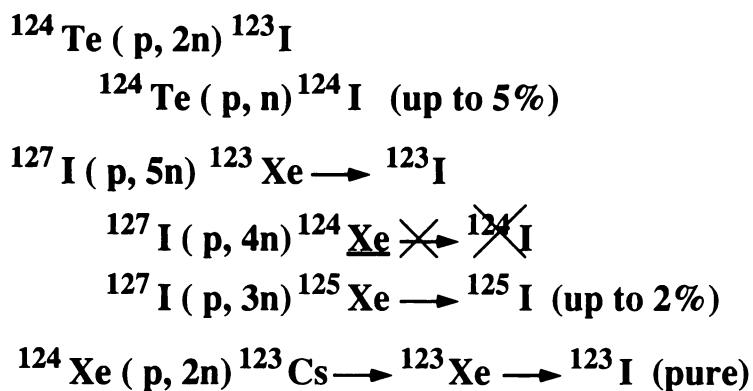
Another limited class of radioisotopes is produced by neutron activation. This process entails placing target atoms in a nuclear reactor, where they are bombarded with thermal neutrons. Nuclear transformation induced by neutron capture results in the addition of 1 to the mass number of the isotope. The excess energy of the newly formed isotope is released as gamma radiation. An example of a radioisotope produced by neutron activation is strontium-89. Figure 2 shows the production process of Sr-89 with the traditional equation and the standard nuclear shorthand.

Desirable properties of radioisotopes produced by neutron activation are the wide variety of isotopes that can be produced and moderate cost. Undesirable properties of such radioisotopes as potential imaging agents are particulate emission (beta decay) and low specific activity (stable target atoms are mixed with their radioisotope products). However, radioisotopes produced by neutron activation (eg, phosphorus-32, Sr-89) can potentially be used as therapeutic radiopharmaceuticals in cases in which beta emission is a desired characteristic.

A larger class of radioisotopes can be produced with a cyclotron. A cyclotron accelerates charged particles (eg, protons) in an oscillating electromagnetic field, whereupon they bombard target atoms. Nuclear transformation induced by particle capture usually results in a radioisotope of a different element with the emission of one or more nucleons (ie, protons or neutrons). An example of a radioisotope produced with a cyclotron is I-123. Figure 3 shows one production process for I-123 with the traditional equation and the standard nuclear shorthand.

Figure 4. Three schemes for cyclotron production of I-123. Note that the first production scheme also yields unwanted I-124 as an impurity from a side reaction. The second scheme avoids the production of I-124 (because the intermediate isotope is stable) but does yield some unwanted I-125 as an impurity from a side reaction. The third scheme results in essentially pure I-123. The underlined term is a stable isotope. Crossed-out terms indicate a lack of occurrence. Cs = cesium, n = neutron, p = proton.

$$^{124}Te\,(\,p,\,2n)\,^{123}I$$

$$^{124}Te\,(\,p,\,n)\,^{124}I \quad (\text{up to } 5\%)$$

$$^{127}I\,(\,p,\,5n)\,^{123}Xe \longrightarrow {}^{123}I$$

$$^{127}I\,(\,p,\,4n)\,^{124}\underline{Xe} \not\longrightarrow {}^{124}I$$

$$^{127}I\,(\,p,\,3n)\,^{125}Xe \longrightarrow {}^{125}I \quad (\text{up to } 2\%)$$

$$^{124}Xe\,(\,p,\,2n)\,^{123}Cs \longrightarrow {}^{123}Xe \longrightarrow {}^{123}I \quad (\text{pure})$$

Desirable properties of radioisotopes produced with a cyclotron are the wide variety of isotopes that can be produced, the choice of production methods, and high specific activity. It is also important that cyclotron-produced radioisotopes decay by means of electron capture or positron emission. Undesirable properties of radioisotopes produced with a cyclotron are potential impurities from side reactions (Fig 4) and relatively high cost. The particular scheme to be used for radioisotope production is chosen by weighing the level of purity against the cost associated with each scheme.

Because of the substantial desirable properties of radioisotopes produced with a cyclotron, several of these radioisotopes are routinely used for radiopharmaceuticals. Examples of single-photon-emitting radioisotopes commonly used in conventional nuclear medicine are gallium-67, indium-111, I-123, and Tl-201. Examples of dual-photon-emitting radioisotopes commonly used in positron emission tomography are carbon-11, nitrogen-13, oxygen-15, and fluorine-18.

A very limited class of radioisotopes is obtained from radioisotope generators, which are produced by one of the methods summarized above. Generators provide a short-lived daughter radioisotope, which is the decay product of a longer-lived parent radioisotope. The term *generator* refers to the physical device in which the short-lived daughter radioisotope can be chemically separated from the longer-lived parent radioisotope. A slang term sometimes used for a generator is a *cow*. The separation process by

which the daughter radioisotope is extracted from the generator is referred to as elution. A slang phrase sometimes used for elution is "milking the generator."

Figure 5 illustrates the production-elution kinetics of an Mo-99/Tc-99m generator. Mo-99, the parent radioisotope, undergoes radioactive decay with a half-life of 66 hours. As it decays, it forms Tc-99m atom by atom. The Tc-99m thus formed decays more rapidly (half-life = 6 hours); therefore, its activity builds up over time and reaches a maximum at approximately 24 hours, at which time the generator can be eluted (ie, all of the Tc-99m can be extracted). During the next 24 hours, more Tc-99m will be created so that the generator can be eluted again the next day, and so on. Mo-99/Tc-99m generators are typically eluted every morning to provide a daily supply of Tc-99m. The useful life of an Mo-99/Tc-99m generator is 1-2 weeks. Figure 6 shows a cross section of one type of Mo-99/Tc-99m generator.

In general, desirable properties of radioisotopes obtained from generators are ready availability, relatively low cost, high specific activity, and the variety of types of decay (which are not related to the production method). Undesirable properties of radioisotopes obtained from generators are the limited variety of parent-daughter pairs and the potential for "generator breakthrough" of parent radioisotope in the eluate.

Although numerous raidoisotope generators have been developed, only three are currently commercially available for routine radiopharmaceutical use. Of these, the most important
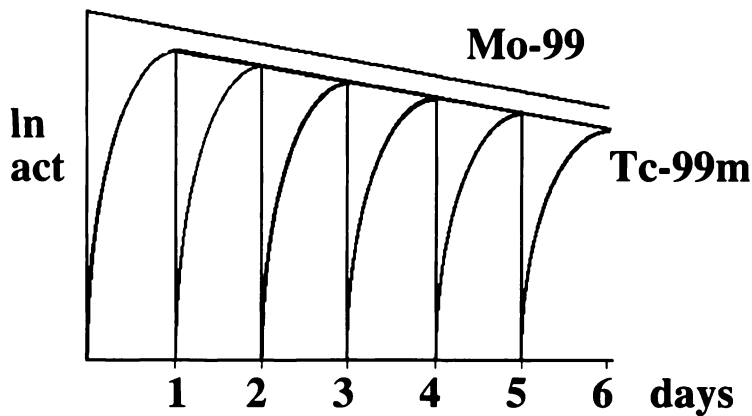
Figure 5. Buildup and daily elution profile for an Mo-99/Tc-99m generator. *ln act* = natural logarithm of activity (measured in gigabecquerels or millicuries).
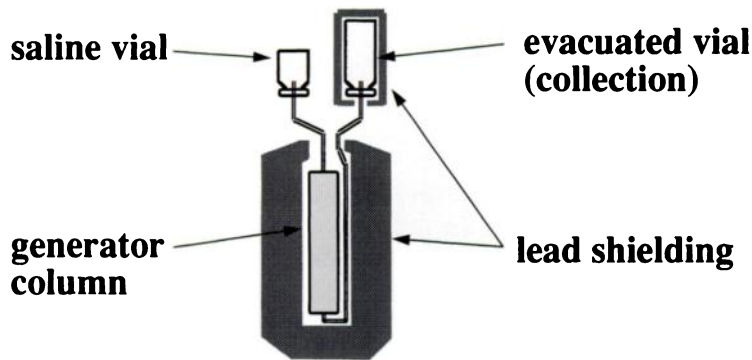

Figure 6. Schematic vertical cross section of one type of Mo-99/Tc-99m generator. Mo-99 is placed (by the manufacturer) on an ion exchange column surrounded by lead shielding. Tubing connects the column to two needles. To elute the generator, a unit-dose vial of normal saline solution (eg, 5 mL) is placed on one needle and an evacuated collection vial (eg, 30 mL) enclosed in a lead vial shield is placed on the other needle. The vacuum in the collection vial draws the normal saline solution through the column, where it extracts the Tc-99m and is then collected in the shielded collection vial. Mo-99 is retained on the ion exchange column because of differences in molecular charge (−2 for molybdate vs −1 for pertechnetate) and solubility (molybdate is not readily soluble in sodium chloride injection). This simple elution process takes only approximately 3–5 minutes.

generator is the Mo-99/Tc-99m generator. Tc-99m has several very desirable physical and chemical characteristics. More than 80% of all nuclear medicine procedures performed in the United States use radiopharmaceuticals labeled with Tc-99m. Because the parent, Mo-99, has a half-life of just under 3 days, Mo-99/Tc-99m generators are usually replaced every week. A less common generator is the rubidium-81/krypton-81m generator. Because krypton is an inert gas, its routine use is limited to lung venti-

lation studies. The short parent half-life requires that this generator be replaced every day. A third generator is the Sr-82/Rb-82 generator. Rb-82 is a positron-emitting chemical analogue of potassium; routine use of Rb-82 is limited to positron emission tomographic studies of myocardial perfusion. The long half-life of Sr-82 allows this generator to be used for a month or longer before it is replaced.

■ CHEMISTRY OF TECHNETIUM AND RADIOLABELING PROCESSES

As previously stated, the majority of nuclear medicine procedures use radiopharmaceuticals labeled with Tc-99m. Technetium is element 43 in the periodic table and is a transition metal in the position immediately below manganese. An unusual element, technetium is not found in nature and none of its isotopes are stable. Technetium was discovered and first produced in 1937 and derives its name from the Greek word *technētos*, which means "artificial." Thus, *technetium* literally translates as "artificial element," and technetium was the first man-made element. Tc-99m is formed from the decay of Mo-99. The *m* in *Tc-99m* denotes the metastable state and refers to the fact that the nucleus is in an "excited" energy state and decays to form Tc-99 (which has a half-life of 200,000 years).

Technetium is obtained from the generator in the chemical form of sodium pertechnetate. Pertechnetate contains one technetium atom and four oxygen atoms; as a molecular ion, incorporated technetium has a valence or oxidation state of +7, so the molecular ion has an overall charge of −1. Technetium in this pertechnetate form is chemically very stable and does not readily react with or label onto other compounds. The first step in preparing Tc-99m radiopharmaceuticals is to use stannous chloride as a reducing agent to reduce the technetium to a lower valence or oxidation state (eg, +3, +4, or +5). In a reduced state, technetium atoms can be chelated with ligand molecules to form Tc-99m-labeled radiopharmaceuticals. These labeling procedures are usually carried out with commercially prepared "reagent kits."

A typical reagent kit contains vials of a lyophilized mixture of stannous ion (which serves as the reducing agent) and the ligand compound to be radiolabeled. For many common radiopharmaceuticals, preparation consists of simply adding Tc-99m pertechnetate solution to the reagent kit vial, in which the technetium is rapidly reduced and immediately chelated with the ligand compound to yield the desired Tc-99m product. Figure 7 shows the proposed structure of a Tc-99m chelate. Preparation of a radiopharmaceutical may require heating (eg, boiling) to drive the labeling reaction. Some radiopharmaceuticals are prepared with multiple ingredients that must be mixed in a specific sequence.

■ PURITY STANDARDS AND QUALITY CONTROL TESTING

Because of their short half-lives, Tc-99m radiopharmaceuticals require preparation of the final product either on-site (ie, in-house) or locally (eg,
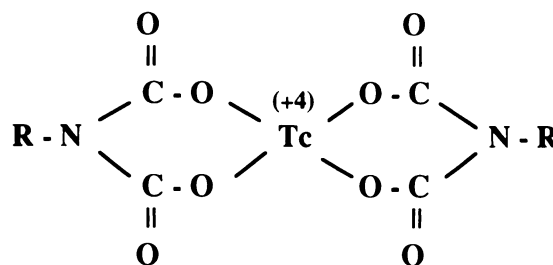

Figure 7. Proposed structure of a dimeric Tc-99m chelate. The molecule on the left chelates the reduced technetium atom with two bonds. The molecule on the right also chelates the technetium atom with two bonds. Because two distinct molecules both chelate the same technetium atom, this example is referred to as a dimeric chelate. R = radical.

a commercial nuclear pharmacy). The pharmacist or physician in charge has the responsibility to ensure that these products meet acceptable standards for strength, quality, and purity. Thus, a radiopharmaceutical quality control program should be implemented.

The term *radioassay* refers to measurement of the amount of radioactivity in a given container (eg, a vial or syringe). The Nuclear Regulatory Commission requires that each patient dose of a radiopharmaceutical be assayed for radioactivity content before administration. The radioassay procedure involves placing the dose (eg, a syringe) into a dose calibrator, which measures the radioactivity (eg, in megabecquerels or millicuries). By regulation, each dose of a therapeutic radiopharmaceutical (eg, I-131) must be within ±10% of the prescribed dose; as a standard of practice, each dose of a diagnostic radiopharmaceutical also must be within ±10% of the prescribed dose. If an assayed dose is excessive or insufficient, the dose is iteratively adjusted and assayed until it is an acceptable quantity.

Radionuclidic purity is defined as the fraction of activity due to the specified radionuclide. Radionuclidic impurity is the fraction of an unwanted radionuclide. Radionuclidic impurities include unwanted radioisotopes associated with radionuclide production (eg, I-124 is produced in Te-123 [p,2n] production of the target radionuclide I-123) and parent radioisotopes produced by breakthrough from a generator column during elution (eg, Mo-99 in the Tc-99m eluate). Radionuclidic impurities can be observed and measured by such means as gamma spectroscopy (identification of characteristic energies in a gamma energy spectrum) (Fig 8) or the differential attenuation of the characteristic photon energies emitted (Fig 9).

Radionuclidic impurities can result in adverse consequences such as degradation of image
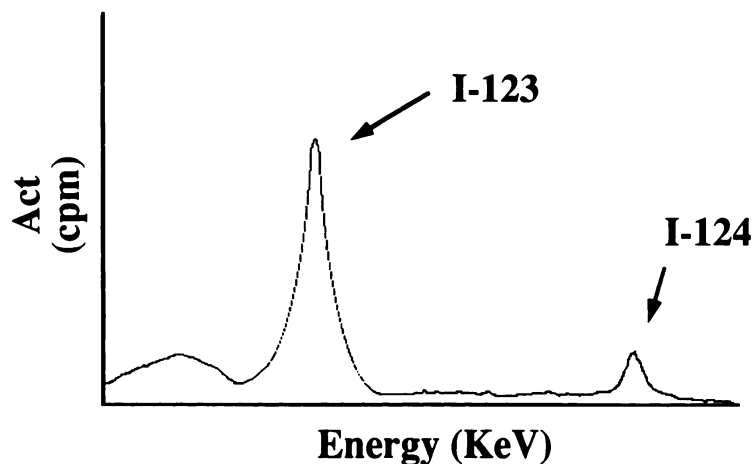
I-123

I-124

Act (cpm)

Energy (KeV)

Figure 8. Sketch of the gamma spectrum of an I-123 production sample. A radionuclidic impurity is detected as the small peak at the higher gamma energy, which corresponds to the gamma emissions of I-124. The amount of the impurity can be determined from the area under the peak and the photon-counting efficiency of the detector. *Act* = activity.

~ 6 mm ──► Pb shield

direct assay in dose calibrator

Tc ──►
Mo ──► ~ 30 %
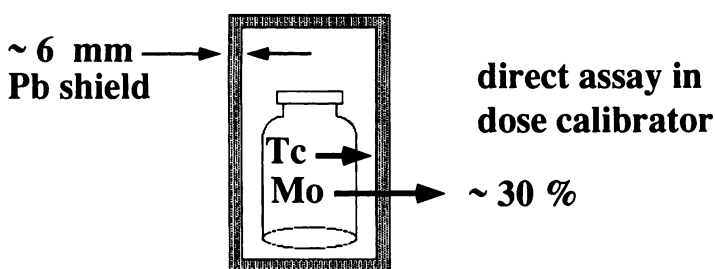
Tc-99m γ = 140 KeV   > 20 HVLs
Mo-99 γ = 740, 780 KeV   < 2 HVLs

Figure 9. Basis for determination of Mo-99 breakthrough in a Tc-99m eluate with the differential attenuation technique. A Tc-99m generator eluate vial is placed in a specifically designed lead canister, which provides more than 20 half-value layers (*HVL*) of attenuation for the 140-keV gamma rays of Tc-99m. This thickness of lead effectively reduces these emissions to undetectable levels. However, this same thickness of lead provides less than 2 half-value layers of attenuation for the higher-energy gamma rays of Mo-99 but allows almost 30% of them to be transmitted. This canister assembly can be placed directly into a dose calibrator, which measures the amount of Mo-99 transmitted. To correct for the attenuation, the dose calibrator reading is multiplied by 3.5. *Pb* = lead.

quality and, more important, an increase in the radiation dose to the patient. Consequently, limits have been established for radionuclidic purity. Limits for radionuclidic impurities in specific radiopharmaceuticals are provided in *United States Pharmacopeia* (USP) monographs. For example, the limit for Mo-99 in a Tc-99m generator eluate is 0.15 μCi Mo-99 per mCi Tc-99m (0.15 kBq Mo-99 per MBq Tc-99m) at the time of administration.

The responsibility for meeting FDA radionuclidic purity regulations and ensuring compliance with the specified limits rests with the manufacturer. In the special case of Mo-99/Tc-99m

generators, the Nuclear Regulatory Commission further requires verification of acceptable radionuclidic purity by the user, who must test each generator eluate for Mo-99. The user must establish a written procedure describing how this testing is to be performed, and the testing must be performed only by trained personnel. Documentation of this training must also be maintained, and records of the test results must be maintained for at least 3 years.

Chemical purity is defined as the fraction of the desired (nonradioactive) substances present relative to the specified chemicals. Chemical
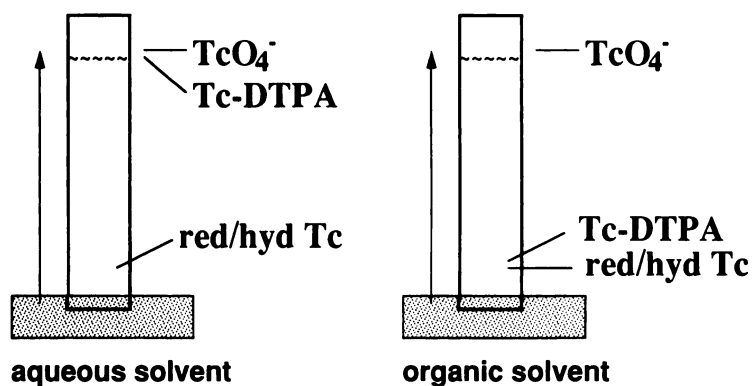
Figure 10. Radiochemical quality control testing of Tc-99m diethylenetriaminepentaacetic acid (*DTPA*) by using two instant thin-layer chromatography strips in different solvents. For each strip, one drop of the Tc-99m DTPA solution is spotted near the bottom. The bottom tip of each strip is then placed in the desired solvent. As the solvent migrates up the strip, soluble radiochemical species are carried with it, while insoluble species remain behind. The radioactivity at each location on the strip can then be measured with a suitable radiation detector. Reduced-hydrolyzed (*red/hyd*) Tc-99m impurity is detected as an insoluble species at the origin when an aqueous solvent is used; Tc-99m pertechnetate impurity is detected as a soluble species at the solvent front when an organic solvent is used. The radiochemical purity of Tc-99m DTPA is then calculated by subtraction of these impurity fractions.

impurity is the fraction of unwanted (nonradioactive) substances relative to the specified chemicals. Causes of chemical impurities include the breakthrough of substances from a generator column during elution (eg, aluminum ion in a Tc-99m eluate) and contamination by reagents used in the production process. Chemical impurities can be detected with a variety of chemical analysis techniques such as photospectrometry, evaluation with dye-impregnated paper, and gas or liquid chromatography.

Chemical impurities can have adverse consequences such as toxic effects or interactions with radiopharmaceuticals. For example, aluminum ion can interact with Tc-99m sulfur colloid to form flocculent particles that embolize in the lungs or with Tc-99m bone agents to form colloidal precipitates that are phagocytosed by the liver. Consequently, limits have been established for chemical purity and are detailed for specific radiopharmaceuticals in USP monographs. For example, the limit for aluminum ion in a Tc-99m generator eluate is 10 µg of aluminum per milliliter of Tc-99m solution. The responsibility for meeting FDA chemical purity requirements and ensuring compliance with the specified limits rests with the manufacturer. Verification of acceptable chemical purity by the user is recommended in certain cases to meet professional practice standards.

Radiochemical purity is defined as the fraction of activity in the specified chemical form. Radiochemical impurity is the fraction of the desired radionuclide that is in the wrong chemical form. Radiochemical purity is also referred to as labeling efficiency. Causes of radiochemical impurities include suboptimal radiolabeling procedures (eg, excess Tc-99m pertechnetate remaining in a Tc-99m-labeled radiopharmaceutical) and decomposition of prepared radio-
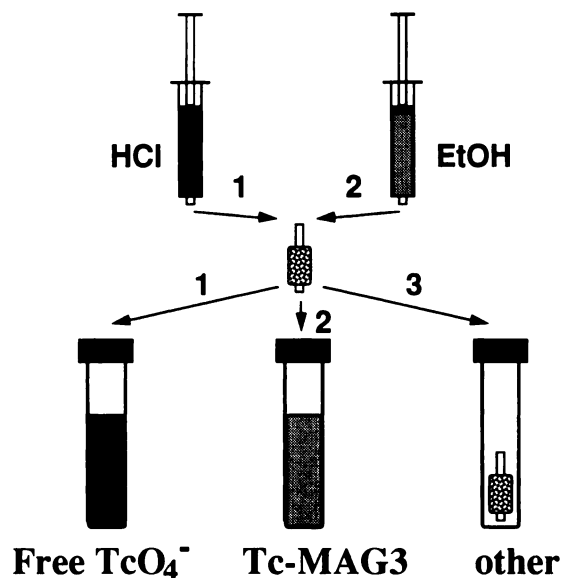
HCl   **EtOH**

1   2

1   ↓2   3

Free TcO₄⁻   Tc-MAG3   other

Figure 11. Radiochemical quality control testing of Tc-99m MAG₃ with minicolumn chromatography. A few drops of Tc-99m MAG₃ solution are placed in the minicolumn. Hydrochloric acid is then passed through the column to extract the Tc-99m pertechnetate impurity, which is collected in a test tube. Next, an alcohol solution is passed through the column to extract the desired Tc-99m MAG₃, which is collected in a second test tube. The column itself, which still contains the other radiochemical impurities, is placed in a third test tube. The radioactivity in each test tube is then measured with a suitable radiation detector. The radiochemical purity of Tc-99m MAG₃ is calculated as the fraction of the total in the second test tube.

pharmaceuticals (eg, Tc-99m pertechnetate and reduced-hydrolyzed Tc-99m species resulting from the breakdown of a Tc-99m–labeled radiopharmaceutical). Radiochemical impurities can be observed by separating them with various chemical separation techniques (eg, thin-layer chromatography, column chromatography) and then measured by means of the radioactivity associated with each of the separated species.

Because of their biodistribution, radiochemical impurities can have adverse consequences such as degradation of image quality and inter-

ference with image interpretation. Consequently, limits have been established for radiochemical purity in specific radiopharmaceuticals and are detailed in USP monographs. Although there are several exceptions, most radiopharmaceuticals must have radiochemical purity of greater than 90%. The responsibility for meeting FDA requirements for radiochemical purity and ensuring compliance with the specified limits rests with the manufacturer. Verification of acceptable radiochemical purity by the user is required by the FDA (package insert instructions) for a few radiopharmaceuticals (eg, Tc-99m mercaptoacetyltriglycine [MAG₃], Tc-99m hexamethyl-propyleneamine oxime [HMPAO]). Verification of acceptable radiochemical purity by the user is recommended in other cases to meet professional practice standards.

Instant thin-layer chromatography is the most commonly used procedure for radiochemical quality control testing of Tc-99m radiopharmaceuticals (Fig 10). This procedure makes use of silica gel supported on glass fiber strips. Separation of radiochemical species is based on differences in solubility (ie, the soluble species move up the strip with the solvent, while insoluble species remain at the spot of placement). When an aqueous solvent is desired, normal saline solution (0.9% sodium chloride) is typically used; when an organic solvent is desired, acetone or methyl ethyl ketone is typically used. Figure 11 illustrates radiochemical quality control testing of Tc-99m MAG₃ by using minicolumn chromatography.

Pharmaceutical purity refers to the quality of other physical properties of the product. For example, the particle size distribution of Tc-99m MAA is an important purity parameter. Causes of incorrect particle size include manufacturing defects and clumping. Substantial alterations in particle size are readily detected by viewing a hemocytometer slide in an ordinary light microscope (Fig 12). The most significant adverse

consequence of abnormally large particles is iatrogenic pulmonary embolism. Because of this safety issue, limits have been established for the particulate size of Tc-99m MAA products. As detailed in the USP monograph for this product, more than 90% of the MAA particles must be in the size range of 10-90 μm and none of the MAA particles can be larger than 150 μm. The responsibility for meeting FDA pharmaceutical purity requirements and ensuring compliance with the specified limits rests with the manufacturer. Verification of acceptable pharmaceutical purity by the user is recommended in certain cases to meet professional practice standards.

Biologic purity refers to the quality of properties related to microorganisms and their products. Injectable radiopharmaceuticals must be sterile (ie, free of microorganisms) and apyrogenic (ie, free of bacterial endotoxins that cause fevers, etc). Methods of sterility testing and bacterial endotoxin testing are given in the USP. In brief, sterility testing involves the incubation of product samples in two growth media for 14 days; endotoxin testing involves the incubation of product samples in limulus amebocyte lysate for 1 hour. The responsibility for meeting FDA biologic purity requirements and ensuring compliance with the specified limits rests with the manufacturer. Professional practice standards mandate the use of an aseptic technique during handling by the user so that sterility and apyrogenicity will be maintained. In the special case in which compounding of a radiopharmaceutical involves the use of raw materials (eg, radiopharmaceuticals for positron emission tomography), the user is legally obligated to perform this quality control testing.

■ SUMMARY

A radiopharmaceutical is a radioactive drug: It has both a radioactive component and a drug component. Radioisotopes used in radiopharmaceuticals are produced by nuclear reactors, cyclotrons, or generators. The majority of radiopharmaceuticals are Tc-99m chelates prepared by using reagent kits. Quality control testing is used by manufacturers and users to ensure or verify appropriate radioassay and radionuclidic, chemical, radiochemical, pharmaceutical, and biologic purity.

■ SUGGESTED READINGS

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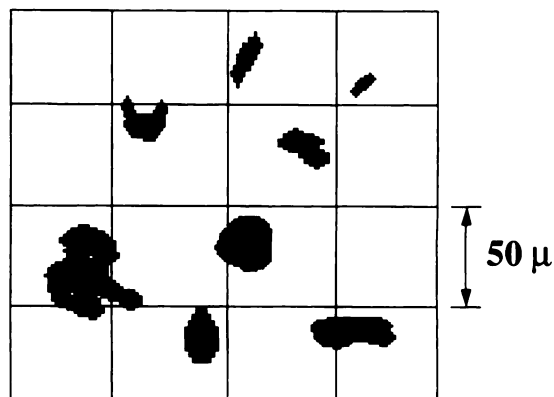

Figure 12. Microscopic determination of Tc-99m MAA particle size on a hemocytometer slide. The grid etched on the slide has a spacing of 50 μm. Relative to the grid, the MAA particles in this illustration range in size from approximately 10 μm to approximately 50 μm.

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