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Preparation and Dispensing Problems Associated with Technetium Tc-99m Radiopharmaceuticals

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STATEMENT OF OBJECTIVES

The purpose of this lesson is to increase the reader's knowledge and understanding of problems associated with the preparation and dispensing of Tc-99m radiopharmaceuticals and the corresponding effects/manifestations of these problems.

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

1. Describe common Tc-99m radiochemical impurities and their clinical manifestations.
2. Describe preparation problems associated with using Tc-99m generator eluates.
3. Describe other common problems encountered when radiolabeling Tc-99m kits.
4. Discuss the incidence of preparation problems associated with Tc-99m radiopharmaceuticals.
5. Describe common problems associated with dispensing of Tc-99m radiopharmaceuticals.

COURSE OUTLINE

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INTRODUCTION

In contrast to conventional drugs, Tc-99m labeled radiopharmaceuticals have several unique characteristics that are potentially problematic in their preparation and dispensing:

1. Their preparation involves chemical reactions that may produce undesired radiochemical impurities;
2. Their emitted radiation, especially at high intensities, may produce radiolytic effects that can result in undesired impurities;
3. Their chemical properties, especially in combination with their small mass quantities, may result in undesired adsorption to container components or interaction with trace contaminants leached therefrom.

These problems may subsequently result in unexpected alterations in biodistribution and/or inadequate localization in organs of interest, and thereby interfere with diagnostic interpretation.

The purpose of this lesson is to briefly describe many of these common problems, including the underlying causes and possible methods of minimization/avoidance. Although many of these problems have been described in past reviews on this topic,[1-4] this lesson aspires to update and reorganize such information in order to enhance understanding of the subject and to provide a ready reference.

COMMON RADIOCHEMICAL IMPURITIES AND THEIR CLINICAL MANIFESTATIONS

In addition to the desired product, Tc-99m radiopharmaceuticals may also contain various radiochemical impurities. Each of these impurities, being a different chemical species, exhibits a biodistribution in the body different from the desired radiopharmaceutical with resultant unintended localization in other various organs and tissues. Hence, depending on the specific parameters of the imaging procedure, the radiochemical impurity may interfere with diagnostic interpretation of the images by masking disease, mimicking disease, or otherwise resulting in non-diagnostic image quality. Also, radiochemical impurities may impart unnecessary radiation exposure to non-target organ(s).

The predominant radiochemical impurity associated with most Tc-99m radiopharmaceuticals is free, unlabeled Tc-99m in the chemical form of pertechnetate ion (i.e., TcO_4^-). Pertechnetate distributes throughout the vasculature and interstitial fluid, and concentrates primarily in the stomach, intestinal tract, urinary tract, thyroid gland, and salivary glands. A second radiochemical impurity associated with some Tc-99m radiopharmaceuticals is insoluble Tc-99m in the chemical form of technetium hydroxides or technetium labeled stannous hydroxide (also referred to as hydrolyzed-reduced technetium). These species are in the physical form of colloid particles which are phagocytized by cells of the reticuloendothelial system located primarily in the liver, spleen, and marrow. A third radiochemical impurity associated with a few Tc-99m radiopharmaceuticals is large aggregates of particles. Particles larger than 10 microns become physically lodged in the first capillary bed they encounter; i.e., following intravenous injection, they lodge in the pulmonary capillaries.

A variety of other radiochemical impurities may also be formed during preparation

and/or decomposition of certain Tc-99m radiopharmaceuticals. Impurities that are hydrophilic, ionized, non-protein bound, and less than 5,000 daltons molecular weight tend to be excreted in the urine by glomerular filtration.[5] On the other hand, impurities that are lipophilic, possess both polar and nonpolar groups, and have a molecular weight of 300-1,000 daltons tend to be excreted by the liver into the bile.[5] To describe yet another potential problem, Tc-99m can adventitiously radiolabel red blood cells if stannous ion and pertechnetate are both present in the circulation in sufficient concentrations.

Many of these potential problems can be detected by the routine, standard practice of performing quality control testing on each radiopharmaceutical preparation and thereby assuring that it complies with applicable specifications for purity before it is administered to patients. Unfortunately, some problems are not detectable by routinely used quality control techniques, occur after dispensing, occur *in vivo*, or are otherwise unknown at the time of use. Therefore, knowledge of common problems is essential for nuclear medicine personnel, including nuclear pharmacists, who are involved in trouble-shooting images with unexpected biodistribution.

PROBLEMS ASSOCIATED WITH Tc-99m GENERATOR ELUATES

Tc-99m generator eluates have been associated with a variety of radiopharmaceutical problems encountered during and after the radiolabeling process. Because many of these problems may be caused by more than one mechanism, and because contributing factors are generally present in combination, assignment of a problem to a single factor or mechanism is rarely appropriate. Nonetheless, understanding the effects of individual contributing factors and mechanisms aids in understanding the resulting effects that may occur in multifactorial situations.

Inadequate Stannous:Technetium Molar Ratio

Tc-99m is obtained from Mo-99/Tc-99m generators as sodium pertechnetate (i.e., $Na^{+}TcO_4^{-}$), a chemical form in which technetium (Tc) has an oxidation state, or valence, of 7+ (VII). This chemical form of Tc is relatively non-reactive and is not chelated by other ligand molecules. Hence, for nearly all Tc-99m labeled radiopharmaceuticals, the Tc(VII) pertechnetate species must first be reduced to a lower oxidation state, such as (I), (IV), or (V), using stannous ion (i.e., Sn^{2+}) as a reducing agent. Once in a reduced oxidation state, the Tc is more reactive and can be readily chelated by various ligand molecules to form Tc-99m labeled radiopharmaceuticals. For these reactions to proceed with near-complete yield, the amount of stannous reductant must be sufficient to interact with all of the pertechnetate; i.e., there must be an adequate stannous:technetium molar ratio.

One exception to this radiolabeling process is Tc-99m sulfur colloid. This particular radiopharmaceutical involves chemical covalent bonds in the formation of technetium sulfide molecules rather than coordination complexation with chelating ligands as described above.

The desired stannous:technetium molar ratio can be foiled by the presence of excessive technetium and/or by inadequate stannous, as follows:

1) Excessive Tc-99m

   An excessive amount Tc-99m pertechnetate added to a reagent vial, or kit, may result in unacceptably high amounts of residual, unreacted free pertechnetate. This problem has been reported for a variety of products, especially those kits* containing relatively small amounts of stannous ion

* throughout this article, for the sake of brevity, each "kit for the preparation of technetium Tc 99m [generic name]" is simply referred to as "[generic name]"

such as exametazime,[6] mertiatide,[7] and red blood cells.[8] However, because stannous is nominally in stochiometric excess even in these cases (see Table 1), the decreased radiolabeling is more likely related to radiolytic effects (*vide infra*) than it is to technetium mass effects.

2) Excessive Tc-99

Tc-99 is always present in Tc-99m samples. Tc-99 is a decay product of Mo-99 (approximately 14% of Mo-99 decay bypasses the metastable state [i.e., Tc-99m] and goes directly to the ground state [i.e., Tc-99]) and is also, of course, the transition product remaining after Tc-99m decay. Tc-99 has a sufficiently long half-life (i.e., 210,000 years) that its rate of decay can be considered, for practical purposes, to be negligible. The relative number of atoms in a Mo-99/Tc-99m generator during a period of in-growth is

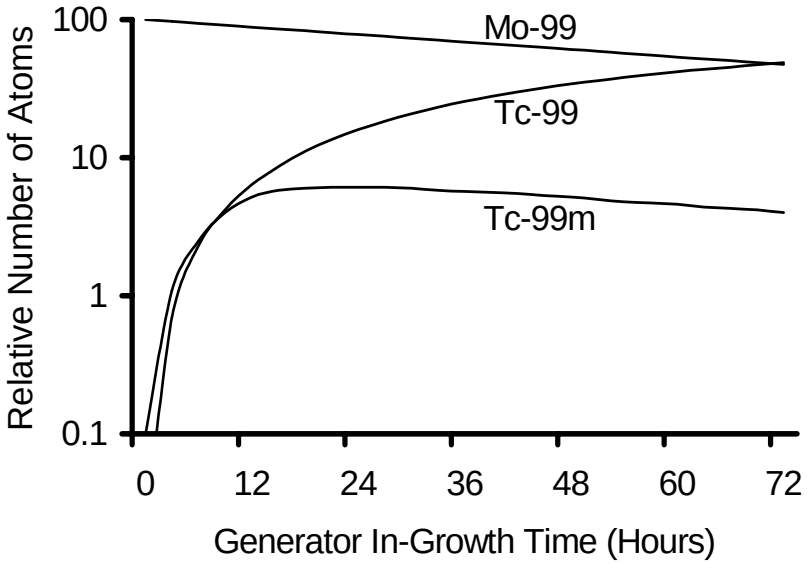
Table 1. Reductive Capacity of Selected Kits for the Preparation of Tc-99m Radiopharmaceuticals* (modeled after Verbeke[35])

Kit	$SnCl_2 \cdot 2H_2O$ (µg)	Maximum Recommended Activity (mCi Tc-99m)	Molar Ratio Sn:Tc (24-hr Generator Build-up, Fresh Eluate)	Molar Ratio Sn:Tc (24-hr Generator Build-up, 12 Hour Aged Eluate; or 72-hr Generator Build-up, Fresh Eluate)
pyrophosphate	2800	100	18,200	4550
gluceptate	700	300	1517	379
mebrofenin	465	100	3023	756
succimer	380	40	6175	1544
arcitumomab	290	30	6283	1571
disofenin	240	100	1560	390
medronate	170	200	550	138
pentetate	150	160	609	152
in vitro red cell	96	100	624	156
apcitide	89	50	1157	289
sestamibi	75	150	325	81
bicisate	72	100	468	117
aggregated albumin	70	50	910	228
depreotide	50	50	650	162
mertiatide	50	100	325	81
tetrofosmin	30	240	81	20
exametazime	7.6	54	91	23

Note: This table is not intended to provide information on all kit products and formulations; in situations where multiple formulations of a given kit are available from multiple manufacturers (e.g., pyrophosphate kits), only one representative kit is described. Package inserts for specific kits should be consulted for precise information regarding each particular kit's formulation.

shown in Figure 1. Note that Tc-99m atoms outnumber Tc-99 atoms initially, but that Tc-99 predominates after about 10 hours. One way to describe this relationship is with the use of the term mole fraction. The mole fraction of Tc-99m is defined as the number of Tc-99m atoms divided by the total number of Tc (i.e., Tc-99m plus Tc-99) atoms. A simplified list of Tc-99m mole fractions for selected combinations of generator in-growth times and eluate ages (i.e., times post-elution) is presented in Table 2.

Figure 1. Relative Number of Atoms in a Mo-99/ Tc-99m Generator.



The mole fraction of Tc-99m is essentially an indicator of specific activity. As the Tc-99m mole fraction decreases, there is a corresponding increase in the fraction of Tc-99. Tc-99, which is chemically identical to all other Tc isotopes, competes with Tc-99m for stannous reduction and chelation reactions, resulting in unacceptably high amounts of residual, unreacted free Tc-99m pertechnetate. Hence it is not surprising that excessive amounts of Tc-99, such as in the first eluate of a new generator, in the eluate of a generator with prolonged in-growth time, or in an aged eluate, can interfere with the radiolabeling of nearly all radiopharmaceuticals of this type. This problem has been reported more frequently for those kits containing relatively small amounts of stannous ion,[9] such as albumin aggregated,[10] exametazime,[6] mertiatide,[11,12] red blood cells,[8,13] and sestamibi.[14] However, because stannous is nominally in stochiometric excess even in these cases (see Table 1), radiolytic effects (*vide infra*) may also contribute to the decreased radiolabeling.

3) Oxidation of stannous ion

Stannous ion is readily oxidized to stannic ion by atmospheric oxygen, dissolved oxygen, or radiolytic products such as free radicals and peroxides which may be present in pertechnetate solutions (*vide infra*). Kits nominally contain a stochiometric excess of stannous salt lyophilized and sealed in an atmosphere of nitrogen or argon; however, introduction of these species during reconstitution (e.g., entry of air during needle puncture, dissolved oxygen present in aqueous diluent, radiolytic products in pertechnetate solutions) can oxidize stannous ion and may decrease reductive capacity below the threshold needed for a satisfactory radiolabeling process. In these situations, unacceptably high amounts of residual, unreacted free pertechnetate will result. Although oxidation of stannous ion may be problematic for any stannous-containing product, the frequency and severity of this effect is inherently more pronounced in kits, such as those listed in the previous example, that contain relatively small amounts of stannous ion.

Table 2. Mole Fractions for Tc-99m.

Generator in-growth time (hr)	Eluate age (hr)	Tc-99m Mole Fraction
24	0	0.28
24	6	0.14
24	12	0.07
48	0	0.13
48	6	0.07
48	12	0.03
72	0	0.08
72	6	0.04
72	12	0.02

Similarly, inadvertent entry of oxidizing agents used for diaphragm antisepsis prior to needle entry can result in oxidation of stannous ion. For example, unacceptably low radiolabeling of Tc-99m mertiatide has been linked to H_2O_2 contamination from use of an antiseptic product containing hydrogen peroxide to cleanse the vial diaphragm.[15]

Standardly, 0.9% sodium chloride injection (normal saline) is used for elution of Tc-99m generators and in the preparation or dilution of many Tc-99m radiopharmaceuticals. Only preservative-free normal saline should be used for these purposes because the chemicals in bacteriostatic normal saline may cause oxidation of stannous ion or reduced Tc-99m.[16,17]

A recent controversy in nuclear pharmacy practice is the fractionating (or splitting) of kits. Although originally undertaken as a cost-cutting measure, fractionating kits has also been cited as an important option for continued provision of radiopharmaceuticals in situations involving limited availability of commercial kits (e.g., extended back order).[18] Typically, fractionation entails reconstitution of the lyophilized kit with normal saline, transfer of aliquots into other containers, and storage of these aliquots for later radiolabeling. Other issues like sterility and adequate mass of active ingredient aside, fractionated vials may be especially susceptible to stannous oxidation because of inadvertent entry of atmospheric oxygen and the presence of oxygen dissolved in the normal saline diluent. Stannous ion rapidly degrades in solution at room temperature.[19] Decreased radiochemical purity, paralleling decreased stannous ion following storage of fractionated vials, appears to be especially pronounced for exametazime and mertiatide.[19] Some strategies that have been employed to minimize this problem include the use of nitrogen-purged normal saline for reconstitution, minimization of reconstitution and fractionation volumes, limitation on bore size of needles used to enter vials, maintenance of a nitrogen atmosphere in the storage containers, addition of antioxidants, storage at refrigerator or freezer temperatures, and assignment of a conservative (short) storage/beyond-use time. In some situations, augmentation of fractionated kits with supplemental stannous ion has been used to restore the reductive capacity in individual aliquots to levels adequate to provide satisfactory radiolabeling.[20]

4) Inadequate stannous ion

Administration of inadequate stannous ion is a potential problem in the process of radiolabeling red cells *in vivo*. For example, if the stannous pyrophosphate injection is partially infiltrated, the amount of stannous in the bloodstream may be insufficient to reduce all of the subsequently injected Tc-99m pertechnetate, thus preventing that fraction of Tc-99m pertechnetate from being able to radiolabel red cells. Similarly, if the stannous injection is administered through certain catheters or tubing, a substantial fraction of the stannous may bind to components of the

device and not be available for reduction of Tc-99m pertechnetate.[21] In either situation, the result will be sub-optimal radiolabeling of red cells with corresponding increased amounts of residual, unreacted free pertechnetate.

Radiolytic Effects

Radiation interacts with water molecules to produce ions, free radicals, and peroxides (see Figure 2). Hydroxyl free radicals and peroxides are capable of oxidizing stannous ion and reduced Tc, whereas aqueous electrons and hydrogen free radicals are capable of reducing many metal ions and metal complexes.[5,22] The magnitude of these effects is directly related to the radiation levels.[22-25] For example, the rate of peroxide production increases linearly with increasing activity or radioactive concentration (see Figure 3). The presence of oxygen further promotes the production of peroxides[23-25] (see Figure 4).

Figure 2. Radiation Interactions with Water.

$$\sim\!\!\sim\!\!> H_2O \longrightarrow H_2O^+ + e^-_{(aq)}$$

$$H_2O^+ \longrightarrow H^+ + OH\bullet$$

$$e^-_{(aq)} + H_2O \longrightarrow OH^- + H\bullet$$

$$OH^* + OH^* \longrightarrow H_2O_2$$

Predominant radiolytic effects can be summarized as follows:

1) Interference with radiolabeling procedure

   Hydroxyl free radicals and peroxides may interfere with Tc radiolabeling procedures because of their ability to readily oxidize stannous ion. Because production of these species is related to radiation levels, they are most abundant in highly concentrated pertechnetate solutions. Peroxides also tend to build up over time. Hence this interference is most likely when preparing products that contain relatively small amounts of stannous ion using the first eluate from a new generator, the eluate from a generator with prolonged in-growth time, or pertechnetate that has aged for several hours since elution. This interference has been reported in the radiolabeling of various kits, including aggregated albumin,[10] exametazime,[26] red cells,[13] and sestamibi.[14]

2) Decomposition and oxidation

   Hydroxyl free radicals and peroxides can interact with Tc-complexes to cause decomposition and oxidation of reduced Tc resulting in production of free pertechnetate.

   Although radiolytic decomposition and oxidation occurs with nearly all Tc-99m radiopharmaceuticals, this problem is more pronounced for those products possessing relatively weak coordination complexation bonds. High amounts of radiation promote radiolytic decomposition and oxidation because of increased production of free radicals and peroxides. Hence most products exhibit increased radiolytic production of free pertechnetate impurity when prepared with excessive amounts of radioactivity or maintained at excessive radioactive concentrations. This problem has been reported for many Tc-99m radiopharmaceuticals including, for example, Tc-99m exametazime,[27] Tc-99m gluceptate,[28] Tc-99m mertiatide,[7] and Tc-99m phosphate bone agents.[29]

   Radiolytic decomposition occurs over time, so prolonged storage will generally manifest increased production of impurities. [The expiration time of the preparation is established, in part, by the rate of radiolytic decomposition.] On the other hand, this effect can be inhibited by the presence of free radical scavengers or antioxidants which preferentially interact with the free radicals and peroxides. For

Figure 3. Rate of Peroxide Production Related to Radioactivity Levels of Tc-99m. Adapted from Molinski.[25]

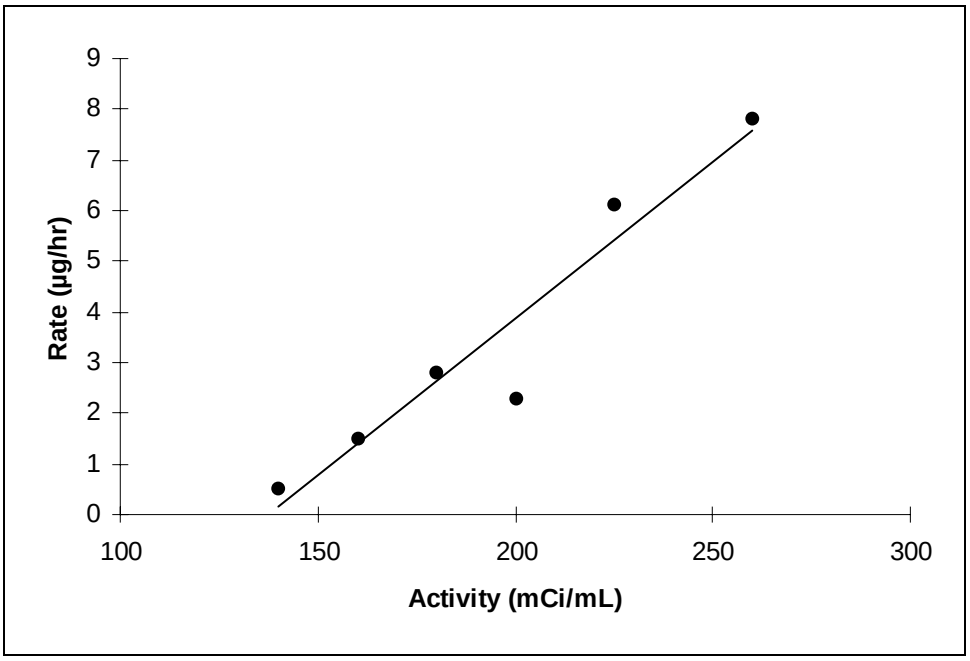
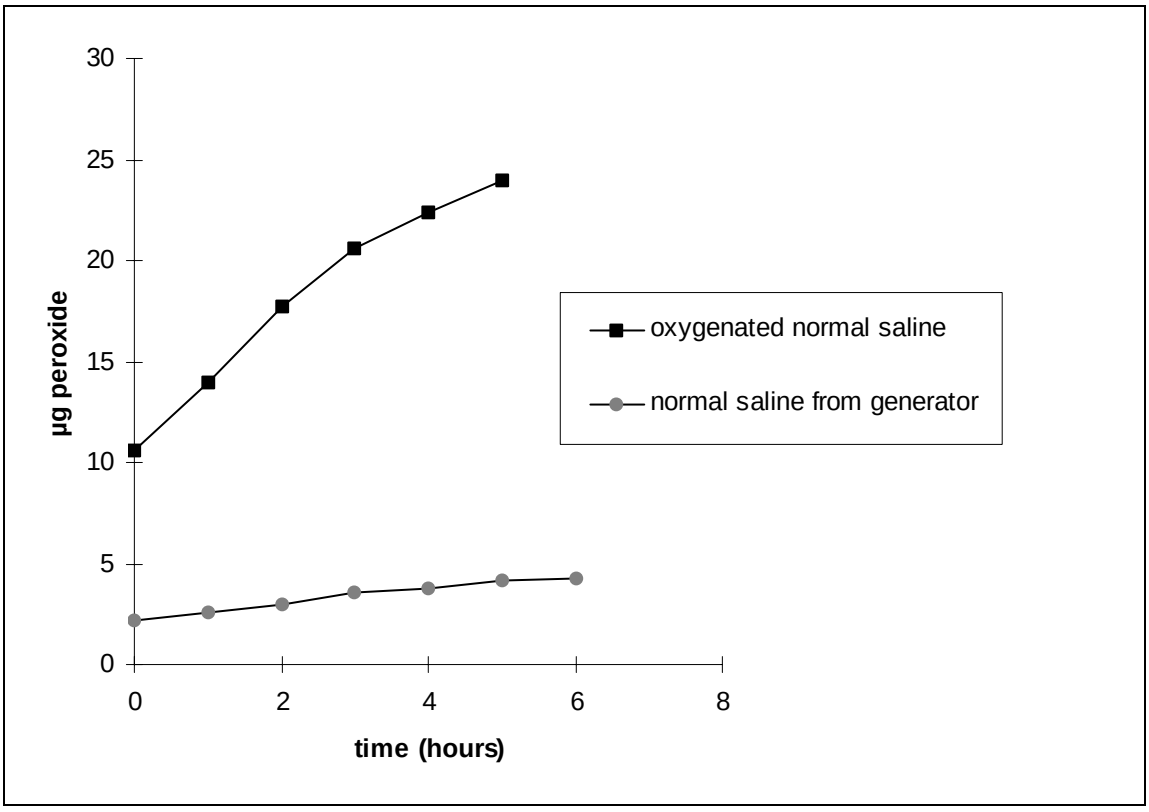


Figure 4. Effect of oxygen on the production of peroxide. Adapted from Molinski.[25]



example, ascorbic acid substantially reduces radiolytic decomposition of Tc-99m diphosphonate bone agents.[30] Radiolytic decomposition may also be inhibited by reducing the storage temperature in order to slow the rate of diffusion for the free radicals. For example, decomposition of high activity Tc-99m gluceptate preparations can be substantially slowed by storage at 2^{o} – 8^{o} C.[31]

3) Reduction

Although radiolytic decomposition and oxidation is of primary concern for most traditional Tc-99m radiopharmaceuticals, radiolytic reduction is a key mechanism in the decomposition of several newer Tc-99m radiopharmaceuticals. Aqueous electrons and hydrogen free radicals formed from the radiolysis of water are capable of reducing many metal ions and metal complexes. For example, in Tc-99m tetrofosmin, these species can reduce Tc(V) in the desired $Tc(V)O_2(tetrofosmin)_2$ complex to produce other unwanted complexes such as Tc(IV) tetrofosmin, $Tc(III)Cl_2(tetrofosmin)_2$, and $Tc(I)(tetrofosmin)_3$ [22] This excessive reduction can be minimized by avoiding high radioactive concentrations (i.e., minimizing production of reductive free radicals) and by purposeful addition of air (i.e., oxygen) to interact with these reductive species as they are formed.[22,32,33] Similarly, purposeful addition of air in the preparation of Tc-99m mertiatide stabilizes the Tc(V)oxo intermediate prior to the formation of the desired Tc(V) mertiatide and inhibits its further reduction to other unwanted complexes such as Tc(IV)mertiatide.[22,34,35]

Reductive decomposition is also a major concern for Tc-99m exametazime. The primary lipophilic complex is readily converted to a secondary hydrophilic complex via nucleophile-induced polymerization.[22] This process, involving reductive free radicals and oxy-stannous species, can be inhibited by the presence of a stabilizing agent, such as methylene blue, which is an oxidizing agent and free radical scavenger.[22]

Compromised Integrity

One manufacturer incorporates a dye-impregnated disk under the generator column inside its shielding. In the event of loss of integrity of the column seals, the eluate will come in contact with the disk and will be discolored yellow.[36,37] Hence, a yellow colored eluate indicates compromised integrity of the column and compromised sterility of the eluate. Additionally, the toxicity of the dye is unknown.[37] Therefore, any eluate exhibiting discoloration upon visual inspection should not be used in humans.

Recommendations

In order to minimize the above problems associated with Tc-99m generator eluates, a number of precautions are generally recommended for the preparation of Tc-99m radiopharmaceuticals, especially those containing relatively small amounts of stannous ion:

1) Use eluates from generators which have in-growth times of no more than 24 hours whenever possible.
2) Avoid the use of aged Tc-99m eluates, especially those more than 12 hours old.
3) Avoid adding excessive Tc-99m activity to kits.
4) Avoid maintaining excessive concentrations of radioactive solutions; i.e., dilute solutions to lower radioactive concentrations whenever possible.
5) Avoid adding air (i.e., oxygen) to vials unless otherwise directed.
6) Avoid use of bacteriostatic normal saline for preparation or dilution of Tc-99m radiopharmaceuticals.
7) Choose kit products that contain free radical scavengers or other stabilizing

agents (e.g., antioxidants) whenever available.

8) Consider storage at low temperatures (e.g., refrigeration) unless otherwise impractical.
9) Avoid the practice of fractionating kits; if fractionation is necessary, employ appropriate strategies to inhibit oxidation of stannous ion.
10) Do not use discolored eluates.

OTHER COMMON PROBLEMS INVOLVED IN RADIOLABELING KITS

Improper Heating

Several Tc-99m radiopharmaceuticals require heating as a step in their preparation. Inadequate heating, caused by insufficient incubation temperature or insufficient incubation time, may not provide the necessary energy to drive the reaction to completeness and therefore results in unacceptably high amounts of residual, unreacted free pertechnetate. This problem has been reported for a variety of Tc-99m radiopharmaceuticals, including Tc-99m mertiatide,[7] Tc-99m sestamibi,[38] and Tc-99m sulfur colloid.[39] Conversely, excessive heating may produce gas pressures inside sealed vials sufficiently high to cause rupture of the septum, ejection of the stopper, or breakage of the glass walls. This problem can be nearly eliminated by assuring that substantial negative pressure (i.e., a partial vacuum) exists in the vial prior to heating.[40]

The particle size distribution of Tc-99m sulfur colloid is also influenced by heating parameters. Minimal heating produces a particle size distribution favoring small particles, and therefore has been recommended as one procedure for preparing Tc-99m sulfur colloid suitable for lymphoscintigraphy.[41] Excessive heating, on the other hand, produces a particle size distribution favoring large particles which, if greater than 10 microns, effect embolization of pulmonary capillaries.

Improper Mixing Order

When preparing Tc-99m radiopharmaceuticals, the reducing agent (i.e., Sn^{2+}) and the chelating ligand should be mixed together before Tc-99m pertechnetate is added. If Sn^{2+} and Tc-99m pertechnetate are combined first, insoluble Tc-99m hydroxides or Tc-99m tin colloids may be formed, with resultant liver uptake.[42-47] This potential problem is obviated with the use of commercial kits, which contain a lyophilized mixture of Sn^{2+} and chelating ligands, that are to be reconstituted with Tc-99m sodium pertechnetate.

The preparation of some radiopharmaceuticals involves mixing of ingredients in a specific sequence in order to optimize the intended chemical reactions. If the sequence is not correctly followed, poor or negligible radiolabeling may result. For example, the preparation of Tc-99m sulfur colloid involves the heat-driven reaction of thiosulfate and acid to form elemental sulfur, with concurrent formation of Tc_2S_7 as a coprecipitate; phosphate buffer is added after boiling and cooling to neutralize excess acid. If the acid and buffer components are inadvertently switched, the intended reaction will not proceed and the resulting product will consist of primarily unreacted free pertechnetate with little or no Tc-99m sulfur colloid.[10]

Similarly, the *in vitro* radiolabeling of red cells involves an ordered series of steps: following incubation of blood with stannous chloride, sodium hypochlorite and citrate are added to oxidize and chelate excess extracellular stannous ion (which would otherwise interfere with radiolabeling red cells by reducing pertechnetate before it enters the cell) prior to incubation with pertechnetate. If the sodium hypochlorite is mixed with the stannous chloride prior to addition of blood, it will prematurely oxidize the stannous and thus result in a product consisting of primarily unreacted free pertechnetate with negligible radiolabeling of Tc-99m to the red cells.[10]

As stated earlier, the preparation of many Tc-99m radiopharmaceuticals includes dilution with normal saline. In addition to minimizing radiolytic decomposition, dilution is often desirable in order to optimize the volume associated with the handling and administration of a patient dosage.[48] Hence, as a matter of practice, kits reconstituted with relatively concentrated Tc-99m sodium pertechnetate are frequently post-diluted to achieve a standardized concentration or volume.[48] Moreover, reconstitution of certain kits (e.g., aggregated albumin, pentetate, sulfur colloid) with concentrated Tc-99m sodium pertechnetate followed by post-dilution with normal saline may actually improve the radiochemical purity of the final product as compared to standard preparation procedures.[49,50] For tetrofosmin, however, reconstitution with concentrated Tc-99m sodium pertechnetate followed by dilution with normal saline may produce various radiochemical impurities, due to radiolytic effects as described above that occur during the time of high radioactive concentration prior to dilution. Therefore, optimal radiolabeling of tetrofosmin requires that Tc-99m sodium pertechnetate be pre-diluted with normal saline.[32,51]

A practice-related issue associated with dilution methods is radiation dose to hands. Using two separate syringes for reconstituting reagent kits, one for normal saline and the other for Tc-99m sodium pertechnetate, rather than the standard method of using one syringe containing diluted Tc-99m sodium pertechnetate significantly reduces the radiation dose to the fingers.[52,53] The greatest reduction in finger dose is achieved with a predilution method (i.e., adding normal saline to the vial prior to adding Tc-99m sodium pertechnetate).[52,54,55] It is important to note that such a procedural alteration, when used with caution, does not significantly effect the radiochemical purity and stability of several Tc-99m radiopharmaceuticals, including Tc-99m medronate, Tc-99m mertiatide, and Tc-99m sestamibi.[55]

Reagent Concentration

For certain Tc-99m radiopharmaceuticals, improper reagent/component concentration, either too low or too high, can result in radiolabeled products of decreased radiochemical purity. For example, the rate and extent of radiolabeling red cells with Tc-99m are affected by cell concentration. The rate-limiting factor appears to be the facilitated transport of Tc-99m into red cells via the band 3 protein anionic transport system present in the cell membrane.[56] Hence, an unusually low concentration of red cells, and thus transport sites, will result in poor radiolabeling with Tc-99m. This problem has been observed in situations involving patients with severely low hematocrits, or, more commonly, low red cell concentration due an inadequate blood volume and/or an excessive Tc-99m sodium pertechnetate volume used in the *in vitro* labeling method.[8,10] Similarly, suboptimal radiolabeling of leukocytes with Tc-99m exametazime may occur when using an inadequate number of cells,[57-61] a large incubation volume (i.e., low cell concentration),[62,63] or an inadequate concentration of Tc-99m exametazime (i.e, large reconstitution volume for preparation of Tc-99m exametazime).[60,62,64,65]

For a few products, excessive reagent concentration (i.e., inadequate preparation/ dilution volume) may result in undesirable effects. Decreased radiolabeling and lessened stability of Tc-99m tetrofosmin result when total preparation volumes are smaller than directed;[66,67] production of other radiochemical impurities is due to concentration-dependent radiolytic effects as discussed above as well as reactions directly caused by tetrofosmin acting as a reducing agent. Similarly, decreased radiolabeling of Tc-99m mertiatide occurs when total preparation volumes are smaller than directed.[7] In the procedure for radiolabeling leukocytes with Tc-

99m exametazime, improved labeling efficiencies can be achieved by using a lower concentration of exametazime (e.g., one-half to one-fifth of an exametazime vial labeled with Tc-99m) compared to using the entire contents of a vial labeled with Tc-99m, in the incubating cell suspension.[68,69] Occasionally, excessive reagent concentration may also be an important factor relating to solubility. For example, an inadequate preparation volume for Tc-99m disofenin may produce cloudiness, due to precipitation of poorly soluble disofenin.[70]

Incubation/Time Delays

Although most Tc-99m chelates are formed very rapidly, some complexation reactions require substantial incubation time. In these latter reactions, radiolabeling usually follows an exponential curve, with plateaus achieved after several minutes. For example, incubation times of up to 10-20 minutes may be required to reach radiolabeling plateaus for several Tc-99m radiopharmaceuticals, including Tc-99m iminodiacetic acid derivatives for hepatobiliary imaging, Tc-99m pentetate, and Tc-99m succimer, presumably because of slow progression from the initial rapidly-formed mononuclear complex to the final dinuclear complex (dimer).[71] For albumin products, such as Tc-99m albumin aggregated, a similar incubation time is required to allow pertechnetate ions to diffuse into the protein's tertiary structure where stannous reduction and chelation takes place.[72] An incubation time of 10-20 minutes is also required for Tc-99m labeling of red cells, where the transport of pertechnetate ions across the cell membrane appears to be the rate-limiting factor.[56] Maximal radiolabeling of leukocytes with Tc-99m exametazime also requires an incubation time of about 20 minutes.[60,73] The quality of bone images is significantly improved if Tc-99m medronate is incubated at least 30 minutes before administration, apparently related to the slow formation of a complex with more rapid elimination kinetics;[74,75] brief sonication of the vial produces similar results as prolonged incubation.[76]

Many of the newer Tc-99m radiopharmaceuticals are prepared via rapid initial formation of an intermediate complex (i.e., Tc-99m weakly chelated by a transfer ligand) from which the final product is slowly formed via exchange reactions.[67] Examples of transfer ligands used in commercial kits include acetate [arcitumomab], citrate [sestamibi], edetate [bicisate, depreotide], glucoheptonate [apcitide, depreotide], gluconate [tetrofosmin], and tartrate [arcitumomab, mertiatide]. Due to relatively slow exchange reactions, incubation times of 15-30 minutes are required for preparation of Tc-99m bicisate and Tc-99m tetrofosmin. Exchange reactions can be promoted by heating, so incubation in a boiling water bath is recommended for preparation of Tc-99m apcitide, Tc-99m depreotide, Tc-99m mertiatide, and Tc-99m sestamibi to facilitate the exchange from the transfer ligand to the final product ligand. In addition to promoting exchange reactions, heating (i.e., boiling) is also needed in the preparation of Tc-99m apcitide, Tc-99m mertiatide, and Tc-99m sestamibi to cleave off protective groups and free up binding sites for complexation with Tc. Inadequate incubation may result in unacceptably large amounts of radiochemical impurities in the form of residual intermediates (i.e., transfer ligands).[67]

On the other hand, excessive incubation times or excessive time delays between preparation steps can produce undesirable effects for certain Tc-99m radiopharmaceuticals. For example, unacceptable radiochemical purity of Tc-99m mertiatide may result if there is an excessive time delay (i.e., a few minutes) before the addition of air or before the boiling step.[7] Similarly, a time delay of several minutes before adding the methylene blue stabilizer to a freshly reconstituted vial of Tc-99m exametazime may result in de-

creased radiochemical purity.[22] In these examples, excessive delays between preparation steps allow radiolytic effects to proceed relatively unimpeded and result in increased production of radiochemical impurities. In the preparation of Tc-99m sulfur colloid, an excessive delay following the addition of Tc-99m sodium pertechnetate and hydrochloric acid to the reagent vial before the boiling step may allow acid reduction of pertechnetate and formation of the chelate Tc-99m edetate (Zabel P, personal communication, July 24, 2001).

Commercial Source

The commercial source of generators, kits, and other ingredients may affect the radiochemical purity and/or the biodistribution of various radiopharmaceuticals. A specific kit that yields a highly labeled product when prepared with Tc-99m eluate from one brand of generator may demonstrate substantially lower radiolabeling when prepared with the eluate from a different manufacturer's generator. One explanation for differences may be related to the concentration of oxidizing species produced from the radiolysis of water. For example, the lower labeling efficiency of Tc-99m sestamibi observed when prepared with the eluate from a wet-column generator is likely related to oxidation of stannous by oxidizing species formed from radiolysis of water in the generator column.[14] Other factors, however, may be involved in certain situations. For instance, the poor labeling efficiency of Tc-99m mertiatide reported with the use of one company's generator[7] was traced to the presence of chemical contaminants leached from its vial stoppers. Similarly, the poor radiochemical purity of some Tc-99m antibody conjugates prepared with pertechnetate eluates from certain generators was shown to coincide with the presence of 2-mercaptobenzothiazole, a chemical used in manufacturing the non-halogenated butyl stoppers of the collection vials.[77]

In addition to generator elution vials, other vials with different compositions, presumably as a result of different chemicals leached therefrom, may be implicated in poor radiolabeling reactions. For example, significant differences in the stability of stannous chloride solutions have been observed in vials with different types of elastomeric closures.[78] Also, poor radiolabeling of Tc-99m exametazime, of Tc-99m red cells, and of Tc-99m mertiatide have been associated with certain sources of normal saline used for dilution.[12,26,61,79,80] This interference may be explained, albeit not yet substantiated, by the oxidizing effects of free radicals formed from organic substances (e.g., butylated hydroxytoluene) leached from the plastic.[81]

Even with comparable radiolabeling yields, kits from different commercial sources may result in significant differences in biodistribution and elimination kinetics. For example, various Tc-99m pentetate products exhibit significant differences in protein binding and glomerular filtration rates.[82] The frequency of gastric, hepatic, gallbladder, and intestinal localization is greater with unstabilized Tc-99m medronate products than with Tc-99m medronate products stabilized with antioxidants such as ascorbic acid.[83,84] Also, variations in lung-to-background ratios for Tc-99m aggregated albumin products may be related to differences in particle size distribution and/or soluble radiochemical impurities that are not detected with usual thin layer chromatography tests.[85,86]

Bacteriostatic Preservatives

Because sterility of products for parenteral administration is essential, it might be surmised that bacteriostatic normal saline be used in the preparation and dilution of injectable radiopharmaceuticals. Unfortunately, bacteriostatic normal saline used in the preparation of many Tc-99m radiopharmaceuticals may adversely affect their radiochemical purity, stability, and biodistribution. For example, dilution of Tc-99m pertechnetate with

bacteriostatic normal saline has been reported to produce an increased percentage of insoluble, colloid impurities.[17,87] Biodistribution studies using Tc-99m medronate prepared with bacteriostatic normal saline, in comparison to preparation with preservative-free normal saline, found significantly lower uptake in the skeleton with correspondingly higher uptake in other organs such as blood, muscle, and liver.[17,87]

Most of these effects can be traced to reactions with benzyl alcohol, the most commonly used preservative in bacteriostatic normal saline. In addition to its oxidizing effects described earlier, it is theorized that benzyl alcohol may be transformed by radiolytic oxidation to benzaldehyde, a weak reducing agent, which may be capable of reducing pertechnetate to lower oxidation states with the resultant formation of hydrolyzed-reduced technetium.[87] Because of these potential deleterious effects, only preservative-free normal saline should be used in the preparation of Tc-99m radiopharmaceuticals.

Possible contamination of generator columns or eluates with bacteriostats from needle protectant vials could potentially interfere with elution yield or radiolabeling of kits. For example, isopropyl alcohol contamination of alumina generator columns can substantially decrease expected elution yields of Tc-99m sodium pertechnetate,[88,89] and unacceptably low radiolabeling of mertiatide kits has been linked with generator eluates contaminated with bacteriostats from the guard vial.[15] The use of 0.2% parabens as a bacteriostat for generator needle covers, however, appears to be suitable with no deleterious effects on generator performance and no effects on the radiochemical purity when used to radiolabel aggregated albumin, mertiatide, pyrophosphate, sestamibi, or tetrofosmin kits.[89]

Other Diluents

Because of potential deleterious effects from bacteriostatic agents as described above, preservative-free normal saline is the standard solution used in the preparation Tc-99m radiopharmaceuticals. Other stock intravenous solutions, such as 5% dextrose injection or 5% dextrose and 0.45% sodium chloride injection, should not be used for this purpose. For example, preparation of Tc-99m medronate and Tc-99m mebrofenin using Tc-99m pertechnetate diluted with 5% dextrose injection can result in abnormally high activity in kidneys, cardiac blood pool, and soft-tissue background.[90] This altered biodistribution has been ascribed to the competitive formation of Tc-99m dextrose during the radiolabeling process. It is interesting to note, however, that the radiolabeling of Tc-99m tetrofosmin does not appear to be affected by 5% dextrose injection, presumably because ligand exchange reactions favor the transchelation of technetium by tetrofosmin.[90]

Leukocytes labeled with Tc-99m exametazime are typically resuspended in cell-free plasma for subsequent patient administration. Although resuspension in other solutions, such as certain salt solutions, may somewhat improve the labeling efficiency,[91] a plasma environment is beneficial for the functional integrity of the leukocytes.[92] Furthermore, patient procedures using Tc-99m leukocytes suspended in plasma demonstrate less non-specific bowel uptake compared to those using Tc-99m leukocytes suspended in other media.[93]

Aluminum

Excessive concentrations of aluminum contamination, generally related to breakthrough from alumina generator columns, may interact with several Tc-99m radiopharmaceuticals via chemical reactions. Examples of these interactions with aluminum include Tc-99m diphosphonates (colloidal precipitation resulting in liver localization), Tc-99m pentetate (dissociation resulting in alterations in glomerular filtration measurements), Tc-99m sodium pertechnetate (complexation resulting in decreased thyroid up-

take and prolonged soft tissue retention), Tc-99m red cells (agglutination), and Tc-99m sulfur colloid (flocculation resulting in pulmonary microembolism).[3] Excessive aluminum contamination was frequently a problem with generators produced using low specific activity Mo-99 obtained from neutron activation of Mo-98 that required relatively large alumina columns.[25] Modern generators are produced using high specific activity Mo-99 obtained as a fission byproduct that require much smaller alumina columns.[25] Because of this change and other improvements in generator manufacturing processes that consistently ensure compliance with United States Pharmacopeia limits for aluminum contamination, excessive aluminum contamination is extremely rare nowadays and these problems are now essentially of historical significance.[25]

Filtration

The performance of lymphoscintigraphy and sentinel node localizations using conventional Tc-99m sulfur colloid may be limited by retention of large particles (i.e., > 100-200 nanometers) at the site of injection.[94-98] Therefore, the use of "filtered" Tc-99m sulfur colloid (i.e., obtained from filtration of Tc-99m sulfur colloid through 0.1 or 0.22 micron filters) has become standard practice in many settings for use in lymphoscintigraphy procedures. Because only a fraction of the Tc-99m sulfur colloid particles passes through the filter whereas all of the free pertechnetate in the sample passes through the filter, the percentage of free pertechnetate in the filtrate will be higher than in the original sample.[94,99] Excessive free pertechnetate impurity may interfere with lymphoscintigraphy because it can be absorbed into the blood rather than flowing through the lymphatic channels and localizing in lymph nodes.

Specific Activity/Mass

The specific activity of some Tc-99m radiopharmaceuticals may have important effects on their biodistribution. The effects of low specific activity (excessive mass) on radiopharmaceutical biodistribution are most pronounced when the mechanism for localization involves saturatable processes involving a limited number of receptor sites, transport systems, enzymes, or other interactive biological substances responsible for the localization. In these circumstances, target-to-background radioactivity ratios will decrease as saturation occurs.

For example, administration of an excessive number of Tc-99m damaged red cells in certain clinical situations may overload the sequestering ability of the spleen.[100] Administration of an excessive number of Tc-99m sulfur colloid particles (i.e., low specific activity Tc-99m sulfur colloid) for lymphoscintigraphy may result in less radioactivity localized in lymph nodes.[101] Additionally, progression of radioactivity on to second tier nodes may be observed when large numbers of particles pass into sentinel nodes, presumably due to saturation of phagocytic function in the sentinel nodes.[95,98] Hence, use of Tc-99m sulfur colloid prepared with high specific activity may offer some advantages for lymphoscintigraphy.[101]

On the other hand, excessive specific activity may also effect the biodistribution of certain Tc-99m radiopharmaceuticals. For example, administration of inadequate peptide mass of Tc-99m apcitide may result in decreased accuracy for detection of deep vein thrombosis.[102] Therefore, preparation of all Tc-99m radiopharmaceuticals should involve procedures that address specific activity as appropriate.

Summary of Preparation Problems

A listing of many reported problems associated with preparation of current Tc-99m radiopharmaceuticals is presented in Appendix 1.

INCIDENCE OF PREPARATION PROBLEMS

The actual incidence of preparation problems for Tc-99m radiopharmaceuticals is unknown. It varies, of course, from site to site, depending on many variables such as the particular products used, type and extent of deviations from package insert instructions for preparation, and staff knowledge and experience. Hence, isolated reports and limited surveys are unlikely to be representative of general practice. Moreover, problems are substantially under-reported to voluntary reporting systems; for example, a total of only 40 instances of poor radiochemical purity of radiopharmaceuticals was reported in Europe throughout the years 1988-1995.[4] Therefore, these problems are undoubtedly much more frequent than generally appreciated.

Survey studies attempt to provide somewhat more perspective as to the incidence of problems. For example, the number of Tc-99m radiopharmaceuticals with unacceptable radiochemical purity has been reported, by seven individual sites, to be in the range of 0.2 - 0.8%.[10,103,104] However, as discussed above, these results cannot be extrapolated to other locations and situations. For instance, in certain circumstances, the radiolabeling failure rate for one Tc-99m radiopharmaceutical was reported to be 100%![14]

In a 13-month study of factors affecting Tc-99m mertiatide kit failures, an overall incidence of unacceptable radiolabeling of 25% was observed.[12] Radiolabeling failures were associated with the use of Tc-99m sodium pertechnetate obtained as the first eluate from a new generator, the use of normal saline obtained from certain plastic ampules, and certain lots of manufactured mertiatide kits.

The incidence and probable causes of substandard Tc-99m radiopharmaceuticals have been followed for many years at the University of Iowa Hospitals and Clinics' nuclear medicine department, where radiopharmaceuticals are routinely prepared for in-house use. During the seventeen-year period of 1986-2002, there were 77 out of 29,927 (0.26%) Tc-99m radiopharmaceutical preparations that were substandard (see Table 3). Most of these preparation problems involved kits containing relatively small amounts of stannous ion: aggregated albumin, exametazime, *in vitro* red cells, and mertiatide. The majority (64%) of the substandard preparations were associated with the use of Tc-99m sodium pertechnetate obtained from a generator with >48 hours build-up (e.g., new generator) and/or Tc-99m sodium pertechnetate aged more than 12 hours (e.g., evening call back situation). Hence, the presence of excessive Tc-99 (i.e., a low mole fraction of Tc-99m) and the presence of excessive products from the radiolytic ionization of water appear to be important reasons for substandard radiolabeling. However, because preparations of high quality were frequently produced when several different kits were prepared using Tc-99m sodium pertechnetate from a generator with >48 hours build-up and/or Tc-99m sodium pertechnetate aged >12 hours, other factors such as trace contaminants and lot variability must also play important roles in the radiolabeling reactions. Additionally, some preparation problems, such as improper mixing order or inadequate heating, resulted from human error or inattention to written procedures.

Prior to circa 1985, package inserts for Tc-99m generators did not state an expiration time for the eluate, while the United States Pharmacopeia specified a maximum expiration time for Tc-99m sodium pertechnetate of 48 hours.[105] Hence, expiration times (up to a maximum of 48 hours) for Tc-99m eluates were often established based on the Mo-99 concentration therein.[106] Currently, however, package inserts for Tc-99m generators state the expiration time for an eluate to be 12 hours. Use of a Tc-99m eluate after 12 hours may be considered to be a deviation from package insert instructions.[107]

Table 3. Incidence and Probable Causes of Substandard Tc-99m Radiopharmaceuticals Prepared at the University of Iowa 1986-2002.

Product	Number of Substandard Preparations (% of Substandard Preparations)	Number of Substandard Problems per Probable Causative Factor			
		Pertechnetate from a Generator with >48 Hours Build-up	Pertechnetate Aged >12 Hours	Both >48 Hours Generator Build-up and Aged >12 Hours	Other
Tc-99m aggregated albumin	43 (56%)	14	16	9	1 – defective vial (no particles) 3 – pertechnetate aged >6 hours
Tc-99m *in vitro* red cells	12 (16%)	1	1	3	1 – wrong mixing order (syringes I and II reversed) 1 – excessive volume (4 mL Tc 99m) 2 – inadequate red cell concentration (patient hematocrit <30%) 1 – excessive hemolysis during blood withdrawal 1 – blood obtained from whole blood transfusion bag 1 – unknown
Tc-99m exametazime	5 (6%)	–	–	–	1 – Tc-99m aged >6 hours 4 – unknown (first few production lots when initially marketed)
Tc-99m mertiatide	4 (5%)	1	–	–	2 – inadequate heating 1 – unknown
Tc-99m sulfur colloid	4 (5%)	–	–	–	2 – wrong mixing order (acid and buffer reversed) 1 – excessive volume (inadequate heating?) 1 – unknown
Tc-99m disofenin	3 (4%)	1	1	–	1 – unknown
Tc-99m sestamibi	3 (4%)	–	–	–	2 – inadequate heating 1 – delay >10minutes before heating
Tc-99m tetrofosmin	2 (3%)	2	–	–	
Tc-99m depreotide	1 (1%)	–	–	–	1 – unknown

In summary, the incidence of substandard Tc-99m radiopharmaceuticals encountered in clinical practice is generally low, although it is variable among products, personnel, and practices. A substantial fraction of the problems that have been reported tend to involve the use of Tc-99m pertechnetate containing excessive amounts of Tc-99 and/or oxidizing impurities to prepare kits that contain relatively small amounts of stannous ion. Other reported problems have been the result of human procedure error. Also, intentional deviations from package insert instructions can potentially be an important cause of substandard preparations. Therefore, a routine quality control program involving testing for radiochemical purity before patient administration should be adopted as a standard of practice. Moreover, such quality control testing, at least for older products, has been shown to be cost effective.[104]

DISPENSING PROBLEMS

As stated in the introduction, some problems are not related to preparation factors but rather are related to subsequent dispensing activities. (In this context, dispensing refers to activities associated with the provision of individual patient doses withdrawn from previously prepared products.) Like the product preparation problems described above, depending on the specific radiopharmaceuticals and the specific parameters of the imaging procedure, these dispensing problems may interfere with diagnostic interpretation of the images by masking disease, mimicking disease, or otherwise resulting in non-diagnostic image quality, or may impart unnecessary radiation exposure to non-target organ(s).

Decomposition During Storage

Decomposition of radiopharmaceuticals is characterized by four mechanisms: internal radiation effects (i.e., radiation emitted from one molecule directly affecting that same molecule), direct radiation effects (i.e., radiation emitted from one molecule directly affecting a different molecule), indirect radiation effects (i.e., radiation emitted from one molecule indirectly affecting a different molecule), and nonradiolytic chemical effects (e.g., hydrolysis). Of primary significance in Tc-99m radiopharmaceutical solutions are the indirect radiation effects resulting from the ionization of water (*vide supra*). Decomposition of virtually all Tc-99m radiopharmaceuticals will occur if sufficient time is allowed; however, the rate of decomposition varies widely from one Tc-99m radiopharmaceutical to another and from one preparation and/or storage factor to another. Therefore, in addition to following proper preparation and storage recommendations, Tc-99m radiopharmaceuticals should be used as soon after preparation as possible to avoid decomposition problems.

Dispensing Tc-99m radiopharmaceuticals in plastic syringes, rather than in glass vials, is commonplace. It should be noted, however, that the radiochemical purity of many Tc-99m radiopharmaceuticals may decrease more rapidly when stored in plastic syringes compared to glass vials.[108,109] The mechanism of this effect is not well defined, but may be related to greater oxygen permeability of plastic or leaching of certain chemicals from the plastic or rubber plunger tip. In certain circumstances, this faster rate of decomposition in plastic syringes may necessitate assigning a shorter expiration time.[109] Therefore, the stability of each particular Tc-99m radiopharmaceutical in each particular syringe should be ascertained so as to assign a revised expiration time if appropriate.

For Tc-99m radiopharmaceuticals involving living cells, prolonged storage or excessive delay before reinjection may lead to decreased cell viability and functional localization, as has been observed with In-111 labeled leukocytes.[110,111] Also, Tc-99m steadily elutes out of Tc-99m [exametazime] leukocytes over time.[112,113] Therefore, Tc-99m leukocytes should be reinjected as soon as

possible after the radiolabeling procedure is complete.

Agitation

Agitation, including that caused by transportation, may have deleterious effects on several radiopharmaceuticals. Excessive agitation of Tc-99m radiopharmaceutical solutions may enhance radiolytic decomposition and oxidation by increasing the air/water interface and promoting the dissolution of atmospheric oxygen in the solution.[114] This appears to be especially important for Tc-99m radiopharmaceuticals that contain small amounts of stannous ion, such as exametazime.[115] For Tc-99m radiopharmaceuticals containing soluble protein (e.g., albumin, antibodies), excessive agitation can result in the production of foam and encourages denaturation, aggregation, and precipitation.[114] Vigorous agitation of Tc-99m sulfur colloid can result in a substantial increase in mean particle size.[116] Agitation may also result in a greater fraction of Tc-99m sestamibi and Tc-99m antibodies adhering to the walls of the vial.[114,117] For radiolabeled blood cells, excessive agitation during transportation may damage the cells and cause leaching of Tc-99m from them.[118] Therefore, care must be taken during transportation to avoid excessive agitation.

Sedimentation of Particles

Particulate radiopharmaceuticals for perfusion lung imaging tend to settle or sediment with time. The rate of sedimentation is variable, and depends in large part on the particular manufactured product.[119] Therefore, before a dosage is withdrawn, the vial should be gently inverted several times to resuspend the particles. Failure to do this may result in withdrawal of an unexpectedly low activity per volume, a slightly higher percentage of free Tc-99m pertechnetate impurity in the withdrawn dosage, and/or an inadequate number of particles of optimal lung imaging. Similarly, Tc-99m aggregated albumin products may settle in syringes (e.g., unit doses) especially if substantial time elapses between dosage preparation and patient administration. If the syringe is stored needle-down, and then the needle is changed immediately prior to injection, a substantial portion of the dose may be lost in the discarded needle (Quinton T, personal communication, September 15, 2003). Therefore, syringes containing Tc-99m aggregated albumin should be stored on their sides or needle-up, and the syringe should be inverted a few times prior to administration to resuspend particles that may have settled during storage. Note: such resuspension must be gentle because vigorous agitation or shaking will result in the formation of foam in the vial.

Adsorption to Container Walls

Some Tc-99m radiopharmaceuticals have a tendency to adsorb over time to the surface of glass storage vials, thus resulting in unexpectedly low activity per volume and a slightly higher percentage of free Tc-99m pertechnetate impurity. This phenomenon has been reported for several Tc-99m radiopharmaceuticals, including Tc-99m aggregated albumin,[120,121] Tc-99m sestamibi,[117] Tc-99m succimer,[122] and Tc-99m sulfur colloid.[120,123] Tc-99m tetrofosmin also adsorbs to the walls and rubber stopper of glass storage vials, with increased adsorption related to storage time, contact between the solution and the rubber stopper, agitation, and low concentration of tetrofosmin.[124]

Many Tc-99m radiopharmaceuticals have a tendency to adsorb to the surface of plastic syringe barrels and/or the tips of their plungers, thus resulting in unexpected reductions in the dosage actually administered. In some situations, this unexpected reduction in administered dosage may be significant and potentially result in images of non-diagnostic quality. The fraction of Tc-99m radiopharmaceutical retained in the syringe is highly variable, and is influenced by excipients in the formulation, the type and composition of

the syringe, the length of time in the syringe, and amount of agitation.[125-127]

Relatively low syringe retention occurs with most Tc-99m radiopharmaceuticals, including Tc-99m bicisate, Tc-99m exametazime, Tc-99m medronate, Tc-99m mertiatide, Tc-99m oxidronate, Tc-99m pentetate, Tc-99m sodium pertechnetate, and Tc-99m succimer.[126-128] However, significant syringe retention (e.g., 10-50%) can be observed in some combinations of radiopharmaceutical product, syringe product, and storage conditions for Tc-99m aggregated albumin,[121,126,127,129] Tc-99m sestamibi,[126,130,131] and Tc-99m tetrofosmin.[125-127,132] Enhanced retention of lipophilic myocardial perfusion radiopharmaceuticals in syringes constructed with elastomeric plunger tips appears to be related to greater adsorption to the elastomeric component of the plunger.[126,127,132] For Tc-99m sestamibi, flushing the syringe with normal saline may remove up to 70% of this retained activity.[131] Nonetheless, syringe products that demonstrate unacceptably high retention of specific radiopharmaceuticals should not be used for dispensing of those radiopharmaceuticals.

Interaction with Container Components

Occasionally a Tc-99m radiopharmaceutical can interact with a container component or with chemical contaminants leached therefrom. For example, administration of stannous pyrophosphate through certain catheters or tubing for *in vivo* red cell labeling may result in substantial binding of stannous to the walls of the device and thereby produce poor radiolabeling of red cells with corresponding increased amounts of residual, unreacted free pertechnetate.[21] In some instances, chemical impurities leached from the rubber tips of plungers in certain syringes can be labeled with Tc-99m and subsequently show kidney localization.[133] A similar problem has been reported that involved the formation of a sticky glue-like substance inside a syringe containing a Tc-99m iminodiacetic acid hepatobiliary agent, but which did not occur when a different brand of syringe was used.[4]

Interaction with Antiseptics

Another problematic interaction relates to the inadvertent entry of antiseptic solution into the Tc-99m radiopharmaceutical vial during needle puncture. When the vial diaphragm is swabbed with excessive antiseptic, a small puddle often remains on the surface of the rubber septum. If sufficient time is not allowed for complete evaporation or drying, a small volume of the antiseptic may enter the vial when penetrated with a needle. This antiseptic contamination may then react or interfere with the radiopharmaceutical contents.

Various detrimental interactions due to contamination with antiseptics have been reported. Povidone-iodine (a complex of iodine and polyvinyl pyrrolidinone) has been reported to inhibit the Tc-99m sulfur colloid labeling reaction to result in products with unacceptably low radiochemical purity.[134] Chlorhexidine acetate has been reported to have caused the aggregation of Tc-99m sulfur colloid particles with consequent pulmonary embolization.[135] Chlorhexidine gluconate has been associated with kidney localization, which is thought to be from formation of Tc-99m gluconate.[135] An antiseptic solution of chlorhexidine and cetrimide has been reported to cause colloidal precipitation of Tc-99m succimer with consequent uptake in liver and spleen.[136] Isopropyl alcohol has been noted to cause a time-related breakdown of Tc-99m oxidronate with consequent uptake of free pertechnetate in the stomach.[137] Isopropyl alcohol can also interfere with elution of Tc-99m sodium pertechnetate from generator systems, whereas parabens do not.[88] A mixture of hydrogen peroxide and isopropyl alcohol has been reported to produce poor radiochemical purity of Tc-99m mertiatide because of stannous oxidation by peroxide.[15]

Based on these reports, it is recommended that antiseptics known to cause problems with certain radiopharmaceuticals be avoided for those products. Generally, alcohol antiseptics (e.g., 70% ethanol or isopropanol) are preferred over those containing iodine or other strong oxidizing agents. With the use of any antiseptic, it is essential that excessive pooling on the septum surface be avoided, and that the antiseptic solution be allowed to dry completely before any needle puncture is performed.

Summary of Dispensing Problems

A listing of many reported problems associated with dispensing of current Tc-99m radiopharmaceuticals is presented in Appendix 2.

CONCLUSION

This review was intended to describe many of the preparation and dispensing problems associated with Tc-99m radiopharmaceuticals, including the underlying causes and possible methods of minimization/avoidance. The reader is encouraged to apply these factors to explore potential problems that are likely to be encountered with other radiopharmaceuticals, especially new agents, or when deviating from package insert instructions for preparation of established products. Nonetheless, preparation problems that are detected by quality control testing and unexpected or unexplainable cases of altered radiopharmaceutical biodistribution will occasionally occur, and these should be monitored closely and documented by the healthcare professionals involved. It is important that these product-related problems be reported to the manufacturers and to the regulatory agencies (e.g., via MedWatch: The FDA Medical Products Reporting Program), and, as appropriate, disseminated in professional communications. The widespread reporting of such problems in a timely manner will contribute to improved safety and efficacy of radiopharmaceuticals.

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APPENDIX 1. REPORTED PROBLEMS ASSOCIATED WITH PREPARATION OF CURRENT TC-99M RADIOPHARMACEUTICALS

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
99mTc-generators	source of alumina (contains reducing agents)	↓ pertechnetate yield	Molinski VJ. *Int J Appl Radiat Isot* 1982;33:811-819.
	source of plastic components (leaches plasticizers, produces reducing gases)	↓ pertechnetate yield	Boyd RE. *Int J Appl Radiat Isot* 1982;33:801-809. Molinski VJ. *Int J Appl Radiat Isot* 1982;33:811-819.
	bacteriostats such as benzyl alcohol (accelerate radiation induced reduction)	↓ pertechnetate yield	Molinski VJ. *Int J Appl Radiat Isot* 1982;33:811-819.
	reflux of isopropyl alcohol through elution needle down into the column	↓ pertechnetate yield	Anon. *Eur J Nucl Med* 1996;23:BP27-BP31. Professional Services staff. personal communication. St. Louis:Mallinckrodt Medical. June 18, 1997. Anon. *Eur J Nucl Med* 1999;26:BP33-BP38. Bushman MJ, et al. *J Nucl Med* 2000;41(suppl):251P. Anon. *Eur J Nucl Med* 2002;29:BP13-BP19.
	obstruction or kinking of tubing inside generator	↓ pertechnetate yield	Anon. *Eur J Nucl Med* 1996;23:BP27-BP31.
	exposure to extreme cold (frozen eluent)	↓ pertechnetate yield	Anon. *Eur J Nucl Med* 1996;23:BP27-BP31.
	residual moisture in a "dry column" generator	↓ pertechnetate yield	Anon. *Eur J Nucl Med* 1996;23:BP27-BP31.
	inadequate vacuum in elution vial	↓ yield	Anon. *Eur J Nucl Med* 1995;22:BP29-BP33.
	interlot variability	↑ Mo-99 breakthrough	Anon. *Eur J Nucl Med* 1996;23:BP27-BP31.
	discolored eluate	indicator of compromised integrity/sterility	Hung JC. *J Nucl Med* 2001;42:827-828. Taylor MR, et al. *J Nucl Med* 2001;42:828-829.
99mTc-pertechnetate	Al+3	sustained blood pool activity	Shukla SK, et al. *Eur J Nucl Med* 1977;2:137-141. Wang TST, et al. *J Nucl Med* 1978;19:381-383.
	stannous ion	↑ liver and spleen uptake	Subramanian, et al. *J Nucl Med* 1970;11:365-366. Francis MD, et al. *Int J Nucl Med Biol* 1981;8:145-152.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	preparation/dilution with bacteriostatic saline	↑ blood pool, liver, and spleen activity	Study KT, et al. *J Nucl Med Technol* 1981;9:115-116.
99mTc-antibodies	variability in commercial source of antibody (damage during purification)	alterations in liver and/or kidney uptake	Louw WKA, et al. *Eur J Nucl Med* 1993;20:96-100.
	preparation with first eluate of a new generator and/or use of "aged" eluate	↓ radiochemical purity	Decristoforo C, et al. *Eur J Nucl Med* 1993;20:565-566. McGhee B. Presentation at the American Pharmaceutical Annual Meeting, Los Angeles, CA, Mar. 8, 1997.
	variations in incubation times and temperatures	↓ radiochemical purity	McGhee B. Presentation at the American Pharmaceutical Annual Meeting, Los Angeles, CA, Mar. 8, 1997.
	"rough" mechanical handling during reconstitution	antibody denaturation or aggregation; ↑ liver uptake	Reske Sn, et al. *Eur J Nucl Med* 1990;17:38-41. Grabenstein JD. *Hosp Pharm* 1996;31:1387-1401.
	shaking (↑ air/water interface)	air oxidation, ↓ radiochemical purity; ↑ adsorption to container	Grabenstein JD. *Hosp Pharm* 1996;31:1387-1401.
	incomplete dissolution of ligand	↓ radiochemical purity	McGhee B. Presentation at the American Pharmaceutical Annual Meeting, Los Angeles, CA, Mar. 8, 1997.
	settling with prolonged storage (failure to resuspend)	↓ withdrawn activity	Grabenstein JD. *Hosp Pharm* 1996;31:1387-1401.
	commercial source of vials (thio impurities are leached from the stoppers of some brands of evacuated vials)	↓ radiochemical purity	Sanderson JA, et al. *J Nucl Med* 1991;32:1102. McGhee B. Presentation at the American Pharmaceutical Annual Meeting, Los Angeles, CA, Mar. 8, 1997.
	column filtration performed at excessive rate of flow	↓ radiochemical purity and/or yield	McGhee B. Presentation at the American Pharmaceutical Annual Meeting, Los Angeles, CA, Mar. 8, 1997.
	method of radiolabeling	differences in blood clearance, liver uptake, kidney/urinary excretion	Hnatowich DJ, et al. *J Nucl Med* 1993;34:109-119.
99mTc-apcitide	inadequate peptide mass administered	↓ accuracy for detection of deep vein thrombosis	Aten EM, et al. *Eur J Nucl Med* 1997;24:947.
99mTc-albumin aggregated (MAA)	soluble protein	↑ blood pool activity	McLean JR, et al. *J Nucl Med Technol* 1977;5:28-31. McLean JR, et al. *Int J Nucl Med Biol* 1979;6:142-143.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	particles with size smaller than capillaries and/or Tc-99m labeled albumin	↑ liver uptake and/or hepatobiliary excretion	Subramanium G, et al (eds). *Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1975; 267-281. McLean JR, et al. *J Nucl Med Technol* 1977;5:28-31. Arroyo A, et al. *J Nucl Med Technol* 1994;22:122. Arroyo A, et al. *Clin Nucl Med* 1997;22:42-45.
	clumping of particles	focal hot spots in lungs	McLean JR, et al. *J Nucl Med Technol* 1977;5:28-31. Strout B, et al. *Monthly Scan* 1978;December:1-2.
	mean particle size	differences in biologic half-life in lungs	Vinberg N, et al. *Nucl Med Commun* 1990;11:719-720.
	inadequate number of particles	perfusion defects, especially peripheral patchiness	Heck LL, et al. *Radiology* 1974;113:675-679. Dworkin HJ, et al. *J Nucl Med* 1977;18:260-262.
	excessive number of particles	↑ risk of toxicity	Heck LL, et al. *Radiology* 1974;113:675-679. Dworkin HJ, et al. *J Nucl Med* 1977;18:260-262.
	preparation with first eluant from a new generator	↑ free pertechnetate	Ponto JA. *J Nucl Med Technol* 1998;26:262-264.
	preparation with "aged" pertechnetate	↑ free pertechnetate; ↑ uptake in thyroid, stomach, breasts	Ponto JA. *J Nucl Med Technol* 1998;26:262-264. Sherigar RM, et al. *Clin Nucl Med* 1998;23:700-701.
	mixing order	↑ free pertechnetate	Bolstad DM, et al. *J Nucl Med Technol* 1992;20:109.
	inadequate incubation time	↓ radiochemical purity	Vanbilloen HP, et al. *Eur J Nucl Med* 1993;20:465-472. Cheng KT, et al. *J Nucl Med Technol* 1994;22:173-177.
	excessive volume of pertechnetate and/or normal saline	↓ rate of labeling, ↓ radiochemical purity	Cheng KT, et al. *J Nucl Med Technol* 1994;22:173-177.
	commercial source of kits	variable radiochemical purity	Levit N. *Monthly Scan* 1979;November:1. Callahan RJ, et al. *J Nucl Med Technol* 1986;14:206-209. Rose MR, et al. *Eur J Nucl Med* 1997;24:89-90.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	commercial source of kits	differences in mean particle size and particle size distribution	Redfern MG, et al. *J Nucl Med Technol* 1996;24:165. Mallol J, et al. *Nucl Med Commun* 1997;18:87-88.
	commercial source of kits and/or containers	differences in adsorption of particles to vial or syringe	Palmer AM. *Nucl Med Commun* 1985;6;550. Bolster AA, et al. *Nucl Med Commun* 1994;15:188-191. Rose MR, et al. *Eur J Nucl Med* 1997;24:89-90. Goransson M, et al. *Eur J Nucl Med* 1997;24:1059.
	commercial source of kits	differences in lung clearance	Rose MR, et al. *Eur J Nucl Med* 1997;24:89-90.
	interlot and intralot variability	↑ free pertechnetate, ↑ thyroid and stomach uptake	Anon. *Eur J Nucl Med* 1996;23:BP27-BP31. Petry N. Personal communication. November 7, 2002.
	interlot variability	presence of large aggregates	Anon. *Eur J Nucl Med* 1995;22:BP29-BP33. Anon. *Eur J Nucl Med* 1996;23:BP27-BP31.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate	McLean JR, et al. *J Nucl Med Technol* 1977;5:28-31.
99mTc-bicisate (ECD)	excessive pertechnetate activity	↑ radiochemical purity	Verbeke K, et al. *Nucl Med Commun* 1997;18:535-539.
	inadequate stannous	↓ radiochemical purity, ↑ free pertechnetate	Afshan A, et al. *Eur J Nucl Med* 1994;21:991-995. Green JM, et al. *J Nucl Med Technol* 1994;22:21-26. Nicolini M, et al (eds). *Technetium and Rhenium in Chemistry and Nuclear Medicine 4*. Padova: Servizi Grafici Editoriali, 1995;547-550.
	excessive stannous	↓ radiochemical purity	Green JM, et al. *J Nucl Med Technol* 1994;22:21-26. Nicolini M, et al (eds). *Technetium and Rhenium in Chemistry and Nuclear Medicine 4*. Padova: Servizi Grafici Editoriali, 1995;547-550.
	inadequate reagent concentration (excessive reaction volume)	↓ radiochemical purity	Nicolini M, et al (eds). *Technetium and Rhenium in Chemistry and Nuclear Medicine 4*. Padova: Servizi Grafici Editoriali, 1995;547-550.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	inadequate incubation time	↓ radiochemical purity	Green JM, et al. *J Nucl Med Technol* 1994;22:21-26. Nicolini M, et al (eds). *Technetium and Rhenium in Chemistry and Nuclear Medicine 4*. Padova: Servizi Grafici Editoriali, 1995;547-550.
	predilution of pertechnetate in syringe vs. post-dilution in vial	no difference in labeling efficiency or stability	Bogsrud TV, et al. *J Am Pharm Assoc* 1998;38:273. Bogsrud TV, et al. *Clin Nucl Med* 1998;23:562.
	variations in incubation temperatures (heating)	alterations in radiochemical purity	Hung JC, et al. *J Nucl Med* 1996;37(suppl):142P-143P. Hung JC, et al. *Eur J Nucl Med* 1997;24:655-659.
	radiolytic decomposition/hydrolysis	↓ radiochemical purity	Green JM, et al. *J Nucl Med Technol* 1994;22:21-26.
	improper pH	↓ radiochemical purity, ↑ free pertechnetate	Afshan A, et al. *Eur J Nucl Med* 1994;21:991-995.
	photolytic degradation	↓ radiochemical purity	Green JM, et al. *J Nucl Med Technol* 1994;22:21-26.
99mTc-exametazime (HMPAO)	excessive 99Tc/first eluate of a new generator	↓ labeling efficiency, ↑ free pertechnetate, ↓ stability	Neirinckx RD, et al. *J Nucl Med* 1987;28:191-202. Brandau W, et al. *J Nucl Med* 1990;31:2075-2076. Gagnon A, et al. *J Nuc Med* 1991;32:1103.
	preparation with "aged" or low specific activity pertechnetate	↓ labeling efficiency, ↓ stability	Neirinckx RD, et al. *J Nucl Med* 1987;28:191-202. Bayne VJ, et al. *Nucl Med Commun* 1989;10:29-33. Ballinger JR, et al. *J Nucl Med* 1990;31:118-122. Brandau W, et al. *J Nucl Med* 1990;31:2075-2076. Millar AM. *Nucl Med Commun* 1992;13:306-311. Millar AM. *Am J Hosp Pharm* 1993;50:103-106. Piera C, et al. *J Nucl Med* 1995;36:706. Ponto JA. *J Nucl Med Technol* 1998;26:262-264.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	preparation with excessive Tc-99m activity	↓ labeling efficiency, ↓ stability	Neirinckx RD, et al. *J Nucl Med* 1987;28:191-202. Lang J, et al. *Eur J Nucl Med* 1989;15:424. Ballinger JR, et al. *J Nucl Med* 1990;31:118-122. Corlija M, et al. *J Nucl Med* 1990;31(suppl):806. Ballinger J. *J Nucl Med* 1990;31:1892. Gagnon A, et al. *J Nuc Med* 1991;32:1103. Tubergen K, et al. *J Nucl Med* 1991;32:111-115.
	inadequate stannous	↓ radiochemical purity	Solanki C, et al. *Nucl Med Commun* 1994;15:718-722. Kumar V, et al. *J Nucl Med* 1996;37(suppl):83P. Baker RJ. *J Nucl Med* 1996;37(suppl):84P. Kumar V. *J Nucl Med* 1997;38:1664. Decristoforo C, et al. *Nucl Med Biol* 1998;25:675-583. Baker RJ. *Nucl Med Commun* 1999;20:287-293.
	excessive stannous (high Sn+2:Tc ratio)	↓ stability, ↑ reduced-hydrolyzed Tc	Hung JC, et al. *J Nucl Med* 1988;29:1568-1576. Lang J, et al. *Eur J Nucl Med* 1989;15:424. Ramamoorthy N, et al. *Nucl Med Biol* 1993;20:307-310. Solanki C, et al. *Nucl Med Commun* 1993;14:1035-1040. Solanki C, et al. *Nucl Med Commun* 1994;15:718-722.
	excessive volume/ inadequate concentration	↓ radiochemical purity	Sampson CB, et al. *Nucl Med Commun* 1991;12:719-723.
	inadequate mixing of pertechnetate and HMPAO solutions	↓ radiochemical purity	Morrissey GJ, et al. *J Nucl Med* 1993;34:151-155.
	intra- and inter-lot variability	↓ labeling efficiency	Ballinger JR, et al. *J Nucl Med* 1990;31:118-122. Ponto JA. *Am J Hosp Pharm* 1990;47:2511-2513. Seifert S, et al. *Nucl Med Biol* 1995;22:1063-1066.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	radiolytic decomposition (esp. without addition of stabilizing agent)	↓ radiochemical purity; ↓ brain:parotid ratio	Hung JC, et al. *J Nucl Med* 1988;29:1568-1576. Piera C, et al. *J Nucl Med* 1990;31:127-128. Ballinger JR, et al. *J Nucl Med* 1990;31:118-122. Tubergen K, et al. *J Nucl Med* 1991;32:111-115. Ramamoorthy N, et al. *Nucl Med Biol* 1993;20:307-310. Weisner PS, et al. *Eur J Nucl Med* 1993;20:661-666. Papos M, et al. *Nucl Med Biol* 1994;21:893-895. Mang'era KO, et al. *Eur J Nucl Med* 1995;22:1163-1172. Kumar V, et al. *J Nucl Med* 1996;37(suppl):83P. Barthel H, et al. *Eur J Nucl Med* 1996;23:1200. Tsai CS, et al. *Nucl Med Commun* 1996;1:76-79. Wang SJ, et al. *Eur J Nucl Med* 1997;24:1040. Solanki C, et al. *Nucl Med Commun* 1998;19:567-572. Verbeke K, et al. *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine.* 1999; pp435-446. Burke JF. Presentation at the American Pharmaceutical Association Annual Meeting, San Francisco, CA, Mar. 18, 2001. Thom J, et al. *Nucl Med Commun* 2002;23:408. Siddig SMA, et al. *Nucl Med Commun* 2002;23:1224.
	excessive time delay before addition of the methylene blue stabilizer	↓ labeling efficiency, ↓ stability	Burke JF. Presentation at the American Pharmaceutical Association Annual Meeting, San Francisco, CA, Mar. 18, 2001.
	dissolved oxygen (shaking vial)	↓ labeling efficiency, ↓ stability	Lang J, et al. *Eur J Nucl Med* 1989;15:424. Karesh SM. *J Nucl Med Technol* 1989;17:215-218. Bayne VJ, et al. *Nucl Med Commun* 1989;10:29-33.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	commercial source of normal saline	↓ labeling efficiency, ↑ free pertechnetate, ↓ brain:parotid ratio	Brandau W, et al. *J Nucl Med* 1990;31:2075-2076. Hammersley PAG, et al. *Nucl Med Commun* 2001;25:981-986.
	alkaline pH	↓ stability, ↑ free pertechnetate	Hung JC, et al. *J Nucl Med* 1988;29:1568-1576.
	refrigerated vial not at room temperature	↓ rate of labeling	Karesh SM. *J Nucl Med Technol* 1989;17:215-218.
	storage of "fractionated" kits, esp. differences in storage temperature	↓ radiochemical purity	Piera C, et al. *J Nucl Med* 1990;31:127-128. Hawkins T, et al. *Nucl Med Commun* 1991;12:1045-1055. Tikofsky RS, et al. *J Nucl Med Technol* 1993;21:57-60. Kumar V, et al. *J Nucl Med* 1996;37(suppl):83P. Baker RJ. *J Nucl Med* 1996;37(suppl):84P. Decristoforo C, et al. *Nucl Med Biol* 1998;25:675-583. Baker RJ. *Nucl Med Commun* 1999;20:287-293.
99mTc-(HMPAO) leukocytes	inadequate HMPAO concentration	↓ labeling efficiency	Danpure HJ, et al. *J Nucl Med* 1987;28:694. Solanki KK, et al. *Nucl Med Commun* 1988;9:753-761. Sampson CB, et al. *Nucl Med Commun* 1991;12:719-723. Vanlic-Razumenic N, et al. *Nucl Med Biol* 1992;19:251-256.
	excessive quantity of HMPAO reagent	↓ labeling efficiency	Ozker K, et al. *Eur J Nucl Med* 1995;22:182-183. Osker K, et al. *Nucl Med Commun* 1996;17:342-345.
	decreased fraction of Tc-99m HMPAO as primary, lipophilic complex	↓ labeling efficiency	Papos M, et al. *Nucl Med Biol* 1994;21:893-895. Sampson CB. *Nucl Med Commun* 1996;17:648-658. Wang SJ, et al. *Eur J Nucl Med* 1997;24:1040.
	inadequate number or concentration of leukocytes (or excessive incubation volume)	↓ labeling efficiency	Danpure HJ, et al. *J Nucl Med* 1987;28:694. Mortelmans L, et al. *J Nucl Med* 1989;30:2022-2028. Ballinger JR, et al. *Nucl Med Biol* 1990;17:443. Ecclestone M, et al. *Eur J Nucl Med* 1990;16:299-302.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
			Vanlic-Razumenic N, et al. *Nucl Med Biol* 1992;19:251-256. Papos M, et al. *Nucl Med Biol* 1994;21:893-895. Sampson CB. *Nucl Med Commun* 1996;17:648-658. Hung JC, et al. *J Nucl Med* 1998;39(suppl):243P. Hung JC, et al. *Nucl Med Commun* 1998;19:981-987. Farto JCA, et al. *Nucl Med Commun* 1999;20:965. Hammersley PAG, et al. *Nucl Med Commun* 2001;25:981-986. Georges B, et al. *Eur J Nucl Med* 2002;29(suppl): S197.
	inadequate incubation time	↓ labeling efficiency	Danpure HJ, et al. *J Nucl Med* 1987;28:694. Mortelmans L, et al. *J Nucl Med* 1989;30:2022-2028. Vanlic-Razumenic N, et al. *Nucl Med Biol* 1992;19:251-256.
	suspension in other (eg, salt solution) media vs. plasma	↓ functional integrity; ↑ non-specific bowel uptake	Roddie ME, et al. *Radiology* 1988;166:767-772. Plaza P, et al. *Eur J Nucl Med* 2002;29(suppl): S318. Martin-Comin J. *Nucl Med Commun* 2002;23:1039-1040.
	excessive plasma	↓ labeling efficiency	Ecclestone M, et al. *Eur J Nucl Med* 1990;16:299-302. Hung JC, et al. *J Nucl Med* 1997;38(suppl):112P-113P. Hung JC, et al. *J Nucl Med* 1998;39(suppl):243P. Cardoso VN, et al. *Nucl Med Commun* 2002; 23:715-720.
	excessive amount of red cells and/or platelets	↑ labeled RBCs or platelets (↑ blood pool retention)	Danpure HJ, et al. *J Nucl Med* 1987;28:694. Sampson CB. *Nucl Med Commun* 1996;17:648-658. Hammersley PAG, et al. *Nucl Med Commun* 2001;25:981-986.
	excessive amount of lymphocytes	↓ neutrophil labeling; ↑ labeled lymphocytes	Hammersley PAG, et al. *Nucl Med Commun* 2001;25:981-986.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	eosinophilia	↓ neutrophil labeling; ↑ uptake in lymph nodes and skin	Puncher MRB, et al. *Eur J Nucl Med* 1994; 21:1175-1182. Vasanawala MS, et al. *Clin Nucl Med* 2003;28:389-391.
	various methods for leukocyte separation	differences in cellular contaminants, esp. red cells and platelets	Thorson LM, et al. *J Nucl Med Technol* 1995; 23:282-288.
	use of dextran as erythrocyte sedimentation agent	adverse reactions (flushing, shortness of breath)	Anon. *Eur J Nucl Med* 1995;22:BP29-BP33. Rodrigues M. *Eur J Nucl Med* 1996;23:857-858.
	improper pH	↓ labeling efficiency	Danpure HJ, et al. *J Nucl Med* 1987;28:694. Solanki KK, et al. *Nucl Med Commun* 1988;9:753-761. Vanlic-Razumenic N, et al. *Nucl Med Biol* 1992; 19:251-256.
	lysis of red cells	↓ labeling efficiency; no significant differences in stability, viability, or function *in vitro*; but ↓ peak recovery and ↑ liver uptake *in vivo*	Hung JC, et al. *J Nucl Med* 2002;43(suppl):381P. Hung JC, et al. *J Nucl Med* 2003;44(suppl):317P-318P.
	use of stabilized vs. unstabilized Tc-99m HMPAO	no significant differences in labeling efficiency, stability, viability	Hung JC, et al. *Nucl Med Commun* 1998;19:981-987. Hung JC, et al. *J Nucl Med* 2002;43(suppl):381P. Hung JC, et al. *J Nucl Med* 2002;43:928-932.
	use of stabilized vs. unstabilized Tc-99m HMPAO	possible decrease in chemotactic function; ↑ uptake in marrow (may be technique dependent?)	Iglesias F, et al. *Nucl Med Commun* 1999;20:967. Roca M, et al. *J Nucl Med* 2001;42:505-508. Hung JC, et al. *J Nucl Med* 2002;43(suppl):381P. Hung JC, et al. *J Nucl Med* 2002;43:928-932. Hung JC, et al. *J Nucl Med* 2003;44(suppl):317P-318P.
99mTc-(HMPAO) platelets	inadequate platelet concentration	↓ labeling efficiency	Danpure HJ, et al. *Nucl Med Commun* 1988;9:267-272.
	inadequate incubation time	↓ labeling efficiency	Danpure HJ, et al. *Nucl Med Commun* 1988;9:267-272.
	excessive concentration of ACD-plasma in labeling medium	↓ labeling efficiency	Danpure HJ, et al. *Nucl Med Commun* 1988;9:267-272.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	variations in centrifugation parameters	differences in radiochemical purity; differences in cellular contaminants, esp. WBCs	Navaratnam T, et al. *J Nucl Med Technol* 1997;25:156.
99mTc-gluceptate (GH)	improper pH	↑ free pertechnetate	Chi SL, et al. *J Nucl Med* 1978;19:520-524.
	improper mixing order	↑ free pertechnetate or ↑ liver uptake	Chi SL, et al. *J Nucl Med* 1978;19:520-524.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate	Chi SL, et al. *J Nucl Med* 1978;19:520-524. Porter WC, et al. *Monthly Scan* 1978;September:1. Zbrzeznj DJ, et al. *Am J Hosp Pharm* 1981; 38:1499-1502. Collins HR, et al. *Pharm Pract* 1983;18:A-12.
99mTc-hepatobiliary iminodiacetic acid (IDA) derivatives	pH >5.5	↓ rate of labeling	Nunn AD, et al. *J Nucl Med* 1981;22:P-52.
	inadequate incubation time	↓ free pertechnetate, ↑ blood pool activity	Nunn AD, et al. *J Nucl Med* 1981;22:P-52. Ponto JA, et al. *Am J Hosp Pharm* 1981;38:1939-1941. Steigman J, et al. *The Chemistry of Technetium in Medicine.* Washington, DC: National Academy. 1992.
	inadequate volume	cloudiness (precipitation?)	Sullivan RM. Professional communication letter. North Billerica: DuPont. May 5, 1988.
	low ligand concentration	↓ rate of labeling	Nunn AD, et al. *J Nucl Med* 1981;22:P-52.
	preparation with 5% dextrose	↓ liver uptake; ↑ uptake in kidney, cardiac blood pool, soft-tissue background	Al-Enizi E, et al. *J Nucl Med Technol* 2003;31:33-36.
	radiolytic decomposiiton and/or oxidation	↑ free pertechnetate	Nunn AD, et al. *J Nucl Med* 1981;22:P-52. Jovanovic V, et al. *Eur J Nucl Med* 1981;6;375-378. Majewski W, et al. *J Nucl Med Technol* 1981; 9:116. Lecklitner ML, et al. *Clin Nucl Med* 1985;10:468-474. Hupp BD, et al. *J Nucl Med Technol* 1986;14:202-205.
	photolytic degradation from exposure of kit to light	↓ radiochemical purity	Chilton HM. *J Nucl Med Technol* 1994;22:261.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
99mTc-mertiatide (MAG3)	preparation with excessive amount of Tc-99m activity	↓ radiochemical purity, ↓ stability, ↑ hepatobiliary excretion	Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Szlaczky LA, et al. *J Nucl Med* 1992;33:990. Thorson LM, et al. *Nucl Med Commun* 1992;13:832-837. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74.
	preparation with first eluate of a new generator	↑ free pertechnetate	Anon. *Eur J Nucl Med* 1995;22:BP29-BP33. Stringer RE, et al. *Nucl Med Commun* 1996;17:993.
	preparation with "aged" eluate	↓ radiochemical purity	Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74. Hung JC, et al. *Nucl Med Commun* 1995;16:157-160.
	radiolytic decomposition	↓ radiochemical purity	Nosco D, et al. *Technetium and Chemistry in Chemistry and Nuclear Medicine 3*. 1990;385-392. Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74. Verbeke K, et al. *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine.* 1999;435-446. Burke JF. Presentation at the American Pharmaceutical Association Annual Meeting, San Francisco, CA, Mar. 18, 2001.
	storage time of final product prior to administration	conversion of radiochemical impurity from renal excretion compound to hepatobiliary excretion compound	Chatterjee M, et al. *Nucl Med Biol* 1996;23:867-872.
	inadequate Sn+2 (esp. with fractionation and storage)	↓ radiochemical purity	Decristoforo C, et al. *J Nucl Med* 1996;37:1912-1913. Kumar V. *J Nucl Med* 1997;38:1664. Decristoforo C, et al. *Nucl Med Biol* 1998;25:675-583.
	storage of reconstituted product at room temperature	↓ radiochemical stability compared to storage at freezer temperature	Kiratli PO, et al. *J Nucl Med Technol* 2003;31:74-75.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	preparation in small total volume	↓ radiochemical purity, ↑ hepatobiliary excretion	Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74. Shattuck LA, et al. *J Nucl Med* 1994;35:349-355. Arroyo A, et al. *J Nucl Med Technol* 2003;31:18-20.
	inadequate volume of air added during preparation	↓ radiochemical purity	Nosco D, et al. *Technetium and Chemistry in Chemistry and Nuclear Medicine 3*. 1990;385-392. Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74. Verbeke K, et al. *Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine.* 1999;435-446. Burke JF. *APhA Annual Meeting*. March 18, 2001. Arroyo A, et al. *J Nucl Med Technol* 2003;31:18-20.
	predilution of pertechnetate in syringe vs. postdilution in vial	no difference in labeling efficiency or stability	Bogsrud TV, et al. *J Am Pharm Assoc* 1998;38:273. Bogsrud TV, et al. *Clin Nucl Med* 1998;23:562. Bogsrud TV, et al. *Nucl Med Comun* 1999;20:61-65.
	excessive delay before adding air during preparation	↓ radiochemical purity	Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74. Arroyo A, et al. *J Nucl Med Technol* 2003;31:18-20.
	excessive delay before heating during preparation	↓ radiochemical purity	Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74. Arroyo A, et al. *J Nucl Med Technol* 2003;31:18-20.
	inadequate heating	↓ radiochemical purity	Hung JC, et al. *J Nucl Med Technol* 1991;19:176-179. Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
			Anderson R, et al. *J Nucl Med Technol* 1994; 22:114. Noll B, et al. *Nucl Med Biol* 1995;22:1057-1062. Wemmenhove BL. *Eur J Nucl Med* 1996;23:1256. Ponto JA. *J Nucl Med Technol* 1998;26:262-264.
	excessive pressure in vial during heating	breakage of vial	Hung JC, et al. *J Nucl Med Technol* 1991;19:176-179.
	loss of argon atmosphere in vial	↓ radiochemical purity	Fleming WK, et al. *J Nucl Med* 1992;33:1915.
	commercial source of Tc-99m pertechnetate used for preparation	↓ radiochemical purity	Nosco D, et al. *J Nucl Med* 1992;33:1033-1034. Nosco DL, et al. *J Nucl Med Technol* 1993;21:69-74. Decristoforo C, et al. *J Nucl Med* 1996;37:1912-1913. Stringer RE, et al. *Nucl Med Commun* 1997;18:294.
	commercial source of saline (glass vials vs. plastic bags)	↓ radiochemical purity if saline from plastic bags	Murray T, et al. *Eur J Nucl Med* 1997;24:991.
	commercial source of saline (esp. certain plastic containers)	↓ radiochemical purity	Stringer RE, et al. *Nucl Med Commun* 1996;17:993. Anon. *Eur J Nucl Med* 1998;25:BP3-BP8. Millar AM, et al. *Nucl Med Commun* 1998;19:475-477. Spendley PJ. *Nucl Med Commun* 2001;22:447-448. Halliburton L. personal communication. March 14, 2003.
	hydrogen peroxide antisepsis of vial septum	↓ radiochemical purity	Stringer RE, et al. *Nucl Med Commun* 1997;18:294.
	alkaline pH	↑ impurities, ↑ hepatobiliary excretion	Bannister KM, et al. *J Nucl Med* 1990;31:1568-1573. Noll B, et al. *Nucl Med Biol* 1995;22:1057-1062.
	photolytic degradation from exposure of kit to light	↓ radiochemical purity	Chilton HM. *J Nucl Med Technol* 1994;22:261. Arroyo A, et al. *J Nucl Med Technol* 2003;31:18-20.
99mTc-pentetate (DTPA)	excessive 99Tc	↑ free pertechnetate	Colombetti LG, et al. *Nuklearmedizin* 1977;16:271-274.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	inadequate stannous	↑ free pertechnetate	McKuskick KA, et al. *J Nucl Med* 1973;14:113-114. Colombetti LG, et al. *Nuklearmedizin* 1977;16:271-274. Robins PJ, et al. *J Nucl Med* 1979;20:653.
	improper mixing order	↑ free pertechnetate	Levit N. *Monthly Scan* 1979;November:1.
	inadequate incubation time	↑ protein binding, ↑ blood pool retention	Blauenstein P, et al. *Eur J Nucl Med* 1983;8:A46. Russell CD, et al. *J Nucl Med* 1986;27:560-2. Steigman J, et al. *The Chemistry of Technetium in Medicine.* Washington, DC: National Academy. 1992.
	radiolytic decomposition and/or oxidation (influenced by temperature)	↑ free pertechnetate (thyroid, stomach, salivary glands)	Cooper PA, et al. *J Nucl Med Technol* 1975;3:208-209. Levit N. *Monthly Scan* 1979;November:1. Robins PJ, et al. *J Nucl Med* 1979;20:653. Millar AM. *Nucl Med Commun* 1983;4:368-371. Sampson CB. *Nucl Med Commun* 1984;5:239. Waldman DL, et al. *J Nucl Med* 1985;26:P131. Hammes RJ, et al. *J Nucl Med* 1988;29:980. Anon. *Eur J Nucl Med* 1999;26:BP33-BP38.
	oxidation from exposure to air	↑ free pertechnetate (thyroid, stomach, salivary glands)	Sampson CB. *Nucl Med Commun* 1984;5:239. Sampson CB (ed). *Textbook of Radiopharmacy --Theory and Practice.* Langhorne, PA: Gordon and Breach Science Publishers. 1994: 145-151.
	excessive dilution	↓ stability, ↑ free pertechnetate	Levit N. *Monthly Scan* 1979;November:1. Sampson CB. *Nucl Med Commun* 1984;5:239.
	commercial source of Tc-99m pertechnetate	differences in labeling efficiences	Sampson CB. *Nucl Med Commun* 1984;5:239.
	commercial source of reagent kits	differences in labeling efficiences, stability, and renal excretion rates	Atkins HL, et al. *Radiology* 1971;98:674-677. Levit N. *Monthly Scan* 1979;November:1. Carlsen JE, et al. *J Nucl Med* 1980;21:126-129.

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			Russell CD, et al. *J Nucl Med* 1983;24:722-727. Sampson CB. *Nucl Med Commun* 1984;5:239. Hammes RJ, et al. *J Nucl Med* 1988;29:980.
	commercial source of reagent kits	differences in protein binding and glomerular filtration rates	Russell CD, et al. *J Nucl Med* 1983;24:722-727. Hammes RJ, et al. *J Nucl Med* 1988;29:980. Rehling M, et al. *Eur J Nucl Med* 1998;25:856. Rehling M, et al. *Nucl Med Commun* 1998;19:495. Rehling M, et al. *Nucl Med Commun* 2001;22:617-623.
	interlot variability	↑ free pertechnetate (thyroid, stomach, salivary glands)	Millar AM. *Nucl Med Commun* 1983;4:368-371.
	excessive Al+3	dissociation; ↑ free pertechnetate (stomach, intestines); altered GFR results	Specht HD, et al. *J Nucl Med* 1987;28:383-386.
	storage temperature	↑ free pertechnetate	Lerthirunwong C, et al. *Nucl Med Biol* 1992; 19:727-735.
	pentasodium salt of DTPA used for intrathecal use	chelation of Ca and Mg ions in CSF; adverse neurological effects	Verbruggen AM, et al. *Eur J Nucl Med* 1994; 21:261-263. Sampson CB (ed). *Textbook of Radiopharmacy--Theory and Practice, Second Edition.* Langhorne, PA: Gordon and Breach Science Publishers. 1994: 285-298.
99mTc-pyrophosphate and diphosphonates	presence of excessive Tc-99m pertechnetate	persistent blood pool activity (labeled RBCs)	Lewis SE, et al. *Nuclear Cardiology--1980.* Kalamazoo, MI: Upjohn. 1979: 20-23.
	preparation with excessive Tc-99m activity	↑ rate of radiolytic decomposition, ↓ radiochemical purity	Beightol RW, et al. *J Nucl Med Technol* 1983;11:173-176. Cheng KT, et al. Presentation at APhA Annual Meeting, March 18-21, 1995; Orlando, FL.
	excessive 99Tc	slow blood pool clearance	Van Duzee BF, et al. *Clin Nucl Med* 1981;6(suppl):P148.
	Al+3	↑ liver uptake, ↑ kidney uptake	Chaudhuri TK. *Radiology* 1976;119:485-486. Chaudhuri TK. *Int J Nucl Med Biol* 1976;3:37-40. Zimmer AM, et al. *Radiology* 1978;126:813-816.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
			Jaresko GS, et al. *J Nucl Med Technol* 1980;8:160-161. Dugal B, et al. *J Nucl Med* 1996:37:1920.
	commercial source of kits	variations in bone:soft tissue ratios; variations in stomach, liver, gallbladder, and/or intestional localization; variations in overall image quality	Fordham EW, et al. *Atlas of Total Body Radionuclide Imaging. Volume II.* Philadelphia: Harper & Row. 1982: 1587-1667. Najafi A, et al. *J Nucl Med* 1985;26:524-530. Seevers RH, et al. *J Nucl Med* 1985;26:P130. Gouaillardouu D, et al. *Appl Radiat Isot* 1987;38:103-106. Simon TR, et al. *J Nucl Med* 1990;31:829. Simon TR, et al. *Nucl Med Biol* 1990;17:793-795.
	commercial source of 99mTc-pertechnetate	variable ↑ free pertechnetate; differences in soft tissue localization	Conway JJ, et al. *J Nucl Med* 1982;23:P109. Van Duzee BF, et al. *Pharm Pract* 1983;18:A-11. Coupal JJ, et al. *J Nucl Med* 1986;27:1067.
	alkaline pH	↑ liver, kidney, and/or stomach uptake	Schumichen C, et al. *Nuklearmedizin* 1977;16:100-103. Schumichen C, et al. *Nuklearmedizin* 1977;16:157-162. Hoogland DR, et al. *Med Imaging* 1977;2:39.Zimmer AM, et al. *Radiology* 1978;126:813-816. Francis MD, et al. *In J Nucl Med Biol* 1981;8:145-152. Vanlic-Razumenic N, et al. *Nuklearmedizin* 1982;21:150-156.
	excessive acid pH	↑ free pertechnetate or ↑ liver localization	van den Brand JAGM, et al. *Int J Appl Radiat Isot* 1982;33:917-928. Dugal B, et al. *J Nucl Med* 1996:37:1920.
	inadequate stannous	↓ labeling efficiency, ↑ free pertechnetate	Yano Y, et al. *J Nucl Med* 1973;14:73-78. Tofe AJ, et al. *J Nucl Med* 1974;15:69-74. Sorenson JA (coord). *Radiopharmaceuticals II: Proceedings of the 2nd International Symposium on Radiopharmaceuticials.* New York: Society of Nuclear Medicine. 1979: 637-644. Kowalsky RJ, et al. *Am J Hosp Pharm* 1981;38:1722-1726.

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			Kroesbergen J, et al. *Nucl Med Biol* 1987;14:37-41. Decristoforo C, et al. *Nucl Med Biol* 1998;25:675-683.
	excessive stannous	↑ liver and soft tissue uptake	McCormick MV, et al. *J Nucl Med Technol* 1976;4:189-192 Zimmer AM, et al. *Radiology* 1978;126:813-816. Sorenson JA (coord). *Radiopharmaceuticals II: Proceedings of the 2nd International Symposium on Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1979: 637-644.
	preparation with bacteriostatic saline	↑ free pertechnetate	Study KT, et al. *J Nucl Med Technol* 1981;9:115-116.
	preparation with 5% dextrose	↑ uptake in kidney, bladder, cardiac blood pool, gallbladder, soft-tissue background	Al-Enizi E, et al. *J Nucl Med Technol* 2003;31:33-36.
	antiseptic contamination	↑ free pertechnetate (stomach)	Peterson EM, et al. *J Nucl Med* 1986;27:1090.
	improper mixing order	↑ blood pool activity; ↑ liver uptake	Yano Y, et al. *J Nucl Med* 1973;14:73-78. van den Brand JAGM, et al. *Int J Appl Radiat Isot* 1982;33:917-928.
	pre-dilution vs. post-dilution	no difference in labeling efficiency or stability	Bogsrud TV, et al. *J Nucl Med Technol* 1998;26:124-125. Bogsrud TV, et al. *Clin Nucl Med* 1998;23:562. Bogsrud TV, et al. *J Am Pharm Assoc* 1998;38:273. Bogsrud TV, et al. *Nucl Med Comun* 1999;20:61-65.
	inadequate or prolonged incubation time	↓ bone uptake, ↑ soft tissue uptake	Henkin RE, et al. *Radiology* 1980;135:464-466. Darte L. *Nuklearmedizin* 1981;20:51-63. Wilson MA, et al. *J Nucl Med* 1981;22:518-521. Van Duzee BF, et al. *J Nucl Med* 1982;23:P99. Buell U, et al. *J Nucl Med* 1982;23:214-217. Van Duzee BF, et al. *Pharm Pract* 1983;18:A-11. McCullough RW, et al. *Nucl Med Commun* 1985;6:548-549.

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			Goomer NC, et al. *Eur J Nucl Med* 1999;26:1633-1634.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate	Yano Y, et al. *J Nucl Med* 1973;14:73-78. McCormick MV, et al. *J Nucl Med Technol* 1976;4:189-192 Zimmer AM, et al. *J Nucl Med Technol* 1977;5:54-55. Billinghurst MW, et al. *J Nucl Med* 1979;20:138-143. Dhawan V, et al. *J Nucl Med* 1979;20:791-793. Sorenson JA (coord). *Radiopharmaceuticals II: Proceedings of the 2nd International Symposium on Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1979: 637-644. Tofe AJ, et al. *J Nucl Med* 1980;21:366-370. Kowalsky RJ, et al. *Am J Hosp Pharm* 1981;38:1722-1726. Francis MD, et al. *In J Nucl Med Biol* 1981;8:145-152. Coupal JJ, et al. *J Nucl Med* 1981;22:153-156. Der M, et al. *J Nucl Med* 1981;22:645-646. Hesslewood SR. *Nuklearmedizin* 1981;20:3-6. Majewski W, et al. *J Nucl Med Technol* 1982;10:111. Beightol RW, et al. *J Nucl Med Technol* 1983;11:173-176. Hupp BD, et al. *J Nucl Med Technol* 1986;14:202-205. Sampson CB (ed). *Textbook of Radiopharmacy --Theory and Practice.* Langhorne, PA: Gordon and Breach Science Publishers. 1994: 145-151. Woods WV, et al. *Clin Nucl Med* 1995;20:92.
	addition of air to vial	↑ free pertechnetate	Majewski W, et al. *J Nucl Med Technol* 1982;10:111. Beightol RW, et al. *J Nucl Med Technol* 1983;11:173-176.
	excessive mass/ concentration of the diphosphonate	↓ bone uptake	De Ligny CL, et al. *Nucl Med Biol* 1993;20:23-29.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	low ligand concentration	↓ labeling efficiency, ↓ bone uptake; ↑ soft tissue and kidney uptake	Schumichen C, et al. *Nuklearmedizin* 1977;16:157-162. van den Brand JAGM, et al. *Int J Appl Radiat Isot* 1982;33:917-928. Inoue O, et al. *Nuklearmedizin* 1982;21:121-125. Vanlic-Razumenic N, et al. *Nuklearmedizin* 1982;21:150-156. Kroesbergen J, et al. *Nucl Med Biol* 1987;14:37-41.
	improper Sn/ligand ratio	↓ bone uptake; ↑ lung uptake(?)	van den Brand JAGM, et al. *Int J Appl Radiat Isot* 1982;33:917-928. Vanlic-Razumenic N, et al. *Nuklearmedizin* 1982;21:150-156. Tatum JL, et al. *Clin Nucl Med* 1985;10:16-18. Gouaillardouu D, et al. *Appl Radiat Isot* 1987;38:103-106. Kroesbergen J, et al. *Nucl Med Biol* 1987;14:37-41.
	excessive dilution	↓ bone uptake, ↑ soft tissue uptake	McCullough RW, et al. *Nucl Med Commun* 1985;6:548-549.
	storage temperature	↓ free pertechnetate; ↓ bone uptake, ↑ soft tissue uptake	McCullough RW, et al. *Nucl Med Commun* 1985;6:548-549. Lerthirunwong C, et al. *Nucl Med Biol* 1992;19:727-735.
99mTc-red blood cells (RBC)	excessive 99Tc , such as first eluant from a new generator (especially with ACD)	↓ labeling efficiency, ↑ free pertechnetate	Smith TD, et al. *J Nucl Med* 1975;16:570-571. Smith TD, et al. *J Nucl Med*1976;17:126-131. Porter WC, et al. *J Nucl Med* 1983;24:383-387. Wilson ME, et al. *J Nucl Med* 1992;33:306-307. Srivastava SC, et al. *J Nucl Med* 1992;33:307-308. Wolfangel RG. *J Nucl Med* 1992;33:308. Kelly MJ, et al. *J Nucl Med* 1991;32:1090. Wolfangel RG, et al. *J Nucl Med* 1992;33:989. Hung JC, et al. *J Nucl Med Technol* 1992;20:107.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
			Kelly MJ, et al. *J Nucl Med* 1992;33:2222-2225. Ponto JA. *J Nucl Med Technol* 1998;26:99-100.
	preparation with "aged" pertechnetate	↓ labeling efficiency, ↑ free pertechnetate	Ponto JA. *J Nucl Med Technol* 1998;26:262-264.
	excessive Tc-99m activity used in preparation	↓ rate and extent of labeling	Wolfangel RG, et al. *J Nucl Med* 1992;33:989.
	inadequate stannous	↓ radiochemical purity, ↑ free pertechnetate	Smith TD, et al. *J Nucl Med* 1976;17:126-131. Zimmer AM, et al. *Nuklearmedizin* 1979;18:241-246. Feldkamp M, et al. *J Nucl Med Technol* 1991; 19:50. Rastovac M, et al. *Nucl Med Commun* 1991; 12:461-464. Stallings LE, et al. *J Nucl Med Technol* 1997;25:44-48.
	deterioration of stannous pyrophosphate due to lack of refrigeration	↓ radiochemical purity	Adalet I, et al. *Eur J Nucl Med* 1994;21:173-175.
	excessive stannous	↓ radiochemical purity, ↑ plasma activity, ↑ spleen uptake	Eckelman W, et al. *J Nucl Med* 1971;12:310-311. Bardy A, et al. *J Nucl Med* 1975;16:435-437. Smith TD, et al. *J Nucl Med* 1976;17:126-131. Zimmer AM. *Am J Hosp Pharm* 1977;34:264-267. Zimmer AM, et al. *Nuklearmedizin* 1979;18:241-246. Callahan RC, et al. *J Nucl Med* 1982;23:P109. Zanelli GD. *Nucl Med Commun* 1982;3:155-161. Rastovac M, et al. *Nucl Med Commun* 1991;12:461-464.
	excessive extracellular Sn^{+2}	↓ radiochemical purity, ↑ plasma activity	Van Hembert F, et al. *Eur J Nucl Med* 2000;27:1218.
	Al+3	RBC agglutination	Lin MS, et al. *J Nucl Med* 1971;12:297-299.
	very acidic pH	RBC hemolysis	Lin MS, et al. *J Nucl Med* 1971;12:297-299.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	inadequate incubation time for Sn+2 and RBCs	↓ radiochemical purity	Zimmer AM, et al. *Nuklearmedizin* 1979;18:241-246. Staub RF, et al. *J Nucl Med* 1985;26:P130-P131. Kelly MJ, et al. *J Nucl Med* 1991;32:1090. Kelly MJ, et al. *J Nucl Med* 1992;33:2222-2225.
	inadequate incubation time for Tc-99m and "tinned" RBCs	↓ radiochemical purity, ↑ free pertechnetate	Zimmer AM. *Am J Hosp Pharm* 1977;34:264-267. Zimmer AM, et al. *Nuklearmedizin* 1979;18:241-246. Billinghurst MW, et al. *J Radioanalyt Chem* 1980;59:579-584. Froelich JW, et al. *J Nucl Med* 1980;21:P44. Callahan RJ, et al. *J Nucl Med* 1981;22:P70. Callahan RJ, et al. *J Nucl Med* 1982;23:P109. Callahan RJ, et al. *J Nucl Med* 1990;31:2004-2010. Kelly MJ, et al. *J Nucl Med* 1991;32:1090. Kelly MJ, et al. *J Nucl Med* 1992;33:2222-2225.
	incubation at lower than 37o	↓ rate of labeling, ↑ free pertechnetate	Callahan RJ, et al. *J Nucl Med* 1981;22:P70. Callahan RJ, et al. *J Nucl Med* 1982;23:P109.
	improper mixing order	↓ radiochemical purity	Smith TD, et al. *J Nucl Med* 1976;17:126-131. Wolfangel RG, et al. *J Nucl Med* 1992;33:989. Massler J, et al. *J Nucl Med Technol* 1996;24:165-166. Ponto JA. *J Nucl Med Technol* 1998;26:99-100.
	inadequate volume of blood and/or low RBC concentration	↓ rate and extent of labeling	Callahan RJ, et al. *J Nucl Med* 1982;23:P109. Gerson B, et al. *J Nucl Med Technol* 1988;16:9-11. Kelly MJ, et al. *J Nucl Med* 1991;32:1090. Kelly MJ, et al. *J Nucl Med* 1992;33:2222-2225. Wolfangel RG, et al. *J Nucl Med* 1992;33:989.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
			Marton S, et al. *Eur J Nucl Med* 1999;26:993.
	large volume of Tc-99m pertechnetate solution used in preparation	↓ rate and extent of labeling	Wolfangel RG, et al. *J Nucl Med* 1992;33:989. Ponto JA. *J Nucl Med Technol* 1998;26:99-100.
	heparin vs. ACD (for modified in vivo labeling)	↓ labeling efficiency, ↑ extravascular activity, ↑ urinary excretion	Porter WC, et al. *J Nucl Med* 1983;24:383-387.
	ACD vs. heparin (for in vitro labeling)	↓ stability, ↓ blood:background ratio	Chowdhury S, et al. *J Nucl Med Technol* 1991; 19:118. Bonacorrsi J, et al. *J Nucl Med Technol* 1992; 20:107.
	excessive amount of ACD	↓ labeling efficiency, ↑ splenic sequestration	Mayer K, et al. *J Nucl Med* 1971;11:455-458. Wolfangel RG, et al. *J Nucl Med* 1992;33:989. Hung JC, et al. *J Nucl Med Technol* 1992;20:107. Hung JC, et al. *Am J Hosp Pharm* 1994;51:2699-2701.
	EDTA as an anticoagulant	↓ labeling efficiency	Gerson B, et al. *J Nucl Med Technol* 1988;16:9-11. Bernardo-Filho M, et al. *Nucl Med Commun* 1994;15:730-734.
	EDTA as a tin sequesterant	↓ blood pool retention, ↑ splenic uptake	Ryo UY, et al. *J Nucl Med* 1976;17:133-136. Kelbæk H, et al. *Eur J Nucl Med* 1989;15:333-335. Srivastava SC, et al. *Semin Nucl Med* 1990;20:41-51.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate	Zimmer AM. *Am J Hosp Pharm* 1977;34:264-267. Zimmer AM, et al. *Nuklearmedizin* 1979;18:241-246. Torres MA, et al. *J Nucl Med* 1996;37(suppl):199P.
	photolytic degradation from exposure of kit to light	↓ radiochemical purity	Chilton HM. *J Nucl Med Technol* 1994;22:261.
	use of Teflon or polyurethane catheter (cannula) for in vivo labeling	↓ radiochemical purity; rapid blood pool clearance	Millar AM, et al. *Eur J Nucl Med* 1983;8:502-504. Hambye AS, et al. *Eur J Nucl Med* 1995;22:61-67. Eising EG, et al. *Eur J Nucl Med* 1995;22:587.

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			Verbeke K, et al. *Eur J Nucl Med* 1997;24:448.
	commercial source of normal saline	↓ labeling efficiency, ↑ free pertechnetate	Ponto JA, et al. *J Nucl Med Technol* 1990;19:107-108.
99mTc-RBC, damaged	low heating temperature	↓ spleen uptake, ↑ blood pool activity	Early PJ, et al. *Textbook of Nuclear Medicine Technology, 3rd ed.* St. Louis: CB Mosby. 1979:363-370. Som P, et al. *Radiology* 1981;138:207-209.
	high heating temperature	↓ spleen uptake, ↑ liver uptake	Early PJ, et al. *Textbook of Nuclear Medicine Technology, 3rd ed.* St. Louis: CB Mosby. 1979:363-370. Som P, et al. *Radiology* 1981;138:207-209.
	inadequate heating time	↓ spleen uptake, ↑ blood pool activity	Early PJ, et al. *Textbook of Nuclear Medicine Technology, 3rd ed.* St. Louis: CB Mosby. 1979:363-370. Som P, et al. *J Nucl Med* 1980;21:P44. Armas RR, et al. *J Nucl Med* 1980;21;413-416. Som P, et al. *Radiology* 1981;138:207-209. Valk PE, et al. *J Nucl Med* 1984;25:965-968.
	excessive heating time	↓ spleen uptake, ↑ liver uptake	Early PJ, et al. *Textbook of Nuclear Medicine Technology, 3rd ed.* St. Louis: CB Mosby. 1979:363-370. Som P, et al. *J Nucl Med* 1980;21:P44. Som P, et al. *Radiology* 1981;138:207-209.
	large volume heated	↓ spleen uptake, ↑ blood pool activity	Atkins HL, et al. *Radiology* 1980;136:501-503.
	alterations in microwave heating parameters	alterations in hepatic uptake and blood clearance	O'Donoghue JP, et al. *Clin Nucl Med* 1994;19:933.
	low specific activity	↓ spleen uptake, ↑ blood pool activity	Atkins HL, et al. *Radiology* 1980;136:501-503.
99mTc-sestamibi (MIBI)	preparation with excessive and/or "aged" Tc-99m, esp. from the first eluation of a new generator	↓ radiochemical purity	Herold TJ, et al. *J Nucl Med* 1993;34:148P. Hung JC, et al. *Nuc Med Biol* 1995;22:949-951 Porter WC, et al. *J Nucl Med Technol* 1995;23:279-281. Hung JC, et al. *Nucl Med Biol* 1995;22:949-951. Baker RJ. *J Nucl Med* 1996;37(suppl):84P. Hung JC, et al. *Nucl Med Biol* 1996;23:599-603.

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	inadequate Sn+2 (esp. with fractionation and storage)	↓ radiochemical purity	Baker RJ. *J Nucl Med* 1996;37(suppl):84P. Decristoforo C, et al. *J Nucl Med* 1996;37:1912-1913. Kumar V. *J Nucl Med* 1997;38:1664.
	inadequate heating	↓ radiochemical purity	Taillefer R, et al. *J Nucl Med* 1989;30:865. Gagnon A, et al. *J Nucl Med Technol* 1991;19:90-93. Hung JC, et al. *J Nucl Med* 1991;32:2162-2168. Wilson ME, et al. *Nucl Med Commun* 1993;14:544-549. Parrott SJ, et al. *J Nucl Med* 1994;35(suppl):138P. Anderson R, et al. *J Nucl Med Technol* 1994;22:114. Hung JC, et al. *J Nucl Med Technol* 1996;24:141-142. Porter WC, et al. *Nucl Med Technol* 1996;24:142. Ponto JA. *J Nucl Med Technol* 1998;26:262-264.
	excessive pressure inside vial during heating	ejection of vial stopper or breakage of vial	Gagnon A, et al. *J Nucl Med Technol* 1991;19:90-93. Hung JC, et al. *J Nucl Med* 1991;32:2162-2168. Hung JC, et al. *J Nucl Med* 1992;33:176-178.
	excessive delay before heating	↓ radiochemical purity	Ponto JA. *J Nucl Med Technol* 1998;26:262-264.
	exposure to air	↓ radiochemical purity	Hayes AC. *J Nucl Med Technol* 1992;20:84-87.
	commercial source of Tc-99m pertechnetate used for preparation (esp. wet column generators)	↓ radiochemical purity	Decristoforo C, et al. *J Nucl Med* 1996;37:1912-1913. Hung JC, et al. *Nucl Med Biol* 1996;23:599-603. Varelis P, et al. *Nucl Med Commun* 1998;19:615-623.
	pre-dilution vs. post-dilution	no difference in labeling efficiency or stability	Bogsrud TV, et al. *J Nucl Med Technol* 1998; 26:124-125. Bogsrud TV, et al. *Clin Nucl Med* 1998;23:562. Bogsrud TV, et al. *J Am Pharm Assoc* 1998;38:273. Bogsrud TV, et al. *Nucl Med Comun* 1999;20:61-65.

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			Johnson G, et al. *Nucl Med Commun* 2001;22:461.
	additional dilution after preparation	no effect on radio-chemical purity and stability	Cooper MS, et al. *Nucl Med Commun* 2003;24:469.
	agitation	↑ adsorption to vial	Millar AM. *Nucl Med Commun* 1989;10:247.
99mTc-succimer (DMSA)	alkaline pH	rapid urinary excretion	Krejcarek GE, et al. *J Nucl Med* 1976;17:565. Krejcarek GE, et al. *J Labeled Compd Radiopharm* 1977;13:157. Ikeda I, et al. *J Nucl Med* 1977;18:1222-1229. Hata N, et al. *J Nucl Med* 1983;24:P126-P127. Jeghers O, et al. *Appl Radiat Isot* 1987;38:13-18.
	low ligand concentra-tion	↓ kidney uptake, ↑ bone uptake	Ikeda I, et al. *J Nucl Med* 1977;18:1222-1229.
	inadequate incubation time	↓ kidney uptake, ↑ bone uptake	Ikeda I, et al. *J Nucl Med* 1977;18:1222-1229. Steigman J, et al. *The Chemistry of Tech-netium in Medicine.* Washington, DC: National Academy. 1992.
	radiolytic decomposi-tion and/or oxidation	↑ free pertechnetate, ↓ kidney uptake, ↑ liver uptake	Ikeda I, et al. *J Nucl Med* 1977;18:1222-1229. Taylor A, et al. *J Nucl Med* 1980;21:1190-1193. Vanlic-Rasumenic N. *Nuklearmedizin* 1981;20:46-49. Ponto JA, et al. *View Box* 1983;2:1-2.
	commercial source of container	differences in adsorp-tion onto walls and stoppers of glass vials	Millar AM. *Nucl Med Commun* 1984;5:195-199.
	contamination with antiseptic	↑ liver/spleen uptake	Murray T, et al. *Nucl Med Commun* 1986;7:505-510.
	photolytic degradation from exposure of kit to light	↓ radiochemical purity	Chilton HM. *J Nucl Med Technol* 1994;22:261.
	variation in Sn+2 amount and/or pH	variation in radio-chemical purity, rela-tive fractions of Tc(III) and Tc(V) species	Hirano T, et al. *Eur J Nucl Med* 1994;21:82-85. Kobayashi H, et al. *Eur J Nucl Med* 1995;22:559-562. Washburn LC, et al. *Nucl Med Biol* 1995;22:689-691.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	oxygen bubbled into vial	conversion of Tc(III) to Tc(V) species; ↓ renal uptake	Kobayashi H, et al. *Eur J Nucl Med* 1995;22:559-562. Washburn LC, et al. *Nucl Med Biol* 1995;22:689-691.
99mTc-sulfur colloid	excess 99Tc	↑ free pertechnetate	Albers JW, et al. *J Nucl Med Technol* 1974;2:14-17.
	inadequate Tc activity/mass	↓ labeling efficiency	Sorenson JA (coord). *Radiopharmaceuticals II: Proceedings of the 2nd International Symposium on Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1979: 15-23.
	variations in Tc content (Tc-99 + Tc-99m)	differences in particle size distribution	Eshima D, et al. *J Nucl Med* 1996;37(suppl):84P. Eshima D, et al. *J Nucl Med* 1996;37:1575-1578.
	Al+3	↑ lung uptake	Larson SM, et al. *J Nucl Med* 1966;7:817-826. Dworkin HJ, et al. *Am J Roentgenol Rad Ther* 1967;101:557-560. Weinstein MB, et al. *J Nucl Med* 1970;11:767-768. Haney TA, et al. *J Nucl Med* 1971;12:64-68. Staum MM. *J Nucl Med* 1972;13:386-387. Adams EH, et al. *J Nucl Med* 1972;12:707-708. Bobinet DD, et al. *J Nucl Med* 1974;15:1220-1222. Early PJ, et al. *Textbook of Nuclear Medicine Technology, 3rd ed.* St. Louis: CV Mosby. 1979: 544-570. Study KT, et al. *J Nucl Med Technol* 1984;12:16-18. Zabel PL, et al. *J Nucl Med* 1986;27:942.
	alkaline pH	↑ free pertechnetate	Andrews GA, et al (eds). *Radioactive Pharmaceuticals*. Oak Ridge: US Atomic Energy Commission. 1966: 67-91. Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820.
	commercial source of kits	variable ↑ free pertechnetate; differences in liver uptake and liver:lung ratios	Albers JW, et al. *J Nucl Med Technol* 1974;2:14-17. Subramanium G, et al (eds). *Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1975; 236-245. Levit N. *Monthly Scan* 1979;November:1.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	commercial source of 99mTc-pertechnetate	variable ↑ free pertechnetate; differences in liver uptake and liver:lung ratios	Subramanium G, et al (eds). *Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1975; 236-245.
	incorrect order of mixing	↑ free pertechnetate	Haney TA, et al. *J Nucl Med* 1971;12:64-68. Feezer B. *Monthly Scan* 1979;March:1-2. Ponto JA. *J Nucl Med Technol* 1998;26:262-264.
	excessive delay after adding pertechnetate and acid before boiling	↓ radiochemical purity, formation of Tc-99m EDTA	Zabel P. Personal communication. July 24, 2001.
	inadequate heating (inadequate time and/or temperature)	↓ radiochemical purity, ↑ free pertechnetate	Larson SM, et al. *J Nucl Med* 1966;7:817-826. Haney TA, et al. *J Nucl Med* 1971;12:64-68. Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820. Sorenson JA (coord). *Radiopharmaceuticals II: Proceedings of the 2nd International Symposium on Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1979: 15-23. Frier M, et al. *Eur J Nucl Med* 1981;6:255-260. Morrissey GJ, et al. *J Nucl Med Technol* 1992;20:159-162. Anderson R, et al. *J Nucl Med Technol* 1994;22:114. Eshima D, et al. *J Nucl Med* 1996;37:1575-1578.
	inadequate boiling time	↓ spleen uptake	Larson SM, et al. *J Nucl Med* 1966;7:817-826. Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820.
	excessive boiling time	↑ particle size, ↑ lung uptake	Larson SM, et al. *J Nucl Med* 1966;7:817-826. Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820. Morrissey GJ, et al. *J Nucl Med Technol* 1992;20:159-162.
	low specific activity	↓ liver uptake, ↑ bone marrow uptake	Atkins HL, et al. *J Nucl Med* 1969;10:319-320.
	excessive pressure in vial	rupture of rubber septum	Evdokimoff VN. *Health Physics* 1980;39:573-574. Morrissey GJ, et al. *J Nucl Med Technol* 1992;20:159-162.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	heating large volume	↑ free pertechnetate	Haney TA, et al. *J Nucl Med* 1971;12:64-68.
	variations in heating times	differences in particle size distribution	Eshima D, eta l. *J Nucl Med* 1996;37(suppl):84P. Eshima D, et al. *J Nucl Med* 1996;37:1575-1578. Smith F, et al. *J Nucl Med* 1996;37(suppl):301P. Rao SA, et al. *Eur J Nucl Med* 1998;25:1164.
	reheating after buffering	↓ particle size	Steigman J, et al. *The Chemistry of Technetium in Medicine.* Washington, DC: National Academy Press. 1992; 11-14.
	preparation using microwave heating	↑ lung uptake	Hollar BS, et al. *J Nucl Med Technol* 1995;23:77-81.
	radiolytic decomposition	↑ free pertechnetate	Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820.
	filtration (e.g., for use in lymphoscintigraphy)	↓ radiochemical purity	Hung JC, et al. *J Nucl Med* 1995;36:1895-1901. Corrigan P, et al. *J Nucl Med Technol* 1997;25:153. Rao SA, et al. *Eur J Nucl Med* 1998;25:1164.
	particle size > 100-200 nanometers (when used for lymphoscintigraphy)	retention at site of injection	Wilhelm AJ, et al. *Eur J Nucl Med* 1999;26(suppl):S36-S42. Eshima D, et al. *Semin Nucl Med* 2000;30:25-32. Mariani G, et al. *J Nucl Med* 2001;42:1198-1215. Uren RF, et al. *J Nucl Med* 2003;44:570-582.
	routine vs. very high specific activity (when used for lymphoscintigraphy)	↓ uptake in sentinel nodes, ↑ progression on to second tier nodes	Wilhelm AJ, et al. *Eur J Nucl Med* 1999;26(suppl):S36-S42. Krynyckyi BR, et al. *J Nucl Med* 2001;42(suppl): 295P-296P. Mariani G, et al. *J Nucl Med* 2001;42:1198-1215. Krynyckyi BR, et al. *Clin Nucl Med* 2002;27:92-95. Zhang Z, et al. *J Nucl Med* 2003:44(suppl):100P-101P.
	sterilization of vial septum with iodinated antiseptics	↑ free pertechnetate	Fisher SM, et al. *J Nucl Med* 1977;18:1139-1140.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	chlorhexidine antisepsis of vial septum	aggregation of particles, ↑ lung uptake	Theobald AE (ed). *Radiopharmacy and Radiopharmaceuticals*. London: Taylor and Francis. 1985: 189-205.
	particle clumping	↑ lung uptake	Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820. Stadalnik RC. *Semin Nucl Med* 1980;10:106-107.
99mTc-tetrofosmin	excessive radioactive concentration or inadequate total volume of preparation	↓ radiochemical purity	McKay BF, et al. *J Nucl Med Technol* 1996;24:164. Hammes RJ, et al. *J Nucl Med.* 2002;43(suppl):42P-43P.
	preparation with excessive Tc-99m activity	↓ radiochemical stability	McKay BF, et al *J Nucl Med Technol* 1997;25:149. McKay BF, et al. *Clin Nucl Med* 1997;22:578. Cagnolini A, et al. *Nucl Med Biol* 1998;25:435-439.
	maintaining nitrogen atmosphere	↓ radiochemical stability compared to adding room air (oxygen)	Anon. *Myoview ™ 12 Hour Preparation: Questions and Answers.* Arlington Heights, IL: Nycomed Amersham. 1999. Burke JF. Presentation at the American Pharmaceutical Association Annual Meeting, San Francisco, CA, Mar. 18, 2001. Jones JM, et al. *J Nucl Med Technol* 2003;31:125.
	inadequate Sn+2 (?) (esp. with fractionation and storage)	↓ radiochemical purity	Saponaro R, et al. *Eur J Nucl Med* 2001;28:1229.
	inadequate incubation	↓ radiochemical purity	Bastien SA, et al. *J Nucl Med* 1999;40(suppl):153P. Bastein SA, et al. *Nucl Med Commun* 1999;20:480. Burke JF. Presentation at the American Pharmaceutical Association Annual Meeting, San Francisco, CA, Mar. 18, 2001.
	pre-dilution vs. post-dilution	↓ rate of labeling with post-dilution	Bastien SA, et al. *J Nucl Med* 1999;40(suppl):153P. Bastein SA, et al. *Nucl Med Commun* 1999;20:480. Anon. *Myoview ™ 12 Hour Preparation: Questions and Answers.* Arlington Heights, IL: Nycomed Amersham. 1999.
	additional dilution after preparation	no effect on radiochemical purity and stability	Goransson M, et al. *Eur J Nucl Med* 1999;26:1207. Cooper MS, et al. *Nucl Med Comun* 2003;24:469.

Radiopharmaceutical	Preparation Problem	Effect/Manifestation	References
	low tetrofosmin concentration	↑ adsorption to vial	Graham D, et al. *Nucl Med Commun* 1997;18:335.
	radiolytic decomposition	↓ radiochemical purity	McKay BF, et al. *Clin Nucl Med* 1997;22:578. Cagnolini A, et al. *Nucl Med Biol* 1998;25:435-439. Burke JF. Presentation at the American Pharmaceutical Association Annual Meeting, San Francisco, CA, Mar. 18, 2001.
	agitation	↑ adsorption to vial and rubber stopper	Graham D, et al. *Nucl Med Commun* 1997;18:335.
	inadequate mass (excessive fractionation)	↓ radiochemical purity and stability	Sdraiati C, et al. *J Nucl Med Technol* 1998;26:128.
	heating (above room temperature)	↓ radiochemical purity (Tc reduced from +5 to +3)	Kronauge JF. Presentation at the American Pharmaceutical Association Annual Meeting, Los Angeles, CA, Mar. 8, 1997.
Misc. -- preparation using heat block	variable heating rate of vial contents dependent on the configuration of the vial in the heating block	variability in reaction yields	Baldwin RM, et al. *J Nucl Med* 1995;36(suppl): 151P-152P.

APPENDIX 2. REPORTED PROBLEMS ASSOCIATED WITH DISPENSING OF CURRENT TC-99M RADIOPHARMACEUTICALS

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
Tc-99m sodium pertechnetate	preparation/dilution with bacteriostatic normal saline	↑ blood pool, liver, and spleen activity	Study KT, et al. *J Nucl Med Technol* 1981;9:115-116.
Tc-99m aerosol	relatively larger particle (droplet) size; commercial source of aerosolizing device	↓ peripheral penetration, ↑ central deposition	Phipps P, et al. *Eur J Nucl Med* 1987;13:183-186. Miki M, et al. *Nucl Med Commun* 1992;13;553-562. O'Doherty MJ, et al. *Eur J Nucl Med* 1993;20:1201-1213.
	commercial source of aerosolizing device	differences in radioaerolization efficiency	Cutrera P, et al. *Clin Nucl Med* 1999;24:628.
	variations in oxygen/air flow rates	variations in droplet size and thus airway distribution	Schuster K, et al. *J Nucl Med Technol* 1987;15:97-98. Diot P, et al. *J Nucl Med* 1997;38(suppl):180P.
	addition of 10% ethanol	↑ efficiency of radioaerosol delivery	Schuster K, et al. *J Nucl Med Technol* 1987;15:97-98. Sirr SA, et al. *J Nucl Med* 1986;27:1500. Porter WC, et al. *J Nucl Med* 1990;31:894. Sirr SA, et al. *J Nucl Med* 1985;26:643-646.
	relative humidity	variations in deposition rate and/or distribution	Phipps P, et al. *Eur J Nucl Med* 1987;13:183-186.
	density of carrier gas	peripheral lung penetration is inversely related to density of gas	Donaghy TA, et al. *J Nucl Med Technol* 1994;22:113.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate (altered respiratory clearance)	Waldman DL, et al. *J Nucl Med* 1985;26:P131. Waldman DL, et al. *J Nucl Med* 1987;28:378-382. Huchon GJ, et al. *J Nucl Med* 1987;28:894-902.
Tc-99m albumin aggregated	inadequate number of particles	perfusion defects, especially peripheral patchiness	Heck LL, et al. *Radiology* 1974;113:675-679. Dworkin HJ, et al. *J Nucl Med* 1977;18:260-262.

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
	excessive number of particles	↑ risk of toxicity	Heck LL, et al. *Radiology* 1974;113:675-679. Dworkin HJ, et al. *J Nucl Med* 1977;18:260-262.
	inadequate incubation time	↓ radiochemical purity	Cheng KT, et al. *J Nucl Med Technol* 1994;22:173-177.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate	McLean JR, et al. *J Nucl Med Technol* 1977;5:28-31.
	settling of particles and/or adsorption to vial	↓ number of particles in suspension, ↓ activity per volume withdrawn from vial	Millar AM, et al. *Nucl Med Commun* 1985;6:115-116. Palmer AM. *Nucl Med Commun* 1985;6:550. Coupal JJ, et al. *J Nucl Med* 1988;29:904. Anon. *Eur J Nucl Med* 1998;25:BP3-BP8.
	settling of particles in syringe/needle, especially if stored needle-down	if needle is changed immediately prior to injection, ↓ in administered dose	Quinton T. Personal communication. September 15, 2003.
	adsorption to syringe	↓ activity actually injected	Gunasekera RD, et al. *Eur J Nucl Med* 1996;23:1250. Jansson BA, et al. *J Nucl Med Technol* 1998;26:196-199. Gunasekera RD, et al. *Nucl Med Commun* 2001;22:493-497. Tudor M, et al. *Nucl Med Commun* 2003;24:461-462.
	administration via an intravenous lock filled with normal saline instead of heparin	"hot" spots in lungs (probably due to residual thrombus at the catheter tip)	Telepak RJ, et al. *Clin Nucl Med* 2000;25:231.
Tc-99m antibodies	shaking (↑ air/water interface)	air oxidation, ↓ radiochemical purity; ↑ adsorption to container	Grabenstein JD. *Hosp Pharm* 1996;31:1387-1401.
	settling with prolonged storage (failure to resuspend)	↓ withdrawn activity	Grabenstein JD. *Hosp Pharm* 1996;31:1387-1401.
Tc-99m bicisate	radiolytic decomposition/ hydrolysis	↓ radiochemical purity	Green JM, et al. *J Nucl Med Technol* 1994;22:21-26.
	retention in syringe	↓ activity injected	Koslowsky IL. *J Nucl Med* 2000;41(suppl):251P.

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
Tc-99m exametazime	radiolytic decomposition	↓ radiochemical purity; ↓ brain:parotid ratio	Ballinger JR, et al. *J Nucl Med*1990;31:118-122. Tubergen K, et al. *J Nucl Med* 1991;32:111-115. Ramamoorthy N, et al. *Nucl Med Biol* 1993;20:307-310. Weisner PS, et al. *Eur J Nucl Med* 1993;20:661-666. Kumar V, et al. *J Nucl Med* 1996;37(suppl):83P. Mang'era KO, et al. *Eur J Nucl Med* 1995;22:1163-1172. Barthel H, et al. *Eur J Nucl Med* 1996;23:1200. Papos M, et al. *Nucl Med Biol* 1994;21:893-895. Wang SJ, et al. *Eur J Nucl Med* 1997;24:1040. Koslowsky IL, et al. *J Nucl Med* 2000;41(suppl): 251P. Thom J, et al. *Nucl Med Commun* 2002;23:408.
	retention in syringe	↓ activity injected	Koslowsky IL, et al. *J Nucl Med* 2000;41(suppl): 251P.
	dissolved oxygen (shaking vial)	↓ labeling efficiency, ↓ stability	Lang J, et al. *Eur J Nucl Med* 1989;15:424. Karesh SM. *J Nucl Med Technol* 1989;17:215-218. Bayne VJ, et al. *Nucl Med Commun* 1989;10:29-33.
	type of aerosolization for inhalation	↓ radiochemical purity; altered lung clearance	Yu TW, et al. *J Nucl Med* 1994;35(suppl):244P.
Tc-99m (exametazime) leukocytes	prolonged storage/delay before reinjection	↓ labeling efficiency (Tc-99m elutes from cells over time)	Torres MA, et al. *Eur J Nucl Med* 1997;24:1041. Becker W, et al. *Nucl Med Commun* 1998;9:435-447.
	prolonged storage/delay before reinjection	↓ cell viability, ↓ localization at site of infection [anticipated based on observations with In-111 leukocytes]	Forstrom L. Presented at the Fourth Annual Midwestern Cell Labeling Conference, Iowa City, IA. November 5, 1983. Paavola PC, et al. *J Nucl Med Technol* 1995;36:126.
	suspension in other (eg, salt solution) media vs. plasma	↓ functional integrity; ↑ non-specific bowel uptake	Roddie ME, et al. *Radiology* 1988;166:767-772. Martin-Comin J. *Nucl Med Commun* 2002;23:1039-1040.

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
	excessive agitation (eg, during transportation)	cell damage, leaching of Tc-99m from cells	Cooper MS, et al. *Nucl Med Commun* 2003;24:468.
Tc-99m (exametazime) platelets	prolonged storage/ delay before re-injection	↓ labeling efficiency (Tc-99m elutes from cells over time)	Danpure HJ, et al. *Nucl Med Commun* 1988;9:267-272.
Tc-99m gluceptate	radiolytic decomposition and/or oxidation	↑ free pertechnetate	Chi SL, et al. *J Nucl Med* 1978;19:520-524. Zbrzeznj DJ, et al. *Am J Hosp Pharm* 1981;38:1499-1502. Collins HR, et al. *Pharm Pract* 1983;18:A-12. Porter WC, et al. *Monthly Scan* 1978;September:1.
Tc-99m hepatobiliary iminodiacetic acid derivatives	radiolytic decompositon and/or oxidation	↑ free pertechnetate	Nunn AD, et al. *J Nucl Med* 1981;22:P-52. Lecklitner ML, et al. *Clin Nucl Med* 1985;10:468-474. Jovanovic V, et al. *Eur J Nucl Med* 1981;6;375-378. Majewski W, et al. *J Nucl Med Technol* 1981;9:116. Hupp BD, et al. *J Nucl Med Technol* 1986;14:202-205.
	storage in plastic syringe	↑ free pertechnetate	Hupp BD, et al. *J Nucl Med Technol* 1986;14:202-205.
	interaction between hepatobiliary agent and syringe components	formation of a sticky glue-like substance	Theobald AE (ed). *Radiopharmacy and Radiopharmaceuticals*. London: Taylor and Francis. 1985: 189-205. Sampson CB (ed). *Textbook of Radiopharmacy—Theory and Practice, Third Edition.* Amsterdam:Gordon and Breach. 1999; 187-194.
Tc-99m mertiatide	prolonged storage time of final product prior to administration	conversion of radiochemical impurity from renal excretion compound to hepatobiliary excretion compound	Chatterjee M, et al. *Nucl Med Biol* 1996;23:867-872.
	hydrogen peroxide antisepsis of vial septum	↓ radiochemical purity	Stringer RE, et al. *Nucl Med Commun* 1997;18:294.
Tc-99m pentetate	inadequate incubation time	↑ protein binding, ↑ blood pool retention	Russell CD, et al. *J Nucl Med* 1986;27:560-2. Blauenstein P, et al. *Eur J Nucl Med* 1983;8:A46.

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
	radiolytic decomposition and/or oxidation (influenced by temperature)	↑ free pertechnetate (thyroid, stomach, salivary glands)	Cooper PA, et al. *J Nucl Med Technol* 1975;3:208-209. Levit N. *Monthly Scan* 1979;November:1. Robins PJ, et al. *J Nucl Med* 1979;20:653. Waldman DL, et al. *J Nucl Med* 1985;26:P131. Sampson CB. *Nucl Med Commun* 1984;5:239. Millar AM. *Nucl Med Commun* 1983;4:368-371. Hammes RJ, et al. *J Nucl Med* 1988;29:980.
	oxidation from exposure to air	↑ free pertechnetate (thyroid, stomach, salivary glands)	Sampson CB. *Nucl Med Commun* 1984;5:239. Sampson CB (ed). *Textbook of Radiopharmacy --Theory and Practice.* Langhorne, PA: Gordon and Breach Science Publishers. 1994: 145-151.
	storage in plastic syringe	↑ free pertechnetate	Hupp BD, et al. *J Nucl Med Technol* 1986;14:202-205.
	excessive dilution	↓ stability, ↑ free pertechnetate	Levit N. *Monthly Scan* 1979;November:1. Sampson CB. *Nucl Med Commun* 1984;5:239.
	storage temperature	↑ free pertechnetate	Lerthirunwong C, et al. *Nucl Med Biol* 1992;19:727-735.
	pentasodium salt of pentetate used for intrathecal use	chelation of calcium and magnesium ions in cerebral spinal fluid; adverse neurological effects	Verbruggen AM, et al. *Eur J Nucl Med* 1994;21:261-263. Sampson CB (ed). *Textbook of Radiopharmacy--Theory and Practice, Second Edition.* Langhorne, PA: Gordon and Breach Science Publishers. 1994: 285-298.
Tc-99m pyrophosphate and diphosphonates	antiseptic contamination	↑ free pertechnetate (stomach)	Peterson EM, et al. *J Nucl Med* 1986;27:1090.
	inadequate or prolonged incubation time	↓ bone uptake, ↑ soft tissue uptake	McCullough RW, et al. *Nucl Med Commun* 1985;6:548-549. Henkin RE, et al. *Radiology* 1980;135:464-466, Buell U, et al. *J Nucl Med* 1982;23:214-217. Darte L. *Nuklearmedizin* 1981;20:51-63. Wilson MA, et al. *J Nucl Med* 1981;22:518-521.

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
			Van Duzee BF, et al. *J Nucl Med* 1982;23:P99. Van Duzee BF, et al. *Pharm Pract* 1983;18:A-11.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate	Kowalsky RJ, et al. *Am J Hosp Pharm* 1981;38:1722-1726. Francis MD, et al. *In J Nucl Med Biol* 1981;8:145-152. Billinghurst MW, et al. *J Nucl Med* 1979;20:138-143. Sorenson JA (coord). *Radiopharmaceuticals II: Proceedings of the 2nd International Symposium on Radiopharmaceuticals.* New York: Society of Nuclear Medicine. 1979: 637-644. Yano Y, et al. *J Nucl Med* 1973;14:73-78. Der M, et al. *J Nucl Med* 1981;22:645-646. Dhawan V, et al. *J Nucl Med* 1979;20:791-793. Beightol RW, et al. *J Nucl Med Technol* 1983;11:173-176. Coupal JJ, et al. *J Nucl Med* 1981;22:153-156. McCormick MV, et al. *J Nucl Med Technol* 1976;4:189-192 Zimmer AM, et al. *J Nucl Med Technol* 1977;5:54-55. Tofe AJ, et al. *J Nucl Med* 1980;21:366-370. Hesslewood SR. *Nuklearmedizin* 1981;20:3-6. Majewski W, et al. *J Nucl Med Technol* 1982;10:111. Hupp BD, et al. *J Nucl Med Technol* 1986;14:202-205. Sampson CB (ed). *Textbook of Radiopharmacy --Theory and Practice.* Langhorne, PA: Gordon and Breach Science Publishers. 1994: 145-151. Woods WV, et al. *Clin Nucl Med* 1995;20:92.
	addition of air to vial	↑ free pertechnetate	Majewski W, et al. *J Nucl Med Technol* 1982;10:111. Beightol RW, et al. *J Nucl Med Technol* 1983;11:173-176.
	excessive dilution	↓ bone uptake, ↑ soft tissue uptake	McCullough RW, et al. *Nucl Med Commun* 1985;6:548-549.

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
	storage in plastic syringe	↑ free pertechnetate	Zimmer AM, et al. *Pharm Practice* 1982;17:A-17. Beightol RW, et al. *J Nucl Med Technol* 1983;11:173-176. Hupp BD, et al. *J Nucl Med Technol* 1986;14:202-205. Woods WV, et al. *Clin Nucl Med* 1995;20:92.
	storage temperature	↑ free pertechnetate; ↓ bone uptake, ↑ soft tissue uptake	McCullough RW, et al. *Nucl Med Commun* 1985;6:548-549. Lerthirunwong C, et al. *Nucl Med Biol* 1992;19:727-735.
Tc-99m red blood cells	deterioration of stannous pyrophosphate due to lack of refrigeration	↓ radiochemical purity	Adalet I, et al. *Eur J Nucl Med* 1994;21:173-175.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate	Zimmer AM. *Am J Hosp Pharm* 1977;34:264-267. Zimmer AM, et al. *Nuklearmedizin* 1979;18:241-246.
	use of Teflon or polyurethane catheter (cannula) for in vivo labeling	↓ radiochemical purity; rapid blood pool clearance	Millar AM, et al. *Eur J Nucl Med* 1983;8:502-504. Hambye AS, et al. *Eur J Nucl Med* 1995;22:61-67. Eising EG, et al. *Eur J Nucl Med* 1995;22:587. Verbeke K, et al. *Eur J Nucl Med* 1997;24:448.
Tc-99m sestamibi	exposure to air	↓ radiochemical purity	Hayes AC. *J Nucl Med Technol* 1992;20:84-87.
	dilution and withdrawal of patient dosage immediately after preparation while vial contents are still hot	stomach uptake	Pendleton D, et al. *J Nucl Med Technol* 1993;21:46.
	agitation	↑ adsorption to vial	Millar AM. *Nucl Med Commun* 1989;10:247.
	adsorption to vial	↓ activity per volume withdrawn from vial	Millar AM. *Nucl Med Commun* 1989;10:247..

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
	adsorption to syringe	↓ activity actually injected	Jansson BA, et al. *J Nucl Med Technol* 1998;26:196-199. Hurless L. *J Am Pharm Assoc* 2000;40:310. Hurless LM, et al. *J Nucl Med* 2000;41(suppl):250P-251P. Cheng K and Ngo T. *J Am Pharm Assoc* 2002;42:306. Mayes C. *Nucl Med Commun* 2003;24:468.
Tc-99m succimer	inadequate incubation time	↓ kidney uptake, ↑ bone uptake	Ikeda I, et al. *J Nucl Med* 1977;18:1222-1229.
	radiolytic decomposition and/or oxidation	↑ free pertechnetate, ↓ kidney uptake, ↑ liver uptake	Ikeda I, et al. *J Nucl Med* 1977;18:1222-1229. Vanlic-Rasumenic N. *Nuklearmedizin* 1981;20:46-49. Taylor A, et al. *J Nucl Med* 1980;21:1190-1193. Ponto JA, et al. *View Box* 1983;2:1-2.
	commercial source of container	differences in adsorption onto walls and stoppers of glass vials	Millar AM. *Nucl Med Commun* 1984;5:195-199.
	contamination with antiseptic	↑ liver/spleen uptake	Murray T, et al. *Nucl Med Commun* 1986;7:505-510.
	oxygen bubbled into vial	conversion of Tc(III) to Tc(V) species; ↓ renal uptake	Kobayashi H, et al. *Eur J Nucl Med* 1995;22:559-562. Washburn LC, et al. *Nucl Med Biol* 1995;22:689-691.
Tc-99m sulfur colloid	sterilization of vial septum with iodinated antiseptics	↑ free pertechnetate	Fisher SM, et al. *J Nucl Med* 1977;18:1139-1140.
	chlorhexidine antisepsis of vial septum	aggregation of particles, ↑ lung uptake	Theobald AE (ed). *Radiopharmacy and Radiopharmaceuticals*. London: Taylor and Francis. 1985: 189-205.
	radiolytic decomposition	↑ free pertechnetate	Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820.
	particle settling and/or adsorption to vial	↓ activity per volume withdrawn from vial	Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820. Elliot AT, et al. *Nucl Med Commun* 1990;11:375-381. Cohen MB, et al. *J Nucl Med* 1969;10:395-396. Porter WC, et al. *Am J Hosp Pharm* 1975;32:1141-1143. Millar AM, et al. *Nucl Med Commun* 1985;6:115-116.

Radiopharmaceutical	Dispensing Problem	Effect/Manifestation	References
	adsorption to walls of plastic syringe	↓ dose administered	Corrigan P, et al. *J Nucl Med Technol* 1997;25:153.
	particle clumping	↑ lung uptake	Kelly WN, et al. *Am J Hosp Pharm* 1973;30:817-820. Stadalnik RC. *Semin Nucl Med* 1980;10:106-107.
	variable incubation time	variable particle size	Boudreau R, et al. *Eur J Nucl Med* 1983;8:335-337.
	filtration (e.g., for use in lympho-scintigraphy)	↓ radiochemical purity	Hung JC, et al. *J Nucl Med* 1995;36:1895-1901. Corrigan P, et al. *J Nucl Med Technol* 1997;25:153.
Tc-99m tetrofosmin	prolonged storage/radiolytic decomposition	↓ radiochemical purity; ↓ uptake in breast cancer cells	McKay BF, et al. *Clin Nucl Med* 1997;22:578. Cagnolini A, et al. *Nucl Med Biol* 1998;25:435-439. Oh S, et al. *Clin Nucl Med* 1999;24:469.
	commercial source of syringe	variation in adsorption, especially to plunger; ↓ activity actually injected	Gunasekera RD, et al. *Eur J Nucl Med* 1996;23:1250. Jansson BA, et al. *J Nucl Med Technol* 1998;26:196-199. Bartosch R, et al. *Eur J Nucl Med* 1998;25(suppl): S29. Coupal JJ, et al. *J Nucl Med* 2003;44(suppl):320P. Gunasekera RD. *Nucl Med Commun* 2001;22:493-497.
	adsorption to vial	↓ activity per volume withdrawn from vial	Graham D, et al. *Nucl Med Commun* 1997;18:335.
	adsorption to syringe	↓ activity actually injected	Jansson BA, et al. *J Nucl Med Technol* 1998;26:196-199. Gunasekera RD. *Nucl Med Commun* 2001;22:493-497.
	storage temperature	radiochemical stability is the same for refrigeration vs. room temperature	Jones JM, et al. *Eur J Nucl Med* 1995;22:944.

QUESTIONS

1. Which of the following **is NOT** a potential result of a Tc-99m radiopharmaceutical preparation problem?
   a. ↑ uptake in thyroid, salivary, and stomach from excessive free pertechnetate impurity
   b. ↑ uptake in liver, spleen, and marrow from excessive insoluble hydroxides impurity
   c. ↑ uptake in lungs from excessive large particulates impurity
   d. ↑ uptake in gallbladder from excessive hydrophilic, ionized, >5000 daltons molecular weight impurity

2. Regarding Tc-99m and Tc-99, a mole fraction of 0.5 occurs at an in-growth time of approximately ___ hours in a Mo-99/Tc-99m generator.
   a. 6
   b. 10
   c. 24
   d. 66

3. Which of the following generator eluates contains the SMALLEST mole fraction of Tc-99m?
   a. generator in-growth = 24 hours, eluate age = 12 hours
   b. generator in-growth = 48 hours, eluate age = 6 hours
   c. generator in-growth = 72 hours, eluate age = 1 hour
   d. all of the above are approximately equivalent

4. Based on stannous content, which of the following kits would be expected to best tolerate preparation using the first eluate of a new generator?
   a. bicisate
   b. exametazime
   c. mebrofenin
   d. mertiatide

5. Strategies to minimize radiolytic decomposition and formation of free pertechnetate include each of the following, EXCEPT:
   a. addition of ascorbic acid.
   b. dilution to a lower radioactive concentration.
   c. replacement of nitrogen atmosphere with sterile room air.
   d. storage at refrigerator/freezer temperatures.

6. For which of the following Tc-99m radiopharmaceuticals is reductive decomposition **NOT** a major concern?
   a. Tc-99m exametazime
   b. Tc-99m mertiatide
   c. Tc-99m sestamibi
   d. Tc-99m tetrofosmin

7. For certain Tc-99m generators, a yellow colored eluate indicates:
   a. compromised integrity of the column.
   b. excessive aluminum contamination.
   c. excessive Mo-99 contamination.
   d. excessive peroxide content.

8. For which of the following kits is predilution, rather than post-dilution, with normal saline an important preparation factor?
   a. medronate
   b. pentetate
   c. sestamibi
   d. tetrofosmin

9. Which of the following factors is LEAST likely to result in a poor radiochemical purity of Tc-99m red cells labeled *in vitro*?
   a. elevated white blood cell count
   b. large volume of pertechnetate
   c. low hematocrit
   d. small volume of blood sample

10. For which of the following kits could an inadequate total volume result in solubility problems?
    a. disofenin
    b. gluceptate
    c. mertiatide
    d. tetrofosmin

11. An incubation time of 10-20 minutes for Tc-99m labeling of red cells is required to allow:
    a. diffusion of reduced technetium into the tertiary structure of protein components.
    b. ligand exchange of technetium from an intermediate complex.
    c. progression from the initial rapidly-formed mononuclear complex to the final dinuclear complex.
    d. transport of pertechnetate ions across the cell membrane.

12. Which of the following kits utilizes citrate as a transfer ligand?
    a. apcitide
    b. depreotide
    c. red blood cells
    d. sestamibi

13. Which of the following Tc-99m radiopharmaceuticals might contain Tc-99m edetate as a radiochemical impurity?
    a. Tc-99m arcitumomab
    b. Tc-99m bicisate
    c. Tc-99m mertiatide
    d. Tc-99m tetrofosmin

14. Which of the following kits **does NOT require** heating for the purpose of cleaving off protective groups and freeing up binding sites for complexation with Tc-99m?
    a. apcitide
    b. depreotide
    c. mertiatide
    d. sestamibi

15. Contamination of Tc-99m generator columns with which of the following has been implicated in cases of poor elution yields?
    a. benzyl alcohol
    b. isopropyl alcohol
    c. parabens
    d. peroxide

16. In order to best maintain functional integrity, Tc-99m leukocytes should be resuspended in:
    a. 0.9% sodium chloride injection
    b. Hank's balanced salt solution
    c. phosphate buffered saline
    d. plasma

17. Which of the following Tc-99m labeled radiopharmaceuticals is **LEAST** affected by changes in specific activity?
    a. Tc-99m apcitide – detection of deep vein thrombosis
    b. Tc-99m pentetate – determination of glomerular filtration rate
    c. Tc-99m sulfur colloid – localization in sentinel lymph node
    d. Tc-99m damaged red cells – sequestration in spleen

18. Surveys of preparation problems resulting in unacceptable radiochemical purity suggest that important contributing factors include each of the following, EXCEPT:
    a. normal saline for dilution obtained from glass vials.
    b. kits containing relatively small amounts of stannous ion.
    c. Tc-99m sodium pertechnetate obtained as the first eluate from a new generator.
    d. Tc-99m sodium pertechnetate more than 12 hours old.

19. Which of the following is the most significant mechanism for decomposition of Tc-99m radiopharmaceuticals?
    a. direct radiation effects
    b. indirect radiation effects
    c. internal radiation effects
    d. non-radiolytic chemical effects

20. For which of the following Tc-99m radiopharmaceuticals is agitation of LEAST concern?
    a. Tc-99m arcitumomab
    b. Tc-99m leukocytes
    c. Tc-99m pyrophosphate
    d. Tc-99m sestamibi

21. Which of the following Tc-99m radiopharmaceuticals has the greatest tendency to adsorb over time to the surface of glass storage vials?
    a. Tc-99m medronate
    b. Tc-99m pentetate
    c. Tc-99m pertechnetate
    d. Tc-99m sulfur colloid

22. For which of the following Tc-99m radiopharmaceuticals can significant syringe retention be a concern?
    a. Tc-99m bicisate
    b. Tc-99m exametazime
    c. Tc-99m mertiatide
    d. Tc-99m tetrofosmin

23. Retention of Tc-99m radiopharmaceuticals in syringes is influenced by:
    a. amount of agitation.
    b. length of time in syringe.
    c. type and composition of syringe.
    d. all of the above.

24. Which of the following is preferred as an antiseptic for vial diaphragms?
    a. chlorhexidrine
    b. ethyl alcohol
    c. hydrogen peroxide
    d. povidone-iodine

25. Tc-99m radiopharmaceutical preparation problems:
    a. always result in false positive image interpretations.
    b. are always detected by quality control testing.
    c. are always the result of human error.
    d. are likely to be encountered with new radiopharmaceuticals and when deviating from package insert instructions for preparation of established products.

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