Radiopharmaceutical Production and Quality Control*

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With the development of shorter-lived, organ-specific radiopharmaceuticals, much of the manufacture and quality control of these products have shifted from commercial manufactures to individual nuclear medicine laboratories. Recognizing this fact, the Nuclear Regulatory Commission (NRC) is encouraging quality assurance by proposing that "an authorized physician may permit technicians and other paramedical personnel to perform the preparation and quality control testing of radiopharmaceuticals . . ." (1).

Cohen (2) has catagorized pharmaceutical controls into chemical, biological, and physical. Figure 1 is a diagram of these controls. In each control a degree of purity is implied and is often determined by comparison to a standard.

Chemical controls.

A. *Radiochemical purity.* May be defined as that portion of the stated radionuclide in the stated chemical form. This can be assessed in the nuclear medicine laboratory by several techniques. It is applicable to Tc^{99m}-pertechnetate compounds where the degree of tag to an organ-specific molecule must be evaluated.

Radiochemical impurities may be demonstrated in those images where organs other than the target organ are visualized due to a free (unbound) radioactive component of a labeled product. Visualization of thyroid on lung imaging (Fig. 2) or stomach with kidney (Fig. 3) and bone (Fig. 4) imaging are examples of these. Reagent "kits" labeled with radionuclides should be at least 90% bound for optimum organ visualization. The assessment of binding can be accomplished in the laboratory by the use of gel filtration and/or thin-layer chromatographic techniques. Labeled reagent kits may contain small molecules (free Tc^{99m}-pertechnetate), larger labeled molecules, and a reduced technetium fraction which is considered neither free nor bound to an organ-specific molecule. To determine the percentage of each component in this three-phase system by employing the gel filtration technique, 1-2 μl of the material is placed at the top of a gel column and eluted with a suitable solvent. Heavy molecules which do not enter the gel meshwork will be eluted first, after the void volume. Light molecules will follow several milliters later. Reduced technetium, if present, will bind to the gel and can be removed by oxidation with 0.1% H_2O_2. This fraction can be subsequently collected with additional volumes of solvent. The fractionated volumes are counted and quantitation of each component may be determined.

Thin-layer chromatography employs the use of suitable media strips to which is spotted 5μl of the radioactive material 2.5 cm from the bottom of the strip. The strip is dried and placed in a developing tank containing a suitable solvent system (Fig. 5). The solvent is allowed to ascend the strip until the front is at approximately 14 cm. Solvent systems chosen provide for the bound material to remain approximately at the origin (point of application) while free activity migrates to the level of the solvent front. Using this method, Rf (reference factor) may be determined. These factors are ratios of distance

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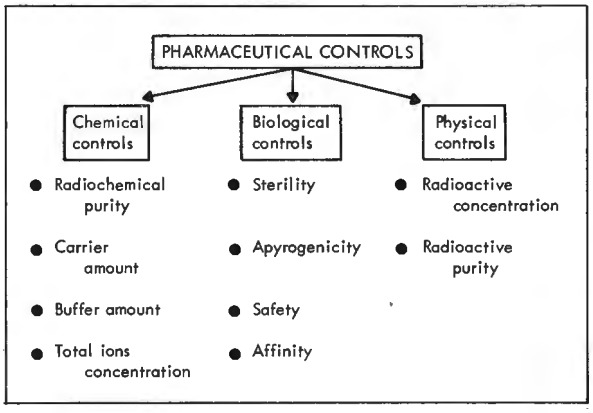


Fig. 1—Diagram of the radiopharmaceutical controls.

traveled by the radioactive entities to that traveled by the solvent front. Labeled molecule Rf are approximately 0–0.1 while that of free species 0.8–1.0. Solvent systems may be single or multiple components and provide for good separation of labeled molecules and free ionic species.

Strips are removed from developing tanks, air dried, and analyzed for quantitation of components in the sample. Strips may be cut into 1 cm widths and placed into gamma well counters to determine presence and, therefore, identity of activity on the strip. The origin (2.5–3.5 cm) of acceptable radiopharmaceuticals contains 90% of the counts. A radiochromatogram well adapter can be used and is less time consuming (3). Radioscanchromatographs can provide this information by producing a graph with peaks of activity demonstrating location and quantitation of radioactive components.

Figure 6 is a chromatograph of Tc^{99m}-Polyphosphate® (New England Nuclear) used as the bone scanning agent in Figure 4. The chromatograph demonstrates activity at the origin representing

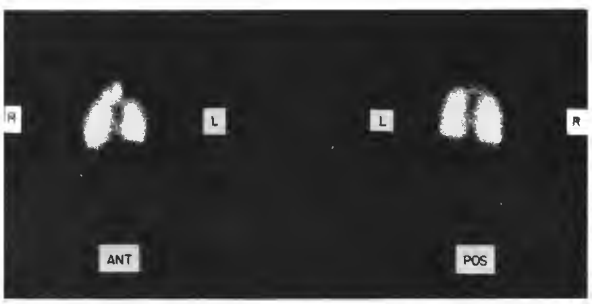


Fig. 2—I^{131}-macroaggregated albumin (Abbott) lung image demonstrating thyroid uptake of free radioiodine.

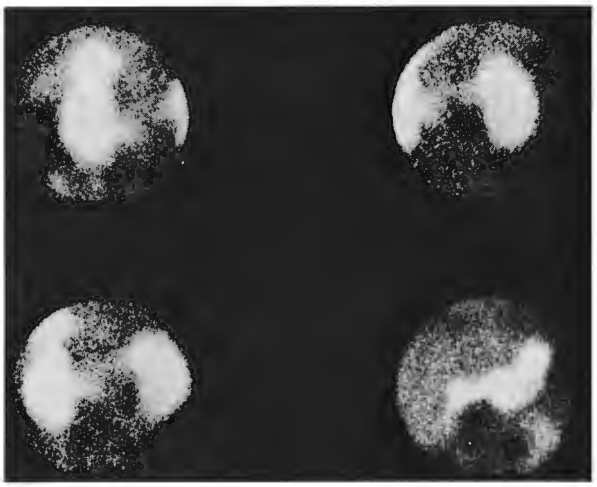


Fig. 3—Tc^{99m}-Renotec (Squibb) kidney image demonstrating stomach uptake of free Tc^{99m}-pertechnetate. (Image provided courtesy Dr. H. T. Haden, McGuire VA Hospital, Richmond, Va.)

Tc^{99m}-pertechnetate bound to phosphate complexes, activity between origin and solvent front demonstrating reduced pertechnetate and/or labeled metabolized phosphates, and a second but less prominent

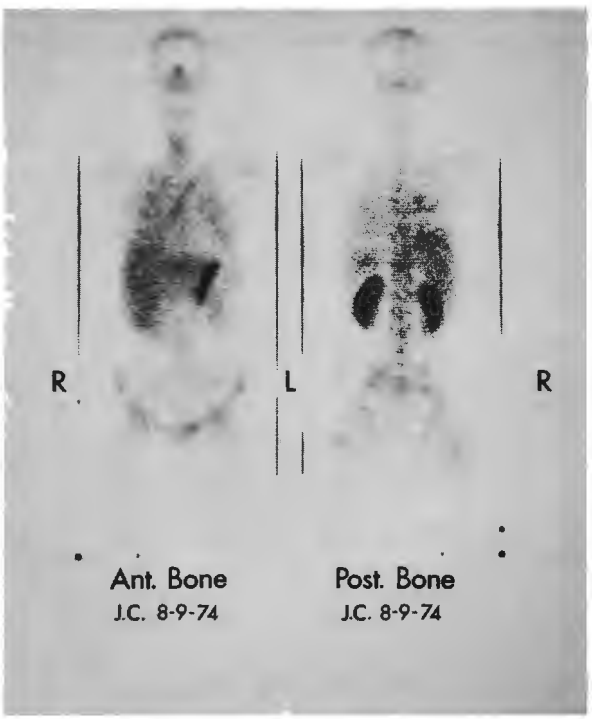


Fig. 4—Tc^{99m}-Polyphosphate® (New England Nuclear) bone image demonstrating stomach uptake of free Tc^{99m}-pertechnetate. Increased activity in liver probably associated with a reduced technetium species in blood pool.

Recommended Chromatography Solvents

Preparation	Solvent	Rf BTc	Rf FTc
Tc99m (Sn) DTPA	Acetone	0.0	1.0
	Butyl acetate	0.0	0.8
Tc99m (Sn) Gluco-heptonate	M.E.K.	0.0	1.0
Tc99m - HSA	Methanol, 85%	0.0	0.8
Tc99m - MAA	Methanol, 85%	0.0	0.8
Tc99m - Polyphosphate	Acetone	0.0	1.0
	Butyl acetote	0.0	0.8
Renotec*	Butanol: Ethanol: Water (2:2:1)	0.1	0.7
Tc99m - Sulfur Colloid	Methanol, 85%	0.1	1.0

*Eastman TLC Cellulose #6064 media; all others, Gelman ITLC Type SG

Fig. 5—Chromatography solvent systems recommended for the determination of bound (BTc) and free (FTc) components of technetium-99m kit preparations. Each system provides reproducible Rf values used in the identification and quantitation of each component.

peak at the solvent front demonstrating free pertechnetate.

Figure 7 compares the chromatographs of Tc^{99m}-Polyphosphate® (NEN) to that of Osteoscan® (Proctor and Gamble). Technetium-99m-pertechnetate obtained from a 400 millicuries fission Mo^{99}-Tc^{99m} generator was used to prepare each of the above bone imaging agents. The Tc^{99m}-Polyphosphate® chromatogram demonstrated 98.5% of the pertechnetate bound to the phosphate complex. With Osteoscan®, the chromatograph demonstrated a reduced and/or labeled metabolized phosphate component of approximately 40%. The manufacturer claimed that the nitrogen atmosphere in the vial was lost through the rubber closure with oxidation of the Sn(II) reducing agent. (Recently the manufacturer has adopted a butyl rubber closure which has resolved this problem.)

Figure 8 is a chromatograph of Tc^{99m}-Sn-Glucoheptonate® (NEN). With methyl ethyl ketone (MEK) solvent, peak activity was found at the origin corresponding to the bound component. No free pertechnetate was demonstrated. The manufacturer claimed the material may be subject to colloid formation with some resultant localization of activity in the liver. The material was chromatogramed in a physiologic saline solution demonstrating no colloid at the origin.

B. *Carrier amount.* May be defined as stable or long-lived isotopes of the nuclide present at the time of administration of the radiopharmaceutical. Carrier, if present in large quantities, alters the distribution of the nuclide in vivo or adds to radiation burden if it is radioactive. Manufacturers prepare compounds that are "carrier-free." This has come to mean that no other isotope of the nuclide has been intentionally added.

C. *Buffer amount.* The pH of radiopharmaceuticals should be adjusted to provide for stable complexes as well as physiologic suitability. Most radiopharmaceuticals are adjusted in the range of pH 4.0 to 8.8.

D. *Total ions concentrations.* Radiochemical solutions after production may contain various metals or metaloids as contaminants. These contaminants may be imparted from apparatus and reagent materials even if very pure. Complexation of the radiochemical with these traces give chemically unstable radioactive solutions. A standard of 80μg/ml of these ions has been set; however, the current state of the art is to prepare products with less than 1μg/ml.

Of the potential nonradioactive ionic impurities present in Tc^{99m}-pertechnetate eluent, aluminum [Al (III)] has produced the most concern. Toxicology of Al (III) of potential doses administered appears minimal (Fig. 9); however, it has been reported to cause flocculation of Tc^{99m}-sulfur colloid preparations as well as agglutination of red blood cells during the labeling process (4). Current NRC standards limit the presence of this ion to 10μg (fission Mo^{99}) and 20μg (activation Mo^{99}) per milliliter of generator

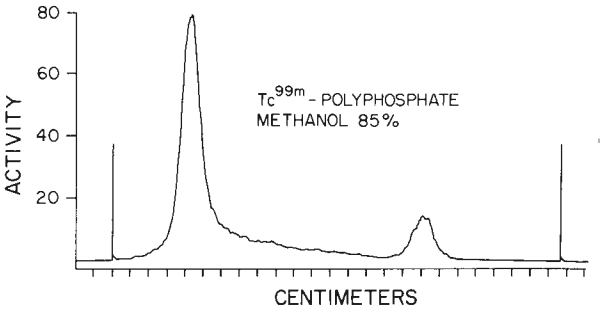


Fig. 6—Chromatograph of Tc^{99m}-Polyphosphate® used to produce bone image in Figure 4 demonstrates bound, reduced, and free components of the radiopharmaceutical.

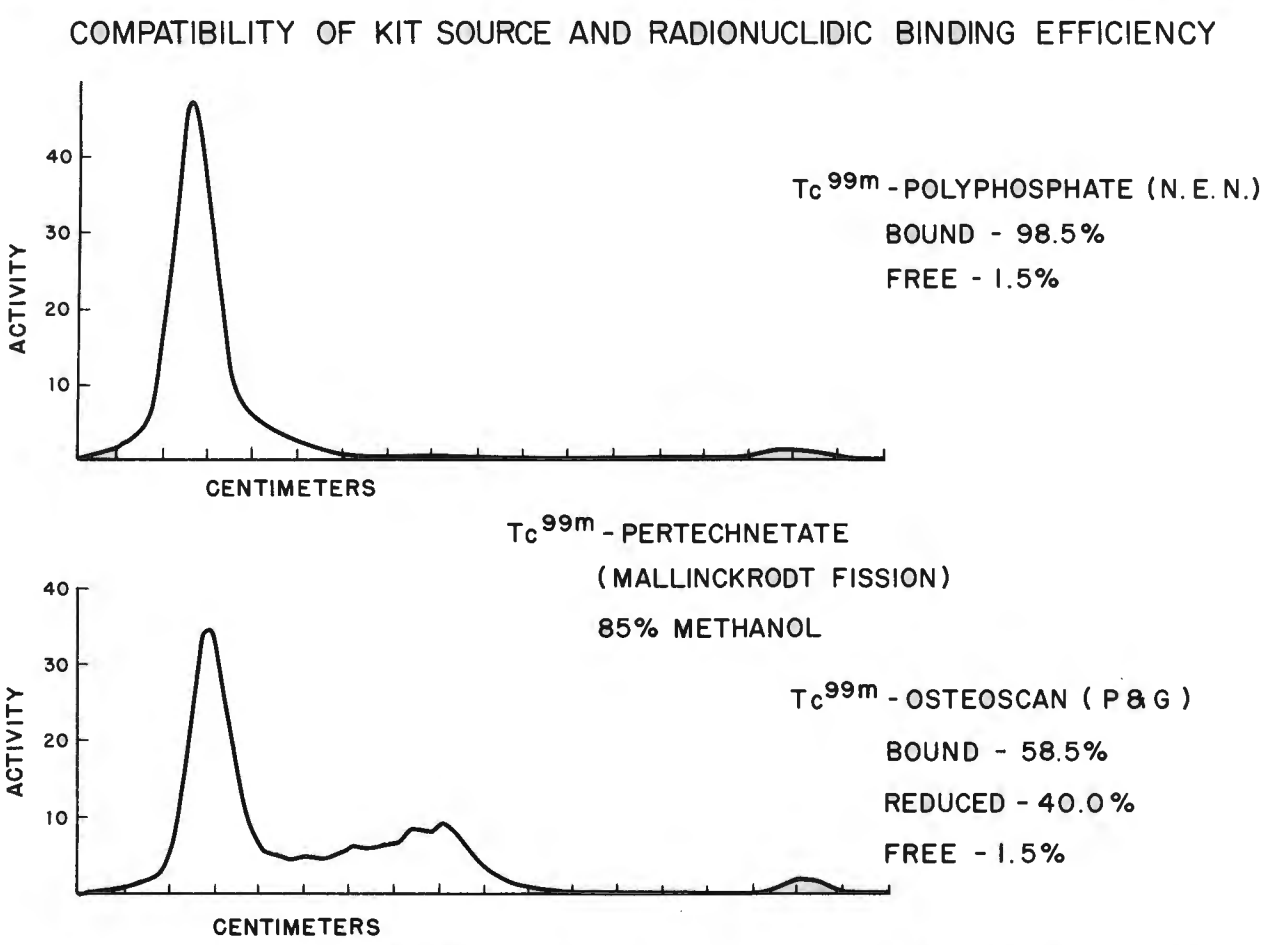


Fig. 7—Comparison of chromatographs obtained after preparation of two commercially available bone imaging agents; Tc^{99m}-Polyphosphate® (New England Nuclear), Tc^{99m}-Osteoscan® (Proctor and Gamble).

eluent. This represents a more stringent requirement from a previous 500μg Al (III)/10 millicuries Tc^{99m}-pertechnetate limitation.

To determine at what concentration of Al (III) flocculation of sulfur colloid would occur, Al (III) solution was prepared by dissolving 99+% aluminum metal in HCl. Aluminum (III)-Tc^{99m}-pertechnetate solutions were prepared such that Al (III) concentration ranged from 10μg/ml to 1000μg/ml of Tc^{99m}-pertechnetate in saline (Fig. 10). A control using Al (III) free pertechnetate was also prepared. Technetium-99m-sulfur colloid (Squibb) were prepared by standard methods incorporating each of the Al (III)-Tc^{99m}-pertechnetate solutions as the radioactive source. Final sulfur colloid volumes were 8 ml giving resultant Al (III) concentrations of 0 to 12.50 mg%. Aluminon reagent (aurin-tricarboxylic acid) test strips (NEN) were evaluated for suitability in the detection of Al (III) contamination at levels associated with sulfur colloid flocculation (Fig. 11). Colloid aggregation was determined by placing 0.1 ml of each sample on a standard hemocytometer chamber and observation under light microscopy (Fig. 12).

Two hundred microcuries (0.2 ml) of each of the sulfur colloid preparations were injected into 250 g female Sprague-Dawley rats via a femoral vein. Scintiphotos were obtained using the Searle Radiographics Pho-Gamma HP camera fitted with a pinhole collimator to demonstrate distribution of the radiocolloid (Fig. 13).

Preparations of sulfur colloid from 0 to 0.63 mg% Al (III) demonstrated no aggregation. Aluminon test papers demonstrated an increase in the presence of Al (III) with each increase in ion concentration. Scintiphotos of test animals demonstrated

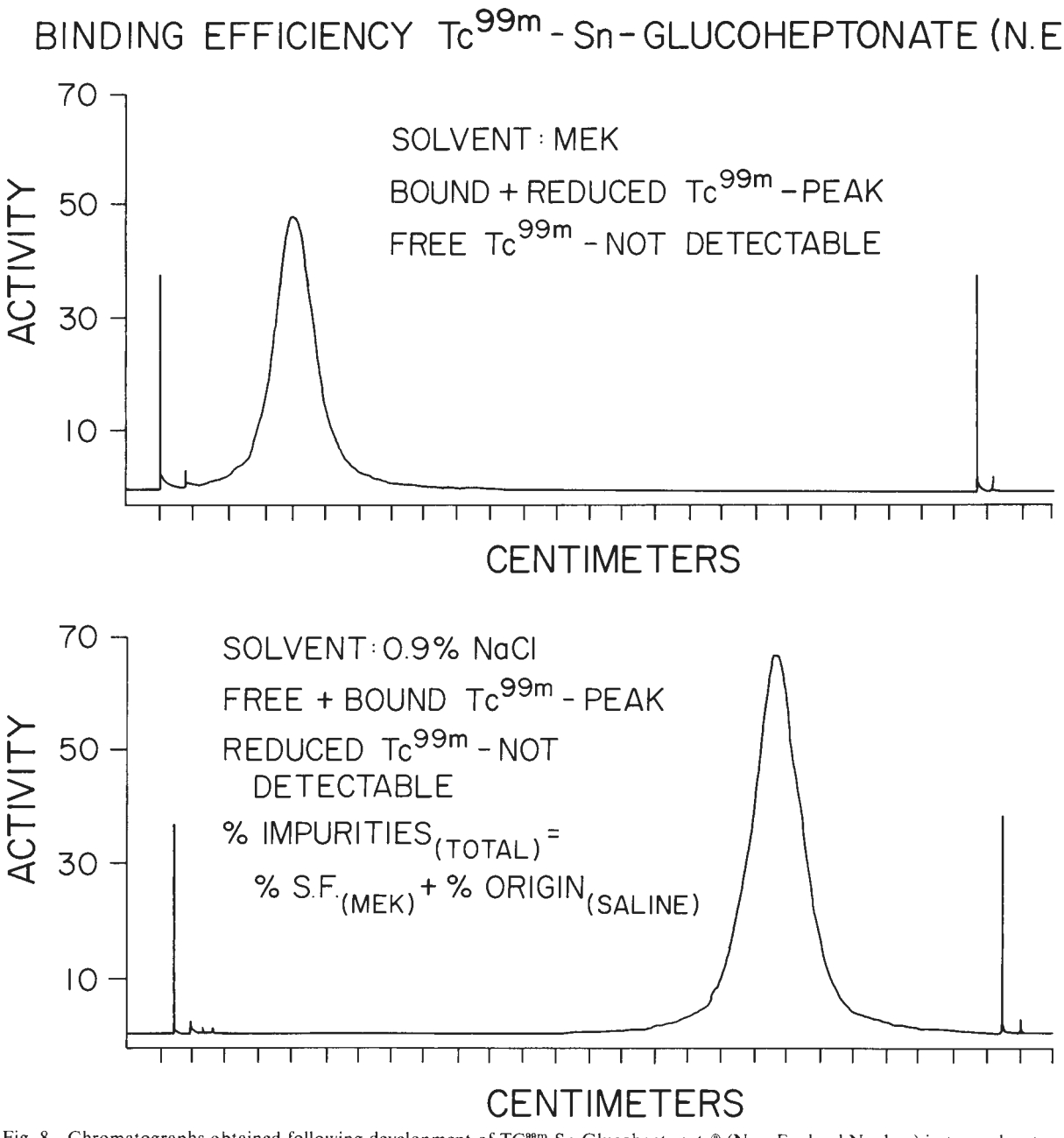


Fig. 8—Chromatographs obtained following development of TC^{99m}-Sn-Glucoheptonate® (New England Nuclear) in two solvent systems. Upper chromatograph demonstrates absence of free pertechnetate. Lower chromatograph demonstrates absence of colloid.

distribution of radiocolloid to liver with no uptake in lung. At 0.94 mg% Al (III), some colloid aggregation was present with minimum uptake of colloid in the lung of test animal. At 1.56 mg% Al (III), aggregate size became critical with scintiphotos demonstrating significant quantities of radiocolloid in lung. Lung uptake of radiocolloid increased at 3.13 mg% Al (III). Test materials containing 6.25 mg% and 12.50 mg% Al (III) demonstrated larger aggregates; however, these materials were not administered to test animals because aggregates would be limited to the inside diameter (254μ) of the 25 G needle.

Liver, lung, and spleen from each test animal were excized and counted using a Picker well counter.

TOXICOLOGY ALUMINUM CONTAMINATION IN PERTECHNETATE

A.E.C. LIMIT - 10μg./ml. $NaTcO_4$

I.V. LD_{50} OF ALUMINUM (AS $AlCl_3$) IN MICE IS 79 mg./Kg. (EQUIVALENT TO ABOUT 20 mg. ALUMINUM/Kg.)

I.V. LD_2 OF ALUMINUM (AS $AlCl_3$) IN MICE IS 55 mg./Kg. (EQUIVALENT TO 14 mg. ALUMINUM/Kg.)

Fig. 9—Nuclear Regulatory Commission (AEC) allowable limit for aluminum ion contamination in Tc^{99m}-pertechnetate. Limit is within a margin of safety for administration to man.

Ratios of counts for liver: lung and liver: spleen were calculated (Fig. 14) and demonstrated good correlation with Squibb Institute reports for the control material. At Al (III) concentration of 0.13 mg% to 0.94 mg%, there was a general increase in liver: lung with a corresponding general decrease in liver: spleen. Sulfur colloid used in liver imaging vary in size from mμ to 1 μ. Up to 15% of the material may normally localize in bone marrow attributable to the smaller end of colloid size range. With increasing concentrations of Al (III), smaller colloid may aggregate providing for more liver localization. Similarly, as the colloid size continues to increase, more of the material may localize in spleen, which is capable of phagocytizing colloid larger than that by liver.

At the critical concentration of 1.56 mg% Al (III), liver: lung was 0.32:1 demonstrating on a per-gram basis three times the activity of radiocolloid in lung as compared to liver. At 3.13 mg% Al (III), activity in the lung increased to 16 times that of liver.

μg. Al + 3	μg. Al + 3/ml. Tc99m04 (mg. %)		μg. Al + 3/ml. Kit* (mg. %)	
10	10	(1.0)	1.25	(0.13)
25	25	(2.5)	3.13	(0.31)
50	50	(5.0)	6.25	(0.63)
75	75	(7.5)	9.38	(0.94)
125	125	(12.5)	15.63	(1.56)
250	250	(25.0)	31.25	(3.13)
500	500	(50.0)	62.50	(6.25)
1000	1000	(100.0)	125.00	(12.50)

* FINAL PREPARATION = 8 ml.

Fig. 10—Concentration of aluminum ion in radioactive solutions. Center panel expresses aluminum concentration present in Tc^{99m}-pertechnetate. Third panel expresses aluminum concentration present following preparation of sulfur colloid kit.

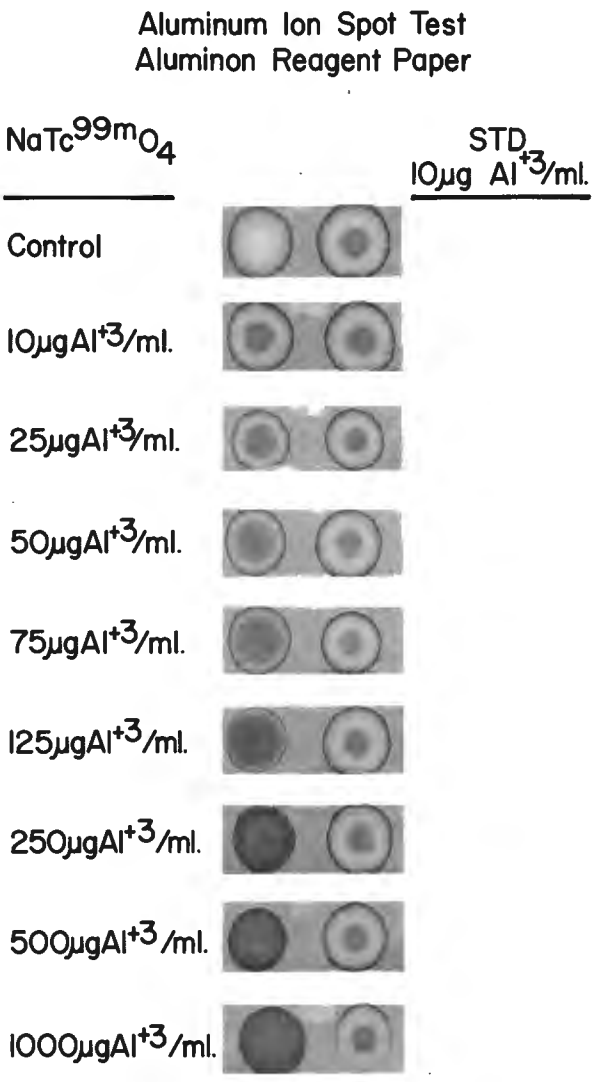


Fig. 11—Change in aluminon spot test with increasing concentration of aluminum ion.

In conclusion, the Aluminon test papers were adequate in detecting Al (III) concentration, and the maximum allowable concentration of Al (III) in Tc^{99m}-pertechnetate was found to be 75μg/ml. The current standard is well within this value.

Biological Controls. The United States Pharmacopeia (USP) specifications for all parenteral products includes the absence of viable forms of bacteria, viruses, yeast, and molds as well as pyrogenic substances. Therefore, radiopharmaceuticals administered parenterally must also be of this quality.

A. *Sterility.* Many of the radiopharmaceuticals

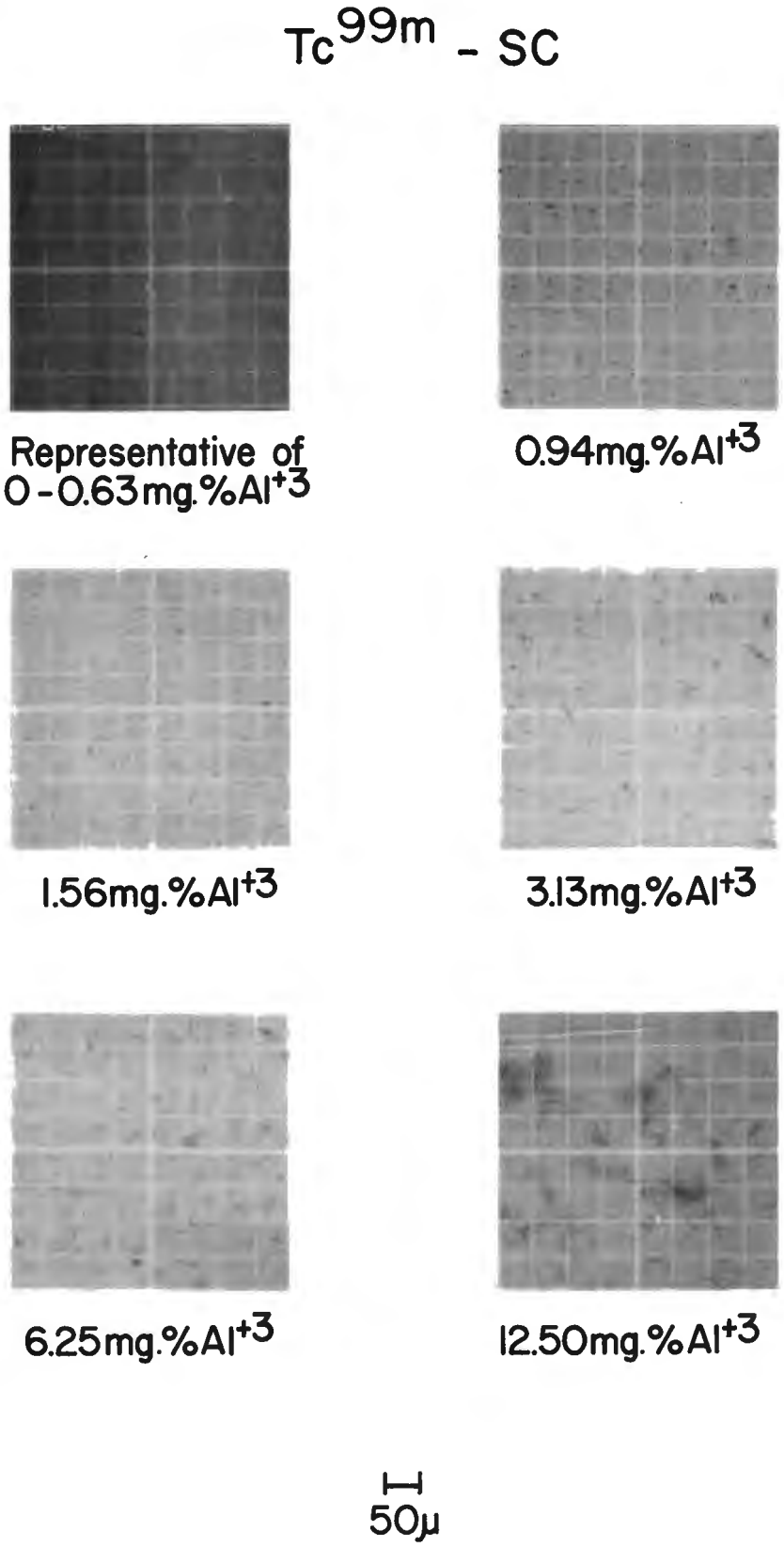
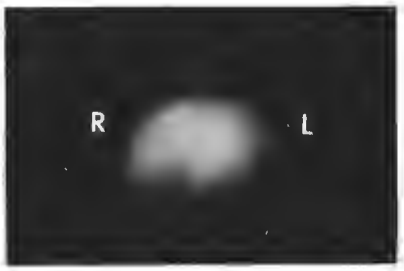


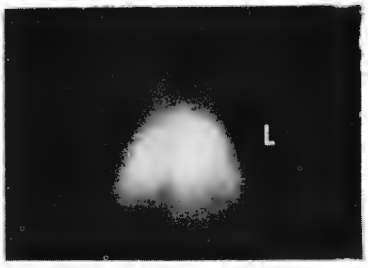
Fig. 12—Effect of increasing concentration of aluminum ion on colloid aggregation. Magnification is 10X.

0mg.% Al^{+3}



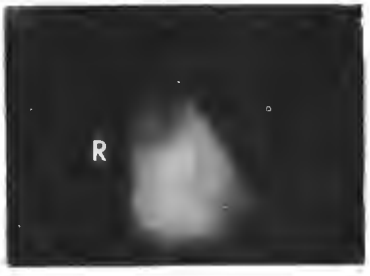
0.13mg.% Al^{+3}

0.31mg.% Al^{+3}

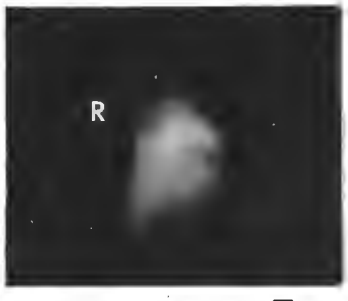


0.63mg.% Al^{+3}

0.94mg.% Al^{+3}



1.56mg.% Al^{+3}



3.13mg.% Al^{+3}

Fig. 13—Effect of increasing concentration of aluminum ion on radiocolloid distribution in rat. Anterior views obtained with Searle Radiographics-HP gamma camera fitted with a pin-hole collimator. Each image represents the accumulation of 100,000 counts.

Effect of Al^{+3} Content in Tc99m - Sulfur Colloid on Distribution Ratios* in Rat Organs (per gram wt.)

mg. % Al^{+3}	Liver:Lung	Liver:Spleen
0	4.73:1	1.23:1
0.13	6.73:1	6.43:1
0.31	5.23:1	4.77:1
0.63	3.46:1	1.83:1
0.94	4.81:1	1.59:1
1.56	0.32:1	1.16:1
3.13	0.06:1	0.37:1

* 20 min. post-injection (i.v.)

Fig. 14—Ratios of liver:lung and liver:spleen counts obtained from excized rat organs. Ratios are expressed per-gram weight of organ.

used as diagnostic agents in nuclear medicine are intended for parenteral administration. Pharmaceuticals of this type must meet USP requirements in that they are sterile, apyrogenic, and of acceptable pH (5).

Methods of sterilization vary and selection is dependant upon stability of the compound and its label. Terminal sterilization in an autoclave and membrane filtration are two of the more commonly used methods employed to sterilize radiopharmaceuticals. With each of the above methods, however, samples must be taken and tested to confirm sterility.

The USP method requires innoculation of the radiopharmaceutical into fluid thioglycolate and Soybean-Casein Digest medias. A 7-day incubation period at 30 to 35°C with fluid thioglycolate and 20 to 25°C with Soybean-Casein Digest without evidence of viable organisms indicates a sterile preparation. It becomes apparent that activity of radiopharmaceuticals with short physical half-lives would significantly decay before the product was approved for clinical use. Under this circumstance, the dilemma of whether to administer the preparation may be minimized if asceptic technique were employed and previous materials tested after-the-fact demonstrated sterility.

Work by Deland and Wagner (6) has shortened the determination of sterility to within acceptable time for short-lived nuclides. Test materials are innoculated in thioglycolate broth containing C^{14} glucose. Viable organisms, if present, would metabolize the labeled sugar to $C^{14}O_2$ which is detected and recorded, demonstrating the presence of microbial contamination. This procedure, although not an official test, has reduced lag time from days to 1–3 hours.

B. *Apyrogenicity.* Pyrogens of microbial origin, are mucopolysaccharide molecules present as the result of bacterial, viral, fungal, or yeast contamination. The substances are heat-stable and therefore resistant to destruction by terminal sterilization. When administered by some injection route, they may produce in man such symptoms as mono-or biphasic fever, chills, malaise, mild to moderate pain in the joints, and leukopenia, or other less well-defined clinical signs, such as apprehension, pallor, and substernal oppression (7). Sensitivity of the human body to administration of pyrogens by the intrathecal route is such that the biologic insult of this type increases 4000-fold as compared to the intravenous route (8).

The USP method for the detection of pyrogens relies upon rectal temperature change in the pre- to post-innoculated rabbit. Controls for the test are stringent and include:

1. Use of healthy, mature rabbits each weighing not less than 1.5 kg that have maintained this weight for one week.
2. Control temperature of each rabbit used does not vary by more than 1°C from each other. No animal may be used with a control temperature exceeding 39.8°C.
3. Animals must be housed individually, free from excitement, in an environmental temperature that does not vary by more than ± 3°C.
4. Animals may not be used more than once every 48 hours.
5. Animals may not be used before 2 weeks having been given a test sample that was pyrogenic.
6. Animals not used for pyrogen testing during a 14-day period must be sham tested 1–3 days before use.
7. Test material administered may not exceed 10 ml.

Test material is injected into the marginal ear vein of three animals. Rectal temperatures are

recorded at hourly intervals for three hours post injection. If none of the test animals show an individual temperature rise of 0.6°C or more above its control temperature and if the sum of the temperature rises in all three animals does not exceed 1.4°C, the test material meets the requirement of apyrogenicity. If the above criteria are not met, the test must be repeated with five rabbits. If not more than three of the eight rabbits show temperature rises of 0.6°C or more and if the sum of the eight temperature rises does not exceed 3.7°C, the product under test meets the requirement for apyrogenicity.

Pyrogen testing by the USP method is difficult, time consuming, and generally not amenable to small laboratories. Cooper et al (9), have introduced an in vitro test based on the detection of endotoxin through gelation of Limulus polyphemus lysate prepared from blood amebocytes. Test results may be obtained in 1 hour which represents time saved with respect to short-lived nuclides. This test is significantly more sensitive than the official test; however, it is subject to false positive results if the preparation to be tested contains Ca (II). The problems of adopting a more sensitive test must be justified in view of the fact that no documentation exists of pyrexia following administration of materials found apyrogenic by the USP test. The question of how sensitive pyrogen testing must be deserves further investigation.

C. *Safety.* With the administration of pharmaceuticals in radioactive form, safety includes radiation-absorbed doses received by target and nontarget organs that are within acceptable limits. The product must also be nontoxic in doses administered with respect to formed cells in blood as well as organs to which the material will be distributed.

D. *Affinity.* Radioactive compounds used in organ imaging localize by various physiological mechanisms. Control of the physiochemical characteristics of the radiopharmaceutical are needed to assure affinity of the product for target organs.

Soloway and Davis (10) reviewed radiopharmaceuticals currently used for organ imaging and have catagorized their biological basis for localization. In vitro quality control testing is essential to predetermine that organs of interest will be visualized. Poor affinity demonstrated by suboptimal images must frequently be repeated, therefore, necessitating subsequent dosing with radionuclides and increased radiation burden to patients.

Perfusion lung imaging is dependant upon blood flow to that organ with capillary and terminal arteriolar blockage by radiolabeled particles. Particles for this purpose must be larger than that of red blood cells (7μ) to prevent arterial distribution after intravenous administration. To avoid an unnecessarily long, effective half-life in lung, as well as optimum patient safety, particles should be limited in size to 50μ. Particle size determination can be easily accomplished in the laboratory using light microscopy as a routine check.

Images of liver and spleen are dependant upon blood flow to these organs with phagocytosis of radiocolloid by reticuloendothelial cells. Colloid of 0.6μ and 1.0μ are necessary for localization in liver and spleen respectively. Although colloid may not be visualized by light microscopy, the test serves as a negative check for aggregates so large that they might localize in lung.

Radioactive materials have been used to delineate special anatomic or biochemical compartments. Labeled serum albumin has been used in the past for cisternography and currently for blood pool imaging. Care must be taken not to denature the protein by excessive labeling or chemical manipulation.

Stannous chloride [Sn(II)] has become a useful reducing agent in the preparation of technetium-labeled radiopharmaceuticals. Yano et al (11), in studies with the bone imaging agent Tc^{99m}-Sn-EHDP, found optimum molar ratio of Sn (II):EHDP for greater bone localization and rapid soft tissue clearance. They reported the importance in the order of combination of EHDP, Sn (II) and Tc^{99m}-pertechnetate such that poor formulation resulted in radiocolloid formation with localization in liver. Poor localization of other technetium products with significant uptake in thyroid has been noted when stannic chloride [Sn(III)] forms on crystal surfaces of the reducing agent.

Physical Controls.

A. *Radioactive concentration.* Refers to the activity concentration of the product with respect to activity per unit volume. Activity concentration can be easily determined using a dose calibrator. This instrument has an overall accuracy of 5% and is designed to quantitate many of the more commonly used radionuclides.

B. *Radioactive purity.* This term should be discontinued in favor of the more accurate term "radionuclide purity." It may be defined as that proportion of the total activity that is present as the stated radionuclide.

The NRC limit for Mo^{99} contamination has been set at 1 microcurie Mo^{99} per millicuries Tc^{99m}-pertechnetate and 5 microcuries per dose of Tc^{99m}-pertechnetate. On a milligram basis the amount of Mo^{99} necessary for a lethal dose or LD_{50} dose in test animals is large as compared to what can be eluted from an intact generator system (Fig. 15). However, on an equal activity basis using the MIRD system (12, 13), radiation burden from Mo^{99} is 35 times greater as compared to Tc^{99m}. It has also been demonstrated that parent Mo^{99} produced by neutron activation of Mo^{98} results in Cs^{134} contamination.

Radioactive contaminants of Mo^{99}-Tc^{99m} generator systems may be detected radiometrically. Molybdenum-99 emits 740 and 780 kev gammas as well as other less energetic photons. A 4 mm lead shield adapter inserted in the ion chamber of the dose calibrator would absorb all but 0.0002% of Tc^{99m} gamma (140 kev) and 50% of Mo^{99} gamma (14). It is fortuitous that Mo^{99} activity can be read directly on the Tc^{99m} setting when the pertechnetate source is placed in the lead adapter. The method allows for quantitation of the Mo^{99} activity which should not exceed 0.1% of the Tc^{99m} activity. Cesium-134 emits 605 and 796 kev gammas which penetrate the 4 mm lead shield and will be quantitated with the Mo^{99} reading.

In-House Preparation of Radiopharmaceuticals.

Present day practice of nuclear medicine relies upon readily available organ-specific radiopharmaceuticals. Exhaustive research of natural and man-made radionuclides has resulted in a handful that demonstrate organ specificity with patient safety. As a result, research has been directed toward the labeling of molecules with radionuclides of near-ideal properties for organ selectivity. Technetium-99m having suitable physical, chemical, and biological properties enjoys an active role in organ imaging. Since 1961, many Tc^{99m}-labeled compounds have been introduced which have broadened the diagnostic capabilities of nuclear medicine and/or improved radiation burden as compared to previously used radionuclides.

Much of this research has resulted in the commercial availability of kit preparations where simple asceptic techniques are employed to produce the desired Tc^{99m} radiopharmaceutical. With the commercial availability of Mo^{99}-Tc^{99m} generators, daily delivery, or MEK extraction techniques, a continuous supply of Tc^{99m}-pertechnetate is at hand for the preparation of kits. The commercial availability of these tools has been a boon to many institutions which might not be able to provide this diagnostic service. This availability, however, is not without cost, and newer formulations with clinical merit may take months before they become commercially available, thereby limiting diagnostic studies to current available preparation.

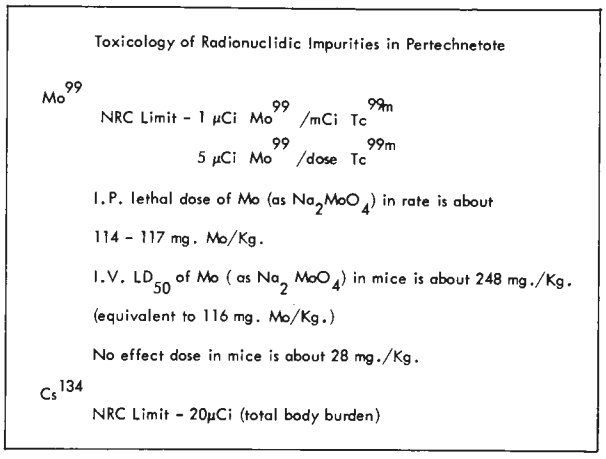


Fig. 15—Nuclear Regulatory Commission maximum allowable limits for radionuclidic impurities in Tc^{99m}-pertechnetate.

Radiopharmaceutical scientists (radiopharmacist, radiochemist) have paralleled the growth of nuclear medicine consultants by providing efficacious radiopharmaceutical diagnostic agents. In-house preparation of radiopharmaceuticals by these individuals have allowed for the availability of newer agents in nuclear medicine practice. Institutions preparing radiopharmaceuticals are increasing, and those without this technical capability may benefit under a cost-sharing program (15).

Several formulations are available for the preparation of the more routinely used imaging agents. The following are currently used at the Medical College of Virginia Hospitals. Drug-adverse reactions have not been reported for any of the products since clinical initiation.

PREPARATION OF TC99M-SULFUR COLLOID KIT (16)

Solution A:

To 100 ml of Sterile Distilled Water add:

1. 400 mg Sodium Thiosulfate
2. 750 mg Gelatin
3. 850 mg Potassium Monohydrogen Phosphate (Dibasic)
4. 200 mg Disodium Edetate

Stir and warm the mixture gently to dissolve the gelatin. After solution is complete, pipette exactly 3 ml of the solution into each 30 ml serum vials. Seal the vials with rubber closures and aluminum caps (twice boiled in sterile distilled water for not less than 30 minutes and autoclaved, wrapped in aluminum foil) and autoclave Solution A for 15 minutes at 20 PSIG pressure.

Solution B:
Sterilize 1-3 ml of exactly 0.5N HCl solution in serum vials by autoclaving for 15 minutes at 20 PSIG pressure.

Solution C:
To 100 ml Sterile Distilled Water add:
1. 1.20 g Sodium Hydroxide pellets
2. 2.8 g Sodium monohydrogen phosphate

Mix well until solution is complete. Do not autoclave. Sterilize by filtration using 0.22μ membrane filter.

Preparation of Tc99m MAA Kit (16)

A. Prepare Albumin Sodium Acetate solution in distilled water such that it contains 10 mg/ml of HSA, 100 mg/ml of Sodium Acetate. Sterilize by membrane filtration (0.22μ size).
B. Prepare Stannous Chloride solution in 1N HCl such that it contains 5 mg/ml of stannous chloride. Sterilize by membrane filtration (0.22μ size).
C. To an empty sterile serum vial containing a small magnetic stirrer mix 5 ml of Solution A with 19 ml of Sterile Water for Injection. Mix well. Add 1 ml of Solution B. The pH should be approximately 5.5.
D. Macroaggregate the Albumin in the above solution in a water bath at 80°C±1 for 12 minutes with stirring.
E. Cool and mix the aggregates well. Each ml of this preparation now contains:
   1. 2 mg HSA as aggregates (denatured)
   2. 200μg Stannous Chloride as hydroxide
   3. 20 mg Sodium Acetate as buffer
F. Transfer under aseptic conditions 1 ml each of this solution to presterilized empty serum vials and store under refrigeration.

Preparation of Tc99m-Labeled Human Serum Albumin (17)

Materials:

I. Kit (consists of 3 sterile pyrogen-free vials).
   Vial "A"—20 ml vial containing 0.85 ml of 1N HCL with two 1-inch lengths of Zr wire inserted through the diaphragm.
   Vial "B"—5 ml containing approximately 1 ml of HSA 25%.
   Vial "C"—5 ml vial containing approximately 2 ml of Sodium Bicarbonate 3.75% and Sodium Hydroxide 2.0% in sterile pyrogen-free water for injection.
II. Lead pig (for housing 200 ml vial during procedure).
III. D.C. power source with external leads adapted with alligator clips capable of providing 100 milliamps constant current at 3–5 volts.

Procedure:

I. Place vial "A" in lead pig; electrically insulate the top of the container by covering top of lead pig and aluminum band with masking tape. Rubber diaphragm is left exposed.
II. To vial "A" aseptically add 5.5 ml of pertechnetate in normal saline (oxident free). Remove 5.5 ml air.
III. To vial "A" aseptically add 0.1 ml of HSA from vial "B" using a 1 ml TB syringe adapted with a 21 G needle. Flush syringe several times and remove 0.1 ml of air.
IV. Immediately connect electrodes to power supply leads by means of alligator clips.
V. Invert vial allowing contents of vial to come in contact with both electrodes.
VI. Using circular motion gently agitate the inverted vial. Pass 100 milliamps of current for exactly 42 seconds; continue to agitate vial inverted position for an additional 15 seconds after electrolysis is completed.
VII. Remove leads from electrodes, reinvert vial to upright position and allow vial "A" to incubate at room temperature for at least 30 minutes.
VIII. Add to vial "A" 1.2 ml of vial "C". Remove an equivalent amount of air.
IX. Pass the product through a 0.22μ

membrane filter and collect in a sterile empty vial.

Radiopharmaceuticals, whether prepared in-house or obtained commercially, should be subjected to quality control testing. If the limitations of image interpretations are instrumentation, technique, adequate patient history, and radiopharmaceutical quality, equal attention must be payed to all.

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