June 12, 1985

MS16
P5

Ms. Jenny M. Johansen
Nuclear Regulatory Commission
Nuclear Materials Safety Section B
631 Park Avenue
King of Prussia, Pennsylvania 19406

Att: Mail Control No. 03754

Dear Ms Johansen:

Regarding your letter dated May 30, 1985, the following additional information is submitted in support of Cadema's reagent kit distribution authorization:

1. NDA 19,180 for Antimony Trisulfide Colloid (Lymph-Scan) is not as yet approved by the FDA. The FDA assigns a NDA number when a firm submits and they receive an NDA application. The original IND number is then deleted and the new NDA number is used in all future correspondence. The original sponsor of this drug was Union Carbide Corp. which sold its Medical Division to Medi Physics/Cintichem. In February 1982, the drug was transferred to Cadema Medical under a royalty arrangement. (Attachment 1. is a copy of the letter from the FDA giving IND approval for studies using this kit).

2. Attachment 2. is a letter from the FDA stating that we may proceed with the Red Blood Cell Kit.

3. Attachment 3 contains pages 2, 3, 4, and 5 of the October 15, 1984, letter from the FDA regarding our Pentatate Sodium (DTPA) kit. The kit is still under IND 24, 406 until further clinical studies are accumulated.

4. Attachment 4 is the cover letter regarding Cadema's response to the chemistry questions contained in the Albumin Colloid Reagent Kit application. We continue to wait for FDA written approval to resume clinicals. In a recent phone conversation (June 11, 1985) with Mr. Robert West, Consumer Safety Officer for the FDA's Division of Oncology and Radiopharmaceuticals, he stated that Cadema may continue the Albumin Colloid clinicals. He does not know when we will receive written approval. For confirmation of this conversation, you may call him at: (301) 443-4260.

Cadema Medical Products, Inc.
P.O. Box 250, Middletown, New York 10940
914/343-7474

03754

5. Included in the original appendices were labels and artwork of labels to be placed on the vial and the shielded lead container. ASC, RBC, and Albumin Colloid labels were attached. Artwork for the DTPA label was also included. Two of these investigational preparation labels containing the words, "Caution Radioactive Material," are provided for each vial in a kit. One label is to be attached to the vial; the other to the lead shield. At our next printing, we will modify the package inserts to specify the use of these labels as well as iterate the radiation safety instructions as outlined in Attachment 5.

6. The outer box label and package insert will contain the licensing statement as stated in 10 CFR 32.73 (a) (5) (i i) and will contain the radiation safety procedures for processing the kit. These changes will be made at the next label and package insert reorder point or within 9 months, whichever is shorter. Attachment 5 shows drafts of both the licensing statement and the radiation safety instructions for each product that will be incorporated with the outer labels and package inserts.

If you have any further questions, please call me at: 1-800-422-3362.

Very truly yours,

CADEMA MEDICAL PRODUCTS, INC.

Maurice E Bordoni

M. E. Bordoni
President

MEB/pmw
Enclosures

cc: Mr. E. Lieberman
Mr. J. Burke

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Attachment I

Food and Drug Administration
Rockville MD 20857

IND 13,717

JAN 17 1983

Cadema Medical Products, Inc.
Attention: Mr. E. Lieberman
Office of the President
Post Office Box 230
Middletown, New York 10940

Dear Mr. Lieberman:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND 13,717) submitted pursuant to section 505 (i) of the Federal Food, Drug, and Cosmetic Act for the compound Technetium Tc 99m Antimony Trisulfide Colloid Kit and to the letters from this Division (the most recent of which was dated December 7, 1982) informing you of the Agency's decision to cease distribution of the drug until certain manufacturing and controls data could be evaluated.

We acknowledge the receipt of your amendment to the Exemption dated December 21, 1982 which provides further clarification of your manufacturing and controls procedures.

We have completed our review of this amendment as submitted and have concluded that the drug may be distributed to the various investigators and their studies may proceed. Cadema Medical Products, Inc. was informed of this decision during a telephone conversation between Mr. Henrkern and Mr. Abel of this Division on December 30, 1982.

The hold on the distribution of the kit is being lifted with the understanding that you will correct and respond to the following deficiencies:

1. DMF 4636 should be updated within four weeks to correct the discrepancies and to reflect the proposed changes as per your commitment indicated in your letter dated December 16, 1982. In the future, please address all such communications directly to the Division to facilitate their review.

2. The Notice should provide the accuracy, precision, sensitivity, and specificity of all of the proposed release test methods.

3. As indicated in the FDA letter dated December 7, 1982, no data on the new lots generated by various contractors or subcontractors are provided to ensure the continued safety of the drug and to show that the appropriate standards of identity, quality, strength, and purity of the drug product have been established and maintained. Please provide such data on at least three consecutive lots as soon as each lot becomes available.

9. It is recommended that the application be sequentially paginated in an appropriate manner for reference and review purposes.

10. Please note that the letter of authorization from Becton Dickinson Pharmaceutical System to refer in your behalf to their appropriate DMF(s) is not included in your application.

Sincerely yours,

William J. Gyarfas, MD., Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of New Drug Evaluation
National Center for Drugs and Biologics

DEPARTMENT OF HEAL● & HUMAN SERVICES ● Public Health Service

Attachment 2

Food and Drug Administration
Rockville MD 20857

IND 12,003

AUG 6 1984

Cadema Medical Products, Inc.
P.O. Box 250
Middletown, New York 10940

Attention: M. E. Bordoni
President

Dear Mr. Bordoni:

Please refer to the Notice of Claimed Investigational Exemption for a New Drug (IND 12,003) submitted pursuant to section 505 (i) of the Federal Food, Drug, and Cosmetic Act for the diagnostic radiopharmaceutical Technetium Tc 99m Red Blood Cell Labeling Kit. The Notice was originally submitted to this Administration by the Brookhaven National Laboratory of the Associated Universities, Inc.

We acknowledge the receipt of your amendment dated July 17, 1984 which provides for a transfer of the sponsorship of IND 12,003 from Brookhaven Laboratories to Cadema Medical Products, Inc.

In order to complete the transfer, please provide the following additional material:

1. We await the letter from Ms. Margaret Bogossian, Patent Counsel for Brookhaven National Laboratory, stating that all rights have been assigned or transferred to the new sponsor.

2. You have submitted a FDA Form 1571. However, the form which was submitted was unsigned. We enclose another form for you to complete, sign, and return.

3. We note that there will be no change in the manufacturing and controls of the kit at this time. The kit will continue to be manufactured by Brookhaven National Laboratories but will be distributed by Cadema Medical Products, Inc. beginning in September 1984. Please submit copies of the labeling which you intend to affix to the finished drug product for our review before initiating distribution.

4. Please submit a specific commitment that distribution of the product as manufactured in your facilities will not be initiated until the proper manufacturing and controls information has been submitted and accepted by this Division.

5. Please submit your estimated target date for the submission of your New Drug Application (NDA) for the product. As provided in the new drug regulations, clinical trials should not be unduly prolonged. The data accumulated by the extensive list of investigators you have provided should prove adequate to evaluate the safety and effectiveness of the product and an NDA should be submitted promptly.

Sincerely yours,

John F. Palmer

John F. Palmer, M.D.
Acting Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

August 10, 1984

Mr. Robert West
Consumer Safety Officer
Division of Oncology
and Radiopharmaceutical Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: BNL IND # 12003 FOR A RED BLOOD CELL LABELING KIT

Dear Mr. West:

The following are the responses to the Division's questions regarding the RBC Kit as stated in a letter dated August 6, 1984.

1. QUESTION: We await the letter from Ms. Margaret Bogossian, Patent Counsel for Brookhaven National Laboratory stating that all rights have been assigned or transferred to the new sponsor.

1. RESPONSE: As of this writing, the Division should have received the letter from Brookhaven Patent Counsel stating all rights have been assigned to Cadema Medical (attached as Appendix I is my copy of Brookhaven's letter to you).

2. QUESTION: You have submitted a FDA Form 1571. However, the form which was submitted was unsigned. We enclose another form for you to complete, sign and return.

2. RESPONSE: Attached in Appendix II is a signed FDA Form 1571.

3. QUESTION: We note that there will be no change in the manufacturing and controls of the kit at this time. The kit will continue to be manufactured by Brookhaven National Laboratories but will be distributed by Cadema Medical Products, Inc., beginning in September 1984. Please submit copies of the labeling which you intend to affix to the finished drug product for our review before initiating distribution.

3. RESPONSE: Appendix III contains Cadema's drug product labels for your review.

Cadema Medical Products, Inc.
P.O. Box 250, Middletown, New York 10940
914/343-7474

4. QUESTION: Please submit a specific commitment that distribution of the product as manufactured in your facilities will not be initiated until the proper manufacturing and controls information has been submitted and accepted by this Division.

4. RESPONSE: Cadema will not distribute the RBC Kit if manufactured in our own facilities until the proper manufacturing and control information has been submitted and accepted by the Division.

5. QUESTION: Please submit your estimated target date for your New Drug Application (NDA) for the product. As provided in the new drug regulations, clinical trials should not be unduly prolonged. The data accumulated by the extensive list of investigators you have provided should prove adequate to evaluate the safety and effectiveness of the product and an NDA should be submitted promptly.

5. RESPONSE: Cadema has targeted January 1, 1985, as the date to file the New Drug Application. At present we are working with Brookhaven Labs to determine the status and quality of their clinical trials. Based on the results of this review and input from the Division, a determination will be made regarding final clinical disposition(see letter to investigators in Appendix IV).

Thank you for your prompt and helpful reply to Cadema's RBC submission.

Very truly yours,

CADEMA MEDICAL PRODUCTS, INC.

Maurice E Bordoni

M. E. Bordoni

MEB/pmw
Enclosures

Attachment 3

CLINICAL:

1. Please supply data which demonstrates that only 3 millicuries out of the total of 30 millicuries of drug administered are deposited in the lung and that the biological half-life is one hour in humans for the aerosol study. If this data is not available, the dosimetry values should be recalculated based on a dose of 30 millicuries of drug accumulating in the lung (100%) and a 6 hour half-life.

2. The device described does not appear to have a "large particle trap" as outlined in Joplin's article. The bacterial filter described in the Venti-Scan advertisement is said to trap exhaled air only.

3. The clinical protocols are improperly described and should be rewritten. For example, the word "in" should be deleted under high probability (page 80) and "with X-ray of chest showing no pulmonary lesion" inserted. In addition, please define clearly the first sentence following low probability. As it currently reads, it is supposed to be an abnormal X-ray finding.

4. Please state what types, other than "diffuse and focal",may be detected on page 81 under high probability.

CHEMISTRY:

1. The description of your facilities in Middletown, New York does not provide for a QC lab or equipment necessary to carry out the biodistribution or radiochemical purity test on the drug.

2. There is no statement from Envirotest regarding their repsonsibility to carry out the indicated analytical procedures.

3. Based on the resumes presented in your IND and DMF, a number of the personnel are employed at other places than your company. A person responsible for the quality control and release of the drug is not clearly indicated.

4. No information is provided on the synthesis of the new drug substance, sodium DTPA. Details of the synthesis, isolation, purification, and identification and quality control by your supplier should be made available for review and support of your Notice.

5. Specifications and tests for acceptance of the raw material sodium DTPA are inadequate. Requirements for assay should provide values rather than plus or minus 5% of the value reported on the label. It should be shown that the assay method has been validated and that it is accurate, sensitive, specific and reproducible. Impurities should be determined and limits set for acceptable raw material.

6. In the master log the conditions for freeze drying should be specified and the criteria for a satisfactory dried product should be indicated.

7. The commitment letters from Bell-More do not include their testing the drug for clarity and particulates nor do they indicate that samples will be sent directly to Dutchland for pyrogen testing.

8. No information is provided on the composition of the Tompkins closure for the packaged drug.

9. A specifiction of 80% radiochemical purity of the reconstituted drug is not consistent with a minimum radiochemical purity of 90% as specified for this drug in USP.

10. A specification for the moisture content of the packaged vial should be proposed and then substantiated based on the proposed stability studies.

11. The LAL endotoxin test should be considered in the controls for the drug since the USP monograph includes this test.

12. Although the pH range specification of 3.8-7.0 is within the USP range for this drug, it is recommended that a tighter range be considered as a specification since in the Master Record the drug is manufactured to have a range of 4.0 +/- 0.2 in the bulk solution. Based on the literature, the radioactive drug has various structures depending on the pH and its biodistribution will vary depending on the conditions under which it is prepared.

13. Since the drug is to be administered as an aerosol, controls should be performed on the drug after it has been aerosolized under the conditions proposed for use.

14. The specification for sodium DTPA of plus or minus 20% in the packaged drug appears wider than necessary since in manufacturing the range of this component is held to +5%, -0%.

15. The analytical methods should be validated to show accuracy, sensitivity, specificity and reproducability.

16. Information should be provided on the standard EDTA used in standardization of the zinc nitrate used in the sodium DTPA assay.

17. It should be shown that there is no interference in the stannous assay due to the presence of the the DTPA in the drug. It has been reported in the literature that DTPA from some sources contains impurities that affect redox reactions.

18. The presentation of the procedure for the determination of total tin on page 123 appears to have part of another procedure included.

19. Although the method for the determination of the moisture content of the vial of drug (p 125) does not have specifications, the QC batch record on page 127 states the acceptance requirements that each vial must be ± 10% of the mean. This requirement should be expressed in mg per vial.

20. Your radiochemical purity method stated that the Rf value of the bound Tc 99m will be 0.2, but USP states that the drug complex remains at the point of application in the same system. Please resolve this apparent contradiction.

21. The method for bioassay on page 130A is incomplete since it does not indicate:

    a. the site of administration
    b. the age, sex, and weight of the mice to be used
    c. how the mice are sacrificed.
    d. the instrument(s) to be used for counting the organs for radioactivity.
    e. the justifiction for the specifications which differ from those in USP.

22. There should be a test to assure a nitrogen atmosphere in the vial of the packaged drug.

23. Your stability testing protocol should provide for studies on both the new drug substance, sodium DTPA, as well as the drug in the package form and its reconstituted form. Although you have stated that the sodium DTPA has a shelf life of two years, no data is presented to substantiate this.

24. Stability studies on the packaged drug should include a determination of radiochemical purity and the presence of a nitrogen atmosphere in the sealed vials in addition to those proposed.

25. Tests on the reconstituted drug should be performed on samples prepared from the packaged drug of various ages and demonstrate that the reconstituted drug is suitable for use, as specified in the directions in the package insert, a few minutes after preparation, one hour after preparation for glomerular filtration rate, and 6 hours after preparation at expiry.

26. An explanation should be provided as to your recommendation to store the reconstituted drug at room temperature while the USP monograph for this drug calls for storage at 2-8°C.

27. Although this drug is being used in an investigational stage, it is recommended that the labels and labeling contain the accepted USAN name for the kit in addition to your proprietary name. Please refer to USAN 1984, page 527 for the proper nomenclature in item 1 of your Notice.

28. In part 7.5 (pages 62-70) of your Notice, if the exact structure of the complex is unknown, the structure of the sodium DTPA could be included in the description section of the package insert.

29. In the package insert described on page 65 of your Notice, the procedure for the determination of the free pertechnetate appears incomplete and further information should be provided for the investigator. On page 70 of the same insert, the storage temperature of the reconstituted drug should be indicated as well as that for the packaged drug.

30. Under item 7.6 of the aerosol protocol, the drug preparation on page 87 calls for the addition of up to 100 millicuries in 5 ml of solution to the vial which would yield a concentration of 20 millicuries per vial, while on page 88 the directions call for adding 4 ml of drug at a concentration of 10 millicuries per milliliter to the nebulizer. The difference in concentration should be explained.

31. Information should be presented on the validation of the system used to measure the droplet size of the aerosol.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions, the agreement to provide for any significant changes to your clinical protocol by means of an amendment, and the submission of a progress report detailing the course of your study at intervals not to exceed one year.

Sincerely yours,

John F. Palmer

John F. Palmer, M.D.
Acting Director Division of Oncology
and Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

Attachment 4

November 19, 1984

John F. Palmer, M.D.
Acting Director, Division of Oncology
and Radiopharmaceutical Drug Products
Bureau of Drugs (HFD-150)
Rockville, MD 20857

Re: IND 22,683

Dear Dr. Palmer:

The attached is the response to the chemistry questions outlined in your letter of April 5, 1984 to Cadema Medical Products, Inc. regarding Notice of Clinical Investigational Exemption for New Drug, (IND 22,683) Technetium Tc-99m Albumin Colloid Kit. We have changed the name of the drug to conform to the applicable USAN name. The labels, package insert, and clinical protocols have been revised with the new nomenclature.

Enclosed as Exhibit I is the revised clinical protocol for the Phase III studies.

We have answered the agency's questions with respect to the chemistry questions and would appreciate a quick and affirmative reply in order to continue our clinical studies.

Sincerely,

Alfred K. Thornton, Ph.D.
Chief Chemist

T:jdr

Cadema Medical Products, Inc.
P.O. Box 250, Middletown, New York 10940
914/343-7474

Attachment 5

Exhibit 7.1

~~OUTER~~ BOX LABEL

THIS ARTWORK IS
100 % ACTUAL SIZE: 3" x 6 3/4"

BACKGROUND - ~~PMS~~ WHITE
BLACK COPY - PROCESS BLACK

CAUTION: NEW DRUG diagnostic/sterile/pyrogen-free

LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE

TECHNETIUM Tc 99m DTPA Multi-dose

Kit for use in preparation of TECHNETIUM Tc 99m PENTETATE

contents of kit

10 STERILE REACTION VIALS
(10 cc, silver aluminum overseal), each containing a lyophilized mixture of 10 mg Na_5 DTPA, 0.55 mg $SnCl_2 \cdot 2H_2O$ under a nitrogen atmosphere, pH was adjusted to 4 with hydrochloric acid.

Use within 6 hours after preparation.

Store kit at 15-30°C.

Only for administration after reconstitution with additive-free Sodium Pertechnetate Tc 99m.

CAUTION: INVESTIGATION DRUG
TO BE USED BY QUALIFIED INVESTIGATORS ONLY

CADEMA MEDICAL PRODUCTS, INC.
MIDDLETOWN, N.Y. 10940

Made in U.S.A.

LF250-1
3-84

Lot Number and Expiration Date will be stamped on each kit at the time of final kit assembly.

The DTPA reagent kit is approved for use by the U.S. NRC pursuant to 35.14 and 35.110 Group III of 10 CFR Part 35.

DTPA PREPARATION

FINAL DRUG FORM

1. Do not use with solutions of sodium pertechnetate Tc 99m containing oxidizing agents.

2. Complete and affix the DTPA radiation warning label to the reaction vial.

3. Swab the top of the DTPA vial closure with isopropyl alcohol and let dry.

4. Use waterproof gloves during the preparation procedure.

5. Place the DTPA vial in a suitable lead shield that has a fitted lead cap.

6. Using a shielded syringe, aseptically inject 1.0-5.0 mL, up to 100 millicuries, into the reaction vial. Relieve the excess pressure in the vial by withdrawing an equal volume of air.

7. With lead cap in place, mix the solution by shaking vigorously for at least 30 seconds before use.

8. Complete and affix the radioactive contents (warning label) to the vial shield.

9. Aseptically, using a shielded syringe, withdraw material for use.

10. Assay radioactivity content of each patient dose prior to administration.

11. Do not use more than one (1)hour after preparation for use in estimating glomerular filtration rate.

12. Do not use more than six (6) hours after preparation.

Package Insert and Outer Box Label to also include statement:

The DTPA kit is approved for use by the U. S. NRC pursuant to 35.14 and 35.110 Group III of 10 CFR Part 35.

Cadema Medical Products, Inc.
P.O. Box 250, Middletown, New York 10940
914/343-7474

CAUTION: NEW DRUG — **Diagnostic/Sterile/Pyrogen-free**

Limited by Federal Law to Investigational Use — **MULTI-DOSE**

Albumin Colloid Kit (TcmAC)

Contains: Normal Serum Albumin (Human) prepared by a manufacturer licensed to do so by the Bureau of Biologics, and found to be nonreactive for hepatitis B surface antigen (HB_sAg) by FDA required test.

Contains: No bacteriostatic preservative.

Do not use after six hours from time of preparation.

Store Kit at (15-30°C)

Read accompanying literature for recommended adult dosage and preparation procedures before use.

Store prepared drug at refrigerator temperature (2-8°C).

Only for intravenous use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc-99m.

Lot #
Exp.

CONTENTS:

10	Sterile Reaction Vials, each containing in lyophilized form:	
	Human Serum Albumin (Soluble Albumin 10.0 mg. Albumin Colloid 1.0 mg)	11.0 mg
	Pluronic F68 (Surfactant)	2.0 mg
	Total Tin as Stannous Chloride DiHydrate	0.2 mg
	Dibasic Sodium Phosphate	< 2.5 mg
	Hydrochloric Acid	< 0.1 mL
10	Radioactive Labels (Symbol)	
20	Pressure-sensitive labels for final Albumin Colloid Kit injection preparation.	
1	Package Insert	

Manufactured for:
CADEMA MEDICAL PRODUCTS, INC.
MIDDLETOWN, NY 10940

By:
BELLMORE LABORATORIES
Hampstead, MD

Rev. MF 160
12/30/84
Made in U.S.A.

The Albumin Colloid kit is approved for use by the U.S. NRC pursuant to 35.14 and 35.110 Group III of 10 CFR Part 35.

ALBUMIN COLLOID PREPARATION

FINAL DRUG FORM

1. Do not use with solutions of sodium pertechnetate Tc 99m containing oxidizing agents.

2. Complete and affix the Albumin Colloid radiation warning label to the reaction vial.

3. Swab the top of the Albumin Colloid vial closure with isopropyl alcohol and let dry.

4. Use waterproof gloves during the preparation procedure.

5. Place the Albumin Colloid vial in a suitable lead shield that has a fitted lead cap.

6. Using a shielded syringe, aseptically inject 1.0-5.0 mL, up to 100 millicuries, into the reaction vial. Relieve the excess pressure in the vial by withdrawing an equal volume of air.

7. With lead cap in place, mix the solution by shaking vigorously for at least 30 seconds before use.

8. Complete and affix the radioactive contents (warning label) to the vial shield.

9. Aseptically, using a shielded syringe, withdraw material for use.

10. Assay radioactivity content of each patient dose prior to administration.

11. Do not use more than one (1) hours after preparation for use in estimating glomerular filtration rate.

12. Do not use more than six (6) hours after preparation.

Package Insert and Outer Box Label to also include statement:

The Albumin Colloid kit is approved for use by the U. S. NRC pursuant to 35.14 and 35.110 Group III of 10 CFR Part 35.

CHARACTERISTICS

To correct or physical decay of this radionuclide, the fractions that remain at selected time intervals after the time of calibration are shown in Table 3.

TABLE 3

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	8	.399
1	.891	9	.355
2	.795	10	.317
3	.708	11	.282
4	.631	12	.252
5	.563		
6	.502		
7	.447		

*Calibration Time

CLINICAL PHARMACOLOGY

Following interstitial administration, Technetium Tc-99m Antimony Trisulfide Colloid slowly migrates out of the injection site into the channels to the regional lymph node groups. Transport can be phagocytic as well as direct through the channels. The uptake of the colloidal particles by a lymph node depends upon the integrity of the node and the patency of the lymphatic vessels feeding the node.

INDICATIONS AND USAGE

Technetium Tc-99m Antimony Trisulfide Colloid injection is used as an agent for imaging lymphatic drainage in patients with breast cancer or malignant melanoma.

CONTRAINDICATIONS

None known.

WARNINGS

The contents of the two syringes are intended only for use in preparation of the Technetium Tc-99m Antimony Trisulfide Colloid injection and are **not to be directly administered to the patient.**

The contents of the kit are not radioactive. However, after the Sodium Pertechnetate Tc-99m is added, adequate shielding of the final preparation must be maintained.

This radiopharmaceutical preparation should not be administered to children, to patients who are pregnant or during lactation, unless the expected benefits to be gained outweigh the potential hazards.

PRECAUTIONS

The components of the kit are sterile and pyrogen-free. It is essential that the user follows the directions carefully and adheres to strict aseptic procedures during preparation of the radiodiagnostic agent.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females. Any teratogenic potential or adverse effects on the fetus are not known. It is not known whether this drug is excreted in human milk. Safety and effectiveness in children have not been established.

[redacted]netium Tc-99m Antimony Trisulfide Colloid, because it is radioactive, must be handled with care. Appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should be taken to minimize radiation exposure to patients, consistent with proper patient management.

DOSAGE AND ADMINISTRATION

Internal Mammary Dosage: Volume to be injected is 0.1 to 0.2 milliliters, but is not to exceed 0.3 milliliters, containing a minimum of 500 microcuries Technetium Tc-99m, but not to exceed a maximum of 1000 microcuries Technetium Tc-99m.

Malignant Melanoma Dosage: Two (2) to four (4) injections will be given circumferentially surrounding the primary tumor or recent excision site. A total of 0.8 mL but not less than 0.4 mL Technetium Tc-99m Antimony Trisulfide Colloid containing up to a maximum 1000 uCi, will be injected. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by a nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate agency authorized to license the use of radionuclides.

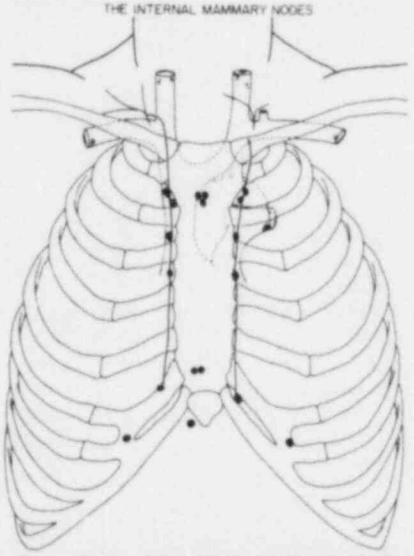

Fig. 1. Diagram of diaphragmatic, parasternal, and substernal lymphatics displayed by subcostal radiocolloid injection.

[redacted]

RADIATION DOSIMETRY

The estimated absorbed radiation doses from a 1000 microcurie interstitial injection of Technetium Tc-99m Antimony Trisulfide Colloid is as follows:

General calculations, using the MIRD information,* and making the "worst assumption," yield the following results:

a. If all the injected dose is in and remains in the bladder, then the radiation dose to the testes, ovaries, and uterus is 0.04, 0.06, and 0.14 rads respectively.

b. If a blood vessel is penetrated and the 1000 microcuries of Technetium Colloid is in the liver and that is the radiation source, then the dose to the testes, ovaries and uterus is 0.0006, 0.004, and 0.004 rads, respectively.

Summarized, it would be:

TABLE I

1000 uCi 99mTc in	Radiation Dose, Rads to: Testes	Ovaries	Uterus
Bladder	0.04	0.06	0.14
Liver	0.0006	0.004	4.004

This is the calculated radiation dose when 1000 microcuries are injected:

TABLE II

INFINITE DOSES FOR Tc-99m IN SINGLE-SOURCE ORGAN**

Absorbed Radiation Dose rads/1000 microcuries	Source in Liver	Source in Bladder
Target		
Testes	0.0006	0.04
Ovaries	0.004	0.06
Liver	0.40	0.00014
Red Marrow	0.0014	0.02
Bone (Total)	0.001	0.008
Blood	0.02	0.0016
Total Body	0.02	0.0016
Bladder (Wall)	0.00014	1.4
Uterus	0.004	0.14

* MIRD Pamphlet No. 11, (1975)
MIRD Pamphlet No. 1, Revised (1976)

**MIRD Pamphlet No. 11, Society of Nuclear Medicine (1976)

Radiation Dose to Skin at Injection Site

1. **Radiation Dose to Skin**
   Assumption:
   Radius of Technetium sphere at injection site, 1.5 cm.
   Mass 9 grams.
   Dose to skin (using Technetium Tc-99m, 0.3 rads per uCi per gram) = 32 rads to skin.
2. **Radiation Dose to Lymph Node**
   Assumption:
   Lymph node is sphere.
   Diameter of lymph node, 0.5 cm.
   Mass of lymph node, 60 mg.

0.4% of injected dose in a lymph node. (Ege's data). The dose to a lymph node would be about 20 rads. In both of the above cases, the effective half-life was taken to be equivalent to the physical half-life. Regardless of whether the source was assumed to be a point source, or a line source (10 centimeters long) the results are the same within the accuracy of the estimate.

To the accuracy of the approximation used:

D 0.06 rads

(D) Infinite Dose

If 0.3 milliliters of the Technetium Tc-99m labeled Antimony Sulfide Colloid were injected and there was a maximum amount of 50 millicuries in the vial, then 2.08 millicuries would be injected.

The maximum radiation dose would then be $\frac{2.08}{0.5}$

or approximately four times that listed in Table I. Notwithstanding this maximum dosage, the level of radiation is comparatively lower for various organs than for many other procedures commonly performed in Nuclear Medicine.

The "worst" total dose of 32 millirads to the female-gonads is lower than the gonadal dose from a typical administration of Technetium labeled diethylene triamine pentaacetic acid, technetium labeled polyphosphate, technetium as pertechnetate (all 180 millirads dose to the gonads), and far less than Selenium-75 or Selenomethionine (1,700 millirads). The reference for all of these values is the **British Journal of Radiology**, (London), page 201, March 1977. "The Application of the "Ten-Day Rule" in Radiopharmaceutical Investigations," R. E. Ellis et al.

HOW SUPPLIED

The Technetium Tc-99m Antimony Trisulfide Colloid Kit is supplied as a sterile, pyrogen-free kit consisting of five reaction vials, each containing 0.2 mL of 0.5N Hydrochloric Acid, 5 syringes (labeled "A"), each containing 1.2 mL of an aqueous solution of 0.67 mg of Antimony as Trisulfide, 3.2 mg of Povidone and 1.0 mg. of Potassium Tartrate; five syringes (labeled "B") each containing 0.5 mL aqueous buffer solution of 24.7 mg. of Dibasic Sodium Phosphate, 2.7 mg. of Monobasic Sodium Phosphate.

KIT CONTENTS

- 5 Sterile Reaction Vials, each containing 0.2 mL of 0.5N Hydrochloric Acid.
- 5 Sterile Syringes (labeled "A") each containing 1.2 mL of an aqueous solution of 0.67 mg of Antimony as Trisulfide, 3.2 mg. of Povidone and 1.0 mL of Potassium Tartrate
- 5 Sterile Syringes (labeled "B") each containing 0.5 ml aqueous buffer solution of 24.7 mg of Dibasic Sodium Phosphate 2.7 mg. of Monobasic Sodium Phosphate.
- 5 Radioactive Symbol labels.
- 10 Pressure-sensitive labels for final Technetium Tc-99m Antimony Trisulfide Colloid injection preparation.
- 1 Package Insert

STORAGE

Store kit contents at room temperature (15-30°).

PREPARATION

The following directions must be carefully followed for optimum preparation of the drug.

1. Aseptically swab rubber septum of shielded 10 cc. vial containing 0.2 mL of 0.5N Hydrochloric Acid.
2. Aseptically inject 0.5 mL of Sodium Pertechnetate Tc-99m in isotonic saline up to 15 mCi..
3. Maintaining aseptic technique, add the contents of syringe (labeled "A"), Antimony Trisulfide Colloid preparation to the 10 cc. vial containing the Technetium Tc-99m and 0.2 mL of 0.5N Hydrochloric Acid.
4. Shake the shielded vial by hand for three seconds.
5. Using forceps, remove vial from shield and immerse vial into a shielded boiling water bath for 30 minutes.
6. Remove vial from water bath, place in lead shield, and vent using a 10 cc. syringe with a 20-gauge needle, CAUTION.
7. Using aseptic technique, immediately inject the contents of the syringe (labeled "B"), containing the Buffer Solution into the shielded vial.
8. Cool the shielded vial to room temperature for approximately 15 minutes.
9. It is recommended that with proper shielding and equipment, the final formulation be tested for radiochemical purity (percent Technetium Tc-99m binding) and each patient dose be visually inspected for foreign matter. If the radiochemical purity is not adequate or foreign matter is observed in the patient dose, it is recommended that the patient dose be discarded. Do not use preparation after six hours. STORE PREPARED DRUG AT ROOM TEMPERATURE.
10. It is recommended that the radioactivity content of each patient dose be checked prior to administration.

DISPOSAL

The residual materials may be discarded in accordance with Federal, State or local regulations.

Manufactured for
CADEMA MEDICAL PRODUCTS, INC.
Middletown, N.Y. 10940
By: BELL-MORE LABS, INC.
Hampstead, Maryland 21074

October 1984

Cadema Medical Products, Inc.
P.O. Box 250, Middletown, New York 10940
914/343-7474

CAUTION: NEW DRUG
Limited by Federal Law to Investigational Use

LYMPH-SCAN
TECHNETIUM Tc-99m ANTIMONY TRISULFIDE COLLOID KIT

DESCRIPTION

Contains: 5 reaction vials, each containing 0.2 mL of 0.5N Hydrochloric Acid; 5 syringes containing 1.2mL aqueous solution of 0.67 mg. Antimony as Trisulfide, 3.2 mg of Povidone, 1.0 mg. of Potassium Tartrate and 5 syringes containing 0.5 ml aqueous buffer solution of 24.7 mg. of Dibasic Sodium Phospate, 2.7 mg. of Monobasic Sodium Phosphate. All components are sterile and pyrogen free. When a solution of sterile pyrogen-free Sodium Pertechnetate Tc-99m in isotonic saline is mixed with these components, following the instructions provided with the kit, Technetium Tc-99m Antimony Trisulfide Colloid injection is formed. The resulting product is intended for interstitial injection.

PHYSICAL CHARACTERISTICS

Technetium Tc-99m decays by isomeric transition with a physical half-life of 6.02 hours (1). Photons that are useful for detection and imaging are listed in Table 1.

TABLE 1
PRINCIPAL RADIATION EMSSION DATA

Radiation	Mean % Disintegration	Mean Energy (keV)
Gamma -2	87.9	140.5

(1) Dillman, L. T. and Von der Lage, F.D. Radionuclide Decay Schemes and Nuclear Parameters for use in Radiation – Dose Estimation, MIRD Pamphlet No. 10, p. 62 (1975).

EXTERNAL RADIATION

The specific gamma ray constant for Tc-99m is 0.8R/mCi-hr at 1 cm. The first half value thickness of lead (Pb) for Tc-99m is 0.2mm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. For example, the use of 2.7mm of Pb will decrease the external radiation exposure by a factor of about 1,000.

TABLE 2
RADIATION ATTENUATION BY LEAD SHIELDING

Shield Thickness (Pb)mm	Coefficient of Attenuation
0.2	0.5
0.95	10^{-1}
1.8	10^{-2}
2.7	10^{-3}
3.6	10^{-4}
4.5	10^{-5}

1. Complete and affix the pressure sensitive radioactive warning label to the reaction vial.

2. Use waterproof gloves during the preparation procedure.

3. Place the reaction vial in a suitable lead shield that has a fitted lead cap.

4. Aseptically swab rubber septum of shielded 10 cc. vial containing 0.2 mL of 0.5N Hydrochloric Acid.

5. Using a shielded syringe aseptically inject 0.5 mL of Sodium Pertechnetate Tc-99m in isotonic saline up to 15 mCi.

6. Maintaining aseptic technique, add the contents of syringe (labeled "A"), Antimony Trisulfide Colloid preparation to the 10 cc. vial containing the Technetium Tc-99m and 0.2 mL of 0.5N Hydrochloric Acid.

7. After placing lead cap on the reaction vial, shake the vial by hand for three seconds.

8. Using forceps, remove vial from shield and immerse vial into a shielded boiling water bath for 30 minutes.

9. Remove vial from water bath, place in lead shield cap and vent using a 10 cc. syringe with a 20-gauge needle. CAUTION.

10. Using aseptic technique, immediately inject the contents of the syringe (labeled "B"), containing the Buffer Solution into the shielded vial.

11. Cool the shielded vial to room temperature for approximately 15 minutes.

12. It is recommended that with proper shielding and equipment, the final formulation be tested for radiochemical purity (percent Technetium Tc-99m binding) and each patient dose be visually inspected for foreign matter. If the radiochemical purity is not adequate or foreign matter is observed in the patient dose, it is recommended that the patient dose be discarded. Do not use preparation after six hours. STORE PREPARED DRUG AT ROOM TEMPERATURE.

13. Complete and affix the radioactive warning label to the vial shield.

14. It is recommended that the radioactivity content of each patient dose be assayed prior to administration.

The DTPA reagent kit is approved for use by the U. S. NRC pursuant to 35.14 and 35.110 Group III of 10 CFR Part 35.

OUTER BOX LABEL

FOR

ANTIMONY SULFUR COLLOID

;AUTION: NEW DRUG
IITED BY FEDERAL LAW TO INVESTIGATIONAL USE

diagnostic/sterile/pyrogen-free

LYMPH-SCAN Multi-dose

ECHNETIUM Tc 99m ANTIMONY TRISULFIDE COLLOID KIT

contents

5 vials containing 0.2 ml of sterile 0.5 N Hydrochloric acid. 5 syringes each containing 0.67 mg Antimony as Trisulfide, 3.2 mg Povidone, 1.0 mg Potassium Tartrate, 1.2 ml Sterile Water. 5 syringes each containing 24.7 mg Dibasic Sodium Phosphate, 2.7 mg Monobasic Sodium Phosphate, 0.5 ml Sterile Water.

procedure

1. Aseptically swab rubber septum of shielded 10 cc vial containing 0.2 ml of 0.5N Hydrochloric Acid.
2. Aseptically inject 0.5 milliliters of Sodium Pertechnetate Tc 99m* in isotonic saline up to 15 millicuries.
3. Maintaining aseptic technique, add the contents of syringe labeled "A" containing the Antimony Trisulfide Colloid preparation to the 10 cc vial containing the Technetium Tc 99m and 0.2 milliliters of 0.5 normal Hydrochloric Acid.
4. Shake the shielded 10 cc vial by hand for three seconds.
5. Using forceps, remove vial from shield and immerse vial into a shielded boiling water bath for 30 minutes.
6. Remove vial from water bath, place in lead shield, and vent using a 10 cc syringe with a 20 gauge needle. CAUTION:
7. Using aseptic technique, immediately inject the contents of the syringe labeled "B" containing the Buffer Solution (supplied) into the shielded vial.
8. Cool the shielded vial to room temperature (approximately 15 minutes).
9. The preparation is now ready for use. Do not use after 6 hours.

Store prepared drug at room temperature (18-25 °C).

*The material should be oxidant and additive-free.

Store kit at room temperature (18-25 °C).

Only for patient use after reconstitution with additive and oxidant-free Sodium Pertechnetate Tc 99m.

Read accompanying literature before preparation and patient use.

Do not use preparation after 6 hours from the time of formulation.

CADEMA MEDICAL PRODUCTS, INC.
MIDDLETOWN, N.Y. 10940

Made in U.S.A.

Rev. LF150-1
Date 4-83

The ASC kit is approved for use by the

U.S. NRC pursuant to 35.14 and 35.110

Group III of 10 CFR Part 35.

September 1984

Cadema Medical Products, Inc.

P.O. Box 250, Middletown, New York 10940
914/343-7474

CAUTION: NEW DRUG

Limited by Federal Law to Investigational Use

The BNL Red Blood Cell Kit

for preparing Tc-99m Labeled RBC's

Description:

The kit consists of 6 unit dose vacutainer tubes, 10 mL. Each partially evacuated to draw up to 6 mL, containing a sterile, pyrogen-free lyophilized mixture of 2.0 µg of tin, 3.7 mg of Sodium Citrate, 5.5 mg of Dextrose and 0.11 mg of Sodium Chloride (maximum).

Physical Characteristics

Technetium Tc-99m decays by isomeric transition with a physical half-life of 6.02 hours. (1) The principle photon that is useful for detection and imaging studies is listed in Table I.

Table I. principal radiation emission data

radiation	mean % /distintigration	mean energy (keV)
Gamma-2	88.96	140.5

(1) Martin, M.J. ed., Nuclear Decay Data for Selected Radionuclides, ORNL-5114, p. 24 (March 1976).

EXTERNAL RADIATION

The specific gamma ray constant for Technetium Tc-99m is 0.8 R/millicurie-hour at 1 cm. The first half-value thickness of lead (Pb) for Technetium Tc-99m is 0.2 mm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of Pb is shown in Table II. For example, to facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of 2.5 mm of Pb will decrease the external radiation exposure by a factor of about 1,000.

Table II. radiation attenuation by lead shielding

shield thickness lead (Pb) mm	coefficient of attenuation
0.2	0.5
0.8	10-1
1.6	10-2
2.5	10-3
3.3	10-4

Molybdenum Mo-99 decays to Technetium Tc-99m with a Molybdenum Mo-99 half-life of 2.75 days. The physical decay characteristics of Molybdenum Mo-99 are such that only 86.8% of the decaying Molybdenum Mo-99 atoms form Technetium Tc-99m. Generator elutions may be made at any time, but the amount of Technetium Tc-99m available will depend on the time interval since the last elution. Approximately 47% of maximum Technetium Tc-99m is reached after 6 hours and 95% after 24 hours. To correct for physical decay of Technetium Tc-99m, the fractions that remain at selected intervals of time are shown in Table III.

Table III. Physical Decay Chart: Technetium-99m, Half-Life 6.02 hours

hours	percent	hours	percent
0*	100.00	8	39.8
1	89.1	9	35.5
2	79.4	10	31.6
3	70.8	11	28.2
4	63.1	12	25.1
5	56.2	18	12.6
6	50.1	24	6.3
7	44.7		

*Calibration time

Pharmacology:

When the heparinized whole blood is mixed with the kit contents, the stannous ion is taken up by the red blood cell fraction of the blood. The excess stannous ion is complexed by the edition of EDTA. The mixture is centrifuged to separate the plasma from the red cell fraction. A specified volume of packed red cells is transferred to a vial containing pertechnetate. The Technetium Tc-99m labels the red cells by the stannous reduction mechanism. The labeled cells are reintroduced into the blood stream by intravenous injection. The labeled cells remain in the blood providing excellent images of the cardiac blood pool.

Indications and Usage

Technetium Tc-99m labeled red blood cells can be used for gated blood pool imaging; studying ejection fractions; detection of gastro intestinal bleeding; detection of abdominal masses; changes in pulmonary blood volume and venography.

Contraindications:

None known.

Warnings:

None known.

Contents of the vacutainer are intended only for use in the preparation of Technetium Tc-99m labeled RBC's and are not to be administered directly to the patient. The contents of the kit are not radioactive. However after the Sodium Pertechnetate Tc-99m is added adequate shielding of the final preparation must be maintained.

Technetium Tc-99m labeled RBC's as well as other radioactive drugs, must be handled with care, and appropriate safety measures should be used to minimize radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers.

The components of the Technetium Tc-99m BNL-RBC Kit are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during addition of solutions and the withdrawal of doses for patient administration.

The labeling reactions involved in preparing the agent depends upon maintaining the tin in the reduced state. Any oxidant present in the Sodium Pertechnetate Tc-99m supply may thus adversely affect the quality of the prepared agent. Hence, Sodium Purtechnetate Tc-99m containing oxidants, or other additives, should not be employed without first demonstrating that it is without adverse effect on the properties of the resulting agent.

Carcinagenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc-99m RBC affects fertility in males or females.

Pregnancy Category C:

Animal reproductive studies have not been conducted with Technetium Tc-99m BNL-RBC. It is also not known whether Technetium Tc-99m BNL-RBC can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Technetium Tc-99m BNL-RBC should be given to a pregnant woman only if clearly needed.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers:

Tc-99m is excreted in human milk during lactation. Therefore, formula feedings should be substituted for breast feedings.

Pediatric Use:

Safety and effectiveness in children below the age of 18 have not been established.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Adverse Reactions:

No adverse reactions specifically attributable to the use of Technetium Tc-99m BNL-RBC have been reported.

Drug Abuse and Dependence:

There is no report of any drug abuse or dependence with this diagnostic agent.

Overdosage:

Increased radiation exposure would be expected if an overdosage of the diagnostic agent occurred.

Dosage and Administration:

The suggested intravenous dose range of Technetium Tc-99m BNL-RBC in the average patient (70 kg) is: 10-20 millicuries.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Technetium Tc-99m BNL-RBC is prepared by simply withdrawing 4 mL of patient blood into a **heparinized syringe** and adding it to the kit. Mixing immediately to dissolve the freeze dried solids in the blood and gently rotating for five minutes at room temperature. Add 1 mL of the EDTA solution; centrifuge the tube; remove a small volume of packed red cells and transfer to the reaction vial containing the sodium pertechnetate. Incubate the Technetium Tc-99m mixture for 10 minutes. Shielding should be utilized when preparing the Technetium - RBC mixture.

Radiation Dosimetry:

The estimated absorbed radiation dose (2) to an average patient (70kg) from an intravenous injection of a maximum dose of 20 millicuries of Technetium Tc-99m BNL-RBC are shown in Table IV.

TABLE IV

Tissue	Patient Absorbed radiation dose (rads/20 millicuries)
Blood/Total Body	0.222
Liver/Liver	0.378
Spleen/Spleen	0.380
Kidney/Kidney	0.276
Heart/Heart Wall and Contents	1.120
Lung/Lung	0.340
Bladder/Bladder (empty)	0.254
Bladder/Bladder (4 hr. hold, no void)	2.866
Testes/Bladder (empty)	0.174
Testes/Bladder (4 hr. hold, no void)	0.236
Ovaries/Ovaries (Bladder empty)	0.296
Ovaries/Ovaries (Bladder, 4 hr. hold, no void)	0.392
Total Body/Total Body	0.296

(2) R. Loevinger, M. Berman: A Revised Scheme for Calculating the Absorbed Dose from Biologically Distributed Radionuclides. MIRD Pamphlet No. 1, Revised. New York, Society of Nuclear Medicine, March (1976).

How Supplied:

Technetium Tc-99m BNL-Red Blood Cell Kit is supplied as a sterile, pyrogen-free kit containing 6 vacutainer tubes. Each tube contains a lyophilized mixture of 2.0 µg of Tin; 3.7 mg of Sodium Citrate; 5.5 mg of Dextrose and 0.11 mg (maximum) Sodium Chloride.

Kit Contents:

6 Sterile unit dose vacutainer tubes (10 mL) each containing 2.0 µg Tin; 3.7 mg Sodium Citrate; 5.5 mg Dextrose; 0.11 mg Sodium Chloride; Lyophilized.

12 Pressure-Sensitive Labels for final Technetium Tc-99m BNL-RBC.

1. Package insert.

Preparation:

Procedure for Preparing Tc-99m-Labeled Red Blood Cells Using the BNL Red Blood Cell Kit

Use aseptic techniques throughout the procedure.

1. Add 1-3 mL (smallest possible volume is preferable) of saline Tc-99m pertechnetate to a shielded sterile and pyrogen-free 10-15 mL pharmaceutical vial and assay. Store in a lead shield (up to 100 mCi) (see Note a).

2. Draw 4 mL of patient blood into a **heparinized syringe** and add to kit (see note f). Up to 6 mL blood may be used if the hematocrit is low.

3. Mix immediately to dissolve the freeze-dried solids in the blood and gently rotate the tube for five minutes at room temperature.

4. Add 1 mL of a 4.4% EDTA (ethylenediamine tetraacetic acid, disodium or calcium disodium salt) solution (see Note b). Draw an equal volume of air to avoid pressure buildup in the tube.

5. Mix briefly by gently inverting about 5 times, and centrifuge the tube upside down 5 minutes at 1300 x G (2900 RPM for 14 cm spin radius; full speed setting on International Clinical Centrifuge Model CL 20928m).

6. Maintain the tube in the inverted position to avoid disturbing the packed RBC's. Using a standard 20G Sterile needle and a 2-3 mL sterile disposable syringe, withdraw 1.25-2.0 mL of RBC's (depending on volume of whole blood used) and transfer to the premeasured technetium prepared in (1). To remove the RBC's from the upside-down vacutainer tube, make sure the plunger of the 3-mL syringe is pushed all the way into the syringe barrel before puncturing the vacutainer stopper – injection of air into the settled RBC's will resuspend the cells. Once the needle has just penetrated the vacutainer stopper, remove the RBC's in one smooth plunger withdrawal movement – ejection of cells from the syringe back into the vacutainer tube will resuspend the remaining cells and the operation cannot be continued without recentrifugation (see Note c).

7. Incubate the technetium-RBC mixture for ten minutes at room temperature with gentle mixing.

8. Assay and dilute appropriately for injection. Cell separation and yield determination at this point (Note h) consistently give 98+ % yields. (see note d for preparation of damaged cells for splenic studies.)

Notes on the BNL-RBC Kit

a. Instant Tc-99m solutions and the first milking from a new generator or over the weekend are not recommended for use with the kit without first testing labeling yield with desired amount of Tc-99m activity.

b. Only a fraction of the tin in the kit is taken up by the RBC. Extracellular stannous tin (in the plasma) depresses the Tc-99m labeling of RBC and has to be removed. The EDTA through its chelating action and partly through oxidative and other possible mechanisms effectively sequesters the extracellular tin and thus reduces the stannous tin content of plasma trapped within the packed centrifuged RBC to a minimum level.

To prepare the EDTA solution for use with this kit, take any commercially available disodium EDTA or calcium disodium EDTA solution for injection (for example: Endrate, Edetate disodium injection, USP, 15% solution in water, pH7, Abbott Laboratories, North Chicago, Il 60064, USA), and dilute with sterile water for injection to give a final concentration of 4.4%.

Alternately, an in-house EDTA preparation can be used if desired. To prepare this, weigh out 4.4 g disodium EDTA or calcium disodium EDTA (reagent grade) and dissolve in sterile water for injection or distilled water, under stirring, and make up the volume to 100 mL. Sterilize this solution by autoclaving.

Aliquots of the sterile 4.4% EDTA solution (either in-house or commercial) can be dispended into a number of individual sterile vials and stored in the refrigerator for subsequent use.

c. Blood volume has been chosen so that the operator need not worry about the plasma-cell interface – some RBC's will be left behind. The removal of 1.25 - 2.0 mL of RBC's does not create any appreciable vacuum in the closed tube.

d. The described procedure yields an excellent agent for blood pool imaging and red cell mass studies. Substitution of the following for step 7 produces an ideal splenic agent: Incubate the technetium-RBC mixture 15 minutes at 49°C with gentle mixing.

e. A slightly modified procedure, involving the use of 1 mL blood., allows for the use of the BNL-RBC kit in pediatric applications (undamaged as well as heat-damaged cells). For details, contact the kit suppliers.

f. The kit does not contain heparin. Therefore, a heparinized syringe must be used for drawing the patient's blood. The syringe should be coated with dilute heparin solution so that approximately 100 units of heparin are present in the syringe before drawing blood.

g. The labeling parameters have been optimized for use with human red blood cells. It is advisable to contact kit supplier prior to use other than with human blood.

h. It is recommended that the labeling yield determinations be carried out while acquiring familiarity with the labeling procedure during initial stages, or when the history of technetium solutions is not known, e.g., when using instant technetium. The following procedure is satsifactory.

Draw an aliquot (0.1 - 0.5 mL) of the well-mixed labeled red blood cell suspension into a syringe and add to a tube containing 2 mL saline. Mix briefly and centrifuge for 5 min. at 1300 X G. Withdraw supernatant solution carefully with a long disposable Pasteur Pipet or a spinal needle and transfer to another tube. Count supernatant solution and red blood cells and calculate the yield as follows:

$$\text{Percent labeling yield} = \frac{\text{Activity in RBC's} \times 100}{\text{Act. RBC} + \text{Act. Supernat. Sol.}}$$

The Tc-99m activity should be measured in a dose calibrator unless the sample has been allowed to cool down to 1 µCi in which case a NaI gamma counter can be used.

Storage:

Store Kit at room temperature (15-30°C)

Disposal:

The residual materials should be discarded in accordance with Federal, State and Local regulations.

For further information or if any problems are encountered, please contact: Cadema Medical Products, Inc. (914) 343-7474

Manufactured for

CADEMA MEDICAL PRODUCTS, INC.
Middletown, N.Y. 10940

By BROOKHAVEN NATIONAL LABORATORIES
Upton, N.Y. 11973

CAUTION: NEW DRUG — Diagnostic/Sterile/Pyrogen-free

Limited by Federal Law to Investigational Use — UNIT DOSE

BNL Red Blood Cell Kit for the preparation of Technetium Tc-99m labeled Red Blood Cells.

Contains: No bacteriostatic preservative.

Store Kit at (15-30°C)

Before use, read accompanying literature for recommended dosage and preparation procedures.

Only for intravenous use after reconstitution with patient blood: additive and sterile, non-pyrogenic, oxidant-free sodium pertechnetate Tc-99m, in accordance with preparation procedure.

Contents:

6 vacutainers, evacuated to draw up to 6 milliliters and each containing in lyophilized form:

Total tin	2.0 µg
Sodium Citrate	3.7 mg
Dextrose	5.5 mg
Sodium Chloride (maximum)	0.11 mg

12 Labels for final technetium TC-99m Red Blood Cell Kit injection preparation.

1 Package Insert

MANUFACTURED FOR
CADEMA MEDICAL PRODUCTS, INC.
MIDDLETOWN, NEW YORK 10940

By BROOKHAVEN NATIONAL LABORATORIES
UPTON, NEW YORK 11973

LF 610
6/84
Made in U.S.A.

The Red Blood Cell Kit is approved for use by the U.S. NRC pursuant to 35.14 and 35.110 Group III of 10 CFR Part 35.

Lot #

Exp. Date

Cadema Medical Products, Inc.

P.O. Box 250, Middletown, New York 10940

914/343-7474

RBC

PREPARATION

Procedure for preparing Tc-99m - labeled Red Blood Cells Using the BNL Red Blood Cell Kit.

Use aseptic techniques throughout the procedure.

1. Complete and affix the RBC radiation warning label to the reaction vial.

2. Use waterproof gloves during the preparation procedure.

3. Place the RBC vacutainer in a suitable lead shield that has a fitted lead cap.

4. Using a shielded syringe, add 1-3 mL (smallest possible volume is preferable) of saline Tc-99m pertechnetate to a shielded sterile and pyrogen-free 10-15 mL pharmaceutical vial and assay. Store in a lead shield (up to 100 mCi) (see Note a).

5. Draw 4 mL of patient blood into a heparinized syringe and add to kit (see note f). Up to 6 mL blood may be used if the hematocrit is low.

6. Place a lead cap on the vacutainer lead shield prior to mixing the contents by rotation.

7. Mix immediately to dissolve the freeze-dried solids in the blood and gently rotate the tube for five minutes at room temperature.

8. Add 1 mL of a 4.4% EDTA (ethylenediamine tetraacetic acid, disodium or calcium disodium salt) solution (see Note b). Draw an equal volume of air to avoid pressure buildup in the tube.

9. Mix briefly in the capped lead shield by gently inverting about five times, and centrifuge the tube upside down five minutes at 1300 x G (2900 RPM for 14 cm spin radius; full speed setting on International Clinical Centrifuge Model CL 20928m).

10. Maintain the tube in the inverted position to avoid disturbing the packed RBC's. Using a standard 20 G Sterile needle and a 2-3 mL sterile shielded disposable syringe, withdraw 1.25-2.0 mL of RBC's (depending on volume of whole blood used) and transfer to the premeasured technetium prepared in (1). To remove the RBC's from the upside-down vacutainer tube, make sure the plunger of the 3 mL syringe is pushed all the way into the syringe barrel before puncturing the vacutainer stopper - injection of air into the settled RBC's will resuspend the cells. Once the needle has just penetrated the vacutainer stopper, remove the RBC's in one smooth plunger withdrawal movement - ejection of cells from the syringe back into the vacutainer tube will resuspend the remaining cells and the operation cannot be continued without recentrifugation (see Note c).

11. Incubate the technetium-RBC mixture for ten minutes at room temperature with gentle mixing.

12. Complete and affix the radioactive contents label to the vial shield.

13. Assay and dilute appropriately prior to injection. Cell separation and yield determination at this point (Note h) consistently give 98 +% yields. (see note d for preparation of damaged cells for splenic studies).

The DTPA reagent kit is approved for use by the U. S. NRC pursuant to 35.14 and 35.110 Group III of 10 CFR Part 35.