L+L= 20841
030- 21252

APPENDIX A

NRC FORM 313
(1-84)
10 CFR 30, 32, 33, 34, 35 and 40

U.S. NUCLEAR REGULATORY COMMISSION
APPROVED BY OMB
3150-0120
Expires: 5-31-87

APPLICATION FOR MATERIAL LICENSE 02512

INSTRUCTIONS: SEE THE APPROPRIATE LICENSE APPLICATION GUIDE FOR DETAILED INSTRUCTIONS FOR COMPLETING APPLICATION. SEND TWO COPIES OF THE ENTIRE COMPLETED APPLICATION TO THE NRC OFFICE SPECIFIED BELOW.

FEDERAL AGENCIES FILE APPLICATIONS WITH:

U.S. NUCLEAR REGULATORY COMMISSION
DIVISION OF FUEL CYCLE AND MATERIAL SAFETY, NMSS
WASHINGTON, DC 20555

ALL OTHER PERSONS FILE APPLICATIONS AS FOLLOWS, IF YOU ARE LOCATED IN:

CONNECTICUT, DELAWARE, DISTRICT OF COLUMBIA, MAINE, MARYLAND, MASSACHUSETTS, NEW JERSEY, NEW YORK, PENNSYLVANIA, RHODE ISLAND, OR VERMONT, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION I
NUCLEAR MATERIAL SECTION B
631 PARK AVENUE
KING OF PRUSSIA, PA 19406

ALABAMA, FLORIDA, GEORGIA, KENTUCKY, MISSISSIPPI, NORTH CAROLINA, PUERTO RICO, SOUTH CAROLINA, TENNESSEE, VIRGINIA, VIRGIN ISLANDS, OR WEST VIRGINIA, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION II
MATERIAL RADIATION PROTECTION SECTION
101 MARIETTA STREET, SUITE 2900
ATLANTA, GA 30323

IF YOU ARE LOCATED IN:

ILLINOIS, INDIANA, IOWA, MICHIGAN, MINNESOTA, MISSOURI, OHIO, OR WISCONSIN, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION III
MATERIALS LICENSING SECTION
799 ROOSEVELT ROAD
GLEN ELLYN, IL 60137

ARKANSAS, COLORADO, IDAHO, KANSAS, LOUISIANA, MONTANA, NEBRASKA, NEW MEXICO, NORTH DAKOTA, OKLAHOMA, SOUTH DAKOTA, TEXAS, UTAH, OR WYOMING, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION IV
MATERIAL RADIATION PROTECTION SECTION
611 RYAN PLAZA DRIVE, SUITE 1000
ARLINGTON, TX 76011

ALASKA, ARIZONA, CALIFORNIA, HAWAII, NEVADA, OREGON, WASHINGTON, AND U.S. TERRITORIES AND POSSESSIONS IN THE PACIFIC, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION V
MATERIAL RADIATION PROTECTION SECTION
1450 MARIA LANE, SUITE 210
WALNUT CREEK, CA 94596

PERSONS LOCATED IN AGREEMENT STATES SEND APPLICATIONS TO THE U.S. NUCLEAR REGULATORY COMMISSION ONLY IF THEY WISH TO POSSESS AND USE LICENSED MATERIAL IN STATES SUBJECT TO U.S. NUCLEAR REGULATORY COMMISSION JURISDICTION.

1. THIS IS AN APPLICATION FOR (Check appropriate item)

- [X] A. NEW LICENSE
- [ ] B. AMENDMENT TO LICENSE NUMBER _____
- [ ] C. RENEWAL OF LICENSE NUMBER _____

2. NAME AND MAILING ADDRESS OF APPLICANT (Include Zip Code)

CADEMA MEDICAL PRODUCTS, INC.
569 North St., P. O. Box 250
Middletown, N. Y. 10940

3. ADDRESS(ES) WHERE LICENSED MATERIAL WILL BE USED OR POSSESSED.

Address where Reagent Kits will be used or possessed: 569 North St.
Middletown, N.Y. 10940

4. NAME OF PERSON TO BE CONTACTED ABOUT THIS APPLICATION

MAURICE E. BORDONI

TELEPHONE NUMBER: 1-800-422-3362

SUBMIT ITEMS 5 THROUGH 11 ON 8½ x 11" PAPER. THE TYPE AND SCOPE OF INFORMATION TO BE PROVIDED IS DESCRIBED IN THE LICENSE APPLICATION GUIDE.

5. RADIOACTIVE MATERIAL. a. Element and mass number, b. chemical and/or physical form, and c. maximum amount which will be possessed at any one time. Reagent Kits See Attached Sheets

6. PURPOSE(S) FOR WHICH LICENSED MATERIAL WILL BE USED. See Attached Sheet

7. INDIVIDUAL(S) RESPONSIBLE FOR RADIATION SAFETY PROGRAM AND THEIR TRAINING AND EXPERIENCE. Not Applicable

8. TRAINING FOR INDIVIDUALS WORKING IN OR FREQUENTING RESTRICTED AREAS Not Applicable

9. FACILITIES AND EQUIPMENT. Not Applicable

10. RADIATION SAFETY PROGRAM 10.3 of guide See Attached Sheet

11. WASTE MANAGEMENT. Not Applicable

12. LICENSEE FEES (See 10 CFR 170 and Section 170.31)
FEE CATEGORY Reagent Kits | AMOUNT ENCLOSED $700.00

13. CERTIFICATION. (Must be completed by applicant) THE APPLICANT UNDERSTANDS THAT ALL STATEMENTS AND REPRESENTATIONS MADE IN THIS APPLICATION ARE BINDING UPON THE APPLICANT.

THE APPLICANT AND ANY OFFICIAL EXECUTING THIS CERTIFICATION ON BEHALF OF THE APPLICANT NAMED IN ITEM 2, CERTIFY THAT THIS APPLICATION IS PREPARED IN CONFORMITY WITH TITLE 10, CODE OF FEDERAL REGULATIONS, PARTS 30, 32, 33, 34, 35, AND 40 AND THAT ALL INFORMATION CONTAINED HEREIN, IS TRUE AND CORRECT TO THE BEST OF THEIR KNOWLEDGE AND BELIEF.

WARNING: 18 U.S.C. SECTION 1001 ACT OF JUNE 25, 1948, 62 STAT. 749 MAKES IT A CRIMINAL OFFENSE TO MAKE A WILLFULLY FALSE STATEMENT OR REPRESENTATION TO ANY DEPARTMENT OR AGENCY OF THE UNITED STATES AS TO ANY MATTER WITHIN ITS JURISDICTION

SIGNATURE--CERTIFYING OFFICER	TYPED/PRINTED NAME	TITLE	DATE
Maurice E. Bord	MAURICE E. BORDONI	PRESIDENT	4/15/85

14. VOLUNTARY ECONOMIC DATA

a. ANNUAL RECEIPTS
- [ ] <$250K
- [ ] $250K–$500K
- [X] $500K–$750K
- [ ] $750K–1M
- [ ] $1M–3.5M
- [ ] $3.5M–7M
- [ ] $7M–10M
- [ ] >$10M

b. NUMBER OF EMPLOYEES (Total for entire facility excluding outside contractors) 7

c. NUMBER OF BEDS Not Applicable

d. WOULD YOU BE WILLING TO FURNISH COST INFORMATION (Dollar and/or staff hours) ON THE ECONOMIC IMPACT OF CURRENT NRC REGULATIONS OR ANY FUTURE PROPOSED NRC REGULATIONS THAT MAY AFFECT YOU? (NRC regulations permit it to protect confidential commercial or financial--proprietary--information furnished to the agency in confidence)

[X] YES [ ] NO

FOR NRC USE ONLY

TYPE OF FEE	FEE LOG	FEE CATEGORY	COMMENTS	APPROVED BY
APPL.	May 5 I	~~3~~ 3D	Dist only - Kits will not contain byproduct material	Frances Brown
AMOUNT RECEIVED	CHECK NUMBER			DATE
$700	613			5/15/85

PRIVACY ACT STATEMENT ON THE REVERSE

03754

5/17/85

"OFFICIAL RECORD COPY"

8507230582 850626
REG1 LIC30
31-20841-01MA PDR

ML10

MAY 02 1985

Application No.

5. and 6.

A. Lymph-Scan ASC Kit used to prepare Technetium Tc-99m labeled Antimony Trisulfide Colloid.

B. RBC Kit used to prepared Technetium Tc-99m-labeled red blood cells.

C. DTPA Kit used to prepare Technetium Tc-99m-labeled pentatate sodium.

D. TcmaC Kit used to prepare Technetium Tc-99m-labeled microalbumin colloid.

Section 10.3.1

Completed applications of reagent kits to FDA and FDA responses.

DEPARTMENT OF HEALTH & HUMAN SERVICES

file NDA

Public Health Service

Food and Drug Administration
Rockville MD 20857

2.a

2.a.i

2.a.ii

2 a iii

2.b

2.c

2.d.i

2.d.ii

MAR 1 4 1984

NDA 19-180

Cadema Medical Products, Inc.
Attention: E. Lieberman
P.O. Box 250
Middletown, New York 10940

Dear Mr. Lieberman:

We are pleased to acknowledge the receipt of your new drug application submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for the following diagnostic radiopharmaceutical:

Name of Drug:	Technetium Tc 99m Antimony Trisulfide Colloid Kit
Date of Application:	November 30, 1983
Date of Receipt	December 9, 1983
Our Reference Number	NDA 19-180

We will correspond with you further after we have had the opportunity to study the application. Should you have any questions prior to our contacting you, please call:

Mr. Robert L. West
Pharmacist, Consumer Safety Officer
(301) 443-4260

All future communications concerning this new drug application should be addressed as follows:

National Center for Drugs and Biologics
Office of Drug Research and Review
Division of Oncology and Radiopharmaceutical Drug Products (HFN-150)
Attention: Document Control Room # 17-B-28
5600 Fishers Lane
Rockville, Maryland 20852

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
National Center for Drugs and Biologics

'ARTMENT OF HEALTH, EDUCATION, AND WELFARE
LIC HEALTH SERVICE
D AND DRUG ADMINISTRATION
5 FISHERS LANE
KVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0003

NEW DRUG APPLICATION *(DRUGS FOR HUMAN USE)*

(Title 21, Code of Federal Regulations, § 314.1)

of applicant Cadema Medical Products, Incorporated

lress P. O. Box 250, 569 North St., Middletown, N. Y. 10940

December 7, 1983

ıe of new drug Technetium Tc-99m Antimony Trisulfide Colloid

Original application (regulation § 314.1).

☐ Amendment to original, unapproved application (regulation § 314.6)

Abbreviated application (regulation § 314.1(f)).

☐ Amendment to abbreviated, unapproved application (regulation § 314.6).

☐ Supplement to an approved application (regulation § 314.8).

☐ Amendment to supplement to an approved application.

The undersigned submits this application for a new drug pursuant to section 505(b) of the Federal Food, Drug, and ıetic Act. It is understood that when this application is approved, the labeling and advertising for the drug will prescribe, nmend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the e is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or ı prescribes, recommends, or suggests a dosage for use of the drug will contain the same information for its use, ding indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant warnings, ds, contraindications, side effects, and precautions, as that contained in the labeling which is part of this application in d with §201.100 (21 CFR 201.100). It is understood that all representations in this application apply to the drug ıced until an approved supplement to the application provides for a change or the change is made in conformance with provisions of §314.8 of the new-drug regulations.

Attached hereto, submitted in the form described in §314.1(e) of the new-drug regulations, and constituting a part of ication are the following:

Table of contents. The table of contents should specify the e number and the page number in which the complete and ed item is located and the volume number and the page er in which the summary of that item is located (if any).

Summary. A summary demonstrating that the application is rganized, adequately tabulated, statistically analyzed (where priate), and coherent and that it presents a sound basis for proval requested. The summary should include the following ıation: (In lieu of the outline described below and the tion described in Item 3, and expanded summary and tion as outlined in §314.1(d) of the new-drug regulations e submitted to facilitate the review of this application.)

Chemistry.

Chemical structural formula or description for any new-drug nce.

Relationship to other chemically or pharmacologically l drugs.

Description of dosage form and quantitative composition.

Scientific rationale and purpose the drug is to serve.

Reference number of the investigational drug notice(s) which this drug was investigated and of any notice, ug application, or master file of which any contents are ncorporated by reference to support this application.

Preclinical studies. (Present all findings including all adverse ences which may be interpreted as incidental or not ılated. Refer to date and page number of the investigational otice(s) or the volume and page number of this application complete data and reports appear.)

Pharmacology (pharmacodynamics, endocrinology, olism, etc.).

Toxicology and pathology: Acute toxicity studies; subacute toxicity studies; reproduction and teratology studies; us studies.

e. Clinical studies. (All material should refer specifically to each clinical investigator and to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found.)

i. Special studies not described elsewhere.

ii. Dose-range studies.

iii. Controlled clinical studies.

iv. Other clinical studies (for example, uncontrolled or incompletely controlled studies).

v. Clinical laboratory studies related to effectiveness.

vi. Clinical laboratory studies related to safety.

vii. Summary of literature and unpublished reports available to the applicant.

3. Evaluation of safety and effectiveness. *a.* Summarize separately the favorable and unfavorable evidence for each claim in the package labeling. Include references to the volume and page number in the application and in any documents incorporated by reference where the complete data and reports may be found.

b. Include tabulation of all side effects or adverse experience, by age, sex, and dosage formulation, whether or not considered to be significant, showing whether administration of the drug was stopped and showing the investigator's name with a reference to the volume and page number in the application and any documents incorporated by reference where the complete data and reports may be found. Indicate those side effects or adverse experiences considered to be drug-related.

4. Copies of the label and all other labeling to be used for the drug (a total of 12 copies if in final printed form, 4 copies if in draft form):

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

ncerning any other treatment given previously or concurrently,
d a full statement of adverse effects and useful results observed,
gether with an opinion as to whether such effects or results are
tributable to the drug under investigation and a statement of
here the underlying data are available for inspection. Ordinarily,
e reports of clinical studies will not be regarded as adequate
less they include reports from more than one independent,
mpetent investigator who maintains adequate case histories of
adequate number of subjects, designed to record observations
d [illegible] evaluation of any and all discernible effects
tributable to the drug in each individual treated and comparable
cords on any individuals employed as controls. An application
r a combination drug may be refused unless there is substantial
idence that each ingredient designated as active makes a
ntribution to the total effect claimed for the drug combination.
cept when the disease for which the drug is being tested occurs
th such infrequency in the United States as to make testing
practical, some of the investigations should be performed by
mpetent investigators within the United States.

d. Attach as a separate section a completed Form FD-1639,
ug Experience Report (obtainable, with instructions, on request
om the Food and Drug Administration, Department of HEW.
00 Fishers Lane, Rockville, Maryland 20852), for each adverse
perience or, if feasible, for each subject or patient experiencing
e or more adverse effects, described in Item 12c, whether or not
l information is available. Form FD-1639 should be prepared by
applicant if the adverse experience was not reported in such
m by the investigator. The Drug Experience Report should be
ss-referenced to any narrative description included in Item 12c.
lieu of a FD Form 1639, a computer-generated report may be
mitted if equivalent in all elements of information with the
ntical enumerated sequence of events and methods of
npletion; all formats proposed for such use will require initial
iew and approval by the Food and Drug Administration.

e. All information pertinent to an evaluation of the safety and
ctiveness of the drug received or otherwise obtained by the
plicant from any source, including information derived from
er investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application and related drugs. An adequate summary may be acceptable in lieu of a reprint of a published report which only supports other data submitted. Reprints are not required of reports in designated journals, listed in §310.9 of the new-drug regulations, about related drugs; a bibliography will suffice. Include the evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

f. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

g. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in Item 6, 7, or 8 of the application.

h. In vivo bioavailability data or information to permit waiver of this requirement in accordance with Subpart B of Part 320 (21 CFR Part 320, Subpart B).

13. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

Observe the provisions of §314.8 of the new-drug regulations concerning supplemental applications.

14. [Reserved]

15. The applicant is required to submit an environmental impact analysis report analyzing the environmental impact of the manufacturing process and the ultimate use or consumption of the drug pursuant to §6.1 of this chapter.

Cadema Medical Products, Inc.
(Applicant)

Per E. Lieberman
(Responsible official or agent)

Chief Executive Officer
(Indicate authority)

ning: A willfully false statement is a criminal offense. U.S.C. Tittle 18, sec. 1001.)

ote: This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or authorized representative does not reside or have a place of business within the United States, the application must also sh the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing intaining a place of business within the United States.

APPENDIX I

BROOKHAVEN NATIONAL LABORATORY
ASSOCIATED UNIVERSITIES, INC.
Upton, Long Island, New York 11973

(516) 282-7338
FTS 666-

Office of the Director

July 26, 1984

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

Re: Brookhaven National Laboratory IND No. 12003 for a
Red Blood Cell Labeling Kit

Dear Mr. West:

This is to inform you that Brookhaven National Laboratory and Cadema Medical Products, Inc. have entered into an agreement, effective June 1, 1984, by which Brookhaven transferred its IND No. 12003 to Cadema Medical Products, Inc. This agreement was approved by the U. S. Department of Energy as required by Brookhaven's contract with DOE. Under the terms of the agreement, Brookhaven conveys to Cadema the IND, copies of all correspondence currently in Brookhaven's possession relating to this IND, and all background data relating to toxicology, pharmacology, clinical studies and manufacturing techniques for the red blood cell kit.

Brookhaven is taking this opportunity to formally notify the FDA of the transfer in ownership from Brookhaven to Cadema of IND No. 12003. Please be advised that all other notifications and submissions required by the FDA concerning the red blood cell kit will now be the responsibility of Cadema.

Sincerely yours,

Margaret C. Bogosian
Patent Counsel

MCB:am
cc: M. Bordoni, Cadema Medical Products, Inc.

APPENDIX II

IND 12,003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0910-0014

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE: No drug may be shipped or study initiated unless a complete statement has been received. *(21 CFR 312.1(a)(2)).*

Name of Sponsor CADEMA MEDICAL PRODUCTS, INC. Date July 16, 1984

Address 569 NORTH ST., MIDDLETOWN, N.Y. Telephone (914) 343-7474

Name of Investigational Drug RED BLOOD CELL KIT (BNL)

FOR A DRUG:

Food And Drug Administration
Office of New Drug Evaluation *(HFN-106)*
5600 Fishers Lane
Rockville, Maryland 20857

FOR A BIOLOGIC:

Food and Drug Administration
Office of Biologics *(HFN-823)*
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Sir:

The sponsor, CADEMA MEDICAL PRODUCTS, INC., submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, or each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to under-

take the phase of the investigation outlined in section 10 [illegible]he "Notice of Claimed Investigational Exemption for a New Dru[illegible] (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed Form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. [illegible]ical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man - only animal and in vitro data are available - with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phas[illegible] following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review board (IRB). The sponsor must give assurance that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the pr[illegible]ed clinical study. The sponsor must also provide assurance that th[illegible]vestigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FDA-1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, and additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 25.1 of this chapter.

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

Maurice E Bordoni

SPONOR	PER MAURICE E. BORDONI
[illegible] Cadema Medical Products, Inc. 569 North St., Middletown, N.Y. 10940	INDICATE AUTHORITY PRESIDENT

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 24,406

OCT 15 1984

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

Attention: Maurice Bordoni
President

Dear Mr. Bordoni:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND 24,406) submitted pursuant to section 505 (i) of the Federal Food, Drug, and Cosmetic Act for the diagnostic radiopharmaceutical Technetium Tc 99m Diethylenetriamine Pentaacetic Acid Reagent Kit (Pentetate).

The protocol as submitted provides for a study to demonstrate the effectiveness of the drug when it is administered intravenously in a dose of 3 to 5 millicuries for kidney imaging and glomerular filtration rate estimation and also in a dose of 10 to 20 millicuries for brain imaging or renal perfusion studies. A separate protocol provides for a study to demonstrate the safety and efficacy of the drug when it is administered as an aerosol for the purpose of lung imaging. A dose of between 10 and 30 millicuries will be used for this purpose in conjunction with a baffled nebulizer system.

We note that Technetium Tc 99m DTPA when used for renal scanning and function studies by the intravenous route is included on the well-established list of radiopharmaceuticals as found in 21 CFR 310.503. Therefore two adequate and well controlled clinical studies are not required for NDA approval for this purpose although clinical concordance with commercially available Tc 99m DTPA kits must be demonstrated. However, two adequate and well controlled clinical studies are required for NDA approval of the aerosol dosage form for inhalation. It is the intention of this IND to provide the necessary clinical data prior to an NDA submission.

We have completed our review of your submission and have concluded that your clinical studies may proceed. However, in order to complete your submission, please respond to the following comments and requests:

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

FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0030

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor Cadema Medical Products, Inc.

Address P. O. Box 250, 569 North St., Middletown, N.Y., 10940 - Tel. No. (914) 343-7474

Date June 18, 1984

Name of Investigational Drug Technetium Tc-99m Diethlyenetriamine Pentaacetic Acid Reagent Kit (Penetate)

ITEM 1

Commissioner
Food and Drug Administration
Bureau of Drugs (BD-22)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

The sponsor, CADEMA MEDICAL PRODUCTS, INC., submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto, in triplicate, are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of pre-existing information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of three copies of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of claimed investigational exemption for a new drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD 1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies.

b. *Clinical trial.* This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. It is understood that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. It is understood that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver.

Very truly yours,

SPONSOR	PER
Cadema Medical Products, Inc. P.O. Box 250, 569 North Street, Middletown, N.Y., 10940	Maurice Bordoni
	INDICATE AUTHORITY
	President

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Received
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IND 22,683

MAY 11 1984

Tcmac

Fill TcMAAC
#22683

E. Lieberman
Chief Executive Officer
Cadema Medical Products, Inc.
P. O. Box 250
Middletown, New York 10940

Dear Mr. Lieberman:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND 22,683) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for the diagnostic radiopharmaceutical Technetium Tc 99m Mini-Microaggregated Albumin Colloid Reagent Kit, and to the latest letter from this Division dated April 5, 1984 informing you that your clinical study was being maintained on clinical hold for safety reasons.

We acknowledge the receipt of your resubmitted Notice which is dated April 10, 1984.

We have completed our review of your submission and have concluded that your clinical study may proceed under the revised protocol as submitted on April 10, 1984. However, the study may not be expanded beyond the original 40 patients until the chemistry deficiencies contained in our letter of April 5, 1984 have been responded to in a satisfactory manner, and permission as been granted by this Division.

We request that you indicate the complete name of the drug on page 128 of the protocol under the Dosage and Administration section.

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 substantial change to your 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0014

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE: No drug may be shipped or study initiated unless a complete statement has been received. *(21 CFR 312.1(a)(2)).*

Name of Sponsor CADEMA MEDICAL PRODUCTS, INC. Date _____

Address P. O. Box 250, 569 North St., Middletown, N.Y. 10940 Telephone (914) 343-7474

Name of Investigational Drug Technetium Tc-99m Mini-Microaggregated Albumin Colloid Reagent Kit

FOR A DRUG:

Food And Drug Administration
Office of New Drug Evaluation *(HFN-106)*
5600 Fishers Lane
Rockville, Maryland 20857

FOR A BIOLOGIC:

Food and Drug Administration
Office of Biologics *(HFN-823)*
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Sir:

The sponsor, CADEMA MEDICAL PRODUCTS, INC., submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, or each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to under-

take the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations phase 3 investigators may be added and the form supplemented by rapid communication methods, and the revised Form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man - only animal and in vitro data are available - with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review board (IRB). The sponsor must give assurance that an IRB that complies with the requirements set forth in Part of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FDA-1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, and additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 25.1 of this chapter.

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

SPONSOR Cadema Medical Products, Inc. P. O. Box 250 - 569 North St. Middletown, N. Y. 10940	PER E. Lieberman INDICATE AUTHORITY Chief Executive Officer

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

Section 10.3.2

Four reagent kits are listed in this Approval application.

Four reagent kits are manufactured and distributed as IND's.

Two of the four reagent kits (Pentatate Sodium and Micro Albumin colloid are listed in Group III of 35.100 of 10 CFR Part 35.

Section 10.3.3

In response to 32.73 (a) (3) of 10 CFR Part 32, the reagent kits are packaged in a manner that is appropriate for their use in physicians' offices and community hospitals.

Attached find:

a. the radionuclide to be used with the reagent kits

b. the chemical and physical form of the components of each reagent kit

c. the packaging of the reagent kits (samples shown in Section 10.3.4)

Section 10.3.4

In response to 32.73 (a) 4 and 5 and 20.203 of 10 CFR Part 20, attached find samples of labels, package insert, physician's protocol and packaging components.

APPENDIX I

ANTIMONY TRISULFIDE COLLOID REAGENT KIT

2 a.1 Chemistry

1. The name of the drug is Technetium Tc-99m Antimony Trisulfide Colloid (USAN) (Lymph Scan).

The Antimony Trisulfide Colloid is prepared by adding Antimony Potassium Tartrate ($KSbO\ C_4H_4O_6 - \frac{1}{2}H_2O$) to sterile water saturated with Hydrogen Sulfide Gas.

Although the precise chemical structure of Antimony Trisulfide Colloid is unknown, it is generally postulated to be $Sb_2\ S_3$.

The formed colloid has a particle size of 4 to 12 millimicrons (40 - 120 Angstroms). This small colloidal size is essential to assure effective flow with lymph fluid through small lymph channels and uptake by the lymph nodes. The polyvinylpyrrolidone (PVP) which is added to the preformed colloid coats the particle and prevents agglomeration of the colloid.

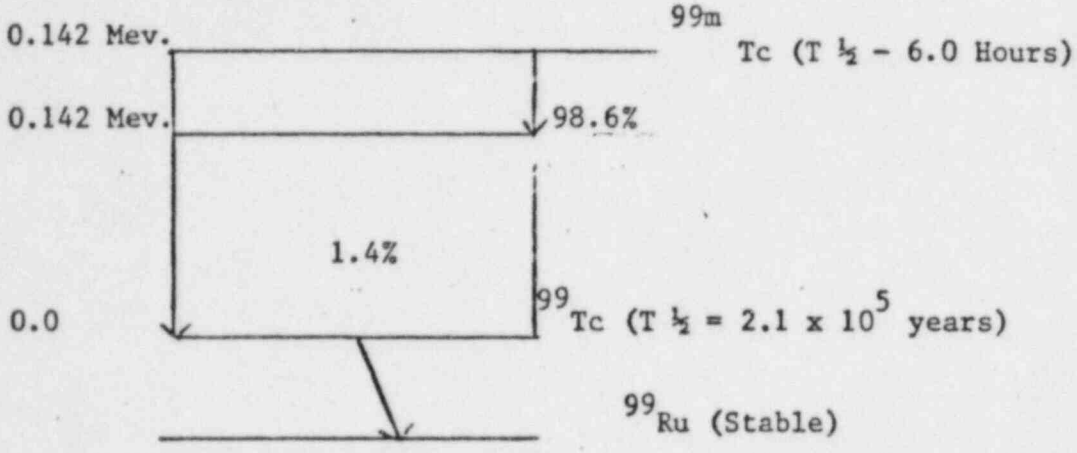
The drug is prepared from a kit containing 10 syringes and 5 vials. Five of the syringes contain a premeasured solution of preformed Antimony Trisulfide Colloid and five contain a premeasured solution of phosphate buffer. The five vials contain a premeasured volume of 0.5 N Hydrocholoric Acid.

The radioisotope Technetium Tc-99m is added to the vial containing 0.5 N Hydrochloric Acid.

Technetium Tc-99m, in the presence of strong acid and heat is reduced to a lower valance state and as a result, labeling to the Antimony Trisulfide Colloid is affected. After labeling the Antimony Sulfide ligand, excess acid in the solution is neutralized by the addition of a buffering solution.

The Technetium 99m in the drug is a radionuclide with a six-hour half-life. It is obtained by eluting it with saline from its longer-lived parent, Molybdenum Mo-99.

The decay scheme for ^{99m}Tc is:-



The radioactive isotope, Technetium Tc-99m is identified through its half-life and emission characteristics. Chemically, Technetium belongs to the group VII B of the periodic table with manganese and rhenium. It is similar to rhenium in chemical reactions. The mechanism for binding the Technetium to the Antimony Trisulfide Colloid is not known at this time.

The finished drug is administered interstitially to the patient.

RADIOCHEMICAL PURITY

The radiochemical purity is determined by assending radiochromotography.

The Technetium Tc-99m radioactivity bound to the Antimony Trisulfide Colloid has an R.f. equal to 0. Any unbound Technetium Tc-99m activity will be found at the solvent from R.F.=0.8 to 1.0.

The recommended radiochromotographic procedure is in Item 8N of the NDA, page 409.

QUANTITATIVE COMPOSITION OF THE FINISHED DRUG

Since the activity, per unit volume, of Sodium Pertechnetate, Tc-99m added to the 10 milliliter vial containing the 0.2 milliliters of 0.5 N Hydrochloric Acid and 1.2 milliliters of Antimony Trisulfide Colloid is variable, no composition of the final drug can be given. A typical addition of 0.5 milliliters of Sodium Pertechnetate Tc-99m containing 15 millicuries, together with 0.5 milliliters of buffer solution would yield the following:

FINISHED DRUG CONCENTRATIONS

Volume Additions (mL)	ASC Syringe System
Tc-99m Pertechnetate in 0.9% saline	0.5
HCl	0.2
ASC Colloid	1.2
Buffer	0.5
Saline, 0.9%	---
Final Volume	2.4

Reactants	Per 10cc. Vial 2.4 mL	Per mL
*Sodium Pertechnetate Tc-99m	15 mCi	6.25 mCi
Antimony as Trisulfide	0.67 mg	0.28 mg
Potassium Tartrate	1.0 mg	0.42 mg
Povidone	3.2 mg	1.33 mg
Sodium Phosphate, Monobasic	2.7 mg	1.13 mg
Sodium Phosphate, Dibasic	24.7 mg	10.29 mg
Sterile Water for Injection	1.7 mL	0.71 mg
**Isotonic Saline	0.5 mL	0.21 mL
0.5 N Hydrochloric Acid	0.2 mL	0.08 mL

*Not in kit as supplied ** Total for Sodium Pertechnetate Tc-99m solution

Per 0.3 mL (Injection Volume)

Tc-99m	1.88 mCi
Sb as Sb_2S_3	0.084 mg
	0.126 mg
	0.399 mg
	3.09 mg
	0.33 mg
	0.022 mmole

Dosage Form

The generally recommended dosage form for the interstitial injection is 500 to 1000 microcuries of Technetium Tc-99m.

2 a.iii KIT DESCRIPTION

Technetium Tc-99m Antimony Trisulfide Colloid Reagent Kit is supplied in a multidose form without Sodium Pertechnetate Tc-99m. When made up in accordance with the preparation instructions, each multidose kit has sufficient material to make five multidose preparations.

Packaged in one box, the contents are as follows:

QUANTITY	DESCRIPTION
5	2.25 cc. syringes (labeled "A"), each containing 1.2 mL of stabilized Antimony Trisulfide Colloid preparation (0.67 mg. of Antimony as Trisulfide, 3.2 mg. of Povidone, 1.0 mg. of Potassium Tartrate, 1.2 Sterile Water for Injection).
5	10 cc. vials, each containing 0.2 mL of 0.5 N Hydrochloric Acid.
5	2.25 cc. syringes (labeled "B"), each containing 0.5 mL of Phosphate buffer solution (24.7 mg. of Dibasic Sodium Phosphate, 2.7 mg. of Monobasic Sodium Phosphate, 0.5 mL Sterile Water for Injection.

OUTER BOX LABEL

FOR

ANTIMONY SULFUR COLLOID

CAUTION: NEW DRUG

LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE

diagnostic/sterile/pyrogen-free

LYMPH-SCAN Multi-dose

TECHNETIUM 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

Rev. LF150-1

Made in U.S.A. Date 4-83

PATIENT RECORD LABEL

FOR

ANTIMONY SULFUR COLLOID

INVESTIGATIONAL PREPARATION
diagnostic/sterile/pyrogen-free
TECHNETIUM Tc 99m
ANTIMONY TRISULFIDE COLLOID

activity _____ millicuries
volume _____ ml
concentration _____ millicuries/ml
time & date prepared _____
prepared by _____ lot. no. _____

Store prepared drug at room temperature. Rev. L201-1
Read brochure before use. Date 4-83

CAUTION
NEW DRUG
Limited by Federal Law to Investigational use.

RADIOACTIVE MATERIAL

CADEMA MEDICAL PRODUCTS, INC.
MIDDLETOWN, NY 10940

VIAL LABEL

FOR

ANTIMONY SULFUR COLLOID

CAUTION: NEW DRUG—LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE.

0.5 N Hydrochloric Acid
For Preparation of Technetium
Tc 99m Antimony Trisulfide Colloid Kit

Contains 0.2 ml of 0.5 N Hydrochloric Acid.
Not for use in humans in present form.
See brochure for preparation and use.
Sterile/pyrogen-free.
Store at 18-25 °C.

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

REV. LC151-1
Made in U.S.A. DATE 4-83

A

Sterile Pyrogen-free
CAUTION: NEW DRUG-LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE
For the preparation of
Technetium Tc 99m Antimony Trisulfide Colloid Kit
An aqueous solution containing 0.67 mg Sb as Sb_2S_3, 3.2 mg Povidone, 1.0 mg Potassium Tartrate, 1.2 ml Sterile Water for Injection.
Store at 18-25 °C.
Not for use in humans in present form.
See brochure for preparation and use.
CADEMA MEDICAL PRODUCTS, INC., MIDDLETOWN, N.Y. 10940
REV. LC152-1
Made in U.S.A. DATE 4-83

B

Sterile Pyrogen-free
CAUTION:NEW DRUG-LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE.
For the preparation of
Technetium Tc 99m Antimony Trisulfide Colloid Kit
An aqueous solution containing 24.7 mg Sodium Phosphate, Dibasic; 2.7 mg Sodium Phosphate, Monobasic; 0.5 ml Sterile Water for Injection.
Store at 18-25 °C.
Not for use in humans in present form.
See brochure for preparation and use.
CADEMA MEDICAL PRODUCTS, INC., MIDDLETOWN, N.Y. 10940
REV. LC153-1
Made in U.S.A. DATE 4-83

PACKAGE INSERT

FOR

ANTIMONY SULFUR COLLOID

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}

APPENDIX II

RED BLOOD CELL REAGENT KIT

Revised 1/25/82

1. Drug: Autologous red blood cells labeled with technetium-99m, using the reagent kit vial.

2. List of components:

Human blood from the patient
Technetium-99m as sodium pertechnetate
Sodium chloride 0.9%, injection, U.S.P.
Sterile water for injection, U.S.P., pyrogen-free
Trisodium citrate
Tin wire
Dextrose
Vacutainer tube, 100 x 15 mm, 10 ml capacity
20 G, hypodermic needle

3. Quantitative composition of the kit:

2.0 µg tin
3.67 mg trisodium citrate-dihydrate
5.50 mg dextrose (anhydrous)
0.11 mg sodium chloride (maximum)

The kit contains ±10% of the above stated quantities of reagents.

4. Source, purity, and composition of components used:

(i) 0.9% Sodium chloride injection, U.S.P. (normal saline), Travenol Laboratories, Inc., Deerfield, Ill.

(ii) Tin wire, 0.5 mm diameter, M5N (99.999%), Alfa Products, Ventron Corporation, 152 Andover St., Danvers, Mass.

(iii) Trisodium citrate, dihydrate, U.S.P., Amend Drug and Chemical Company, Irvington, New Jersey, or Mallinckrodt, Inc., Paris, Kentucky

(iv) Dextrose (anhydrous), U.S.P., J. T. Baker Chemical Company, Phillipsburg, New Jersey

(v) Sterile water for injection, U.S.P., pyrogen-free, Travenol Labs., Inc., Deerfield, Illinois

(vi) Sterile Vacutainer tubes, 100 x 15 mm, 10 ml capacity, Becton & Dickinson Co., Rutherford, New Jersey

The identity and the purity of the tin wire are confirmed by atomic emission spectroscopy. The other chemicals listed above are tested by standard U.S.P. procedures. (See Appendix 1 for methods and results of analysis.)

9. Procedure for using the kit to prepare ^{99m}Tc-labeled RBC's:

(For details, see Appendix 8.)

(i) One to three ml of saline ^{99m}Tc pertechnetate is added to a sterile, pyrogen-free, 15 ml pharmaceutical vial and the activity assayed. The vial is stored in a lead shield.

(ii) Four ml (or up to six ml in case of low hematocrit) of the patient's blood is drawn into a heparinized syringe and added to the kit tube.

(iii) Gentle mixing is carried out for 5 min at room temperature, to dissolve the freeze-dried solids in the blood.

(iv) (10-x) ml of sterile saline is added to the blood (x = ml blood used in step (ii)). CAUTION: To avoid pressure buildup inside the Vacutainer tube, (10-x) sterile saline is drawn into a 20 ml syringe, the hypodermic needle is pushed through the stopper and with the tube upright so that the blood will not be drawn back into the syringe, the syringe plunger is pulled back to 2(10-x)ml mark. The created vacuum allows the saline to be drawn into the tube.

(v) After brief mixing, the tube is centrifuged upside down for 5 min at 1300 x G.

(vi) The tube is maintained in the inverted position to avoid disturbing the packed RBC's. 1.25-2 ml of RBC's are withdrawn using a 20G needle. The needle should just penetrate the stopper.

(vii) The RBC's are transferred to the premeasured technetium from step (i).

(viii) The technetium-RBC mixture is incubated for 5 min at room temperature, with gentle mixing.

(ix) The suspension is assayed and diluted appropriately for injection. Cell separation and yield determination at this point should give 97% or better labeling yield. (See Appendix 8 for labeling yield determination.)

(x) A splenic agent can be conveniently prepared by replacing step (viii) with a 15-min incubation at 49.5°C, with gentle mixing.

10. Assay and Calibration Procedures:

(i) Identity: Each patient's blood is drawn and marked separately during all stages of preparation.

(ii) Radioactivity per unit volume of the $^{99m}TcO_4^-$ used in the preparation is determined daily as described in IND 4316. Radioactivity of the ^{99m}Tc-labeled red cells is determined before injection into the patient with a well type ionization chamber (Capintec dose calibrator, Capintec, Inc., 63 E. Sanford Blvd., Mount Vernon, New York).

(iii) Chemical analysis: (For details, see Appendices 1 and 5.) The quantity of chemicals present in each kit vial is as follows:

2.0 µg tin
3.67 mg trisodium citrate, dihydrate
5.50 mg dextrose (anhydrous)
0.11 mg sodium chloride (maximum)

The total tin is based on the tin wire weight and is occasionally determined by atomic absorption spectrometry. Several kit vials are selected from each batch randomly, and reconstituted with 1 N HCl. The tin content is then measured individually for each selected vial by comparison with suitable standards having identical chemical composition. The analysis for trisodium citrate, and dextrose is carried out by standard U.S.P. procedures.

The stock stannous citrate solutions, before the dispensing operation, are analyzed for Sn(II) by either (a) iodate titration in 1 N HCl with a potentiometric end point detection, or (b) molybdenum-blue colorimetric procedure (for details of both methods, see Appendix 1). A more relevant test for the presence of adequate amount of Sn(II) in the kits, in the right chemical form, is the final labeling yield determination under loading conditions (addition of sufficient technetium-99 pertechnetate to $^{99m}TcO_4^-$ in order to mimic the worst possible situation, where the presence of maximum Sn(II) in the kit would be required to produce quantitative reduction of technetium and give $\gtrsim$ 97% labeling yield). This test is a more reliable indicator of the efficacious performance of the kits for the intended applications.

(iv) Sterility and apyrogenicity: Sterility and pyrogen testing of the $^{99m}TcO_4^-$ solutions, and of random samples of kit vials from each lot is performed from time to time by independent testing laboratories (sterility: Liuzzi Microbiology Laboratory, Islip, New York; pyrogen testing: Leberco Laboratories, Roselle Park, New Jersey). The design of the kit system, the components, and the recommended method, all assure a uniform, easy-to-follow aseptic procedure throughout the whole operation. Pyrogen-free chemicals are employed during kit preparation, and strictly aseptic conditions are maintained. All glassware is sterilized prior to use. The stannous stock solution before dispensing is filtered through a sterile 0.22 µm Millipore filter and the filter is always tested immediately afterwards. (Typical test results -- Appendices 4 and 5).

(v) Labeling yield determinations: An aliquot of the well-mixed labeled RBC suspension as in steps (9-viii) or (9-x) above is diluted with 1 or 2 ml normal physiological saline and centrifuged for 5 min at 1300 G. The supernatant and the red cells are separated and the ^{99m}Tc activity in each phase is counted using either an ionization chamber or a well-type NaI scintillation counter. A total of $\geq$ 97% technetium-99m activity is routinely found incorporated into the RBC's using the described procedure. (For details, see Appendix 8.)

11. Animal evaluations:

Red blood cells labeled with ^{99m}Tc according to this method have been administered to numerous dogs, goats, rabbits, and rats without any unfavorable reactions whatsoever. (See Appendix 9 for typical results.)

12. Patient Radiation Dose and Safety of Clinical Studies:

Under normal usage, the radiation dose to the patient will be 13 mrads/mCi expressed as a dose to the patient's blood. As a spleen imaging agent, the dose to the spleen is 1.0 rad/mCi. Tin is considered to be practically non-toxic (S. Moeschlin, Poisoning, Grune and Stratton, New York, 1965, p. 115). The normal level of tin in the blood is 13 µg/100 ml (Biological Handbook, Blood and other Blood Fluids, Federation of American Societies for Experimental Biology, Washington, D.C., 1961, p. 21). The lethal dose for animals is 25-30 mg/kg body weight (W.S. Specter, Ed., Handbook of Toxicology, Vol. I, W. B. Saunders Co., Philadelphia, 1956, p. 300). Based on animal toxicity data, the maximum amount of tin administered to a patient is $\leq 1.14 \times 10^{-6}$ times that of a toxic dose. In fact only 20-40% of the total tin in the kit is incorporated into the red cells using the described labeling procedure. The information about the safety of these studies was submitted to, and the study subsequently approved by, the Clinical Investigation Committee and by Dr. E. P. Cronkite, Chairman of the Medical Department of the Brookhaven National Laboratory at that time.

PROTOCOL FOR USING BNL RBC KIT:

THE BNL RED BLOOD CELL KIT FOR PREPARING ^{99m}Tc-LABELED RBC's

Description of Kit Components:

1 Vacutainer reagent tube 100 x 15/16 mm - 10-ml capacity, evacuated to draw up to 6 ml and containing:

2.0	µg tin
3.67	mg sodium citrate
5.50	mg dextrose
0.11	mg sodium chloride (maximum)

Potential Applications for BNL-RBC Labeling Kit

Labeled Cells

1. Nuclear Cardiology
2. Blood Pool Imaging
3. Red Cell Mass
4. Red Cell Mass
5. Detection of G.I. Bleeding
6. Detection of Hemangiomas

Heat Damaged Cells (See Note d)

1. Spleen Imaging
2. Accessory Spleen Localization
3. Detection of G.I. Bleeding

Procedure for Preparing ^{99m}Tc-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 ^{99m}Tc pertechnetate to a sterile and pyrogen-free 10-15 ml pharmaceutical vial and assay. Store in a lead shield (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).

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 appropiately for injection. Cell separation and yield determination at this point (Note h) consistently give 98+% yields. (See Note d for prepartion of damaged cells for splenic studies.)

NOTES ON THE BNL RBC KIT

a. Instant ^{99m}Tc solutions and the first milking from a new generator are not recommended for use with the kit without first testing labeling yield with desired amount of ^{99m} Tc 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 ^{99m}Tc-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, taken any commercially available disodium EDTA or calcium disodium EDTA solution for injection (for example: Endrate, Edetate disodium injection, USP, 15% solution in water, pH 7, 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 prepartation 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 dispensed into anumber 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.

ntly modified procedure, involving the use of 1 ml blood, allows for the
the BNL RBC kit in pediat applications (undamaged as well as
damaged cells). For details, contact the kit suppliers.

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

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.

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 satisfactory.

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 @ 1300 X G. Withdraw supernatant solution carefully
with a long disposable Pasteur pipet or a spinal needle and transfer to another
tube. Make volumes in both tubes same with water. Count supernatant solution
and red blood cells and calculate the yield as follows:

$$\text{Percent labeling yield} = \frac{\text{Activity in RBC's X 100}}{\text{Activity in RBC's + Activity in supernatant solution}}$$

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

Brookhaven National Laboratory does not assure the suitability of the kits for human
use. Any such use is the responsibility of the experimenter.

For further information or if any problems are encountered, please contact the
following:

Suresh C. Srivastava
(516)282-4459
FTS 666-4459
Building 801
Brookhaven National Laboratory
Upton, NY 11973

Revised 10/12/83.

PACKAGE INSERT

FOR

RED BLOOD CELLS

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}

VIAL LABEL

FOR

RED BLOOD CELLS

Sterile/Diagnostic/Pyrogen-free Unit Dose
CAUTION: NEW DRUG–LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE
BNL Red Blood Cell Kit for the preparation of
Technetium Tc-99m Labeled Red Blood Cells
A lyophilized mixture containing 2.0 μg Total Tin, 3.7 mg Sodium Citrate, 5.5 mg Dextrose, 0.11 mg Sodium Chloride (maximum).
Store at 15-30°C.
Not for use in humans in present form.
See brochure for preparation and use.
Manufactured
for CADEMA MEDICAL, INC., Middletown, N.Y. 10940
by Brookhaven National Labs, Upton, N.Y. 11973
Made in U.S.A. Rev. LC602
6/84

PATIENT RECORD LABEL

FOR

RED BLOOD CELLS

INVESTIGATIONAL PREPARATION
diagnostic/sterile/pyrogen-free
BNL RED BLOOD CELL KIT

activity_____millicuries
volume_____ml
concentration_____millicuries/ml
time and date prepared_____
prepared by_____lot no._____

Read brochure before use

Rev. L604
Date 6/84

Manufactured
for CADEMA MEDICAL, INC., Middletown, N.Y. 10940
by Brookhaven National Labs, Upton, N.Y. 11973

CAUTION
NEW DRUG
Limited by
Federal Law to
Investigational use.

RADIOACTIVE
MATERIAL

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

OUTER BOX,

OUTER BOX LABEL

FOR

RED BLOOD CELLS

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 **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.

Lot #

Exp. Date

APPENDIX III

PENTATATE SODIUM REAGENT KIT

ITEM 1

THE DESCRIPTIVE NAME OF THE DRUG INCLUDING CHEMICAL NAME, STRUCTURE, AND METHOD AND ROUTE OF ADMINISTRATION OF NEW DRUG SUBSTANCE.

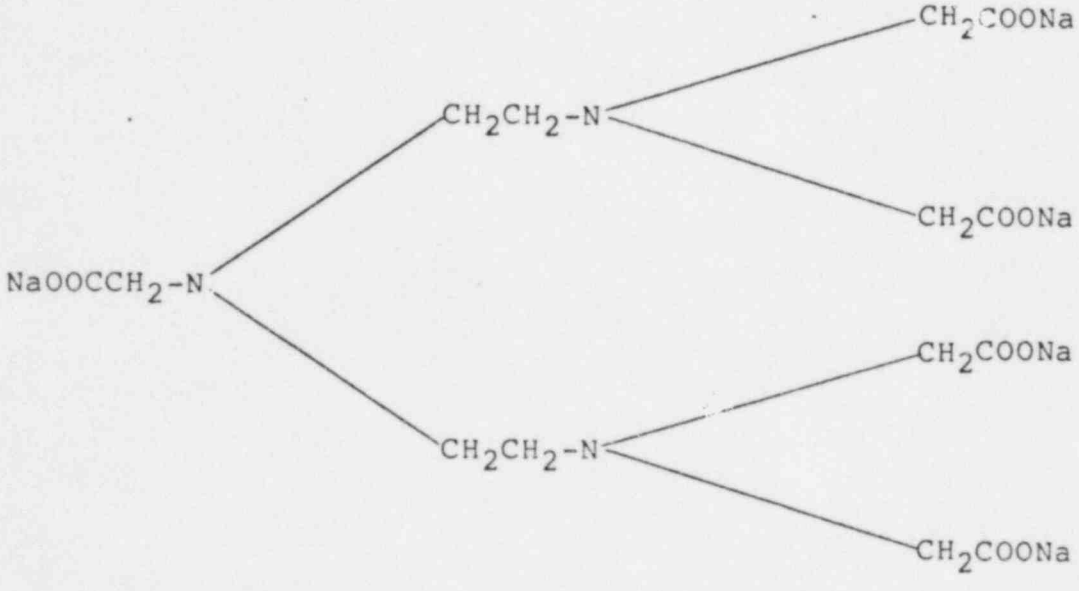
1a. Descriptive name, chemical name and structure of drug substance.

The USAN name of the drug substance is PENTETATE and the full finished USAN drug name is Technetium Tc 99m Pentetate.

The chemical name of the drug is Technetium -99m Diethylenetriamine Pentaacetic Acid (DTPA). The chelate, which is formed by the end user prior to administration, consists of three reactants:

1) Sodium Pertechnetate - Tc 99m ($Na^{+99m}TcO_4^-$)

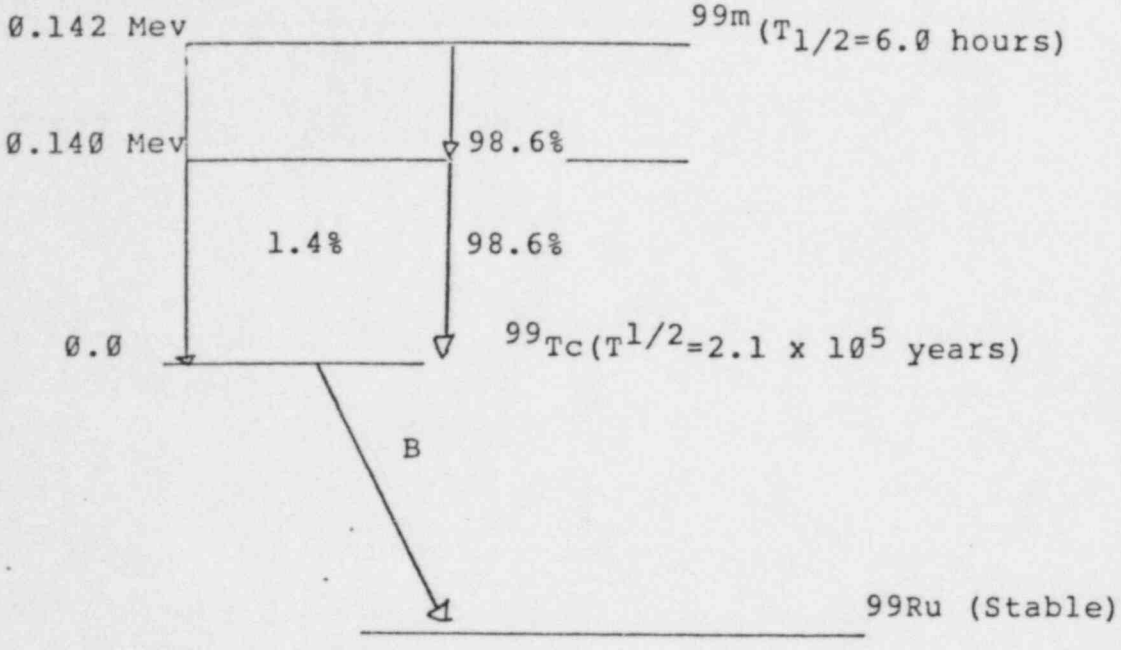
2) Na_5 DTPA



3) $SnCl_2$ (Sn++)

The formulation shall be the same for all indications and routes of administration.

The decay scheme of $^{99}Tc^{m}$ is as follows:



Technetium Tc-99m is identified through its half-life and emission characteristics, above. Tc-99m DTPA can be identified and assayed by paper chromatography.

Chemically, Technetium belongs to Group VII-B in the periodic table with Manganese and Rhenium and is quite similar to Rhenium in its reactions.

The various Chelates of DTPA, such as Na_5 DTPA, act as chelating agents for many radioisotopes and are used in treating radiation poisoning.

Biologically, Tc-99m DTPA resembles other radioisotope chelates of DTPA, including In - 113m-DTPA. These complexes are uniformly distributed throughout the extracellular space With transient accumulation in the kidneys.

ITEM 2

COMPONENTS USED IN THE MANUFACTURE OF THE DRUG

QUALITY CONTROL CODE		GRADE
A102	Sterile Water for Injection	U.S.P.
A103	Hydrochloric Acid	U.S.P.
A116	Stannous Chloride	U.S.P.
A117	Na_5-DTPA	Quality Control Approved
A118	Nitrogen Gas	U.S.P.
	*Sodium Technetium Tc 99m	U.S.P.
	**Isotonic Saline	U.S.P.

* Not in final product

** Not supplied in kit.

For a full description of raw material control code numbers, please refer to CADEMA DMF # 4636.

Alternatives

No alternative components are anticipated

ITEM 3

QUANTITATIVE COMPOSITION OF THE KIT

The Technetium Tc-99m Pentetate (DTPA) will be supplied as a multidose kit consisting of 10 multidose reaction vials, each containing a sterile, pyrogen-free lyophilized mixture of 10 mg. of Pentasodium diethylenetriamine pentaacetic acid, 0.55 mg. stannous chloride under a nitrogen atmosphere. Prior to lyophilization, the pH was adjusted with hydrochloric acid.

QUANTITATIVE COMPOSITION OF THE FINISHED DRUG

Since the activity of the sodium pertechnetate Tc 99m added to the vial is variable, no composition of the final drug can be given. A typical addition of four milliliters of isotonic saline, containing 20 millicuries/milliliter of sodium pertechnetate Tc-99m, would yield the following composition for the finished drug:

Material	Amount
Na_5 DTPA	2.5 mg/mL
$SnCl_2$-$2H_2O$	0.14 mg/mL
Hydrochloric Acid	pH adjustment to 4.0
* Technetium Tc 99m	20.0 mCi/mL
**Isotonic Saline (0.9%)	q.s. to 4.0 mL

Reasonable variations (1 to 5%) may be expected to occur in product preparation during the investigational stages.

* Not in kit as supplied
** Total for Sodium Pertechnetate Tc-99m Solution

PREPARATION OF THE FINAL DRUG FORM

The following directions must be carefully followed for optimum preparation of the Technetium Tc-99m Pentetate injection:

1. Affix radioactive symbol label to reaction vial.

2. Aseptically inject 1.0-5.0mL of sterile Sodium Pertechnetate Tc-99m, up to 100 millicuries, into the reaction vial. Relieve the excess pressure in the vial by withdrawing an equal volume of nitrogen. Mix the solution by shaking vigorously for at least 30 seconds before use.

3. Affix the descriptive label to the dose vial shield. Maintain adequate shielding of the radioactive preparation. After reconstitution, store at 15 to 30 degrees centigrade. Do not use the prepartion after six hours from the time of formulation

5.1 COMPONENT QUALITY CONTROL

1. Components

The drug will be dispensed into a 10 mL serum finish Type I glass vial and stoppered with a 20 mm gray butyl septum and sealed with an aluminum crimp. The suppliers of these components are listed:

10 mL Type I glass vials Serum Finish	Kimble Glass Division Morristown, N. J.
	Wheaton Glass Co. Millville, N. J.
20 mm Gray Butyl Septum	Tompkins Rubber Blue Bell, PA
	The West Co. Phoenixville, N.J.
20 mm Aluminum Crimp	The West Co. Phoenixville, N.J.

Manufacturers certificates of quality will be used to document the individual component specifications.

Attached are copies of component specifications from the various component manufacturers.

Compatibility studies have not been started. As part of the on going in vitro studies, the compatibility of the drug to the vial and closure will be documented. A separate study will also be conducted demonstrating the capability of the septa to withstand multiple punctures. These studies will commence in the early stages of the stability program.

OUTER BOX LABEL

FOR

PENTETATE SODIUM

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.

ITEM 7.3.a

ITEM 7.3

PATIENT RECORD LABEL

FOR

PENTETATE SODIUM

Exhibit 7.2.a 4

FINISHED DRUG LABEL

INVESTIGATIONAL PREPARATION

TECHNETIUM 99m

DTPA Multi-dose

diagnostic/sterile/pyrogen-free

TECHNETIUM Tc 99m PENTETATE

Do not use after 6 hours. Store Finished Drug at 15-30°C.

activity _____ millicuries volume _____ ml

concentration _____ millicuries/ml

time & date prepared _____

prepared by _____

lot number _____

CAUTION
NEW DRUG—Limited by Federal law to investigational use.

RADIOACTIVE MATERIAL

Cadema Medical Products, Inc.

569 NORTH STREET
MIDDLETOWN, N. Y. 10940

L 254,
3-84

THIS ARTWORK IS
200 % ACTUAL SIZE: 1 3/4" x 4"

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

VIAL LABEL

FOR

PENTETATE SODIUM

Exhibit 7.2

REACTION VIAL LABEL

THIS ARTWORK IS
200 % ACTUAL SIZE: 1¼" x 2⅞"

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

CAUTION: INVESTIGATIONAL NEW DRUG

Diagnostic/Sterile/Pyrogen-free

TECHNETIUM 99m

DTPA Multi-dose — Kit for use in preparation of TECHENTIUM Tc 99m PENTETATE

Vial contains a lyophilized mixture of 10 mg Na_5DTPA, 0.55 mg $SnCl_2 \cdot 2H_2O$ under a nitrogen atmosphere. pH was adjusted to 4 with hydrochloric acid.

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

Use within 6 hours after preparation. Store at 15-30°C.

C M P

Cadema Medical Products, Inc.

848 NORTH STREET
MIDDLETOWN, N. Y. 10940

Made in U.S.A.

LC 252
3-84

and Expiration Date will be stamped on each vial label at the time of labeling each vial. Lot Number

ITEM 7.6
ITEM 7.5
ITEM 7.4
ITEM 7.3.a
ITEM 7.3
ITEM 7.2.a

PACKAGE INSERT

FOR

PENTETATE SODIUM

CMPI DTPA KIT (Chelate)

(for use in the preparation of
Technetium Tc 99m DTPA)

DIAGNOSTIC

DESCRIPTION

The kit contains 10 vials, each vial containing 10 mg sterile, pyrogen-free sodium salt of Diethylenetriamine-pentaacetic Acid (DTPA) and 0.55 mg. Stannous Chloride.

Administration is by intravenous injection or by aerosolization for diagnostic use. The product as supplied is sterile and pyrogen-free. When sterile, pyrogen-free Sodium Pertechnetate Tc 99m is added to the vial, a chelate, Technetium Tc 99m DTPA is formed.

The precise structure of stannous diethylenetriamine-pentaacetic complex is unknown at this time.

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 studies are listed in Table I.

Table I.

Principal Radiation Emission Data

Radiation	Mean % Disintegration	Mean Energy (keV)
Gamma -2	89.07	140.5

EXTERNAL RADIATION

The specific gamma ray constant for Technetium Tc 99m is 0.8 R/mCi-hr at 1 cm. The first half value layer is 0.2 mm of Pb. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 2.7 mm. thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

Table II

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) Kochlee, David C., "Radioactive Decay Data Tables," DOE/TIC-11026,108

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

Table III

Physical Decay Chart; Technetium Tc 99m
half-life, 6.02 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.777	5	0.563
-4	1.584	6	0.502
-3	1.412	7	0.447
-2	1.259	8	0.399
-1	1.122	9	0.355
0*	1.000	10	0.317
1	0.891	11	0.282
2	0.795	12	0.252
3	0.708	18	0.126
4	0.631	24	0.063

*Calibration Time

CLINICAL PHARMACOLOGY

Following its intravenous administration Technetium Tc 99m DTPA rapidly distributies itself throughout the extracellular fluid space from where it is (promptly) cleared from the body by glomerular filtration. There should be little or no binding of the chelate by the renal parenchyma. A variable percentage of the Technetium Tc 99m DTPA binds to serum proteins; this ranges from 3.7% following the single injection to approximately 10% if the material is continuously infused. Although the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured glomerular filtration rate which is lower than the glomerular filtration rate as determined by inulin clearances.

Technetium Tc 99m DTPA tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. The chelate does not accumulate in the choroid plexus.

Since Technetium Tc 99m DTPA is excreted by glomerular filtration, the images of the kidneys obtained in the first few minutes after injection represent the vascular pool within the kidney. Subsequent images of the kidneys represent radioactivity which is in the urine of both the collecting system and the renal pelvis.

INDICATION AND USAGE

Technetium Tc 99m DTPA may be used to perform kidney imaging, brain imaging, to assess renal perfusion to estimate glomerular filtration rate and lung ventilation.

CONTRAINDICATIONS

None known.

WARNINGS

The contents of the reaction vial are intended only for use the preparation of Technetium Tc 99m DTPA and are not to be directly administered to the patient.

Any sodium pertechnetate Tc 99m solution which contains an oxidizing agent is not suitable for use in the preparation of Technetium Tc 99m DTPA.

The contents of this kit are not radioactive, however, after sodium pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained.

PRECAUTIONS

Technetium Tc 99m DTPA as well as other radioactive drugs must be handled with care and appropriate safety measures should be used to minimize external radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to patients consistent with proper patient management.

To minimize radiation dose to the bladder, the patient should be encouraged to void when the examination is completed and as often thereafter as possible for the next 4-6 hours.

Technetium Tc 99m DTPA for use in estimating glomerular filtration rate should be formulated within one (1) hour prior to clinical use.

Technetium Tc 99m DTPA for use in imaging must be formulated within six (6) hours prior to clinical use. For optimal results this time should be minimized. Intervals longer than one hour should be the exception.

Pregnancy Category C

Adequate reproductive studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus.

Technetium Tc 99m DTPA should be used in pregnant women only when 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

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken while a patient is on the drug since many drugs are excreted in human milk.

Pediatric Use

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

General

Technetium Tc 99m DTPA should not be administered to children or to patients who are pregnant, or to nursing mothers unless the benefits to be gained outweigh the potential hazards.

ADVERSE REACTIONS

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

DOSAGE AND ADMINISTRATION

The suggested dose range for I.V. administration to be employed in the average patient (70 kg) is:

Kidney imaging and glomerular filtration rate estimation:
3 to 5 mCi.

Brain imaging or renal perfusion: 10 to 20 mCi.

For Aerosol lung imaging:

(a) Pre-Perfusion	10-15 mCi in 4 mL
(b) Post-Perfusion	15-30 mCi in 4 mL

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 and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

The components of the CADEMA Technetium TC 99m DTPA Kit (Chelate) are supplied sterile and non-pyrogenic. Aseptic procedures normaly employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during addition of pertechnetate solution and the withdrawal of doses for patient administration.

Technetium Tc 99m DTPA is prepared by simply adding 2-8 mL of Sodium Pertechnetate Technetium 99m solution to the vial and swirling for about one minute. Shielding should be utilized when preparing the Technetium Tc 99m DTPA. Radiochemical purity should be checked prior to patient administration, using the following or equivalent procedure:

DETERMINATION OF FREE PERTECHNETATE IN TECHNETIUM Tc 99m LABELED DTPA

1. Mark a 1 x 5 cm Gelman ITLC-SG strip at 1 cm from one end and 1.5 cm from the other end with a pencil.
2. Place one mL of 85% Methanol into a glass vial.
3. Spot the preparation at the 1 cm. line and dry the spot with nitrogen.
4. Immediately place the strip into the vial and allow to develop in the capped vial until the solvent front reaches the top of the strip.
5. Remove the strip and allow it to air dry.

Radiation Dosimetry

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

Table Iv. Radiation Doses

Patient

Tissue	Absorbed Radiation Dose (rads/20 millicuries	
Kidneys		1.7
Bladder Wall	2.0 hour void	2.2
	4.8 hour void	5.4
Testes	2.0 hour void	0.15
	4.8 hour void	0.20
Ovaries	2.0 hour void	0.22
	4.8 hour void	0.32
Whole Body		0.13

Target	Hospital Technician preparation of drug*	Administering drug* (20 mCi)
Extremity Dose	0.84 milli rem	1.7 milli rem
Whole Body Dose	0.01 milli rem	0.004 milli rem

*Using shielded vial and syringes

(2) "S"Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and organs, MIRD pamphlet No. 11, 1975.

Radiation Dosimetry (Cont'd)

Aerosol Administration

The estimated absorbed dose [2] to an average patient (70 kg) from inhaling 3 millicuries of Technetium Tc-99m Pentetate Aerosol is shown in Table V.

Table V. ESTIMATED RADIATION DOSE FROM INHALED AEROSOL

ORGAN	ABSORBED DOSE (rads/mCi)	ABSORBED DOSE (rads/3 mCi)
Lung [1]	0.050	0.15
Bladder [2]	0.555	1.7
Kidneys	0.042	0.13
Testes	0.016	0.048
Ovaries	0.019	0.057
Whole Body	0.016	0.048
Lens of Eye	0.016	0.048

These estimates are based on the following assumptions:

(1) One hundred percent of the administered activity is instantly and uniformly taken up by the lung.

(2) The biological half-life of activity in the lung is ~ 1 hour.

(3) For all organs (other than lung and eye) instantaneous appearance of activity in the blood is assured. However, since the biological clearance from the lung is not instantaneous, the values are very conservative.

(4) The dose to the eye lens is taken to be the same as the absorbed dose for the whole body.

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1. Based on: "S" Absorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Organs; MIRD Pamphlet No. 11, Soc. of Nucl. Med., Oct. 1975.

2. With the exception of the lung doses, all other doses are based on: Method of Calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides. Supplement No. 1, MIRD Pamphlet No.1, J. Nucl. Med., pg. 7, 1968

adema Technetium Tc 99m DTPA Kit is supplied as a sterile, yrogen-free kit containing 10 vials. Each vial contains 10 g. of sodium salt of DTPA and 0.55 mg. of $SnCl_2$, The is djusted with HCl or NaOH prior to lyophilization. Following yophilization the vials are sealed under a nitrogen tmosphere.

Directions

reparation of Technetium Tc 99m DTPA is done by the olloiwng aseptic procedure:

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

2. Remove the central metal disc from the Technetium Tc 99m DTPA vial and swab the top of the vial closure with alcohol to sterilize the surfac

3. Place the vial in a suitable radiation shield suitably labeled and identified.

   With a suitable syringe, aseptically obtain 2-8 mL of suitable sterile, non-pyrogenic sodium pertechnetate Tc 99m.

4. Aseptically add the sodium pertechnetate Tc 99m solution to the vial.

5. Swirl the contents of the vial for one minute and let stand 1-2 minutes.

6. Record date and time of preparation.

7. Aseptically withdraw material for use.

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

9. Do not use more than six (6) hours after preparation for imaging.

10. Do not use if solution is cloudy.

Storage

Before reconstitution, store at room temperature (15 to 30 degrees centigrade) and protect from light.

Disposal

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

APPENDIX IV

MICRO ALBUMIN COLLOID REAGENT KIT

ITEM I

DESCRIPTION OF THE DRUG

NAME

The name of the drug is Technetium Tc-99m MMAA (Mini-Microaggregated Human Serum Albumin Colloid Reagent Kit). Hereinafter referred to as Mini-Microaggregated Albumin Colloid.

Technetium Tc-99m is reduced to the pentavalent oxidation state by Stannous Ion and tagged to the Albumin Colloid. The chemical structure of the drug is not known at present.

The drug is prepared from a kit containing vials of Mini-Microaggregated Albumin Colloid in lyophilized form and from Sodium Pertechnetate Tc-99m from hospitals or central pharmacies. When mixed, Technetium Tc-99m Mini-Microaggregated Albumin Colloid is formed. It is in a sterile, isotonic saline solution.

INDICATIONS

The proposed indication of the Technetium Tc-99m Mini-Microaggregated Albumin Colloid is imaging areas of functioning reticuloendothelial cells in the liver, spleen, and erothyropoietic bone marrow.

ADMINISTRATION

The method of administration is intravenous.

ITEM 2

COMPONENTS USED IN THE MANUFACTURE OF THE DRUG

QUALITY CONTROL CODE	COMPONENT	GRADE
A 102	Sterile water for injection	U.S.P. or equivalent
A 103	Hydrochloric Acid	U.S.P. or equivalent
A 105	Normal Human Serum Albumin 25%	U.S.P.
A 109	Pluronic F88 (Surfactant)	Quality Control approved
A 114	Dibasic Sodium Phosphate	Reagent grade or equivalent
A 116	Stannous Chloride	Reagent grade or equivalent
A 118	*Nitrogen Gas	Quality Control approval
	**Sodium Pertechnetate Tc 99m	U.S.P. or equivalent
	**Isotonic Saline	U.S.P. or equivalent

* - Not in final product

** - Not supplied in kit

ALTERNATIVES

No alternative components are anticipated.

ITEM 3

QUANTITATIVE COMPOSITION OF THE REAGENT KIT

HOW SUPPLIED

The Technetium Tc-99m Mini-Microaggregated Albumin Colloid Reagent Kit as supplied to the investigator consists of the following components:

QUANTITY	DESCRIPTION
10	10 ml. vials each containing Mini-Microaggregated Albumin Colloid in lyophilized form, sterile, pyrogen-free.

KIT CONTENTS

The quantitative composition of the reagent kit per vial is as follows:

Mini-Microaggregated Albumin Colloid	Per 10 cc. Vial
Human Serum Aggregated Albumin Colloid	1.0 mg.
Pluronic F88 Surfactant	2.0 mg.
Stannous Chloride ($Sn\ Cl_2 \cdot 2H_2O$)	0.2 mg.
Sodium Phosphate Anhydrous ($Na_2\ HPO_4$)	3.0 mg.
Hydrochloric Acid	0.0025 ml
Human Serum Albumin	10.0 mg.

ITEM 3

QUANTITATIVE COMPOSITION OF THE FINISHED DRUG

Since the activity per unit volume of the Sodium Pertechnetate Tc-99m added to the 10 cc vial containing the Mini-Microaggregated albumin colloid is variable, no composition of the final drug can be given. A typical addition of 5 mL Sodium Pertechnetate Tc-99m, containing 50 millicuries would yield the following:

	Per 10 cc Vial	Per mL
*Sodium Pertechnetate Tc-99m	50 mCi	10 mCi
Human Serum Aggregated Albumin Colloid	1.0 mg.	0.2 mg.
Human Serum Albumin	10.0 mg.	2.0 mg.
Pluronic F88 Surfactant	2.0 mg.	0.4 mg.
Stannous Chloride ($SnCl_2.2H_2O$)	0.2 mg.	0.04 mg.
Sodium Phosphate, Anhydrous	3.0 mg.	0.6 mg.
Hydrochloric Acid	0.0025 mL.	0.0005 mL
**Isotonic Saline	5.0 mL.	1.0 mL.

Reasonable variations (1% to 5%) may be expected to occur in product preparation during the investigational stages.

*Not in kit as supplied

**Total for Sodium Pertechnetate Tc-99m solution

PREPARATION OF THE FINAL DRUG FORM

The following directions must be carefully followed for optimum preparation of the Technetium Tc-99m Mini-Microaggregated Albumin Colloid injection:

1. Affix radioactive symbol label to reaction vial.
2. Aseptically inject 1.0-5.0 ml of sterile Sodium Pertechnetate Tc-99m, up to 100 millicuries, into the reaction vial. Relieve the excess pressure in the vial by withdrawing an equal volume of air. Mix the solution by shaking vigorously for at least 30 seconds before use.
3. Affix the descriptive label to the dose vial shield. Maintain adequate shielding of the radioactive colloid preparation. (After reconstitution, store at 4^0 to 8^0C.). Do not use the preparation after six hours from the time of formulation.

RADIATION DOSIMETRY

DOSE CALCULATIONS FOR Tc-99m MMAA

A. General Information and Assumptions

1. Dose calculation will be carried out as recommended by MIRD Communication, Society of Nuclear Medicine.[1]

2. Biological Distribution Data.[2]

   (a) The dose will be calculated for two extremes in the distribution of Tc-99m MMAA ^{tm}.

	Distribution 1	Distribution 2
Liver (% of admin. act.)	90%	70%
Spleen (% of admin. act.)	5%	15%
Marrow (% of admin. act.)	5%	15%

   (b) Instantaneous uptake by the liver, spleen and red marrow will be assumed and the biological half-life of the Tc-99m MMAA ^{tm} is infinitely long compared to the physical half-life of Tc-99m. The effective half-life is equal to the physical half-life of Tc-99m.

3. Radiopharmaceutical

   (a) No radionuclidic impurities present.

   (b) No radiochemical impurities present - free Tc-99m, etc.

   (c) Intravenously administered in a sterile/pyrogen-free form.

4. Anatomical - mass and location of organs:[3]

Total Body	70,036 gm.
Liver	1,833
Spleen	176
Red Marrow[2]-for mass	1,500
Testicles	38
Ovaries	8.8

5. Nuclear Decay Scheme Data[4]

Radiation Type, i	Designation	Mean Energy (MeV), E_i	Δ_i g-rad/μ Ci-hr
Nonpenetrating Radiations	n-p	--	0.0362
K x-rays	1	0.0187*	0.003i
Gamma 2	)	0.1405	0.2643
Gamma 3	) 2	0.1427	0.0001

*Weight mean energy

6. Organs to be treated as target and as source organs:

	Dose From		
Dose To	Liver	Spleen	Skeleton
Liver	x	x	x
Spleen	x	x	x
Red Bone Marrow+	x	x	x
Total Body	**	**	**
Ovaries***	x	x	x
Testicles***	x	x	x

\+ Activity is located in red marrow, but for computation of penetrating component of self-irradiation will assume activity in skeleton to get the absorbed fraction, Ø.

** For total body dose calculation assume activity uniformly distributed in the body.

*** Reciprocity will be used to calculate Ø.

7. Absorbed Fraction Data [5]

Target Organs	Source in Liver 0.019 MeV	0.14 MeV
Liver	.807	.161
Spleen	<.001**	<.001**
Total Marrow*	.007	.018

Target Organs	Source in Spleen 0.019 MeV	0.14 MeV
Liver	<.001**	.007
Spleen	.605	.072
Total Marrow*	.006	.018

Target Organs	Source in Skeleton 0.019 MeV	0.14 MeV
Liver	<.001**	.005
Spleen	<.001**	.001**
Total Marrow*	.326	.061

Target Organs	Source in Total Body 0.019 MeV	0.14 MeV
Total Body	.940	.319

Target Organ	Source in Testicle(2) 0.019 MeV	0.14 MeV
Liver+	<.001**	.0002

Target Organ	Source in Ovaries (2) 0.019 MeV	0.14 MeV
Liver+	<.001**	0.0037

*~~F~~for total marrow will be used for sources in various organs to obtain for red marrow.

+ All admin. act. will be assumed to be in testicles or ovaries for reciprocity calc.using the the liver as target organs .

** ~~<~~<.001 neglected in these dose calculations.

D. Summary of Dose Calculations

	Rad/mCi Administered Activity	
	Distribution #1 Liver - 90% Spleen & Marrow	Distribution #2 Liver - 70% Spleen & Marrow
ORGAN	each 5%	each 15%
Liver	0.35	0.27
Spleen	0.14	0.42
Red Marrow	0.042	0.070
Total Body	0.015	0.015
Testicles	0.0003	0.0003
Ovaries	0.005	0.005

Determine the Rf value by the following:

$$Rf = \frac{\text{Activity Distance from Origin (cm)}}{\text{Solvent Front Distance from Origin (cm)}}$$

Rf 0.9-1.0 = FREE
Rf 0 -0.1 = BOUND

RADIATION DOSIMETRY

The estimated absorbed radiation dose[2] to an average patient (70 kg), from an intravenous injection of 8 millicuries of Tc-99m Albumin Colloid is shown in Table 4.

Table 4. Radiation Doses

Organ	Radiation Absorbed Dose (rads/8 mCi)
Liver	2.7
Spleen	1.7
Red Marrow	0.22
Testes	0.01
Ovaries	0.05
Total Body	0.15

[2]Method of Calculation "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975)

HOW SUPPLIED

The Albumin Colloid Kit is supplied as a sterile, pyrogen-free kit consisting of: Ten reaction vials, each containing 11.0 mg. of Human Serum Albumin (Soluble Albumin 10.0 mg., Albumin Colloid 1.0 mg.), 2.0 mg. of Pluronic F68 and 0.2 mg. of Stannous Chloride DiHydrate.

KIT 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

STORAGE

Before reconstitution, store at room temperature (15-30° C) and protect from light.
The components of the Technetium Tc-99m Albumin Colloid 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 pertechnetate solution and the withdrawal of doses for patient administration.
Technetium Tc-99m Albumin Colloid is prepared by adding 1-5 mL. of oxidant-free Sodium Pertechnetate Technetium Tc-99m solution to the vial and swirling for about one minute. Shielding should be utilized when preparing the Technetium Tc-99m Albumin Colloid.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc-99m ALBUMIN COLLOID

The preparation of Technetium Tc-99m Albumin Colloid Kit is done by the following aseptic procedure:

a. Waterproof gloves should be worn during the preparation procedure. Remove the central metal disc from the Technetium Tc-99m Albumin Colloid Kit vial and swab the top of the vial closure with alcohol to disinfect the surface.
b. Place the vial in a suitable radiation shield suitably labeled and identified.
c. With a sterile syringe, aseptically obtain 1-5 mL. maximum 75 millicuries, of a suitable oxidant-free, sterile non-pyrogenic Sodium Pertechnetate Tc-99m injection.
d. Aseptically add the Sodium Pertechnetate Tc-99m solution to the vial. Swirl the contents of the vial for one minute and let stand 1-2 minutes. Record date and time of preparation.
e. Inspect the vial for foreign particulates. Do not administer if foreign particulates are found in the vial.
f. Prior to withdrawing an aliquot, re-suspend the colloid by repeatedly inverting the shielded vial for 15 seconds.
g. Aseptically withdraw material for use within six (6) hours of preparation. The vial contains no bacteriostatic preservative.
h. After reconstitution, store at 2-8° C and protect from light.

DISPOSAL

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

Manufactured for:
CADEMA MEDICAL PRODUCTS, INC.
Middletown, N.Y. 10940
by: BELLMORE LABORATORIES, INC.
Hampstead, M.D. 21074

January 1985

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

Aubumin Colloid Kit (TcmAC)
DIAGNOSTIC: FOR INTRAVENOUS USE
NEW DRUG LIMITED BY FEDERAL LAW
TO INVESTIGATIONAL USE

DESCRIPTION

Each vial of Albumin Colloid Kit contains a sterile, pyrogen-free, lyophilized mixture of 11 mg. of Human Serum Albumin (Soluble Albumin 10.0 mg., Albumin Colloid 1.0 mg.), 2.0 mg. of Pluronic F68, and 0.2 mg. of total tin as Stannous Chloride DiHydrate.
The Human Serum Albumin used in this kit was non-reactive when tested for hepatitis B antigen (HB_1Ag) by radiommunossay. Prior to lyophilization, the pH is adjusted to pH 6.8 with a solution of dibasic sodium phosphate.
Reconstitution of the kit with sterile, non-pyrogenic, and oxidant-free Sodium Pertechnetate Tc-99m injection provides an aqueous suspension of Technetium Tc-99m Albumin Colloid for injection.
Administration is by intravenous injection for diagnostic use, after reconstitution with Sodium Pertechnetate Tc-99m. The product, as supplied, is sterile and pyrogen free.
The precise structure of the stannous technetium albumin colloid complex is unknown at this time.

PHYSICAL CHARACTERISTICS

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

Table 1. Principal Radiation Emission Data

Radiation	Mean % / Disintegration	Mean Energy(keV)
Gamma–2	89.07	140.5

[1]Kocher, David C., "Radioactive Decay Data Tables" DOE/TIC – 11026, 108

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 0.2 mm. 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 2.7 mm of Pb will decrease the external radiation exposure by a factor of about 1,000.

PACKAGE INSERT FOR
ALBUMIN COLLOID KIT

OUTER BOX
+
OUTER BOX LABEL
FOR
ALBUMIN COLLOID KIT

SAMPLE

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.

VIAL LABEL FOR

ALBUMIN COLLOID KIT

SAMPLE

TECHNETIUM Tc-99m (TcmAC)

TECHNETIUM Tc-99m (TcmAC) Multi-Dose
Diagnostic/ Sterile/ Pyrogen-free Caution: New Drug
VIAL FOR THE PREPARATION OF Limited by Federal Law
ALBUMIN COLLOID KIT To Investigational Use
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 (HBsAg) by FDA required test.
Vial contains: Total tin as Stannous Chloride DiHydrate 0.2 mg, Human Serum Albumin 11.0 mg (Soluble Albumin 10.0 mg, Albumin Colloid 1.0 mg), Pluronic F68 2.0 mg, Hydrochloric Acid < 0.1 mL, pH adjusted to 6.8 with Dibasic Sodium Phosphate < 2.5 mg, lyophilized. Contains no bacteriostatic preservative.
Do not use after six hours from time of preparation.
Read accompanying literature for recommended adult dosage and preparation procedures before use.
Store prepared drug at refrigerator temperatures (2-8°C).
Only for intravenous use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc-99m.
Manufactured for:
CADEMA MEDICAL PRODUCTS, INC. MIDDLETOWN, NY 10940 Rev. MC161
by Belmore Laboratories, Hampstead, MD 12/30/84

SAMPLE

TECHNETIUM Tc-99m (TcmAC)

TECHNETIUM Tc-99m (TcmAC) Multi-Dose
Diagnostic/ Sterile/ Pyrogen-free Caution: New Drug
VIAL FOR THE PREPARATION OF Limited by Federal Law
ALBUMIN COLLOID KIT To Investigational Use
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 (HBsAg) by FDA required test.
Vial contains: Total tin as Stannous Chloride DiHydrate 0.2 mg, Human Serum Albumin 11.0 mg (Soluble Albumin 10.0 mg, Albumin Colloid 1.0 mg), Pluronic F68 2.0 mg, Hydrochloric Acid < 0.1 mL, pH adjusted to 6.8 with Dibasic Sodium Phosphate < 2.5 mg, lyophilized. Contains no bacteriostatic preservative.
Do not use after six hours from time of preparation.
Read accompanying literature for recommended adult dosage and preparation procedures before use.
Store prepared drug at refrigerator temperatures (2-8°C).
Only for intravenous use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc-99m.
Manufactured for:
CADEMA MEDICAL PRODUCTS, INC. MIDDLETOWN, NY 10940 Rev. MC161
by Belmore Laboratories, Hampstead, MD 12/30/84

PATIENT RECORD LABEL

FOR

ALBUMIN COLLOID KIT

SAMPLE

INVESTIGATIONAL PREPARATION
diagnostic/sterile/pyrogen-free
TECHNETIUM Tc-99m (TcmAC)
ALBUMIN COLLOID KIT

activity _____ millicuries
volume _____ ml
concentration _____ millicuries/ml
time & date prepared _____
prepared by _____ lot no. _____
Read brochure before use.

Manufactured for:
CADEMA MEDICAL PRODUCTS, INC. MIDDLETOWN, NY 10940 Rev. M301
by Bellmore Laboratories, Hampstead, MD Date 12/30/84

CAUTION
NEW DRUG
Limited by Federal Law to investigational use.

RADIOACTIVE MATERIAL

CADEMA MEDICAL PRODUCTS, INC.
MIDDLETOWN, NY 10940

INVESTIGATIONAL PREPARATION
diagnostic/sterile/pyrogen-free
TECHNETIUM Tc-99m (TcmAC)
ALBUMIN COLLOID KIT

activity _____ millicuries
volume _____ ml
concentration _____ millicuries/ml
time & date prepared _____
prepared by _____ lot no. _____
Read brochure before use.

Manufactured for:
CADEMA MEDICAL PRODUCTS, INC. MIDDLETOWN, NY 10940 Rev. M301
by Bellmore Laboratories, Hampstead, MD Date 12/30/84

CAUTION
NEW DRUG
Limited by Federal Law to investigational use.

RADIOACTIVE MATERIAL

CADEMA MEDICAL PRODUCTS, INC.
MIDDLETOWN, NY 10940

SAMPLE

PHASE III PROTOCOL

FOR

ALBUMIN COLLOID KIT

EXHIBIT 7.7

CAUTION: NEW DRUG LIMITED BY FEDERAL LAW

TO

INVESTIGATIONAL USE

PHASE III PROTOCOL

TECHNETIUM Tc-99m MINI-MICROAGGREGATED ALBUMIN COLLOID REAGENT KIT

INTRODUCTION

The chemical name of the drug is Technetium Tc-99m Mini-Microaggregated Albumin Colloid Reagent Kit.

It is prepared by heat denaturation of a solution of Normal Human Serum Albumin.

HOW SUPPLIED

The Technetium Tc-99m Mini-Microaggregated albumin colloid kit is supplied as a sterile pyrogen-free kit consisting of: Ten reaction vials; each containing 1.0 mg. of aggregated albumin (Human), 10.0 mg. of Normal Human Serum Albumin, and 2.0 mg. of Pluronic F88 and 0.2 mg. of Stannous Chloride Di hydrate.

KIT CONTENTS

10 Sterile reaction Vials, each containing in lyophilized form:

Aggregated Albumin (Human)	-	1.0 mg.
Normal Human Serum Albumin	-	10.0 mg.
Pluronic F88 (Surfactant)	-	2.0 mg.
Stannous Chloride Di hydrate	-	0.2 mg.

10 Radioactive Labels (Symbol)

10 Pressure-sensitive labels for final Technetium Tc-99m Albumin Colloid Reagent Kit injection preparation.

1 Package Insert

MATERIAL NEEDED

Imaging Instrument: Gamma Camera
Collimator: Parallel Hole or LEAP
Sterile Syringes and Needles
Sodium Pertechnetate Tc-99m in isotonic saline

STORAGE

Store kit contents at [redacted] temperature (4-8^0).

DISPOSAL

The residual material may be discarded in ordinary trash provided the vials and syringes read background with an appropriate low range survey meter. All identification labels should be destroyed before discarding.

INDICATIONS

The proposed indication of the Technetium Tc-99m Mini-microaggregated Albumin Colloid is imaging areas of functioning reticuloendothelial cells in the liver, spleen and erothypoeitic bone marrow.

CONTRAINDICATIONS

None known.

PATIENT SELECTION CRITERIA

Pregnant or lactating patients and persons under 18 years of age are not to be considered for this study.

PRECAUTION

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

Adequate reproduction studies have not been performed in animal to determine whether this drug effects 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.

Technetium Tc-99m Mini-microaggregated Albumin Colloid, because it is radioactive, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to patients, consistent with proper patient management.

PRE-INJECTION TESTS
Blood Pressure, pulse, temperature.

DOSAGE AND ADMINISTRATION

The suggested intravenous dose range used in the average patient (70 kg) is 1 to 8 millicuries of Technetium Tc-99m Mini-Microaggregated Albumin Colloid injection.

When orally administered, the Technetium Tc-99m Albumin Colloid injection is not absorbed from the G. I. tract. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should only be used 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.

PREPARATION

The following directions must be carefully followed for optimum preparation of the Technetium Tc-99m Mini-Microaggregated Albumin Colloid injection.

1. Affix radioactive symbol label to reaction vial.

2. Aseptically inject 1.0-5.0 mL of sterile Sodium Pertechnetate Tc 99m, up to 100 Millicuries which must contain less than 10 micrograms of aluminum into the reaction vial. Relieve the excess pressure in the vial by withdrawing an equal volume of air. Mix the solution by shaking vigorously for at least 30 seconds before use.

3, Affix the descriptive label to the dose vial shield. Maintain adequate shielding of the radioactive colloid preparation. (After reconstitution, store at 4-8^{0}C). Do not use the preparation after six hours from the time of formulation.

IMAGING

Static anatomic imaging is to be performed after intravenous administration of the drug.

The study should be started about five minutes after injection. Blood clearance is impaired in cirrhosis, and a delay of several minutes may imporve the counting statistics.

A minimum of three views are required:

Anterior, Right Lateral, and Posterior.

POST-INJECTION TESTS

Blood pressure, pulse and temperature are to be recorded approximately five minutes and 60 minutes following injection.

ADVERSE REACTIONS

The patients will be monitored for any adverse reactions or side effects immediately post-injection, and for the duration of the protocol.

If any adverse reactions are observed after injection, the blood pressure, temperature, and pulse should be monitored until symptoms or signs have disappeared. The time of the adverse reaction after injection will be recorded as well as the duration of the reaction.

The question of the relationship of the adverse reaction to the drug administration will be determined by the investigator after thorough consideration of all the facts that are available to him.

Significant and serious adverse reactions will be reported to Cadema Medical Products by telephone (914) 343-7474.

CLINICAL EVALUATION SHEET

It is the responsibility of the documented Principal Investigator to prepare and submit to Cadema the original completed Clinical Evaluations Sheet for each clinical study performed with the product. All completed Clinical Evaluations Sheets, signed and dated by the Investigator, will be forwarded to Cadema Medical Products, Inc., 569 North St., Middletown, N.Y. 10940.

SPECIAL NOTES

The Clinical Evaluation Sheets must be:

1. Legible.
2. Completed in BLACK INK.
3. All blank spaces completed.
4. Signed by the principal investigator or initialed by the principal investigator if signed by the co-investigator.

INSTITUTIONAL APPROVAL

The study will not be initiated until an Institutional Review Committee has reviewed and approved the study.

INFORMED CONSENT

Written informed consent must be obtained from each subject prior to entrance into the study.

The basic elements of informed consent are:

A. This is an investigational new drug.

B. A fair explanation of the procedure to be followed.

C. Explanation that no long-term health benefits may accrue to the subject as a result of this particular study.

D. A description of the attendant discomforts and risks.

E. An offer to answer any inquiry concerning the procedures.

F. An instruction that the subject is free to withdraw consent and discontinue participation in the project or activity at any time and for any reason whatsoever, without prejudice.

In addition, the agreement entered into by the subject should include no exculpatory language to which the subject is made to waive, or to appear to waive, any legal rights, or to release the institution or its agents from liability for negligence. Signed "informed" consent will be obtained in the manner and by use of forms usually employed by the investigator, and approved by the investigator's peer review committee on Human Research.

DURATION OF STUDY

Phase III will be completed within 6 months following the initiation of clinical trials.

Application has been filed with the U.S. Nuclear Regulatory Commission for distribution of this radiopharmaceutical to persons licensed pursuant to Section 35.14 and Section 35.100, Group III, of CFR 10, Part 35, or under equivalent licenses of agreement states; and is still pending.

PHASE III CLINICAL REPORT ON TECHNETIUM Tc-99m MINI-MICROAGGREGATED ALBUMIN COLLOID REAGENT KIT

HOSPITAL _____ INVESTIGATOR _____ DATE _____

PATIENT Name or Initials _____ Hospital Admission No. or Social Security No. _____

Age _____ Sex _____ Weight _____ lbs Height _____

PRE-INJECTION CLINICAL DATA

Blood Pressure _____ Pulse _____ Temperature _____

Initial Clinical Diagnosis: _____

INJECTION DATA (I.V. Injection)

Time of Injection (1) _____

Lot No. _____ *Activity Injected (1) _____ mCi Volume Injected _____ mL

Source of Sodium Pertechnetate Tc 99m _____

IMAGE INFORMATION

Summarize the image information including: the views and times (after injection) of imaging; the anatomical areas images; type of instrumentation; and collimation.

_____

_____

_____

_____

_____

QUALITY OF IMAGES (1 to 5, 5 being best): _____

*Obtained by measuring activity in syringe pre and post-injection.