E.I. DU PONT DE NEMOURS & CO. (INC.)
MEDICAL PRODUCTS DEPARTMENT

March 30, 1987

U. S. Nuclear Regulatory Commission
Region I
Attn: Dr. John Glenn
Materials Licensing Section
631 Park Avenue
King of Prussia, PA 19406

Gentlemen:

This is a request for amendments to six (6) of our USNRC Materials Licenses.

- All six require a change to reflect the proper business name,
- Two of the six require a change to reflect the proper manufacture and distribution facility street address,
- One of the six requires a change in the list of diagnostic reagent kits authorized for manufacture and distribution to medical licensees.

Please note the following business address;

E. I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

549 Albany Street
Boston, MA 02118

and amend the following DuPont, Boston Area, USNRC Materials Licenses, to reflect the current business name:

20-00320-19
20-00320-18MD
20-00320-17MA
20-00320-16MD
20-00320-15G
20-00320-14E

"OFFICIAL RECORD COPY"

In addition, please modify the following licenses;

20-00320-17MA
20-00320-14E

to specify the proper Billerica facility address

331 Treble Cove Road
N. Billerica, MA 01862

for the manufacture and distribution of the licensed products.

Finally, please modify the following license,

20-00320-17MA

to reflect changes in our diagnostic reagent kit approval list for distribution.

Two reagent kits must be removed from the list as they will no longer be offered as part of our product line,

- Stannous Phytate Reagent Kit (IND9713)
  [Reference License Item B]
- "Cardolite ^{TM}", Human Serum Albumin Kit (IND 12 899)
  [Reference License Item E].

A new diagnostic reagent kit must be added to the list,

Kit Trade Name

"Cardiolite^{TM}", Technetium Tc99m RP30A (IND 28,333)

Radiopharmaceutical Prepared From Kit

Technetium 99m labeled 2-methoxyisobutyl isonitrile

Enclosed for your review is the RP30A kit monograph and samples of the most recent version of the product labels. Final product labels specifying the Cardiolite^{TM} name are to be prepared prior to product distribution. All other information on the final labels will remain the same.

A check has been included to cover the processing fees for these license modifications. The total check amount, $540.00, is based on a review of the various fee categories for each license as supplied by Ms. Sandra Kimberly, USNRC License Fee Management Staff, Office of Administration.

Please contact me if you require additional information.

Sincerely,

Francis E. Roy, Jr.
Associate Radiation Protection Officer

FER/jb
Enc.

DOMESTIC

December 1986

E.I. du Pont de Nemours & Co.
Diagnostic Imaging Division
331 Treble Cove Road
N. Billerica, Massachusetts 01862

Kit for the preparation of TECHNETIUM Tc99m RP-30A for Diagnostic Use

DESCRIPTION: Each vial contains 1mg of $[Cu(MIBI)_4]BF_4$ (Where MIBI = 2-methoxy isobutyl isonitrile); 0.075mg stannous chloride, dihydrate; 1mg L-cysteine hydrochloride, monohydrate; 2.6mg sodium citrate, dihydrate; and 20mg mannitol. The pH is 5.3 to 5.9 prior to lyophilization. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reacting with sodium pertechnetate Tc99m injection. The precise structure of the technetium complex is $Tc99m[MIBI]_6^+$ where MIBI is 2-methoxyisobutyl isonitrile.

PHYSICAL CHARACTERISTICS

Technetium Tc99m 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 1.

Table 1. Principle 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(1981).

EXTERNAL RADIATION

The specific gamma ray constant for Tc99m is 5.4 microcoulombs/Kg-MBq-hr (0.78R/mCi-hr) at 1cm. The first half value layer is 0.017cm of Pb. 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. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

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

Table 3. Physical Decay Chart; Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	8	.398
1	.891	9	.355
2	.794	10	.316
3	.708	11	.282
4	.631	12	.251
5	.562		
6	.501		
7	.447		

*Calibration Time

CLINICAL PHARMACOLOGY: Tc99m RP-30A is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in proportion to regional blood flow, analogous to thallous chloride Tl-201. Animal cross-over experiments using, Tl-201 and Tc99m RP-30A have confirmed that the myocardial distribution of Tc99m RP-30A correlates well with regional myocardial perfusion.

Scintigraphic images obtained in animals and man after the intravenous administration of Tc99m RP-30A have been comparable to those obtained with Tl-201 in normal, infarcted and transiently ischemic myocardial tissue.

The major metabolic pathway for clearance of Tc99m RP-30A is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty percent of the injected dose is cleared through the renal elimination in 24 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that eighty percent of the injected dose clears with a $t_{1/2}$ of 1.5 to 1.9 minutes at stress and rest respectively. At five minutes post injection about 8% of the injected dose remains in circulation. The myocardial $t_{1/2}$ is approximately six hours, rest and stress, while the $t_{1/2}$ for the liver is 1.2 hours after a rest injection and 2.5 hours after a stress injection. The ideal imaging time, reflecting the best compromise between heart count rate and contrast, is approximately 1-2 hours after a rest injection and 1/2-2 hours after a stress injection. There is no evidence for change in myocardial distribution (redistribution), therefore imaging at delayed times is possible.

Myocardial uptake which is coronary flow dependent is 2.8% of the injected dose. Animal studies have shown that uptake is not blocked when the sodium pump mechanism is inhibited. However, hypoxia reduces the level of myocardial extraction. Animal studies have also indicated that ischemic tissues do not exhibit normal extraction for up to five hours after the stress event.

INDICATIONS AND USAGE: Technetium Tc99m RP-30A may be useful in the diagnosis and localization of myocardial infarction.

Technetium Tc99m RP-30A may be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease.

Technetium Tc99m RP-30A may be useful in the assessment of global ventricular function.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure. Exercise stress testing should only be performed under the supervision of a qualified physician and in a laboratory equipped with the appropriate support and resuscitation apparatus.

PRECAUTIONS: Contents of the vial are intended only for use in the preparation of Technetium Tc99m RP-30A and are not to be administered directly to the patient without first undergoing the preparative procedure.

Technetium Tc99m RP-30A, as well as other radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel and patients.

Technetium Tc99m RP-30A should be be used with six (6) hours after preparation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential. A normal and a sensitized Ames test has demonstrated no mutagenic changes induced by exposure to RP-30A.

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

ADVERSE REACTIONS: No adverse reactions specifically attributable to the use of Technetium Tc99m RP-30A have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for intravenous administration, after preparation with oxidant-free sodium pertechnetate Tc99m injection, in the average patient (70 kg) is 370-1110MBq (10-30mCi). The patient dose should be measured by a suitable radioactivity calibration system just prior to administration. Radiochemical purity should be checked prior to patient administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

RADIATION DOSIMETRY: The projected radiation doses to organs and tissues of an average patient (70 kg) per 1110MBq (30mCi) of Technetium Tc99m RP-30A injected intravenously are shown in Table 4.

Table 4. Radiation Absorbed Doses from Tc99m RP-30A

	Estimated Radiation Absorbed Dose			
	STRESS		REST	
Organ	Rads/30mCi	mGy/1110MBq	Rads/30mCi	mGy/1110MBq
Bladder	1.65	16.5	2.34	23.4
Small Intestine	0.20	2.0	0.30	3.0
Upper Large Intestine Wall	0.20	2.0	0.39	3.9
Lower Large Intestine Wall	0.22	2.2	0.36	3.6
Gallbladder	0.19	1.9	0.19	1.9
Heart Wall	0.78	7.8	0.81	8.1
Kidneys	1.29	12.9	2.46	24.6
Liver	0.29	2.9	0.39	3.9
Lungs	0.57	5.7	0.57	5.7
Spleen	0.63	6.3	0.75	7.5
Thyroid	1.71	17.1	2.85	28.5
Ovaries	0.23	2.3	0.27	2.7
Testes	0.14	1.4	0.14	1.4
Red Marrow	0.25	2.5	0.25	2.5
Total Body	0.18	1.8	0.19	1.9

HOW SUPPLIED: Du Pont's Kit for the preparation of Technetium Tc99m RP-30A Kit is supplied in kits of ten (10) vials, sterile and pyrogen-free, each vial containing in lyophilized form:

$[Cu(MIBI)_4]BF_4$	1.0mg
Stannous Chloride, Dihydrate	0.075mg
Mannitol	20.0mg
Sodium Citrate, Dihydrate	2.6mg
L-Cysteine Hydrochloride, Monohydrate	1.0mg

The pH is between 5.3-5.9 prior to lyophilization. The contents of the vial are lyophilized and stored under nitrogen. Store at room temperature (15-30°) before and after reconstitution. Technetium Tc99m RP-30A contains no perservatives. Protect from light. Included in each ten (10) vial kit is one (1) product monograph and twelve (12) radiation labels.

The components of the Kit for the preparation of Tc99m RP-30A are supplied sterile and non-pyrogenic. Aseptic procedures normally used 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 Tc99m RP-30A is prepared by adding no more than 2.78GBq (75mCi) of additive-free non-pyrogenic Sodium Pertechnetate Tc99m Injection in 1-3ml to the vial and boiling for ten minutes. Appropriate shielding should be used during the preparation of the Technetium Tc99m RP-30A.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m RP-30A

Preparation of the Technetium Tc99m RP-30A from the Kit for the preparation of Technetium Tc99m RP-30A is done by the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the Technetium Tc99m RP-30A Kit vial and swab the top of the vial closure with alcohol to disinfect the surface.
2. Place the vial in a suitable radiation shield appropriately labeled with date, time of preparation, volume and activity.
3. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic sodium pertechnetate Tc99m solution [max. 2.78GBq (75mCi)] in approximately 1 to 3ml.
4. Aseptically add the sodium pertechnetate Tc99m solution to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
5. Swirl the contents of the vial for a few seconds.
6. Place the vial with the lead shield upright in a boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again.
7. Remove the shielded vial from the water bath and allow to cool for fifteen minutes.

8. Examine vial contents for particulates and/or discoloration prior to injection.
9. Aseptically withdraw material using a sterile shielded syringe. Use within six (6) hours of preparation.
10. Radiochemical purity should be checked prior to patient administration.

This reagent kit is supplied under IND #28-333. This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed pursuant to Sections 35.14 and 35.100, Group III, of 10 CFR Part 35, or under equivalent licenses of Agreement States.

E.I. du Pont de Nemours & Co.
Diagnostic Imaging Division
331 Treble Cove Road
North Billerica, Massachusetts 01862
Tel: Toll Free 800-225-1572
(For Massachusetts and International, call 617-482-9595)

511798

RADIO-TLC METHOD FOR QUANTITATION OF Tc99m RP-30A

QUALITY CONTROL STUDIES

The preparation and quality control of the agent should follow the below procedure. QC results should be recorded in the appropriate place on the Case Report Form.

1.0 CONTENTS

2.0 MATERIALS

2.1 Baker-Flex Aluminum Oxide plates, # 1B-F, pre-cut to 2.5cm x 7.5cm
2.2 Ethanol, Absolute
2.3 Capintec, or equivalent instrument for measuring radioactivity in the 20-300mCi range.
2.4 1cc Syringe with a 26 gauge needle
2.5 Small developing tank with cover, (100ml beaker covered with Parafilm®, is sufficient)
2.6 Boiling water bath

3.0 PREPARATION OF Tc99m RP-30A

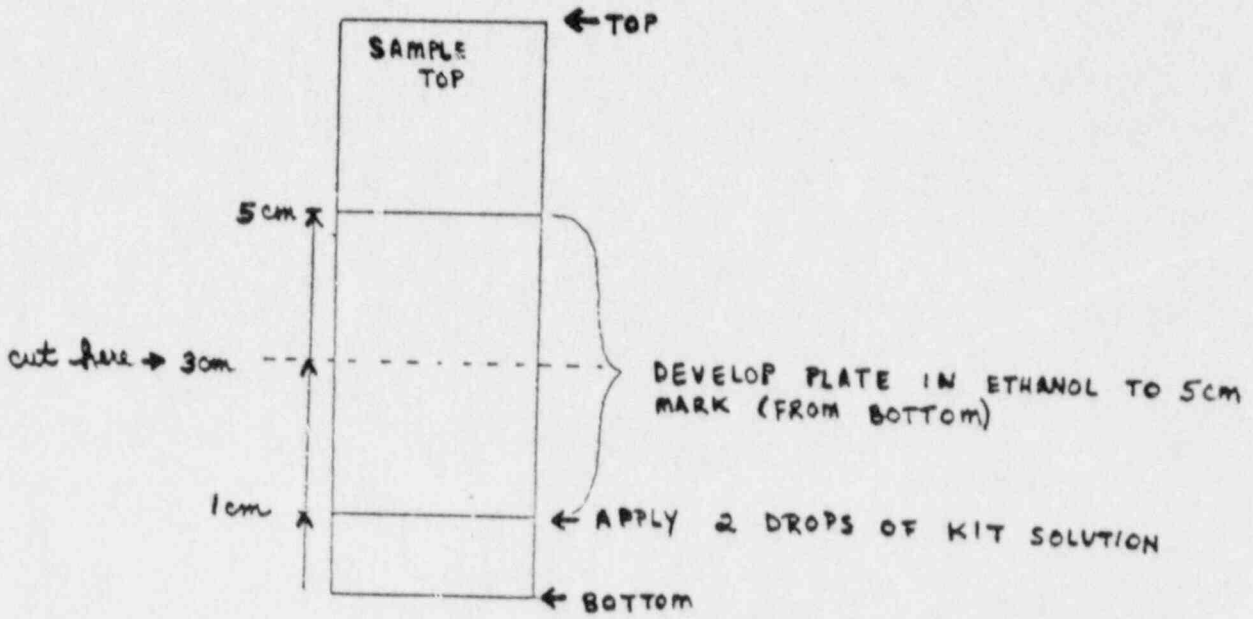
3.1 Add 1.0 to 3.0ml of Tc99mTcO_4 containing 25-75 mCi to the vial.
3.2 Shake the vial briefly.
3.3 Put the vial in a boiling water bath for 10 minutes.
3.4 After heating, allow the vial to cool in its lead shield for 15 minutes.

4.0 PROCEDURE

4.1 Pour enough Ethanol into the developing tank (beaker) to have a depth of 3-4mm of solvent. Cover the tank (beaker) and allow it to equilibrate for approximately 10 minutes
4.2 Apply 1 drop of Ethanol, using a 1cc syringe with a 26 guage needle onto the Aluminum Oxide TLC plate, 1cm from the bottom.
4.3 Apply 2 drops of the kit solution, on top of the ethanol spot, on the same plate.
4.4 Develop the plate a distance of 4cm from the spot.
4.5 Cut the strip 3cm from the bottom, and measure each piece in the Capintec. See Figure 1.
4.6 Calculate the % Tc99m RP-30A as:

% Tc99m RP-30A=(uCi Top Portion)/(uCi Both Pieces) x 100

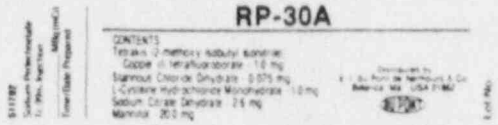
FIGURE 1 - PLATE DIAGRAM



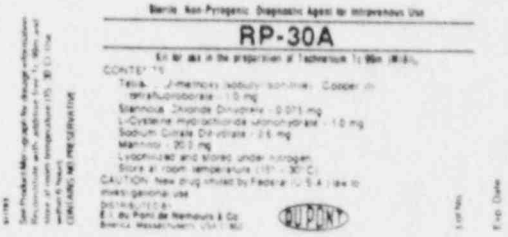
Cardiolite™

Technetium 99m RP30A (IND 28,333)

Product Labels



Vial Label



Box Label

TRI-SM-C

E. I. du Pont de Nemours & Company

INCORPORATED
DISBURSEMENTS
WILMINGTON, DELAWARE 19898

06303785

93-142/929

DATE	CHECK NUMBER	AMOUNT
01/02/87	06303785	$*********540.00

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US GOVT
OFFICE OF THE CONTROLLER
US NUCLEAR REGULATORY COMM
WASHINGTON DC 20555

E I DU PONT DE NEMOURS & COMPANY
DISBURSEMENT ACCOUNT

TO
FIRST INTERSTATE BANK OF COLSTRIP
COLSTRIP, MONTANA

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"6303785" 1:0929014261: 00 422 3"

00-000-002343820 DUPONT ACCOUNTS PAYABLE 06303785

VOUCHER NO	INVOICE NO	PURCHASE ORDER NO	DATE	GROSS	DISCOUNT	NET
MN8122 RELEASE:	121986 000000006	YNEN61355	12-19-86	540.00	.00	540.00
TOTALS				540.00	.00	540.00

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INCORPORATED
DISBURSEMENTS
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