medi+physics®
MEDI-PHYSICS, INC., RICHMOND, CALIF.
SUBSIDIARY OF HOFFMANN-LA ROCHE INC.

August 3, 1987

U.S. Nuclear Regulatory Commission
Region I
Nuclear Materials Safety Section B
Division of Radiation Safety and Safeguards
631 Park Avenue
King of Prussia, Pa. 19406

Re: Approval No. 29-15360-~~02MA~~ ~~03MD~~

Medi-Physics, Inc. would like to amend our Reagent Kit Distribution Approval No 29-15360-~~02MA~~ ~~03MD~~ to add the reagent kit MPI Pyrophosphate manufactured by E.R. Squibb, Inc. under license number 29-15360-01, and used for the preparation of Tc99m Pyrophosphate injection.

Enclosed is a check for two hundred and thirty dollars ($230) to cover the ammendment fee. Should there be any questions regarding this request, please contact me at (201) 757-0500.

Sincerely yours,

MEDI-PHYSICS, INC.

Gary Ziola
Radiation Protection Officer
South Plainfield Facility

bp

Log Aug 7th
Check No. 64679
Amount $230 - $110 refunded
Type of Fee Amdt
Date Check Received 9/8/87
Date Completed
By: Kimberly

See 8/24/87 ltr for fee info

"OFFICIAL RECORD COPY" ML18

08 SEP 1987

medi+physics®

MEDI-PHYSICS, INC., RICHMOND, CALIF.
SUBSIDIARY OF HOFFMANN-LA ROCHE INC.

August 24, 1987

Log Aug. 7 F
Remitter
Check No. 64674
Amount $230 (Refunded $110)
Fee Category 3D
Type of Fee AMD
Date Check 9/8/87
Date Complete
By: A. Kimberley

* This fee accompanied the 8/3/87 ltr.

Ms. Doris Foster
U.S. Nuclear Regulatory Commission
Region I
Nuclear Materials Safety Section B
Division of Radiation Safety and Safeguards
631 Park Avenue
King of Prussia, PA 19496

Re: Approval No. 29-15360-~~03MD~~

In accordance with the letter dated 8/3/87, the additional information is submitted in application for amendment of Approval No. 29-15360-03MD to distribute reagent kit MPI Pyrophosphate for use in the preparation of Tc99 Pyrophosphate injection.

1. This product is manufactured by E.R. Squibb, Inc. of New Brunswick, New Jersey.

2. The NDA number for this product is 17-680.

3. This product is manufactured, labelled and packaged in accordance with the Federal Food and Drug Act, and is redistributed by MPI with no changes in these criteria.

4. Please see attachment for copies of the F.D.A. approved labelling for this product, all effective July 17, 1987.

If there are any additional questions, please do not hesitate to contact me at (201) 757-0500.

Thank you,

MEDI-PHYSICS, INC.

Gary Ziola
Associate R.S.O.
South Plainfield Facility

bp
#87-040
Attachments

"OFFICIAL RECORD COPY"

ML18.

27 AUG 198

~~107724~~
08120

IMS 16
K2

medi+physics
ROCHE a subsidiary of Hoffmann-La Roche Inc.

Medi-Physics, Inc.
140 East Ridgewood Avenue
P.O. Box 289
Paramus, New Jersey 07653-0289

Direct Dial 201-599-8926

November 16, 1987
RA-K-3410

Mr. Jack Davis
U.S. Nuclear Regulatory Commission
Region I
Nuclear Material Safety Section
Division of Radiation Safety
631 Park Avenue
King of Prussia, Pennsylvania 19406

Dear Mr. Davis: **Re: Control No. 107724**

On behalf of Medi-Physics, Inc., 900 Durham Avenue, South Plainfie New Jersey, the following additional information is presented in support of an amendment to our Medical Application (MA) license.

This amendment provides for the addition of "MPI Pyrophosphate Kit" to our license. This kit is manufactured by Squibb Diagnostics for Medi-Physics, Inc. under NDA 17-680. A copy of the NDA approval letter from the FDA to Squibb is attached.

In regard to your comment on the reference to the proper CFR part for licensure by the U.S. Nuclear Regulatory Commission, MPI will revise with our next printing the appropriate 10 CFR Part 35.200 reference. This change will obviously be made no later than March 31, 1989.

Thank you for your assistance in this matter.

Sincerely,

MEDI-PHYSICS, INC.

John Kerins

John Kerins
Director
Quality Assurance and
Regulatory Affairs

JK:kd
Enclosures

"OFFICIAL RECORD COPY"

ML10

19 NOV 1987

~~107724~~
10812-0

29-15360-03 MD

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 17-680

OCT 20 1976

E. R. Squibb & Sons, Inc.
Attention: Norman W. Lavy, M.D.
Georges Road
New Brunswick, New Jersey 08902

Gentlemen:

Reference is made to your new drug application dated September 9, 1975, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Phosphotec (Technetium Tc 99m Pyrophosphate-Tin Complex Kit).

We also acknowledge receipt of your additional communication dated August 27, 1976, providing Final Printed Labeling.

The application was filed on August 30, 1976.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the drug when available.

Sincerely yours,

M. J. Finkel

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

Enclosures

BETWEEN: C. James Holloway, Chief
License Fee Management Branch
Office of Resource Management

030-16024
02512
11/89

John E. Glenn, Chief
Nuclear Materials Safety & Safeguards Section B
Division of Radiation Safety and Safeguards

LICENSE FEE TRANSMITTAL

A. REGION

1. APPLICATION ATTACHED

Applicant/Licensee: Medi-Physics Ltd

Application Dated: 8/24/87 ✓

Control No.: 107724

License No.: 29-15360-~~03 AD~~

2. FEE ATTACHED

Amount: 0

Check No.: _____

8/3 letter to be forthcoming -- original ltr was lost by HQ when sent for logging in.

3. COMMENTS

See previously check for 29-15360-02MA Returned

Signed _____

Date 9/1/87

B. LICENSE FEE MANAGEMENT BRANCH

1. Fee Category and Amount: 3D $120

2. Correct Fee Paid. Application may be processed for:

Amendment ✓

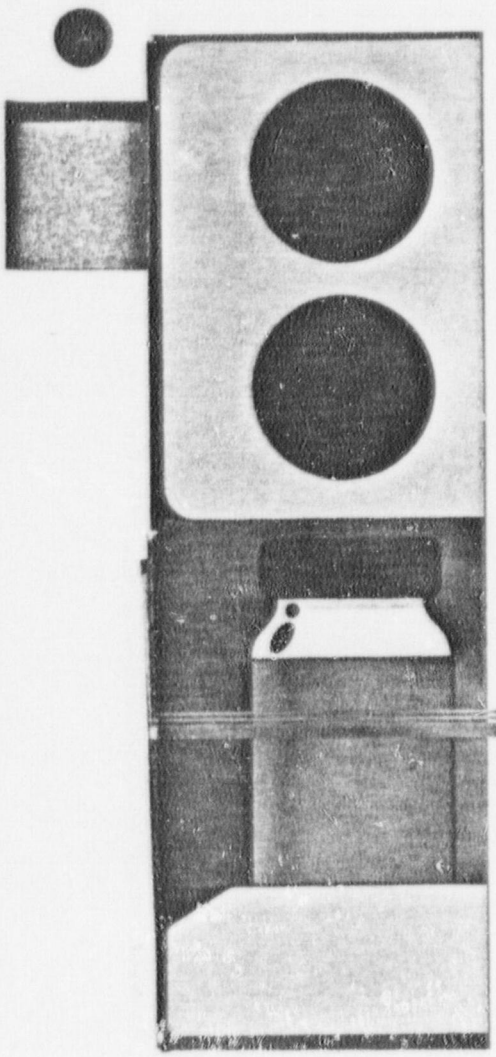
Renewal _____

License _____

Signed Sandra Kimberley

Date 9/9/87

REGION I FORM 213
(MARCH 1987)



TECHNETIUM Tc 99m

PYRO

MPI
PYROPHOSPHATE KIT
Kit for the Preparation of
Technetium Tc 99m Pyrophosphate

diagnostic/sterile/pyrogen-free

CAUTION: Federal (USA) law prohibits dispensing without prescription.

Contains no preservative

Store at 2°—8°C

Procedures for reconstitution of MPI Pyrophosphate Kit—See insert

Dosage: See insert

For intravenous use

CONTENTS OF KIT
10 STERILE REACTION VIALS
Each reaction vial provides a sterile, nonpyrogenic lyophilized powder containing 40 mg sodium pyrophosphate and 0.4 mg stannous fluoride (minimum) and 0.9 mg total tin (maximum) as stannous fluoride; pH adjusted with sodium hydroxide or hydrochloric acid prior to lyophilization.
10 PRESSURE-SENSITIVE LABELS
for final preparation of Technetium Tc 99m Pyrophosphate
1 PACKAGE INSERT

Manufactured by Squibb Diagnostics
New Brunswick, NJ 08903 for

medi+physics®

a subsidiary of Hoffmann-La Roche Inc.
Medi-Physics, Inc., Paramus, NJ 07652

Made in USA
LB146A / 0741O

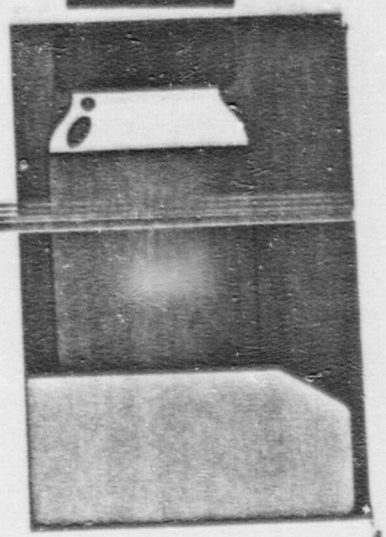
TECHNETIUM Tc 99m

PYRO

MPI PYROPHOSPHATE KIT
Kit for the Preparation of
Technetium Tc 99m Pyrophosphate

TECHNETIUM Tc 99m

PYRO



MPI PYROPHOSPHATE KIT
Kit for the Preparation of
Technetium Tc 99m Pyrophosphate

J4-200A

Issued April 1987

"OFFICIAL RECORD COPY"

MPI Pyrophosphate Kit

Kit for the Preparation of Technetium Tc 99m Pyrophosphate

For Diagnostic Use

DESCRIPTION

Each reaction vial contains 40 mg sodium pyrophosphate (equivalent to 23.9 mg anhydrous sodium pyrophosphate) and 0.4 mg stannous fluoride (minimum) and 0.9 mg total tin (maximum) as stannous fluoride; the product does not contain a preservative. The pH of the product is adjusted with sodium hydroxide or hydrochloric acid prior to lyophilization. At the time of manufacture, the air in the vial is replaced with a nitrogen gas atmosphere. When sterile, nonpyrogenic sodium pertechnetate Tc 99m solution is added to the vial, a diagnostic agent, technetium Tc 99m pyrophosphate, is formed for intravenous administration; the structure of this radiolabeled complex is unknown.

The product as supplied is sterile and nonpyrogenic.

PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] The principal photon that is useful for detection and imaging studies is shown in Table 1.

TABLE 1

Principal Radiation Emission Data

Radiation	Mean % per 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 Tc 99m is 0.78 R/hour-millicurie at 1 cm. The first half-value layer is 0.017 cm of lead (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 millicurie amounts of this radionuclide, the use of a 0.25 cm 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	Attenuation Factor
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 technetium Tc 99m, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

TABLE 3

Physical Decay Chart:
Tc 99m half-life 6.02 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	8	0.398
1	0.891	9	0.355
2	0.794	10	0.316
3	0.708	11	0.282
4	0.631	12	0.251
5	0.562	18	0.126
6	0.501	24	0.063
7	0.447		

*Calibration Time

CLINICAL PHARMACOLOGY

Bone and Cardiac Imaging

Following intravenous administration of the technetium Tc 99m pyrophosphate skeletal uptake occurs as a function of blood flow to bone and bone efficiency in extracting the complex. Bone mineral crystals are generally considered to be hydroxyapatite, and the complex appears to have an affinity for the hydroxyapatite crystals in bone. It is theorized that the complex also reacts with the mitochondrial calcium crystals, produced within infarcted myocardial cells which are believed to be hydroxyapatite; this phenomenon usually does not persist beyond six days after the occurrence of an infarction.

Clearance of the radioactivity from the blood is quite rapid with skeletal uptake and urinary excretion being the principal mechanisms of clearance. At two hours following intravenous injection, approximately 55 percent of the injected dose has localized in bone; at four hours approximately 10 percent of the dose remains in the vascular system, decreasing to about 7 percent at 24 hours. The average urinary excretion was observed to be about 38 percent of the administered dose after eight hours increasing to an average of about 44 percent at 24 hours. A minimum amount of uptake has been observed in soft-tissue organs, most notably the kidneys.

Blood Pool Imaging

The *in vivo* tagging of MPI Pyrophosphate Kit results in the radiolabelling of red blood cells. Approximately 76 percent of the injected activity remains in the blood pool between 30 and 60 minutes after injection of sodium pertechnetate Tc 99m, thereby permitting excellent images of the cardiac chambers.

Maximum blood radioactivity levels occur in about 30 minutes; the initial biological half-life is approximately 18 hours. There is virtually no biological elimination of the agent after approximately six hours.

INDICATIONS AND USAGE

Bone Imaging

MPI Pyrophosphate Kit (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) may be used as a bone imaging agent to delineate areas of altered osteogenesis.

Cardiac Imaging

MPI Pyrophosphate Kit is a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction. The infarction is best visualized one to six days after onset of symptoms. False-negative images can occur if imaging is done too early in the evolutionary phase of the infarct or too late in the resolution phase. The

incidence of false-positives may range from 5 to 9 percent and of false-negatives from 6 to 9 percent but may vary even more depending on selection criteria of patient populations.

Blood Pool Imaging
MPI Pyrophosphate Kit is also a blood pool imaging agent which may be used for gated cardiac blood pool imaging.

CONTRAINDICATIONS
None known.

WARNINGS
Preliminary reports indicate impairment of brain scans using sodium pertechnetate Tc 99m injection which have been preceded by a bone scan using an agent containing stannous ions. The impairment may result in false-positive or false-negative brain scans. It is recommended, where feasible, that brain scans precede bone imaging procedures. Alternatively, a brain-imaging agent such as technetium Tc 99m pentetate may be employed.

PRECAUTIONS
General
The lyophilized contents of the MPI Pyrophosphate Kit reaction vial are to be administered to the patient only as an intravenous solution (see PROCEDURES FOR RECONSTITUTION OF MPI PYROPHOSPHATE KIT).

Any sodium pertechnetate Tc 99m solution which contains an oxidizing agent is **not** suitable for use with MPI Pyrophosphate Kit (Kit for the Preparation of Technetium Tc 99m Pyrophosphate).

When reconstituted with sodium pertechnetate Tc 99m, MPI Pyrophosphate Kit must be used within 6 hours. **When reconstituted with Sodium Chloride Injection USP** for blood pool imaging, use the solution within 30 minutes.

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

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.

Bone Imaging
Both prior to and following administration of the technetium Tc 99m pyrophosphate, the patient should be encouraged to drink fluids and to void as often as possible thereafter to minimize radiation exposure to the bladder and background interference during imaging.

Cardiac Imaging
The patient's cardiac condition should be stable before beginning the cardiac imaging procedure. If not contraindicated by the patient's cardiac status, patients should be encouraged to drink fluids and to void as often as possible in order to reduce unnecessary radiation exposure to the bladder. Interference from chest wall lesions such as breast tumors and healing rib fractures can be minimized by employing the three recommended projections (see DOSAGE AND ADMINISTRATION). False-positive and false-negative myocardial scans may occur; therefore, the diagnosis of acute myocardial infarction depends on the overall assessment of laboratory and clinical findings.

Blood Pool Imaging
The reconstituted agent should be injected by direct venipuncture. Heparinized catheter systems should be avoided, as interference with red blood cell tagging will result.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to determine any carcinogenic potential or impairment of fertility in males or females.

Teratogenic Effects: Pregnancy Category C
Animal reproduction studies have not been conducted with technetium Tc 99m pyrophosphate. It is also not known whether technetium Tc 99m pyrophosphate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Technetium Tc 99m pyrophosphate should be administered to a pregnant woman only if clearly needed.

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

Nursing Mothers
Caution should be exercised when technetium Tc 99m pyrophosphate is administered to a nursing woman. Technetium Tc 99m is excreted in human milk during lactation; therefore, formula feedings should be substituted for breast-feedings.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Some hypersensitivity reactions have been associated with pyrophosphate use.

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

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

Intravenous doses for an average adult (70 kg) are as follows:

Bone Imaging
The suggested dose is 370 to 555 MBq (10 to 15 mCi).

Following reconstitution, Technetium Tc 99m Pyrophosphate is injected intravenously over a 10- to 20-second period. Imaging may be started at one hour after administration; however, for optimal results bone imaging should be performed two to four hours following administration.

Cardiac Imaging
The suggested dose is 370 to 555 MBq (10 to 15 mCi) administered intravenously over 10 to 20 seconds and within 24 hours to six days after the onset of symptoms suggestive of acute myocardial infarction.

Imaging is recommended at 45 to 60 minutes postinjection. It is suggested that scans be obtained in at least three projections (e.g., anterior, lateral, and left anterior oblique).

Blood Pool Imaging

The suggested dose is 41 mg (contents of one reaction vial) of MPI Pyrophosphate Kit (see PROCEDURE FOR RECONSTITUTION) administered intravenously, followed 15 to 60 minutes later by the intravenous administration of 740 MBq (20 mCi) of sodium pertechnetate Tc 99m. Administration should be made by direct venipuncture and not by heparinized catheter systems. Cardiac pool imaging should be initiated 15 to 30 minutes after the administration of sodium pertechnetate Tc 99m.

Radiation Dosimetry

The effective half-life was assumed to be equal to the physical half-life for all calculated values. The estimated absorbed radiation doses to an average adult (70 kg) from an intravenous injection are shown in Table 4 and 5.

TABLE 4
Bone and Cardiac Imaging

	Estimated Absorbed Radiation Doses	
	Technetium Tc 99m Sodium Pyrophosphate	
Target Organ	(mGy/555 MBq)	(rads/15 mCi)
Total Body†	2.3	0.23
Kidneys	7.1	0.71
Bone Marrow	5.7	0.57
Skeleton*	8.1	0.81
Bladder Wall		
2 hour void	14.8	1.48
4.8 hour void	34.5	3.45
Testes		
2 hour void	1.5	0.15
4.8 hour void	2.3	0.23
Ovaries		
2 hour void	1.4	0.14
4.8 hour void	2.3	0.23

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††If patient voids frequently after radiopharmaceutical is administered, this dose will be reduced slightly.

*Dose at point of highest uptake may be a factor of 10 higher.

TABLE 5
Blood Pool Imaging*

	Estimated Absorbed Radiation Doses	
	Sodium Pertechnetate Tc 99m 30 min. Post injection with Pyrophosphate	
Target Organ	(mGy/740 MBq)	(rads/20 mCi)
Total Body	3.2	0.32
Spleen	3.6	0.36
Bladder Wall†	24	2.4
Testes	2.4	0.24
Ovaries	4.6	0.46
Blood	10.4	1.04

*Assume 75% of the Sodium Pertechnetate Tc 99m labels red blood cells and the other 25% remains as pertechnetate.

†If 25% excreted with 1 hour T_b.

Method of Calculation: MIRD Dose Estimate Report No. 8, J Nucl Med 17:74-77, 1976.

HOW SUPPLIED

MPI Pyrophosphate Kit (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) is supplied in a kit containing 10 reaction vials (5 mL size), 10 pressure-sensitive labels, and 1 package insert.

Storage

Store the MPI Pyrophosphate Kit (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) at 2° to 8°C. The reconstituted preparation should be refrigerated since the product does not contain a preservative. When reconstituted with sodium pertechnetate Tc 99m, MPI Pyrophosphate Kit must be used within 6 hours. When reconstituted with Sodium Chloride Injection USP for blood pool imaging, use the solution within 30 minutes.

PROCEDURES FOR RECONSTITUTION OF MPI PYROPHOSPHATE KIT

Procedural Precautions

The contents of the MPI Pyrophosphate Kit reaction vial are sterile and nonpyrogenic. Aseptic procedures should be used during reconstitution of MPI Pyrophosphate Kit and the withdrawal of doses for intravenous administration. The introduction of air into the vial during the reconstitution step should be avoided.

The MPI Technetium Tc 99m Generator may be used as the source of sodium pertechnetate Tc 99m solution; other sources which have been shown by the user to be compatible with the ingredients of MPI Pyrophosphate Kit (Kit for the Preparation of Technetium Tc 99m Pyrophosphate) may also be used.

Reconstitution

Bone and Cardiac Imaging

Technetium Tc 99m pyrophosphate must be used within 6 hours.

1. Waterproof gloves should be worn during the preparation procedure.
2. Allow the contents of the reaction vial to come to room temperature.
3. Place reaction vial in an appropriate lead shield with a fitted cover.
4. Swab the rubber closure of the reaction vial with a germicide.
5. Using a shielded syringe, slowly inject 2 to 4 mL (up to 2775 MBq (75 mCi)) of sterile sodium pertechnetate Tc 99m solution into the reaction vial. In determining the amount of technetium Tc 99m radioactivity to be used, the labeling efficiency, number of patients, administered radioactive dose and radioactive decay must be taken into account. NOTE: If sodium pertechnetate Tc 99m solution must be diluted for use with MPI Pyrophosphate Kit (Kit for the Preparation of Technetium Tc 99m Pyrophosphate), only Sodium Chloride Injection USP (without preservatives) should be used.
6. Secure the lead shield cover. Shake the vial gently to bring the lyophilized material into solution.

7. Record the time and date of preparation and the radioconcentration and volume of the solution on the pressure-sensitive label.
8. Affix the pressure-sensitive label to the shield.
9. Using proper shielding, examine vial contents. If the solution is not clear and free of particulate matter and discoloration on visual inspection, it should not be used.
10. Maintain adequate shielding of the radioactive preparation including the use of appropriate shielded syringes.
11. Radioassay of technetium Tc 99m pyrophosphate may be accomplished conveniently by using an ionization chamber-type dose calibrator.

Blood Pool Imaging

When reconstituted with Sodium Chloride Injection USP, MPI Pyrophosphate Kit should be used within 30 minutes.

1. Allow the contents of the reaction vial to come to room temperature. Swab the top of the rubber closure with a germicide.
2. Slowly inject 2 to 3 mL Sodium Chloride Injection USP (without preservatives) into the reaction vial.
3. Shake the vial gently to bring the lyophilized material into solution.
4. If the solution is not clear and free of particulate matter and discoloration on visual inspection it should not be used.

This reagent kit is approved for use by persons licensed by the US Nuclear Regulatory Commission pursuant to Sections 35.14 and 35.100 Group III of 10 CFR Part 35 or under equivalent licenses of Agreement States.

J4-200A

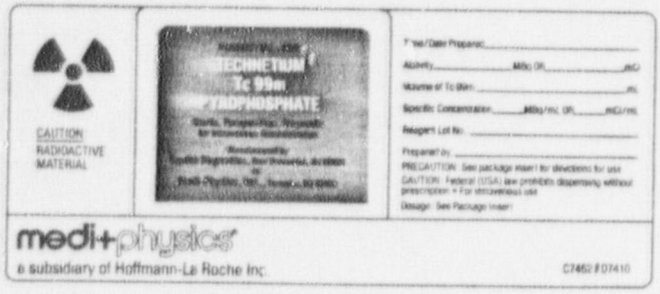
Manufactured By:
Squibb Diagnostics New Brunswick, NJ 08903
For
MEDI-PHYSICS, Inc.
140 East Ridgewood Ave., Paramus, NJ 07653

Issued April 1987

Printed in USA

MPI PYROPHOSPHATE KIT

29-15360-03A



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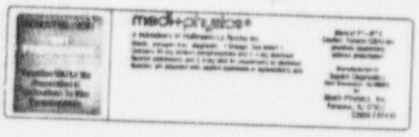

VIAL LABEL 40-4801

"OFFICIAL RECORD COPY"

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~~107724~~

PACKAGE INSERT 43-4801

ML1B.

MPI PYROPHOSPHATE KIT

29-15360-03A2

"OFFICIAL RECORD COPY"

KIT BOX

108120

~~107724~~

ML1B

Note To: License Fee Management Section, ADM

From: Region I

Subject: VOIDED APPLICATION

Control Number 107724

Applicant Medi-Physics, Inc

Date Voided 87 12 17

Reason for Void:

Transferred to CN 108120

New license to be issued 29-15360-04AM

Signature Date 12/17/87

Attachment:
Official Record Copy
of Voided Action

OK. LFMB

"OFFICIAL RECORD COPY"

ML10.