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

030-11164

I

Log May 1
Remitter
Check No. 052017796
Amount $120
Fee Category 3D
Type of Fee AMD
Date Check Rec'd. 5-11-89
Date Completed
By: S. Kimberly

April 12, 1988

U.S. Nuclear Regulatory Commission
Region I
Nuclear Materials Section B
475 Allendale Road
King of Prussia, PA 19406

Attention: C. Thor Oberg

Gentlemen:

As we discussed on Friday, April 7, 1989, please expedite this license amendment request.

A new DuPont xenon vial will be introduced to the medical user marketplace by the DuPont Medical Products Department.

As of April 24, 1989, customers will begin to receive DuPont Xenon-133 gas in vials manufactured from tubing stock instead of the current vial manufactured by a molding process. The only physical changes, as a result of this modification, is that the new vial wall thickness will be slightly less and the new gas volume will be 3 cc per vial rather than the existing 2 cc gas volume per vial.

The following information is attached for your review:

1. DuPont, Greater Boston Area, USNRC Materials License Number 20-00320-21.

2. Food and Drug Administration Approval NDA 17-284/S006 for the DuPont Xenon-133 3 cc tubing glass vial.

3. Communication from DuPont Regulatory Affairs to the Food and Drug Administration, dated February 13, 1989 that includes engineering drawings and leak test data for the new vials.

4. DuPont Xenon-133 package insert.

5. Labels for the Xenon vial and lead shields.

6. Operation Instructions for Calidose Dispenser.

The DuPont USNRC Materials License number 20-00320-16MD should be amended to authorize the distribution of this new 3 cc xenon tubing vial to persons licensed pursuant to Section 35.57 and Section 35.200 of Title 10 CFR Part 35 or under equivalent licenses of Agreement States.

MEDICAL PRODUCTS DEPARTMENT
331 Treble Cove Road, No. Billerica, MA 01862 Telephone 508-667-9531

110552

OFFICIAL RECORD COPY MIL 10

APR 13 1989

A check is enclosed in the amount of $120 for the license amendment processing fee as specified for Fee Category 3D of Title 10 CFR Part 170, Section 170.31.

Due to an existing critical business situation, we request your office expedite the processing of this license information.

Please contact me if you require any additional information.

Sincerely,

Francis E. Roy Jr.
Health Physicist

FER:dlw

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-284/S006

FEB 24 1989

RECEIVED

E.I. DuPont De Nemours & Co (Inc.)
Medical Products Dept.
331 Treble Cove Road
No. Billerica, MA 01862

Attention: Thomas J. Mullins
Regulatory Affairs Specialist

Dear Mr. Mullins:

We acknowledge the receipt on February 14, 1989 of your supplemental new drug application dated February 13, 1989 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenon Xe-133 Gas.

The supplemental application provides for (a) changing the immediate container from a 2cc molded glass vial to a 3 cc tubing glass vial, and (b) changing the "How Supplied" section of the package insert to state "3 ml" vial.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

for Eric B. Sheinin, Ph.D. 2/24/89
Supervisory Chemist
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

13 February 1989

John Palmer, M.D.
Director
Division of Oncology &
Radiopharmaceuticals (HFN-150)
Office of Drug Evaluation I
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RE: NDA #17-284
XENON Xe-133 GAS
SUPPLEMENT #S-006

EXPEDITED REVIEW
REQUESTED

REF: RA/MP/Xeno/01/89

Dear Dr. Palmer:

Pursuant to 21 CFR 314.70 (b) (2) (VIII) and 21 CFR 314.70 (b) (3), Du Pont Diagnostic Division is submitting a Supplement to NDA #17-284, Xenon Xe-133 Gas. The Supplement involves replacing the current 2 cc product vial with a 3 cc product vial.

An expedited review of this Supplement is requested as the current Wheaton 2 cc product vial is no longer manufactured, nor is there any available stock (please reference Wheaton's 3 February 1989 letter, attached). Additionally, Du Pont's inventory of the Wheaton 2 cc vials will be exhausted the week of 17 April 1989.

The 3 cc tubing vial was selected as a replacement for the current 2 cc molded vial for the following reasons:

- The 3 cc vial consists of Type I borosilicate glass and complies with the prescribed requirements of the U.S. Pharmacopeia XXI and its supplements (please reference Wheaton's 28 October 1988 letter certifying compliance to USP XXI Type I Glass requirements, attached). Please note that attempts to obtain an authorization to reference Wheaton's DMF were unsuccessful as Wheaton does not have a DMF on file with the FDA.

- The outside dimensions of the 3 cc vial and the 2 cc vial are substantially equivalent; with the range of the 3 cc vial dimensions falling within the specified tolerances of 2 cc vial dimensions. Please reference the attached Wheaton vial drawings and dimension specification comparison.

- The finished dimensions of both vials are identical and the finish is compatible with the current closure system.

- Xenon Xe-133 Gas is an inert gas with no glass adhesion characteristics. Accordingly, the increase in internal volume represented by the 3 cc vial would have no impact upon the identity, quality, efficacy, purity or strength of the drug product.

Please note that it is Du Pont's intent to utilize the current closure and closure system with the proposed 3 cc tubing vial.

To demonstrate the integrity and stability of using the proposed 3 cc tubing vial with the current closure system, three lots of approximately 200 vials each were manufactured by current practices. A control lot consisting of the current 2 cc vial and closure system was also manufactured.

The test lots and the control lot were analyzed at manufacture and then at 20 days to determine the Xenon Xe-133 Gas leak rate. The leak rate was determined to be 0.12%/day, 0.10%/day and 0.03%/day, respectively, for the test lot and 0.07% for the control lot. All lots, test and control, were well within the 0.5%/day leak rate specification. Please reference Table 1 through Table 5 which are attached.

A copy of the proposed package insert is also enclosed in this submission.

This supplement involves no other changes in the manufacture or quality control of the product.

We look forward to the timely review of this submission.

Please do not hesitate to contact me, or J. D. Bernardy, Manager, Regulatory Affairs and Compliance, should you require any additional information.

Sincerely,

Thomas J. Mullins
Regulatory Affairs

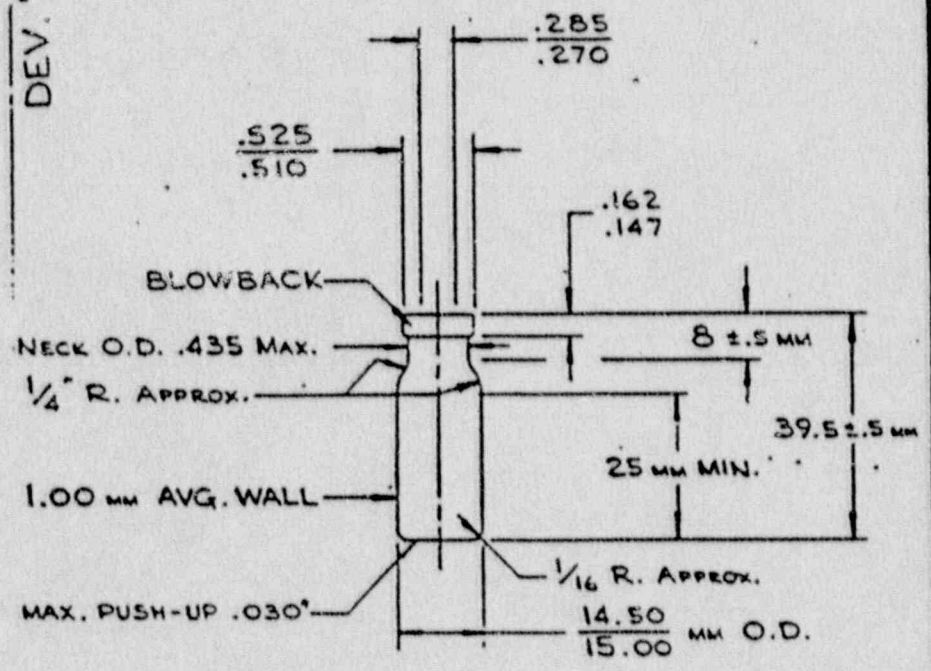
/dmd

Attachments

DIMENSION SPECIFICATION COMPARISON

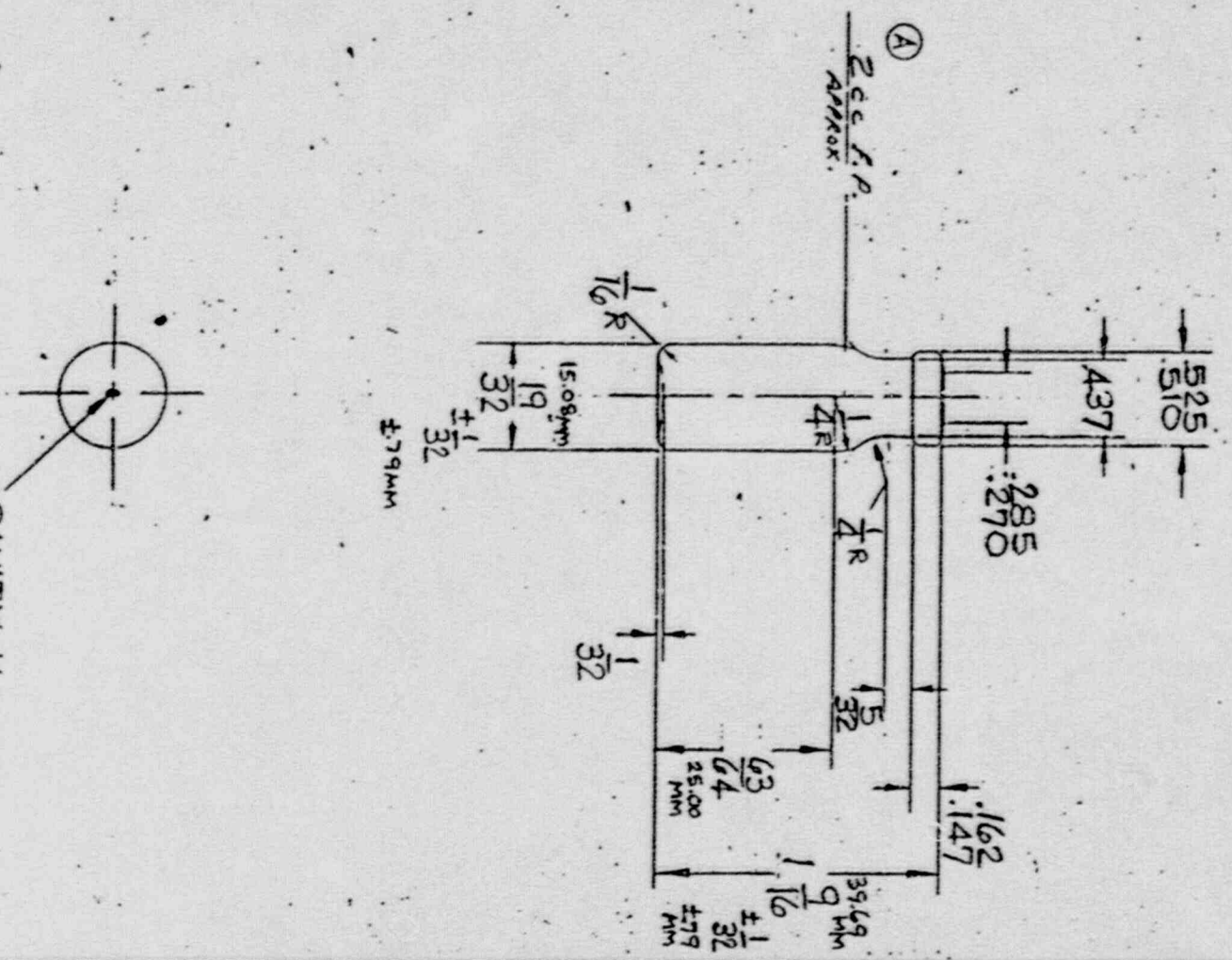
	3 cc Vial	2 cc Vial
Diameter of mouth:	0.270" - 0.285"	0.270" - 0.285"
Diameter of lip:	0.510" - 0.525"	0.506" - 0.525"
Height of vial:	1.535" - 1.575"	1.532" - 1.594"
Diameter of vial body:	0.571" - 0.591"	0.563" - 0.625"
Height of lip:	0.147" - 0.162"	0.147" - 0.162"

DEV. #87-155-01



TYPE I GLASS

CUSTOMER WHEATON SCIENTIFIC	SOLD ACCORDING TO	DATE DRAWN 6-4-87	
TITLE DIM. DUP S-329	SCALE: FULL UNLESS OTHERWISE NOTED	DRAWN BY SP	
PRACTICAL FILL 3 cc	APPROX. WGT.	CHECKED BY [illegible]	REVISIONS
CAPACITY SPECIFICATION	WHEATON TUBING PRODUCTS MILLVILLE, N.J.		DRAWING NO: E-
FINISH 13 MM A/S WITH BLOWBACK			



WHEATON

NOV 16 1978

ISSUED

CUSTOMER	MOLD REGISTER NO. S-329	DATE DRAWN 9-19-68	
TITLE ROUND SERUM	SCALE: FULL UNLESS OTHERWISE NOTED	DRAWN BY D.C.H.	REDRAWN
PRACTICAL FILL 2 cc	APPROX. WGT. 1/4 oz.	CHECKED BY	REVISIONS
CAPACITY SPECIFICATION 2.1 - 2.7 cc B.O.N.	WHEATON GLASS COMPANY MILLVILLE, N.J.		DRAWING NO.: E-2766-A
FINISH 13 MM. A/S			

± 1/64 ALLOWANCE

TABLE 1

SUMMARY

TUBING VIAL Xe-133 GAS LEAK RATE DATA

lot 88-001-A

Initial Average, t = 0	40.34 mCi
Decayed Initial Average, Theoretical	2.87 mCi
Final Average, t = 20 days	2.80 mCi
Leakage Rate, %/day	0.12%/day

lot 88-001-B

Initial Average, t = 0	42.92 mCi
Decayed Initial Average, Theoretical	2.98 mCi
Final Average, t = 20 days	2.92 mCi
Leakage Rate, %/day	0.10%/day

lot 88-001-C

Initial Average, t = 0	42.82 mCi
Decayed Initial Average, Theoretical	3.04 mCi
Final Average, t = 20 days	3.02 mCi
Leakage Rate, %/day	0.03%/day

CONTROL

Initial Average, t = 0	31.68
Decayed Initial Average, Theoretical	2.25
Final Average, t = 20 days	2.22
Leakage, Rate, %/day	0.07%

TABLE 2

Xe-133 INITIAL ASSAY, t = 0 DAYS

(IN MILLICURIES)

lot 88-001-A

	Beginning of Lot	Middle of Lot	End of Lot	Compilation of Lot Data
# of Vials	67.00	70.00	70.00	207.00
Average	40.51	40.29	40.21	40.34
Min	37.40	37.50	36.10	36.10
Max	48.90	43.10	43.10	48.90
Std. Dev.	1.30	0.79	1.08	1.08
Var	1.70	0.63	1.16	1.17
% RSD	3.22	1.96	2.68	2.68

lot 88-001-B

# of Vials	70.00	65.00	68.00	203.00
Average	41.74	41.95	42.08	41.92
Min	39.70	38.50	38.90	38.50
Max	43.40	47.60	45.80	47.60
Std. Dev.	0.84	1.14	1.24	1.09
Var	0.70	1.30	1.55	1.20
% RSD	2.00	2.72	2.96	2.61

lot 88-001-C

# of Vials	68.00	68.00	70.00	206.00
Average	43.28	41.92	43.25	42.82
Min	37.30	39.20	38.70	37.30
Max	64.00	49.00	45.40	64.00
Std. Dev.	3.04	1.52	1.03	2.14
Var	9.22	2.32	1.06	4.57
% RSD	7.01	3.63	2.38	4.99

TABLE 3

Xe 133 FINAL ASSAY, t = 20 DAYS

(IN MILLICURIES)

lot 88-001-A

	Beginning of Lot	Middle of Lot	End of Lot	Compilation of Lot Data
# of Vials	67.00	70.00	70.00	207.00
Average	2.82	2.80	2.79	2.80
Min	2.63	2.38	2.53	2.38
Max	3.38	3.01	2.97	3.38
Std. Dev.	0.09	0.08	0.07	0.08
Var	0.01	0.01	0.01	0.01
% RSD	3.23	2.76	2.64	2.92

lot 88-001-B

# of Vials	70.00	65.00	68.00	203.00
Average	2.91	2.91	2.93	2.92
Min	2.74	2.70	2.68	2.68
Max	3.00	3.06	3.19	3.19
Std. Dev.	0.06	0.06	0.09	0.07
Var	0.00	0.00	0.01	0.01
% RSD	2.03	2.14	3.01	2.46

lot 88-001-C

# of Vials	68.00	68.00	70.00	206.00
Average	3.05	2.96	3.06	3.02
Min	2.65	2.79	2.73	2.65
Max	3.34	3.20	3.22	3.34
Std. Dev.	0.10	0.07	0.07	0.09
Var	0.01	0.01	0.00	0.01
% RSD	3.20	2.47	2.22	3.00

TABLE 4

Xe-133 GAS

CONTROL DATA (mCi) IN MOLDED GLASS VIAL

Initial Assay t = 0 days		Final Assay t = 20 days	
# of Vials	98	# of Vials	96
Average	31.68	Average	2.22
Min	8.90	Min	2.04
Max	36.40	Max	2.33
Std. Dev.	0.83	Std. Dev.	0.04
Var	0.69	Var	0.00
% RSD	2.62	% RSD	1.80

TABLE 5

LEAKAGE RATE FORMULA

$$\text{Leakage Rate Per Day} = \frac{\dfrac{\text{Theoretical Decayed Initial Average} - \text{Final Average}\ (t = 20\ \text{Days})}{\text{(Theoretical Decayed Initial Average)}}}{\text{Number of Days}} \times 100\%$$

SAMPLE CALCULATION

Using Data From Lot 80-001-A

$$\text{Leakage Rate Per Day} = \frac{\dfrac{2.87 - 2.80}{2.87}\ \text{mCi}}{20\ \text{Days}} \times 100\%$$

$$= \frac{0.12\%}{\text{Day}}$$

WHEATON

1501 NORTH TENTH STREET
MILLVILLE, NEW JERSEY 08332, U.S.A.
TELEPHONE 1-609-825-1100 FAX 1-609-825-1888
TLX 84 1295 (WHEATON MIL)

February 3, 1989

Ms. Debra Gillis
E.I. DuPont de Nemours & Co., Inc.
NEN Products
331 Treble Cove Road
No. Billerica, MA 01862

Dear Ms. Gillis:

Subject: Wheaton Item No. 223713 [2 ml Bottle]

To confirm our telephone conversation of yesterday, Wheaton no longer produces the above bottle and stock is no longer available.

If I can be of any further assistance, please contact me at extension 2655.

Very truly yours,

WHEATON

Heidi Weaztergom

Heidi Weaztergom
Customer Service Representative

HW:lmj

cc: Tom Doyle

WHEATON TUBING PRODUCTS
PRODUCERS OF THE GOLD BAND AMPULE
A DIVISION OF WHEATON INDUSTRIES

MILLVILLE, NEW JERSEY 08332
TELEPHONE 609 825 2222
TWX 510 687 7555
FAX 609 825 7835

October 28, 1988

Mr. Mitch Hollander
E.I. DUPONT DE NEMOURS INCORPORATED
NEN Products Divsion
601 Treble Cove Road
North Billerica, MA 01862

Dear Mitch:

We hereby certify that all the listed containers comply to the requirements of Type I quality glass as set forth in the XXI Revision of the U.S. Pharmacopoeia, and supplements thereto, in the section titled "Chemical Resistance - Glass Containers".

When tested in accordance with the provisions of the U.S.P. XXI Powdered Glass Test, the results are within the maximum limit of 1.0ml prescribed for U.S.P. Type I Glass.

ITEM NO.	QUANTITY	ORDER NO.	DATE OF SHIPMENT
2703-B34B	137,200	LNEN62210-0060	10/21/88

Very truly yours,
WHEATON INDUSTRIES

Marcia Reed

(Mrs.) Marcia Reed

MR/dw

WHEATON TUBING PRODUCTS
PRODUCERS OF THE GOLD BAND AMPULE
A DIVISION OF WHEATON INDUSTRIES

MILLVILLE, NEW JERSEY 08332
TELEPHONE 609 825 2222
TWX 510 687 7555
FAX 609 825 7835

October 28, 1988
(dict. 10/26/88)

Mr. Mitch Hollander
E.I. DUPONT DE NEMOURS INCORPORATED
NEN Products Division
601 Treble Cove Road
North Billerica, MA 01862

Subject: Purchase Order LNEN62210-0060

Dear Mitch:

I wish to advise that we have made shipment against subject purchase order under date of October 21, 1988.

This shipment consisted of 35 cartons packed at 3,920 pieces each for a total shipped of 137,200 pieces of the 3cc Tubing Serum Vial 2703-B34B, your Code 699020.

This shipment went forward from Easton, MD via Red Star Trucking.

Please find attached herewith the signed copies of the Glass Certification covering this shipment of vials.

Very truly yours,

Marcia Reed

(Mrs.) Marcia Reed

MR/dw
Attachment

1888 1988

January 1989

XENON Xe 133 GAS

FOR DIAGNOSTIC USE

DESCRIPTION: Du Pont's XENON Xe 133 Gas is supplied in a mixture of xenon gas (5%) in carbon dioxide (95%). It is contained within septum sealed glass vials and is suitable for inhalation in the diagnostic evaluation of pulmonary function and imaging, as well as assessment of cerebral blood flow. Xenon Xe 133 Gas is reactor-produced as a by-product of Uranium U235 fission. Each vial contains the labeled amount of Xenon Xe 133 radioactivity at the time of calibration. The contents of the vial are in gaseous form, contain no preservatives, and are ready for use.

Xenon Xe 133 is chemically and physiologically related to elemental Xenon, a non-radioactive monoatomic gas which is physiologically inert except for anesthetic properties at high doses.

PHYSICAL CHARACTERISTICS

Xenon Xe-133 decays by beta and gamma emissions with a half-life of 5.245 days.[1] Significant radiations which are emitted by the nuclide are listed in Table 1.

Table 1. Principal Radiation Emission Data from Xenon-133

Radiation	Mean Energy (KeV)	Mean % per Disintegration
Beta-2	100.6	99.3
Ce-K-2	45.0	53.3
Ce-L-2	75.3	8.1
Ce-M-2	79.8	1.7
Gamma-2	81.0	36.5
$K_{\alpha 2}$X-ray	30.6	13.6
$K_{\alpha 1}$X-ray	31.0	25.3
K_{β}X-ray	35.0	8.1

[1]Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC-11026, p. 136, 1981.

EXTERNAL RADIATION

The specific gamma ray constant for Xenon Xe 133 is 3.6 microcoulombs/Kg-MBq-hr (0.51R/hr-mCi) at 1 cm. The first half value thickness of lead is 0.0035cm. 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 2. For example, the use of 0.20cm of Pb will decrease the external radiation exposure by a factor of 1,000.

Table 2. Radiation Attenuation by Lead Shielding

cm of Pb	Radiation Attenuation Factor
0.0035	0.5
0.037	10^{-1}
0.12	10^{-2}
0.20	10^{-3}
0.29	10^{-4}

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

Table 3. Xenon Xe 133 Physical Decay Chart (Half-Life 5.245 days)

Day	Fraction Remaining	Day	Fraction Remaining
0 *	1.000	8	.349
1	.877	9	.302
2	.768	10	.268
3	.674	11	.235
4	.591	12	.206
5	.518	13	.181
6	.452	14	.157
7	.398		

*Calibration Day

CLINICAL PHARMACOLOGY: Xenon Xe 133 is a readily diffusible gas which is neither utilized nor produced by the body. It passes through cell membranes and freely exchanges between blood and tissue. It tends to concentrate more in body fat than in blood, plasma, water or protein solutions. In the concentrations used for diagnostic purposes it is physiologically inactive. Inhaled Xenon Xe 133 Gas will enter the alveolar wall and enter the pulmonary venous circulation via the capillaries. Most of the Xenon Xe 133 that enters the circulation from a single breath is returned to the lungs and exhaled after a single pass through the peripheral circulation.

INDICATIONS AND USAGE: Inhalation of Xenon Xe 133 gas has proved valuable for the evaluation of pulmonary function and for imaging the lungs. It may also be applied to assessment of cerebral flow.

CONTRAINDICATIONS: None known.

WARNINGS: Xenon Xe 133 Gas delivery systems, i.e., respirators or spirometers, and associated tubing assemblies must be leakproof to avoid loss of radioactivity into the environs not specifically protected by exhaust systems.

Xenon Xe 133 adheres to some plastics and rubber and should not be allowed to stand in tubing or respirator containers. The unrecognized loss of radioactivity from the dose for administration may render the study non-diagnostic.

PRECAUTIONS:

General

Xenon Xe 133, as well as [illegible] radioactive drugs, must be handled with care and appropriate safeguards should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to patients consistent with proper patient management.

Exhaled Xenon Xe 133 gas should be controlled in a manner that is in compliance with the appropriate regulations of the government agency authorized to license the use of radionuclides.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential or whether Xenon Xe 133 affects fertility in males or females.

Pregnancy Category C

Animal reproductive studies have not been conducted with Xenon Xe 133 Gas. It is also not known whether Xenon Xe 133 Gas can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xenon Xe 133 Gas should be given to a pregnant woman only if clearly needed.

Ideally, examination using radiopharmaceuticals, especially those elective in nature in 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 Xenon Xe 133 is excreted in human milk. Many drugs are excreted in human milk, therefore formula feedings should be substituted for breast feeding, because of the potential for adverse reactions in nursing infants.

Pediatric Use

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

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

ADVERSE REACTIONS: Adverse reactions related to the use of this agent have not been reported to date.

DOSAGE AND ADMINISTRATION: Xenon Xe 133 gas is administered by inhalation from closed respirator systems or spirometers.

The suggested activity range employed for inhalation by the average adult patient (70kg) is:

Pulmonary function including imaging: 74-1110MBq (2-30mCi) in 3 liters of air.

Cerebral blood flow: 370-1110MBq (10-30mCi) in 3 liters of air.

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

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to an average patient (70kg) for pulmonary perfusion and cerebral blood flow studies from a maximum dose of 1110 MBq (30mCi) of Xenon Xe 133 in 3 liters of air are shown in Table 4.

Table 4. Radiation Doses

	Effective Half-time	Lungs*	Brain	Whole Body
		mGy/1110MBq (rads/30mCi)		
Pulmonary Perfusion	2 min.	2.5 (0.25)	0.014 (0.0014)	0.027 (0.0027)
Cerebral Blood Flow	5 min.	6.3 (0.63)	0.035 (0.0035)	0.066 (0.0066)

*99% of activity is in lungs.

[2]Method of Calculation: A Schema for Absorbed-Dose Calculation for Biologically Distributed Radionuclides, Supplement No. 1, MIRD pamphlet No. 1, *J. Nucl. Med.*, p.7 (1968).

HOW SUPPLIED: The Xenon Xe 133 gas is supplied as part of the Celidose™ system, consisting of 3ml vial dose vials and the Celidose dispenser™ for shielded dispensing.

Normally vials containing either 370-740MBq (10 or 20mCi)/vial, packed up to 5 vials per shield tube, are supplied. Vial sets containing up to 3700MBq (100mCi)/vial are available.

Store at room temperature (15-30°C).

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

E.I. du Pont de Nemours & Co.
331 Treble Cove Rd., Billerica, MA, USA 01862
Tel. Toll Free 800-225-1572
(For Mass. & International, Call 617-482-9595)

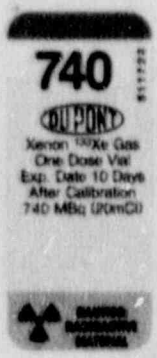
[1]U.S. Patent 3648775 [2]Canadian Patent 999,263 Patented 1976
Printed in U.S.A.

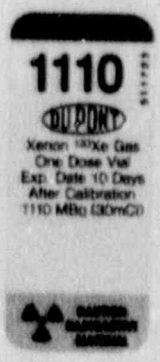
DUPONT

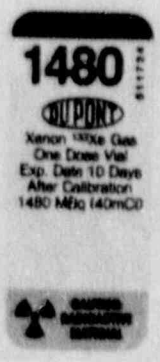
511893

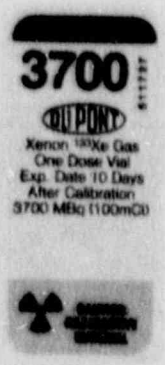
DuPont
Xenon-133 Gas

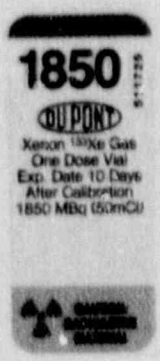
Vial Labels

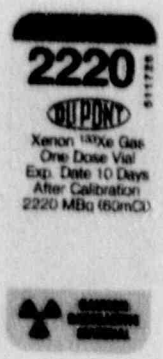












DuPont
Xenon-133 Gas

Shield Label

511716 Diagnostic Agent
XENON Xe 133 GAS

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. (℞)
See Package Insert for dosing information.
U.K. PL/5849/0005 Canadian Lic. #145
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, U.S.A. 01862

No. of Vials:
Total Activity:

Calib. Noon E.T.:
Exp. Noon E.T.:
Lot No.:

CAUTION:
RADIOACTIVE MATERIAL

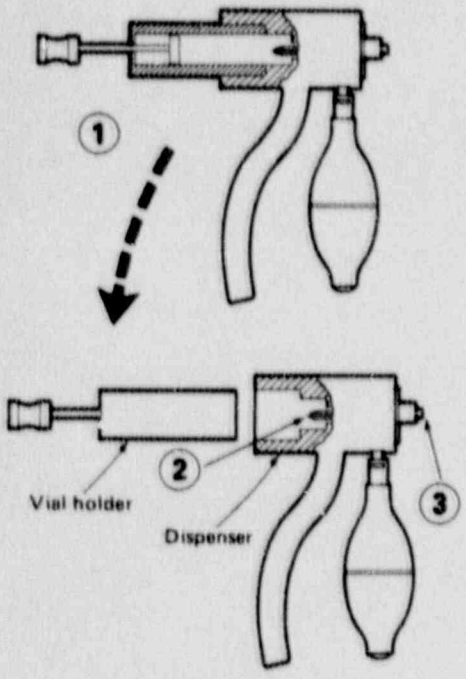
No. of Vials:
Total Activity:

Calib. Noon E.T.:
Exp. Noon E.T.:
Lot No.:

XENON Xe 133 GAS
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

PULL

Operation Instructions for CALIDOSE™ DISPENSER For Use with XENON Xe 133 Gas



Loading

1 Separate shielded vial holder from dispenser.

2 Check Huber point needles inside the dispenser body to insure that they are not blocked (if necessary, clean by pushing a fine wire through needles).

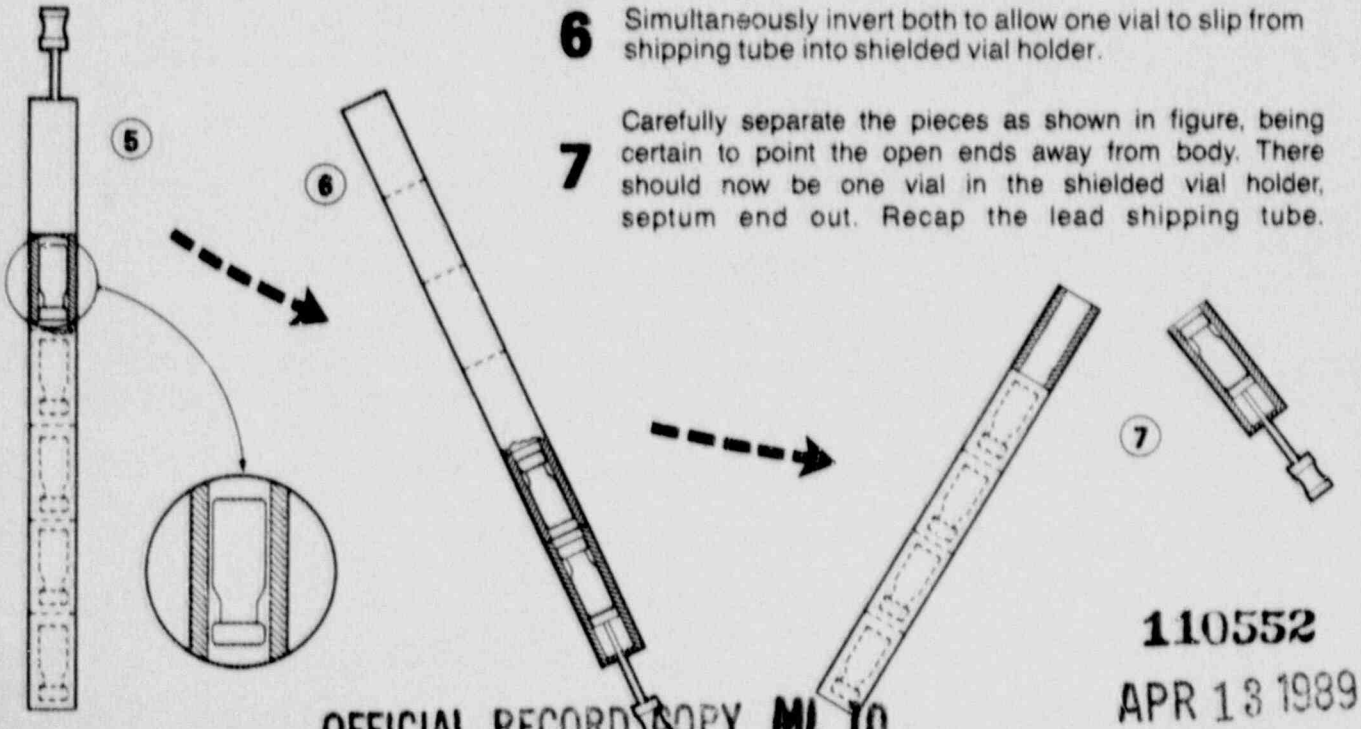
3 Attach a hypodermic needle (or other connector) securely to Luer Lock fitting on front end of dispenser.

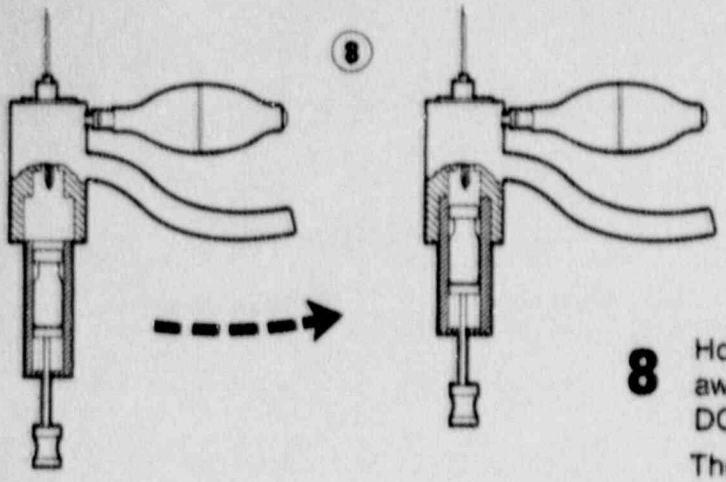
4 Remove the cap of the Xenon Xe 133 lead shipping tube, being careful to point opened tube away from body.

5 Place the open end of the shielded vial holder tightly against the open end of the shipping tube.

6 Simultaneously invert both to allow one vial to slip from shipping tube into shielded vial holder.

7 Carefully separate the pieces as shown in figure, being certain to point the open ends away from body. There should now be one vial in the shielded vial holder, septum end out. Recap the lead shipping tube.

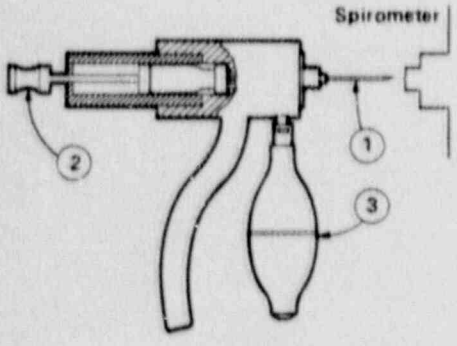




8 Holding the shielded vial holder upright (and pointed away from body), insert it into the dispenser until seated. DO NOT PUSH PLUNGER IN AT THIS TIME.

The loaded CALIDOSE Dispenser is now ready for use and can be put aside until needed. Note that appropriate radiation protection precautions should be taken with loaded unit.

Using



1 Affix the CALIDOSE Dispenser to a spirometer or related breathing apparatus.

2 Puncture septum of loaded vial by pushing plunger into dispenser.

3 Immediately squeeze the rubber bulb, and then release.

4 Detach CALIDOSE assembly from breathing apparatus.

Storing

Remove vial holder from dispenser. The previously used vial will not contain enough residual Xenon Xe 133 to be harmful, and may be removed by hand for disposal in the radioactive waste. Replace vial holder in dispenser for easy storage.

Statement

This CALIDOSE™ Dispenser is a device protected by U.S. Patent 3,848,773, and Canadian Patent 999,263 Patented 1976. It is to be used solely for the purposes of dispensing Du Pont's Xenon 133 gas .

E. I. du Pont de Nemours & Co.

331 Treble Cove Road, Billerica, Massachusetts, USA 01862
CALL TOLL-FREE: 800-225-1572 Telex: 94-0996
(In Massachusetts and International: 617-482-9595)

511788

DUPONT

Printed in U.S.A.

NRC Form 374
(5-84)

U.S. NUCLEAR REGULATORY COMMISSION

MATERIALS LICENSE

Amendment No. 07

Pursuant to the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974 (Public Law 93-438), and Title 10, Code of Federal Regulations, Chapter I, Parts 30, 31, 32, 33, 34, 35, 40 and 70, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, possess, and transfer byproduct, source, and special nuclear material designated below; to use such material for the purpose(s) and at the place(s) designated below; to deliver or transfer such material to persons authorized to receive it in accordance with the regulations of the applicable Part(s). This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954, as amended, and is subject to all applicable rules, regulations and orders of the Nuclear Regulatory Commission now or hereafter in effect and to any conditions specified below.

Licensee	
1. E. I. DuPont de Nemours & Co., Inc. Medical Products Department Boston Area	In accordance with letter received November 6, 1987, 3. License number 20-00320-21 is amended in its entirety to read as follows:
2. 549 Albany Street Boston, Massachusetts 02118	4. Expiration date November 30, 1990
	5. Docket or Reference No. 030-28902

6. Byproduct, source, and/or special nuclear material	7. Chemical and/or physical form	8. Maximum amount that licensee may possess at any one time under this license
A. Any byproduct material with atomic numbers 1-83	A. Any	A. 200 curies of each radionuclide with atomic numbers 1 to 83, with a total possession limit of 5,000 curies
B. Krypton 85	B. Any	B. 10,000 curies
C. Molybdenum 99	C. Any	C. 6,000 curies
D. Americium 241	D. Any	D. 960 curies
E. Xenon 133	E. Any	E. 2,500 curies
F. Nickel 63	F. Any	F. 1,000 curies
G. Sulfur 35	G. Any	G. 1,000 curies
H. Carbon 14	H. Any	H. 1,500 curies
I. Cesium 137	I. Any	I. 500 curies
J. Phosphorus	J. Any	J. 550 curies
K. Strontium 90	K. Any	K. 500 curies
L. Hydrogen 3	L. Any	L. 150,000 curies
M. Any byproduct material with atomic nos. 84-94	M. Any	M. 60 millicuries each radionuclide with atomic nos. 84-94
N. Any byproduct material listed in Schedule B 10 CFR 30.71	N. Any	N. Not to exceed limits specified in Schedule B. 10 CFR 30.71

9. Authorized use

A. through M.
(1) Research and Development as defined in Section 30.4(q) of 10 CFR 30.
(2) For possession, use, and processing incident to manufacture of radiochemicals, radiopharmaceuticals and sealed sources.
(3) For storage prior to distribution of manufactured radiochemicals, radiopharmaceuticals and sealed sources.
(4) For packaging and distribution of manufactured radiochemicals, radiopharmaceuticals, and sealed sources to persons authorized to receive the licensed material pursuant to the terms and conditions of specific licenses issued by the Nuclear Regulatory Commission or Agreement States.

8903140780

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number: 20-00320-21

Docket or Reference number: 030-28902

Amendment No. 07

(Item 9. continued)

(5) For use in calibration of E. I. DuPont NEN Products instruments.
(6) For storage as radioactive wastes.

A. Licensed material possessed at the Boston Site will not exceed 10 Curies per nuclide and 100 Curies total of nuclides with atomic number 3 through 83.

G. Licensed material possessed at the Boston Site will not exceed 200 Curies, S-35. Licensed material possessed at the Westwood Site shall not exceed 400 millicuries, S-35.

H. Licensed material possessed at the Boston Site will not exceed 500 Curies, C-14. Licensed material possessed at the Westwood site shall not exceed 100 millicuries, C-14.

J. Licensed material possessed at the Boston Site will not exceed 90 Curies, P-32. Licensed material possessed at the Westwood Site shall not exceed 150 millicuries, P-32.

L. Licensed material possessed at the Boston Site will not exceed 100,000 Curies, H-3. Licensed material possessed at the Westwood Site shall not exceed 500 millicuries, H-3.

M. Licensed material possessed at the Boston Site will not exceed 50 millicuries per nuclide with atomic numbers 84 through 94.

N. For demonstration by sales persons at customers facilities, anywhere in the United States where the Nuclear Regulatory Commission has jurisdiction.

A. through M. Licensed material possessed at the Billerica Site will not exceed the limits specified after the Boston Site limits are subtracted from the maximum amount.

A. through M. Sealed sources can be returned to the NEN Products, Billerica Site for the purpose of refurbishment or disposal. All such return shipments will be handled in compliance with the conditions of the NEN Products USNRC By-product Materials License, as well as applicable DOT regulations.

CONDITIONS

10. A. Licensed material may be used at the Boston Facility; Building locations at 549 and 575 Albany Street; 100 E. Canton Street; and 120 and 123 E. Dedham Street, Boston, Massachusetts.

B. Licensed material may be used at the Billerica Facility; 331 Treble Cove Road, N. Billerica, Massachusetts. Buildings designated as Nos. 100, 150, 200, 250, 300, 325, 350, 375, 400, 500 and 600.

C. Licensed material in Item 6.N. may be used at and at temporary job sites of the licensee anywhere in the United States where the U. S. Nuclear Regulatory Commission maintains jurisdiction for regulating the use of licensed material.

D. Licensed material as authorized by Items 9.G., 9.H., 9.J. and 9.L. for the Westwood Site may be use at licensee's facilities, 240 University Avenue, Westwood, Massachusetts.

11. A. Licensed material shall be used by, or under the supervision of, individuals designated by the respective Boston or Billerica Site Radioisotope Committee.

(11. continued) CONDITIONS

B. The Radiation Protection Officer for the activities authorized by this license is Dennis O. Dumas.

12. This license does not authorize commercial distribution to persons exempt from licensing, to persons generally licensed or for medical use pursuant to Sections 35.14 and 35.31, of 10 Part 35.

13. A(1) Each sealed source or detector cell acquired from another person and containing licensed material, other than hydrogen 3, with a half-life greater than 30 days and in any form other than gas shall be tested for contamination and/or leakage before use. In the absence of a certificate from a transferor indicating that a test has been made within 6 months before the transfer, a sealed source or detector cell received from another person shall not be put into use until tested.

(2) Notwithstanding the periodic leak test required by this condition, any licensed sealed source or detector cell is exempt from such leak tests when the source or detector cell contains 100 microcuries or less of beta and/or gamma emitting materials or 10 microcuries or less of alpha emitting material.

(3) Except for alpha sources, the periodic leak test required by this condition does not apply to sealed sources that are stored and not being used. The sources excepted from this test shall be tested for leakage before any use or transfer to another person unless they have been leak tested within 6 months before the date of use or transfer.

B. Each sealed source or detector cell fabricated by the licensee shall be inspected and tested for construction defects, leakage, and contamination prior to use or transfer as a sealed source or detector cell. If the inspection or test reveals any construction defects or 0.005 microcurie or greater of contamination, the source shall not be used or transferred as a sealed source or detector cell until it has been repaired, decontaminated and retested.

C. Each sealed source containing licensed material, other than hydrogen 3, with a half-life greater than 30 days and in any form other than gas shall be tested for leakage and/or contamination at intervals not to exceed 6 months except that each source designed for the purpose of emitting alpha particles shall be tested at intervals not to exceed 3 months.

D. The test shall be capable of detecting the presence of 0.005 microcurie of radioactive material on the test sample. The test sample shall be taken from the sealed source or detector cell or from the surfaces of the device in which the sealed source or detector cell is permanently or semipermanently mounted or stored on which one might expect contamination to accumulate. Records of leak test results shall be kept in units of microcuries and maintained for inspection by the Commission. Records may be disposed of following Commission inspection.

(13. continued) CONDITIONS

E. If the test required by Subsection A. or C. of this condition reveals the presence of 0.005 microcurie or more of removable contamination, the licensee shall immediately withdraw the sealed source or detector cell from use and shall cause it to be decontaminated and repaired or to be disposed of in accordance with Commission regulations. A report shall be filed within 5 days of the date the leak test result is known with the U. S. Nuclear Regulatory Commission, Region I, ATTN: Chief, Nuclear Materials Safety and Safeguards Branch, 631 Park Avenue, King of Prussia, Pennsylvania 19406, describing the equipment involved, the test results, and the corrective action taken.

14. The licensee shall not use licensed material in or on humans beings or in field applications where activity is released except as provided otherwise by specific conditions of this license.

15. Experimental animals administered licensed materials or their products shall not be used for human consumption.

16. A. Detector cells containing titanium tritide foil shall only be used in conjunction with a properly operating temperature control mechanism which prevents foil temperatures from exceeding 225 degrees Centigrade.

B. Detector cells containing scandium tritide foil shall only be used in conjunction with a properly operating temperature control mechanism which prevents foil temperatures from exceeding 325 degrees Centigrade.

17. In lieu of using the conventional radiation caution colors (magenta or purple on yellow background) as provided in Section 20.203(a)(1), of 10 CFR Part 20, the licensee is hereby authorized to label detector cells and cell baths, containing licensed material and used in gas chromatography devices, with conspicuously etched or stamped radiation caution symbols without a color requirement.

18. The licensee may transport licensed material in accordance with the provisions of 10 CFR Part, "Packaging and Transportation of Radioactive Material".

19. Pursuant to Section 20.302, 10 CFR Part 20, the licensee is authorized to exceed the 1 curie limit in Section 20.303(d), 10 CFR Part 20, provided that for the Boston site:

A. Not more than 12 curies total of hydrogen 3 and 1 curie total of all other byproduct material shall be released during any 12 consecutive months, and;

B. All releases to the sewerage system shall be in accordance with the procedures described in the licensee's application dated July 17, 1985, excluding Item 15.J.5. paragraphs 2. and 3.

(Continued) CONDITIONS

20. The licensee shall maintain and execute the response measures of his Radiological Contingency Plan for the Boston Site as revised in its entirety dated June, 1985 and attached to letter dated July 26, 1985 and Addendum Item 8 described in letter dated October 16, 1985. The licensee shall also maintain implementing procedures for his Radiological Contingency Plan as necessary to implement the plan. The licensee shall make no change in his Radiological Contingency Plan that would decrease the response effectiveness of the plan without prior Commission approval as evidenced by license amendment. The licensee may make changes to his Radiological Contingency Plan without prior Commission approval if the changes do not decrease the response effectiveness of the plan. The licensee shall maintain records of changes that are made to the Plan without prior approval for a period of two years from the date of the change and shall furnish the Chief, Nuclear Materials Safety and Safeguards Branch, Division of Radiation Safety and Safeguards, U.S. Nuclear Regulatory Commission, Region I, 631 Park Avenue, King of Prussia, Pennsylvania 19406, a report, in duplicate, containing a description of each change with six months after the change is made.

21. A. At the licensee's Boston Site no more than 15 curies of phosphorus-32 shall be used or stored in any building unless radiation detection systems and alarms to continuously monitor possible effluent releases are installed and operated.

B. Notwithstanding the requirements of Condition A above; the licensee is not required to comply with Condition 21.A. with respect to phosphorus-32 wastes stored in non-combustible drums when the drums are porvided with sprinkler protection.

22. The licensee shall maintain and execute the response measures of his Radiological Contingency Plan for the Billerica Site as revised in its entirety dated June, 1985, and attached to letter dated July 26, 1985. The licensee shall also maintain implementing procedures for his Radiological Contingency Plan as necessary to implement the Plan. The licensee shall make no change in his Radiological Contingency Plan that would decrease the response effectiveness of the plan without prior Commission approval as evidenced by license amendment. The licensee may make changes to his Radiological Contingency Plan without prior Commission approval if the changes do not decrease the response effectiveness of the plan. The licensee shall maintain records of changes that are made to the Plan without approval for a period of two years from the date of the change and shall furnish the Chief, Nuclear Materials Safety and Safeguards Branch, Division of Radiation Safety and Safeguards, U.S. Nuclear Regulatory Commission, Region I, 631 Park Avenue, King of Prussia, Pennsylvania 19406, a report, in duplicate, containing a description of each change within six months after the change is made.

NRC Form 374A (5-84) U.S. NUCLEAR REGULATORY COMMISSION

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number: 20-00320-21

Docket or Reference number: 030-28902

Amendment No. 07

(Continued) CONDITIONS

23. The licensee may possess up to 10 curies of Iodine-125 waste in any building at the Billerica Site without installation of radiation detection systems and alarms to continuously monitor possible effluent releases from associated ventilation systems, provided, the material is stored as waste in non-combustible drums and the drums are provided with sprinkler protection.

24. Except as specifically provided otherwise in this license, the licensee shall conduct its program in accordance with the statements, representations, and procedures contained in the documents including any enclosures, listed below. The Nuclear Regulatory Commission's regulations shall govern unless the statements, representations and procedures in the licensee's application and correspondence are more restrictive than the regulations.

A. Letter dated December 17, 1984
B. Application dated July 17, 1985
C. Letter dated October 16, 1985
D. Letter dated January 21, 1986
E. Letter dated September 12, 1986
F. Letter received February 5, 1987
G. Letter dated June 29, 1987
H. Letter dated August 6, 1987
I. Letter dated August 26, 1987
J. Letter dated October 9, 1987
K. Letter dated November 30, 1987

For the U.S. Nuclear Regulatory Commission

Date 23 FEB 1988

By Original Signed By
Jack Davis

Nuclear Materials Safety and
Safeguards Branch, Region I
King of Prussia, Pennsylvania 19406

AMS-18
89-04-17

BETWEEN:

LICENSE FEE MANAGEMENT BRANCH, ARM
AND
REGIONAL LICENSING SECTIONS

(FOR LFMS USE)
INFORMATION FROM LTS

PROGRAM CODE: 02512
STATUS CODE: 2
FEE CATEGORY: 3D
EXP. DATE: 19890131
FEE COMMENTS: _____

LICENSE FEE TRANSMITTAL

A. REGION I

1. APPLICATION ATTACHED
APPLICANT/LICENSEE: E. I. DU PONT DE NEMOURS & CO., INC
RECEIVED DATE: 890413
DOCKET NO: 3011164
CONTROL NO.: 110552
LICENSE NO.: 20-00320-16MD
ACTION TYPE: AMENDMENT

2. FEE ATTACHED
AMOUNT: $120.00
CHECK NO.: 052017796

3. COMMENTS

SIGNED B. J. Brown
DATE 89-04-17

B. LICENSE FEE MANAGEMENT BRANCH (CHECK WHEN MILESTONE 03 IS ENTERED / T)

1. FEE CATEGORY AND AMOUNT: 3D $120

2. CORRECT FEE PAID. APPLICATION MAY BE PROCESSED FOR:
AMENDMENT ✓
RENEWAL _____
LICENSE _____

3. OTHER _____
_____

SIGNED A Kimberly
DATE 5/4/89