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Medical Products Division/3M

3M Center
St. Paul, Minnesota 55101
612/733 1110

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3M

June 30, 1981

U. S. Nuclear Regulatory Commission
License Management Branch
Division of Fuel Cycle and Material Safety
Washington, D.C. 20555

Attention: Joseph Del Medico

Re: Control No. 07845, Application for Amendment of Materials License No. 22-00057-59MD

Dear Mr. Del Medico:

This letter is to provide clarifying information in support of our license amendment application of May 1, 1981, for I-125 Seeds in Carrier, model 6720. Included in this letter are responses to those items discussed in our telephone conversations of June 26 and 30, 1981, and July 1 1981.

ITEM 1

Have the prototype tests for I-125 Seeds models 6701 and 6711, described on pages 8 through 15 of the May 1, 1981, submission been repeated for this document? Are these data the same as those previously submitted?

Response

The prototype tests described in the May 1, 1981, document are the same as those submitted in license amendment applications of March 15, 1979, and February 8, 1980, for models 6701 and 6711, respectively. The data were repeated for the convenience of the reviewer. No additional prototype tests were performed for the purposes of this submission, since both I-125 Seeds are currently licensed for distribution.

ITEM 2

If the portion of carrier containing I-125 Seeds is removed from the stainless steel shielding ring, is

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APPENDIX/ Item 12

it possible to replace them? Should there be directions for storage of the product after its removal from the ring?

Response

I-125 Seeds in Carrier is intended to be used (implanted) immediately after its removal from the stainless steel shielding ring. If this is not possible, for some reason, the user should not attempt to replace the product in the ring. Instead, the product should be placed in a sterile stainless steel tray with cover for storage until use. This container will effectively attenuate the radiation, while maintaining sterility of the product.

Instruction to the user regarding this procedure will be added to the 'Precautions' section of the product package insert, as paragraph 5 under 'Preparation for Use'. The text is as follows:

> In the event that I-125 Seeds in Carrier is not used (implanted) immediately following its removal from the stainless steel shielding ring, the product should be placed in a sterile stainless steel tray with cover for storage until use. The tray cover should be secured and the tray labeled to denote radioactive content, with care taken to prevent loss or inadvertant disposal of the product.

ITEM 3

With regard to the source return policy described in the package insert, in what container does the customer return I-125 Seeds in Carrier? Please submit the instructions that you supply to customers who wish to return I-125 Seeds in Carrier.

Response

The container which will be supplied to customers for return of I-125 Seeds in Carrier is a lead container, a schematic diagram for which is presented in Attachment A to this letter.

The information which is supplied to individuals wishing to return I-125 Seeds in Carrier to 3M consists of the following documents: 1) a "Dear Customer" letter containing instructions for packaging and shipping, as

well as a decay chart for iodine - 125; 2) two Radioactive - white labels; 3) one address label; and 4) one shipper's certification form. Copies of this information are also presented in Attachment A.

ITEM 4

In package inserts for I-125 Seeds, there is a paragraph in the 'Treatment' section describing precautions to be taken in the event that a seed sloughs off. Should such a paragraph be included in the package insert for I-125 Seeds in Carrier?

Response

The radioactive sources in this product are held in position within the carrier, and the entire unit is placed into the tumor to be treated. The probability that an I-125 Seed would be released from this carrier and subsequently slough from the tumor is negligible. For this reason, precautions were not included in the package insert draft for the product.

We have reviewed our original position, however, and, in the interest of radiation safety, are revising the package insert to include precautions, in the unlikely event that seed sloughing from this product occurs. The text, to be added to 'Precautions', as paragraph 2 under 'Treatment of Patient', is as follows:

> All patients should be advised of the possibility that, during a course of treatment, one or more I-125 Seeds might slough off and become detached as a tumor regresses and becomes smaller. Under these circumstances, any bandages or linens which come into contact with the site of the implant should be scrutinized for small metallic seeds ($\frac{1}{4}$ of an inch long). Patients should be advised that whenever seeds are found, they should be picked up [redacted] a spoon and placed in a jar or [redacted] container, and placed in an [redacted] ssible area in the home. The radiation center should be notified of such an event as soon as possible after its occurrence.

ITEM 5

It was suggested that several statements in the package insert for I-125 Seeds in Carrier be highlighted.

Response

We have considered the agency suggestions that certain statements be highlighted. In this regard, several statements will be revised editorially and appear in capital letters, as described below.

in the 'Warnings' section,

I-125 SEEDS IN CARRIER IS SHIPPED STERILE AND MUST NOT BE RESTERILIZED.

in the 'Precautions' section, paragraph 4 under 'Preparation for Use',

. . . In addition, I-125 SEEDS IN CARRIER SHOULD BE HANDLED ONLY WITH FORCEPS, with as much distance as practical between sources and the operator. Spacing of seeds may be adjusted using forceps to manipulate the seeds within the carrier. WHEN USING FORCEPS CARE MUST BE TAKEN NOT TO CRUSH THE SEEDS.

in the 'Precautions' section, paragraph 2 under 'Application to Patient',

WHEN CUTTING THE CARRIER MATERIAL TO THE DESIRED LENGTH DURING IMPLANTATION, CARE MUST BE TAKEN TO AVOID CRUSHING OR RUPTURING AN I-125 SEED . . .

A typed draft of the package insert for I-125 Seeds in Carrier containing these statements, as well as revisions described in responses to items 2 and 4, is enclosed with this letter, as Attachment B.

We appreciate your expeditious review of this application. If you have additional questions or concerns, please feel free to contact me (612/733-6421).

Sincerely yours,

Jacquelyn D. Bush

Jacquelyn D. Bush
Sr. Regulatory Compliance Coordinator
Medical Products Division/3M
3M Center, Bldg. 270-4A-05
St. Paul, Minnesota 55144

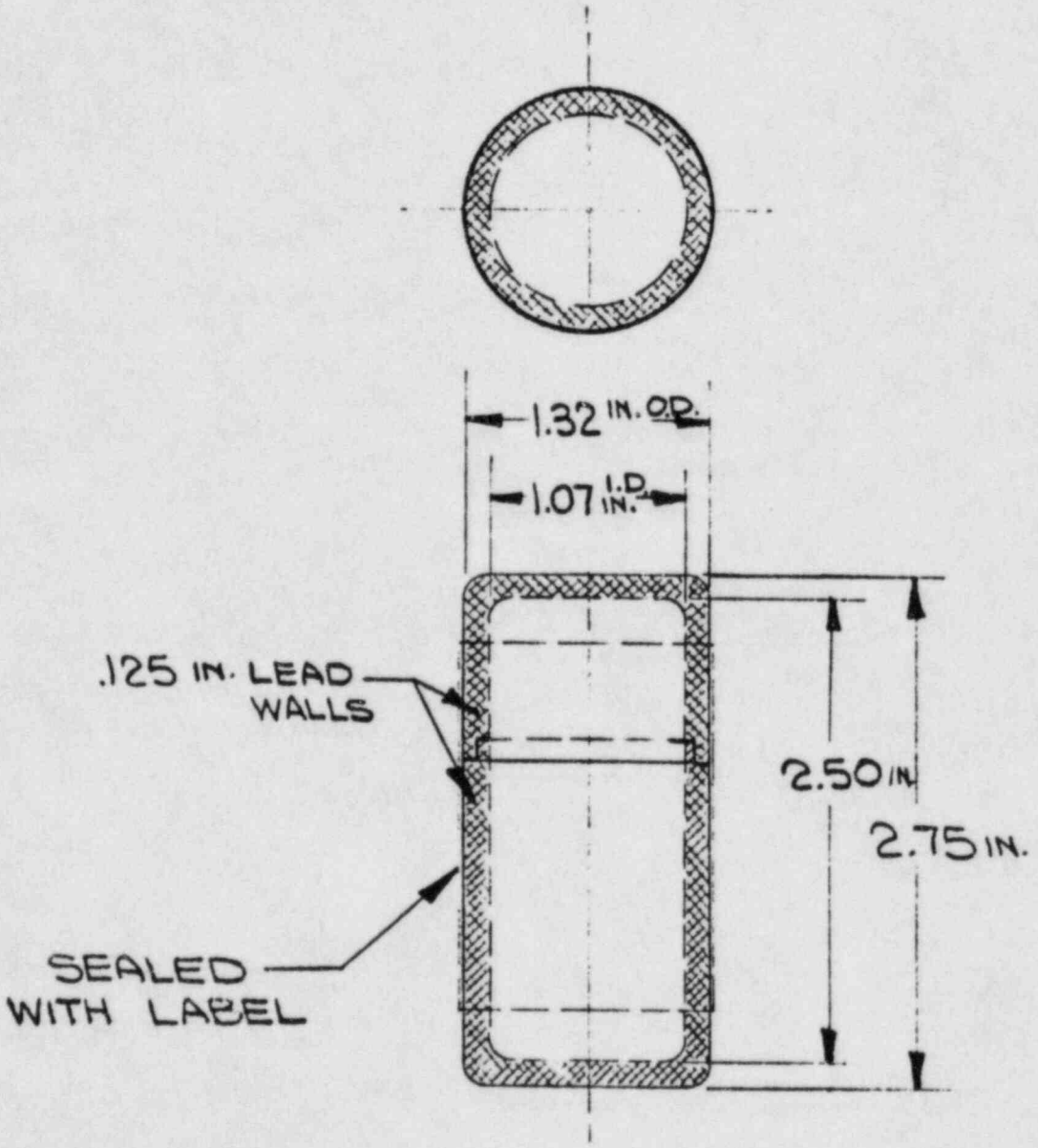
JDB:tmf

Enclosures: 2

ATTACHMENT A

Customer Information Pertaining to Return Policy
for I-125 Seeds in Carrier

LEAD SHIPPING CONTAINER
I-125 SEEDS^{R}



Medical Products Division/3M

3M Center
St. Paul, Minnesota 55101
612/733 1110

3M

Dear Customer:

We have your request for the shipment of I-125 Seeds in Carrier to Medical Products Division/3M for the purpose of disposal. Shipment of radioactive materials is controlled by a number of government agencies, including the Department of Transportation and the Nuclear Regulatory Commission. These regulations require proper packaging for shipment, marking, labeling and certification of the packages by the shipper. You, as a shipper, are responsible to see that these regulations are met.

We are providing you a package with a shielded container which should be adequate for the shipment of your iodine to 3M. However, final determination of the adequacy is your responsibility as the shipper. It is legally required that you monitor the package you ship for contamination and external radiation dose rate prior to presenting it for shipment to 3M.

Please prepare the shipment in the following manner:

1) If not done previously, remove the I-125 Seeds in Carrier from the stainless steel shielding ring.

2) Place I-125 Seeds in Carrier to be returned in the screw cap glass vial supplied by 3M, and label the vial showing "I-125" and the radioactivity content.

3) Place the vial of seeds in the lead container provided. Tape the container securely, and label it.

4) Center the container in the carton/foam assembly provided, and tape the carton closed.

5) Complete the two Radioactive White I Labels provided, and affix to opposite sides of the carton. Enclosed is a decay factor chart which may be helpful in determining the approximate activity of the Iodine seeds.

6) Affix the address label which we have provided.

7) The preparation of the shipper's certification for radioactive materials is critical. Please fill out this form as follows:

A. Check the block indicating "cargo aircraft".

B. Under "Proper Shipping Name," write in Radioactive Material, N.O.S., and Iodine-125.

C. Under "Radionuclide," enter I-125.

D. Under "Group," enter III.

E. Under "Form," enter I-125, absorbed on resin, and solid.

F. Under "Activity," enter the total activity of the Iodine-125 you are shipping.

G. Enter the number of packages in the next column.

H. Enter "White I' in the Category column.

I. Enter "N/A" in the Transpore Index column, since this column is not applicable for this shipment.

J. Enter "Type A" in the next column.

K. In the lower left-hand corner, enter your name and address as the shipper.

L. In the lower right-hand corner, print name of the person responsible for the shipment, and print this person's title. Then, sign the certificate in the block indicated. Because some air carriers insist on two originals, lift the first copy of the certification, and sign the second copy again.

The back copy of the certification can be kept for your records; the other four copies should be delivered with the package to the carrier.

These instructions should be adequate for the shipment of these materials to us. If you are in doubt, please do not make the shipment. Call W. F. Pollock at 612-633-9420 if you have any questions.

Sincerely,

Wendell F. Pollock

Wendell F. Pollock
Supervisor
Materials Control

WFP:mem
enclosure-1

One mCi Equivalent I-125 Seed

Half life: 60 days

Days after assay	Decay factor
0	1.000
2	0.977
4	0.955
6	0.933
8	0.912
10	0.891
12	0.871
14	0.851
16	0.832
18	0.813
20	0.794
22	0.776
24	0.759
26	0.741
28	0.724
30	0.708
32	0.692
34	0.676
36	0.661
38	0.646
40	0.631
42	0.617
44	0.603
46	0.589
48	0.575
50	0.562
52	0.550
54	0.537
56	0.525
58	0.513
60	0.501
62	0.490
64	0.479
66	0.468
68	0.457
70	0.447
72	0.437
74	0.427
76	0.417
78	0.407
80	0.398
82	0.389
84	0.380
86	0.372
88	0.363

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From **General Offices/3M**
3M Center
St. Paul, MN 55144

3M

Radiation Therapy Products
Medical Products Division/3M
Building 590
Twin Cities Army Ammunition Plant
New Brighton, MN 55112

Form 6550-F

RADIOACTIVE MATERIAL, N.O.S.

34-7014-1007-7

Form 13906-2

SHIPPER'S CERTIFICATION FOR RADIOACTIVE MATERIALS

The two completed and signed white copies of this certification shall be handed to the carrier. Retain pink for your file.

(Use block letters)

WARNING: Failure to comply in all respects with the applicable regulations of the Department of Transportation, 49-CFR, CAB 82 and, for international shipments, the IATA Restricted Articles Regulations may be a breach of the applicable law, subject to legal penalties. This certification shall in no circumstance be signed by an IATA Cargo Agent or a consolidator for international shipments.

This shipment is within the limitations prescribed for: *(mark one)*

☐ passenger aircraft and contains radioactive material intended for use in, or incident to, research, or medical diagnosis or treatment.

☐ cargo-only aircraft

NATURE AND QUANTITY OF CONTENT					PACKAGE			
Proper Shipping Name	Radionuclide	Group	Form	Activity		Category	Transport Index	Type
For U.S. Shipments, See Section 2, CAB 82, Tariff 6-D	Name or Symbol of Principal Radioactive Content	Group Number of Groups I to VII	Chemical Form and Physical State (Gas/ Liquid/Solid) or Special Form, or Special Encapsulation	Number of Curies or Milli-curies	Number of Packages	I – White or II – Yellow or III – Yellow Label	For Yellow Label Categories Only	Industrial or Type A or Type B

ADDITIONAL INFORMATION REQUIRED FOR FISSILE MATERIALS ONLY

EXEMPTED FROM THE ADDITIONAL REQUIREMENTS FOR FISSILE MATERIALS SPECIFIED IN 7.1 OF PART 2 OF THE IATA RESTRICTED ARTICLES REGULATIONS ☐
NAMES, PLUS QUANTITY IN GRAMS, OR CONCENTRATION OR ENRICHMENT IN U2??

NOT EXEMPTED: FISSILE CLASS I ☐ FISSILE CLASS II ☐ FISSILE CLASS III ☐

Additional certificates obtained by the Shipper when necessary:

- Special Form Encapsulation Certificate(s) ☐
- Type "B" Packaging Certificate(s) ☐
- Certificate(s) for Fissile Material ☐
- Certificate(s) for Large Radioactive Source ☐
- Government Approvals/Permits ☐

Special Handling Information

I hereby certify that the contents of this consignment are fully and accurately described above by Proper Shipping Name and are classified, packed, marked, labelled and in proper condition for carriage by air according to applicable national governmental regulations, and for International Shipments the current IATA Restricted Articles Regulations.

Name and full address of Shipper	Name and title of person signing Certification
Minnesota Mining and Manufacturing Co.	
Date	Signature of the Shipper (see WARNING above)

Air Waybill No.*	Airport of Departure*	Airport of Destination*

*This box is optional for completion by issuing carrier.

ATTACHMENT B

Revised Package Insert for I-125 Seeds in Carrier
Model 6720

Medical Products Division/3M

3M Center
St. Paul, Minnesota 55101
612/733 1110

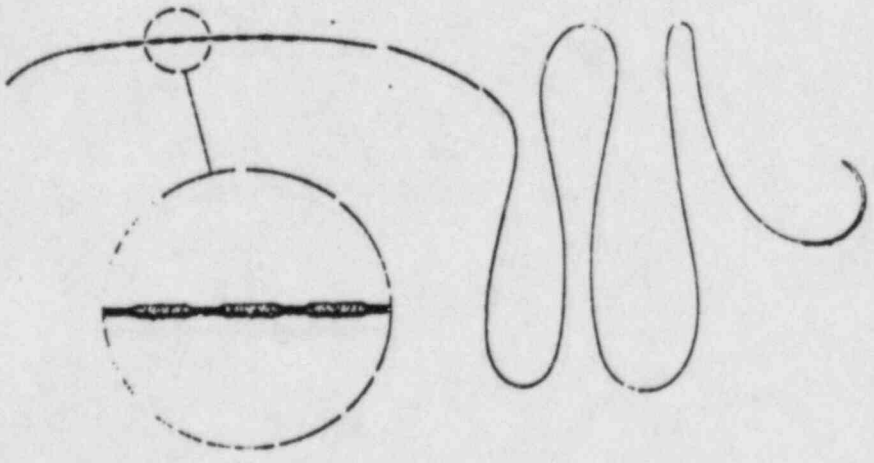
3M

I-125 SEEDS[R] IN CARRIER

NO. 6720

DESCRIPTION

I-125 Seeds in Carrier consists of a group of I-125 Seeds (up to 20) housed at a fixed distance (0.5 to 1.5 cm center to center) within a braided, synthetic, absorbable carrier. The I-125 Seeds consist of a welded titanium capsule containing iodine-125 absorbed onto either anion exchange resin spheres or a silver rod. The carrier material housing the I-125 Seed is a synethetic absorbable suture material, #1 Vicryl[R] (polyglactin 910). Seeds are spaced at the distal 2 to 30 cm of the carrier, from which the core has been removed. A surgical needle is attached to the opposite end.



Physical Characteristics

Iodine-125 has a half-life of 60.2 days and decays by electron capture with the emission of characteristic X-rays and Auger electrons. The electrons are absorbed by the titanium wall of the I-125 Seed. The principal radiation emissions are X-rays of 27.4 keV and 35.5 keV.

To correct for the physical decay of Iodine-125, the decay factors at selected days after the assay date are shown in table below.

Decay Chart Iodine-125, Half-Life 60.2 Days

Days	Decay Factor	Days	Decay Factor	Days	Decay Factor
0	1.000	24	0.759	48	0.575
2	0.977	26	0.741	50	0.562
4	0.955	28	0.724	52	0.550
6	0.933	30	0.708	54	0.537
8	0.912	32	0.692	56	0.525
10	0.891	34	0.676	58	0.513
12	0.871	36	0.661	60	0.501
14	0.851	38	0.646	62	0.490
16	0.832	40	0.631	64	0.479
18	0.813	42	0.617	66	0.468
20	0.794	44	0.603	68	0.457
22	0.776	46	0.589	70	0.447

Radiation Protection

The half value thickness of lead for iodine-125 is 0.025 mm. Thus, a 0.25 mm lead sheet will provide > 99% reduction in exposure.

ACTIONS

I-125 Seeds emit X-rays of 27.4 and 35.5 keV. The clinical efficacy of the sources derives solely from the interaction of these ionizing radiations with the tissue being treated.

Dose distribution around each individual seed is not isotropic. This anisotropy should be included in dose distribition calculations.

Intramuscular implantation studied in rats show that the absorption of the carrier in I-125 Seeds in Carrier is minimal until about the 40th post-operative day. Absorption is essentially complete between the 60th and 90th day.

INDICATIONS

I 125 Seeds in Carrier is indicated for permanent interstitial implantation of selected tumors which are localized, either unresectable or residual after excision of the primary lesion, and of low to moderate radiosensitivity.[1,2,3]

I-125 Seeds in Carrier may be indicated for use concurrent with or at the completion of other treatment modalities, such as external beam radiation therapy or chemotherapy.

CONTRAINDICATIONS

As with other brachytherapy sources, treatment of tumors in generally poor condition (e.g. ulcerated) is not recommended with I-125 Seeds in Absorbable Carrier.

WARNINGS

I-125 SEEDS IN CARRIER IS SHIPPED STERILE AND MUST NOT BE RESTERILIZED.

PRECAUTIONS

Preparation for Use

I-125 Seeds in Carrier is radioactive, and appropriate precautions must be taken when handling these devices. All steps of the implantation procedure should be planned in advance to minimize radiation exposure to personnel consistent with published exposure limits.[4]

Personnel monitoring is required for individuals working with I-125 Seeds in Carrier. A film badge or TLD dosimeter worn on the body and, for handling, a ring badge will provide adequate monitoring.

Sterile I-125 seeds in carrier is contained within a stainless steel shielding ring. This ring is provided in a moisture-resistant foil pouch within a gas permeable bag. The shielding ring effectively attenuates all radioactivity, eliminating the need for additional shielding.

All manipulations involving I-125 Seeds in Carrier should be carried out behind shielding of such size and thickness as will adequately shield the operator. DIRECT CONTACT WITH THE SOURCES SHOULD BE AVOIDED. In addition, I-125 SEEDS IN CARRIER SHOULD BE HANDLED ONLY WITH FORCEPS, with as much distance as practical between sources and the operator. Spacing of seeds may be adjusted using forceps to manipulate the seeds within the carrier. WHEN USING FORCEPS, CARE MUST BE TAKEN NOT TO CRUSH THE SEEDS.

In the event that I-125 Seeds in Carrier is not used (implanted) immediately following its removal from the stainless steel shielding ring, the product should be placed in a sterile stainless steel tray with cover for storage until use. The tray cover should be secured and the tray labeled to denote radioactive content, with care taken to prevent loss or inadvertant disposal of the product.

Although I-125 Seeds have a high structural integrity, it is possible, through rough handling, high temperatures, or crushing, that a seed could leak or be ruptured. If such a rare occurrence does happen, the area should be closed off, the seeds packaged into a sealed container, and the area decontaminated. Decontamination can be confirmed by taking "wipe" samples of the immediate area. Personnel movement should be controlled to avoid spread of any radioactive contamination. Whenever a source is damaged, personnel working in the area should undergo a thyroid scan to assure that they have not been contaminated by contact, ingestion, or inhalation of Iodine-125.

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Application to Patient

I-125 Seeds in Carrier should be used only by individuals 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.

WHEN CUTTING THE CARRIER MATERIAL TO THE DESIRED LENGTH DURING IMPLANTATION, CARE MUST BE TAKEN TO AVOID CRUSHING OR RUPTURING AN I-125 SEED. Radiation detection equipment capable of detecting 30 keV X-rays should be available whenever I-125 Seeds in Carrier is being handled.

All practical physical protection should be provided during the implantation procedure. Frequently, however, protective barriers are not practical in the surgery. In this circumstance, operators must rely upon distance and speed to minimize radiation exposure.[4]

Treatment of Patient

All patients should be informed of the nature of I-125 Seed implants and the expected period of time during which radiation precautions will be necessary. Patients, their close associates, and associated medical personnel should be instructed in the necessary radiation safety procedures required for someone who has received an I-125 Seed implant. Guidelines for necessary precautions have been established by National Council on Radiation Protection and Measurements and are detailed in NCRP Reports.[4,5,6,7,8]

All patients should be advised of the possibility that, during a course of treatment, one or more I-125 Seeds might slough off and become detached as a tumor regresses and becomes smaller. Under these circumstances, any bandages or linens which come into contact with the site of the implant should be scrutinized for small metallic seeds (1/4 of an inch long). Patients should be advised that whenever seeds are found, they should be picked up with a spoon and placed in a jar or other container, and placed in an inaccessible area in the home. The radiation center should be notified of such an event as soon as possible after its occurrence.

Accountability/Disposal

Iodine-125 is an accountable radioactive material. I-125 Seeds in Carrier should, therefore, be strictly controlled and stored in a locked safe. If any significant material cannot be accounted for, the loss must be reported to the federal or state licensing agency.

When disposal is indicated, I-125 Seeds in Carrier should be transferred to an authorized radioactive waste disposal agency. I-125 Seeds should never be disposed of in normal waste.

An I-125 Seed disposal service is provided by 3M Radiation Therapy Products. Customers wishing to dispose of I-125 Seeds in Carrier in this manner must contact the 3M Company for approval and specific shipping container and forms.

Material approved for return must comply with Department of Transportation regulations (49 CFR Parts 171-177) regarding packaging and labeling. Shipments are to be directed to: 3M/Radiation Therapy Products, TCAAP Building 590, New Brighton, Minnesota, 55112.

Leak Testing

I-125 Seeds are leak tested prior to loading in Carrier and the results are shown on the shipment identification papers which accompany each shipment.

ADVERSE REACTIONS

No adverse reactions involving I-125 Seeds in Carrier have been reported.

DOSAGE AND ADMINISTRATION

The total activity of I-125 Seeds in Carrier required for any given treatment depends upon the tumor volume and the previous radiation history of the tumor site. Established practice[11] should be followed for the calculation of the total activity to be implanted, the proper placement of the sources within the tissue, and the evaluation of the radiation dose distribution achieved.

Dose distribution around each individual seed is not isotropic.[10] This anisotropy should be accounted for in dose distribution calculations.

Iodine-125 has a 60.2 day half-life. Decay corrections must be made in order to calculate properly the activity of the seeds on the day they are implanted. Seeds are movable within the carrier to enable the practitioner to establish the correct seed-to-seed spacing based on the isotopic decay curve.

Directions for Use

I-125 Seeds in Carrier is supplied with an attached surgical needle. With the patient appropriately anesthetized, a qualified practitioner may place the seeds in carrier throughout the tumor volume according to a preplanned geometric arrangement. The implantation of I-125 Seeds in Carrier does not require use of conventional I-125 Seed applicators.

HOW SUPPLIED

I-125 Seeds in Carrier is available sterile with an activity per seed of 0.20 to 1.0 mCi comp. The product is supplied as a group of 10 seeds with the same nominal activity spaced at a fixed distance of 1.0 cm

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within a braided, synthetic, absorbable carrier. Other configurations of I-125 Seeds in Absorbable Carrier (with the number of seeds varying up to 20 at interseed distances of 0.5 to 1.5 cm) are available upon special request.

I-125 Seeds in Carrier is packaged within a stainless steel shielding ring in a moisture-resistant foil wrapper, which is subsequently enclosed in a breathable Steri-lok® BAG. A label is attached to the Steri-lok bag which indicates the isotope, amount of activity, number of seeds, and assay date.

I-125 Seeds in Carrier is sterile when shipped.

LICENSING

I-125 Seeds® are licensed by the U.S. Nuclear Regulatory Commission for distribution to persons licensed pursuant to §§35.14 and 35.100 Group VI of 10 CFR Part 35 or under equivalent licenses of Agreement States.

Federal law restricts this device to sale by or on the order of a physician.

REFERENCES

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