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Medical Products Division/3M

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3M

May 30, 1979

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

Re: Control No. 99111

Dear Mr. DelMedico:

Backup info in a Supplemental File on the same shelf as license

This letter is to provide additional information in support of our license amendment application regarding the distribution of I-125 Seeds. Included in this information, as Part A, are responses to questions and concerns noted in your letter of May 11, 1979. Responses to requests made by Mr. Earl Wright, following the sealed source review, are presented as Part B.

PART A

REQUEST 1

Please submit actual color samples (not photocopies) of all labels that you will use to comply with the provisions of 10 CFR 32.72 and 10 CFR 20.203.

Response

Actual color samples of all labels which will be used in the packaging the labeling of I-125 Seeds to comply with the provisions cited are presented in Attachment I of this submission. These printed labels, including one vial label and two labels to be affixed to lead storage containers for the models 6701 and 6702, respectively, replace photocopies of labels originally submitted on pages 15 and 17 of the March 15, 1979, license amendment application.

REQUEST 2

The radiation safety instructions provided in your package insert are scattered among several headings and do not appear to follow a logical format. For example, instructions concerning adequate shielding for personnel appear underneath a paragraph warning that the seeds are not sterile. Instruction for personnel monitoring then appear four paragraphs later.

The information and instructions that your package insert provides concerning radiation safety should be organized into specific procedures that follow a

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logical sequence and that are organized under an appropriate subheading.

In his sealed source review, Mr. Wright has requested greater emphasis on warning against direct contact with the sources. Your revised instructions should reflect this emphasis. You should consider the use of bold face type, etc.

The revised instructions should also include detailed information for maintaining radiation safety precautions (e.g., shielding, distance, use of forceps) during the various types of sterilization processes. The special emphasis on temperature and pressure limitations requested by Mr. Wright might logically be included with this information.

Please revise your package insert such that it includes the information requested above and resubmit it for review.

Response

The package inserts, provided in the March submission, contained information on I-125 Seeds in a format and order recommended by the U.S. Food and Drug Administration. Because I-125 Seeds are regulated by FDA as a medical device, we have continued to follow this format and order in a general way in revising the text, on the basis of comments resulting from your review.

With regard to the observation that radiation safety instructions are scattered among several headings, we have gathered this type of information under a single heading entitled 'Precautions'. This section contains instructions previously presented in the insert under the headings 'Leak Testing' and 'Returns'. In addition, we have organized information within the 'Precautions' section into specific procedures, identified by subheadings, which we believe follow a logical sequence with respect to clinical application of the product. These subheadings include Preparation for Use/Sterilization, Application to Patient, Treatment of Patient, Accountability/ Disposal, and Leak Testing.

In response to Mr. Wright's request pertaining to warning against direct contact, the following paragraph, which places greater emphasis on this warning, has been added to the 'Precautions' section under Preparation for Use/Sterilization.

> All manipulations involving I-125 Seeds 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 should be handled only with forceps, with as much distance as practical between sources and the operator. I-125 SEEDS SHOULD NOT BE PICKED UP WITH THE HANDS.

In addition, instructions have been revised, as requested, to provide additional information for maintaining radiation safety precautions during sterilization processes. These instructions have been organized into the following paragraphs.

> I-125 Seeds are NOT sterile when shipped and as such must be sterilized with steam (autoclave) or ethylene oxide (EO) before implantation. Regardless of the method selected, I-125 Seeds should be placed in an adequately shielded container prior to placement in the sterilization chamber. Manipulation of the seeds prior to or following sterilization should be carried out behind

shielding of such size and thickness as will adequately shield the operator. In addition, I-125 Seeds should be handled only with forceps, with as much distance as practical between sources and the operator. Autoclaves should be equipped with traps or other means to prevent seed loss through the drain hole.

I-125 Seeds have been designed to withstand normal autoclave temperature and pressure variations from 121°C at 30 PSI to 138°C at 50 PSI. I-125 SEEDS ARE NOT INTENDED TO BE STERILIZED USING DRY HEAT AND SHOULD NOT BE SUBJECTED TO TEMPERATURES AND PRESSURES IN EXCESS OF THESE LIMITS (138° C and 50 PSI).

Copies of the package inserts for I-125 Seeds, models 6701 and 6702, which have been revised as described above, are presented in Attachment II of this submission. This replaces information originally submitted on pages 22-31 of our March 15, 1979, license amendment application.

REQUEST 3

Please submit a sample of the instructions and forms that you supply to individuals who return iodine-125 seeds to your company. Also, please describe the container that you provide for this service.

Response

The information which is supplied to individuals wishing to return I-125 Seeds 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 presented in Attachment III of this submission.

The container which will be supplied to customers for return of seeds is a lead "pig", a schematic diagram for which is presented on page 16 of our March 15, 1979, license application amendment.

REQUEST 4

Your promotional brochure on iodine-125 seeds indicates that the seeds may be used in surface applicators, particularly for treatment of intraocular tumors. This section should caution that persons licensed by the Nuclear Regulatory Commission pursuant to Sections 35.14 and 35.100 Group VI of 10 CFR Part 35 or under equivalent licenses of Agreement States may use iodine-125 seeds only for interstitial treatment of cancer.

The promotional brochure also states that NRC has classified iodine-125 seeds as a "well established clinical procedure". You should substitute the licensing statement specified in 10 CFR 32.74 (a) (3) in place of this information.

Please describe the changes that you will make in your promotional brochure to fulfill the needs identified above.

Response

Two text changes, described below, will be made in the promotional brochure for I-125 Seeds at its next printing (anticipated during the fourth quarter), to fulfill the needs identified in this request.

1. The section entitled 'Surface Applicators' is being revised, by the addition of the suggested text, to read:

   The success of I-125 Seeds in permanent implants has led to investigations of iodine-125 in surface applicators, particularly for treatment of intraocular tumors[8]. At this time, however, persons licensed by the Nuclear Regulatory Commission pursuant to Sections 35.14 and 35.100 Group VI of 10 CFR Part 35 or under equivalent licenses of Agreement States may use iodine-125 seeds only for interstitial treatment of cancer.

2. The first paragraph in the section entitled 'Licensing' is replaced by the following statement.

   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.

With regard to point 5 of the letter, we understand that the promotional brochure has been submitted for review to the advisory committee on the Medical Use of Isotopes.

PART B

REQUEST 1

A description of the method to be used for identification of seeds with respect to contained activity. (For example Appendix D of NCRP No. 40 discusses a procedure for using gold plating for identifying activity).

Response

I-125 Seeds are supplied as a group of seeds with an assay within a stated activity range on the assay date. The group of seeds is identified with respect to contained activity by a label affixed to the glass, screw-cap vial in which they are contained. A sample of this vial label is presented in Attachment I of this submission.

I-125 Seeds are not identified individually according to contained activity. Although we have considered at length identification systems, in addition to group labeling, nevertheless we have concluded, for reasons discussed below, that none of these systems is a feasible addition to our current method.

The primary argument against color-coding, electroplating, or engraving I-125

Seeds is the dynamic nature, specifically the 60-day half-life, of their contained isotope. Whereas radioactive decay is of no practical concern in the color coding of radium needles, as described in Appendix D of NCRP No. 40, because of the 1620 year half-life of radium - 226, such decay is critical when considering an identification system for I-125 Seeds.

Let us assume that a color coding system were established for I-125 Seeds. As noted in our March 15, 1979, license amendment application, I-125 Seeds are supplied to customers in groups of seeds with a stated activity range, the size of which is typically 0.05 mCi. Suppose that a group of seeds having a labeled activity range of 0.50 - 0.54 mCi were identified by coloring them green. Eight days later, the seeds would have fallen, by radioactive decay, into the next lower activity range, 0.45 - 0.49, which we had previously chosen to color red. As a result of this decay, I-125 Seeds, although correctly labeled at the time of their manufacture, would frequently be color-coded incorrectly with respect to contained activity by the time they were shipped to customers. This would constitute a misbranding situation.

Radioactive decay of the seeds would continue following shipment. I-125 Seeds may be inventoried for several week following their receipt by the Radiation Therapist. In this situation, it would be necessary for the therapist to determine the activity of seeds at the time of use, by applying the correct decay factor (supplied in the package insert) to the assigned I-125 Seed activity and assay date, as stated on the vial label and certification sheet included with the shipment.

An alternative to color-coding or electroplating which we have considered is the engraving or stamping of individual seeds with an identification code. We do not believe this is feasible because of the small physical dimensions of the seed. Furthermore, it is felt that engraving might reduce the integrity of the thin (0.051 mm) seed wall, thereby jeopardizing seed contents.

For reasons discussed above, and because we believe that the extra handling required to identify 500 or more seeds per day on an individual basis would result in undue radiation exposure to manufacturing personnel, we feel that our existing seed assay method (i.e. dividing seeds into various assay ranges) and packaging and labeling methods are adequately controlled to assure receipt by our customers of properly identified seeds.

REQUEST 2

Results of impact and percussion tests of prototype sources conducted per ANSI N44.1-197 (see ANSI N44.1 paragraphs 4.2.2 and 4.2.3).

Response

As requested, I-125 Seeds have been subjected to prototype tests for impact and percussion, described in ANSI N44.1-1973, paragraphs 4.2.2 and 4.2.3, respectively. These tests, identified as D and E, are in addition to those three described on pages 07 - 10 of our March 15, 1979, license amendment application.

Following the test procedures, I-125 Seeds were subjected to a leak test, according to a procedure outlined on page 07 of the March submission.

The two additional tests, and resulting experimental data, are described below. Seeds evaluated were of the model 6701 configuration, with separate seeds evaluated in each test procedure.

D. Impact Test

Each I-125 Seed was positioned above a 30-foot (9.1 meter) length of hollow, 5/8" (inside diameter) conduit, constructed from 3 - 10 foot lengths coupled with metal connectors. This was necessary to avoid loss of small (~1/4") sources. Each seed was then dropped vertically, through the tubing, onto a 9 x 12 x 1.5 cm thick steel plate. Following the test, each seed was visually inspected for damage and then dropped into a 1 dram vial containing 3 ml of wash solution, and assayed for removable radioactivity.

No damage to the seeds, such as bending or denting, was observed. Data tabulated below indicate that the I-125 Seeds maintain their integrity under the conditions of the impact test.

TABLE 4. Results of Impact Testing of I-125 Seeds

Sample No.	Lot No.	Activity(mCi)	Removable Activity*
1	010	0.35-0.39	1.8×10^{-6} µCi
2	010	0.35-0.39	0 µCi
3	010	0.35-0.39	1.4×10^{-6} µCi

*Determined following 20 hours' soak in wash solution. "0µCi" indicates that the removable activity was indistinguishable from background.

E. Percussion Test

Each I-125 Seed was positioned horizontally on a 1.5 cm thick lead plate, which was supported by an aluminum plate resting on a tile floor. A 2.5 cm (diameter) steel rod weighing 1.42 kg was dropped vertically on the seed, positioned in the center of the impact circle, from a height of 1 meter. Following the test, each seed was inspected for damage, then dropped into a 1 dram vial containing 3 ml of wash solution, and assayed for removable radioactivity.

Visual inspection indicated that the seed configuration was altered significantly by the test (see attached photograph). The central portion of the seed, between the end welds, was crushed flat except for a slight elevation at the location of the gold ball contained within. The end welds did not appear to lose their integrity (i.e. separate from the titanium can). The crushed seed left an impression in the lead plate.

Data tabulated below indicate that the I-125 Seeds maintain their integrity under the conditions of the percussion test.

TABLE 5. Results of Percussion Testing of I-125 Seeds

Sample No.	Lot No.	Activity(mCi)	Removable Activity*
1	010	0.35-0.39	0 μCi
2	010	0.35-0.39	1.4×10^{-6} μCi
3	010	0.35-0.39	0 μCi

*Determined following 20 hours' soak in wash sholution. "0 μCi" indicates the removable activity was indistinguishable from background.

REQUEST 3

Clarification of the quality control procedures to be used. For example include copies of mil. STD 105 and explain how it is used in your quality control program.

Response

A copy of Military Standard (Mil. Std.) 105D (29 April 1963), entitled Sampling Procedures and Tables for Inspection by Attributes, is presented in Attachment IV of this submission. Published by the Department of Defense, this document provides a description of defect classification, definitions of terms associated with sampling and inspection, sampling plans, and statistical reference tables.

Mil. Std. 105D is used in our quality control program to determine the sample size (number of I-125 Seeds) to be tested for each lot of material produced. In addition, the document provides, in the reference tables, information which allows us to make a statistically-based Accept-Reject decision for the lot. The following example illustrates in more detail these operations, which are performed for all Quality Control procedures involving I-125 Seeds.

Assume that a lot consisting of 2465 I-125 Seeds is to be visually inspected for uniform welds with no holes. The test procedures described on page 13 of our March 15, 1979, license amendment application indicates that the sample size is to be determined according to Mil. Std. 105, Level II, AQL 1.0. The first step is to determine the sample size code letter from Table 1 of the document; for a Level II inspection of the specified lot size, the proper code letter is "K". Using this information, we proceed to Table II-A, Single Sampling Plans for Normal Inspection. The sample size code letter "K" in the first column of this table corresponds to a sample size of 125, as read from the adjacent column.

Using the same table and reading across from "K" to the column headed "AQL 1.0", we observe Acceptance-Rejection numbers of 3 and 4, respectively. This means that if 3 or less defective seeds are found in the representative sample of 125 seeds, the lot is considered to meet the test specification, and hence, is accepted. However, if 4 or more defective seeds are found, the specification is not met and the lot is rejected. If this occurs the entire lot is returned to production personnel for a 100% visual inspection (retest), and then subsequently resubmitted to Quality Control for sampling and testing, as described above.

REQUEST 4

Copies of instructions to users which have been revised to forcefully state precaution to avoid direct handling of the seeds and temperature limitations for use. We have noted that your temperature tests data shows that the iodine absorbed into the Dowex resin begins to volatize at temperatures above 250°C. Users should be instructed to avoid temperatures in excess of a temperature range you consider acceptable to prevent volatilization. Is it possible for autoclave temperatures to exceed this temperature either under normal or abnormal conditions?

Response

Radiation safety instructions to users have been revised, as requested, 1) to caution against direct handling of seeds, and 2) to state more forcefully temperature limitations for their use. The specific text changes pertaining to these cautions are presented below and, in addition, are discussed, along with other revisions in the 'Precautions' section of the package insert, in response to Request 2, Part A above.

> All manipulations involving I-125 Seeds 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 should be handled only with forceps, with as much distance as practical between sources and operator. I-125 SEEDS SHOULD NOT BE PICKED UP WITH THE HANDS.
>
> I-125 Seeds have been designed to withstand normal autoclave temperature and pressure variations from 121°C at 30 PSI to 138°C at 50 PSI. I-125 SEEDS ARE NOT INTENDED TO BE STERILIZED USING DRY HEAT AND SHOULD NOT BE SUBJECTED TO TEMPERATURES AND PRESSURES IN EXCESS OF THESE LIMITS (138°C and 50 PSI).

Normal autoclave conditions would not exceed the temperature and pressure limitations noted above. In the event that an autoclave malfunctioned, however, the water contained therein would evaporate, resulting in a pressure drop to one atmosphere and an increase in temperature. To the best of our knowledge, this temperature would not exceed 250°C, at which temperature the integrity of the source is not compromised. We base this on results of our temperature tests, which you cite, which indicate that, although volatilization of iodine-125 begins at temperatures of 250°C, nevertheless the integrity of the titanium can is retained, and no iodine-125 is detected in routine leak tests of the sources.

With regard to point 5 of sealed source review, it is our understanding that, although models 6701 and 6702 fail to meet the 800°C temperature requirement of ANSI 44.1, nevertheless that requirement was not intended to apply to I-125 Seeds.

In addition to these five written points pertaining to the sealed source evaluation, Mr. Wright, in his telephone conversation of 4/27/79 with Mr. R. Wissink of 3M, requested several copies of our promotional brochure for use in preparation of NRC's certificate of registration. Please be advised that five copies of the brochure are included as an enclosure to this letter.

In addition to these points raised following NRC review of our March 15, 1979, license amendment application, we have noted, in reviewing the submission, that

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the model 6702 I-125 Seed was incorrectly described with respect to the number of resin spheres contained within the titanium capsule. Instead of three resin spheres, as stated on page 04, a model 6702 I-125 Seed consists of a cylindrical titanium capsule containing three to five resin spheres with adsorbed iodine-125, welded at both ends. A schematic diagram of the model 6702 seed, which accurately reflects this construction, is presented in Attachment V of this submission. This diagram replaces that originally submitted on page 06 of the March 15, 1979, application.

If there are additional questions or requests for information, please feel free to contact me (612/733-6421). Your continued expeditious review of this application is appreciated.

Sincerely yours,

Jacquelyn D. Bush

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JDB/
Enclosures

c: E. G. Wright
Procedures and Certification Branch