MILLS BIOPHARMACEUTICALS INC.

120 N.E. 26TH STREET
OKLAHOMA CITY, OKLAHOMA 73105
405-525-3141
405-5253143 Fax

June 29, 2001

John Jankovich, Ph. D. , Sr. Engineer
Materials Safety and Inspection Branch
Division of Industrial and
Medical Nuclear Safety
Office of Nuclear Materials Safety
And Safeguards

SUBJECT: June 15, 2001 letter requesting additional information on Model Pd-103 seeds

Dear Dr. Jankovich:

Additional information requested.

1. Engineering Design:

1.1. Please clarify the physical dimensions both for the I-125 seeds and for the Pd-103 seeds. Specifically, Registration Certificate No. NR-1081-S-101-S, dated December 1, 1999, authorized I-125 seeds to be manufactured with the external dimensions of 4.9 mm in length and 0.96 mm in diameter with a wall thickness of 0.06 mm. The application states these dimensions as 4.5 mm, 0.8 mm, and 0.05 mm respectively. Please confirm that (a) the dimensions of the I-125 seeds will be manufactured with the latter dimensions.

Response: The I-125 and the Pd-103 seeds will be manufactured to 4.5 mm, 0.8 mm, and 0.05 mm nominal external dimensions.

1.2. Please clarify the number of seeds both in the I-125 and Pd-103 models. The Registration Certificate No. NR-1081-S-101-S, dated December 1, 1999, authorized the use of three to five I-125 seeds. Your application stated, "all models have five silver seeds." Please clarify the discrepancy. If you always use five seeds, but some of the seeds are inert for spacing purposes within the capsule, please state so.

Response: Both I-125 and Pd-103 models contain five silver spheres. All silver spheres are coated with radioactivity, i.e. we do not manufacture the sources with inert spheres for spacing purposes.

1.3. Please clarify the maximum activity for the Model 125SH I-125 seeds. The Registration Certificate No. NR-1081-S-101-S, dated December 1, 1999, authorized a maximum activity of 5.55 GBq (150 millicuries). You have also committed to such a maximum value in your letter dated October 1, 1999. However, the application shows a maximum activity of 5.55 GBq (150 millicuries) + 10%. Do you intend to increase the maximum activity with 10% for I-125? If so, please provide information that the design is sufficient for such an activity regarding capsule design, capsule testing, and radiation protection.

Response: No. The maximum activity is 5.55 GBq (150 millicuries).

1.4. Please confirm that the maximum activity for the Palladium Model 103SH is 185 MBq (5 millicuries) + 10%.

Response: The maximum activity is 185 MBq (5 millicuries). This will provide consistency between the I-125 and the Pd-103 sources as to the maximum limits of activity.

2. FDA Approval: Please provide a copy of FDA Form 510(k) or pre-market approval form FDA for the Pd-103 models. Please note that without FDA approval, NRC cannot issue a registration certificate for the Pd-103 seeds.

   Response: We have submitted the 510(k) to the FDA and have received a 510(k) number (K011427) see attached letter dated May 09, 2001. Mills Biopharmaceuticals, Inc. commits and confirms that no product will be placed into commercial distribution until both the U.S. NRC and the U.S. FDA has approved thru the Registration Certificate (U.S. NRC) and Premarket Notification in accordance with Section 510(k)(FDA).

   Please note that the U.S. FDA would not approve the 510(k) for I-125 seeds until either we made the above statement or sent your approval to the U.S. FDA.

3. Labeling: Please confirm that the label materials and the placement of labels are identical to those for the I-125 models.

   Response: The labeling materials and the placement of labels are identical to those for the I-125 models.

4. Conditions of Use:

   4.1. Please state the working life for the sources, i.e. the length of time that the Pd-103 sources may be used. Please provide information similar to what you have provided for the I-125 seeds in your letter dated October 1, 1999.

   Response: Therapeutic brachytherapy seed sources are designed for permanent implantation and therefore remain in the patient indefinitely. Therefore, post implantation the working life of the source is best characterized as indefinite. Pre implantation the working life of the source is based upon the sources ability to provide effective therapeutic radiation. Based upon these criteria the working life should be classified as 170 days or 10 half-lives pre implantation.

   4.2. Please specify the maximum temperature and pressure for sterilization or autoclaving.

   Response: Sources are designed to be sterilized using ethylene oxide or steam autoclaves at normal autoclave temperature and pressure variations up to 138° C (280° F) and 35 psi (241.3 kPa).

5. Prototype Testing: Please describe the prototype tests that you have conducted on your Pd-103 models and provide the test results. IF no prototype tests were conducted, please specify in detail the operational experience, including failures or leaks, with your I-125 models and explain why the operational experience is applicable to the Pd-103 models.

   Response: The two models (I-125 and Pd-103) are constructed identically from the same titanium, silver spheres, assembly, and welding processes. Although the production lines are different the equipment design, construction, and operation are for all intent and purposes identical. Therefore, the sources are identical except for the radioisotope. We have been producing the I-125 models for almost two (2) years without a source failure or leak. We believe the operational experience with the I-125 models; design similarities to the I-125 models, and manufacturing process similarities to the I-125 models indicate the Pd-103 models will have an equivalent robust character.

6. Quality Assurance: The application showed that the leak test period is to be reduced from 18 hours to 4 hours. Please delineate the rationale for the change and provide data that support the change.

Response: We have been producing the I-125 models for almost two (2) years without a source failure or leak. See also response to number 5 above. The American National Standard for leak-testing radioactive brachytherapy sources ANSI N44.2-1973 recommends a four hour testing procedure on page 10 under the Appendix and is provided as follows:

A1.3 Immersion Test (2). To minimize radioactive contamination of the apparatus used in the immersion test, the source should indicate less than 50 nanocuries of removable contamination by the wipe test (see A1.2) prior to immersion testing. Immerse the source in a solvent, which will not attack the material of which the outer surface of the source is made and, which under the conditions of this test, has been demonstrated to be effective in removing the radionuclide involved. Examples of such solvents include distilled water and weak solutions of detergents or chelating agents. Heat the solution to 50° C + 10° C and keep it at this temperature for at least 4 hours. Remove the source and measure the total activity in the solvent using appropriate radiation detection equipment. This test is not appropriate for testing sources containing radium (see Section A2).

7. Instructions to Users: Please provide a user manual or instructions that includes the Pd-103 models.

Response: See Attached. Please note that the attached package insert was submitted to the U.S. FDA and could change pursuant to changes requested by their review.

Sincerely,

Stanley L. Mills, Ph.D., R.Ph.
President and CEO

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

May 09, 2001

MILLS BIOPHARMACEUTICALS, INC.
120 N.E. 26TH ST.
OKLAHOMA CITY, OK 73105
ATTN: DR. STANLEY MILLS

510(k) Number: K011427
Received: 08-MAY-2001
Product: MBI PD-103 SL; MBI PD-103 SH

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

On January 1, 1996, FDA began requiring that all 510(k) submitters provide on a separate page and clearly marked "Indication For Use" the indication for use of their device. If you have not included this information on a separate page in your submission, please complete the attached and amend your 510(k) as soon as possible. Also if you have not included your 510(k) Summary or 510(k) Statement, or your Truthful and Accurate Statement, please do so as soon as possible. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers Assistance (DSMA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the Document Mail Center will not be considered as part of your official premarket notification submission. Because of equipment and personnel limitations, we cannot accept telefaxed material as part of your official premarket notification submission, unless specifically requested of you by an FDA official. Any telefaxed material must be followed by a hard copy to the Document Mail Center (HFZ-401).

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Staff
Office of Device Evaluation
Center for Devices and Radiological Health

Brachytherapy Sources in an appropriate container and the plastic cap on the glass vial should be removed to allow steam or ethylene oxide to access the Pd-103 Brachytherapy Sources.

Pd-103 Brachytherapy Sources Storage and Disposal

For disposal, Pd-103 Brachytherapy Sources should be transferred to an authorized radioactive waste disposal agency. Radioactive Pd-103 Brachytherapy Sources should never be disposed in normal waste. We provide Pd-103 Brachytherapy Source disposal service to our U.S. customers as a separate service. Customers wishing to use this service should contact us. We will **NOT** accept any Pd-103 Brachytherapy Sources for disposal without prior approval. In general, material approved for return must comply with Department of Transportation regulations (49 CFR Parts 171-177) regarding packaging and labeling. You, as the shipper, are responsible to see that these regulations are met.

Licensing

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

Specifications: Pd-103 Brachytherapy Sources

Model:	**103SL and 103SH**
Dimensions	4.5 mm long, 0.8 mm OD, 0.05 mm wall nominal
Encapsulation	titanium
Carrier for Pd-103	silver spheres 0.5 mm diameter nominal
X-ray Marker	Silver spheres
Photon Energies	Characteristic X-rays at 20-23 keV
Assay Method	Well re-entrant chamber calibrated using an Pd-103 Brachytherapy Source Standard of the same Model which is traceable to the NIST.
Exposure Rate	1.293 $\mu Gy\ m^2\ /h$ = mCi
Source Strength	Apparent activity in mCi or MBq and air kerma strength. These are descriptive of output and not contained activity. Attenuation of titanium and internal components is approximately 55%.
Source Strengths	0.37 MBq to 185 MBq or (0.1 mCi to 5.00 mCi)

Revision: FO-.00
Date: 30 Apr 2001

Pd-103 Brachytherapy Sources
Model 103SL & 103SH
for Interstitial Radiation Therapy

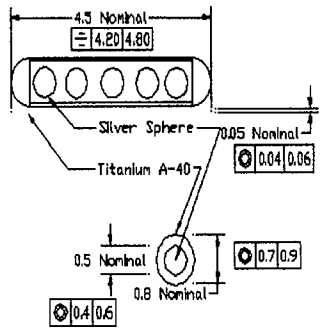
Manufactured By:
Mills Biopharmaceuticals, Inc.
120 N.E. 26th Street
Oklahoma City, Oklahoma 73105
405-525-3141 FAX: 405-525-3143

General Information

Description

Pd-103 Brachytherapy Sources

Nominal dimensions are 4.5 mm in length and 0.8 mm in diameter. The cylindrical metal casing is titanium having a nominal wall thickness of 0.05 mm laser welded at both ends. Both model 103SL and 103SH contain silver spheres, which are coated with palladium-103 and provide X-ray contrast.



How Supplied

Pd-103 Brachytherapy Sources are available with apparent activities from 3.7 MBq (0.1mCi) to 185 MBq (5.0 mCi) of Pd-103 per Brachytherapy Source. Pd-103 Brachytherapy Sources are labeled with apparent activity ranges in MBq-GBq; total activity in MBq-GBq; assay date; number of Pd-103 Brachytherapy Sources and Pd-103 Brachytherapy Source lot number. The sources are contained in a lead "vial shield" similarly labeled. The shield label has precautionary regulatory statements pertaining to licensing of the Pd-103 Brachytherapy Sources.

Indications

Pd-103 Brachytherapy Sources with apparent activities between 3.7 MBq (0.1 mCi) to 78 MBq (2.11 mCi) are indicated for permanent interstitial treatment of tumors which are unresectable or residual after excision of the primary lesion, localized, slow growing, and exhibit low to moderate radiosensitivity. Intra-abdominal, intrathoracic and superficial tumors may be treated with Pd-103 Brachytherapy Sources containing apparent activities within this range. Tumors commonly treated are prostate (early stage), pancreas, head, neck, and lung.

Pd-103 Brachytherapy Sources, containing apparent activities greater than 78 MBq (2.11mCi), are indicated for temporary interstitial treatment of tumors which are unresectable or residual after excision of the primary lesion, localized, and exhibit moderate radiosensitivity. Temporary implants are indicated in breast, brain and eye tumors.

Pd-103 Brachytherapy Sources are indicated for treatment of residual tumors and recurrent tumors following external radiation therapy, hyperthermia, or chemotherapy or concurrent with these treatment modalities.

Implant Devices

Permanent implants: Pd-103 Brachytherapy Sources are implanted using an Pd-103 Brachytherapy Source "applicator" attached to a 18 gauge or larger needle. Temporary implants: Pd-103 Brachytherapy Sources are usually loaded into plastic tubing or other devices (e.g., eye plaques) to facilitate afterloading procedures and Pd-103 Brachytherapy Source recovery.

Pd-103 Brachytherapy Source Dosimetry, Implant Activity and Number

This device is to be administered to humans by physicians licensed to dispense drugs in the practice of medicine. Each physician should use established practices for the calculation of the total activity to be implanted, number of seeds, and placement of seeds. Considerations should be given to the tumor volume, previous/current radiation history, physical parameters associated with this Pd-103 Brachytherapy source, and patient specific information to determine the appropriate dosage. Dose distribution around Pd-103 Brachytherapy Sources is not isotropic. This anisotropy should be included in dose distribution calculations.

Physical Properties

Titanium encapsulation of Pd-103 Brachytherapy Sources insures good tissue compatibility and minimal self-absorption of the low-energy photons. Palladium-103 has a half-life of 16.99 days and decays by electron capture with the emission of characteristic x-rays at 20-23 keV and Auger electrons. The titanium wall absorbs the electrons. Table 1 shows the decay of Palladium-103.

Table 1. Palladium-103 Decay Table

Days	Decay Factor	Days	Decay Factor	Days	Decay Factor	Days	Decay Factor
1	0.9600	9	0.6927	17	0.4998	25	0.3506
2	0.9216	10	0.6650	18	0.4798	26	0.3462
3	0.8848	11	0.6384	19	0.4606	27	0.3324
4	0.8494	12	0.6129	20	0.4422	28	0.3191
5	0.8155	13	0.5884	21	0.4245	29	0.3063
6	0.7829	14	0.5649	22	0.4076	30	0.2941
7	0.7516	15	0.5423	23	0.3913	31	0.2823
8	0.7215	16	0.5206	24	0.3756	32	0.2710

Radiation Safety

Radiation Protection

The 20-23 keV photons of palladium-103 are substantially absorbed by a high Z material, but exhibit desirable penetration in tissue. Pliable thin lead sheet 0.25 mm (0.01 inches) reduces the external exposure by > 99.9%.

Always wear a film badge, use long reverse pressure forceps or tongs, lead shielding, and leaded glass "L" shields when handling or storing Pd-103 Brachytherapy Sources. Survey the preparation area with an appropriate survey meter while checking, unpacking, handling and processing Pd-103 Brachytherapy Sources. It is important to maintain an accurate Pd-103 Brachytherapy Source count. In the case of a loss of a Pd-103 Brachytherapy Source(s), or accidents involving a Pd-103 Brachytherapy Source(s), report the event immediately to the appropriate regulatory authority. Reduce your handling time, increase your distance from the source, and use shielding when possible to reduce your radiation exposure.

Quality Assurance

Inspection

Each Pd-103 Brachytherapy Source is visually inspected, gauged for proper length and diameter, cleaned and leak tested, assayed (and assigned to an assay range) prior to shipment.

Leak Testing

Pd-103 Brachytherapy Sources are leak tested prior to shipment and have passed a leak test showing <0.005 μCi of removable palladium-103. This leak test value is printed on the Certification form that accompanies each shipment. For Palladium 103, leak testing at 6 months is not required due to the short half-life (17days). The licensee shall, however, test each such source for leakage before any reuse or transfer. Either of the following procedures are recommended: 1) Soak Test-Immerse the seed in water or EDTA solution at 50 degrees centigrade for at least 4 hours and measure the activity in the liquid. 2) Wipe (Swab)Wipe the external surfaces of the seed with a premoistened absorbant material such as cotton swab or filter paper. The activity removed is measured.

Calibration

Each production Pd-103 Brachytherapy Source is measured by comparison in a fixed geometry with a Pd-103 Brachytherapy Source of the same model which has been calibrated by the NIST. For this comparison, we use a well re-entrant ionization chamber. NIST reports air kerma strength of Pd-103 Brachytherapy Source standards in units of micrograys meters squared per hour (μGy m^2/h) with an overall uncertainty of about +/- 5%.

Prior to using the NIST Pd-103 Brachytherapy Sources for calibration, we convert the stated air kerma strength into "apparent activity" in mCi using an equivalence of 1 mCi (apparent) = 1.293 U (μGy m^2h). Apparent activity is a measure of output and not contained activity. Following calibration, each Pd-103 Brachytherapy Source is assigned to one of several activity ranges.

Additional Information

Warnings

Pd-103 Brachytherapy Sources Intended for Permanent Implant

Do not force a Pd-103 Brachytherapy Source into (or from) any implant tube, needle, or cartridge; doing so may damage the wall or end, potentially causing release of palladium-103 into the environment and into body fluids should the Pd-103 Brachytherapy Source be implanted. If visibly damaged in any way, discard it immediately to radioactive waste and check the area for contamination.

UNDER NO CIRCUMSTANCES SHOULD YOU IMPLANT VISIBLY DAMAGED Pd-103 BRACHYTHERAPY SOURCES.

Contraindications

It is **not** recommended that Pd-103 brachytherapy sources be implanted in tissue sites where structural instability might lead to source migration.

Adverse Reactions

Reported adverse events associated with brachytherapy include but are not limited to impotence, urinary incontinence, proctitis, transient dysuria and increased urinary frequency.

Pd-103 Brachytherapy Sources Intended for Temporary Implant and Reuse

Use a vented chemical hood, which has adequate airflow up the stack and a filtered exhaust when loading, or removing the Pd-103 Brachytherapy Sources from plastic or rubber afterloading catheters. If a chemical hood is not available, a plastic glove box specifically designed for work with radioactive iodine may be substituted provided it is properly vented. If a razor blade, scalpel, or other sharp tool is used to remove Pd-103 Brachytherapy Sources, avoid contacting or cutting a Pd-103 Brachytherapy Source. The potential exists for all Pd-103 Brachytherapy Sources, which are damaged (nick, cut, slice, or other type of damage) to release Palladium-103 into the environment.

To assure that Pd-103 Brachytherapy Sources have not been damaged following removal from the afterloading catheters, a contamination survey should be conducted using a radiation monitor capable of detecting 20-23 keV photons. This survey should include wipe (or leak) tests of Pd-103 Brachytherapy Sources and an overall area survey.

Pd-103 Brachytherapy Sources Sterilization

Pd-103 Brachytherapy Sources and Applicator Magazine Cartridges are NOT sterile when shipped. Before implantation, they must be sterilized using steam or ethylene oxide (EtO).

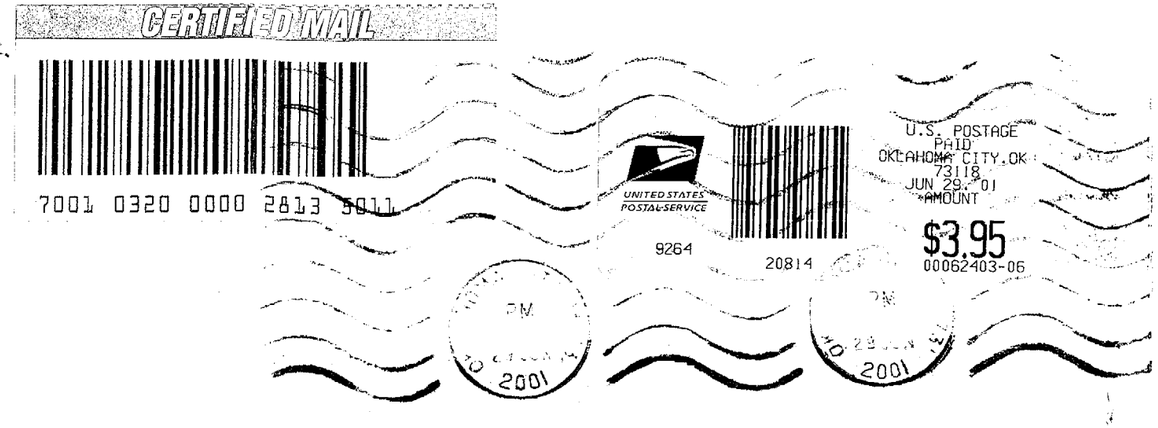
DO NOT USE DRY HEAT OR CHEMICAL STERILIZATION

Steam Sterilization (autoclave): Use the normal cycle (121°C at 15 psi for 15 to 30 minutes) or the flash cycle (133°C at 30psi for about 3 minutes).

DO NOT EXPOSE Pd-103 BRACHYTHERAPY SOURCES TO TEMPERATURES AND PRESSURES IN EXCESS OF 138°C AND 35 PSI.

Ethylene Oxide (EtO) Sterilization: use cycle and aeration times recommended by the sterilizer's manufacturer or use those determined at the Institution. Sterilize the Pd-103

Mills Biopharmaceuticals Inc.
120 NE 26th street
Oklahoma city, oklahoma
73105



RESTRICTED DELIVERY
REQUESTED

U.S. Nuclear Regulatory commission.
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Division of Industrial & Material Nuclear.
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11545 Rockville pike.
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Rockville, Maryland
20850