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16751 Trans Canada Hwy.,
Kirkland, QC., H9H 4J4

FACSIMILE TRANSMISSION

Addressee: Mr. William Ward
Company: NRC
Fax No: (301) 415-5369

Date: October 25, 2001

Sender: Carolyne Desrosiers Clarke
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Number of Pages (including cover) 13

Message:

Mr. Ward,

We are pleased to provide the attached responses to the questions regarding our application for Brachyseed Pd-103 brachytherapy source.

Please do not hesitate to contact Dr. Richard Flanagan at (514) 630-7043 should you require additional information.

Thank you again for your timely attention to this matter.

Regards,

A handwritten signature in black ink, appearing to be "Carolyne Desrosiers Clarke".

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Questions and Responses
DraxImage Inc. Brachyseed Pd-103 brachytherapy source application
October 25, 2001

1. ***Two different summary data sheets were submitted, one with the letter has a Rockville address for AAC Consulting Group. The one in the notebook has the same Bethesda address that certificate NR-1121-S-101-S has, except that the suite number is now 850, vice 800 as on that certificate. Which address is correct?***

The correct address for our US Agent is: AAC Consulting Group
7361 Calhoun Place
Suite 500
Rockville, Maryland
20855

The address for our US Distributor, which should appear on the certificate is:
Cytogen Corporation
600 College Road East
Princeton, NJ 08540
Tel: 1 800 833-3533

2. ***For devices marketed in the United States, we must have the U.S. address on the labels. The labels you provided in Section 4 of your application for the Pd-103 list DraxImage, Inc. in Canada. These labels must have the address for the U.S. distributor, as listed on the certificate on the label. Please change the labels to show the U.S. distributor name.***

NOTE: We realize that the SSD Certificate of Registration previously issued to you, NR-1121-S-101-S, for the LS-1 model iodine-125 seeds, had labels with DraxImage, Inc. in Canada on them. Accepting the labels without the U.S. distributor name on them was an oversight on our part. We will contact you separately about correcting this situation.

Please see the attached revised labels and package insert to which the U.S. distributor name has been added.

The address for our US Distributor is: Cytogen Corporation
600 College Road East
Princeton, NJ 08540

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3. ***Section 2 - Conditions of Use, and Section 5, Prototype Testing, state classification is ISO/98/C53211. Appendix 3, section 1 states it is ISO/99/C53211. Date of standard is 1999. Please confirm that first classification is a typographical error and that the second classification is correct.***

We confirm that the first classification is a typographical error and that the second classification is correct. We apologize for the error.

4. ***Label material description was not specified. The April 12, 2000 Request for Additional Information for the LS-1 source, question 8, asked whether the label material would be durable. The response did not clearly state the durability. NR-1121-S-101-S stated labels would be legible and made of durable material for the LS-1. Please describe the label's durability.***

Please refer to response 14 for a description of the labels' composition and durability.

Question 8 for the LS-1 source read:

In Section 4, per 10CFR 32.74(a)(2)(viii), please provide the radiation safety instructions for the handling and storing the source. These instructions are to be included on a durable label attached to a permanent storage container for the source. If these instructions are lengthy for such label, they may be summarized on the label and printed in detail on a brochure which is referenced on the label.

The instructions for the handling and storing of both LS-1 and Pd-1 sources are, in fact, quite lengthy for the container labels. Therefore, they are provided in detail on the package insert which is referenced on both the shipping and storage pot label as well as the warning insert.

5. ***Appendix 3, Sections 1.0, 2.0, and 2.4, mention ISO 2929:1999(E) as the standard. Please confirm that this is a typographical error in referencing ISO 2919:1999(E).***

We confirm that this is a typographical error in referencing ISO 2919:1999(E) and apologize for the error.

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6. ***Package Insert isodose contour plot does not have units specified. The units are specified in Section 6, Radiation Profiles, Figure 5a. Please specify units on the package insert.***

The units have been specified on the attached revised Package Insert.

7. ***Basis for Radiation Profile calculations not specified. Please specify how the calculations given in Section 6, Radiation Profiles, paragraph 6.3, were determined.***

Measurements of the dose were carried out using Monte Carlo modeling by Drs Gordon Chan of the Ottawa Regional Cancer Center, Ontario and William Prestwich of McMaster University, Hamilton, Ontario. The dose distribution in water of the seed was simulated using Cyltran code of the Integrated Tiger Series, version 2.1.

Also, would the concerns regarding hospital personnel exposures due to implantation and removal of these Pd-103 sources be the same as those discussed in the correspondence for the LS-1 iodine-125 source?

Yes.

8. ***Section 7, Quality Control, Page 17 discusses counting the iodine-125 removed from the source. This appears to be a copy of your BrachySeed™ iodine-125 application which has not been updated for the Pd-103 source. Please provide a new page 17 which correctly identifies the radioisotope being counted as Pd-103.***

Please see the attached revised p.17.

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9. ***In your application review checklist, you checked "The applicant is manufacturer and distributor" row. In my email of 10/24/01, I discussed the need for a US distributor. Please confirm who is the manufacturer, who is the distributor and who the NRC would inspect and take enforcement action against should NRC regulations be violated.***

The manufacturer is : DRAXIMAGE Inc.
16751 TransCanada Highway
Kirkland, QC Canada H9H 4J4
1 888 633-5343

The address for our **US Distributor**, which should appear on the certificate is:

Cytogen Corporation
600 College Road East
Princeton, NJ 08540
Tel: 1 800 833-3533

Mr. Ward states in his e-mail of October 24, 2001 that the NRC cannot inspect manufacturing facilities outside of the US, nor can it adequately enforce the regulations outside of the US. Therefore, we assume that Cytogen would be subject of any inspection by the NRC.

10. ***In Section 3.1 of your application, you stated that "Figure 2 on page 6 is a micrograph..." Figure 2 shows the labeling. No copy of the micrograph(s) was provided in the application. Please provide a copy of the micrographs mentioned in section 3.1.***

Please see attached micrographs.

11. ***In Section 3 of your application, you stated that aluminum spacers may be substituted for titanium spacers. Have you performed an analysis of the effect of the use of the various materials (titanium tubing, aluminum spacer, platinum/iridium marker) used and the potential for corrosion between them? What were the results of that analysis?***

We have decided not to use aluminum spacers.

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- 12. *In Section 3.5.2, what is the applying force used to close the end caps?***

Approximately 75 psi is used to close the end caps.

It should be noted that the apparatus used to press the end shells together is molded to the shape of the seed in order to avoid any seed deformation. This is confirmed by inspection of each assembled seed.

- 13. *In Section 4, Labeling: The outer container label should provide the source model number, not isotope name in the statement of "The U.S. Nuclear Regulatory Commission has approved distribution of BrachySeedPd-103..." The LS-1 label was correct in this regard.***

Please see attached revised labels.

- 14. *In my questions provided on 10/24/01, I asked about the durability of the labels. In order to clarify that question, we are asking the following. What are the label's material, size, and how is the labeling wording added (etched, engraved on metal)? Please note that the label and wording must be legible and durable.***

The labels are manufactured by a local printer using permanent colored inks and a clear lacquered finish on white paper stock with a permanent self-adhesive backing. Two labels are used; one on the inner vial containing the sources, and one on the outer lead shielding. The inner label is 30 mm by 40 mm and the outer label is 75 mm by 40 mm. All wording on both labels is legible to the naked eye. Lot-specific data such as calibration date and lot number are added to the label by hand using permanent ball point pens. We consider the durability of these labels more than adequate for these short-lived brachytherapy sources

- 15. *In Section 6, page 14, Figure 4 states, "BrachySeed™ Pd-103 (DraxImage model LS-1) Photon Spectrum." Please clarify this figure, is it for the Pd-103, or I-125, and what significance does it have to your application?***

It should read: (DRAXIMAGE model Pd-1). The photon spectrum shows that the emission from the assembled seed is identical to the spectrum from Pd-103 itself. This information is used in modeling for Monte Carlo calculations.

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- 16. *In Appendix 6, Quality Manual, section 2.2, how often are internal audits and supplier/contractor audits performed?***

Quality Operations SOP RPH_2045: Audit Program describes the yearly audit schedule. An internal audit of each department is required at least once per year. Outside suppliers and contractors are audited on a schedule that varies according to the material or service provided. Suppliers of active ingredients are typically audited once every two years.

- 17. *In Appendix 6, Quality Manual, section 8.1, what fraction of your raw materials and finished products are tested? If not 100%, how do you decide what is tested?***

BrachySeed sources (finished product) are submitted to 100% in-process testing. A minimum of three representative sources is tested from each shipment of finished sources, and all shipments undergo a Quality Control inspection before release. All lots of raw materials and seed components are tested before use. The number of components sampled from each lot received is determined according to a pre-established statistical sampling plan based on ANSI/ASQC standard Z1.4-1993. The sampling plan is listed in the product specification sheet for each component.

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Registration of BrachySeed™Pd-103**

then placed on a hotplate and the temperature of the fixture plate is raised over a period of 10-20 minutes to 135-140°C as measured by a thermocouple probe which can be inserted at two positions on the plate. The absolute pressure inside each recess containing a source and solution is thereby raised to above 3 atmospheres. The fixture plate is removed from the heater and allowed to cool to room temperature. It is then disassembled and the solution from each recess is pumped sequentially to a shielded counting cell where the amount of Pd-103 removed from the source is measured using a calibrated sodium iodide detector. Sources associated with solutions showing greater than 5 nCi of Pd-103 activity are rejected.

Experience to date indicates that positive tests (>5 nCi) will seldom occur. Monitoring, decontamination and replacement routines will ensure that all equipment is contamination-free before it is involved in any further leak test process.