



UNITED STATES
NUCLEAR REGULATORY COMMISSION

REGION III
2443 WARRENVILLE ROAD, SUITE 210
LISLE, ILLINOIS 60532-4352

FEB 06 2012

Laura T. Smith, M.S., DABR
Radiation Safety Officer
St. John Macomb-Oakland Hospital
Macomb Center
11800 E. 12 Mile Road
Warren, MI 48093

Dear Ms. Smith:

This letter refers (1) to your facsimile letter received on November 6, 2011 and (2) to emails and phone conversations conducted between November 29, 2011, and January 27, 2012.

As we have noted via email, **we have voided your request to amend your NRC License No. 21-01190-05, adding yttrium-90 (Y-90) SIR-Spheres for manual brachytherapy, including the request to add Philip Adler, M.D., as an Authorized User for Y-90 microspheres.** This action is based on the three issues identified below. An annotated copy of the 10 CFR 35.1000 guidance, "Microsphere Brachytherapy Sources and Devices," is attached for your convenience, including annotations for your specific situation. This "void" is without prejudice to resubmission.

(1) The information provided for Dr. Adler does not demonstrate that Dr. Adler qualifies as an interventional radiologist. The documentation of Dr. Adler's interventional radiologist status must include dates for the completion of at least one year of supervised clinical experience in interventional radiology, including the name and license number of the supervising individual.

(2) The letter dated January 25, 2012, signed by Eric A. Wang, M.D., lacks either documentation of Dr. Wang's status as an Authorized User (AU), or SIRTEX letterhead. The documentation of Dr. Adler's work experience must include dates of that experience, together with documentation of the supervising individual's status as an AU or as an official manufacturer representative.

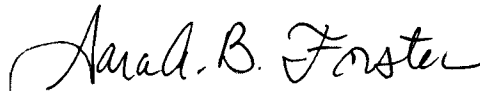
(3) The letter submitted on November 6, 2011, lacks required commitments, as described on pages 3- 5 of the guidance identified above. These commitments must be submitted with any request to add SIR-spheres to your license.

Should you choose to resubmit your request, please resubmit the application in its entirety, and ensure that a senior management representative signs your amendment request, in accordance with 10 CFR 35.12(a). Include the telephone number and fax number of at least one person who serves as a point of contact with the request.

If you have any questions or require clarification on any of the information stated above, you may contact us at (630) 829-9887.

In accordance with 10 Code of Federal Regulations 2.390 of the NRC's "Rules of Practice," a copy of this letter will be available electronically for public inspection in the NRC Public Document Room or from the NRC's Agencywide Documents Access and Management System (ADAMS), accessible from the NRC Web site at <http://www.nrc.gov/reading-rm/adams.html>.

Sincerely,

A handwritten signature in black ink that reads "Sara A.B. Forster". The signature is written in a cursive style with a large, stylized 'S' and 'F'.

Sara A.B. Forster
Health Physicist
Materials Licensing Branch

License No. 21-01190-05
Docket No. 030-02005

Enclosures: Microsphere Brachytherapy Sources and Devices, October 2011
(including annotations)

Microsphere Brachytherapy Sources and Devices

REVISED OCTOBER 2011 *(use the most current guidance when submitting or resubmitting.)*
Questions should be directed to: Ashley Cockerham (240) 888-7129 or

MedicalQuestions.Resource@nrc.gov

(additional information needed is noted, below.)

Licensing Guidance – TheraSphere® and SIR-Spheres® Yttrium-90 Microspheres

Yttrium-90 (Y-90) microspheres are manual brachytherapy sources used for permanent implantation therapy. Y-90 microspheres are regulated under 10 CFR 35.1000 "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material." Consistent with the direction in 10 CFR 35.1000, the NRC has evaluated these devices and determined that licensees must use Y-90 microspheres in accordance with the following requirements, which will be incorporated into the license either through license condition or through incorporation by reference to licensee submittals that include commitments consistent with these requirements. Applicants are reminded that licenses issued pursuant to 10 CFR 35.1000 must still meet the general requirements in 10 CFR Part 35, Subparts A, B, C, L, and M.

Training and Experience

NRC has determined that individuals meeting the guidance provided in both A and B below will be considered qualified and can be authorized for the use of Y-90 microspheres. Applicants may also submit alternative training and experience commitments to be reviewed on a case-by-case basis by NRC staff. The alternative information should include an explanation of why the applicant believes the alternative information demonstrates that the individuals are qualified to be authorized individuals.

The authorized user for Y-90 microspheres (AU):

A)

- 1) Is identified as an authorized user for medical uses in 10 CFR 35.400, "Use of sources for manual brachytherapy," or for medical uses in 35.300, "Use of unsealed byproduct material for which a written directive is required," that includes categories 1, 2, and 3 as listed in 10 CFR 35.390(b)(1)(ii)(G) on one of the following licenses or permits that permit the medical use of byproduct material: A Commission or Agreement State license, a permit issued by a Commission master material licensee, a permit issued by a Commission or Agreement State specific licensee of broad scope, or a permit issued by a Commission master material license broad scope permittee; or
- 2) Meets the training and experience requirements of 10 CFR 35.390 or 10 CFR 35.490; or

3) Is an interventional radiologist who meets the training and experience guidelines as follows:

i) *Interventional radiologist documentation must include documentation re:*
a) American Board of Radiology certification in diagnostic radiology and subspecialty certification in interventional radiology; or

① → b) Three years supervised clinical experience in diagnostic radiology and one additional year of supervised clinical experience in interventional radiology; and

ii) has 80 hours of classroom and laboratory training for byproduct material, including Y-90 microspheres, which may be concurrent with training received in accordance with Item A.1. in:

- a) Radiation physics and instrumentation;
- b) Radiation protection;
- c) Mathematics pertaining to the use and measurement of radioactivity;
- d) Radiation biology; and

② → iii) *Work experience documentation must include documentation re:* has work experience under the supervision of an AU for Y-90 microspheres or a Y-90

- microsphere manufacturer representative involving: *(include All details or SIRTEX letterhead)*
- a) Ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys;
 - b) Performing quality control procedures on instruments used to determine the activity of Y-90 microspheres and performing checks for proper operation of survey meters;
 - c) Evaluation of each patient or human research subject for the dose/activity of Y-90 microspheres to be administered to each treatment site;
 - d) Calculating and measuring the activity and safely preparing the Y-90 microspheres to be delivered to the patient or human research subject;
 - e) Using administrative controls to prevent a medical event involving the use of byproduct material;
 - f) Using procedures to control and to contain spilled byproduct material, including Y-90 microspheres, safely and using proper decontamination procedures; and
 - g) Follow up and review of each patient's or human research subject's case history for Y-90 microspheres; and

B) has successfully completed training in the operation of the delivery system, safety procedures, and clinical use for each type of Y-90 microspheres for which authorization is sought. The additional Y-90 microsphere specific training and experience requirements may be satisfied by satisfactory completion of a training program provided by either:

pathway 1) an AU who is authorized for the type of microsphere for which the individual is seeking authorization. The clinical use experience should include at least three supervised hands-on cases for each type of Y-90 microsphere for which the individual is seeking AU status; or

pathway 2) a Y-90 microsphere manufacturer. The clinical use experience should include at least three supervised hands-on *in-vitro* simulated cases for each type of Y-90 microsphere for which the individual is seeking AU status. *In-vitro* simulated cases should demonstrate issues that are encountered during Y-90 microsphere administration procedures. Following the license amendment that names the individual as an AU for Y-90 microsphere use, the first three patient cases completed by the individual should be hands-on and supervised in the physical presence of a manufacturer representative for each type of Y-90 microsphere for which the individual is authorized.

The applicant must submit documentation for the above training and experience. For individuals obtaining clinical use experience under pathway 1 above, this documentation includes the clinical use cases. For individuals obtaining clinical use experience under pathway 2 above, this documentation includes the *in-vitro* simulated cases and a commitment that each individual will complete at least the first three hands-on patient cases supervised in the physical presence of a manufacturer representative for each type of Y-90 microsphere for which authorization is sought. Additionally for pathway 2, the licensee's commitment will include submitting documentation from the manufacturer to the appropriate NRC Regional Office within 30 days of when these three patient cases have been satisfactorily completed.

In addition, the applicant shall commit to provide training in the licensee's procedures to all individuals involved in Y-90 microsphere use, commensurate with the individual's duties to be performed. This training must be provided to all individuals preparing, measuring, performing dosimetry calculations, or administering Y-90 microspheres.

If the NRC staff revises the training and experience criteria, physicians who were authorized for the medical use of a specific type of Y-90 microsphere under these criteria or previous criteria, do not have to meet the revised criteria for that type of microsphere.


Leak Tests


Leak tests are not required for Y-90 microspheres based on the criteria in 10 CFR 35.67(f).

③ License Commitments - Written Directives, Inventory, Patient Release, Labeling, & Medical Event Reporting

See pages 3-5; these commitments must be provided.

The applicant shall commit to follow all the requirements in 10 CFR Part 35 for brachytherapy sources and manual brachytherapy use, except where replaced by the following licensing commitments:

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- For the purpose of written directives and medical event reporting requirements in the Y-90 microsphere guidance, "prescribed dose" means the total dose (rad or Gy). Alternatively, prescribed activity (mCi or GBq) may be used in lieu of prescribed dose.
 - The written directive shall include the patient or human research subject's name; the date; the signature of an AU for Y-90 microspheres; the treatment site; the radionuclide (including the physical form [Y-90 microspheres]); the prescribed dose/activity; the manufacturer; and, if appropriate for the type of microsphere used, the statement "or dose/activity delivered at stasis."
 - The written directive should specify the maximum dose(s)/activity(ies) that would be acceptable to the specified site(s) outside the primary treatment site due to shunting (e.g. lung and gastrointestinal tract).
 - Administration of Y-90 microspheres must be performed in accordance with the written directive.
 - The licensee shall record the administered dose/activity delivered to the primary treatment site and to the other specified site(s). If the administration was terminated because of stasis, then the total dose/activity to the treatment site is the value of the total dose/activity administered when stasis occurred and the administration was terminated. The record should be prepared within 24 hours after the completion or termination of the administration and must include the name of the individual who made the assessment, the date, and the signature of an AU for Y-90 microspheres, if terminated due to stasis.
 - The licensee shall commit to following the manufacturer's procedures for calculating/documenting the dose to the treatment and other sites, preparing the dose for administration, and performing pre/post vial dose measurements; or submit alternative methods.
 - The semi-annual physical inventory of microsphere aggregates (e.g. vials) should include:
 - 1) the radionuclide and physical form; and
 - 2) unique identification of each vial in which the microspheres are contained; and
 - 3) the total activity contained in each of the vial(s); and
 - 4) the location(s) of the vial(s).
 - The licensee shall retain each semi-annual physical inventory record for three years.
 - The licensee should commit to develop procedures that describe measures taken to ensure that radiation emissions, which may include bremsstrahlung, from each patient or human research subject permits his/her release in accordance with 10 CFR 35.75.
 - The following additional guidance applies when the Y-90 microspheres are placed in vials, syringes, or radiation shields that are not labeled by the manufacturer:
 - 1) Label vials and vial radiation shields with radionuclide and form (e.g., Y-90 microspheres).
 - 2) Label syringes and syringe radiation shields with the radionuclide, form, and therapeutic procedure (e.g., Y-90 microspheres, brachytherapy).
 - The licensee shall commit to report any event, except for an event that results from intervention of a patient or human research subject, in which:

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- 1) the administration of byproduct material results in a dose that exceeds 0.05 Sv (5 rem) effective dose equivalent or 0.5 Sv (50 rem) to an organ or tissue from the use of the wrong radionuclide; or
 - 2) the administration of Y-90 microspheres results in a dose
 - a) that differs from the prescribed dose or the dose that would have resulted from the prescribed activity, as documented in the written directive, by more than 0.05 Sv (5 rem) effective dose equivalent or 0.5 Sv (50 rem) to an organ or tissue, and the total dose/activity administered differs from the prescribed dose/activity, as documented in the written directive, by 20 percent or more; or
 - b) that exceeds 0.05 Sv (5 rem) effective dose equivalent or 0.5 Sv (50 rem) to an organ or tissue from an administration to the wrong individual or human research subject, via the wrong route, or by the wrong mode of treatment; or
 - c) to an organ or tissue other than the treatment site that exceeds by 0.5 Sv (50 rem) to an organ or tissue and by 50 percent or more of the prescribed dose/activity expected to that site from the administration of Y-90 microspheres, if carried out as specified in the written directive
- Additionally, the licensee shall comply with the medical event reporting and notification requirements as described in 10 CFR 35.3045(b)-(g).

Notes to Licensees

Team Approach

Microsphere brachytherapy treatment is usually conducted using a multi-disciplinary team approach. The AU should consult, as necessary, with individuals with expertise in:

- Cancer management (e.g. radiation or medical oncology)
- Catheter placement
- Radiation dosimetry
- Safe handling of unsealed byproduct material

One individual may satisfy more than one of the listed areas of expertise.

Notification for AUs

NRC recognizes that if an AU satisfies the training and experience listed in NRC's licensing guidance for Y-90 microspheres and is currently listed on a Commission or Agreement State medical use license or permit for a specific type of microsphere, the AU should be allowed to work under a different license for the medical use of the same type of microsphere. A limited specific medical use applicant initially

applying for authorization for the medical use of Y-90 microspheres or an existing licensee applying for an amendment may request authorization to notify the NRC in the future that it has permitted an AU to work at its facility without the need to request an additional license amendment, provided the following conditions are met:

- 1) the AU satisfies the training and experience listed in NRC's licensing guidance for Y-90 microspheres; and
- 2) the AU is currently listed for the same type of Y-90 microsphere use on a Commission or Agreement State license, a permit issued by a Commission master material license, a permit issued by a Commission or Agreement State licensee of a broad scope, or a permit issued by a Commission master material license broad scope permittee; and
- 3) the licensee provides NRC a copy of the license or permit on which the AU was originally listed for the specific microsphere use; and
- 4) the licensee provides documentation to NRC for each AU of the above listed conditions no later than 30 days after the date that the licensee allows the AU to work as an AU for the specific type of microsphere.

If this authorization is approved, these notification conditions will be incorporated as license conditions in the licensee's license.

Change in Physical Conditions of Use

If the physical conditions of use exceed those reported in the Sealed Source and Device (SSD) certificate, the limited specific medical use licensee should request an amendment for the new conditions, and a broad scope licensee should perform its own engineering and radiation safety evaluation addressing those differences.

Use of Other Y-90 Microspheres

The SSD safety evaluation for a specific manufacturer's Y-90 microspheres does not cover the use of any other Y-90 microspheres, including the preparation of Y-90 on other microspheres by a commercial nuclear pharmacy, the medical use licensee's authorized nuclear pharmacist, or a physician authorized user qualified to prepare radioactive drugs. The medical use of such a source will require a new SSD certificate (or safety evaluation by the broad scope medical use licensee) that addresses the conditions of use, safety of the new Y-90 microspheres, and compatibility of the new microspheres with microsphere delivery system(s).

The SSD safety evaluation for a given manufacturer's Y-90 microsphere delivery system does not cover the use of that manufacturer's Y-90 microspheres with another manufacturer's delivery system or the use

of another manufacturer's Y-90 microspheres with the given manufacturer's delivery system. Before authorization, the medical use of such a delivery system will require a new SSD certificate (or safety evaluation by the broad scope medical use licensee) that addresses the conditions of use, safety of the microsphere delivery system, and compatibility of the new delivery system with the Y-90 microspheres.

TheraSphere® Use Outside Humanitarian Device Exemption (HDE) Restrictions

The MDS Nordion TheraSphere® Y-90 microspheres are approved by the U.S. Food and Drug Administration (FDA) under the provisions of a "Humanitarian Device Exemption" (HDE No. H9800006), which includes unique restrictions on the medical use of the devices. Nothing in the NRC license relieves the licensee from complying with those FDA requirements.

If the Institutional Review Board that is required to approve and monitor the use of the MDS Nordion TheraSphere® Y-90 microspheres determines that the particular use of TheraSphere® Y-90 microspheres is for research purposes, the licensee must meet the requirements in 10 CFR 35.6, "Provisions for research involving human subjects." (Note: One of the conditions of approval for an HDE is that there be an Institutional Review Board initial review and approval before a humanitarian use device is used at a facility, as well as continuing review of its use.)

Revision of Y-90 Microsphere Radiation Safety Programs to Conform to Changes in This Licensing Guidance

The above licensing guidance may be revised as additional experience is gained regarding the medical use of TheraSphere® and SIR-Spheres® Y-90 microspheres. A licensee currently authorized to use these products that is committed by license condition to following provisions in this guidance existing at the time of commitment must apply for and receive an amendment to its license in order to make changes to conform with the revised provisions.

An applicant initially applying for authorization for the medical use of TheraSphere® and SIR-Sphere® Y-90 microspheres, or a licensee applying for an amendment to conform with revisions may request to incorporate into its license a change process similar to 10 CFR 35.26. Such a change process can allow some future changes to radiation safety programs provided that the change process requires the following conditions to be met for revisions to the radiation safety program:

- 1) the revision is in compliance with the regulations; and
- 2) the revision is based upon NRC's current guidance for TheraSphere® and SIR-Spheres® Y-90 microspheres 35.1000 use posted on the NRC Web site; and
- 3) the revision has been reviewed and approved by the licensee's Radiation Safety Officer and licensee's management; and
- 4) the affected individuals are instructed on the revised program before the change is implemented; and

- 5) the licensee will retain a record of each change for five years; and
- 6) the record will include a copy of the appropriate website guidance, the old procedure, the new procedure, the effective date of the change, and the signature of the licensee management that reviewed and approved the change.

If approved, these conditions for use of updated guidance will be incorporated as license conditions in the licensee's license.

Waste Disposal Issues

In March 2007 NRC staff issued an Information Notice (IN 2007-10) to alert all medical licensees of the presence of radioactive contaminants and possible disposal issues with the two variations of commercially available Y-90 labeled microspheres, TheraSphere® and SIR-Spheres®. Depending on the contaminants, licensees may need to:

- hold the remaining microspheres longer in decay-in-storage in accordance with 10 CFR 35.92; or
- return the microspheres to the manufacturer, if the manufacturer is authorized to receive Y-90 microspheres; or
- transfer the microspheres to an authorized recipient.

IN 2007-10, *Yttrium-90 TheraSpheres® and SIRSpheres® Impurities*, is available on the NRC public website at <http://www.nrc.gov/reading-rm/doc-collections/gen-comm/info-notices/2007/in200710.pdf>.