47-05322-02
03012570
143229

Microsphere Brachytherapy Sources and Devices

REVISED SEPTEMBER 2008

Questions should be directed to: Ashley Tull (240) 888-7129 or
Ronald Zelac (301) 415-7635 or
MedicalQuestions.Resource@nrc.gov

Licensing Guidance – TheraSphere® and SIR-Spheres® Yttrium80 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

The authorized user for Y-90 microspheres (AU) must meet the training and experience requirements of 10 CFR 35.390 or 10 CFR 35.490. Additionally, the AU must have 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 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 to the appropriate NRC Regional Office within 30 days of when these three patient cases have been completed.

In addition, the applicant shall commit to provide training in the manufacturer'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).

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

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:

- 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 and two separate entries:
  1) pre-administration: the date; the signature of the AU; the treatment site; the radionuclide (including the physical form [Y-90 microspheres]); the prescribed doselactivity; and, if appropriate for the type of microsphere used, identify the manufacturer and include the statement "or doselactivity delivered at stasis"; and
  2) after administration but before the patient or human research subject leaves the post-procedural recovery area: the date; the signature of the AU; and the total doselactivity delivered to the

treatment site. If the administration was terminated because of stasis, then the total doselactivity to the treatment site is the value of the total doselactivity administered when stasis occurred and the administration was terminated. Note: The post-administration entries into the written directive are not an amendment to the written directive; rather, these entries complete the written directive.

- The pre-administration 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). The post-implantation written directive should specify the dose(s)/activity(ies) delivered to the specified site(s) outside the primary treatment site due to shunting.
- Administration of Y-90 microspheres must be performed in accordance with the written directive. If the written directive is specified in dose (rad or Gray), the licensee should describe how the total dose to the treatment site, as well as the doses to other sites, will be determined before and upon completion of the administration, to confirm that the administration is performed in accordance with the written directive.
- The semi-annual physical inventory of microspheres 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).
- Procedures should 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:
  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, as documented in the pre-administration 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 doselactivity administered differs from the prescribed doselactivity, as documented in the pre-administration 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 pre-administration portion of 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 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 manufacturer's Y-90 microsphere delivery system does not cover the use of any other delivery system with the Y-90 microsphere brachytherapy device. 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.