UNITED STATES
NUCLEAR REGULATORY COMMISSION
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ALL AGREEMENT STATES, VERMONT, WYOMING

NOTIFICATION OF ISSUANCE OF YTTRIUM-90 MICROSPHERE BRACHYTHERAPY LICENSING GUIDANCE (STC-16-020)

Purpose: To inform the Agreement States that the Yttrium-90 (Y-90) Microsphere Brachytherapy Sources and Devises TheraSphere® and SIR-Spheres® Licensing Guidance, Revision 9, was published in February 2016.

Background: The licensing guidance for Y-90 microsphere brachytherapy was initially published in October 2002 and subsequently revised in 2004, 2007, 2008, 2011, and 2012. Based on recommendations from the Advisory Committee on the Medical Uses of Isotopes (ACMUI), a joint Organization of Agreement States and U.S. Nuclear Regulatory Commission (NRC) working group revised this licensing guidance. The document is intended to be guidance in licensing Y-90 microsphere brachytherapy for applicants, licensees, NRC staff, and Agreement States.

Discussion: This current licensing guidance revision has three major changes based on ACMUI recommendations. These changes (1) remove specifications for gastrointestinal tract and lung dose/activity in the written directive and exclude reporting dose/activity to an organ or tissue other than the treatment site as a medical event when the dose/activity is caused by shunting when the shunting was evaluated prior to treatment in accordance with manufacturer's procedures, (2) specifically exclude reporting of events due to stasis or emergent patient conditions, and (3) allow for interventional radiologists certified by the American Osteopathic Board of Radiology to become Authorized Users.

This licensing guidance revision is available at http://www.nrc.gov/materials/miau/med-use-toolkit.html.

If you have any questions regarding this correspondence, please contact me at 301-415-3340 or the individual named below:

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Yttrium-90 Microsphere Brachytherapy Sources and Devices
TheraSphere® and SIR-Spheres®
Licensing Guidance

February 12, 2016, Revision 9

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Table of Contents

10 CFR 35.1000 Use

Although yttrium-90 (Y-90) microspheres are manual brachytherapy sources used for permanent implantation therapy, Y-90 microspheres have many unique properties that merit radiation safety considerations other than those required by 10 CFR Part 35, Subpart F, "Manual Brachytherapy." These unique properties include their small size; the large number of microspheres used in a treatment; the route of administration; and their use by physician authorized users (AU) in addition to radiation oncologists, including nuclear medicine physicians and interventional radiologists. As a result, Y-90 microspheres are regulated under 10 CFR 35.1000 "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material."

Licensing Guidance

This guidance provides applicants with an acceptable means of satisfying the requirements for a license for the use of TheraSphere® and SIR-Spheres® and is not intended to be the only means of satisfying the requirements for a license. The applicant must submit the information required by 10 CFR 30.33 and 35.12, as described below. The applicant should submit additional information and commitments requested below or may, unless the information is specifically required by regulation, submit alternative information and commitments for review by the U.S. Nuclear Regulatory Commission (NRC) staff to make a licensing determination. The commitments incorporated into the applicant's license by license condition will be reviewed during routine inspections. Applicants are reminded that licenses issued pursuant to 10 CFR 35.1000 must still meet the general requirements in Part 35, Subparts A, B, C, L, and M, except as specified in this guidance. Additionally, applicants must meet applicable requirements of 10 CFR Part 30.

General

Radionuclides, Form, Possession Limits, and Purpose of Use

The applicant shall identify the radionuclides, chemical/physical form, requested maximum possession limit, and purpose of use. NRC Form 313 may be used to submit this information. For example, the following provides the format for an acceptable request.

	TheraSphere®	SIR-Sphere
Radionuclides (Authorization 6)	Yttrium-90	Yttrium-90
Chemical/Physical Form (Authorization 7)	Glass microsphere (manufacturer as listed in Sealed Source and Device Registry NR-0220-D-131-S, TheraSphere®)	Resin microsphere (manufacturer as listed in Sealed Source and Device Registry MA-1229-D-101-S, SIR-Sphere®)
Maximum Possession Limit (Authorization 8)	540 mCi/vial, 2 Ci total	189 mCi/vial, 2 Ci total
Authorized Use (Authorization 9)	TheraSphere® for permanent brachytherapy using delivery system as listed in Sealed Source and Device Registry NR-0220-D-131-S	SIR-Spheres® for permanent brachytherapy using delivery system as listed in Sealed Source and Device Registry MA-1229-D-101-S.

Leak Tests

Leak tests are not required for Y-90 microspheres. The small size and large number of Y-90 microspheres makes leak testing as required by 10 CFR 35.67(b) impractical. Further, if leak testing were practical, licensees would not be required to leak test individual microspheres because the activity of each microsphere is below the threshold in 10 CFR 35.67(f)(3).

Authorized Individuals

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.

Training and Experience

The authorized user for Y-90 microspheres:

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 include the uses described in paragraphs (1), (2), and (3) of 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 materials licensee, a permit issued by a Commission or Agreement State specific licensee of broad scope, or a permit issued by a Commission master materials license broad scope permittee; or
2. Meets the training and experience requirements of 10 CFR 35.390 or 10 CFR 35.490; or
3. Meets the training and experience guidelines as follows:

    i.

        a. Board certification in diagnostic radiology and subspecialty certification in interventional radiology by either the American Board of Radiology or the American Osteopathic Board of Radiology; or
        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.3.i. in:

        a. Radiation physics and instrumentation;

b. Radiation protection;
c. Mathematics pertaining to the use and measurement of radioactivity;
d. Radiation biology; and

iii. has work experience under the supervision of an AU for Y-90 microspheres or training provided by a Y-90 microsphere manufacturer representative involving:
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 and 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 (Appendix S to NUREG-1556, Volume 9 provides additional guidance on this subject);
f. Using procedures to control and to contain spilled byproduct material, including Y-90 microspheres, safely and using proper decontamination procedures (Appendix N to NUREG-1556, Volume 9 provides additional guidance on this subject. The procedures should address any special circumstances that may be encountered, such as electrostatic charge of microspheres and proper survey instrument and survey technique for beta emitters); 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 microsphere for which authorization is sought. This requirement may be satisfied by satisfactory completion of a training program provided by either:

1. (Pathway 1) an AU who is authorized for the type of microsphere for which the individual is seeking authorization. This 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

2. (Pathway 2) a Y-90 microsphere manufacturer. This 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.

Training and Experience Documentation

The applicant must submit documentation of the above training and experience. For individuals obtaining clinical use experience under B.1 (pathway 1) above, this documentation shall include the clinical use cases. For individuals obtaining clinical use experience under B.2 (pathway 2) above, this documentation shall include 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 B.2 (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.

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, and
- safe handling of unsealed byproduct material.

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

Notification

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 requesting 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 to the NRC a copy of the license or permit on which the AU is listed for the specific microsphere use; and
4. the licensee provides documentation of the above listed conditions to NRC for each AU 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.

Grandfathering

If a licensee adopts this revision of Y-90 microsphere training and experience criteria, physicians who are currently authorized for the medical use of a specific type of Y-90 microsphere under previous criteria do not have to meet the revised criteria for that type of microsphere.

License Commitments

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:

Training

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.

Procedures for Administration

The licensee shall commit to following the manufacturer's procedures for calculating and documenting the dose or activity to the treatment site; preparing the dose for administration; determining shunting to non-treatment sites; and performing pre- and post-vial dose measurements; or submit alternative methods.

Administration of Y-90 microspheres must be performed in accordance with the written directive. The licensee shall record the dose or activity delivered to the treatment site. 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 determined the administered dose or activity and the date.

Written Directives

For the purpose of written directive 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. If prescribed activity is used in lieu of prescribed dose, activity should be used for all documentation and evaluations.

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 manufacturer; the prescribed dose or activity; and, if appropriate for the type of microsphere used, the statement "or dose or activity delivered at stasis."

Termination of Treatment Due to Stasis

If the administration was terminated because of stasis, then the total dose or activity to the treatment site is the value of the total dose or 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 determined the administered dose or activity, the date, and the signature of an AU for Y-90 microspheres.

Emergent Patient Conditions

If the procedure must be modified due to emergent patient conditions that prevent administration in accordance with the written directive (e.g., artery spasm or sudden change in blood pressure), the AU should document such changes in the written directive within 24 hours after the completion or termination of the administration. The modification to the written directive should include the reason for not administering the intended dose or activity, the date, and the signature of an AU for Y-90 microspheres.

Medical Event Reporting

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:

- 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
- the administration of byproduct material: to the wrong individual or human research subject; via the wrong route; or by the wrong mode of treatment; or

- the total dose or activity administered differs from the prescribed dose or activity, as documented in the written directive, by 20 percent or more, except when stasis or emergent patient conditions are documented and resulted in a total dose or activity administered that was less than that prescribed; or
- the administration of byproduct material results in dose or activity to an organ or tissue other than the treatment site, as documented in the written directive, except for shunting when shunting was evaluated prior to the treatment in accordance with the manufacturer's procedures.

Additionally, the licensee shall comply with the medical event reporting and notification requirements as described in 10 CFR 35.3045(b)-(g).

Inventory

The semi-annual physical inventory of microsphere aggregates (e.g., vials) should include:

- the radionuclide and physical form; and
- unique identification of each vial in which the microspheres are contained; and
- the total activity contained in each of the vial(s); and
- the location(s) of the vial(s).

The licensee shall retain each semi-annual physical inventory record for three years.

Labeling

The licensee should commit to the following when the Y-90 microspheres are placed in vials, syringes, or radiation shields that are not labeled by the manufacturer:

- Label vials and vial radiation shields with radionuclide and form (e.g., Y-90 microspheres).
- Label syringes and syringe radiation shields with the radionuclide, form, and therapeutic procedure (e.g., Y-90 microspheres, brachytherapy).

Patient Release

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 or her release in accordance with 10 CFR 35.75.

Radiation Protection Program Changes

This 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 a previous revision of this guidance may request a license amendment to commit to following this revision of the guidance instead. The licensee must apply for and receive this license amendment in order to make program changes to conform to this revision of the guidance.

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 this revision of the guidance 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 Medical Uses Licensee Toolkit;
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.

Notes to Licensees

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 or in 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.)

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.

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