



MEMORANDUM

TO: Medical Licensees possessing Yttrium-90 permitted by 180 NAC 7-085

FROM: Julia A. Schmitt, Manager
Radiation Control Program

DATE: February 5, 2020

SUBJECT: Notification of Issuance of Yttrium-90 Microsphere Brachytherapy
Licensing Guidance, Revision 10 (STC-19-073)

Attached is NRC Notification STC-19-073 regarding revision to Yttrium-90 (Y-90) Microsphere Brachytherapy Sources and Devices TheraSphere[®] and SIR-Spheres[®] Licensing Guidance.

This revision makes significant changes to the Authorized User (AU) training and experience (T&E) criteria. We are sending you this notice for informational purposes.

Should you have any questions, please contact our office at 402-471-2168.



UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

November 13, 2019

ALL AGREEMENT STATES

NOTIFICATION OF ISSUANCE OF YTTRIUM-90 MICROSPHERE BRACHYTHERAPY
LICENSING GUIDANCE, REVISION 10 (STC-19-073)

Purpose: To inform the Agreement States that the Yttrium-90 (Y-90) Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance, Revision 10, was published on November 8, 2019.

Background: The licensing guidance for Y-90 microsphere brachytherapy was initially published in October 2002 and subsequently revised in 2004, 2007, 2008, 2011, 2012, and 2016 as operational experience was gained with the novel technology. A revision 10 to the guidance was sought to evaluate previous stakeholder comments not addressed in the 2016 revision and Authorized User (AU) training and experience (T&E) requirements. The T&E pathway which allows AUs to be added to a license prior to completing their first 3 patient cases was evaluated because Agreement State and the U.S. Nuclear Regulatory Commission (NRC) licensing staff thought that after over 10 years of licensing Y-90 microspheres, there should be enough AUs to train future AUs and that the manufacturer was no longer needed.

Discussion: This revision makes significant changes to the T&E section based on public and stakeholder comments and the recommendations of the Advisory Committee on the Medical Uses of Isotopes. Specifically, the T&E criteria was changed to require physicians to receive work experience or training related to the medical use of Y-90 microspheres under the supervision of an AU and to conduct their first three cases in the physical presence of an AU. Previous revisions to the guidance allowed manufacturer representatives to provide all Y-90 microspheres specific training or supervision. The working group determined this change was supported and that training in topics related to medical use of the Y-90 microspheres should be given or supervised by an AU, consistent with other modalities regulated by the NRC. The AU supervising the training may still be an employee or contractor of the manufacturers. It is expected that there may be physicians who are in the process of using a previous revision of this guidance to become an AU; for that reason, the NRC is recommending a 180-day implementation period, resulting in an effective date of May 6, 2020 for this guidance.

Revision 10 was also revised to include the recentness of training requirements, including a reference to 10 CFR 35.59 to be consistent with other modalities and a 1-year timeframe for individuals to finish their first three patient cases for physicians who have not yet completed them. These changes ensure all training occurs in a reasonable timeframe. In addition, revisions were made throughout the document based on comments, including clarifications on medical event reporting, applicable regulations, and waste disposal issues.

The guidance was not revised to remove the option to allow a physician to become an AU prior to completing their first three patient cases. This option was not removed due to significant industry and medical licensee comments that this could cause delay or harm in patient care. Please see the working group response to public comments for more information (Agencywide Documents Access and Management System Accession No. ML19030B536).

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 use the point of contact identified below:

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/RA/

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Office of Nuclear Material Safety
and Safeguards

Enclosure:

Yttrium-90 Microsphere Brachytherapy
Sources and Devices TheraSphere®
and SIR-Spheres® Licensing Guidance,
Revision 10

SUBJECT: NOTIFICATION OF ISSUANCE OF YTTRIUM-90 MICROSPHERE
BRACHYTHERAPY LICENSING GUIDANCE, REVISION 10 (STC-19-073)
DATED: NOVEMBER 13, 2019

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

November 8, 2019, Revision 10

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1. Background

The licensing guidance for yttrium-90 (Y-90) microsphere brachytherapy was initially published in October 2002 and subsequently revised in 2004, 2007, 2008, 2011, 2012, and 2016. Following years of using the Y-90 licensing guidance, a working group composed of Agreement State representatives and U.S. Nuclear Regulatory Commission (NRC) staff was formed to update it based on stakeholder comments. Revision 10 updates the criteria for training and experience, medical event reporting, inventory requirement specifications, and waste disposal issues. Further, Revision 10 was updated to align the guidance with the final Title 10 of the *Code of Federal Regulations* (CFR) Parts 30, 32, and 35 rule, “Medical Use of Byproduct Material— Medical Event Definitions, Training and Experience, and Clarifying Amendments,” which was published in the *Federal Register* on July 16, 2018 (83 FR 33102) and went into effect on January 14, 2019 for NRC licensees. Lastly this guidance adds a new section on surveys and provides new information regarding patient release, cremation, and autopsy. A draft revision was published in the *Federal Register* (82 FR 51655) on November 7, 2017 for public comment. Responses to comments received can be found in Agencywide Documents Access and Management System (ADAMS) Accession No. ML19030B536.

2. 10 CFR 35.1000 Use

Although 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, “Medical Use of Byproduct Material,” Subpart F, “Manual Brachytherapy.” These unique properties include the microspheres’ small size, the large number of microspheres used in a treatment, and the route of administration. As a result, Y-90 microsphere brachytherapy is regulated under 10 CFR 35.1000, “Other medical uses of byproduct material or radiation from byproduct material¹.”

¹ 10 CFR 35.1000 is designated as Compatibility Category D. Agreement States are not required to adopt these regulations for purposes of compatibility but are not prohibited from adopting Compatibility Category D regulations if they so choose. If Agreement States choose to adopt this licensing guidance, references to 10 CFR should be changed to the equivalent Agreement State regulations.

3. Licensing Guidance

This guidance provides applicants with the acceptable means in 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 to meet 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 NRC staff to make a licensing determination. The commitments incorporated into the license by license condition will be reviewed during routine inspections. If an applicant commits to the guidance provided below, the applicant is committing to follow commitments described with the use of the word “should.”

4. General

4.1 Requirements not Specific to 10 CFR 35.1000 Use

Applicants must commit to meet the general requirements in 10 CFR Part 35, Subpart A, “General Information;” Subpart B, “General Administrative Requirements;” Subpart C, “General Technical Requirements;” Subpart L, “Records;” and Subpart M, “Reports,” except as specified in this guidance. Additionally, applicants must meet applicable requirements of 10 CFR Parts 19, “Notices, Instructions and Reports to Workers: Inspection and Investigations;” Part 20, “Standards for Protection Against Radiation;” and Part 30, “Rules of General Applicability to Domestic Licensing of Byproduct Material.”

4.2 Radionuclides, Form, Possession Limits, and Purpose of Use

Pursuant to 10 CFR 35.12, the applicant shall identify the radionuclide, chemical/physical form, requested maximum possession limit, and purpose of use. This information may be submitted under a signed, dated letter or NRC Form 313, “Application for Materials License.” The following table provides the format for an acceptable request.

	TheraSphere®	SIR-Spheres®
Radionuclides (NRC Form 313 Item 5a)	Yttrium-90	Yttrium-90
Chemical/Physical Form (NRC Form 313 Item 5b)	Glass microsphere (current manufacturer as listed in the Sealed Source and Device Registry [e.g., Nordion (Canada), Inc. Model TheraSphere®])	Resin microsphere (current manufacturer as listed in the Sealed Source and Device Registry [e.g., Sirtex Model SIR-Spheres®])
Maximum Possession Limit (NRC Form 313 Item 5c)	X* Ci total	X* Ci total
Purpose of Use (NRC Form 313 Item 6)	TheraSphere® for permanent brachytherapy using delivery system as listed in the Sealed Source and Device Registry	SIR-Spheres® for permanent brachytherapy using delivery system as listed in the Sealed Source and Device Registry

* Based on the maximum amount the applicant anticipates having at one time (i.e., 3 Ci)

4.3 Facility Address and Description

Provide an address of use and description of the location where the Y-90 microspheres will be used and stored.

4.4 Leak Tests

Leak tests are not required for Y-90 microspheres. The small size and large number of Y-90 microspheres make leak testing, as required by [10 CFR 35.67\(b\)](#), impractical. Further, leak testing is not required as the activity of each Y-90 microsphere is below the threshold in [10 CFR 35.67\(f\)\(3\)](#).

5. Training and Experience

5.1 Authorized Users

NRC has determined that individuals meeting the Authorized User (AU) training and experience (T&E) criteria A, B, and C provided below can be authorized for the use of Y-90 microsphere

brachytherapy. Applicants may also submit alternative T&E commitments to be reviewed on a case-by-case basis by NRC staff. The alternative T&E commitments should include an explanation of why the applicant believes the alternative T&E commitments demonstrate that the individuals are qualified to be an AU.

A.

1. Is identified as an AU for medical use in [10 CFR 35.1000](#) for Y-90 microspheres, [10 CFR 35.400](#), "Use of sources for manual brachytherapy," or for medical uses in [10 CFR 35.300](#), "Use of unsealed byproduct material for which a written directive is required," that includes the use described in 10 CFR 35.390(b)(1)(ii)(G)(3) on one of the following licenses or permits that authorizes 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 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. physician
 - a. Experience in diagnostic radiology demonstrated by:
 - (a) Board certification in interventional radiology/diagnostic radiology by the American Board of Radiology (ABR)²; or
 - (b) Board certification in diagnostic radiology by the ABR²; or
 - (c) Board certification in diagnostic radiology by the American Osteopathic Board of Radiology (AOBR)²; or
 - (d) Three years supervised clinical experience in diagnostic radiology; and
 - b. Experience in interventional radiology demonstrated by:
 - (a) Board certification in interventional radiology/diagnostic radiology by the ABR²; or
 - (b) Board subspecialty certification in interventional radiology by the AOBR²; or
 - (c) One year of supervised clinical experience in interventional radiology; and

² As noted on the NRC's [Medical Uses Licensee Toolkit Web site](#), the NRC-approved ABR and AOBR certificates contain the words "AU eligible" above the ABR or AOBR seal. For the purposes of this guidance, the NRC deems the certificates issued without "AU Eligible" to be adequate to meet the T&E guidelines in criteria A.3.i.a and A.3.i.b.

- ii. Has 80 hours of classroom and laboratory training³ for byproduct material requiring a written directive, applicable to Y-90 microspheres, which may be concurrent with training received in accordance with criterion A.3.i in:
 - a. Radiation physics and instrumentation; and
 - b. Radiation protection; and
 - c. Mathematics pertaining to the use and measurement of radioactivity; and
 - d. Radiation biology;
- iii. Has work experience under the supervision of an AU for Y-90 microsphere brachytherapy 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; and
 - 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; and
 - c. Calculating and measuring the activity and safely preparing the Y-90 microspheres to be delivered to the patient or human research subject; and
 - d. Using procedures to control and to contain spilled byproduct material, including Y-90 microspheres, safely and using proper decontamination procedures. The procedures should address any special circumstances that may be encountered, such as the electrostatic charge of Y-90 microspheres and the proper survey instrument and survey technique for beta emitters⁴; and
- iv. Has work experience or training under the supervision of an AU for the type of Y-90 microsphere brachytherapy the applicant is requesting, including:
 - a. Preparing and administering patient dosage. The individual does not have to be the physician who places the micro-catheter or administers patient dosage, but it is necessary that the individual have training in the administration process, including selection of activity of Y-90 microspheres to be administered to each

³ For Board Certified physicians, if the Board Certification is recognized by the NRC on the NRC's Medical Uses Licensee Toolkit Web site for 10 CFR 35.290, 35.390, 35.392, 35.394, and 35.396, the applicant or licensee need not submit detailed documentation of those AUs' classroom and laboratory training to satisfy section A.3.ii. The applicant or licensee need only confirm that the individual has completed training on the use of Y-90 microspheres.

⁴ [Appendix N, "Model Emergency Procedures," NUREG-1556, Volume 9](#) provides additional guidance.

- treatment site and catheter positioning to ensure administration of the Y-90 microspheres is in accordance with the written directive; and
- b. Using administrative controls to prevent a medical event involving the use of byproduct material⁵; and
 - c. Evaluation of patient or research subject's treatments to determine whether the administered dosage was in accordance with the written directive or if a medical event has occurred.

Has successfully completed training in the operation of the delivery system, safety procedures, and clinical use for the type of Y-90 microsphere for which authorization is sought. This requirement may be satisfied by completing a training program provided by the vendor for new users or by receiving training supervised by an AU⁶ who is authorized for the type of Y-90 microsphere for which the individual is seeking authorization. Clinical use training to support unsupervised use should include at least three hands-on patient cases for each type of Y-90 microsphere requested, conducted in the physical presence of an AU⁶ who is authorized for the type of Y-90 microsphere for which the individual is seeking authorization.

However, if a proposed AU cannot complete patient cases prior to authorization; the licensee may request conditional approval with the proposed AU's completion of at least three mock simulated cases. Mock simulated cases should demonstrate issues that are encountered during Y-90 microsphere administration procedures and should be completed by the individual in the physical presence of a manufacturer representative or an AU⁶ who is authorized for the type of Y-90 microsphere for which the individual is seeking authorization. Following conditional approval, the individual should complete the clinical casework described above, including case work, within a year following the license issuance or amendment that names the individual as an AU for Y-90 microsphere use.⁷ The licensee

⁵ Appendix S, "Model Procedures for Developing, Maintaining, and Implementing Written Directives," NUREG-1556, Volume 9 provides additional guidance.

⁶ A physician who is not an AU but who meets the T&E criteria for the applicable type of Y-90 microsphere may be approved to supervise another physician's training or first hands-on patient cases on a case-by-case basis.

⁷ If an individual does not complete patient case work prior to being granted AU status, the date for which they should complete their patient case work by will be listed on the license in the Material and Use table which lists the AUs for the license. The license will be amended when the licensee submits appropriate documentation that the AU has

may submit documentation to the NRC requesting an extension of this timeframe. The supporting documentation should include a commitment to perform continuing T&E (e.g., one additional mock case prior to performing patient cases) in the use of the type of Y-90 microsphere requested until the first three patient cases are completed, and

- C. Has obtained written attestation that the individual has satisfactorily completed the requirements in criteria A and B of this section and is able to independently fulfill the radiation safety-related duties as an AU for the type of Y-90 microsphere requested. The attestation must be obtained from either:
1. An AU⁶ who is authorized for the type of Y-90 microsphere for which the individual is seeking authorization; or
 2. A residency program director who affirms in writing that the attestation represents the consensus of the residency program faculty where at least one faculty member is a physician who is an AU⁶ for the type of Y-90 microsphere brachytherapy being authorized and concurs with the attestation provided by the residency program director. The residency training program must be approved by the Residency Review Committee of the Accreditation Council for Graduate Medical Education or the Royal College of Physicians and Surgeons of Canada or the Council on Postdoctoral Training of the American Osteopathic Association and must include T&E specified in criteria A and B of this section.

In accordance with 10 CFR 35.59, the T&E specified above must have been obtained within the seven years preceding the date of application or the individual must have had related continuing education and experience since the required T&E was completed. Recent training provided under Section B may be sufficient to show recentness of training. This recentness of training requirement applies to all individuals, including those who are board certified or listed as an AU on an NRC or Agreement State license.

5.2 Radiation Safety Officer

The Radiation Safety Officer (RSO) must have training as specified in 10 CFR 35.50, including training in radiation safety, regulatory issues, and emergency procedures for Y-90 microsphere use. An RSO already listed on a license that includes one type of Y-90 microsphere device

completed their patient cases. Absent such documentation, the license may be amended to remove AUs from the license.

does not require additional approval for another type of Y-90 microsphere device but should be familiar with all devices used at the facility.

5.3 Training and Experience Documentation

The applicant must submit documentation of the above T&E for all physicians requesting authorization to use Y-90 microspheres. This documentation shall include the clinical use cases and written attestation and supervising physician T&E, if necessary. For individuals completing the patient cases following the license amendment, this documentation shall include documentation from the manufacturer representative or supervising physician of the three mock 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 an AU⁶ who is authorized for the type of Y-90 microsphere for which the individual is seeking authorization. The documentation should commit to initiating these three cases within six months following the license issuance or amendment that names the individual as an AU for Y-90 microsphere use and complete the three cases within a year. Additionally, for applicants that have individuals completing the patient cases following the license amendment, the applicant's commitment will include submitting documentation from the manufacturer to the appropriate NRC Regional Office within 60 days of when these three patient cases have been satisfactorily completed.

5.4 Team Approach

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

5.5 Notification

The NRC recognizes that, if an AU satisfies the T&E 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 T&E listed in this 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 materials licensee, a permit issued by a Commission or Agreement State licensee of a broad scope, or a permit issued by a Commission master materials license broad scope permittee; and
3. the licensee provides the NRC a copy of the license or permit on which the AU is listed for the specific Y-90 microsphere use; and
4. the licensee provides the NRC documentation of the completion of three patient cases if previously not submitted to the NRC; and
5. 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 Y-90 microsphere.

If this authorization is approved, these notification conditions will be incorporated as license conditions on the license.

5.6 Grandfathering

If a licensee adopts this licensing guidance revision, physicians who are currently authorized for the medical use of a specific type of Y-90 microsphere under T&E criteria listed in previous revisions do not have to meet the revised criteria in this revision for that type of Y-90 microsphere.

6. 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:

6.1 Procedures for Administration

The licensee must have procedures for administration requiring a written directive as specified in 10 CFR 35.41, specifically to ensure high confidence that the patient's or human research subject's identity is verified before each administration and each administration is in accordance with the written directive. As Y-90 microspheres are too small to be calibrated in accordance with 10 CFR 35.432, the licensee shall determine and record the activity of each dosage before medical use in accordance with 10 CFR 35.63 and 10 CFR 35.60 even though Y-90 microspheres are listed as sealed sources in their Sealed Source and Device Registries. The licensee shall commit to following the manufacturer's procedures or submit alternative methods for calculating and documenting the dose or activity to the treatment site; preparing the dose for administration; determining shunting to non-treatment sites; and determining if a medical event has occurred (e.g., performing pre- and post-vial dose measurements with appropriate instrumentation, evaluating post-treatment imaging). For the purpose of this guidance, shunting is defined as blood flow through pathway or bypass due to patient vasculature causing the Y-90 microspheres to flow to an unwanted location. Unexpected dose or activity to an organ or tissue other than the treatment site that is caused by catheter placement during delivery of the Y-90 microspheres is not considered shunting and should be evaluated as a possible medical event.

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 shall be prepared within 24 hours after the completion or termination of the administration and must include the name of the individual who determined the dose or administered activity and the date the record is completed.

6.2 Written Directives

The licensee must complete a written directive, which must be dated and signed by an AU before the administration in accordance with 10 CFR 35.40(a) and 10 CFR 35.40(c) unless a delay in order to provide a written directive would jeopardize the patient's health, as allowed under 10 CFR 35.40(c)(1). The licensee shall retain a copy of the written directive in accordance with 10 CFR 35.2040.

Due to the unique properties of Y-90 microsphere brachytherapy, the following written directive condition should be used instead of 10 CFR 35.40(b).

The written directive shall include the patient or human research subject's name; the treatment site; the radionuclide (including the physical form [Y-90 microspheres]); the model of spheres (e.g. TheraSphere® or SIR-spheres®) or manufacturer; the prescribed dose or activity; and, if appropriate for the type of microsphere used, the statement "or dose or activity delivered at stasis."

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, the activity shall be used for all documentation and evaluations. As described in 10 CFR 35.2, "treatment site" means the anatomical description of the tissue intended to receive a radiation dose, as described in a written directive. For instance, the treatment site may be described as the lobe or segment that is intended to receive the Y-90 microspheres and the tissue that is expected to receive Y-90 microspheres due to shunting. For the purpose of this guidance, stasis is defined as a stoppage or slowdown in the flow of blood. The inability to complete administration due to clogging or kinking of the catheter is not considered stasis.

6.2.1 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 shall 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 signature of an AU for Y-90 microspheres, and the date signed.

6.2.2 *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 shall document such changes in the written directive within 24 hours after the completion or termination of the administration. The modification to the written directive shall include the reason for not administering the intended dose or activity, the signature of an AU for Y-90 microspheres, and the date signed.

6.3 **Medical Event Reporting**

In place of 10 CFR 35.3045(a), the licensee shall commit to report any event, except for an event that is caused by shunting as described in the criteria below, or as a result of patient intervention, as defined in 10 CFR 35.2 as an actions by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration. The criteria for event reporting is:

- 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; and
 - an administration of the wrong radionuclide or type of microsphere; or
 - an administration to the wrong individual or human research subject; or
 - an administration by the wrong route of administration; or
 - an administration by the wrong mode of treatment; or
- the total dose or activity delivered 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
- A dose to the skin or an organ or tissue other than the treatment site that exceeds by 0.5 Sv (50 rem) to an organ or tissue and 50 percent or more of the dose expected from the administration defined in the written directive (excluding shunting as defined in Section 6.1 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\(b\)-\(g\)](#).

6.4 Sealed Source and Device Use

The licensee should commit to use only yttrium-90 microspheres for therapeutic medical uses as approved in the Sealed Source and Device Registries for TheraSphere® and SIR-spheres®, including maximum activity per vial limit.

6.5 Inventory

Due to the short half-life of Y-90 (64 hours) and the fact that microspheres are not managed as individual discrete sources, the requirements in [10 CFR 35.67](#) for semi-annual physical inventory of brachytherapy sources and recordkeeping in [10 CFR 35.2406](#) are not applicable to microspheres. Rather, the requirements for brachytherapy source accountability (10 CFR 35.406), receipt (10 CFR 20.1906), labeling (10 CFR 20.1904 and 10 CFR 35.69), storage (10 CFR 20.1801 and 10 CFR 35.92), and disposal (see the “Waste Disposal Issues” section of this guidance document) are sufficient to ensure accountability of Y-90 in the form of microspheres possessed by a licensee.

6.6 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 the radioactive device (i.e. SIR-spheres®, TheraSphere®); and
- Label syringes and syringe radiation shields with the radioactive device.

6.7 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](#). Guidance for release of patients or human research subjects following administration of radioactive materials may be found in [Regulatory Guide 8.39](#), “Release of Patients Administered Radioactive Materials.”

6.8 Surveys

As the Y-90 microspheres are too small to be seen, licensees should survey, with an appropriate radiation detection survey instrument, all areas that the Y-90 microspheres are prepared for use or administered. The survey should be conducted immediately following each preparation and administration in unrestricted areas and by the end of the day for restricted areas. A licensee should retain a record of each survey for three years and the record should include the date of the survey, the results of the survey, the instrument used to perform the survey, and the name of the individual who performed the survey. Licensees do not need to perform surveys in an area(s) where patients or human research subjects are confined when they cannot be released under 10 CFR 35.75.

6.9 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-Spheres® 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 without a license amendment 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's Medical Uses Licensee Toolkit Web site](#); and
3. the revision has been reviewed and approved by the licensee's RSO 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 the updated guidance will be incorporated as license conditions in the license.

7. Notes to Licensees

7.1 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 shall request an amendment for the new conditions, and a broad scope licensee shall perform its own engineering and radiation safety evaluation addressing those differences.

7.2 Use of Other Y-90 Microspheres

The SSD safety evaluation for a specific manufacturer's Y-90 microsphere does not cover the use of any other Y-90 microspheres, including those prepared by an authorized nuclear pharmacist or an AU 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 the 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.

7.3 TheraSphere® Use Outside Humanitarian Device Exemption (HDE) Restrictions

The Nordion (Canada) TheraSphere® Y-90 glass microspheres are approved by the U.S. Food and Drug Administration (FDA) under the provisions of a "Humanitarian Device Exemption" (HDE No. H980006), which includes unique restrictions on the medical use of the device. Nothing in the NRC regulations relieves the licensee from complying with applicable FDA requirements.

If the Institutional Review Board (IRB), as defined in 45 CFR Part 46, that is required to approve and monitor the use of the Nordion (Canada) 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 the protection of human research subjects." (Note: One of the conditions of approval for an HDE is that there be an IRB initial review and approval before a humanitarian use device is used at a facility, as well as continuing review of its use.)

7.4 Waste Disposal Issues

Y-90 microspheres are known to potentially contain radioactive impurities, some of which are long-lived (i.e., half-lives of greater than 120 days) (Refer to [Information Notice \(IN\) 2007-10](#), "Yttrium-90 Therasphere® and Sirspheres® Impurities"). Due to different manufacturing processes, the activity and radionuclides of the impurities vary for different Y-90 microsphere products. Impurities that have been recently found in reactor-activated microspheres include

small amounts of long-lived radionuclides such as europium-152, europium-154, and cobalt-60.⁸ Impurities that have been recently found from microspheres with generator-produced Y-90 include trace amounts of strontium-90.⁹

Licensees should be aware that the activity and type of impurities can change and be different from that described above. The NRC does not limit manufacturers to specific manufacturing processes, and it is therefore possible for the activity and types of radionuclide impurities to change for both products. Additionally, unused or partially used vials are likely to contain higher activities of impurities.

Although impurities need not be listed on an NRC license; licensees are responsible to ensure the microspheres are handled and disposed of in accordance with 10 CFR [Part 20](#) and [Part 35](#) requirements. Specifically, 10 CFR 35.92 requires that licensees monitor byproduct material with a physical half-life of less than or equal to 120 days at the surface before disposal and determine that its radioactivity cannot be distinguished from the background radiation level with an appropriate radiation detection survey meter before disposal. Therefore, regardless of the length of time they have been allowed to decay, licensees are not permitted to dispose of Y-90 microspheres if radioactivity can be distinguished from the background radiation level with an appropriate radiation detection survey meter.

If waste is determined to contain impurities with a physical half-life of greater than 120 days that can be distinguished from the background radiation level with an appropriate radiation detection survey meter, the licensee may need to use one or more of the following means to dispose of waste associated with the Y-90 microspheres:

- return the Y-90 microspheres to the manufacturer, if the manufacturer is authorized to receive Y-90 microspheres; or
- transfer the Y-90 microspheres to an authorized recipient pursuant to requirements in 10 CFR [Part 20](#) and [Part 30](#).

⁸ J. Metyko, J. Williford, W. Erwin, J. Poston, S. Jimenez. "Long-lived Impurities of ⁹⁰Y-labeled microspheres, TheraSphere and SIR-Spheres, and the impact on patient dose and waste management." *Health Phys.* **103**(3), S204-S208 (2012).

⁹ J. Metyko, W. Erwin, J. Poston, and S. Jimenez. "⁹⁰Sr Content in ⁹⁰Y-labeled SIR-Spheres and Zevalin." *Health Phys.* **107**(5), S177-S180 (2014)

See [Regulatory Issue Summary 2004-17, Revision 1](#), “Revised Decay-in-Storage Provisions for the Storage of Radioactive Waste Containing Byproduct Material,” for more information regarding requirements for holding waste for decay-in-storage.

7.5 Autopsy and Cremation

Y-90 microspheres are permanent implants that are not removed from the body by biological methods. Because Y-90 has a 64-hour half-life, Y-90 will likely have significantly decayed before a patient’s death. Patients treated with Y-90 microspheres will not usually represent an external radiation hazard to persons handling the body. However, in the case of autopsy or cremation, the radiation hazard increases due to the need for individuals to handle tissues that may contain radioactive material, especially if the death occurs soon after treatment with Y-90 microspheres. The National Council on Radiation Protection and Measurements (NCRP) [Report No. 155](#), “Management of Radionuclide Therapy Patients,” December 2006, may contain helpful information for radiation safety considerations associated with autopsy or cremation of patients with permanent implants. Additionally, [NUREG-1556, Volume 9](#), Appendix N, “Model Emergency Procedures,” contains additional guidance regarding autopsy and cremation of patients who have received therapeutic amounts of radionuclides.

8. Notes to Regulators

8.1 Inspection Frequency

Licenses authorizing Y-90 microsphere brachytherapy should be inspected every two years. Per Enclosure 1 to [Inspection Manual Chapter 2800](#), licenses authorizing emerging technology under 10 CFR 35.1000 are assigned a Priority 2 inspection code.

8.2 Program Code

The NRC regions should use program code 02240.

9. Paperwork Reduction Act Statement

This Licensing Guidance provides voluntary guidance for implementing the mandatory information collections in 10 CFR Parts 30 and 35 that are subject to the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et. seq.). These information collection were approved by the Office of Management and Budget (OMB), approval numbers 3150-0017 and 3150-0010. Send comments regarding this information collection to the Information Services Branch (T6-A10M), U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, or by e-mail to Infocollects.Resource@nrc.gov, and to the OMB reviewer at: OMB Office of Information and Regulatory Affairs (3150-0017, 3150-0010), Attn: Desk Officer for the Nuclear Regulatory Commission, 725 17th Street, NW Washington, DC 20503; e-mail: oira_submission@omb.eop.gov.

The NRC may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the document requesting or requiring the collection displays a currently valid OMB control number.

10. Public Protection Notification

The NRC may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the document requesting or requiring the collection displays a currently valid OMB control number

Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres®
Licensing Guidance, Revision 10

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