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Yttrium-90 Microsphere Brachytherapy Sources and Devices

Eye90 Microspheres® Licensing Guidance

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1. Background

This licensing guidance for yttrium-90 (Y-90) microsphere brachytherapy is exclusively for the use of Eye90 microspheres®. At the time of publication of this guidance, Eye90 microspheres® is a new microsphere device approved by the Food and Drug Administration (FDA) under an Investigational Device Exemption (IDE) for clinical trial.

Eye90 microspheres® are permanent implantable radiopaque glass Y-90 microspheres used for treatment of conditions of the liver. The microspheres are provided as a unit dose in 2.5 mL saline, contained in an acrylic shield. The microspheres are delivered to tumor vasculature via a catheter placed under fluoroscopy guidance using a proprietary delivery system comprised of a sterile, single-use delivery device and a re-useable, nonsterile system container. This product is unique to the existing FDA-approved Y-90 microsphere products at the time of publication, due to the radiopaque quality of the microspheres. The AU may choose to use fluoroscopy to directly image the radiopaque microspheres in the tumor vasculature during administration and via any x-ray imaging modality thereafter.

At the time of publication of this guidance, Eye90 microspheres® does not have an SSDR safety certificate.

This document has been adapted from the existing guidance for other microsphere brachytherapy, “Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance” (ML20080J208) revised in March 2020, to reflect necessary changes unique to Eye90 microspheres®, in particular the ability to visualize the microspheres during administration via fluoroscopy. Because this product is new and still being investigated in early clinical trials at the time of publication, a separate guidance was needed to facilitate any necessary future revisions as the NRC and medical communities gain experience with Eye90 microspheres®.

2. 10 CFR 35.1000 Use

Although Eye90 microspheres® are manual brachytherapy sources used for permanent implantation therapy, Eye90 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, Eye90 microspheres® brachytherapy is regulated under 10 CFR 35.1000, "Other medical uses of byproduct material or radiation from byproduct material[1]."

3. Licensing Guidance

This guidance provides applicants with an acceptable means of satisfying the requirements for a license for the use of Eye90 microspheres® 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 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;" Subpart M, "Reports;" and Subpart N, "Enforcement," except as specified in this guidance. Additionally, applicants must meet applicable requirements of 10 CFR Part 19, "Notices, Instructions and Reports to Workers: Inspection and Investigations;" Part 20, "Standards for Protection Against Radiation;"[2] Part 30, "Rules of General Applicability to

[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.

[2] Refer to IN-21-02 for further information regarding compliance with Part 20.

Domestic Licensing of Byproduct Material;" and Part 71, "Packaging and Transformation of Radioactive 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.

	Eye90 Microspheres®	
Radionuclides (NRC Form 313 Item 5a)	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., ABK Biomedical, Inc. Model Eye90 microspheres®])	**For broad scope licensees using the SSD exemption in 10 CFR 35.15(g):** Glass microsphere (current manufacturer as approved for IDE by the FDA [e.g., ABK Biomedical, Inc. Model Eye90 microspheres®])
Maximum Possession Limit (NRC Form 313 Item 5c)	X* Ci total	

Purpose of Use (NRC Form 313 Item 6)	Eye90 microspheres® for permanent brachytherapy using delivery system as listed in the Sealed Source and Device Registry	**For broad scope licensees using the SSD exemption in 10 CFR 35.15(g):** Eye90 microspheres® for permanent brachytherapy using delivery system as described in the FDA-approved IDE research protocol

***** 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 Eye90 microspheres® will be used and stored.

4.4 Leak Tests

Leak tests are not required for Eye90 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 Eye90 microspheres® brachytherapy. Applicants may also submit alternative T&E criteria 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.

   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 ABR[2]; or
      (c) Board certification in diagnostic radiology by the American Osteopathic Board of Radiology (AOBR)[3]; 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 ABR[2]; or
      (b) Board subspecialty certification in interventional radiology by the AOBR[2]; or
      (c) One year of supervised clinical experience in interventional radiology; and

[3] 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 training[4] 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 Eye90 microspheres® brachytherapy or training provided by an Eye90 microspheres® 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 Eye90 microspheres® and performing checks for proper operation of survey meters; and
    c. Calculating and measuring the activity and safely preparing the Eye90 microspheres® to be delivered to the patient or human research subject; and
    d. Using procedures to control and to contain spilled byproduct material, including Eye90 microspheres®, safely and using proper decontamination procedures. The procedures should address any special circumstances that may be encountered, such as the electrostatic charge of Eye90 microspheres® and the proper survey instrument and survey technique for beta emitters[5]; and
iv. Has work experience or training under the supervision of an AU or manufacturer representative[6] for Eye90 microspheres® brachytherapy, 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,

[4] 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.

[5] Appendix N, "Model Emergency Procedures," NUREG-1556, Volume 9 provides additional guidance.

[6] Because there were no licensees approved for Eye90 Microspheres® at the time this licensing guidance was initially published in 2023, there are a limited number of AUs available to provide training. Therefore, training provided by a manufacturer representative will be accepted in lieu of training provided by an AU until [DATE].

including selection of activity of Eye90 microspheres® to be administered to each treatment site and catheter positioning to ensure administration of the Eye90 microspheres® is in accordance with the written directive; and

b. Using administrative controls to prevent a medical event involving the use of byproduct material[7]; 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.

B.

Has successfully completed training in the operation of the delivery system, safety procedures, and clinical use for Eye90 microspheres®. This requirement may be satisfied by completing a training program provided by the vendor for new users or by receiving training supervised by an AU[8] who is authorized for Eye90 microspheres®. Clinical use training to support unsupervised use should include at least three hands-on patient cases for Eye90 microspheres®, conducted in the physical presence of an AU[6, 9] who is authorized for Eye90 microspheres®.

Additionally, if the proposed AU is already trained on the use of another model of microspheres, they must be trained in the specific differences between Eye90 microspheres® and the other model(s) of microspheres for which they are approved, including activity prescription, written directive preparation, microsphere administration, and spill procedures.

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

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

[8] A physician who is not an AU but who meets the T&E criteria for Eye90 microspheres may be approved to supervise another physician's training or first hands-on patient cases on a case-by-case basis.

[9] Because there were no licensees approved for Eye90 microspheres® at the time this licensing guidance was initially published in [YEAR], there are a limited number of preceptors available to provide training and sign attestations. Therefore, the NRC is postponing requiring a written attestation until [DATE HERE]. At that time, attestations will be required for individuals who are not already authorized for use of Eye90 microspheres®. The NRC will continue to review the availability of preceptors and may revise this guidance if it determines that sufficient preceptors have not become available. In addition, all individuals seeking authorization for use of Eye90 microspheres® must submit documentation of successful completion of required training as provided by the manufacturer.

three mock simulated cases. Mock simulated cases should demonstrate issues that are encountered during Eye90 microspheres® administration procedures and should be completed by the individual in the physical presence of a manufacturer representative or an AU[6] who is authorized Eye90 microspheres®. 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 Eye90 microspheres® use. The licensee 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 Eye90 microspheres® 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 Eye90 microspheres®. The attestation must be obtained from either:

1. An AU[6, 7] who is authorized forEye90 microspheres®; 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 AU[6] for Eye90 microspheres® brachytherapy 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 does not require additional approval for another type of Y-90 microsphere device but should be familiar with all radiation safety aspects, including cleaning up spills, associated 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 Eye90 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 AU[7, 8] who is authorized for the Eye90 microspheres®. The documentation should commit to requiring the individual to perform a mock simulated case if six months or more have passed since last performing a hands-on or mock simulated case. 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 Eye90 microspheres® 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 Eye90 microspheres®.

5.5 Notification

The NRC recognizes that, if an AU satisfies the T&E listed in NRC's licensing guidance for Eye90 microspheres® and is currently listed on a Commission or Agreement State medical use license or permit for Eye90 microspheres®, the AU should be allowed to work under a different license for the medical use of Eye90 microspheres®. A limited specific medical use applicant initially applying for authorization for the medical use of Eye90 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 Eye90microspheres®; and
2. the AU is currently listed for Eye90 microspheres® 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 Eye90 microspheres® 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 Eye90 microspheres®.

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 Eye90 microspheres® under T&E criteria listed in previous revisions do not have to meet the revised criteria in this revision for Eye90 microspheres®.

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 Eye90 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 Eye90 microspheres® are not considered to be unsealed byproduct material. 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 Eye90 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 Eye90 microspheres® is not considered shunting and should be evaluated as a possible medical event.

Administration of Eye90 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 Eye90 microspheres® 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. Eye90 microspheres®) 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 Eye90 microspheres® 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 Eye90 microspheres® and the tissue that is expected to receive Eye90 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 Eye90 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 Eye90 microspheres®, and the date signed.

6.*2.3 Termination of Treatment Due to Observed Deposition*

If the AU decides to terminate administration due to observation of undesired radiopaque microsphere deposition, the AU may make an oral revision to a written directive to modify the prescribed dose or activity. The oral revision must be documented as soon as possible in the patient's record. A revised written directive must be signed by an AU within 24 hours of the oral revision and shall include a reason for the termination, the dose or activity delivered, the signature of an AU for Eye90 microspheres®, and the date signed. If the dose delivered to the unintended target exceeds the thresholds for medical event reporting as outlined in Section 6.3, then the licensee shall comply with the medical event reporting and notification requirements as described in 10 CFR 35.3045(b)-(g).

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 only use Eye90 microspheres® for therapeutic medical uses as approved in the SSD registration certificate for Eye90 microspheres®, including maximum activity per vial limit.[10]

[10] At the time of publication of this guidance, Eye90 Microspheres® does not have a Sealed Source and Device (SSD) registration certificate. Note that 10 CFR 35.15(g) exempts licensees possessing a Type A specific license of broad scope from the SSD manufacturer requirement in 10 CFR 35.49(a). Broad scope licensees instead must perform their own internal safety evaluation as mentioned in Section 7.1.

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 Eye90 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. Eye90 microspheres®); 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 Eye90 microspheres® are too small to be seen, licensees should survey, with an appropriate radiation detection survey instrument, all areas that the Eye90 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 Eye90 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 Eye90 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 Eye90 microspheres® 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

At the time of publication of this guidance, Eye90 microspheres® is does not have an SSD registration certificate. Upon issuance of an SSD registration certificate for Eye90 microspheres®, the following guidance applies:

If the physical conditions of use exceed those reported in the SSD registration 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

At the time of publication of this guidance, Eye90 microspheres® is pending an SSD safety evaluation. Upon issuance of an SSD registration certificate for Eye90 microspheres®, the following guidance applies:

The SSD safety evaluation for a specific manufacturer's Y-90 microsphere does not cover the use of any other Y-90 microspheres in its device for administration. The medical use of such a source will require a new SSD registration 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 registration 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 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.[11] Impurities that have been recently found from microspheres with generator-produced Y-90 include trace amounts of strontium-90.[12] While this IN was generated in response to other products, licensees should be prepared to follow similar precautions and procedures when handling waste generated by Eye90 Microspheres®.

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 all Y-90 microsphere 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

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

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

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 Eye90 microspheres®:

- return the Eye90 microspheres® to the manufacturer, if the manufacturer is authorized to receive Y-90 microspheres; or
- transfer the Eye90 microspheres® to an authorized recipient pursuant to requirements in 10 CFR Part 20 and Part 30.

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.

7.4 Autopsy and Cremation

Eye90 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 Eye90 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 Eye90 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.

7.5 Radiation Safety Committee

If a licensee is required to have an RSC in accordance with 10 CFR 35.24(f), then the committee must include an AU for the use of Y-90 microspheres.

8. Notes to Regulators

8.1 Inspection Frequency

Licenses authorizing Eye90 microspheres® 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.

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.