UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION III
2443 WARRENVILLE ROAD, SUITE 210
LISLE, ILLINOIS 60532-4352

September 28, 2021

Wallace O. Furman, CNMT
Radiation Safety Officer
SSM Health DePaul Hospital - St. Louis
Dept. of Nuclear Medicine
12303 DePaul Dr.
Bridgeton, MO 63044

SUBJECT: ADDITIONAL INFORMATION NEEDED REGARDING AMENDMENT REQUEST FOR SSM HEALTH DEPAUL HOSPITAL - ST. LOUIS, NRC LICENSE NO. 24-02490-03

Dear Mr. Furman:

Our office has reviewed the resubmitted request for NRC to amend SSM Health DePaul Hospital - St. Louis's (your) U.S. Nuclear Regulatory Commission (NRC) Materials License, received August 4, 2021, to authorizations for the use of yttrium-90 SIR-Spheres and TheraSphere microspheres, as permitted by Title 10 of the *Code of Federal Regulations* (10 CFR) Section 35.1000. Upon review, our office has determined that additional information is needed to amend the license as requested.

Specifically, the request referenced commitments and information in a superseded 2016 version of NRC's guidance for the referenced use. The request omitted information requested in the current 2021 version of NRC's applicable yttrium-90 microspheres guidance document. Your amendment request is available electronically from NRC's Agencywide Documents Access and Management System (ADAMS) at accession number ML21218A029. The NRC's ADAMS is accessible from the NRC Web site at http://www.nrc.gov/reading-rm/adams.html.

For additional and current guidance, please refer to the NRC's 10 CFR 35.1000 April 20, 2021 publication, "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance," Revision 10.2, pp. 2 through 15. The guidance document is available electronically from the NRC's ADAMS at accession number ML21089A364.

RADIOACTIVE MATERIAL TO BE AUTHORIZED ON THE LICENSE:

1. The requested chemical/physical form, for each of TheraSphere and SIR-Spheres, including source manufacturers and model numbers, is inconsistent with NRC's current licensing guidance, including the Sealed Source and Device Registry (SSDR) Certificates. **For each of TheraSphere and SIR-Spheres, as requested, please indicate the form (glass microsphere or resin microsphere, as applicable), the sealed source manufacturer(s), and the sealed source models.**

2. The requested possession limit listed in the request was listed as 1 Ci overall, rather than for each of TheraSphere or SIR-Spheres. **Please provide the overall maximum per-radionuclide, per microsphere type, possession limit, based on the maximum amount the applicant anticipates having at one time (i.e., either 500 mCi or 1 Ci per microsphere type).**

PURPOSE OF USE TO BE AUTHORIZED ON THE LICENSE:

3. The requested purpose of use referenced one single SSDR certificate, which may have been superseded and does not apply to both TheraSphere and SIR-Spheres. **For each of TheraSphere and SIR-Spheres, as requested, please indicate an accurate and/or more generic purpose of use (e.g. "TheraSphere® for permanent brachytherapy using delivery system as listed in the Sealed Source and Device Registry" and/or "SIR-Spheres® for permanent brachytherapy using delivery system as listed in the Sealed Source and Device Registry," as applicable and as suggested in the current guidance document).**

FACILITIES AND EQUIPMENT:

4. The application included an address and diagram for the location of use. However, the diagrams were unclear as to the specific areas where yttrium-90 microspheres, including waste, would be used and stored. **Please include the address of use and updated facility diagrams with your request. Diagrams should be drawn to scale, show lockable doors, and indicate storage, refrigerators, freezers, waste containers, sewerage drains and work areas on the map. If temporary brachytherapy administration areas will be used, a sample diagram for such patient administration areas may be acceptable.**

INDIVIDUAL(S) RESPONSIBLE FOR RADIATION SAFETY PROGRAM:

5. In the referenced request, it is NRC's understanding that three 10 CFR 35.1000 (limited to yttrium-90 microspheres as SIR-Spheres) authorized users (AUs) were requested: Robert M. Fischer, M.D., Rebecca J. Mueller, M.D., and Andre Strzembosz, M.D. Although some training documentation was included for each of these proposed 10 CFR 35.1000 individuals, NRC's review indicated that documentation was incomplete or illegible. **For continued review of the proposed responsible individuals, please provide the following for:**

   (a) Because Dr. Mueller and Dr. Strzembosz are listed on the referenced license as 10 CFR 35.300 AUs, the following additional information is needed for each individual:

      i. Documentation of 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 emitters; and

ii. **Documentation of 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 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 material; 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

iii. Documentation of 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 AU 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 AU 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 AU 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. 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 the use of the type of Y-90 microsphere requested until the first three patient cases are completed, and

iv. **Written attestation that Dr. Mueller and Dr. Strzembosz have 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:**
   A. An AU who is authorized for the type of Y-90 microsphere for which the individual is seeking authorization; or
   B. 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 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.

(b) Because Dr. Fischer is listed on the referenced license as only a 10 CFR 35.100 and 200 AU, the information needed for Dr. Mueller and for Dr. Strzembosz is needed. In addition, for Dr. Fischer please provide the following documentation of experience in interventional radiology for Dr. Fischer only:
   i. Board certification in interventional radiology/diagnostic radiology by the American Board of Radiology (ABR); or
   ii. Board subspecialty certification in interventional radiology by the American Osteopathic Board of Radiology (AOBR); or
   iii. One year of supervised clinical experience in interventional radiology

Note that the NRC has been alerted to concerns that requiring that clinical case work be conducted in the physical presence of an AU is a significant change from past revisions and if implemented immediately, could cause a delay in training future physicians. Therefore, the NRC is allowing clinical casework to be conducted in the physical presence of a manufacturer representative in place of an AU until November 8, 2021. This manufacturer representative can provide a written attestation that the individual has satisfactorily completed requirements in criteria B. After this date, the casework and written attestation should be completed in the physical presence of an AU.

Also note that, 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.

Further, note that the submitted SirTex letters signed by Shane Allen, Area Sales Director, on March 1, 2021, April 6, 2021, and April 5, 2021, respectively, for Dr. Fischer, Dr. Mueller, and Dr. Strzembosz, are unclear as to which topics requested were covered. Any manufacturer-provided letters should clearly indicate all topics covered in the training, including any mock or clinical yttrium-90 microsphere administrations.

Finally, please note that 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 AU 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 6 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.

6. In the referenced request, NRC was unable to identify any 10 CFR 35.1000 (limited to yttrium-90 microspheres as TheraSphere) AUs requested. If no TheraSphere. **If no TheraSphere AUs are requested, please remove all references to TheraSphere in your response. If TheraSphere AUs are requested, please provide training and experience as described in NRC's guidance document.**

7. In the referenced request, no Radiation Safety Officer (RSO) training and experience was identified, regarding an authorization for yttrium-90 microspheres permitted by 10 CFR 35.1000. **Please provide dates and training provider for RSO training as specified in 10 CFR 35.50, including training in radiation safety, regulatory issues, and emergency procedures for Y-90 microsphere use.**

RADIATION SAFETY PROGRAM:

8. The request omitted Item 6.1, "Procedures for Administration," on pp. 10-11 of the 10 CFR 35.1000 yttrium-90 microspheres licensing guidance. **Please confirm the following statements:**

   (a) "The licensee shall 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." AND

(b) "Administration of Y-90 microspheres shall 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."

9. The request incompletely clarified the definitions of "prescribed dose" and "treatment site," as discussed in Section 6.2, on pp. 11-12 of the guidance document. **Please confirm the following statements:**

(a) "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." AND

(b) "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." AND

(c) "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."

10. The request incompletely clarified the criteria for medical event reporting, as discussed in Section 6.3, on pp. 12-13 of the guidance document. **Please confirm the following statements:**

    (a) "The licensee shall comply with the medical event reporting and notification requirements as described in 10 CFR 35.3045(b)-(g)." AND
    (b) "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.)"

11. The request omitted accountability for yttrium-90 microspheres inventory, as discussed in Section 6.5, on p. 13 of the guidance document. **Please confirm the following statement:**

    "For yttrium-90 microspheres permitted by 10 CFR 35.1000, the licensee shall follow 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."

12. The request omitted information needed to allow the licensee the flexibility to update its program in accordance with future revisions to 10 CFR 35.1000 yttrium-90 microspheres licensing guidance. **If such flexibility is requested, as discussed in Section 6.9, on p. 15 of the guidance document, please indicate the same, and confirm the following:**

    (a) Please indicate that flexibility to update the program is requested; AND
    (b) Confirm that any revisions to the licensee's radiation safety program will assure that:
    i. the revision is in compliance with the regulations; and
    ii. 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
    iii. the revision has been reviewed and approved by the licensee's RSO and licensee's management; and
    iv. the affected individuals are instructed on the revised program before the change is implemented; and
    v. the licensee will retain a record of each change for five years; and

vi. 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.

Please provide a response via a signed and dated letter within 14 days (on or prior to October 12, 2021). For quickest processing, please submit your response as a pdf file attached to an email message. You may also submit a response via fax or via regular mail. If you have any questions regarding this message, please do not hesitate to reach out to me at 630-829-9892.

In accordance with Title 10 of the *Code of Federal Regulations* (10 CFR) Section 2.390 of the NRC's "Rules of Practice and Procedure," a copy of this letter will be available electronically for public inspection in the NRC Public Document Room or from the NRC's ADAMS, accessible from the NRC Web site at https://www.nrc.gov/reading-rm/adams.html.

Sincerely,

Sara A. Forster

Digitally signed by Sara A. Forster
Date: 2021.09.28 19:45:23 -05'00'

Sara A. Forster, M.S.
Health Physicist
Materials Licensing Branch
Division of Nuclear Materials Safety

Docket No.: 030-02308
License No.: 24-02490-03
Control No.: 628103