



December 15, 2023

Secretary, U.S. Nuclear Regulatory Commission  
Washington, D.C. 20555-0001  
ATTN: Rulemakings and Adjudications Staff

**Nuclear Regulatory Commission: Regulatory Basis for Rulemaking on Rubidium-82 Generators, Emerging Technologies, and Other Medical Use of Byproduct Material**

**Docket ID: NRC-2018-0297**

The Society of Interventional Radiology (SIR) is a nonprofit, professional medical society representing approximately 8,000 practicing interventional radiology physicians, trainees, students, scientists, and clinical associates, dedicated to improving patient care through the limitless potential of image-guided therapies. Our members represent the majority of practicing interventional radiologists in the United States and include experts in the treatment of hepatobiliary cancers, such as hepatocellular carcinoma (HCC).

The Society of Interventional Radiology appreciates the opportunity to provide comments on the Regulatory Basis for Rulemaking on Rubidium-82 Generators, Emerging Technologies, and Other Medical Use of Byproduct Material. These comments were additionally reviewed and are endorsed by the Society of Interventional Oncology, a nonprofit medical society supporting and promoting the advancement of interventional oncology as the fourth pillar of cancer therapy worldwide.

Interventional Radiologists are in a unique position within the treatment paradigm for patients requiring yttrium-90 therapy. Our training necessitates that we become experts in the clinical presentation of the underlying disease processes, the pretreatment workup and imaging interpretation, clinical and imaging follow up including interpretation, radiation safety, and technical delivery of the microsource. No other specialty has the same global involvement in the treatment of patients requiring yttrium-90 therapy.

We respectfully ask the NRC to review the comments attached when considering rulemaking. If we can provide any additional information or if you have any questions, please do not hesitate to contact Keith M. Hume, SIR Executive Director, at [khume@sirweb.org](mailto:khume@sirweb.org).

Sincerely,

A handwritten signature in black ink, appearing to read "Alda L. Tam".

Alda L. Tam, MD, MBA, FSIR  
President, Society of Interventional Radiology

cc: Keith Hume, Executive Director, Society of Interventional Radiology

*Question A.7.1:* The NRC is considering defining a “microsource” in § 35.2 as microparticles and microspheres. What types of radiation (such as alpha, beta, gamma) should fit into the definition of “microsource”? Please include comments and a rationale for whether (1) microspheres should be limited to specific types of radiation or certain energies; (2) microsources should be limited to sealed sources with a Sealed Source and Device (SS&D) registry; (3) unsealed microsources should be required to have a SS&D registry; and (4) any additional changes are needed in the current regulations for microsource brachytherapy that would increase flexibility for future microsource brachytherapy.

**Response:**

1. ***Should microspheres be limited to specific types of radiation or certain energies? No.*** A microsource is how the radiation is “packaged.” Meaning, can it be delivered into the body in a small, constrainable, physical device allowing for a defined implantation into a specific area. The type of radiation attached is only relevant in whether it will be clinically effective, but the exact type of radiation is not relevant to the definition of microsource.
2. ***Should microsources be limited to sealed sources with a Sealed Source and Device (SS&D) registry? No.*** Although, we are unaware of any unsealed devices under investigation for therapeutic use in this space, the same reasoning as above holds. If it can be delivered into the body in a constrainable way, allowing for defined implantation into a specific area, it should be included.
3. ***Should unsealed microsources be required to have a SS&D registry? No,*** as we are not sure how this questions differs from those above.
4. ***Are any additional changes needed in the current regulations for microsource brachytherapy that would increase flexibility for future microsource brachytherapy? No.***

*Question A.7.2:* The NRC is considering defining “physiological equilibrium” in § 35.2 to include stasis or other states of equilibrium. Please provide comments on what should be included in a definition of physiological equilibrium or identify other considerations for physiological stop points.

**Response:** Physiologic equilibrium, as defined by stasis or reflux within the target vessel, is not the only end point to consider. Complete administration of the dose should be included if this end point is not defined elsewhere. We also propose the ability to change the scheduled administration intraprocedurally to ensure patient safety. This would allow for unexpected changes in vessel perfusion (from prior chemotherapy, anesthesia administration, spasm, inadvertent vessel injury, etc.), higher residual encountered when smaller microcatheters are required for more distal delivery, inadvertent catheter repositioning, as well as the aforementioned vascular stasis.

*Question A.7.3:* As the complexity of the medical use of byproduct material increases, use of teams in medical care is becoming more common. Please provide comments on the fundamental elements of a successful team-approach program. Section 35.40, “Written directives,” would be amended to clarify that requirements for manual brachytherapy uses under 10 CFR part 35, subpart F, are in § 35.40(b)(6). The NRC is considering listing the subpart I requirements for written directives for microsource manual brachytherapy uses under a new item in § 35.40(b).

**Response: Fundamental elements required for a successful team approach is the utilization of expert knowledge for available sources. In the case of microsource manual brachytherapy, this may include individuals with expertise in:**

- 1. Cancer management: Medical Oncology, Hepatology, Interventional Radiology, Surgical Oncology, Transplant Surgery, and/or Radiation Oncology**
- 2. Catheter placement and imaging: Interventional Radiology**
- 3. Radiation dosimetry: Interventional Radiology, Radiation Oncology, Nuclear Medicine Physicians, Medical Physicists**
- 4. Safe handling of unsealed byproduct material: Radiation safety officer, Nuclear Medicine Physicians, Medical Physicists**

*Question A.7.4:* For microsource manual brachytherapy, please provide comments and a rationale for whether the before-implant written directive should specify the dose or activity.

**Response: For standardization and reproducibility, activity is preferable in the before-implant written directive as it is readily measurable and does not vary depending on volume of tissue treated. Therefore, activity should be utilized for the pre-implant written directive.**

*Question A.7.5:* For microsource manual brachytherapy, please provide comments and a rationale for whether the after-implant written directive should specify the activity administered or the dose delivered to the treatment site.

**Response: For standardization and reproducibility (as above), activity is preferable as it is readily measurable and does not vary depending on volume of tissue treated. Therefore, activity should be utilized for the post-implant written directive.**

*Question A.7.6:* As required by § 35.41 for determining whether a medical event has occurred (as defined in § 35.3045), please comment on whether and why the NRC should require calculating and documenting the activity administered or the activity or dose specifically delivered to the treatment site. By what deadline (e.g., number of hours or days) should this determination be made?

**Response: For standardization and reproducibility, activity is preferable as it is readily measurable and does not vary depending on volume of tissue treated. Therefore, activity should be utilized for the post-implant written directive. With the increasing availability of radiation dosimetry software that allows for post treatment evaluation of tumor uptake and tumor absorbed dose, the time to determination the delivered dose should be extended to afford a reasonable amount to complete this analysis at centers where applicable. In our estimation, 3 business days to complete these calculations is reasonable.**

*Question A.7.7:* For microsource manual brachytherapy, please comment on whether the NRC should require post-treatment imaging to confirm that the treatment was delivered in accordance with the written directive. Why or why not? What other mechanisms are available to confirm that the treatment was delivered in accordance with the written directive?

**Response: Post treatment SPECT and SPECT-CT have not been definitively shown to correlate with oncology outcomes and therefore we do not believe there is scientific evidence to mandate post**

**treatment nuclear imaging for dose delivery confirmation. Currently, intraprocedural angiographic confirmation of the delivery site is adequate for radiation delivery confirmation.**

*Question A.7.9:* Please comment on what types of use should be permitted for microsource manual brachytherapy, including whether the use should be limited to that approved in the sealed source and device registry. Please comment on why unsealed microspheres without a unique delivery system should or should not be allowed.

**Response: Defer; all y90 therapeutics are considered sealed sources.**

*Question A.7.10:* Please comment on why any new requirements for microsource manual brachytherapy should or should not be limited to permanent implants.

**Response: Defer; permanent implants are currently available in the United States. We do not choose to comment on future undeveloped devices.**

*Question A.7.11:* The NRC is considering establishing minimum safety procedures for microspheres and requiring instructions to assure adequate protection of public health and safety. These changes are based on current EMT licensing guidance for yttrium-90 (Y-90) microspheres and expected new uses of microspheres. Please identify and comment on other items that should be included in a new requirement for safety procedures and instructions for microsource manual brachytherapy.

**Response: Additional uses for y90 within the body should not change the safety recommendations to the general public given the short penetration of y90. Even with photon-to-photon interaction, maximum penetration is ~1 cm. All solid organs are greater than 1 cm deep within the body and therefore implantation does not represent a significant exposure risk outside of the intended patient other than the known possibility of leeching, which has been accounted for in post-treatment patient guidelines following the use of resin microspheres. No additional safety precautions should be necessary.**

*Question A.7.12:* The NRC is considering establishing minimum safety precautions (controls) to assure adequate protection of public health and safety. These considerations are based on current EMT licensing guidance for Y-90 microspheres and expected new uses of microspheres. Please identify and comment on other items that should be included in a new requirement for safety precautions (controls) for microsource manual brachytherapy.

**Response: Please see above.**

*Question A.7.13:* The NRC is seeking input on the need for continued conditional approval for AUs of Y-90 microspheres. The current licensing guidance for Y-90 microspheres states that an AU should successfully complete training in the operation of the delivery system, safety procedures, and clinical use for the specific type of Y-90 microsphere for which authorization is sought. The guidance specifies that 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. The guidance allows conditional approval of an AU before completing these three hands-on patient cases if a proposed AU cannot complete patient cases before authorization. This conditional approval was originally added to the

guidance because there were limited Y–90 microsphere licensees and AUs to train future AUs. As the use of Y–90 microspheres has increased significantly, please comment on the continued need for conditional approval for Y–90 microsphere AUs. Indicate why the NRC should or should not continue to allow this pathway for all microspheres and microsources AUs.

**Response: The conditional clause should remain with a defined time period for completion of proctored hands-on cases to allow physicians in more remote areas with less available proctors to treat patient’s within a timely manner. Entirely removing this clause would put patients in rural areas at a disadvantage.**

*Question A.7.14:* The NRC is seeking input on the 80 hours of classroom and laboratory training for interventional radiologists pursuing AU status for Y–90 microsphere and other microsource uses. The NRC in the current EMT licensing guidance for Y–90 microspheres includes a pathway for interventional radiologists to become AUs for Y–90 microspheres use. This pathway requires the interventional radiologist to demonstrate that they have 80 hours of classroom and laboratory training in specific topics and specific work experience important to radiation safety, in addition to demonstrating they have sufficient clinical interventional radiology and diagnostic radiology experience. Please comment on why 80 hours is or is not an appropriate amount of time to ensure these topics are adequately covered. Who should supervise the work experience to ensure the future AUs have adequate radiation safety knowledge and why?

**Response: 80 hours of classroom and laboratory training in the handling, disposal, safety protocols, dosing, and patient selection is adequate for becoming an AU. The y-90 AU pathway is specific for the use of y-90 only, which decreases the scale needed compared to a nuclear medicine or radiation oncologist that will be certified to handle multiple isotopes in a variety of delivery mechanisms. Furthermore, interventional radiologists undergo basic radiation safety and nuclear medicine training as part of their Radiology residency training. Lastly, the 80 hours was chosen as it is compensatory to other subspecialties outside of radiation oncology and nuclear medicine that administer single radioisotopes, for example, cardiology.**

**This training can be supervised by a combination of experts, including medical physicists, nuclear medicine physicians, interventional radiologists, and radiation oncologists.**

*Question A.7.15:* The NRC is seeking input on classroom and laboratory training topics for physicians seeking AU status for all microspheres or other types of microspheres. The NRC, in the current EMT licensing guidance for Y–90 microspheres, provides a pathway for interventional radiologists and physicians that meet the training and experience requirements in §§ 35.390 and 35.490 to become AUs for Y–90 microspheres use. This pathway does not require any classroom and laboratory training or specific work experience for these physicians besides demonstration of successfully completed training in the operation of the delivery system, safety procedures, and clinical use (including hands-on patient cases) for the type of Y–90 microsphere for which authorization is sought. Please identify and comment on any additional classroom and laboratory training topics or specific work experience that should be required for these physicians to become AUs for all microspheres or other types of microspheres in subpart I. What additional training and work experience should be considered, if any, and why?

**Response: No additional training should be considered.**

*Question A.7.16:* The NRC is seeking input on the pathways for physicians to become AUs for use of microspheres and other types of microspheres. The NRC in the current EMT licensing guidance for Y–90



microspheres provides pathways for interventional radiologists and physicians that meet the training and experience requirements in §§ 35.390 and 35.490 to become AUs for Y-90 microsphere use. Please comment on whether and why the NRC should or should not provide additional pathways for other types of physicians to become AUs for use of microspheres or other types of microspheres.

**Response: Interventional Radiologists are in a unique position within the treatment paradigm for patients requiring yttrium-90 therapy. Our training necessitates that we become experts in the clinical presentation of the underlying disease processes, the pretreatment workup and imaging interpretation, clinical and imaging follow-up, radiation safety, and the technical delivery of the microsource. No other specialty has the same global involvement in the treatment of these patients and therefore it makes sense that there is a unique training pathway for our physicians. This is not the case for any other specialty and therefore this alternate pathway is not applicable outside of IR physicians.**

*Question A.7.17:* In most circumstances, are AUs the individuals administering Y-90 microspheres? Is it appropriate for other individuals to administer microspheres under the supervision of an AU? Why or why not?

**Response: Only a physician such as an Interventional Radiologist trained in arterial catheterization and angiography can place the microsource delivery catheter. When an IR physician is the AU, they place this catheter, confirm accurate catheter positioning, and deliver the microspheres. At training institutions, Interventional Radiology residents can participate in this under the supervision of an attending Interventional Radiologist.**

**When the AU is not an Interventional Radiologist, the catheter placement is done by an Interventional Radiologist and the AU must confirm the catheter is in the appropriate position and be present for delivery for the microspheres, though the procedural attending may be the physically administering the microspheres. While this has been standard of care, this may lead to wrong site administration as the AU is not necessarily an expert in angiographic interpretation.**

*Question A.8.1:* Industry is evaluating various novel radionuclide generators. Some novel radionuclide generators may be utilized to compound therapeutic dosages of unsealed byproduct material. The NRC is considering a requirement for licensees to perform breakthrough testing on novel radionuclide generators and report instances when breakthrough exceeds a defined limit. Since breakthrough limits for some novel radionuclide generators have not been established by the United States Pharmacopeia, please explain why it would or would not be sufficient for licensees to develop, implement, and maintain procedures for breakthrough testing and reporting for novel radionuclide generators.

**Response: Defer; Y90-microspheres are assembled by manufacturers so the burden on breakthrough testing is their responsibility.**

*Question A.8.2:* Please comment on the type of T&E that should be required for AUs utilizing novel radionuclide generators and the type of T&E for authorized nuclear pharmacists utilizing novel radionuclide generators.

**Response: Please see above.**

*Question A.8.4:* Due to the increased number and complexity of EMTs, please comment on why the NRC should or should not require continuing education for AUs. If continuing education should be required,



what should it entail, at what frequency should it be acquired, and how should knowledge topics be acquired?

**Response: Continuing Medical Education (CME) is the responsibility of the governing body of each specialty. The American Board of Radiology (ABR) has AU-related CME questions that are comparable to those for all other topics related to our specialty.**

*Question A.8.5:* Please comment on the need for AUs for § 35.200 to have device-specific training on radionuclide generators. If device-specific training is needed, what topics should the training include? Please explain why the training should or should not be specific to the radionuclide generators for which the AUs are supervising the use.

**Response: With the current commercial packaging, the AU does not oversee the generator and therefore this is not necessary.**

*Question A.8.6:* Please comment and provide a rationale for whether physicians authorized for full use under § 35.300 need additional T&E to fulfill their radiation safety-related duties and supervision roles because of expected emerging therapeutic radiopharmaceuticals. Please comment on why additional training is or is not needed on regulatory requirements for emerging therapeutic radiopharmaceuticals. If needed, what topics should the T&E include? What specific training should these AUs be required to have (e.g., vendor training on clinical use and safety procedures) prior to first-time use, if any? Why should they be required or not required to have continuing education?

**Response: The guidelines as currently written are appropriate and include device specific training. Emerging technologies would need to identify appropriate device training pathways similar to those set by current y-90 radiopharmaceutical vendors and device specific orientation should be completed. Given the current process, a minimum of three cases would be recommended.**

*Question A.8.7:* Please comment on why the current AU T&E requirements for use of sealed sources and medical devices for diagnosis in § 35.590 (i.e., 8 hours of classroom and laboratory training in basic radionuclide handling techniques specifically applicable to the use of the device authorized under § 35.500, as well as device-specific training in the use of the device) are or are not appropriate for emerging sealed sources and medical devices containing sealed sources. If AUs for § 35.500 need additional training and work experience on emerging sealed sources and medical devices containing sealed sources for diagnosis, what topics should be covered?

**Response: The guidelines as currently written are appropriate and include device specific training. Emerging technologies would need to identify appropriate device training pathways similar to those set by current y-90 radiopharmaceutical vendors and device specific orientation should be completed. Given the current process, a minimum of three cases would be recommended.**

