February 7, 2018

Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: (Docket ID NRC-2017-0215) Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres®; Comments of the American College of Radiology

The American College of Radiology (ACR)—a professional organization representing more than 35,000 radiologists, radiation oncologists, interventional radiologists, nuclear medicine physicians, and medical physicists—appreciates the opportunity to comment regarding the U.S. Nuclear Regulatory Commission's (NRC) draft tenth revision of the Yttrium-90 (Y-90) microsphere brachytherapy licensing guidance (NRC–2017–0215). The ACR also appreciates NRC's extension of the associated public comment period to allow for more stakeholder consideration and feedback.

ACR Recommendations

A working group of NRC and Agreement State representatives developed the draft tenth revision of the Y-90 microsphere brachytherapy licensing guidance following a period of extensive review and public deliberation by the NRC's Advisory Committee on the Medical Uses of Isotopes (ACMUI). While most of the proposed changes were aligned with ACMUI's recommendations, the NRC/Agreement States deviated from medical experts on the primary issue of whether it is appropriate to remove the manufacturer-provided alternate pathway in Section B of the training and experience (T&E) section. In the current guidance (Rev. 9), individuals can opt to satisfy the three Authorized Use (AU)-supervised patient cases prerequisite by instead:

1. Completing a minimum of three manufacturer-provided simulated (in vitro) cases;
2. Obtaining a license amendment to name the individual as an AU for Y-90 microsphere use; then,
3. Completing the first three patient (in vivo) cases under direct supervision of a manufacturer representative. The clinical experience of the manufacturer representative(s) proctoring the cases is left unspecified.

The NRC's proposed tenth revision would eliminate the above pathway following a two-year grace period—the effect of which would require future trainees to complete three AU-supervised patient cases prior to obtaining AU status. The NRC also proposed to require the clinically-oriented work

experience requirements in Section A(3)(iii)(c) and (e) of the current T&E criteria be completed under AU supervision during those patient cases. The various other work experience requirements in Section A(3)(iii) of the T&E criteria could continue to be satisfied either under AU supervision or via manufacturer-provided training.

The ACR gathered input from nuclear medicine physicians, interventional radiologists, radiation oncologists, medical physicists, and other members regarding NRC's proposed removal of the manufacturer-provided alternate pathway. While there was no clear consensus regarding how NRC's draft revision would impact individuals' ability to complete all work experience prerequisites, there was significant concern regarding the preparedness and ability of the interventional radiology community to provide ample replacement training opportunities within the proposed two-year grace period.

Several ACR members were skeptical about the NRC and ACMUI's discussions regarding the proliferation of additional "mini-fellowship" opportunities that could be provided by broad scope licensees around the country to meet interventional radiologists' demand for supervised work experience within the proposed two-year grace period. This concept is complex and could be frustrated by competitive organization issues, hospital privileging complications, costs and limited resources. Also, this mini-fellowship mechanism may not be best for a given individual's situation because certain individuals/licensees would benefit from completing supervised patient cases within their normal clinical environments and in coordination with their usual team/support staff.

Most ACR stakeholders do not believe NRC should propose a controversial T&E modification that is substantially misaligned with ACMUI recommendations, particularly without a comprehensive, evidence-based understanding of the potential impact on medical stakeholders and patients. The ACMUI's role as a federal advisory committee of independent experts is to advise NRC staff on policy and technical issues that arise in the regulation of the medical uses of radioactive material in diagnosis and therapy. The process through which ACMUI arrived at its recommendations in 2016 was generally deliberative, transparent, and representative of licensees' and patients' interests.

Therefore, the ACR provides the following recommendations to NRC:

- The ACR supports ACMUI's recommendation that NRC should maintain the current flexibility until such time as the impact of any potential change is clearly understood by the agency and stakeholder community. Specifically, individuals should continue to have the option of the manufacturer-provided alternate pathway #2 in Section B of the T&E portion of the Y-90 licensing guidance (Rev. 9).
- Prior to proposing significant changes to the Y-90 T&E criteria in the future, NRC should conduct a current assessment of the AU workforce/customer data from broad scope licensees and product manufacturers. This assessment should explore the size and distribution of the Y-90 AU population, readiness of the community for requirement changes, and any other considerations that could impede patient access. This could potentially be a part of ACMUI's

ongoing efforts to reevaluate all T&E requirements in 10 CFR Part 35, or it could be a standalone assessment conducted by NRC staff of all those authorized for Y-90 use.

The ACR acknowledges the shared concern of NRC and the ACMUI regarding the lack of specified medical training/experience for the manufacturer representatives proctoring patient cases. To address this concern, ACR recommends a clarification that these representatives be:

1. Experienced AUs with the Y-90 microsphere type in question; or,
2. Physicians not approved as AUs on a license but who have expertise in the interventional radiology aspects of the procedure with the Y-90 microsphere type in question. Their clinical experience should include calculation of dosimetry, catheter placement, safe handling of unsealed byproduct material, and administration.

In terms of #2 above, interventional radiologists on multidisciplinary teams are inherently central to these procedures, even when not formally approved on NRC or Agreement State licenses as AUs. Non-AU interventional radiologists should therefore be able to contract with product manufacturers to proctor cases if they have extensive expertise with the specific product and can instruct other physicians about device delivery, calculation of dosimetry, and medical judgement considerations of direct and indirect relevance to NRC's regulatory authority. Experienced interventional radiologists are also well-positioned to advise individuals regarding practice of medicine issues outside of NRC's scope but of the topmost priority to patients, their families, and clinicians.

Finally, the ACR strongly supports NRC's proposal to not impact the status of existing Y-90 AUs with any future modifications to the T&E section of the guidance.

In summary, ACR recommends:

- Maintaining the mechanism of the current alternate pathway #2 in Section B of the T&E criteria (Rev. 9), as recommended by the ACMUI.
- Conducting an assessment of Y-90 AU population, distribution, and availability to supervise in vivo cases before any future NRC proposals to remove the alternate pathway from the guidance.
- Adding the aforementioned experience requirements for manufacturer-representatives proctoring the required documented patient cases.

ACR Responses to NRC Questions in the FRN

(Q1) *Recommended Minimum Clinical Experience:* Due to the complexity of delivery of Y-90 microspheres, the licensing guidance historically and currently recommends that a prospective AU demonstrate he or she has clinical experience with the device. The current recommendation is that 3 patient cases for each type of microsphere should be completed for each prospective authorized user prior to approval. This recommendation is similar to requirements in other therapy modalities, such

as section 35.390 of title 10 of the Code of Federal Regulations (10 CFR). The NRC is seeking specific comments on whether 3 patient cases provide adequate clinical experience for a physician to gain AU status for Y-90 microspheres.

The ACR believes the current minimum of three patient cases with the product is appropriate and aligned with the current requirements of other NRC-regulated therapy modalities. We believe NRC should recommend that manufacturer-representatives/AUs supervising cases be available for appropriate questions for a reasonable period of time following the supervised clinical experience. The three case minimum could be reconsidered during ACMUI's ongoing evaluation of all T&E requirements in Part 35.

(Q2) ***Adding Authorization for Other Microsphere Type:*** **The NRC is seeking comments to determine additional training needed when an AU who is already authorized to use one type of microsphere requests authorization for use of another type of microsphere. For instance, are 3 additional cases for the other type of microsphere necessary for the AU to gain the knowledge to safely administer the new microsphere, or should the number of cases be left to the discretion of the supervising AU?**

The ACR agrees with the NRC's current approach of requiring a separate series of cases per product type. The general consensus among experts is that clinical experience administering one of the two types of Y-90 microspheres is not inherently transferrable to the other due to the distinct delivery systems, dosimetry methods, and other issues. This approach is consistent with existing NRC requirements for radiopharmaceutical therapies of differing radionuclides.

(Q3) ***Written Attestation from Preceptor:*** **Historically, the NRC has not required a written attestation, signed by a preceptor AU, because there was not a sufficient number of AUs to supervise the training and sign the written attestation. However, given that the NRC and Agreement States have licensed Y-90 microsphere brachytherapy AUs for over 10 years, the NRC is seeking comments to determine if there is anything unique about Y-90 microsphere brachytherapy compared to other types of manual brachytherapy that would obviate the need for a written attestation.**

Generally speaking, preceptor attestations are of questionable value to NRC and Agreement State regulators, particularly for recognized board-certified individuals. The preceptor attestation sections of NRC/Agreement State forms are redundant with board certification as well as with other sections of the NRC/Agreement State forms documenting completion of T&E requirements.

Regarding Y-90 microsphere use, ACR believes it would be unduly burdensome in certain situations for manufacturer-trained individuals to obtain attestation statements from AU preceptors. For example, there could be scenarios in which physicians contracted by manufacturers to supervise cases are uncomfortable signing attestations for liability reasons. Instead of mandatory AU-preceptor attestations, ACR recommends that the Y-90 microsphere manufacturers continue to provide documentation demonstrating completion of NRC requirements.

(Q4) *Clinical Experience under the Supervision of a Manufacturer Representative*: The proposed licensing guidance removes the alternate pathway, which allows an individual to become an AU for Y-90 microsphere brachytherapy prior to completing any patient cases if the applicant commits that the first three patient cases completed by that AU will be hands-on and supervised in the physical presence of a manufacturer representative. This alternate pathway remained in the licensing guidance for several years because there were a limited number of AUs who were authorized for each type of Y-90 microsphere, which made it difficult for physicians who were seeking authorization to complete the necessary clinical experience described in Section B under the supervision of another AU already authorized for the use of Y-90 microspheres. The NRC is seeking comments on whether completing the recommended clinical experience under the supervision of AU(s) authorized for the type of microsphere for which the new physician is seeking authorization still presents an undue burden on physicians. Further, the NRC is seeking comments on whether any unique characteristics of Y-90 microsphere brachytherapy warrant continuation of this alternate training pathway. Additionally, the NRC is seeking comments on whether finding licensed facilities at which the physicians could complete this clinical experience would be difficult.

This question is addressed in the "ACR Recommendations" section of this comment submission (pages 1-3).

(Q5) *Timeliness for Completion of In-Vivo Cases:* The NRC is seeking comments on whether the proposed one in-vivo case prior to treating patients would be appropriate if 6 months has passed to ensure recentness of training or whether this proposal could potentially lower licensee's safety standards for the patients being treated.

The ACR does not support the NRC's proposed removal of pathway #2 in Section B of the T&E criteria, or the proposed required timeframe of six months to complete the three supervised patient cases during the two-year grace period. However, we believe it would be appropriate for NRC to advise that individuals strive to complete their manufacturer-proctored in vivo cases as quickly as is appropriate following training. An arbitrary deadline and extension process should not be explicitly required as this would add administrative burden/cost for licensees and regulators without substantiated offsetting benefits.

(Q6) *Medical Event Definition:* The NRC is seeking comments on the definition of medical events (ME) for Y-90 microspheres as provided in the proposed guidance. A primary purpose of ME reporting is to identify the cause of the event in order to correct them and prevent their recurrence. In the last 2 years there have been several MEs reported where the administration of the Y-90 results in dose or activity to the lobe opposite the lobe documented in the written directive. The working group was informed that in some instances, the AU may determine in the interventional radiology suite that they may be unable to deliver the amount of Y-90 microspheres to the intended lobe, but still wish to perform the treatment knowing some dose or activity may go to the lobe opposite the lobe documented in the written directive. The NRC is seeking specific comments on whether the delivery of Y-90 microspheres can be controlled to a specific lobe or location as described in the written directive

and, if not, whether flexibility in the written directive is necessary to avoid reporting of events that cannot be controlled using the current technology. If flexibility is necessary, the NRC is seeking comments on whether the use of dose or activity ranges in the written directive or an ability to change the written directive in the interventional radiology suite prior to administering the Y-90 microspheres would be adequate. This type of revision could be made verbally by the AU, as long as the revision is documented in writing and signed by the AU within 24 hours of providing the revision verbally, consistent with other uses in 10 CFR part 35.

The ACR supports the concept of a formal revision made verbally in the suite then documented in writing within 24 hours, more or less consistent with NRC's most recent approach to low dose rate/permanent implant brachytherapy. As with other brachytherapy modalities, there are anatomical and physiological factors that could require physician-intended variance from the written directive in order to provide optimal care for a given patient. Verbal revisions should be appropriately documented in the written record within 24 hours after the procedure. This type of process would allow for more precision and dynamic decision-making in the suite than the alternative of listing a predetermined dose/activity range in the written directive.

Given the regulatory status of these products, guidance may also be sought from U.S. Food and Drug Administration (FDA) on how intended variances of mutual interest should be documented by the licensee, and what intended variances should be reported to FDA, as these are not medical events.

Thank you in advance for your consideration of these comments. As always, the American College of Radiology welcomes the opportunity for continued dialogue with the NRC. Should you have any questions on the points addressed herein, or if we can otherwise be of assistance, please do not hesitate to contact Gloria Romanelli, ACR Senior Director of Government Relations, at 703-716-7550 / gromanelli@acr.org, or Michael Peters, ACR Director of Legislative and Regulatory Affairs, at 703-716-7546 / mpeters@acr.org.

Sincerely,

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Chair, Board of Chancellors
American College of Radiology