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Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere and SIR-Spheres; Draft Guidance; Extension of Comment Period

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General Comment

Please see attached.

Attachments

Sirtex Response to NRC Proposed Changes FINAL

83 FR 159
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February 7, 2017

RE: Docket ID NRC-2017-0215

To Whom It May Concern:

On November 7, 2017, and January 2, 2018, the U.S. Nuclear Regulatory Commission (NRC) requested public comment on the draft licensing guidance entitled "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance" (82 FR 51655 and 83 FR 159). Sirtex opposes changes to remove the alternate pathway and is providing responses to NRC's questions from the *Federal Register* Notice. See below. Additional Sirtex comments on the proposed guidance changes are included in Enclosure 1.

NRC Question 1

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 three (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.

Sirtex Response 1

Sirtex believes the three (3) patient-case requirement is sufficient and in alignment with requirements for other types of radiation therapy. Sirtex opposes changes to the guidance to require more than three (3) patient cases. The current Sirtex training program is modeled around this same concept as part of the post-market commitment Sirtex has with the U.S. Food and Drug Administration to train all physicians who use SIR-Spheres Y-90 resin microspheres. Sirtex does not recommend any changes to the guidance with regard to the minimum clinical experience requirements for three (3) patient cases.

NRC Question 2

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?

Sirtex Response 2

Sirtex believes that authorization for one type of microsphere should continue to be independent of authorization for another type of microsphere, and Sirtex opposes changes to the guidance to allow cross-over of training for the two Y-90 microsphere brachytherapy products. The microspheres, delivery systems, delivery methods, dosimetry methods, safety considerations, and associated clinical data are different for each product. Training or experience with one product is not sufficient for authorization for the other. Product-specific training and three (3), hands-on, supervised cases should continue to be documented for approval of authorization for each type of microsphere. Sirtex does not recommend any changes to the guidance regarding cross-over of training for different Y-90 microsphere brachytherapy products.

NRC Question 3

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.

Sirtex Response 3

Sirtex continues to believe there are unique aspects about Y-90 microsphere brachytherapy that obviate the need for a written attestation, and as such Sirtex opposes changes to the guidance to require written attestations. The use of Y-90 microspheres is not consistent across fellowship programs, and the type of physician who serves as an AU varies. Physicians who complete residency or fellowship (e.g., interventional radiologists, radiation oncologists, and nuclear medicine physicians) may or may not receive training or hands-on experience with one Y-90 microsphere brachytherapy product, much less both. Furthermore, the type of physician serving as the AU varies from site to site, and a physician in one specialty would not sign an attestation for a physician in another specialty. Sirtex does not recommend any changes to the guidance to require written attestations.

NRC Question 4

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.

Sirtex Response 4

Sirtex believes that completing the recommended clinical experience under the supervision of an AU still presents an undue burden on physicians. Sirtex also believes that there are unique characteristics of Y-90 brachytherapy that warrant continuation of the alternate training pathway. Sirtex opposes changes to the guidance to remove the alternate pathway for the following reasons:

1. Not all interventional radiology, nuclear medicine, and radiation oncology residency or fellowship programs offer hands-on experience for BOTH Y-90 technologies. Some do not provide hands-on training for either. Others may have only one.
2. Not all physicians obtain hands-on experience during residency or fellowship training, even when one or both products may be used at the site.
3. Y-90 microsphere brachytherapy use is not yet incorporated or standardized into a board certification process.
4. Physicians may not initiate a Y-90 microsphere brachytherapy program immediately upon completing a residency or fellowship program and may not be able to obtain the required documentation later, if the program director or other AUs have left the residency or fellowship training program when the physician requests paperwork, possibly years later.
5. AU status is site specific, often influenced by internal politics and not training and experience. For example, some of the most experienced IR physicians operate at a "two physician model" facility where the radiation oncologist or nuclear medicine physician serves as the AU. If the IR wishes to open a Y-90 microsphere brachytherapy program at another location, the IR does not have a pathway to achieve AU status, as a radiation oncologist or nuclear medicine physician typically would not provide attestation to the training and experience of the IR.
6. Agreement States do not always recognize the AU status of a physician from another Agreement State or the NRC. Some states (e.g. CA, IL, TX) have historically created their own guidance for Y-90 microsphere brachytherapy.

In response to NRC's question regarding the difficulty for a physician to find a licensed facility to complete the required clinical case experience, Sirtex notes that this is not only difficult, **it is impossible**. Outside of fellowship, a physician seeking AU status at a new site not yet licensed for Y-90 cannot treat patients at another site where Y-90 is already approved for use. A physician can only practice medicine in the state(s) where he/she is licensed (i.e. medically licensed) and at facilities where he/she is credentialed (e.g. hospital-specific credentialing). Therefore, a physician cannot visit a facility licensed for Y-90 to obtain the required experience performing hands-on supervised casework. This would specifically preclude physicians from obtaining hands-on patient cases at "Centers of Excellence" or during "mini-fellowships". Physicians must have the ability to obtain the required experience at their own facility, which can reasonably and safely be done under the supervision of the manufacturer using the existing alternate pathway. Removing the manufacturer pathway limits patient access to a potentially life-extending treatment option. Sirtex strongly recommends the NRC maintain the alternate pathway.

NRC Question 5

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.

Sirtex Response 5

Sirtex opposes the proposed change to introduce a 6-month recentness of training requirement for *in-vivo* cases, and Sirtex notes that no safety data has been provided to support such a change. Patient availability and referral patterns vary, especially in smaller cities and community hospitals. NRC should not include prescriptive timelines for recentness of training for *in-vivo* patient cases. The completion of the three (3) required cases should be reviewed during regular inspections and does not merit special consideration in licensing.

NRC Question 6

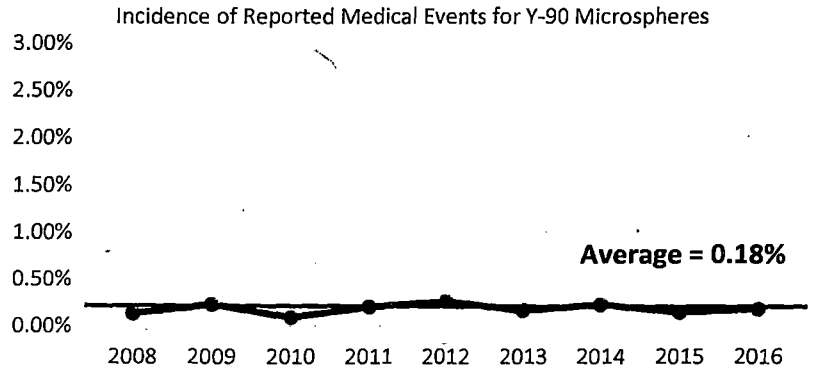
Medical Event Definition: The NRC is seeking comments on the definition of medical events (ME) for Y-90 microspheres as provided in the proposed guidance. A primary purpose of ME reporting is to identify the cause of the event in order to correct them and prevent their recurrence. In the last 2 years 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.

Sirtex Response 6

Sirtex agrees that flexibility in the written directive is necessary to avoid reporting of events that cannot be controlled using the current technology. For SIR-Spheres Y-90 resin microspheres, the delivery of Y-90 microspheres can typically be controlled to a specific lobe or location as described in the written directive; however, microspheres may unexpectedly flow to a non-target site, and a physician may choose to continue to administer the product because the benefit of treatment to the target site outweighs the risk to the non-target site. In these situations, Sirtex recommends the occurrence be documented in the written directive, which is not a change to the written directive *per se*, but rather documentation of the outcome of the procedure. Sirtex agrees that this addition of information in the written directive could be done verbally by the AU, if the written directive is signed by the AU within 24 hours. This is similar to the approach currently used for shunting and stasis, which prevents unnecessary medical event reporting.

Sirtex does not recommend the use of ranges for activities to be administered. This practice would not be consistent with other types of manual brachytherapy and is not necessary for this technology.

Using publicly available data from the ACMUI's website and Y-90 microsphere manufacturer's annual reports, Sirtex notes that the incidence rate of reported medical events remains consistently low. See chart below. While the number of medical events reported for Y-90 microsphere brachytherapy may be generally increasing, the number of doses sold (i.e. procedures performed) also continues to increase. The incidence rate has not statistically significantly changed over the last eight years. The incidence rate for Y-90 microsphere brachytherapy medical events is also comparable to the incidence rate, 0.10%, reported by the International Commission on Radiation Protection for high-dose-rate brachytherapy (Valentin, 2005). Based on this data, there does not appear to be any decrease in safety during Y-90 microsphere brachytherapy procedures, and significant changes to the Y-90 microsphere brachytherapy policy, especially regarding training and experience, are not merited.



In summary, Sirtex opposes the NRC's proposal to remove the alternate pathway as it creates an unnecessary barrier for physicians to achieve AU status without a demonstrable increase in safety. Sirtex has opened more than 300 new sites in the last five years, primarily in smaller cities and community-based hospitals, with each of these sites treating many patients who may not have access to a major metropolitan area or treatment center. These community-based hospital sites are typically not opened by existing AU physicians moving to a new geographical area, and without the alternate pathway, there may be no viable means for a physician to obtain the necessary training and experience to achieve AU status at a new site. Removal of the alternate pathway would limit the ability of physicians to achieve AU status, which would also limit patient access to this potentially life-extending treatment option. Sirtex strongly opposes the removal of the alternate pathway.

Please feel free to contact me or Ashley Cockerham, Regulatory Affairs and Compliance Manager – Americas at acockerham@sirtex.com or (703) 945-5959 with additional questions.

Sincerely,

Shyam Srinivas, M.D., Ph.D.

Shyam Srinivas, M.D., Ph.D.
Chief Medical Officer
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10 CFR 35.1000 Use

Sirtex supports administrative changes in this section to remove language about Authorized Users (AUs) other than radiation oncologists.

Licensing Guidance

Sirtex supports administrative changes in this section, including the footnote on Agreement State compatibility.

General

Radionuclides, Form Possession Limits, and Purpose of Use

Sirtex supports the change to remove the per vial activity limit and to reference the amount approved in the Sealed Source and Device Registry (SSDR). Sirtex also supports the change to remove references to SSDR numbers in the guidance.

Authorized Users

Training and Experience

A.1.

Sirtex supports the addition of AU language for 10 CFR 35.1000 for Y-90 microspheres.

A.3.i.

Sirtex supports the changes to clarify that an Interventional Radiologist (IR) can either be board certified or have the requisite clinical experience in diagnostic radiology and/or interventional radiology and that choosing one pathway for diagnostic radiology does not bind a physician to that same pathway for interventional radiology. Sirtex also supports the addition of the footnote to clarify that board certificates issued without "AU Eligible" are still adequate to meet the requirements in this section.

A.3.ii.

Sirtex supports the addition of the footnote to clarify that certain board-certified IRs do not need a signed letter from a residency or fellowship program to document 80 hours of classroom and laboratory training. Sirtex understands that the required 80 hours of training is inherent in the board certification programs recognized by NRC; however, this is a common request from Agreement State regulators which causes unnecessary delays in licensing and undue burden on potential AUs to obtain additional documentation.

A.3.iii. and iv.

Sirtex supports the change to remove patient evaluation and the use of administrative controls to prevent a Medical Event from the list of work experience items that can be provided by a manufacturer representative with a caveat. Sirtex understands NRC's intent for a clinician to oversee these areas;

however, the Sirtex training program is not set up, nor would it be feasible to have a clinician oversee this work experience *prior* to the license amendment. Sirtex proctors (i.e. clinicians) do provide work experience and training on patient evaluation and medical events during the proctoring process; however, the proctoring process commences *after* the AU has been named on the license. If NRC wishes for a clinician to oversee these two areas, Sirtex proposes that the work experience be combined with the work experience in Section B.

B.

Sirtex does NOT support the removal of the alternate pathway. Physicians must have the ability to obtain the training and work experience in this section *after* being named as an AU on the license with a license commitment to submit additional documentation later. Justification for this practice is provided in the Sirtex responses to NRC's questions in the body of the letter associated with this enclosure.

Sirtex suggests the following:

1. Remove all proposed historical language and the two-year grace period;
2. Reinsert the original alternate pathway language;
3. Add work experience language from the proposed new Section A.3.iv. to Section B; and
4. Delete the now empty Section A.3.iv.

Sirtex does NOT support the addition of the recentness of training requirement. Many Agreement States already try to implement this requirement for board certification and diagnostic radiology or interventional radiology training. This is counterintuitive, as a very experienced physician is an ideal candidate to move into performing the more advanced Y-90 microsphere procedure. Also, Sirtex has a commitment to the U.S. Food and Drug Administration to train every physician who wishes to use the technology, so every physician using SIR-Spheres® Y-90 resin microspheres would have recent training from the manufacturer. While NRC states that training under Section B *may* be sufficient to show a recentness of training, this opens the door to unnecessary interpretation by Agreement States. If the requirement is included in final published guidance, it should be clear that board certification and diagnostic radiology/interventional radiology experience may have been obtained more than 7 years ago and that the recentness of training only applies to the relevant product training and work experience.

Sirtex supports the addition of example license condition language with modifications, as indicated below:

"The following provides a standard license condition that may be used to grant AU status to a physician for Y-90 microsphere use under ~~this~~ the alternate pathway~~ until the pathway is removed~~.

> Physician(s), [insert name(s) of AU(s)], is/are permitted to work as an AU~~s~~ for [TheraSphere® ~~and/or~~ /SIR-Spheres®] yttrium-90 microsphere use in accordance with the letter(s) dated [enter dates of letter(s)]. ~~Within 6 months of being authorized for medical use of each manufacturers' yttrium-90 microspheres, e~~Each AU must complete at least three clinical patient cases, in the physical presence and under the supervision of a manufacturer representative. The licensee shall submit documentation from the manufacturer of each physician's clinical experience within ~~7 months of the date of the amendment adding the authorized user~~ 60 days of the last supervised patient case. ~~Absent such documentation, t~~The license may be amended to remove an AU~~s~~ from the license, if no cases have been completed within 12 months."

Training and Experience Documentation

Sirtex suggests that this section be updated to coincide with the Sirtex proposed language in Section B. NRC should extend the timeframe for submitting documentation of work experience required in Section B from 30 to 60 days. It is difficult for the manufacturer to receive and evaluate the necessary paperwork and then create and issue a regulatory document back to the licensee to comply with the current guidance. A 60-day timeline would allow for appropriate processing of documentation and should not impact NRC or Agreement State inspections that run on yearly, not monthly cycles.

License Commitments

Medical Event Reporting

Sirtex supports the added language for defining shunting.

Inventory

Sirtex supports the additional clarification that the requirements for semi-annual physical inventory and associated recordkeeping are not applicable.

Patient Release

Sirtex supports the concept of providing additional information for the release of patients treated with Y-90 microspheres, as nearly all patients are treated on an outpatient-basis. However, NRC's proposed reference to Regulatory Guide (RG) 8.39 is misleading, as RG 8.39 does not list any values for activities of Y-90 or dose rates for authorizing patient release. As an alternative, Sirtex suggests that NRC include language from RG 8.39 stating that activity and dose rate limits are not applicable to the medical use of Y-90 microspheres because of the minimal exposures to members of the public resulting from activities normally administered.

Notes to Licensees

Waste Disposal Issues

Sirtex does NOT support the addition of the sentence stating NRC has received reports that generator-produced Y-90 microspheres may contain Y-88. The sentence, as proposed, does not include a verifiable, scientific reference, and Y-88 impurities are not possible with current Sirtex manufacturing methods.

Sirtex supports all other information added to this section.

Autopsy and Cremation

Sirtex supports the addition of information regarding autopsy and cremation.