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General Comment

See attached file(s)

Attachments

Y90 Comments

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Overview, Considerations, and Questions
Y-90 Microsphere Guidance/Proposed Rev. 10
December 2017

Background

Y-90 microsphere brachytherapy is regulated by the Nuclear Regulatory Commission (NRC) under 10 CFR 35.1000, which serves as an incubator for new and emerging modalities by regulating the use of those materials via referenced guidance. The general idea is that the Y-90 requirements would remain in guidance and evolve into maturity over the course of numerous revisions. Once fully mature, the requirements would theoretically move from 1000/guidance into the mature areas of Part 35—presumably as either a subsection under 35.390, an entirely new subpart of 35.300, or some other fashion.

The version of the Y-90 guidance currently in effect is Revision 9 (published in early 2016). NRC's latest proposal is the draft 10th revision, released for a 60-day comment period ending January 8, 2018. ACR filed a comment period extension request on December 18, 2017 – we should hear more in the near future.

In the current (Rev. 9) version of the Y-90 guidance, prospective AUs who satisfy the various prerequisites related to training and AU-supervised work experience (or a manufacturer training alternative to that supervised work experience) are then required to receive additional training in the clinical use/operations of the products in question, including completing 3 Authorized User (AU)-supervised patient cases. **As an alternative to 3 AU-supervised cases, trainees can instead complete 3 manufacturer simulations and commit to completing their first 3 patient cases under direct manufacturer supervision.**

For the draft Revision 10, NRC is proposing that: 1) this manufacturer-proctored alternative to AU-supervised patient cases be eliminated after a 2 year grace period; and, 2) that two of the clinically-oriented items in the work experience requirements (related to Written Directive evaluation and Medical Event prevention) be completed only under AU-supervision. The other prerequisites in the Y-90 T&E section would not substantially change, including the nonclinical manufacturer-provided training alternatives to the AU-supervised work experience requirements (i.e., those that involve unpacking/handling, QC of survey meters, activity measurement, and spill containment). Also, manufacturers could still be involved in the clinical use/operations training alongside the AU proctor.

From NRC's perspective, there were several motivations behind the proposal:

- NRC prefers that physicians (in particular, AUs) supervise patient care and provide the clinical aspects of training.
- This proposal is viewed within the agency as a step toward normalization of Y-90 regulation. They ultimately intend for Y-90 requirements to be more similar to the requirements of the other regulated uses that require a Written Directive. Again, the purpose of 1000 is to evolve the requirements for new/emerging modalities and eventually move the fully-baked version of the requirements into the more mature areas of Part 35.
- The manufacturer-proctored flexibility was originally intended to be temporary relief to grow a stable population of AUs. After 10 years (and a 2-year grace period) of the manufacturer-proctored alternative to supervised cases being available, NRC believes the Y-90 AU community is large/mature enough to meet trainees' demand without using non-AU proctors.

- Relative to other NRC-regulated uses, there is a noticeable number each year of Medical Events associated with administrations of Y-90 (they are still statistically insignificant, however).

The NRC's medical advisory committee (ACMUI) was tasked with developing recommendations in 2016 on these draft modifications, including an earlier version of the above proposal. After extensive public deliberation, **ACMUI recommended that NRC maintain the current flexibility.** ACMUI had several concerns about NRC's proposal, including the lack of data demonstrating that the Y-90 AU population was ready to meet demand for supervised cases.

COMMENT: As a proctor for one of the manufacturers, when a proctoring opportunity is posted to the web app, it does not remain on the site for long. There is no question in my mind that there are plenty of AU proctors to supervise new users.

Additionally, ACMUI recommended that NRC could address its uneasiness about non-clinician manufacturer proctors on patient cases by specifying some minimum medical education level for those representatives.

COMMENT: Minimum medical education does not make the manufacturer reps physicians and, consequently, they should not be recommending clinical pathways. Even if the physician performing the procedure has the ultimate responsibility whether to accept this "advice" or not, he will likely not pass the test of the administration if he does not. Consequently, the ultimate responsibility of making the clinical decision rests with the rep, a non-physician.

ACMUI did feel, however, that institutions could/should eventually step in with "mini-fellowship" opportunities if the manufacturer-proctored alternative was eliminated.

COMMENT: This is unlikely to occur as institutions do not want to train their competitors in this medical market. The SIR can hold educational programs to educate these potential users but, in view of the slanted presentations over the last few years, the NRC needs to be assured that these presentations are without bias.

A working group of NRC and Agreement State staff decided not to follow ACMUI's recommendations—in part to use the draft proposal to solicit more feedback from the Y-90 medical community about its readiness level.

To maintain the current flexibility for how the clinical cases can be completed, we need to demonstrate to NRC that the Y-90 AU community is unable to meet trainees' demand for AU-supervised clinical use/operations experience. **We can currently make the following points:**

- *Lack of data...* NRC has not produced sufficient data substantiating that the Y-90 AU community is currently positioned to meet trainees' demand for proctored cases. The availability of quantitative data on AUs is limited because of the added complications of the different license types (e.g., broad scope licenses, Agreement State licenses, etc). NRC must:
    - reach out to broad scope licensees and the two Y-90 microsphere product manufacturers to better understand the denominator and distribution/coverage; and,
    - Engage in a wider data-gathering effort with programs/institutions to make sure any future change does not create unintended consequences. (I.e., NRC should not make changes based on assumptions.)

- *Competition hurdles...* The NRC's belief that the major institutions will step in and adequately meet demand with opportunities is likely overly optimistic because of inter-institutional barriers and facility medical privileging complexities.
- ACMUI publicly discussed, voted, and recommended in 2016 that the NRC maintain the current alternate pathway with some clarification on minimum medical training for manufacturer proctors of in vivo cases. *NRC should adhere to their federal advisory committee's expert recommendations*, which were made following an extensive process with input from stakeholder community.
- ACMUI is currently undergoing a holistic review of all T&E requirements in Part 35. Any guidance changes to the T&E for Y-90 should be reviewed as part of that in-depth, multi-year process—not before.
- NRC should have solicited public comments from stakeholders about NRC's deviation from ACMUI recommendations on this issue via some other mechanism (e.g., an RFI) rather than within the draft Revision 10.

Finding information on the following questions could help us:

- Denominator... How many of these procedures are done each year? How many active AUs are there?
- State of Y-90 penetration... Are mostly the large/broad scope licensees providing this procedure? Many small practices/facilities? Rural coverage?

COMMENT: It has been the announced policy of Sirtex to sell to any hospital that is interested regardless of size. As has been noted, the Medical Event occurrence has risen and it is likely to those physicians who do not have an adequate background and experience with the product. The NRC should consider establishing a floor to the number of Y90 procedures performed annually so that institutions maintain their abilities to perform this complex procedure. I suggest that if an institution does not perform 2-3 per month, they should not be performing this procedure since every procedure becomes a "new" procedure. As was shown in the 1950s with cardiac surgery, the more a hospital performs, the fewer the number of complications. The same is true of Y90.

- AU replacement if/when employees leave or retire... What is currently done in various settings? Complications for licensees replacing AUs?
- Manufacturer proctors... What level of medical training (or what type of medical professional) should be required of an industry representative supervising the in vivo cases? Industry has stated that these representatives are often clinicians themselves– is this generally correct?

COMMENT: Few of the industry reps have a background to qualify them to make medical decisions. Only a few are nurses or interventional technologists, neither of whom are qualified to advise on these procedural or medical decisions.

- Quality of manufacturer simulations and manufacturer-proctored cases? Community confidence in the industry rep proctors?

COMMENT: It is far more likely that a new physician performing this procedure will listen and heed the advice of a physician. There is little confidence in the usual rep; nor should there be. The medical decisions are complex and require much thought and judgement which require an MD.

- Training... How do IR fellowships handle Y-90? What are the complications of integrating AU-proctored cases into those fellowships? Can that be done within the 2 year grace period – if not, what timeframe would be appropriate for programs and fellowship opportunities to evolve to meet demand?

COMMENT: IR fellowships can handle the educational portion of the AU requirements but not the proctored cases since they are in their fellowship and are not an independent physician who is responsible for his own actions. Every hospital environment is different and the fellow should be in his own hospital before the proctored cases should occur.

- NRC proposed requiring manufacturer-proctored trainees to complete their first 3 manufacturer-supervised patient cases within 6 months after training. Would that be a reasonable time frame during the 2-year grace period for trainees in the current pipeline to complete their cases? Is it reasonable to have a "6-months-following-training" requirement even if NRC does not finalize their proposal to eliminate the overall flexibility of the manufacturer-proctored pathway?

COMMENT: This is a bad idea. There are plenty of AUs or IRs well versed in Y90 procedures to train them and the manufacturer has a vested interest in getting them through the cases as quickly as possible to increase sales. And, as mentioned above, the reps have neither the education nor the license to practice medicine and yet their advice can be seen as authoritative since they control if the physician passes has proctorship.

Also, NRC has asked the following additional questions:

- Are 3 AU-supervised patient cases per product enough, or are more cases appropriate? Is it appropriate that they currently require 3 per product, or should cases with TheraSpheres also satisfy the case requirement for SIR-Spheres (or should it be left to the discretion of the supervising AU to decide)?

COMMENT: Because the delivery systems of each product are radically different as is the dose calculation, the AU supervised cases should be 3 of each.

- NRC has not historically required a written statement from an AU-preceptor attesting to trainees' ability to follow regulations as they do for other types of manual brachytherapy – should they? If not, why not?

COMMENT: Since this is no different than other preceptor trained physicians, there should be a written evaluation.

- Would finding licensed facilities at which the physicians could complete AU-supervised clinical experience be difficult if the flexibility were to go away? If so, why?

COMMENT: Proctoring should be done at the hospital where the physician practices. If done elsewhere, the physician is likely distracted and the learning environment does not include the entire team. I have seen both and the physician learns much better in his home hospital environment.

- Medical Event definition... 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 35.

COMMENT: The microspheres can be controlled and the dose measured to each lobe. There is no need for new flexibility. If the dose is unable to be completely given, the written directive can be changed immediately. It is far better to know the exact dose that is applied to each lobe.

Other proposed modifications were in Revision 10 as well, although those were aligned with ACMUI recommendations and thus less likely to be controversial:

- Waste and disposal section
- Autopsy and cremation information
- An additional definition for the term "shunting" to clarify a previous change that was part of Revision 9. Rev. 9 excluded lung shunting from counting as a ME if the lung shunt was evaluated prior to treatment. In draft Rev. 10, shunting would essentially be an unexpected blood flow causing the microspheres to flow to an unwanted direction.

Resources:

- Draft Y-90 guidance/Revision 10: https://www.regulations.gov/document?D=NRC-2017-0215-0002
- *Federal Register* notice re: proposed changes: https://www.federalregister.gov/documents/2017/11/07/2017-24129/yttrium-90-microsphere-brachytherapy-sources-and-devices-therasphere-and-sir-spheres
- ACMUI recommendations on the earlier version of the draft from 2016: https://www.nrc.gov/docs/ML1713/ML17138A352.pdf

COMMENT: I was the first in the US to use Y90 in the Therasphere formulation in about 1999 and the SirSphere product a few months later. I have extensive experience with both products. In all, I have treated well over 1000 patients and have been an active proctor for Sirtex. If I may be of assistance, please contact me:

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