Report of Subcommittee on Emerging Medical Technologies/Rubidium-82 Generator Rulemaking Draft Regulatory Basis

Draft Report

Submitted on: November 18, 2022

Subcommittee Members

Ronald Ennis, M.D.
Richard Green
Hossein Jadvar, M.D., Ph.D.
Megan Shober (Chair)
Zoubir Ouhib
Harvey Wolkov, M.D.

Consultant to Committee: John Fritz Angle, M.D.
NRC Staff Resource: Maryann Ayoade

Charge

ACMUI Chairperson Dr. Darlene Metter established this subcommittee to review and comment on NRC's draft regulatory basis for the Emerging Medical Technologies (EMT) and Rubidium-82 Generator rulemaking.

Background

Although NRC medical regulations in 10 CFR Part 35 cover a wide range of byproduct material uses, medical technologies continue to be developed that have radiation safety concerns not addressed by these requirements.

In 2002, the NRC established 10 CFR 35.1000 so that there would be codified regulatory requirements and a more clearly defined process to obtain regulatory approval for new medical uses of byproduct material.[1] This section provided a mechanism for NRC to license medical technologies that had characteristics or challenges not adequately considered by the other Subparts of 10 CFR Part 35. In practice, as new medical technologies were identified which did not fit into the established Subparts of 10 CFR Part 35, NRC and Agreement States would develop licensing guidance to address the unique features of the technology. In the past 20 years, NRC has issued licensing guidance for 16 emerging medical technologies.[2]

After the Energy Policy Act of 2005 gave NRC regulatory authority over accelerator-produced radioactive material, the NRC identified that rubidium-82 generators were not able to meet

[1] "10 CFR Parts 20, 32, and 35, Medical Use of Byproduct Material; Final Rule" (67 FR 20249; April 24, 2002).
[2] EMT licensing guidance is posted on NRC's Medical Uses Licensee Toolkit: https://www.nrc.gov/materials/miau/med-use-toolkit.html

requirements in 10 CFR 35.60 and 10 CFR 35.63 for measuring patient doses. Due to the 76 second half-life of rubidium-82, the dose calibrator within the rubidium-82 generator measures activity in a dynamic mode (i.e., as fluid flows past the detector) and the measurement results are not available prior to administering the rubidium-82 to the patient. In 2013, NRC issued an enforcement guidance memorandum (EGM-13-003)[3] which authorized NRC staff not to issue violations to licensees for failure to comply with 10 CFR 35.60 and 10 CFR 35.63 if the licensee took certain additional steps to ensure the equipment was working properly, to record dosages administered to patients, and to provide device-specific training to staff.

It has long been the intent of the NRC to amend 10 CFR Part 35 to incorporate these technologies. This proposed rulemaking would accomplish that purpose.

Discussion

In the proposed draft regulatory basis, the NRC outlines its plan to incorporate rubidium-82 generators and many of the emerging medical technologies into 10 CFR Part 35, via modification to existing portions of the rule, and by creating a new Subpart to 10 CFR Part 35 for medical use of microsources.

The ACMUI Emerging Medical Technologies Subcommittee has reviewed the proposed draft regulatory basis. Responses to the specific questions posed by NRC in Appendix A of the draft regulatory basis are included in Appendix 1 of this report. The Subcommittee offers the following additional comments:

- The NRC should evaluate which emerging medical technologies are no longer being distributed in the United States. This information should be stated in Section 3.3 and reflected in the assumptions in Table 7. This information should also inform the proposed rule text.
- Some members of the Subcommittee believe the scope of the proposed rulemaking is ambitious, but reasonable. Other members of the Subcommittee believe the scope of the proposed rulemaking should be limited to products that are in broader use because time and clinical experience are needed to understand the technology and safety issues prior to being able to codify requirements via rulemaking.
- The Subcommittee supports the proposed changes to allow for the use of additional radionuclide generators. In addition, all Subcommittee members agree that gamma knife, microspheres, radioactive seed localization and intravascular brachytherapy (IVB) have extensive histories of clinical use and should be moved out of 10 CFR 35.1000 and into other Subparts of 10 CFR Part 35.
- The Subcommittee believes that medical technologies presenting novel radiation safety hazards should default to 10 CFR 35.1000. NRC should assess the novelty, risk, and

[3] Enforcement Guidance Memorandum—Interim Guidance for Dispositioning Violations Involving 10 CFR 35.60 and 10 CFR 35.63 for the Calibration of Instrumentation to Measure the Activity of Rubidium-82 and the Determination of Rubidium-82 Patient Dosages (EGM-13-003), ML13101A318.

general clinical experience (i.e., beyond clinical trials) when determining whether to move a technology out of 10 CFR 35.1000 and into other parts of 10 CFR Part 35.

- In any case, the Subcommittee cautions the NRC against putting specific requirements in 10 CFR Part 35 which are particular to devices or products that aren't in widespread use (i.e., Alpha DaRT™).
    - The Subcommittee supports adding general requirements for contamination control for liquid or diffusing brachytherapy.
    - The Subcommittee discourages adding training and experience requirements to 10 CFR Part 35 which were designed for products no longer being distributed (i.e., Epi-Rad$_{90}$™ eye applicators).
- The Subcommittee supports the proposed change to the 10 CFR 35.2 definition of "physician."
- The Subcommittee supports the proposed changes to 10 CFR 35.24. Radiation safety committees should include an authorized user (AU) representative for microsource therapy and any future therapeutic emerging medical technologies.
- The Subcommittee cautions the NRC as it considers how to incorporate "treatment regimen" into the written directive regulations. A single written directive should not prescribe a radiopharmaceutical in cycles when the prescribed activity may vary from cycle to cycle, for example based on the patient's weight, bone marrow reserve, or renal or hepatic function.
- The Subcommittee recommends a wholesale re-evaluation of the ophthalmic brachytherapy requirements. The divergent training requirements for physicians and physicists are very complicated, and the Subcommittee recommends streamlining the training requirements. Of particular note, the Subcommittee believes it is not a good practice for a device's applicable training requirements to depend on the prescribed dose. The NRC should consider regulating ophthalmic sources that are intraocular or have shorter half-lives under standard 10 CFR 35.400 manual brachytherapy regulations, since they are significantly more complex than the traditional strontium-90 pterygium applicators. The added complexities may include dose to a specified tissue depth and stricter criteria for source calibration due to rapid decay.
- NRC should re-evaluate when authorized medical physicists (AMPs) should be required. Why do some of the 10 CFR 35.400 uses require an AMP and some do not? What are the specific tasks or skills that must be performed by an AMP? It may be useful to pose this question during the public comment period.
- Submission of procedures for patient immobilization should be part of the licensing process for licensees using gamma stereotactic radiosurgery devices in 10 CFR Part 35, Subpart H. The Subcommittee notes that immobilization methods can also impact emergency response.
- The Subcommittee supports the addition of 10 CFR Part 35, Subpart I (35.700) for microsource brachytherapy.
- In multiple places, Appendix A states, "This section would be amended to require completion of device specific training by the medical physicist applying to be an AMP on

a license authorizing use of this device." The Subcommittee notes that device-specific training is already required for AMPs in 10 CFR 35.51(c).

- In Section 10 CFR 35.415 (page A-6), it states, "this section of the regulation will be amended to require licensees to lock storage of the IVB storage container and to house that storage container in a secure location." The Subcommittee notes that 10 CFR 20.1801 already requires licensees to secure radioactive material from unauthorized access. What is the basis for the additional proposed security requirement?
- In Section 10 CFR 35.3045 (page A-14), the Subcommittee recommends removing the requirement to report as a medical event a radioactive seed localization procedure that uses the wrong radionuclide. Based on the low implanted activity and the short implantation time, the dose effect of the wrong isotope is of minimal consequence.
- In Section 10 CFR 35.610 (page A-24), it states, "This section will be revised to clarify that the AU and AMP, as well as any individual who will operate the unit, are required to have vendor operational and safety training." The Subcommittee recommends also allowing the operational and safety training to be given by an approved AU or AMP.

Conclusion

The Subcommittee supports this rulemaking and applauds the effort it took to develop this draft regulatory basis. The Subcommittee looks forward to continued work on this rulemaking as it progresses.

Respectfully Submitted on November 18, 2022,

Subcommittee on Emerging Medical Technologies/Rubidium-82 Generator Rulemaking Draft Regulatory Basis

Advisory Committee on the Medical Use of Isotopes

Nuclear Regulatory Commission

Appendix 1: Responses to Selected Numbered Questions

Radionuclide generators

Question A.1.1:

For radionuclide generators, RSOs should have general awareness training, including functions and risks. RSOs should know what the potential emergency situations are and know how to respond to them. These responsibilities are inherent to the RSO position and documentation of device-specific training should not be required during licensing.

Question A.1.2:

The regulations should be structured so that certain devices require device-specific training for anyone using or supervising the use of the device. Device-specific training for 10 CFR 35.290 authorized users should be maintained by licensees and should not need to be approved by a regulator or tracked on a license.

Liquid Brachytherapy

Question A.3.1:

Liquid brachytherapy should remain in 10 CFR 35.400. The definition of "manual brachytherapy" in 10 CFR 35.2 already allows for liquid sources. The liquid brachytherapy devices under consideration encapsulate the radioactive liquid in a manner conceptually no different than an encapsulated I-125 seed and therefore belong in 10 CFR 35.400. However, additional regulations are needed to address the potential for radioactive contamination.

Diffusing Sources

Question A.5.1:

10 CFR Part 35, Subpart F should require routine contamination control for brachytherapy sources that are not sealed sources.

Microsources

Question A.8.1:

- The Subcommittee supports the use of the term "microsource." The Subcommittee does not see any reason to exclude particular radiation types or energies from the microsource definition. The Subcommittee encourages NRC to develop regulations which would allow for microsources that are sealed sources and microsources that are unsealed sources (i.e., where the radioactivity is adhered to the surface of the microsource).

- The draft regulatory basis does not address changes to 10 CFR 32.74. This section currently requires medical distributors to receive SSD authorization for 10 CFR 35.1000 technologies (including microspheres). NRC should consider whether to add 10 CFR 35.700 as a reference in 10 CFR 32.74(a).
- Sealed source microsources meet the criteria for SSD registration as described in 10 CFR 32.210, and SSD registration should be required for sealed source microsources. The NRC should seek comment on whether SSD device registration should be required for microsources that are not sealed sources.
- The Subcommittee encourages the NRC to seek comment on the dividing line between microsources and liquid brachytherapy.

Question A.8.2:

The Subcommittee believes that NRC should not define 'physiological equilibrium' and should instead focus on safety measures to prevent non-target embolization.

Question A.8.3:

The Subcommittee cautions the NRC not to regulate licensees' team approaches to medical care. The NRC should focus its efforts on training requirements for individuals who handle licensed material. This is appropriately covered by 10 CFR 35.27 'Supervision.' Licensees should develop, implement, and maintain procedures for microsource use, but the NRC does not need to specifically name "the team approach" in its regulations.

Question A.8.4:

For microsource brachytherapy, the written directive should include both the dose and the activity. Physicians intend to treat patients with a particular dose, and activity is the measurable parameter that allows licensees to determine whether the appropriate amount of radioactive material has been administered. Treatment planning worksheets from microsource manufacturers incorporate both dose and activity.

Question A.8.5:

The post-treatment portion of the written directive should specify the activity administered. The dose delivered to the treatment site is difficult to determine without post-treatment imaging. NRC should ask a question about whether post-treatment imaging should be required and solicit input on whether there are other mechanisms to confirm that the treatment was delivered in accordance with the written directive.

Question A.8.6:

The Subcommittee believes that NRC does not need to specify how a licensee can meet 10 CFR 35.41.

Question A.8.7:

Most of the licensees currently using microsource material do not have authorized medical physicists. The Subcommittee has mixed perspectives on whether an authorized medical physicist should be required for microsources. The Subcommittee encourages NRC to solicit this input during the public comment period.

Question A.8.8:

NRC should not assume that all microsources will be sealed sources. SSD registration (per 10 CFR 32.210) is for sealed sources. Should the microsource section be limited to permanent implants?

Question A.8.9:

35.710 proposes a requirement that prior to the first use for patient treatment of a new delivery system, a licensee shall ensure that vendor operational and safety training is provided to all individuals involved in microsource manual brachytherapy use. The Subcommittee believes that NRC should not restrict who provides the device-specific training. For example, an authorized user who has received training from the vendor on a modified device could provide the training to other staff. There are no other areas of 10 CFR 35 that require training to be provided by the vendors. The Subcommittee also believes that NRC should limit its training requirement to individuals who handle the microsources.

Comment: Questions A.8.9 and A.8.10 appear to be the same. It is not clear what distinguishes “safety procedures” from “safety precautions.” NRC should combine these two questions.

Question A.8.11:

NRC should no longer allow conditional approval of microsource authorized users. Conditional approval is not an option for any other type of medical authorized user. Microsource therapy is well-established and has been an integral part of interventional radiology residencies for many years.

Question A.8.12:

The Subcommittee believes that 80 hours of classroom and laboratory training applicable to microsources is appropriate for interventional radiologists seeking to become microsource authorized users, in addition to the 700 hours of nuclear medicine training already required by radiology residencies.

Question A.8.13:

The NRC should seek comment on the training pathways chosen by current microsource authorized users. The Subcommittee believes that current microsphere training requirements are appropriate for 10 CFR 35.390 and 10 CFR 35.490 authorized users; however, the Subcommittee believes that most microsphere authorized users are interventional radiologists.

Question A.8.14:

This is a great question for public comment. The NRC should also ask whether the individuals injecting the microsources are typically authorized users or individuals working under the supervision of an authorized user.

Other 10 CFR Part 35 Changes

Question A.9.5:

The Subcommittee recommends revising the 10 CFR 35.610 requirement to allow console passwords. The Subcommittee notes that, for example, the Elekta Flexitron high dose rate remote afterloader unit does not have a console key (the key instead goes in the robot).

Question A.9.6:

The Subcommittee notes that proposed changes to 10 CFR 35.615 should not conflict with other regulations, for example 10 CFR 20.1601 (access to high radiation areas) or 10 CFR Part 37 (physical security).