

February 7, 2017

Chairman Kristine L. Svinicki
U.S. Nuclear Regulatory Commission
Mail Stop O-16G4
Washington, DC 20555-0001

Re: Alpha- and Beta-Emitter Training and Experience Requirements

Dear Chairman Svinicki:

I am writing to follow up on past discussions regarding the Nuclear Regulatory Commission's (NRC's) oversight of the administration of therapeutic radiopharmaceuticals, and the recent October meeting of the Advisory Committee on the Medical Use of Isotopes (ACMUI). As we have previously discussed, Spectrum Pharmaceuticals manufactures the biological product Zevalin[®] (ibritumomab tiuxetan) for non-Hodgkin's lymphoma, which has been approved by the Food and Drug Administration (FDA) and is also regulated by the NRC as a beta-emitter therapeutic radiopharmaceutical. We appreciate the time and attention that NRC and the ACMUI have devoted to the review of the appropriate training and experience requirements for Authorized Users (AUs). However, we are concerned that is still no viable pathway for hematologists and oncologists to administer patient-ready doses of alpha- and beta-emitters to the cancer patients that they treat. The current 700-hour "one size fits all" approach is not well-suited to patient-ready doses of alpha- and beta-emitters. As the Society of Nuclear Medicine and Molecular Imaging (SNMMI) noted in its January 24, 2017 letter to the NRC, the 700-hour requirement allows for the coverage of subjects including imaging and diagnostic radiology, which SNMMI believes appropriate for an authorization covering "all parenterals now and in the future." This comment demonstrates that the 700-hour requirement encompasses subjects which are in no way needed for the administration of patient-ready doses of alpha- and beta-emitters prepared at a licensed radiopharmacy. Rather than a broad authorization that seeks to cover many types, a tiered-based approach tailoring the training and experience requirements to the level of safety risk and complexity of administration would be more appropriate.

Current Regulatory Requirements Are Not Commensurate with Safety Profile

Spectrum first notified the NRC in 2011 of the overly broad requirement of 700 hours of training and experience for the administration of patient-ready dose therapies. Stakeholders throughout the current rulemaking process have advocated for a change to the training and experience requirements for the administration of patient-ready doses of alpha- and beta-emitters, which overly burdensome requirements are not commensurate with the safety profile of Zevalin and other patient-ready dose therapies. Spectrum and other stakeholders specifically recommended that the NRC reduce the 700-hour requirement framework as part of the current rulemaking. However, we were very disappointed to learn that the Final Rule on the *Medical Use of Byproduct Material*:

Medical Event Definitions, Training and Experience, and Clarifying Amendments is not expected to address the issue.¹

As testified to by experienced training educators at the recent ACMUI meeting, the current 700 hours of training and experience requirements for the administration of patient-ready doses of alpha and beta-emitter anti-cancer therapies are overly burdensome and not currently aligned with safety precautions needed to administer these doses. The doses are prepared for the individual patient at a licensed radiopharmacy and delivered to the physician on the day of administration in a pre-filled syringe. Unlike other radiolabeled products regulated under the same subpart of the regulations, patient-ready doses of alpha- and beta-emitters do not require mixing or direct handling of radioactive isotopes by the administering physician. NRC and ACMUI have acknowledged that alpha- and beta-emitters have an “exceptional” safety record.

NRC Should Propose a New Tiered-Based Framework

A broad cross-section of stakeholders agree that the current training and experience requirements for alpha- and beta-emitters far exceed the levels needed to ensure safety. The regulations requiring 700 hours of training and experience are outdated, and do not recognize that patient-ready doses are prepared by licensed radiopharmacies and delivered to the physician as a pre-filled syringe on the day the treatment is administered. This point was made clear when neither the NRC nor the ACMUI were able to demonstrate why the training and experience requirements for AU certification to administer patient-ready doses of alpha- and beta-emitters need to be 700 hours. In point of fact, no one has been able to document how the 700-hour threshold was established as a requirement in the first instance. Additionally, there have been no safety incidents with the AUs who became authorized under the previous 80-hour training and experience requirements have been administering alpha- and beta-emitters for years.

There is a growing recognition that a competency-based framework is better suited to assessing training and experience than a strict hours-based requirement. At its October 2016 meeting, the ACMUI heard from leading academic experts in the field of radiation safety education and training, who presented this view.

Recommendations

As was testified to at the October 2016 ACMUI meeting, the issue impacts other alpha and beta-emitters beyond Zevalin. There are numerous alpha- and beta-emitter products in the pipeline. The success of these products in development and innovation for new products is jeopardized by the 700-hour training and experience requirement limiting which physicians can administer the products.

¹ (Docket ID NRC-2008-0175, RIN 3150-AI63)

Our specific recommendations are as follows:

1. **NRC Staff Should Develop Competency-Based Training & Experience Framework**

We appreciate that a subcommittee has been established under the ACMUI to re-evaluate training and experience for all modalities with a focus on competencies. While this is a positive step, it is likely that this process will be lengthy, and the new framework could not be implemented without another full rulemaking process. Because of the negative impact that the current training and experience regulations have on patient access to patient-ready doses of alpha- and beta-emitting radiopharmaceuticals, we recommend that the NRC present to the ACMUI a tiered framework to evaluate the specific category of patient-ready doses of alpha- and beta-emitters first among modalities. The tiered approach should link the safety profile and complexity of administration of the radioimmunotherapy with the appropriate level of training and experience required to administer the therapy safely. This framework should be based closely on the competencies required to administer patient ready doses of these radionuclides.

The NRC could lay out a process and timeline in its current Final Rule by which the Commission staff will develop this framework. This approach would be well within the scope of the ongoing rulemaking.

2. **NRC Staff Should Develop Guidance on Interpretation of Training & Experience Requirements**

The current 700-hour pathway is essentially a bar on practicing medical oncologists and hematologists becoming AUs, as evidenced by the fact that nobody has ever been certified as an AU through the 700-hour pathway. Because the need to address this issue is imminent for cancer patients, we recommend that the NRC take interim steps to make it possible for medical oncologists and hematologists to become AUs under the existing regulatory framework. Specifically, the NRC should issue guidance providing for the application of the training and experience requirements set out in the current regulations at 10 C.F.R. § 35.390 in a manner that reflects the competencies needed to administer alpha- and beta-emitters in patient-ready doses.

Clinicians such as Dr. Jennifer Cultrera of Florida Cancer Specialists, who has presented to the ACMUI about her considerable experience in radioimmunotherapy and the impossibility of becoming an AU under the current training and experience requirements, should be afforded a pathway to demonstrate that they have training and experience equivalent to that which the regulations require. Applying the existing training and experience requirements in a manner focused on patient-ready doses as an interim measure would allow Dr. Cultrera and other experienced clinicians to administer Zevalin and other patient-ready therapies. This guidance would also help to assist the Agreement States in applying their own regulations to patient-ready doses, which are based upon the NRC regulations.

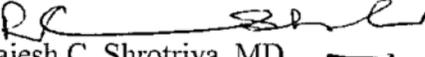
3. NRC Should Modify Training & Experience Requirements for Patient-Ready Doses of Alpha- and Beta-Emitters Through Rulemaking

We recommend that once the tiered competency based requirements are set, NRC should undertake an expedited rulemaking and promulgate those changes without further delay. We respectfully request that the Commission make this a high priority.

In conclusion, we believe that there is no justification for the 700-hour training and experience requirement for the administration of alpha- and beta-emitter patient-ready doses. The NRC has the regulatory authority to modify these outdated requirements and needs to act now. We are eager to work you and the NRC staff to develop a solution and are willing to support efforts to see that physicians have access to the appropriate training in order to learn how to safely handle and administer patient-ready doses of alpha- and beta-emitter therapies.

Thank you for your ongoing attention to this issue.

Sincerely,


Rajesh C. Shrotriya, MD

Cc: NRC Commissioner Jeff Baran
NRC Commissioner Stephen G. Burns

McCloskey, Bridin

Attachments:

Dr. Shrotriya Letter to NRC Chairman Svinicki - February 7, 2017.pdf

From: Clarine Nardi Riddle [<mailto:CNRiddle@kasowitz.com>]

Sent: Wednesday, February 08, 2017 9:10 PM

To: Vietti-Cook, Annette <Annette.Vietti-Cook@nrc.gov>

Subject: [External_Sender] Revised Letter to NRC Chairman Svinicki

Annette,

I hope all is well with you. Would you please substitute the attached letter for the ones FedEx to your office from Dr. Shrotriya? An error was made in the addressee and cc's. Those are the only changes.

Thanks so much,
Clarine

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