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Redefining Cancer Care

October 28, 2015

Advisory Committee on the Medical Use of Isotopes
Subcommittee on Training and Experience for Alpha and Beta Emitters
c/o Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: Training and Experience Requirements for Beta-emitter Radiopharmaceuticals

Dear Members of the ACMUI Subcommittee:

We are writing to follow up on the meeting of the Advisory Committee on the Medical Use of Isotopes (ACMUI) held on October 8, 2015. At the meeting, stakeholders presented on the impact of the current training and experience requirements for beta-emitters on patient access to innovative lifesaving therapies. Additionally, stakeholders stated that the 700 hours of training and experience requirements for Authorized Users (AUs) needs to be re-evaluated by the Nuclear Regulatory Commission (NRC) because it is impacting patient and healthcare access to effective treatment options. We appreciate that the Subcommittee has expanded its charge to evaluate whether the 700 hour requirement is the appropriate level of training for the Alternate Pathway for beta emitters. We believe that the current NRC rulemaking provides the opportunity to modify the existing requirements and to alleviate an adverse impact the regulations have created on patient access to certain radioimmunotherapies. We urge ACMUI to take definitive action and make recommendations for potential changes to the regulations for the benefit of patients.

In response to questions and statements at the ACMUI meeting, Spectrum would like to provide the ACMUI Subcommittee with additional background and information on Zevalin as well as our proposal to modify to 700 hours required to become an AU to at most 80 hours. As set out below, we believe 80 hours is the upper limit of the appropriate level of training for a limited license to administer pre-filled self-contained radiopharmaceuticals like Zevalin. Such an approach would eliminate the unnecessary regulatory barriers currently limiting cancer patient access to effective treatment options, while maintaining training requirements commensurate with the risks of handling Zevalin.

Clinical Background on Zevalin

The topic of AU requirements has been of interest to Spectrum Pharmaceuticals, whose product ZEVALIN® (ibritumomab tiuxetan) is a radioimmunotherapy treatment for non-Hodgkin's lymphoma (NHL) patients. Zevalin was approved by the Food and Drug Administration (FDA) in 2002 for the treatment of patients with relapsed or refractory indolent non-Hodgkin's lymphoma. More recently, in 2009, FDA approved the use of

Zevalin for the treatment of patients with previously untreated follicular non-Hodgkin's lymphoma as consolidation therapy immediately after first-line chemotherapy.

In the Subcommittee report and at the meeting, there were numerous comments regarding the declining utilization of Zevalin due to new competing therapies. However, this in reality is only part of the story. While it is true that there are numerous new therapies for NHL, it is also important to understand that indolent NHL is not a curable disease, and therefore patients will typically require many treatments as they fail available therapies. A typical patient will receive induction chemotherapy and upon relapse will receive a salvage therapy that will hopefully induce another remission and disease-free period. However, it is known that the disease will ultimately relapse again and yet another salvage therapy will be needed. A patient with indolent lymphoma may live many years with their disease, but unfortunately they will need access to different treatment options to induce disease-free remission periods after relapse that typically become shorter with each line of therapy. It is critical, therefore, that all approved, effective treatment options be available and accessible for these patients. In addition, it is essential that multiple therapies with different mechanisms of action be available to help overcome resistance to standard therapies and provide these patients with various effective treatment options.

Currently, only one radioimmunotherapy for NHL remains commercially available, Zevalin. The drug uses the monoclonal mouse IgG1 antibody ibritumomab in conjunction with the chelator tiuxetan, to which a radioactive isotope (yttrium-90) is added. Zevalin is a unique and effective radioimmunotherapy therapy approved by FDA for patients with indolent lymphoma, which has proven safety and efficacy in multiple randomized clinical trials with a long duration of study follow-up. Although it is known to be safe and effective treatment, its clinical use has definitely been markedly limited due to the hurdles resulting from administration logistics, ie, the inability of treating oncologists to administer it. Importantly, unlike many of the newer therapies, Zevalin can maintain NHL patients in remissions lasting many years with only a single course of therapy that consists of just one dose. The National Comprehensive Cancer Network (NCCN) clinical treatment guidelines list Zevalin as one of the few Category 1 options for patients with relapsed or refractory follicular lymphoma, which by definition is only for treatments that, "based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;" the only other Category 1 NCCN recommendation for these patients is intensive combination chemotherapy with FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (NCCN v2.2015). Unlike Zevalin, which is a novel radioimmunotherapy targeting CD20, newer targeted therapies are small molecules that target tyrosine kinase signaling pathways. While these small molecule therapies have the convenience of being oral, they target a different mechanism of action and require continuous treatment that can be associated with chronic side-effects.

It is important to note that Zevalin involves limited physician preparation and handling. Zevalin is delivered to the AU as a patient-ready dose requiring only an acrylic shield and standard radiation precautions. A "hot lab" is not required and patients do not need to be assessed for radiation exposure. Due to the preparation of the patient-ready dose by the radiopharmacy before reaching the administering physician, training requirements for the

physician on dose preparation and the safe handling of radiopharmaceuticals can be more limited. Board certified Hematologists/Oncologists are accustomed to using cytotoxic agents that require specific handling tailored to their risks, and are customarily trained on standard radiation precautions. Limited additional training on the proper handling and disposal of Zevalin should enable them to safely use this product.

Not All AUs Can Administer Zevalin

At the ACMUI meeting, several ACMUI members asked whether the 700-hour requirement has caused a lack of AUs who can administer Zevalin. Dr. Cultrera spoke to the difficulty she has faced finding Authorized Users able to administer Zevalin to her patients outside of the major metropolitan areas with academic medical centers, and based on our discussions with multiple clinical practioners, this is not an isolated instance. In speaking with patient advocates and practitioners across the country, we have found the problem to actually be nationwide. Hematologists and oncologists who wish to offer Zevalin as an appropriate treatment option for their patients outside of major cities are often unable to locate AUs who can administer Zevalin within a reasonable commuting distance for these patients.

Board-certified radiation oncologists and nuclear medicine practitioners, who can achieve Authorized User status through the certification pathway, have also noted that the proctored case requirement is also difficult to meet. Because the use of the treatment option is limited outside of major academic medical centers, it is difficult for practitioners in these areas to locate and participate in the required three case administrations. So while it is possible to find Authorized Users in some areas, these AUs may not be eligible to administer Zevalin specifically, due to a lack of exposure to this treatment option.

Some panel members stated that residency requirements include training and licensure for therapeutic radiopharmaceuticals, so all AUs should be able to administer Zevalin. However, this is not the case. Most nuclear medicine practitioners are AUs, but not all are authorized users under the NRC or equivalent Agreement State Regulations. In addition, not all radiologists or radiation oncologists are listed as AUs on many radioactive material licenses for therapeutics under NRC 35.300 or equivalent Agreement State regulations.

When Zevalin received FDA approval in 2002, the therapy regimen included an Indium -111 Bio-scan, which did require nuclear medicine practitioners to image Zevalin patients. At that time, numerous nuclear medicine, radiation oncologist and radiologists/nuclear practitioners had received education about Zevalin that included low-grade and follicular non-Hodgkin's Lymphoma Disease, Handling, Administration and Radiation Safety. ~~With this said, the actual number of AUs had been estimated as greater than 400.~~ However, since the FDA removed the requirement for an Indium -111 Bio-scan in 2011, nuclear medicine practitioners have shown a lack of interest in offering Zevalin as a therapy option in their departments, resulting in a decrease of radiation oncologist AUs providing Zevalin and other therapeutic radiopharmaceuticals to patients. The lack of AUs in the community setting has decreased in non-metropolitan areas and has created an obstacle to cancer patient access to this effective radiopharmaceutical.

While hospitals and/or academic institutions located in metropolitan cities have AUs, these centers are focused on drug development and clinical trials and do not provide adequate, convenient cancer patient access to radiopharmaceuticals like Zevalin. In 2010, the number of AUs was greater than 400, while today, the number is only about 145 who are willing and working with medical/hematology oncologists to offer Zevalin as a therapeutic option to patients.

#1 Number of known AUs treating Zevalin patients has decreased from >400 AUs to 145 AUs since 2010.

#2 Number of Cities with Known AUs for Zevalin Administration

<u>Hematologists/Oncologists Should Have Access to Appropriate Training Requirements that Enable them to Safely Administer Zevalin</u>

The many hematology and oncology practitioners with whom we have spoken across the country have identified the AU training and experience requirements as the primary hurdle in preventing access of their patients to Zevalin as an effective treatment option. Board certified hematologists and oncologists cannot realistically devote 700 hours of time away from their clinical practices to achieve AU status through the Alternate Pathway for Zevalin, particularly since it is the only radioimmunotherapy used in their practice for a specific group of patients.

As Dr. Cultrera noted in her comments, she does work with nuclear medicine and radiation oncologists at academic medical centers whenever possible. However in her experience, not all patients are located near centers with nuclear medicine AUs to allow for the administration of a radiopharmaceutical product such as Zevalin. The point of the Alternate Pathway is to allow interested oncologists like Dr. Cultrera to be trained and become able to provide Zevalin as a feasible treatment option, which they then can administer to their patients as they routinely do with cytotoxic therapies. Dr. Cultrera mentioned that her colleague Dr. Mace underwent training similar to that proposed in the Alternate Pathway for beta-emitting radiopharmaceuticals before the current requirements went into effect, and he has now been safely administering these products for over a decade.

700 Hours is Not The Appropriate Level of Training for the Risk Associated with Beta-emitter Radiopharmaecuticals

At the meeting several panel members asked how the 700 hours of training and experience was developed. NRC staff explained that the number is set in regulation in § 35.390, but they were not clear on how the number was actually determined. It is our understanding that this number was set to reflect the complete course work that a physician would undertake to specifically become board certified in nuclear medicine, which is a dedicated medical imaging specialty involving the broad use of various radioactive substances in the diagnosis and treatment of disease. As such, the 700 hours include training for all aspects of medical use and safe handling of various radioactive byproduct materials used clinically (nearly 100), including alpha, beta and gamma emitters. As described in the attached chart, Spectrum believes there is ample support that 80 hours of training or less is sufficient and a more appropriate level of training and experience for the risks associated with the administration of a beta-emitter like Zevalin in the hematologist / oncologist setting.

Prior to the 2002 rulemaking, hematologists and oncologists could be licensed as AUs able to administer beta-emitting radiopharmaceuticals such as Zevalin with 80 hours of classroom and laboratory training. A number of the current AUs for Zevalin received AU status under the prior regulations with 80 hours of training and have grandfathered status. These physicians have had an excellent safety record in handling this radioimmunopharmaceutical, like Dr. Cultrera's colleague Dr. Mace.

The proposed Alternate Pathway, requiring at most 80 hours of training and experience for beta-emitters, would mirror the training and experience requirements for those physicians seeking to administer sodium iodide I-131 under the current regulations at § 35.392 and § 35.394. The safety profile of Zevalin is comparable to and in some ways even more favorable than that of sodium iodide I-131. The excellent safety record associated with Zevalin has been recognized by the FDA, which requires only minimal precautionary labelling on the product. Gamma-emitting radiopharmaceuticals such as I-131, in contrast, require more precautionary measures during administration, such as isolation and Geiger counter measurement. Zevalin's safety profile is further enhanced by its unique process of preparation, wherein it is radiolabeled and packaged by a licensed radiopharmacy and then delivered to healthcare providers as a patient-ready dose. Therefore, the physician administering Zevalin is not required to perform the typical radionucleotide handling operations associated with other radiopharmaceuticals, and only has to administer the pre-packaged product to the patient.

There was discussion at the meeting regarding whether a modification to the 700-hour requirement may be included in the final rule. NRC staff indicated that because the proposed rule did not specifically address reducing the 700-hour requirement, it was not subject to public comment. However, the proposed rule did seek public comment on whether the training and experience requirements were having an adverse impact on patient care. Additionally, the proposed rule makes specific revisions to § 35.390. NRC did receive numerous comments from stakeholders advocating for lowering the 700-hour training requirement for AUs to 80 hours or less, and held a public meeting on this issue in February 2015. As such, the changes can be

viewed as a logical outgrowth of the proposed rule. If the Agency determines that an additional comment period must be provided, the Agency rules allow for a post-promulgation comment period. Under 10 CFR § 2.804(d)(2), the NRC can provide a thirty-day post-promulgation comment period. Thus, the NRC has the authority to adopt a training and experience requirement of 80 hours or less at this time.

Emerging Technology Regulation Under 35.1000

One panel member suggested the use of § 35.1000 to address training requirements for beta-emitter radiopharmaceuticals. The NRC's regulations are designed to provide flexibility for emerging technologies, and changes to the regulations would reflect a policy interest in encouraging innovation in alpha- and beta-emitters, a relatively new class of therapeutic radiopharmaceutical products. Alternatively, if the Agency does not pursue a regulatory change in the Final Rule, we request that the NRC pursue licensing Zevalin pursuant to 10 CFR § 35.1000, which gives the NRC broad discretion to regulate emerging technologies. Pursuant to § 35.1000, the NRC could approve Zevalin as an emerging technology as its use is not "specifically addressed" elsewhere in the regulations.

Licensure of Zevalin as an emerging technology pursuant to § 35.1000 would allow applicants to provide materials and seek written approval from the Commission that a requirement of at most 80 hours of training and experience is sufficient for the safe and proper handling and administration of Zevalin.

Regulatory Exemption under 35.19

If ACMUI and the NRC do not believe that the current rulemaking provides an opportunity to address training and experience requirements for Zevalin, Spectrum would like to seek a regulatory exemption for AUs for Zevalin. The NRC has the authority, upon application of any interested person or upon its own authority, to specifically exempt Zevalin from the requirements of 10 CFR § 35.390. Based on the materials presented at both the NRC public meeting in February and ACMUI meetings in June and October, the Commission can determine that such an exemption will not endanger life or the public interest. 10 CFR § 35.19.[1] The Commission has precedent for applying exemptions for new technologies. For example, at the October ACMUI meeting, ACMUI recommended that Ge-68/Ga-68 generators be granted license-specific exemptions from certain DFP requirements until a regulatory solution is reached through a subsequent rulemaking. There, ACMUI found that such an exemption would ensure public health and safety by allowing greater access to needed radiopharmaceuticals. A similar situation is presented here.

[1] *See also* Consolidated Guidance About Materials Licenses: Program-Specific Guidance About Medical Use Licenses, NUREG-1559, 10-1, NRC (Jan. 2008).

Recommendation

Stakeholders at the ACMUI meeting and during the rulemaking comment period have proposed that an alternate training and experience requirement that consists of at most 80 hours would be both commensurate with the actual safety risk for the focused handling of beta-emitter radiophamaceuticals, and also clinically appropriate and achievable for practicing hematologists and oncologists who wish to offer Zevalin as a viable treatment option to their cancer patients; this would eliminate the adverse impact the current regulations have created on patient access to these radioimmunotherapies. Spectrum strongly supports this more focused and appropriate training and experience requirement of no more than 80 hours for beta-emitter products. Spectrum would also support any other revision to the training and experience requirements that would reduce the shortage of AUs by ensuring that training requirements are commensurate with the actual risks, and improve patient access to Zevalin. ACMUI may be aware of alternative requirements that would either reduce training and experience requirements to a reasonable amount and/or reduce the proctored case requirement to a single case for Zevalin or a combination of alpha and beta emitters.

We appreciate the time and attention the ACMUI Subcommittee has devoted to considering these issues, and urge the ACMUI to take definitive action and make recommendations for changes to the regulations for the benefit of patients. We would be pleased to speak with the Subcommittee further, and provide any additional information that the Subcommittee might find helpful as it completes its review. We remain optimistic that the ACMUI will take immediate action in both the interest of cancer patients, and in alignment with the intent to not discourage the use of certain therapeutic options or adversely impact clinical practice.

Sincerely,

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Authorized User
Training and Experience Requirements

Alternate Pathway 35.300 700 Hours	Proposed Alpha and Beta Emitting Pathway At Most 80 Hours
Description of Training Nuclear Medicine residency program provides a broad understanding of general nuclear medicine, as well as advanced subspecialties in nuclear oncology, nuclear cardiology, and molecular imaging. Teaching sessions during service readouts, including emphasis on: • Physics and instrumentation • Radiopharmacy • Clinical technique • Computer applications • Quantitative and semi-quantitative analysis of images • Literature reviews • Correlative imaging • Formulation of differential diagnosis • General Nuclear Medicine • Nuclear Cardiology • PET CT • Rotations in cross sectional imaging including CT and MRI • Research rotations	**Description of Training** • Radiation physics and instrumentation • Radiation protection • Mathematics pertaining to the use and measurement of radioactivity • Chemistry of radioactive material for medical use • Radiation biology **Description of Experience** • Ordering, receiving, and unpacking radioactive material safely and performing the related radiation surveys • Performing quality control procedures on instruments used to determine the activity of dosages and performing checks for proper operation of survey meters • Calculating, measuring and safely preparing patient or human research subject dosages • Using administrative controls to prevent a misadministration involving the use of unsealed radioactive material • Using procedures to contain spilled radioactive material safely and using proper decontamination procedures. • Parenteral administration of any alpha or beta emitter, for which a written directive is required