PUBLIC SUBMISSION

As of: November 19, 2014
Received: November 18, 2014
Status: Pending_Post
Tracking No. 1jy-8fkk-imi6
Comments Due: November 18, 2014
Submission Type: Web

Docket: NRC-2008-0175
Training Requirements for Experienced Radiation Safety Officers and Authorized Medical Physicists

Comment On: NRC-2008-0175-0017
Medical Use of Byproduct Material - Medical Event Definitions, Training and Experience, and Clarifying Amendments

Document: NRC-2008-0175-DRAFT-0050
Comment on FR Doc # 2014-16753

Submitter Information

Name: Anil Hiteshi
Submitter's Representative: Angelique Lee-Rowley, Esq.
Organization: Spectrum Pharmaceuticals, Inc.

General Comment

Please see attached comments on the Proposed Rule from Spectrum Pharmaceuticals, Inc.

Attachments

Final Spectrum Letter to NRC 4317613

SPECTRUM™
PHARMACEUTICALS
Redefining Cancer Care

November 18, 2014

Via e-mail and U.S. Mail

Annette Vietti-Cook
Office of the Secretary
Secretary of the Commission
U.S. Nuclear Regulatory Commission
ATTN: Rulemaking and Adjudications Staff
Washington, DC 20555-0001

Re: Docket ID NRC-2008-0175
Medical Use of Byproduct Material—Medical Event Definitions, Training and Experience, and Clarifying Amendments; Proposed Rule

Dear Secretary Vietti-Cook:

Spectrum Pharmaceuticals appreciates the opportunity to provide comment on the Proposed Rule on "Medical Use of Byproduct Material—Medical Event Definitions, Training and Experience, and Clarifying Amendments" as published in the Federal Register on July 21, 2014. In particular, we would like to focus our comments on the Nuclear Regulatory Commission's oversight of therapeutic radiopharmaceuticals. Spectrum is a company whose mission is to bring pharmaceutical products to patients for unmet medical needs, with a focus on oncology/hematology products. Our product Zevalin® (ibritumomab tiuxetan) is a monoclonal antibody radioimmunotherapy treatment for relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL) and previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy. This rulemaking presents an opportunity for the NRC to clarify the training and experience requirements for physicians that administer potentially life-saving anti-cancer beta emitter products such as Zevalin. As discussed below, we respectfully request that the NRC finalize training and experience requirements to allow Authorized User (AU) status for physicians who undergo 80 hours of classroom and laboratory training.

I. Background on Zevalin

A. Clinical Overview

Zevalin is a CD20 directed monoclonal antibody radioimmunotherapy treatment for relapsed or refractory, low grade or follicular B-cell NHL and previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy. B-cell

NHLs are known to be highly radiosensitive. In February 2002, Zevalin became the first radioimmunotherapy to receive U.S. Food and Drug Administration (FDA) approval.

Zevalin consists of a monoclonal antibody linked to the radioactive isotope yttrium-90, a pure beta emitter. After infusion into a patient, the monoclonal antibody targets the CD20 antigen, which is found on the surface of >90% of B cells. In this manner, cytotoxic beta radiation is delivered directly to the targeted cells and cells within only a 5mm radius.

In September 2009, Zevalin was approved as part of the first-line setting based on results from a 414-patient study that showed a 54% decreased risk of progression with Zevalin. A 130-patient multicenter, randomized, open-label clinical study comparing the efficacy of the Zevalin therapeutic regimen versus rituximab in patients with relapsed or refractory low-grade or follicular NHL showed that the Zevalin therapeutic regimen produced an overall response rate of 83% compared to 55% with rituximab.

B. Administration of Zevalin

Zevalin is administered in an intravenous injection that has three parts: two infusions of rituximab and one injection of Yttrium-90 (Y-90) Zevalin, which must be given within 4 hours of the second dose of rituximab. Rituximab is used to reduce the number of B-cells in the blood and Y-90 Zevalin is given to treat NHL. NHL is typically treated by a hematologist or oncologist in either the hospital outpatient or physician office setting. However, in order for a treating physician that is not an Authorized User licensed by the NRC or an Agreement State to provide a patient with the Zevalin treatment regimen, that physician must refer a patient to an Authorized User to prescribe and administer the radioactive component.

Preparation of the radiopharmaceutical is conducted at a licensed specialty radiopharmacy for the individual patient and delivered to the prescribing physician as a patient-ready dose in a pre-filled syringe. The product has a short half-life and is administered to the patient within 8 hours of radiolabeling. The maximum dose of Y-90 permitted per the product's label is 32 mCi (1184 MBq).

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days). The product of radioactive decay is non-radioactive Zirconium-90. The range of beta particles in soft tissue (χ90) is 5 mm. Radiation emission is beta minus, with a mean 100% per disintegration, and a mean energy of 750-935 keV.

C. Zevalin Has a Demonstrated Safety Record

Since FDA approval in 2002, thousands of patients have been treated with Zevalin. The product has a strong safety record. In recognition of this safety record, in 2011 the FDA revised the label to remove the requirement that clinicians conduct a pre-treatment biodistribution evaluation using Indium-111 Zevalin imaging dose followed by a gamma scan before administering the Zevalin therapeutic dose. This pre-treatment biodistribution evaluation requirement is more commonly referred to as the "bioscan." Some treating clinicians may perform a bioscan based on individual patient characteristics.

Zevalin is the anti-CD20 monoclonal antibody linked to Y-90, which emits using beta radiation. As a beta emitter product, Zevalin has also been subject to oversight and regulation by the NRC. Zevalin has an excellent NRC safety record. Since 2002, there have been only three medical events reported to the NRC involving Zevalin.

As a beta emitting radiotherapy, Zevalin's safety precautions are minimal, as compared to gamma emitting radiopharmaceuticals, such as those using I-131. The Zevalin FDA-approved labeling includes a section for Radionucleotide Precautions that states only, "minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures." No isolation or Geiger counter measurements are required as part of the administration or patient management, as are seen with gamma emitting radiopharmaceuticals. In pharmacokinetic studies of patients receiving the Zevalin therapeutic regimen, the mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

II. Current NRC Regulations Limit Patient Access to Zevalin

In its Notice of Proposed Rulemaking, the NRC has specifically requested comments on whether its regulations "*discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how.*" The NRC's current regulatory framework creates an adverse impact on hematologists and oncologists who would like to administer Zevalin and a patient population that is unable to access the treatment.

The NRC's regulations create a shortage of Authorized Users able to administer Zevalin. Under current regulations, as a drug administered parenterally and used primarily for its beta radiation characteristics, Zevalin can only be administered by an Authorized User who has met the training and experience requirements set forth in 10 CFR 35.396. These requirements involve either board certification or 700 hours of training and experience specifically in radionuclide handling.

The hematologists and oncologists who typically prescribe the Zevalin regimen outside of the hospital setting often do not have the training and experience required to meet the Authorized User requirements and do not work at facilities that have such Authorized Users. They have extensive training and experience, and are frequently board certified, but in different specialized fields. Due to the Y-90 Zevalin being radiolabeled by an expert facility and provided as a patient-ready dose, AUs for Zevalin are not required to perform the typical radionucleotide handling operations.

Spectrum has worked with the relevant professional societies, patient advocacy groups, and NRC staff over the past several years to look at options to expand access to Zevalin. Although the regulations permit hematologists/oncologists to administer the drug under the technical supervision of an Authorized User, such supervisors are not typically available in the clinical hematology/oncology setting. Furthermore, Agreement States often

impose significant regulatory burdens on the technical supervision relationship, making it impractical in the typical clinical setting.

The effect of the regulations is to severely limit patient access to a very safe and effective treatment.

Certain patient populations are particularly negatively affected by a lack of AUs for Zevalin. For example, in rural geographies or other areas where patients must travel great distances to their primary oncologist, and even farther to a specialized facility with an AU, Zevalin is often excluded as a treatment option discussed by the oncologist. This is the same population that would likely benefit from a short course of treatment such as Zevalin, which is completed in 7-9 days, as opposed to additional multi-week cycles of chemotherapy requiring multiple office visits.

It would be a detriment to patients if this important therapy option were to succumb to the same fate as the only other radioimmunotherapy in its class, Bexxar. GSK made the decision to withdraw its NHL treatment Bexxar (I-131 tositumomab) from the market in 2013 due to lack of sales. Bexxar, like Zevalin, was proven safe and effective, but also experienced problems with a lack of Authorized Users as a disincentive to offering radioimmunotherapy as a treatment option.

III. Proposed Rulemaking Adjusts Training and Experience Requirements

Spectrum appreciates the attention and consideration of the NRC staff to these access issues. We have followed the rulemaking process and have carefully reviewed the proposed rule, and specifically the changes to § 35.300, *Use of Unsealed Byproduct Material for Which a Written Directive Is Required,* § 35.390, *Training for use of unsealed byproduct material for which a written directive is required*, and § 35.396, *Training for the parenteral administration of unsealed byproduct material requiring a written directive.*

In the proposed changes to § 35.390, the NRC has addressed an ambiguity that exists under the current regulations as to how the training and experience requirements for certain new technologies should be determined. The proposed language creates a new division among radionuclides to include one category for radionuclides used primarily for electron emission, beta radiation, or photon energy less than 150keV, and a second category for radionuclides used primarily for alpha radiation. The former "any other radionuclide" category is now eliminated, and an explicit direction is added that all radioactive drugs other than those in the identified categories will be reviewed as new technologies under § 35.1000, where the NRC will individually determine the appropriate training and experience requirements.

A. Training and Experience Pathways

In addition to clarifying the categories of radionuclides, the NRC has also proposed changes to the training and experience requirements for the various radionuclides. Spectrum understands the training and experience requirements for administrators of Zevalin under

existing regulations as follows: The options to become an Authorized User for this type of administration are to follow either board certification pathways or alternate pathways to (a) become an Authorized User under § 35.390, or (b) become an Authorized User under § 35.490 or § 35.690 **AND** demonstrate an additional 80 hours training and experience in parenteral administration.

Based on the revisions in the proposed regulations, the NRC has modified the requirements for classroom and laboratory training. As proposed in the rulemaking noticed in the Federal Register, the options for a physician to become an Authorized User for this type of administration are as follows: (a) become an Authorized User under § 35.390, (b) become an Authorized User under § 35.490 or § 35.690, (c) become board certified under § 35.490 or § 35.690, **OR** (d)(1) have "successfully completed 80 hours of classroom and laboratory training, applicable to parenteral administrations listed in § 35.390(b)(1)(ii)(G)" (along with the relevant supervised work experience listed in (d)(2)). The parenteral administrations referenced include "(3) Parenteral administration of any radionuclide that is primarily used for its ... beta radiation characteristics ... for which a written directive is required."

Spectrum strongly supports changes in the proposed rulemaking to permit individuals who have completed the 80 hours of classroom and laboratory training applicable to the parenteral administrations referenced in § 35.396(d)(1) and who have the relevant work experience described in § 35.396(d)(2) to be eligible for Authorized User status to administer Zevalin. Spectrum believes this is an appropriate level of training and experience for administration of Zevalin in the hematologist / oncologist setting.

It should be noted that the pathway requiring 80 hours of training and experience that would be available to those seeking to administer Zevalin under the proposed regulations is the same as that available to those seeking to administer sodium iodide I-131 under the current regulations at § 35.392 and § 35.394. As discussed above, the safety profile of Zevalin is comparable to and in some ways more favorable than that of 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 enhanced by its unique process of administration, wherein it is radiolabeled by a licensed radiopharmacy and delivered as a patient-ready dose, so the administrator of Zevalin is not required to perform the typical radionucleotide handling operations associated with other radiopharmaceuticals. Given these considerations and the favorable safety profile of Zevalin, it is logical that the 80 hour pathway available to administrators of I-131 also be made available to administrators of Zevalin.

B. Case Administrations and Work Experience

The NRC's proposed rulemaking also adjusts the case administration component of the work experience requirement to align with the redefined categories of radionuclides at § 35.390 (b)(1)(ii)(G)(3). The proposed regulation has the unintended consequence of

increasing the burden of the work experience requirement for those seeking to administer therapeutic radiopharmaceuticals such as alpha and beta emitters.

Under the current regulations at § 35.300 et seq., those seeking Authorized User status to administer beta or alpha emitting radiopharmaceuticals can meet the requirements through work experience under a supervising Authorized User involving three cases of administration of such radiopharmaceuticals. Under the proposed regulations, those seeking to administer both types would need work experience in a minimum of six cases of administration, three with alpha emitters and three with beta emitters.

Spectrum is concerned that narrowing the scope of what qualifies as relevant work experience will create an adverse impact on clinical practice, predominantly on those seeking to administer the less common radiopharmaceuticals. These products often treat diseases with limited patient populations and an individual Authorized User may only treat several patients a year. It may prove too burdensome for certain practitioners, particularly those in areas far removed from teaching hospitals and urban centers, to participate in three proctored cases in each of these very specific categories. The result will be to limit patient access to these safe and effective pharmaceuticals among what is already a disadvantaged population.

In its Notice of Proposed Rulemaking, the NRC has specifically requested comments on whether its regulations "discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how." Spectrum believes that the proposed changes would discourage clinicians from seeking authorization to administer these radiopharmaceuticals and would make an already burdensome regulatory scheme more onerous. Spectrum would suggest that the NRC revise its proposed regulations such that the work experience requirement of three proctored cases remain satisfied by relevant experience in either of the proposed revised categories in § 35.390 (b)(1)(ii)(G)(3) or § 35.390 (b)(1)(ii)(G)(4).

IV. Alternatives to Proposed Rulemaking

If Spectrum's reading of the proposed regulation above was not intended to apply to Authorized Users administering Zevalin, the NRC could take this opportunity to address the shortage of authorized individuals able to administer this treatment though alternative modifications to the regulations. This rulemaking addresses training and experience requirements to become an Authorized User, makes specific changes designed to address a likely "shortage of authorized individuals to provide medical care", and restructures the classification of radionuclides, so the context is appropriate.

The NRC's regulations are designed to provide flexibility for emerging technologies, and could be adjusted to recognize that alpha and beta emitters are a new class of therapeutic radiopharmaceutical products. In May 2013 the FDA approved Xofigo for treatment of advanced prostate cancer. Actinium Pharmaceuticals is currently developing an alpha emitter

treatment for leukemia. We expect that in the future there will be more innovative therapeutic radiopharmaceutical agents.

The NRC should create a new training and experience requirement specific to therapeutic radiopharmaceuticals based upon their unique characteristics, typical setting for administration, and safety record (such as was done for sodium iodide I-131 at § 35.392 and § 35.394). The NRC could give license applicants an option to petition NRC for review under § 35.1000 for a drug that technically fits within the four categories listed in § 35.390 (b)(1)(ii)(G), but is deserving of an individualized training and experience requirement review, due to its administration profile and safety characteristics.

Spectrum appreciates the opportunity to comment on the proposed rulemaking. We respectfully request the opportunity to meet with the NRC staff to discuss these modifications of the training and experience requirements for beta emitter products.

Sincerely,

Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
Spectrum Pharmaceuticals, Inc.

11500 South Eastern Ave • Suite 240 • Henderson, NV 89052 • Tel: 702.835.6300 • Fax: 702.260.7405
www.sppirx.com • NASDAQ: SPPI