SPECTRUM™
PHARMACEUTICALS
Redefining Cancer Care

October 02, 2015

Via e-mail and U.S. Mail

Chairman Stephen G. Burns
U.S. Nuclear Regulatory Commission
Mail Stop O-16G4
Washington, DC 20555-0001

Re: Training and Experience Requirements for Alpha and Beta Emitters

Dear Chairman Burns:

We are writing to thank you and your fellow Commissioners for the opportunity to discuss the Nuclear Regulatory Commission's oversight of therapeutic radiopharmaceutical anti-cancer treatments that are regulated by NRC as beta emitters. Spectrum Pharmaceuticals manufactures the biological product Zevalin® (ibritumomab tiuxetan), a radioimmunotherapy treatment for non-Hodgkin's lymphoma (NHL). We are concerned that the current regulations disproportionally impact patient and provider access, relative to the modest safety risk, by restricting Authorized User status for oncologists and hematologists who do not meet the 700 hours of training and experience requirements, which discourages the development and innovation of targeted radioactive anti-cancer biological therapies. We respectfully request that NRC address the training and experience requirements in the Final Rule to allow for a limited authorization of Authorized User status for administration of beta emitters similar to those requirements in place for oral sodium iodine I-131.

National Impact to Patient Access

We believe it is critical for NRC to fully appreciate the extent of the impact of these regulations on patient access to Zevalin, an FDA-approved drug for the treatment of patients with Non-Hodgkins lymphoma, and take immediate action. This is not an isolated issue and we have heard from numerous hematology and oncology providers across the country that the Authorized User (AU) training and experience requirements are the primary hurdle limiting patient access to Zevalin in both rural and urban settings. Board certified hematologists and oncologists are not realistically able to devote 700 hours of time away from their practices to achieve Authorized User status through the alternate pathway, and importantly, this training requirement is not commensurate with the safety risks of handling a beta emitter radioimmunotherapeutic product. Rather, these training and experience requirements are the standard pathway for practitioners who are board certified in nuclear medicine and radiation oncology, who administer and handle radiopharmaceuticals with higher risk profiles, e.g., gamma emitting radiopharmaceuticals.

We appreciate that an ACMUI subcommittee has been convened and has issued a draft report on the current requirement of 700 hours for training and experience for authorized users of alpha and beta emitters. We are concerned, however, that the Subcommittee appears to have reviewed data primarily associated with access at medical centers, which is an incomplete perspective on the issue. As we have presented to ACMUI, the access issues are most acute in the community-based physician setting, where the majority of patients with NHL are treated. 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 simply because it is impractical to coordinate its administration through an AU. The patients

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

who benefit most from a treatment like Zevalin are frequently older and frail and have mobility impairments.

Discouraging Innovation of New Safe and Effective Cancer Therapies

The decrease in the number of Authorized Users across the country to administer Zevalin has interfered with patient access to this effective therapy, and created the disheartening reality that the product will become uneconomical for Spectrum to offer for sale; Spectrum is currently the third owner to market this product. One of the reasons cited by the prior manufacturers for ceasing to market the product was the hurdle for access to Authorized Users based on the current regulations. Additionally, with similar concerns, an earlier radiopharmaceutical product Bexxar (tositumomab and iodine I-131 tositumomab) was withdrawn from the market by GlaxoSmithKline further limiting cancer patient treatment options.

Targeted radioimmunotherapy is an active area of research and development with the potential for new life saving therapies to be developed and approved in this decade. While there is the opportunity in the future for there to be more innovative therapeutic radiopharmaceutical agents, there is growing concern among the biopharma companies and providers that the current regulatory framework is too burdensome for physicians to administer these treatments, which discourages their development. If the regulatory framework is not adjusted now to account for training and experience requirements that are more appropriate and commensurate with the actual risks for using these therapies, there is the real danger that investment in developing these future lifesaving therapies will disappear.

NRC Should Address the Training and Experience Requirements in the Final Rule

NRC has the authority to amend the training and experience requirements as part of its final, ongoing rulemaking process. In its Notice of Proposed Rulemaking, 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.***"

We are very concerned that the ACMUI subcommittee has recommended deferring this charge until the Spring 2016 ACMUI meeting, which will be after the current Rulemaking is expected to be finalized. Spectrum strongly recommends a provision in the Final Rule be implemented now 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.. This would eliminate the unnecessary regulatory barriers that are currently limiting cancer patient access to effective treatment options, while maintaining training requirements commensurate with the risks of handling a beta emitting radiopharmaceutical.

As described in the attached chart, the currently required 700 hours includes training for the handling all aspects of medical use of byproduct materials. Spectrum believes there is ample support that 80 hours of training is a more appropriate level of training and experience for Authorized Users who administer Zevalin in the hematologist / oncologist setting. Prior to the 2006 rulemaking, hematologists /oncologists could be licensed as Authorized Users and be able to administer beta-emitting radiopharmaceuticals such as Zevalin with 80 hours of training. A number of the current Authorized Users for Zevalin received AU status under those regulations with 80 hours of training and have been grandfathered. These physicians have had an excellent safety record of handling these radiopharmaceuticals.

The proposed revision of the regulatory pathway to require 80 hours of training and experience for beta emitters would mirror the extent of training and experience that is currently required for physicians who seek to administer sodium iodide I-131 under the current regulations at § 35.392 and § 35.394. The safety profile of Zevalin is well established and is at least comparable to and in some ways 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 this product. Gamma-emitting radiopharmaceuticals such as I-131, in contrast, require more precautionary measures during administration, such as isolation and Geiger counter measurements. Zevalin's safety profile is further enhanced for Authorized Users by its unique process of administration, wherein it is radiolabeled by a licensed radiopharmacy and delivered as a patient-ready dose, so the Authorized User of Zevalin is not required to perform the typical radionucleotide handling operations associated with other radiopharmaceuticals.

Emerging Technology Regulation under 35.1000

The NRC regulations are designed to provide flexibility for emerging technologies, and, therefore, changes to the regulations would reflect a policy interest in encouraging innovation in the use of FDA-approved beta emitters, a relatively new class of therapeutic radiopharmaceutical products. Alternatively, if the Agency does not pursue a regulatory change in the Final Rule now, we request that NRC grant a license to Zevalin pursuant to 10 CFR § 35.1000, a provision that gives NRC broad discretion to regulate emerging technologies. Pursuant to 35.1000, NRC could approve Zevalin as an emerging technology as its use is not "specifically addressed" elsewhere in the regulations.

In the event that the Commission agrees that Spectrum should petition for licensure of Zevalin as an emerging technology pursuant to 35.1000, applicants would provide the required materials and seek written approval from the Commission that 80 hours of training and experience is sufficient for the safe and proper handling and administration of Zevalin.

Spectrum appreciates the careful attention and consideration of the NRC Commissioners to these important issues. We look forward to meeting with you on October 28th, and would be pleased to address any questions you may have. We remain optimistic that the NRC will take immediate action in both the interest of cancer patients and in alignment with its intent to not discourage the use of certain therapeutic options or adversely impact clinical practice, by implementing a provision in the Final Rule now to permit oncologists who have completed 80 hours of classroom and laboratory training to become eligible for Authorized User status to administer Zevalin..

Sincerely,

cc: NRC Commissioner Jeff Baran
NRC Commissioner William C. Ostendorff
NRC Commissioner Kristine L. Svinicki

APPROVED AS TO LEGAL TERMS
LEGAL DEPT.

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

Authorized **User**

Training and Experience Requirements

Alternate Pathway **35.300** **700 Hours**	**Proposed Alpha and Beta Emitting Pathway** **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