SPECTRUM™
PHARMACEUTICALS
Redefining Cancer Care

March 3, 2016

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

Re: Draft Report on Training & Experience for Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390

Dear Members of ACMUI:

We are writing in advance of the March 10th Advisory Committee on the Medical Use of Isotopes (ACMUI) teleconference to provide our response to the Subcommittee Draft Report on Training and Experience for Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390. While we appreciate the time and attention that the NRC and ACMUI have devoted to this important issue over the past 18 months, we are concerned that the Subcommittee fails to justify why the currently required 700 hours of training and experience is appropriate for an oncologist or hematologist seeking to administer a patient-ready dose of an alpha or beta emitter. Additionally, while the Draft Report acknowledges that the education paradigm has shifted since the 700-hour requirement was established in 2002, the Subcommittee does not recommend a sufficient level of training and experience for Authorized Users (AUs) of patient-ready dose therapies. As discussed in greater detail below, we agree with the Subcommittee's finding that the current requirements are outdated, and urge the Full Committee to make specific recommendations for training and experience for a patient-ready dose.

The Subcommittee Failed to Justify Why 700 Hours of Training and Experience is Appropriate

The Subcommittee was charged with developing a recommendation for the appropriate number of hours of training and experience for a patient-ready dose of alpha and beta emitters. Instead, the Draft Report only notes that "[a]ppropriate T&E requirements for these agents need to be established" and recommends the issue for further study. In particular, the Subcommittee did not address the stakeholder expert commentary regarding appropriate training for AUs for a patient-ready dose. This is a critical distinction because a patient-ready dose does not involve handling or preparation of the radioactive isotopes. Rather, the biological product is prepared by a fully licensed radiopharmacy and delivered to the physician on the day of the scheduled patient appointment.

Corporate Office: 11500 South Eastern Avenue, Suite 240 • Henderson, NV 89052 • Tel: 702.835.6300 • Fax: 702.260.7405 Research & Development: 157 & 153 Technology Drive • Irvine, CA 92618 • Tel: 949.788.6700 • Fax: 949.788.6706
Commercial Office: 31355 Oak Crest Drive, Suite 375 • Westlake Village, CA 91361 • Tel: 818.540.7100
www.sppirx.com • NASDAQ: SPPI

It is our understanding that the 700-hour requirement was set to reflect the complete coursework 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. We believes there is ample support that 80 hours of training or less is sufficient and is 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.

The Subcommittee Found No Safety Issues with Alpha and Beta Emitter Therapies

We agree with the Subcommittee finding of an "exceptional" and "excellent" safety record of alpha and beta emitters. Indeed, the Subcommittee made no mention of any safety incidents or risks associated with the administration of such therapies. However, we disagree with the Subcommittee that the safety record is attributed to AUs "who have successfully completed the rigorous T&E requirements." Notably, at no point in its report did the Subcommittee find that 700 hours of training and experience is necessary to ensure that alpha and beta emitter therapies are safely administered. In particular, the regulations previously required 80 hours of training and experience prior to the 2002 NRC rulemaking, and we are not aware of a single safety event during that time period. Moreover, oncologists who became an AU under the 80-hour alternate pathway continue to administer alpha and beta emitters today without any safety events. This means that physicians who became AUs under the 80 hour requirements have since been administering beta emitters wholly without any safety issue or incident. Contrary to the statement in the Draft Report, "[w]hether or not the safety records would be comparable in the hands of AU's with considerably less T&E [than 700 hours]" is *not* "a matter of conjecture."

The Subcommittee Recognized That the Current Training Paradigm Is Outdated

We agree with the Subcommittee's conclusion that, since it has been "nearly 15 years since the current requirements were established," they are now outdated. It is clear from the Subcommittee's acknowledgement that the training paradigm has shifted that 700 hours is not appropriate and a new training program is needed.

However, we disagree with the Subcommittee's conclusion that establishing a more appropriate educational approach based on competency "is complicated and cannot be completed in weeks or even months." Given the significant involvement of and input from the NRC, ACMUI, the Subcommittee, and numerous stakeholders throughout this process, further delay is unwarranted. Stakeholder input has already demonstrated that competency could be established through programs imposing much less of a burden on practicing physicians.

For example, Kristina Wittstrom, Kara Weatherman, and Nicki Hilliard are experienced nuclear pharmacists and experts in the field of radiation safety education and training. They represent academic training programs that have trained thousands of AUs over the past decades and submitted detailed recommendation to the NRC to "modify the training & experience requirements for authorized users for patient ready alpha and beta emitters to a didactic program which consists of 80 hours of educational material." Course material would be tailored to issues involving the administration of specific patient-ready alpha and beta emitters, and would include a didactic program consisting of 25 hours on Nuclear Physics & Instrumentation; 20 hours on Radiation Biology, 25 hours on Regulations and Radiation Protection, and 10 hours Mathematics Pertaining to Use & Measurement of Radioactivity.

Based on the expert stakeholder commentary, we have prepared the attached proposed regulatory text for a new training and experience paradigm for patient ready doses of alpha and beta emitters.

The Subcommittee Continues to Ignore Patient Access to Needed Therapies

The NRC as well as ACMUI have heard extensive testimony regarding the impact of the current 700-hour training and experience on access to care in certain patient communities. No one maintains that no patients have access. However, the Subcommittee continues to take the position that "it is not possible to conclude that the current T&E requirements are the only, or even the principal, cause of the decreased use of radiopharmaceuticals . . .". ACMUI continues to ignore the letters and expert statements that are contrary to this conclusion. In fact, ACMUI has received letters from, among others, the Leukemia and Lymphoma Society, the Lymphoma Research Foundation, the Community Oncology Alliance, the American Society of Hematology, the Council of Radionuclides and Radiopharmaceuticals, Inc., and Florida Cancer Specialists.

We were pleased to see that Subcommittee Member Laura Weil correctly observed that "[t]he 700 hour T&E requirement effectively limits AUs to those medical specialties that cover the requirements in residency training. Those specialists may simply not be available in the community setting, creating a real barrier to access for those patients who are unable to seek treatment in a larger medical center." In fact, the data displayed in the Subcommittee's report about the decline in the use of Zevalin since 2002 can also be interpreted as evidence that there is an access problem for patients, which is partially caused by the lack of AUs for alpha and beta patient-ready dose therapies outside of major medical centers.

In addition, we noted that NRC Commissioner Svinicki raised concerns about the NRC's actions potentially restricting patient access to medical therapies at a February 25th meeting of the Commission, by stating, "I think we want to just be nuclear geeks, but I just, I don't know that that's practical going forward and it may be that we're just going to have to enmesh ourselves in a community

SPECTRUM™
PHARMACEUTICALS
Redefining Cancer Care

of regulators that is grappling with these issues to make sure that patients have access to things that could be beneficial and that we don't artificially suppress the use."[1]

Furthermore, the report's generalization that the use of older medicines declines "as newer, equally or more effective, agents becomes available" does not apply to Zevalin since the development of new therapies has not replaced the need for alpha and beta emitter therapies. As Dr. Mace noted in his expert statement, because indolent non-Hodgkin's lymphoma (NHL) is a non-curable disease, "it is crucial that proven agents, such as the antibody-bound Beta emitters, be readily available to patients. . . , as optimal improvements in life span and survival will be achieved by employing many different treatments over the course of their disease." Ms. Weil also observed that "NHL patients often live with the disease for many years, and require a varied armamentarium of therapies to address each subsequent recurrence." Supporting those statements about the importance of access to multiple medicines for treating NHL is the **National Comprehensive Cancer Network's** recommendations for radioimmunotherapies as 1st line therapy for the follicular lymphoma form on NHL - particularly for elderly or infirmed patients who may not tolerate other treatment options.[2]
We thank ACMUI for its attention to these issues, and we again request that the ACMUI full committee consider our concerns relating to the Draft Report in advance of the March 10 teleconference. We urge the NRC and ACMUI, in the interest of cancer patients, to act quickly to establish a more appropriate training and experience requirement for becoming an AU able to administer beta emitter therapies in patient-ready doses, and we believe that there is ample information and rationale for establishing an 80 hour didactic course-based requirement for these medicines.

Sincerely,

Allen Yang, M.D., Ph.D.
Spectrum Pharmaceuticals, Inc.
Vice President of Global Clinical Development
157 Technology Drive
Irvine, CA 92618
(949) 743-9287
allen.yang@sppirx.com

[1] NRC's "Briefing on the Strategic Programmatic Overview of the Fuel Facilities and the Nuclear Material Users Business Lines (Public)". Transcript, p. 105. [http://pbadupws.nrc.gov/docs/ML1606/ML16060A375.pdf]
[2] NCCN "Clinical Practice Guidelines in Oncology, Non-Hodgkins Lymphoma, v 4.2014 (8/22/2014)" page 37. [Accessed at http://www.nccn.org/about/nhl.pdf on 3/1/2016]

"Attachment: Proposed Regulatory Text for New Training and Experience for Patient-Ready Doses of Alpha and Beta Emitters."

Training for the Administration of Alpha- and Beta-Emitting Radiopharmaceuticals Prepared as Patient-Ready Doses by Licensed Nuclear Pharmacists at Licensed Radiopharmacies

Except as provided in 35.57, the licensee shall require an authorized user for the administration of pre-prepared patient-ready doses of alpha- and beta-emitting radiopharmaceuticals requiring a written directive to be a physician who--

(a) Is certified by a medical specialty board whose certification process has been recognized by the Commission or an Agreement State and who meets the requirements in paragraphs (c)(1) and (c)(2) of this section. (Specialty boards whose certification processes have been recognized by the Commission or an Agreement State will be posted on the NRC's Web page.); or

(b) Is an authorized user under § 35.390 for uses listed in § 35.390(b)(1)(ii)(G)(2) or equivalent Agreement State requirements; or

(c)(1) Has successfully completed 80 hours of classroom and laboratory training, applicable to the medical use of alpha- and beta-emitting radiopharmaceuticals administered as pre-prepared patient-ready doses for procedures requiring a written directive. The training must include—

(i) Nuclear physics and instrumentation;

(ii) Radiation biology;

(iii) Regulations and radiation protection; and

(iv) Mathematics pertaining to the use and measurement of radioactivity; and

(2) Has completed experiential training exercises, under the supervision of an authorized user who meets the requirements in §§ 35.57, 35.390, [this regulation], or equivalent Agreement State requirements. A supervising authorized user, who meets the requirements in § 35.390(b), must also have experience in administering dosages as specified in § 35.390(b)(1)(ii)(G)(2). The experiential training exercises must involve—

(i) Completion of not less than 10 hours of experiential training in radiation safety techniques, protocols, and procedures;

(ii) Participation in or observation of the administration of the specific radiopharmaceutical to not less than 3 patients; and

(3) Has obtained written attestation that the individual has satisfactorily completed the requirements in paragraphs (c)(1) and (c)(2) of this section, and has achieved a level of competency sufficient to function independently as an authorized user for medical uses authorized under § 35.300. The written attestation must be signed by a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, [this regulation], or equivalent Agreement State requirements. A preceptor authorized user, who meets the requirements in § 35.390(b), must also have experience in administering dosages as specified in § 35.390(b)(1)(ii)(G)(2).