**STATEMENT OF JOSEPH R. MACE, M.D.**
**Medical Oncologist and Licensed Authorized User**
**Florida Cancer Specialists**
**to the**
**Advisory Committee on the Medical Use of Isotopes Subcommittee on Training and Experience for Beta-emitters**

## I. Introduction

1. My name is Joseph Mace, and I am writing to provide the ACMUI Subcommittee with my opinion and recommendations as it reviews the appropriate level of training and experience requirements for hematologists and medical oncologists to safely administer beta-emitters under 10 CFR 35.390. As set out in my statement, I have been an Authorized User for over a decade and have safely administered beta emitters, including Zevalin (ibritumomab tiuxetan), to over 40 patients.

2. I have detailed my training and clinical experience for the Subcommittee. I believe that the information provided in my statement supports a modification to the training and experience requirements to provide a limited authorization for beta emitters prepared by a licensed radiopharmacy and delivered to the hematologist/ medical oncologist in a pre-filled syringe.

3. I strongly urge that the ACMUI Subcommittee consider a modified alternate pathway of requiring 80 hours of training and experience for hematologists/ medical oncologists seeking to administer beta-emitting therapeutic radiopharmaceuticals such as Zevalin.

## II. Academic and Clinical Qualifications

4. I received a Bachelor of Arts with highest honors, from the State University of New York at Binghamton in 1989 and a Doctor of Medicine, *summa cum laude*, from the State University of New York Health Science Center at Syracuse in 1993.

5. I served as a Diagnostic Radiology Resident at the Hospital of the University of Pennsylvania between 1994 and 1996, an Internal Medicine Resident at the State University of New York Health Science Center at Syracuse between 1996 and 1998, and was a Hematology and Medical Oncology Fellow at the University of Michigan Medical Center from 1999 to 2002.

6. Starting in the summer of 2002, I practiced as an Attending Physician at Gulfcoast Oncology Associates in St. Petersburg, FL. I founded both the Gulfcoast Oncology Associates' Clinical Research, and Radioimmunotherapy Programs, and served as director until our merger with Florida Cancer Specialists in February of 2011. I continue to serve as an Authorized User (AU) of radioimmunotherapy agents, treating patients at our St. Petersburg office location. In addition, I travel to several additional Florida Cancer Specialists office locations to administer radioimunitherapy agents, in an effort to expand patient access to these important and effective therapies. I also serve as a Thought Leader for Lymphoma, Leukemia, bone marrow disorders, as well as benign hematology within Florida Cancer Specialists' Clinical Research Program .

**III. Authorized User Training and Experience**

7. I obtained my AU license from the Nuclear Regulatory Commission in 2006, after completing an on-site, eight-day, 100-hour radiation safety and handling course offered through the University of Chicago.[1]

8. This course consisted of didactic lectures and two daily written examinations. Course topics included radiation physics, instrumentation, protection, and biology, as well as mathematics pertaining to radioactivity; and radiopharmaceutical chemistry. Specific characteristics and aspects of use surrounding those radioisotopes that are commonly in use for both medical diagnostic and therapeutic indications, across all medical subspecialities, were reviewed in detail. In part owing to this, and as I explain in greater detail below, the 100-hour course I attended did cover a notable volume of material that was/ is superfluous for those physicians seeking to use/ administer solely beta emitters.

9. I have been safely administering Zevalin at multiple office locations in Florida since I received an AU license in 2006, as discussed above.

**IV. Medical Experience with Beta Emitters**

11. During my fellowship training at the University of Michigan Medical Center, I had the unique opportunity to work closely with Dr. Mark Kaminski in the Lymphoma clinic from 1999 through 2002. During this three year period, the use of radioimmunotherapy was commonplace, and as a result I obtained significant experience with their pharmacology, safe handling, and administration. Upon completing my

[1] Until the regulations were changed in 2002 to require 700 hours of training, one could become an AU with 80 hours of training and experience. Because Florida did not implement the rule until 2006, the 80-horu requirements were grandfathered.

Hematology and Medical Oncology fellowship, and joining Gulfcoast Oncology Associates in St. Petersburg, I was uniquely positioned to enhance the services our practice provided. I felt then, as I do now, that Zevalin offers many advantages for our Non-Hodgkin Lymphoma (NHL) patient population.

12. As compared to conventional chemotherapy regimens, beta emitters such as Zevalin provide an invaluable treatment option for patients NHL. For one, treatment with beta emitters is far less intrusive and cumbersome for patients; It can be completed in approximately one week and involves the administration of one dose of radiolabeled antibodies. In addition, antibody-bound beta emitters target NHL cells highly selectively, which translates into mild and generally well tolerated side effects. Patients do not need to be admitted to a hospital for treatment, and beta emitters such as Zevalin typically do not result in significant adverse impact on patients' quality of life, functional capacity, or their other medical problems. Taken in total, it is the clinical features of Zevalin that make it so appealing to those of us who treat Lymphoma patients on a regular basis, particularly where a large proportion of patents are elderly, and unable to tolerate conventional cytotoxic therapy.

13. Beta emitters are employed at many stages of a NHL patient's clinical course. Their tolerability and efficacy are well established in the setting of indolent NHL, which comprises a large percentage of new NHL diagnoses and, unfortunately, is a non-curable disease. This being said, indolent NHL typically runs a very long clinical course thats can be measured in years to decades, with intermittent treatments required over time. This fact highlights the importance of having as many effective agents in our arsenal as possible. In essence, it is crucial that proven agents, such as the antibody-

bound Beta emitters be readily available to patients with indolent NHL, as optimal improvements in life span and survival will be achieved by employing many different treatments over the course of their disease. The antibody-bound Beta emitters have well established efficacy particularly in those patients who have received many prior conventional chemotherapy agents, where responses to subsequent conventional chemotherapeutic agents is less frequent and of shorter duration.

14. Recognizing this, after I received my AU license I worked to establish a "hot lab" as well as an administration area at our practice location. It soon became clear that the ability to provide Zevalin locally, thereby precluding the need for outside referrals to either radiation oncology or a regional academic center, was of tremendous benefit to our patients. While it might be unusual for a hematologist/ medical oncologist to obtain an AU license for RIT administration, there are clear advantages to doing so. We have a unique understanding of chemotherapy, including its administration, potential short- and long-term side effects, as well as the requisite monitoring both during and after treatment. In addition, a hematologist/ medical oncologist is ideally suited to manage patients who receive Zevalin, and the ability to actually administer this agent (as opposed to referring a patient elsewhere to do so) improves convenience, access, and provides for optimal continuity of patient care.

15. As a result, I received consultations for Zevalin therapy, not only from within Gulfcoast Oncology, but also from physicians outside our practice across the state of Florida. Patients clearly appreciated seeing the same physician for their consultation to review and discuss Zevalin therapy, for the administration of the agent, and for the requisite monitoring over the subsequent two to three months thereafter.

16. I have been administering Zevalin for approximately ten years now and have not had a single safety event. I strongly believe that completing an intensive 100-hour course provided me with more than sufficient training to administer this safe and straight forward therapy.

**V. Shortage of AUs**

17. Since the introduction of the 700-hour training and experience requirements, I have observed an immediate and dramatic impact on access to beta emitters. In my own practice at Florida Cancer Specialists, there are many oncologists who would like to administer beta emitters, however it is not logistically feasible or realistic for them to pursue the 700-hour training requirement. It is difficult to fathom a practicing hematologist/ medical oncologist being able to take an aggregate 700 hours away from patient care, in order to attend a radiation safety and handling course, be it at a brick and mortar facility, or online. In fact, to my knowledge, no oncologist has been able to receive AU status under the alternate pathway of 700 hours, since the regulations went into effect.

18. Accordingly, there is in my opinion, a marked shortage of physician "champions" in any given community who are willing to undertake what is now an extensive number of hours to obtain an AU license. In turn, this decreases patient access to this important and effective therapy.

19. The lack of access to beta emitters is an especially acute problem for the elderly, for whom Zevalin is an especially advantageous treatment option. St. Petersburg has a particularly large population of elderly cancer patients, and owing to this, the incidence of low-grade lymphoma occurs with greater frequency than the national average. Not unexpectedly, a majority of elderly patients are not only less able tolerate

conventional chemotherapy, but are also less mobile, and thus typically cannot manage the rigorous clinic visit schedules associated with these chemotherapies.

20. The problem is severe enough that in order to provide patients with access to beta emitters, I initiated a "traveling AU" program, wherein I see patients in consultation, and for administration of Zevalin at multiple office locations throughout Florida. While the program has been effective in modestly increasing access to beta emitters, increasing the number of oncologist AUs in a given community would be far more impactful. This could be accomplished by lowering the training and experience requirements to a more appropriate level.

**VII. 80 Hours of Training is Sufficient**

21. Based on my own experience with the course, 80 hours of training and experience would sufficiently prepare AUs to administer beta emitters such as Zevalin, which is delivered to the AU as a treatment-ready dose prepared by a licensed radiopharmacy. Its administration is not complex, requiring only an acrylic shield and adherence to standard radiation precautions. It does not even require patient isolation or exposure measurements

22. Zevalin has an excellent safety profile, particularly when compared to cytotoxic chemotherapeutic agents. Rates of nausea, vomiting, alopecia, hepatorenal injury and dysfunction, cardiopulmonary toxicity, neuropathy, and constitutional decline, are all less frequent with Zevalin. Like many cytotoxic chemotherapeutic agents, Zevalin does produce myelosuppression, and once again, it is the medical oncologist/ hematologist who is best prepared to manage this common and expected side effect of NHL therapy.

23. By contrast, the administration of sodium iodide I-131 based therapies is a much more involved process requiring a greater degree of precautionary measures. The patient must be isolated, and anyone handling the patient's fluids must wear protective clothing, including eye protection and a mask. In addition, the patient is not permitted to share toothbrushes, towels, or even a bed with another person. Yet currently, this therapy only requires 80 hours of training to administer.

24. The currently required 700 hours of training is vastly disproportionate to Zevalin's safety profile. Indeed, the requirements contained in 10 CFR 35.390 appear to be aimed at physicians seeking to become board certified in nuclear medicine. Board-certified nuclear medicine practitioners handle an array of radioactive substances in diagnosing and treating a variety of diseases. The course that I completed in 2005 covered topics ranging from diagnostic medical imaging, non-medical radiation uses, historical radiation events, to therapeutic thyroid I-131 administration—all superfluous from the standpoint of radionuclide management and safe handling of Beta emitters. That course was 100 hours, and while I am a strong proponent of general knowledge and academic pursuit, this highlights that 700 hours of training is unnecessarily prohibitive for hematologists/ medical oncologists seeking specifically to administer a limited class of beta-emitting products.

25. By reducing the requirements, practicing hematologists/ medical oncologists who either specialize in, or have an interest in NHL, can feasibly complete the required coursework and have an immediate impact on access within their community. In addition, with less onerous requirements in place, improvement in the

degree of familiarity and comfort with using Zevalin would undoubtedly follow, which in turn would translate into even greater access to these important therapies.

26. I believe the current training and experience requirements should be modified with respect to beta emitters. The course content can be appropriately focused on issues related to the administration and handling of beta emitters in order to lessen the time burden, while still resulting in proficiency on the part of the individual physician.

27. Based on my experience, the relevant components of the 700 hours of training for beta emitters can be successfully encompassed by focused study within an 80 hour course/ pathway. Topics essential to this should include training on:

(a) Radiation physicsand biology

(b) Radiation instrumentation, with particular attention to those used and setting appropriate for beta emitter therapy

(c) Radiation protection

(d) Mathematics pertaining to the use and measurement of radioactivity

(e) Pharmacology and chemistry of radioactive materials in the context of medical use.

(f) Safe handling practices for radioactive material and instrumentation

(g) Performance of standard quality-control procedures on instrumentation (those used to determine the activity of dosage, survey meters, etc.), and on received dose packaging, as well as reviews of personnel badges/ rings, and periodic radiation exposure reports.

(h) Calculation, measurement, and safe preparation of patient or human research subject doses (despite the fact this is performed by a licensed radiopharmacy).

(i) Review of the standard administration practices for specific Beta emitters.

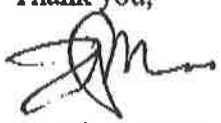
28. In such an 80-hour program, prospective AUs would gain ample experience with the logistics, medical and scientific, as well as administrative aspects and requirements of therapy. This would successfully serve to prevent and/or address adverse events associated with drug misadministration, personnel exposures and decontamination procedures, as well as with procedures for containing spilled radioactive material.

29. The above recommendations can be encompassed and successfully covered with a dedicated 80-hour training and experience requirement. A 700-hour requirement is unnecessary and deprives NHL patients of a valuable treatment option that is needed in many communities.

30. Stakeholders have proposed requiring 80 hours of training and experience to obtain an AU license as part of the current NRC rulemaking on radiolabeled materials, and I fully support this proposal.

31. I appreciate that the ACMUI is taking the opportunity to consider the appropriate training and experience requirements for beta emitters. I urge the ACMUI to consider my experience and recommendations as you prepare your Subcommittee report. I would welcome the opportunity to provide the ACMUI Subcommittee with any additional information that might prove helpful. Please feel free to contact me with any questions.

Thank you,



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