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CORAR

The Council on Radionuclides and Radiopharmaceuticals, Inc.

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Via email February 23, 2016

Advisory Committee on the Medical Use of Isotopes (ACMUI)
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: NRC Training and Experience Requirements for Alpha- and Beta- Emitters

Dear ACMUI Committee Members:

The Council on Radionuclides and Radiopharmaceuticals (CORAR) would like to provide the Advisory Committee on the Medical Use of Isotopes (ACMUI) with additional comments about the training and experience requirements for physicians to safely administer alpha- and beta-emitters that are delivered to them in patient ready doses.

As you know, CORAR's members include the manufacturers and distributors of both FDA approved radiopharmaceuticals, as well as other therapeutic products that are still undergoing research and development. CORAR continues to support the NRC's efforts to update the training and experience regulations, particularly to ensure access and to support technological advances and changes in medical procedures.

As we've noted previously, we continue to hear from providers, patient groups, and our members that the current regulatory framework requiring 700 hours of training before hematologists and oncologists who can become Authorized Users licensed to administer alpha- or beta- emitting radiopharmaceuticals is limiting access to medicines such as Xofigo® (Radium Ra 223 dichloride) and Zevalin® (ibritumomab tiuxetan), as well as raising concerns about the future development of radiopharmaceuticals designed to treat or cure cancers - often in a very precision way.

This letter is about the specific scope of training requirements for Radioisotope Handling and Radiation Safety for physicians wishing to administer intravenous therapeutic radiopharmaceuticals containing alpha- or beta- emitting radioisotopes, which have been prepared by a licensed nuclear pharmacist in a state-licensed radiopharmacy and dispensed to physicians as patient-ready doses. Surely the Advisory Committee members will agree, that as the Advisory Committee and the NRC are evaluating the appropriate level of training and experience for these physicians for their limited use of radionuclide therapies, that the Committee and the NRC consider not only the current state of radiological science, but also how biomedical advancements have produced new valuable drugs for patients and their physicians.

In determining the appropriate amount of time (and scope of content) for Radioisotope Handling and Radiation Safety training that physicians, such as medical oncologists and hematologists, should receive to enable them to safely administer these types of therapeutic drugs, the following factors need to be considered:

- Their limited role in handling these radiolabeled drugs (which would be dispensed and delivered to them in patient-ready doses from a licensed radiopharmacy);
- The radiological safety profiles of radiopharmaceuticals containing alpha- and beta-emitting isotopes; and
- Physician's experience and training in handling toxic non-radioactive chemical therapies, e.g., cytotoxic chemotherapy agents.

CORAR believes that the didactic training required to adequately prepare physicians to safely administer patient-ready doses of alpha- and beta- emitting radiopharmaceuticals would entail about 70-80 hours of classroom and laboratory time, as described in more detail below.

In considering what information should be covered in this training, it should be noted that the didactic training for cardiologists wishing to be added to a radioactive materials (RAM) license as an Authorized User of Diagnostic Radiopharmaceuticals/Radionuclides and/or to be Board Certified in Nuclear Cardiology emphasizes primarily Instrumentation and Physics, Radiopharmacy, and Radiation Safety along with a reasonable amount of Radiobiology and Mathematics Associated with Use of Radioactivity.

For physicians who wish to be added on to a RAM license as an Authorized User of Therapeutic Radionuclides for administering alpha- and beta- emitters as described above, however, the emphasis should change significantly. Emphasis on Instrumentation can be reduced since it historically has covered Imaging Instrumentation, Principles of Scintillation Detection, cameras and scanners, and related topics. That information is not relevant to the administration of non-imageable therapeutic isotopes, but learning about dose calibrator operation and quality control should be on top of the list of important instrumentation topics, along with survey meter operation and quality control and other radiation detection equipment.

Additionally, it is more important to concentrate on Radiation Safety and Radiation Biology, the basics of Radiopharmacy, and in particular, Radionuclide Therapy (basic principles, administration procedures, risks and benefits, radiation safety considerations). Also, the mathematics associated

with use of radioactivity in humans is important since it can help in dose calibration and adjustment, when necessary.

As for the specific areas to cover in this training, considering the didactic lectures and lab training required by the NRC and Agreement States, a course that covers the following areas would be appropriate for physicians who would be administering the therapies described above:

1. Radiopharmacy:

The basics of radiopharmacy, including a comprehensive review of the mechanisms of localization of the drugs, internal radiation dosimetry, waste disposal, radiopharmacology, sterility and apyrogenicity, aseptic technique, quality control procedures, and properties of the ideal therapeutic radiopharmaceutical, as well as an in-depth understanding of the interrelationship between physical, biological, and effective half-lives; it is also valuable to learn the basic operation of a central radiopharmacy and know what to expect when a patient-ready dose of a therapeutic radiopharmaceutical has been received.

2. Radiobiology and Mathematics Associated with Using of Radioactive Materials:

It is very important to understand the biological effects of ionizing radiation in humans, especially when administering therapeutic radiopharmaceuticals. In addition, physicians should be able to perform calculations related to the mathematics associated with the use of radioactivity, including radioactive decay calculations as well as radiation shielding. As part of this understanding, physicians must also know how to convert between the units of the US and SI systems since there is a growing trend now toward reporting doses in the SI System and some radiopharmaceuticals, particularly therapeutic ones, only mention GBq and not mCi.

3. Radiation Safety:

Since these radionuclide therapies will be utilizing only alpha- and beta- emitters, safety issues focusing on particulate-emitting radioisotopes should be emphasized along with safety issues for photon emitters since all particulate emitters have associated X-ray (and sometimes gamma ray) production. Safety discussions should cover detailed information about maximum permissible doses to radiation workers (whole body, extremities, eyes, gonads, internal; organs, etc); definition of a reportable event and a recordable event, and to whom the report should be sent and how soon; discussion of the Declared Pregnant Worker and its associated regulations; radioactive waste disposal limits and procedures as well as reporting requirements in the case of an accidental overdose or underdose of a prescribed therapeutic; how to deal with spills of radioactive materials and decision-making regarding reportability; and relevance of the interrelationship between the physical, biological and effective half-lives.

And of course, it would also be important to include drug administration procedures since there are procedural differences between administering radioactive and non-radioactive drugs, and there is a significant risk related to extravasation of a dose of any cellular toxic medicine designed to be delivered intravenously. Other relevant NRC regulations not included in this paragraph should also

be covered; including a discussion of the various shielding materials appropriate for use with particle emitters, which are typically very different from those used with photon emitters.

4. Instrumentation and Physics:

As noted above, the emphasis for this section should be appropriate for physicians delivering radionuclide therapies rather than conducting diagnostic exams, (e.g. understanding the design and function, and QC for gamma cameras would be of little to no use for these physicians). However, the course should include an extensive review of dose calibrators, including description of mandatory quality control tests, their required frequency, performance of the tests, specifications for determining if the test is a "Pass" or a "Fail"; what to do if there is a failure, and whether or not there is a reporting requirement in the case of a failure. Dose calibrators are much more difficult to use in the case of particle emitters than gamma ray emitters due to the poor penetrability of alpha and beta particles and also due to a dependence on sample geometry. There should also be a comprehensive review of all relevant radiation detection equipment used for monitoring the environment to locate spills; what tests must be performed on the equipment; regulatory requirements for quality control for each type of equipment;

5. Radionuclide Therapy, Including Drug Preparation and Quality Control:

The basics of these areas are important. Even though all dose preparation and quality control procedures will be performed at the central radiopharmacy and the patient-ready dose will be delivered to the healthcare facility, the physician should understand the operation of the central radiopharmacy. An understanding of the inner workings of the central radiopharmacy would enable a physician to communicate effectively with the nuclear pharmacists about their patients and the radiopharmaceutical/radionuclide drugs being prepared and dispensed to them.

In addition, it would be important for physicians to observe the "start-to-finish" performance of 3-4 therapies performed by an authorized user on a RAM license who has had experience in administering these therapies. And (in compliance with current NRC Regulations), the physician wishing to become an AU on a RAM license should perform at least three dose administrations of each radiopharmaceutical under the direct supervision of an authorized user on a RAM license who has had experience in administering these therapies.

Overall, successful completion of a high-quality course including 70 - 80 total classroom hours of didactic and laboratory training covering this material - combined with hands-on experience with dose calibrators and other equipment that these physicians should know how to use, and supervised administrations of alpha- and beta- emitter therapies - would provide adequate training for medical oncologists and hematologists to enable them to safely administer these types of alpha and beta therapies. And since some information in the five areas described above potentially could be covered under more than one area, rather than quantify the numbers of hours that should be dedicated for each topic, it would be better to provide course director flexibility in how they cover the required course material.

In addition, although outside the direct scope of the Committee's and the NRC's role - but appropriate for you to consider as individuals engaged in making public policy - CORAR hopes

that the Committee would also recognize how NRC's current regulations encompass public health and policy factors in the training requirements for physicians administering therapeutic I-131, and apply those same principles to radiotherapies for cancer, so that the number and geographic distribution of physicians who could administer alpha- and beta- emitters as described above - and patient access and treatment options - would expand dramatically.

Thank you for your consideration of this letter.

Sincerely,

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