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Training and Experience Requirements for Different Categories of Radiopharmaceuticals

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General Comment

See attached file(s)

Attachments

AAA comments to NRC final

May Ma
Office of Administration
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Washington, DC 20555-0001

Comments on NRC's Training and Experience Requirements for Different Categories of Radiopharmaceuticals

Docket number: NRC-2018-0230

January 28, 2018

Dear Ms. Ma:

We appreciate the opportunity to comment on training and experience requirements for different categories of therapeutic radiopharmaceuticals and have put significant thought into developing our viewpoint. Advanced Accelerator Applications is a Novartis affiliate that markets radiopharmaceuticals, including Lutathera® (Lu 177 dotatate), a beta/gamma emitting therapeutic drug. We are also actively involved in radiopharmaceutical development, targeting diseases such as prostate cancer.

We believe that the NRC should establish tailored T&E requirements for categories of therapeutic radiopharmaceuticals with similar administration methods and risk profiles. The NRC already has a tailored pathway for administration of oral Iodine-131 therapy, requiring 80 hours of training and an unspecified number of clinical experience hours (10 CFR 35.392 and 10 CFR 35.394). Similarly, the NRC should define an appropriate set of requirements covering alpha, beta, and beta/gamma therapies that are delivered in ready-to-use form and not requiring imaging.

Below are our responses to the specific questions posed:

Tailored Training and Experience Requirements
FR notice Section III.A Question 1: Are the current pathways for obtaining AU status reasonable and accessible?

AAA Comment: The current alternate pathways essentially define two distinct levels of T&E:

A. 80 hours training, plus an undefined amount of work experience for administration of oral Iodine-131 (10 CFR 35.392 and 10 CFR 35.394). When defining this pathway, the NRC noted the strong safety record of the product and the burden that would be placed on patients if their primary physician were unable to administer treatment.
B. 200 hours training, plus 500 hours work experience for administration of a wide variety of therapeutic radiopharmaceuticals including parenteral drugs (10 CFR 35.390). However, the

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training in this category includes a full range of activities in the handling of byproduct material including eluting generators and preparing doses using reagent kits.

Our comments are in regards to alpha, beta, and beta/gamma therapies that are delivered in ready-to-use form by a licensed radiopharmacy or manufacturer and do not require imaging as part of the therapeutic procedure. For this category of radiopharmaceutical, it is unreasonable to require knowledge of how to elute generators and prepare doses using reagent kits, which is typically the work of a nuclear pharmacist. It is also not directly relevant to be trained in diagnostic imaging or general imaging related clinical matters facing a nuclear medicine department.

FR Notice Section III.A Question 2: Are the current pathways for obtaining AU status adequate for protecting public health and safety?

AAA Comment: We believe this is best assessed by the NRC based on the historic safety record observed. To our knowledge, the safety record of therapeutic radiopharmaceuticals in general is excellent.

We would also propose to assess the safety record of physicians who were "grandfathered" into AU status through the previous 80 hours requirement, prior to implementation of the current framework in 2005 (written in 2002, implemented in 2005). This would provide supporting information as to whether the previous pathway posed a public safety risk.

FR Notice Section III.A Question 3: Should the NRC develop a new tailored pathway for these physicians?

AAA Comment: Yes, similar to the tailored pathway for oral I-131, the NRC should tailor a pathway for specialists such as medical oncologists, haematologists, and urologists, who wish to administer non-imaging intravenous therapeutic radiopharmaceuticals delivered in ready to use form. In defining an appropriate level of T&E for this class of radiopharmaceuticals, the NRC should consider:

- The limited role in handling this group of radiopharmaceuticals, which are delivered in patient ready form and do not require reagent kit preparation;
- The radiological safety profile of radiopharmaceuticals containing alpha, beta, and beta/gamma emitting isotopes;
- The experience and training of these physicians in handling other toxic non-radioactive therapies, such as cytotoxic chemotherapy agents.

FR Notice Section III.A Question 4: Should the fundamental T&E required of physicians seeking limited AU status need to have the same fundamental T&E required of physicians seeking full AU status for all oral and parenteral administrations under 10 CFR 35.300?

AAA Comment: Physicians seeking limited AU status should not have T&E requirements that include preparation of doses using generators and reagent kits, or experience in diagnostic imaging.

FR Notice Section III.A Question 5: How should the requirements for this fundamental T&E be structured for a specific category of radiopharmaceuticals?

AAA Comment: We support the outline provided by CORAR (The Council on Radionuclides and Radiopharmaceuticals) in its T&E questionnaire comments provided to NRC on April 27, 2018, as well as the responses being submitted by CORAR to docket NRC-2018-0230.

NRC's Recognition of Medical Specialty Boards

FR Notice Section III.B Question 1: What boards other than those already recognized by the NRC (American Board of Nuclear Medicine [ABNM], American Board of Radiology [ABR], American Osteopathic Board of Radiology [AOBR], Certification Board of Nuclear Endocrinology [CBNE]) could be considered for recognition for medical uses under 10 CFR 35.300?

AAA Comment: We have no comment at this time.

FR Notice Section III.B Question 2: Are the current NRC medical specialty board recognition criteria sufficient?

AAA Comment: We have no comment at this time.

Patient Access

FR Notice Section III.C Question 1: Is there a shortage in the number of AUs for medical uses under 10 CFR 35.300?

AAA Comment: The answer to this question is different when considering our experience only with Lutathera® today, and our expectations for patient access to new therapeutic radiopharmaceuticals anticipated to be available in a few years from now. In one year since launching Lutathera®, we have not seen an issue with patient access, however this is partly due to the nature of the orphan disease that Lutathera® addresses (gastroenteropancreatic neuroendocrine tumors), for which patients are often referred to large academic centers for treatment because local physicians often do not see the volume of cases necessary to become an expert in the disease. It may also be related to the early stage of adoption of the product – meaning, it is hard to tell yet if 20-30% of patients will be left behind when a product is still fairly new.

However, we are concerned about patient access for future therapeutic radiopharmaceuticals in larger disease areas. We find the market research presented by Bayer in their letter to the NRC on July 11, 2018 to be compelling. The analysis shows that out of 27% of patients for which Xofigo was recommended, only 4% of patients received treatment. Within this analysis, 75% of the patients for which Xofigo was recommended did not get referred for treatment, with the main reasons being patient health deterioration, patient refusal, patient unwilling to travel, cost to the patient being too high, limited access to nuclear medicine, and insurance challenges. Even of the patients referred for Xofigo treatment, 37% did not receive treatment, with reasons including health deterioration, cost and insurance challenges, and again patient willingness to travel or be referred to another institution.

We believe, based on this analysis and based on the track record of previous radiopharmaceutical therapies, that when referrals are required fewer patients receive appropriate treatment. It is understandable that some patients want to be treated by their local primary physician. This is an important aspect to consider in defining the accessibility of T&E.

FR Notice Section III.C Question 2: Are there certain geographic areas with an inadequate number of AUs?

AAA Comment: Rural areas require greater travel distances of patients, and therefore lead to a greater problem with patient access.

FR Notice Section III.C Question 3: Do current NRC regulations on AU T&E requirements unnecessarily limit patient access to procedures involving radiopharmaceuticals?

AAA Comment: Yes, we believe very few medical oncologists will take time from their practice to obtain the required 700 hours, resulting in limited access for patients who are unable or unwilling to travel for treatment.

FR Notice Section III.C Question 4: Do current NRC regulations on AU T&E requirements unnecessarily limit research and development in nuclear medicine?

AAA Comment: We believe that the current T&E requirements discourage some physicians from learning about radiopharmaceutical therapies, and that this indirectly reduces clinical participation and slows down innovation in the field. The current T&E requirements could also reduce awareness of this burgeoning class of drugs.

Other Suggested Changes to the T&E Regulations
FR Notice Section III.D Question 1: Should the NRC regulate the T&E of physicians for medical uses?

AAA Comment: We believe that the T&E of physicians is already closely monitored by their professional affiliations and institutions. However, the NRC should still review T&E records during regularly scheduled inspections.

FR Notice Section III.D Question 2: Are there requirements in the NRC's T&E regulatory framework for physicians that are non-safety related?

AAA Comment: As mentioned previously, requirements of elution of generators and use of reagent kits do not impact safety since the activity is out of scope for the category of radiopharmaceuticals considered.

FR Notice Section III.D Question 3: How can the NRC transform its regulatory approach for T&E while still ensuring that adequate protection is maintained for workers, the general public, patients, and human research subjects?

AAA Comment: In addition to the points above, we think that one approach to improving the number of AU's and therefore improving patient access can be through a mid-level practitioner position, such as the Nuclear Medicine Advanced Associate (NMAA). We also think an important role can also be played by nuclear pharmacists in partnership with physicians as advocated by United Pharmacy Partners (UPPI, Inc.) during NRC's open meeting on December 11, 2018.

Finally, NRC should consider the overall readiness of a facility to administer therapeutic radiopharmaceuticals, including qualification of a Supervising Nuclear Medicine Technologist and Radiation Safety Officer. There is always a full team involved in the administration of such a treatment and the qualifications of the supporting personnel are important to consider.

To summarize, we believe that if a tailored set of T&E requirements for non-imaging therapeutic radiopharmaceuticals delivered in patient ready form are established, they will be significantly more accessible for medical oncologists, haematologists, and urologists. We believe that this will lead to greater patient access to radiopharmaceutical therapies without detriment to safety of patients, healthcare providers, and public. Patients who were inclined to travel for treatment can still be referred to Nuclear Medicine departments especially for more complex cases and certainly for treatments requiring the use of imaging and dosimetry.

Sincerely,

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For questions relating to this submission, please contact Theresa Allio at 917-566-5004, or theresa.allio@adacap.com.