July 10, 2018

Douglas Bollock
U.S. Nuclear Regulatory Commission
Mail Stop 0-16G4
Washington, DC 20555-0001

Re: Statement on training and experience for authorized users: Guidance for the Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Use of Isotopes (ACMUI)

Dear Mr. Bollock:

The leadership of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), together with representatives from the American College of Nuclear Medicine (ACNM) and American Society of Radiation Oncology (ASTRO) formed an ad-hoc committee to offer their collective recommendation for potential updates to the 10 CFR 35.390, *Training for use of unsealed byproduct material for which a written directive is required*. We are offering suggestions specifically regarding the basic and clinical knowledge and skills needed for those seeking authorized user status through the "alternate pathway" (10 CFR 35.390(b)) to utilize radioisotopes to provide safe and effective clinical diagnostic and therapeutic results to patients.

With regard to training and experience requirements and the initial determination of competency, it is our opinion that mastery of the curriculum listed below will ensure high quality practice of radionuclide therapy. This didactic instruction and laboratory training is important for safe and effective therapies and should not be minimized. The use of unsealed sources for therapeutic applications is complex and has serious medical and safety risk associated with it, not only for the patient but for their family, and the public at large. As such, we feel it is important to maintain this high quality of training and experience.

Furthermore, we do not have evidence of an authorized user shortage, and there is no hard data to support a potential shortage. Because of broad licensing by the NRC, exact numbers of authorized users across various disciplines is difficult, if not impossible to obtain. While the number of nuclear medicine trainees have declined over the past few years, combined diagnostic radiology and nuclear medicine residencies have developed and are rapidly gaining in popularity, balancing the decline of nuclear medicine residency trainees. Furthermore, thousands of radiation oncologists are authorized users of unsealed source radiotherapies or have an authorized user eligibility specified on their American Board of Radiology (ABR) diploma. In addition, the pipeline of radiation oncologists is strong with 773 currently in residency programs. Of note, this is the same conclusion that was reached in the Statement by the American Society for Radiation Oncology (ASTRO) to the Advisory Committee on the Medical Use of Isotopes (ACMUI) on 3/1/2018.

Given the many authorized users currently available to perform these therapies, it is not surprising that delay in availability of these therapies to patients is rare. This can be seen across many types of radioisotope therapies such as I-131, Ra-223, I-131 ibritumomab, and Strontium-89. It is possible that there is a patient access issue to certain radioisotope therapies, which could be as a result of physician preferences or multiple other causes, but a shortage of authorized users does not appear to be one of them. An example of this is the current availability of Lu-177-Dotatate. Long wait lists at most institutions are due to the ramping up of this therapy at hospitals around the country, primarily due to the complexity of providing the therapy, availability of infusion spaces, and nursing support, but not due to a lack of authorized users available to administer the therapy.

As such, the availability of authorized treating physicians is not a valid reason to consider shortening the training and experience requirements for unsealed radioisotope therapy under 10 CFR 35.390(b). And, indeed, the complexity of the Lu-177-Dotatate therapy further highlights the need for rigorous training.

Detailed in the addendum to this letter is a description of the basic science and clinical training requirements that are necessary for the proper training of an authorized user. It also fully describes the initial certification of competency as well as maintenance of certification. We would like to stress that these training requirements/hours alone are not sufficient. For example, the three mandated experiences for a given therapy are not sufficient by themselves, but rather should be the culmination of many more such experiences in residency and in practice over several years.

Based on the above points, we oppose lowering the training requirements as currently stated in 10 CFR 35.390(b). We thank the ACMUI for the opportunity to provide input and look forward to future discussions.

Sincerely,

Bennett S. Greenspan, MD, M.S.

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Addendum to SNMMI statement on training and experience for authorized users: Guidance for the NRC's ACMUI.

The following are the basic science and clinical training and experience we feel are necessary to have as part of the total training designated in 10 CFR 35.390(b). Below that are the initial competency and maintenance of competency methods we feel are valid.

Basic Science

- Basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material and radionuclides requiring a written directive. Ordering and receiving radiopharmaceuticals.
- Radiation physics: structure of matter, modes of radioactive decay, particle and photon emissions, half-lives and energies. Calculations of radioactive decay. Interactions of radiation with matter, principles of radiation detection, radiation units.
- Mathematics pertaining to the use and measurement of radioactivity, including decay calculations and calculations of organ and whole body dose. Statistics and medical decision making.
- Biochemistry, molecular biology and pharmacology.
- Chemistry of radioactive material for medical use, including: reactor, cyclotron and generator production of radionuclides, radiochemistry, formulation of radiopharmaceuticals.
- Radiation biology: biological effects of ionizing radiation. RBE. Radiation exposure. Radiation biochemistry. Radiation syndromes - Classification of radiation damage. Factors affecting radiation injury. Late effects. Low dose and low dose rate effects. Comparison of risk.
- Instrumentation: Principles of instrumentation used in detection, measurement, and imaging of radioactivity with special emphasis on gamma cameras, including single photon emission computed tomography (SPECT), SPECT/computed tomography (CT), positron emission tomography (PET), and PET/CT systems, and associated electronic instrumentation and computers employed in image production and display. Dose calibrators and survey instruments, including personnel monitoring equipment. Dosage and dose measurements. Quality control of instrumentation – QI, QA, QC, acceptance testing. Artifacts.
- Radionuclide production and quality control. Radiopharmaceutical QC. Radiopharmacology. Radiopharmacy. Surveys and monitoring techniques.
- Radiopharmaceuticals involved in radionuclide therapy and related imaging – biodistribution, mechanisms of localization, potential toxicity. I-131 sodium, Ra-223 dichloride, Sr-89 chloride, Sm-153 EDTMP, Y-90 microspheres, labeled antibodies, Lu-177 Dotatate, Lu-177 PSMA, other alpha and beta-emitting agents.
- Radiation protection, including units, means of reducing radiation exposure, Occupational and public radiation dose limits, shielding and personnel protective equipment (e.g., eye protection, syringe shields). Management of contamination, including spills. Evaluation of patients exposed to potentially dangerous levels of radiation, assisting in the medical management of persons exposed to ionizing radiation, management and disposal of radioactive substances, radiation accident management, and management of radiation safety programs in accordance with federal and state regulations.
- Demonstrate compliance with radiation safety rules and regulations, including Nuclear Regulatory Commission (NRC) or agreement state rules, local regulations, and the ALARA (as low as reasonably

achievable) principle for radiation protection. NRC – 10 CFR 19, 20, 35, especially 10 CFR 35.390. Requirements for training and record keeping. National and international agencies. Restricted and non-restricted areas. Radionuclide therapy written directive. Patient release criteria.
- Medical events – determination of occurrence, evaluation of cause(s) and consequences. Prevention.
- Internal radiation dosimetry, MIRD calculations. Dose calculations – calculations of absorbed doses, therapeutic targets; tumor doses required for effective treatment.

Clinical requirements for radionuclide therapy

- Qualifications of physicians: competence in: patient evaluation - to include: pertinent patient information relevant to the requested procedure using clinical request form, patient interview; chart and computer data base review; Review of relevant imaging studies. Focused physical examination as indicated; and communication with the referring physician if necessary.
- Patient care and procedural skills. History and physical exam.
- Certification in NM, NR, RO, BLS. ACLS desirable.
- Patient selection – Verification of patient identity; Explanation of procedure to the patient. Informed consent. Determination and documentation of pregnancy states. Discussion of risks and benefits of the procedure, including patient education and counseling of expected benefits, possible adverse side effects, radiation safety. Determination of clinical indication. Evaluation of findings – clinical (e.g. operative), pathology, lab values (ex. FT4, TSH, thyroglobulin, WBC, platelets), relevant imaging studies - oncologic studies, including as appropriate studies of sentinel node localization, fluorodeoxyglucose (FDG) imaging, Meta-Iodo-Benzyl-Guanidine (MIBG), somatostatin-receptor imaging, and other agents as they become available. PET, PET/CT, and other hybrid molecular imaging studies for both oncologic and non-oncologic indications.
- Patient preparation: determine desired administered activity, route of administration. Determine required dosimetry. Understand risks specific to each therapeutic radiopharmaceutical, including types of emissions.
- Patient management (along with other physicians as needed) of post-therapy complications.
- Supervision of administration of therapeutic radiopharmaceutical(s) to patient. Radiation protection specific to each therapeutic radiopharmaceutical. Dosimetry.
- Patient release – timing and conditions, provision of radiation precautions, verbal and written.
- Prepare a complete but concise nuclear medicine procedure report.
- Post-therapy follow up. Follow up scintigraphy as necessary.
- Assessment of treatment response.
- Recommend, plan, conduct, supervise, interpret, and report diagnostic and therapeutic nuclear medicine procedures appropriate for the clinical problem or condition.
- Therapeutic administration of radioiodine for both malignant and benign thyroid disease. When appropriate, thyroid studies must include measurement of iodine uptake and dosimetry calculations for radio-iodine therapy.
- Therapeutic administration of other unsealed radiopharmaceuticals for malignant and benign diseases.
- Evaluate radionuclide uptake, biodistribution, metabolism, retention and clearance with quantitative imaging to determine tumor dosimetry and therefore treatment planning.

- Understand fundamentals of imaging molecular targets, processes and events, and existing and emerging molecular imaging techniques, particularly as they relate to current clinical practice of radiopharmaceutical therapy.
- Radiopharmaceutical and/or Clinical Indications (including but not limited to):
  - Hyperthyroidism – I-131 sodium iodide
  - Differentiated thyroid cancer – I-131 sodium iodide
  - Bone pain palliation – Sr-89 chloride, Sm-153 EDTMP
  - Radioembolization for hepatocellular cancer or liver metastases – Y-90 Theraspheres or SIRSpheres
  - Neuroendocrine tumors – I-131 MIBG, Lu-177 Dotatate and other potential PRRT therapies
  - Radiolabeled antibodies
  - Bone metastases - Ra-223 dichloride
  - Prostate cancer – Lu-177 PSMA, (Ac-225 PSMA – currently under active investigation in Europe)
  - Other therapeutic radiopharmaceuticals as they become available for clinical practice.
  - Other potential therapeutic radionuclides currently under investigation:
    - Beta-emitters: Cu-67, Re-186, Re-188, Ho-166
    - Alpha-emitters: Bi-212, Bi-213, At-211, Tb-149, Ac-225

Please note that much of the training delineated above would be obtained within the context of nuclear medicine training programs in Nuclear Medicine or Nuclear Radiology, or training programs in Radiation Oncology. For those physicians who have not had formal training in Nuclear Medicine/Nuclear Radiology or Radiation Oncology and wish to provide radionuclide therapy, the above information is considered essential for competent practice of radionuclide therapy.

Recommendations for initial and maintenance of competency under 35.390(b):

1) Certification process for physicians performing radiopharmaceutical therapy as is already recognized under 10 CFR 35.390 (a) – ABNM or ABR NR or RO certification is sufficient.
2) Participation in Maintenance of Certification for those who became an authorized user through the alternate pathway, similar to 35.390(a).
3) Accreditation of the Nuclear Medicine laboratory. This should include a proficiency testing program that will assess performance of the technologists and physicians.

Future possible evaluation of competency under 35.390(b):

Certification of physicians who have completed a Fellowship in radiopharmaceutical therapy and have passed a certification exam by an accredited medical specialty board.