U.S Nuclear Regulatory Commission
Advisory Committee on the Medical Uses of Isotopes

Subcommittee on Radionuclide Generator
Knowledge and Practice Requirements

Final Report
October 14, 2021

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Subcommittee Charge:

- To review and evaluate the knowledge and practice requirements for eluting, measuring and testing, and processing the eluate from radionuclide generator systems based on the evolution of radionuclide generator distribution.

- To evaluate and determine the appropriateness of the requirements and how best to obtain the required knowledge and practice.

- To evaluate whether and how additional knowledge and practice should be obtained as necessary to supervise the use of any radionuclide generator system.

- Provide considerations and recommendations to staff.

Background:

In 1994, the NRC amended its commercial distribution of radioactive drugs and medical use regulations in 10 CFR Parts 32 and 35, in part, to allow properly qualified nuclear pharmacists and authorized users who are physicians with greater discretion in preparing radioactive drugs containing byproduct material for medical use. The rule, "Preparation, Transfer for Commercial Distribution, and Use of Byproduct Material for Medical Use," resulted in the language presently found in 10 CFR 35.290, "Training for imaging and localization studies." Specifically, 10 CFR 35.290(c)(1)(ii)(G) relative to generators reads:

> *"(G) Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs;"*

Over the last 27 years, the types of radionuclide generators used in clinical nuclear medicine practice, the location where they are housed and used, and the individuals who handle them have all significantly changed.

Molybdenum-99/Technetium-99m (^{99}Mo/^{99m}Tc) generators

Prior to 1972, ^{99}Mo/^{99m}Tc generators were ubiquitous and were found in every clinical nuclear medicine facility. The first centralized radiopharmacy (CRP) opened in 1972 and today there are approximately 300 centralized radiopharmacies in the United States. Over the course of time, the locations of most ^{99}Mo/^{99m}Tc generators migrated from hospital nuclear medicine departments to CRPs as nuclear medicine facilities converted to patient ready unit doses and utilized the services of CRPs for the provision of radiopharmaceuticals. Today approximately 95% of all radiopharmaceuticals used in the United States originate from a CRP. As a result of the consolidation of activities, there are fewer ^{99}Mo/^{99m}Tc generators in use today than were used in the past. It is estimated that the United States utilizes approximately 720 new ^{99}Mo/^{99m}Tc generators weekly, with 90% of them (~660) delivered to CRPs for use under the direction of an authorized nuclear pharmacist (ANP) and 10% of them (~60) delivered to hospital facilities for use under the direction of an authorized user (AU) physician or local ANP.

Strontium-82/Rubidium-82 (^{82}Sr/^{82}Rb) generators

Because of the 75 second half-life of $^{82}RbCl_2$ used for PET myocardial perfusion imaging, all ^{82}Rb generators are in clinical nuclear medicine facilities for use under the direction of an AU physician.

Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generators

It is estimated that currently in the United States, approximately 70% of ^{68}Ge/^{68}Ga generators are delivered to CRPs for use under the direction of an ANP and 30% are delivered to hospital facilities for use under the direction of an AU physician.

The evolution of where radionuclide generators are located has presented challenges for fellows-in-training in residency programs. Many residency programs had made arrangements with commercial radiopharmacies for their fellows-in-training to attend generator training but due to COVID-19 these radiopharmacies have restricted access to their facilities. This increased the knowledge and practice burden affecting fellows-in-training who were unable to attend commercial radiopharmacies to receive generator training due to COVID-19 closures of these facilities.

In June 2020, several professional societies (American Society of Nuclear Cardiology, Society of Nuclear Medicine and Molecular Imaging, American College of Radiology, and the American Society for Radiation Oncology) united to request “that the U.S. Nuclear Regulatory Commission (NRC) consider Title 10 of the Code of Federal Regulations (10 CFR) 35.290(c)(1)(ii)(G), “Training for Imaging and Localization Studies,” as a potential area for regulatory relief during the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (PHE).” This letter states that most of the commercial radiopharmacies that supply portions of this training are closed to visiting trainees because of the COVID-19 PHE and may not reopen for the foreseeable future. This letter further states that they believe that this experience requirement can be satisfied virtually, via demonstrative educational webinars during the duration of the public health emergency. (Agencywide Documents Access and Management System [ADAMS] Accession No. ML20231A931).

Discussion:

The Subcommittee deliberated the intent of the existing Rule language, the knowledge elements necessary for authorized user physicians to possess with regard to generator systems, and various methods of acquiring knowledge of these elements. The Subcommittee recognizes the authorized user physician's role, as described in 10 CFR 35.27, supervising nuclear medicine technologists who may be operating generator systems at clinical sites. Consequently, the Subcommittee believes that authorized users, whether or not they personally use radionuclide generators, must be familiar with how generators work, how breakthrough is tested, and how reagent kits are used to label radioactive drugs. The Subcommittee also believes that it is not necessary for authorized user physicians to have direct hands-on work experience with the generators, although the Subcommittee recognizes that direct work experience is an excellent way to fulfill the training requirements.

In order to facilitate learning, and to provide training programs flexibility to deliver training, the Subcommittee discussed the strengths and limitations of in-person, pre-recorded, or live virtual training opportunities. The Subcommittee believes that training can incorporate any combination of these methods, but the Subcommittee believes it is essential for the training to include an opportunity for physicians to ask questions about the subject material and receive answers in real time. In addition, it is important for the trainer to be able to assess physician learning as the training is progressing. If pre-recorded material is used to deliver a portion of the training, there should also be a live component (whether in-person or via virtual meeting) where trainees and trainers can directly interact.

Consistent with existing regulation, the Subcommittee further believes that it is not necessary to mandate training on *every* radionuclide generator system. Training programs should have the flexibility to modify the training curriculum as the use of generator systems evolves.

Conclusion – Subcommittee Recommendation:

Current rule language in 10 CFR 35.290(c)(1)(ii)(G):

> *(G) "Eluting generator systems appropriate for preparation of radioactive drugs for imaging and localization studies, measuring and testing the eluate for radionuclidic purity, and processing the eluate with reagent kits to prepare labeled radioactive drugs; …"*

Subcommittee proposed revision:

> *(G) "Participating in educational sessions to gain knowledge and provide supervision of – (1) radionuclide generator systems and their operation; (2) the measurement of radionuclidic impurities and acceptable limits; and (3) the use of reagent kits with radionuclide eluate to prepare radioactive drugs."*

The ACMUI unanimously approved this report and its recommendations, as presented during its fall 2021 meeting on October 4, 2021.

Respectfully Submitted on October 14, 2021,
Radionuclide Generator Knowledge and Practice Requirements Subcommittee
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
U.S. Nuclear Regulatory Commission (NRC)