



August 27, 2018

Attn: The Honorable Kristine L. Svinicki
U.S. Nuclear Regulatory Commission
Mail Stop O-16B33
Washington, DC 20555-0001

Subject: 10 CFR 35.390, “Training for use of unsealed byproduct material for which a written directive is required;” recommendations of the American College of Radiology

Dear NRC Chairman Kristine Svinicki:

On behalf of the American College of Radiology (ACR)—a professional organization representing more than 38,000 radiologists, radiation oncologists, interventional radiologists, nuclear medicine physicians, and medical physicists—we are writing regarding ongoing activities within the U.S. Nuclear Regulatory Commission (NRC) and the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI) to reevaluate authorized user (AU) requirements in 10 CFR Part 35, Subpart E—particularly 35.390, *“Training for use of unsealed byproduct material for which a written directive is required.”* This letter outlines specific concerns of ACR on this topic, and proposes an alternative approach going forward.

Concerns Regarding NRC Activities Related to 10 CFR 35.390

The ACR supports and acknowledges the appropriateness of periodic reassessment of 10 CFR Part 35 to provide reasonable assurance of adequate protection of public health and safety. We believe that this process should be driven by the experiences and expertise of medical licensees and regulators, informed by objective and quantitative evidence, and be free from politicization by external companies and groups. We are concerned that the current efforts to reevaluate the training and experience (T&E) requirements in 10 CFR 35.390 appear to have been hastened by external pressures without a sufficient basis in science or the shared experience of current materials licensees. Recent NRC activities to prioritize and rapidly move toward modifying the T&E requirements in 10 CFR 35.390 for prospective AUs without NRC-recognized board certification deviate from the data-driven, risk-informed, deliberative approach warranted by the associated risk and potential destabilizing impact of such a policy.

The ACR believes the arguments in favor of significantly modifying 10 CFR 35.390 to provide a less comprehensive alternate pathway for those without NRC-recognized board certification are

unsubstantiated and should be examined with scientific rigor before the NRC takes any significant action that could negatively impact public health and safety. The recent NRC staff efforts at the Commission's direction to reimagine a radionuclide-specific, "limited scope AU" concept for uses under 10 CFR Part 35, Subpart E do not adequately address the primary questions of whether regulatory revisions are a necessary and justifiable use of limited NRC resources, and whether the perceived benefits outweigh the substantial risks.

A Multidisciplinary Team Model is the Standard of Care in Radiopharmaceutical Therapy

As part of a broad spectrum of cancer therapy modalities, therapy with unsealed radiopharmaceutical sources may promote cures or palliation of disease while minimizing untoward side effects and complications.¹ Examples of these radiopharmaceuticals include Iodine-131 (sodium iodide), Iodine-131 (meta-iodobenzylguanidine MIBG iodine-131), Lutetium-177 DOTA, Yttrium-90 DOTA, Phosphorus-32 (sodium phosphate), Phosphorus-32 (colloidal chromic phosphate), Radium-223 (radium dichloride), Samarium-153 (lexidronam ethylene diamine tetra methylene phosphonic acid [EDTMPA]), Strontium-89 (strontium chloride), Yttrium-90 (ibritumomab tiuxetan), and others in current research.

The predominant medical paradigm for treating patients who may require such therapy utilizes a multidisciplinary team approach so patients benefit from the unique expertise of many medical specialties. Within that framework, public health and safety are optimally protected when unsealed radiopharmaceutical therapies are supervised and performed by appropriately trained and licensed physicians. Typically these are nuclear medicine physicians, radiation oncologists, nuclear radiologists, and certain other diagnostic radiologists with those qualifications in close cooperation and communication with referring physicians responsible for overall clinical management of the patients (such as medical oncologists, etc.), and supported by staff trained and experienced in handling of radioactive materials and imbued with a culture of safety for patients and personnel.²

Lack of Data Indicating AU Shortage

NRC's exploration of less comprehensive, radionuclide-specific, "limited scope" pathways to AU status for therapeutic radiopharmaceuticals implies that the agency believes there is an insufficient AU population performing and supervising radiopharmaceutical therapies in the United States. This presumption has not been supported by publicly accessible, trustworthy data compiled by first-party sources. Indeed, no such datasets currently exist despite questions about the size and distribution of AUs for specific medical uses of isotopes.

¹ ACR, American Association of Physicists in Medicine (AAPM), and Society for Pediatric Radiology (SPR). *ACR-AAPM-SPR Technical Standard for Therapeutic Procedures Using Radiopharmaceuticals*. Available from <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/RadioPharm.pdf>

² American College of Radiology (ACR). *ACR Practice Parameter for the Performance of Therapy with Unsealed Radiopharmaceutical Sources*. Available from: <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/UnsealedSources.pdf?la=en>

In March 2018, an NRC ACMUI subcommittee discussed a potential future AU shortage based on nuclear medicine residency trends combined with an expectation of Lu-177 dotatate popularity. However, those preliminary discussions focused exclusively on previous American Board of Nuclear Medicine (ABNM) trends, without factoring in the American Board of Radiology (ABR) radiation oncology and nuclear radiology pathways to AU status for unsealed radiopharmaceutical sources requiring a written directive. Our current understanding, based on information from the ABR, indicates a potentially increasing trend in the radiation oncologist population and increased expansion of recently revamped nuclear radiology programs. The ACMUI's July 5, 2018 comments to NRC staff found that nearly 900 residents in radiation oncology, nuclear medicine, nuclear radiology, and the redesigned radiology pathway could potentially meet the AU T&E requirements in 10 CFR 35.390 for the 2017-2018 academic year.³ Thus, residency information and observations from the specialties in question contradict the unsubstantiated premise of an impending AU shortage. The increasing clinical use of Lu-177 dotatate, and theranostics in general, should continue to bolster medical student interest in pursuing specialty residencies with radiopharmaceutical therapy expertise. However, there is a need for trustworthy data about currently active AU populations.

The ACR recommends that NRC collaborate with Agreement States and broad-scope licensees to determine the number and distribution of actively practicing AUs with the therapeutic radiopharmaceuticals of interest. Maintaining this dataset should illustrate AU trends over a multi-year period to deduce the stability and growth of the AU population. Changes in AU numbers over time could provide regulators and stakeholders with informed arguments supporting or opposing regulatory revisions and would serve as an accurate baseline for future decision-making.

Other Factors Driving Utilization of Radiopharmaceutical Therapy Unrelated to NRC Regulations

NRC's hastened progression towards a radionuclide-specific, limited scope AU pathway also implies that radiopharmaceutical therapies are underutilized perhaps because of the presumption that AUs are insufficiently accessible under the current T&E prerequisites in 10 CFR 35.390. While there is certainly no trustworthy evidence to suggest chronic underutilization of these modalities resulting from current NRC regulations, there are myriad drivers behind care management decisions by referring clinicians.

While practice guidelines, clinical decision support tools, peer-reviewed literature, and other informational resources can augment decision-making, medical oncologists and other referring physicians responsible for managing patients' care have varying levels of awareness regarding the availability and appropriate use of radiopharmaceutical therapy options. In many cases, alternative treatments not involving radiation dose are available with similar appropriateness ratings and outcomes. In some cases, there could be reluctance by care managers to refer/transfer patients for subspecialty care regardless of the proximity, expertise, or quality of care performed by providers of

³ NRC ACMUI. *Advisory Committee on the Medical Uses of Isotopes Comments on the Draft SECY Paper Entitled "Staff Evaluation of Training and Experience Requirements for Administering Radiopharmaceuticals."* Available from: <https://www.nrc.gov/docs/ML1818/ML18186A517.pdf>

cancer therapies outside their own practices. Economic/insurance drivers and patients' personal views about radiation could also affect referral and treatment decisions. The ACR recommends further exploration of utilization drivers that include partnerships with other federal regulatory agencies with more influence than NRC on radiopharmaceutical therapy utilization, such as the Centers for Medicare and Medicaid Services (CMS).

It is unclear what effects, if any, future modifications to NRC T&E requirements for prospective AUs without NRC-recognized board certification would have on referral patterns and overall use of radiopharmaceutical therapies. NRC regulations are not the sole external consideration for providers interested in providing radiopharmaceutical therapy themselves. A myriad of factors – such as medical standards, appropriate use criteria, practice/procedure guidelines, facility accreditation requirements, quality metrics, insurance/payer requirements, self-referral prohibitions, medicolegal considerations, etc. – influence physician and provider willingness to offer any given treatment. Regardless, if NRC moves forward with the requested revisions to 10 CFR 35.390, it is likely that referring clinicians without subspecialized expertise would be pressured for financial reasons by manufacturers to obtain “limited scope AU” status—those same outreach efforts by manufacturers might be better used to educate the referring provider community about the availability of these therapies provided by subspecialized experts.

Therapeutic Radiopharmaceuticals are Not Simple and Safe—Need for Specialized Expertise

Patients and their families expect that those performing and supervising radiopharmaceutical therapy are providing the right treatment at the right dose at the right time. Nuclear medicine physicians, radiation oncologists, and nuclear radiologists are continuously immersed in radiological considerations as an inherent component of their subspecialized roles on the patient's care team. Such considerations are integrated into every level of training programs, certifications, specialty publications, and day-to-day professional responsibilities. Outliers from other medical specialties who have obtained the necessary T&E and supervised cases under the current 10 CFR 35.390 have acquired basic knowledge to competently manage these tasks in a responsible manner—this is why 10 CFR 35.390 already includes a legitimate T&E alternative pathway to AU status for those from other specialties without NRC-recognized board certification.

With any radionuclide-specific, “limited scope AU” concept, NRC should consider the much higher likelihood of safety issues when enabling the use of therapeutic radiopharmaceuticals in settings with limited expertise and experience in nuclear materials handling, storage, shipping, dosimetry, and waste handling. AUs must be fully prepared to supervise all aspects of the medical use of the unsealed radiopharmaceutical sources in question, prevent potential medical events before they occur, identify and report to regulatory agencies any medical events that have occurred, and mitigate any dangers of spills and contamination.

Prepackaged Unit Dose Distribution Does Not Eliminate Need for Expertise

The core knowledge required to adequately perform AU responsibilities remains the same regardless of whether radiopharmaceuticals are shipped from centralized nuclear pharmacies in unit doses or

prepared on-site in the treatment facilities. Many issues and risks—i.e., improper assay, spillage/contamination, handling unused product, tissue extravasation, etc.—would be more likely to occur in settings where the AU is nominally trained and generally unaccustomed to working with unsealed radiopharmaceutical sources. Less than perfect real-world scenarios, including unexpected situations during the handling of these materials, must be factored into the NRC’s regulatory approach.

Alpha- and Beta-Emitters

NRC should not assume that specific uses regulated under 10 CFR Part 35, Subpart E are safe for general use if they involve alpha- and/or beta-emitters. Many such agents will have a gamma component or be paired with gamma-emitting agents to allow for imaging that is essential for whole body and organ dosimetry and therapeutic decision-making. It is inaccurate to suggest that these radiopharmaceuticals can be handled by nominally trained clinicians in inexperienced facilities without introducing risk to all involved.

Chemotherapy Drugs Are Not Radioactive

It has been argued that medical oncology practices are experienced with administration by oncology nurses of hazardous drugs, such as antineoplastic agents used in chemotherapy. However, nuclear materials pose very different dosage, exposure, handling, storage, waste management, and risk mitigation considerations compared to nonradioactive hazardous materials. While antineoplastic agents are certainly harmful in terms of occupational exposure for oncology nurses when absorbed into the skin/inhaled/ingested, such agents do not carry the same exposure and environmental concerns—much less the same level of public fear and panic—as nuclear materials generally do.

To be clear, the fact that referring physicians may supervise treatments that involve pharmacist preparation and oncology nurse administration of antineoplastic agents or other hazardous drugs in no way prepares them for their responsibilities as an AU of radiopharmaceuticals to protect patients, their staff and facilities, and members of the public from ineffective, accidental, inappropriate, or otherwise unnecessary radiation exposure.

Unintended Implementation Consequences and Considerations for NRC and Agreement State Regulators of Radionuclide-Specific, Limited Scope AU Concept

Beyond the more important medical and public health/safety considerations, the ACR has concerns about the likely disruption within NRC, state regulatory agencies, and licensed facilities created by establishing and overseeing additional complexity and disparate AU levels with varying responsibilities (e.g., “full scope” and “limited scope/radionuclide-specific” AUs).

NRC and Agreement State agencies would need to dedicate additional resources to deal with regulatory revisions and corrections, guidance revisions and new information notices targeted to non-expert AU subpopulations, outreach to new medical communities unaccustomed to NRC’s regulatory paradigm, expanded capabilities for when spills and other adverse issues arise in nontraditional care settings, and so on. With a radionuclide-specific approach, NRC would need to establish a highly prioritized and expeditious timeframe for rulemakings intended to incorporate new radiopharmaceuticals into the

armamentarium of medical licensees and to prevent future delays in patient access to emerging agents tied to the agency's administrative processes. It would be advisable for NRC to establish a more extensive monitoring program to specifically track medical events, trends, and determine any underreporting of medical events that occur under the supervision of limited scope AUs separately from medical events that occur in the more traditional care settings. Additionally, NRC would increase its own exposure to U.S. Government Accountability Office and other external investigations of the agency's licensee vetting processes as numerous new individuals from previously unknown medical settings would be encouraged by manufacturers to seek limited scope AU status. All of the above expanded capabilities would inevitably result in increased fees for materials licensees, and less efficient/timely regulatory oversight.

Summary of ACR Recommendations

In conclusion, the ACR recommends that NRC not pursue regulatory revisions to accommodate the concept of a radionuclide-specific, limited-scope AU status until such time as NRC's time-tested paradigm in 10 CFR 35.390 is shown by data to be problematic for medical licensees or otherwise in immediate need of revision. We recommend that NRC collaborate with all Agreement State agencies and NRC broad-scope licensees to compile a multi-year dataset on the active AU population. NRC should also work with other federal agencies, particularly CMS, to explore other possible radiopharmaceutical therapy drivers and determine if NRC's AU T&E requirements in 10 CFR 35.390 are directly causing a perceived underutilization. Most importantly, we recommend that NRC consider the numerous unintended consequences and likely negative effects on public health and safety, security, and practice of medicine of revising 10 CFR 35.390 to provide a radionuclide-specific, limited-scope AU pathway for nominally trained clinicians.

As always, the American College of Radiology welcomes additional dialog with the NRC Commissioners and staff on these and other issues of shared interest. Please contact Gloria Romanelli, JD, ACR Senior Director, Legislative and Regulatory Relations, or Michael Peters, ACR Director of Legislative and Regulatory Affairs, at (202) 223-1670 or gromanelli@acr.org / mpeters@acr.org, with any questions or concerns.

Respectfully Submitted,



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