SUBJECT: DRAFT FOR REVIEW—EVALUATION OF TRAINING AND EXPERIENCE REQUIREMENTS FOR ADMINISTRATION OF RADIOPHARMACEUTICALS REQUIRING A WRITTEN DIRECTIVE

PURPOSE:

The purpose of this paper is to provide the results of the staff's evaluation of potential changes to the training and experience (T&E) requirements for administration of radiopharmaceuticals under Title 10 of the *Code of Federal Regulations* (CFR), Part 35, "Medical Use of Byproduct Material," Subpart E, "Unsealed Byproduct Material—Written Directive Required."

BACKGROUND:

The regulations in § 35.390, "Training for use of unsealed byproduct material for which a written directive is required," provide three ways a physician can become an AU for unsealed byproduct material requiring a written directive:

> (1) Approval of an individual who is certified by a medical specialty board whose certification process is recognized by the NRC or an Agreement State as meeting the NRC's requirements for T&E, also known as the "board certification pathway."[1]
> (2) Approval based on an evaluation of an individual's T&E—completion of 200 hours of classroom and laboratory training and 500 hours of supervised work experience (including patient casework) for a total of 700 hours T&E, plus preceptor attestation, also known as the "alternate pathway."[2]
> (3) Identification of an individual's approval as an AU on an existing NRC or Agreement State license or permit.

The T&E requirements in the alternate pathway that are the focus of this paper were promulgated in 2002.[3] Since then, some pharmaceutical stakeholders and non-nuclear medicine and non-radiation oncology physicians (herein referred to as "non-traditional" physicians) have asserted that the 700-hour T&E requirement in the alternate pathway is overly burdensome for physicians ineligible for the board certification pathway and prevents these physicians from becoming AUs, and as a result, patient access to certain therapeutic radiopharmaceuticals is being impacted. Providing additional tailored pathways for non-traditional physicians to be authorized to use specific types of radiopharmaceuticals could address these concerns.

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[1] The procedures for recognizing medical specialty boards are available at https://www.nrc.gov/materials/miau/med-use-toolkit/certif-process-boards.html. Currently, specialty boards must show they meet the requirements of the alternate pathway to be recognized by the NRC or an Agreement State.

[2] As defined in § 35.2, "preceptor" means an individual who provides, directs, or verifies T&E required for an individual to become an AU. A preceptor must attest in writing regarding the T&E of any individual to serve as an AU and attest that the individual has satisfactorily completed the appropriate T&E requirements and has achieved a level of competency or a level of radiation safety knowledge sufficient to function independently.

[3] "10 CFR 20, 32, and 35, Medical Use of Byproduct Material; Final Rule" (67 FR 20249; April 24, 2002).

In SRM-M170817[4] the Commission directed the staff to evaluate: (1) whether it makes sense to establish tailored T&E requirements for different categories of radiopharmaceuticals, (2) how those categories should be determined (such as by risks posed by groups of radionuclides or by delivery method), (3) what the appropriate T&E requirements would be for each category, and (4) whether those requirements should be based on hours of T&E or focused more on competency.

In early 2018, the staff began targeted stakeholder outreach to inform their analysis of the radiation safety knowledge topics required for administration of radiopharmaceuticals (ADAMS Accession No. ML18108A266). This analysis and the staff's evaluation of creating tailored AU pathways are documented in SECY-18-0084,[5] which concluded that while it may be feasible to establish tailored T&E requirements for different categories of radiopharmaceuticals, additional outreach to the medical community was needed to determine whether and how to tailor the T&E requirements. The enclosure to this paper provides additional background information, including a summary of prior NRC activities and past stakeholder feedback related to T&E for radiopharmaceuticals.

DISCUSSION:

The staff's stakeholder engagement and subsequent evaluation included whether the NRC's T&E requirements under Subpart E are aligned with the NRC's Medical Policy Statement,[6] whether they are inappropriately impacting patient access to radiopharmaceuticals, whether changes are needed to position the NRC to safely regulate future radiopharmaceuticals, and whether the T&E requirements could be more risk-informed while continuing to ensure the safe and secure use of radioactive material. The staff also considered approaches of our international counterparts as well as evaluated medical event data to determine whether medical events were being caused by inadequate T&E requirements.

The Medical Policy Statement

The staff has continued to focus its efforts on public health and safety in ensuring we implement the tenets of the NRC's Medical Policy Statement. The Medical Policy Statement states that the NRC will regulate the medical uses of radionuclides as necessary to provide for the radiation safety of workers and the general public; the NRC will not intrude into medical judgements affecting patients except as necessary to provide for the radiation safety of workers and the general public; and when justified by the risk to patients, the NRC will regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions.

The NRC staff, some members of the medical community, the Organization of Agreement States (OAS) Executive Board, and some Agreement States have questioned whether reviewing and approving T&E for physicians to become AUs—thus acting as the final arbiter

[4] SRM-M170817, "Staff Requirements – Affirmation Session, 10:30 A.M., Thursday, August 17, 2017, Commissioners' Conference Room, One White Flint North, Rockville, Maryland (Open to Public Attendance)," dated August 16, 2017 (ADAMS Accession No. ML17229B283).
[5] SECY-18-0084, "Staff Evaluation of Training and Experience Requirements for Administering Different Categories of Radiopharmaceuticals in Response to SRM-M170817," dated August 28, 2018 (ADAMS Accession No. ML18135A276).
[6] "Medical Use of Byproduct Material; Policy Statement, Revision" (65 FR 47654; August 3, 2000).

regarding whether a physician can prescribe radiopharmaceuticals—is aligned with the Medical Policy Statement.

Patient Access to Radiopharmaceuticals

The enclosure to this paper discusses concerns brought to the ACMUI by Spectrum Pharmaceuticals and Bayer HealthCare regarding patient access to AUs offering their radiopharmaceuticals. However, the ACMUI contends that the number of existing AUs and medical residents eligible for medical specialty boards recognized by the NRC are sufficient to meet current and future demand for radiopharmaceuticals under § 35.300.[7] The staff mapped the locations of medical licensees authorized to use § 35.300 materials and with at least one AU listed on the license that would be permitted to use any radiopharmaceutical, along with population density data obtained from the 2010 U.S. Census. The maps affirm that § 35.300 licensees are mostly located in more populous areas; the need to travel for specialized health care is a fact-of-life in rural areas and is not limited to radiopharmaceutical procedures. The staff did not draw any conclusions regarding whether the number and location of licensees are sufficient to satisfy patient demand for radiopharmaceuticals—to make this determination would require detailed health care market data and analyses outside the NRC's purview. The NRC regulates medical uses of byproduct material to ensure the safety of workers and the general public, and while patient access concerns were considered by the staff, the NRC cannot regulate T&E with a primary goal of increasing patient access to radiopharmaceuticals or improving geographic distribution of AUs. A discussion of the staff's mapping effort and licensee location maps are contained in "SECY-19-0XX Supplemental Information: Evaluation of § 35.300 Medical Facility Locations," available at ADAMS Accession No. [redacted].

Regulating for the Future of Radiopharmaceuticals

Radiopharmaceutical therapies are expected to increase from 12 percent of the global nuclear medicine market in 2017, to 60 percent by 2030,[8] and emerging radiopharmaceutical therapies will likely become increasingly targeted to individual patients—considering patient anatomy, physiology, and genetic background to determine the most appropriate radiopharmaceutical and prescribed dose.[9] The staff envisions that some emerging targeted radionuclide therapy procedures will include the need for more extensive treatment planning, dosimetry modeling, and evaluation of tumor response. Administration protocols of these emerging radiopharmaceuticals will inherently be more complex. The staff also anticipates that non-traditional physicians such as hematologists, medical oncologists, and urologists will be interested in being both the referring and treating physicians of these targeted radionuclide therapy procedures.

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[7] Page 2 of the ACMUI Subcommittee on T&E for All Modalities final report on T&E for 10 CFR Part 35, Subpart E (ADAMS Accession No. ML19058A598), includes a table depicting the current and average number of resident physicians that are eligible to become § 35.300 AUs through the board certification and alternate pathways.

[8] MEDraysintell "Nuclear Medicine World Market Report & Directory, Edition 2018" available at http://medraysintell.com/resources/Nuclear%20medicine%20Market%20Report%20and%20Directory%202018%20-%20Presentation.pdf.

[9] The Society of Nuclear Medicine and Molecular Imaging, "Fact Sheet: Targeted Radionuclide Therapy and Prostate Cancer," available at http://www.snmmi.org/AboutSNMMI/Content.aspx?ItemNumber=12772.

Risk-Informing T&E for Specific Radiopharmaceuticals

The staff determined that the T&E requirements in the alternate pathway may not be right-sized for certain radiopharmaceuticals. For example, 700 hours of T&E may not be necessary for use of a radiopharmaceutical that is provided to the physician in a unit-dose, patient-specific form, and features an uncomplicated administration protocol, patient release without restrictions, and sufficient operating history demonstrating safe use. Conversely, as discussed above, for certain emerging or future radiopharmaceuticals with complex treatment procedures and higher administered doses, the requirements in § 35.300 might not be sufficient. Tailoring T&E requirements for different categories of radiopharmaceuticals (e.g., alpha- and beta- emitters, any patient-ready radiopharmaceutical, any one parenteral radiopharmaceutical, etc.) would not consider unique aspects of radiopharmaeuticals within these categories that may indicate the need for additional T&E.

Review of Medical Events

The Idaho National Laboratory (INL) performed a study to determine whether there were trends in the number of medical events caused by inadequate training.[10] The review focused on reportable medical events that occurred in FY 2017 and 2018 (86 events total). Of the 86 events, only one event identified inadequate training as the cause, while in three others, inadequate training was inferred. The specific cause of inadequate training was difficult to identify from the reference documents, because they typically identify only that events result from human error, and do not identify why the human error occurred. INL and NRC staff determined that the records/references do not contain enough detailed information to identify how many medical events are caused by inadequate training of medical staff, and the study was inconclusive in identifying any trends regarding medical events caused by inadequate training of medical staff.

Review of International Regulations

The use of radiopharmaceuticals in most European and Asian countries is generally under the practice of nuclear medicine, and diagnostic and therapeutic radiopharmaceuticals are primarily administered by nuclear medicine physician specialists. The international community generally does not regulate the type and amount of T&E for these physician specialists, rather, they require that the physicians administering radiopharmaceuticals have the proper certification as nuclear medicine specialists as set forth by the medical community. "SECY-19-0XX Supplemental Information: International Benchmarking" (ADAMS Accession No. [redacted]) documents the staff's independent research and engement with several international regulators and nuclear medicine societies.

Stakeholder Outreach and Feedback

The NRC staff conducted two public comment periods, including six public comment meetings, to gather stakeholder feedback. The first *Federal Register* notice (83 FR 54380; October 29, 2018) asked whether and how the NRC should tailor T&E, what tailored T&E requirements should consist of, and whether other changes to the NRC's T&E requirements should be considered. The second notice (84 FR 18874; May 2, 2019) asked for feedback on draft regulatory approaches for potentially revising the T&E requirements. In total, the staff received

[10] INL/LTD-19-52843, February 2019, "Nuclear Material Events Database – Review of Medical Events For Inadequate Training (Fiscal Year 2017-2018)," available at ADAMS Accession No. ML19065A234.

approximately 197 written comment submissions and 46 individuals provided oral comments during the public meetings.

Most comments expressed strong support for maintaining the NRC's existing T&E requirements (i.e., status quo) and stated there was no evidence of a shortage of AUs. This support was received from the nuclear medicine and radiation oncology communities and their related medical specialty boards and professional societies.[11] These groups were equally adamant in their opposition to any changes to the T&E requirements, primarily citing concerns about radiation safety and "dilution" of the field of nuclear medicine. The American Medical Association (AMA) also submitted comments strongly supporting the status quo and suggesting that the NRC work with interested medical specialty boards to integrate radiation safety training into their residency programs (ADAMS Accession No. ML19183A338). Similar to the comment from the AMA, several nuclear medicine physicians suggested that the NRC should rely on the nuclear medicine specialty boards and the NRC should only provide "general guidance."[12]

A smaller number of comments expressing support for tailoring the T&E requirements for certain radiopharmaceuticals were received from the radiopharmaceutical industry,[13] the American Society of Hematology, and some non-traditional physicians. These groups advocated for a tiered approach for T&E based on drug safety profile and complexity of administration, and recommended 80 hours of T&E for "unitized, patient-ready" doses of alpha- or beta-emitters. United Pharmacy Partners and the National Rural Healthcare Association advocated partnering authorized nuclear pharmacists (ANPs) with tailored pathway AUs to increase both safety and patient access. Georgia Congressman Buddy Carter advocated for improving rural access to radiopharmaceuticals by considering ANPs for AU status (ADAMS Accession No. ML19018A194).

Public meeting transcripts, meeting summaries, and all written comment submissions are available on www.Regulations.gov under docket ID number NRC-2018-0230. Documentation of the staff's outreach efforts (which included letters and e-mails, newsletter submissions, and conference attendance), detailed comment summaries, commenter tables, and comment binning reports are available in "SECY-19-0XX Supplemental Information: The NRC Staff's Stakeholder Outreach Efforts and Summary of Comments," located at ADAMS Accession No. [redacted].

Agreement State Coordination

The NRC engaged the Agreement States through several letters informing them of the public comment periods and meetings, two government-to-government webinars, e-mails and teleconference coordination with the OAS Executive Board, and updates to the States during the NRC/OAS/Conference of Radiation Control Program Directors (CRCPD) monthly teleconference. The staff also submitted an article soliciting comments on the T&E evaluation in

[11] These included the American College of Radiology, Society of Nuclear Medicine and Molecular Imaging, American College of Nuclear Medicine, American College of Radiation Oncology, American Osteopathic Board of Radiology, American Society for Radiation Oncology, American Association of Physicists in Medicine, American Brachytherapy Society, Health Physics Society, American Society of Radiologic Technologists, the U.S. Oncology Network, and the World Association of Radiopharmaceutical and Molecular Therapy.

[12] These comments are available at ADAMS Accession Nos. ML19190A195 and ML19157A195.

[13] The Council on Radionuclides and Radiopharmaceuticals, Bayer HealthCare, and Spectrum Pharmaceuticals.

the CRCPD's monthly online newsletter (ADAMS Accession No. ML19177A101) and presented on the staff's T&E evaluation at the CRCPD's National Conference on Radiation Control in May 2019 and the OAS Annual Meeting in August 2019.

Generally, the Agreement States oppose any option that would create additional AU pathways or would otherwise add complexity to what are viewed as "already complex" T&E regulations. Most Agreement States find the existing AUs pathways reasonable and accessible for physicians, and they do not see evidence of an AU shortage in their states. However, some Agreement States and the OAS Executive Board indicated that the NRC's regulation of T&E for AUs encroaches on the practice of medicine, and the NRC and the Agreement States could more effectively regulate medical uses under § 35.300 by focusing only on licensees' radiation safety programs and their procedures for ensuring radiopharmaceuticals are administered in accordance with the written directive.[14] In their second comment period submission, the OAS commented that the NRC and Agreement States should no longer review and approve T&E for AUs, and instead licensees should rely on certification by medical specialty boards that physicians are medically competent to use radiopharmaceuticals (ADAMS Accession No. ML19184A590).

ACMUI Coordination

In their draft report dated February 7, 2019 (ADAMS Accession No. ML19039A113), the ACMUI Subcommittee on Training and Experience for All Modalities made the following conclusions: 1) there is no objective data to confirm a shortage of AUs for § 35.300 uses; 2) the Subcommittee does not recommend creation of a new tailored AU pathway; and 3) if the NRC pursues a new tailored AU pathway, candidates for this pathway must acquire all the basic knowledge topics contained in § 35.390, satisfactorily complete an initial formal competency assessment, and maintenance of tailored AU status should require formal periodic competency reassessments. The ACMUI approved the Subcommittee's report, with one dissenting vote, during its public teleconference meeting on February 26, 2019.[15] The Subcommittee issued their final report on T&E for § 35.300 uses on February 27, 2019 (ADAMS Accession No. ML19058A598). The enclosure to this paper discusses the ACMUI's past efforts related to T&E for radiopharmaceuticals.

OPTIONS:

The staff evaluated several options that fall under two general regulatory approaches: 1) a performance-based approach that would remove the current prescriptive T&E requirements and NRC review and approval of AUs; and 2) maintaining and/or enhancing the NRC's existing regulatory framework for T&E.
The options feature a number of variations that the staff would finalize with stakeholders following the Commission's direction, such as whether a formal competency evaluation (preceptor attestation, examination) or additional oversight of the board certification process should be incorporated into any of the options. Options could be approved individually, together, or combined to form new options.

[14] OAS, Colorado, North Carolina, and Wisconsin comments are available at ADAMS Accession Nos. ML19030B764, ML19177A330, ML19170A073, and ML19184A593, respectively.

[15] The meeting summary and transcript for the ACMUI's February 26, 2019 public teleconference are available at ADAMS Accession Nos. ML19072A259 and ML19067A254, respectively.

Approach 1. Removal of Prescriptive T&E Requirements and NRC Review and Approval of AUs

Under Options 1a, 1b, and 1c, the NRC would provide high-level requirements in its regulations for the certification of AUs and would rely on other organizations to approve AUs in accordance with these requirements. AUs would remain responsible for ensuring radiopharmaceuticals they prescribe are administered in accordance with their signed written directive, and regulatory emphasis would be on performance-based inspection of licensees' radiation safety programs to ensure safe and effective handling, storage, use, and security of radiopharmaceuticals. The options under Approach 1 would revise the T&E regulatory framework to address the more immediate issue of the increase in the number and type of radiopharmaceuticals forecasted for the near term The staff could apply this same approach to T&E for other medical modalities in Part 35 during a future rulemaking.

Option 1a, "Specialty Board Credentialing," where physicians must be certified by any medical specialty board to use radiopharmaceuticals.

Option 1b, "Licensee Credentialing," where licensees must develop their own procedures to determine whether their physicians are adequately trained to safely use radiopharmaceuticals. The NRC would review and approve these procedures based on high-level requirements, and the procedures would be enforceable as license conditions.

Option 1c, "NRC-Recognized Specialty Board Credentialing," where physicians must be certified by a medical specialty board recognized by the NRC. The NRC would revise its board certification criteria for the therapeutic use of radiopharmaceuticals to broaden and align it with emerging radiopharmaceuticals.

Pros:

- Would address stakeholder concerns regarding overly burdensome T&E.
- Better alignment with the NRC's Medical Policy Statement than the existing T&E regulatory framework.
- Less licensing resources would be required because the NRC and Agreement States would no longer review and approve T&E for AUs.[16]
- Agile and transformative: provides the flexibility needed to accommodate emerging and future radiopharmaceuticals.
- Option 1c could motivate additional medical specialty boards to seek NRC recognition, thus potentially opening more pathways for physicians to become AUs.
- The OAS Executive Board and some Agreement States support no longer reviewing and approving T&E for AUs.[17]
- The medical community would have more influence in setting T&E requirements.
- Less resources would be required of licensees because they would no longer submit license amendments for AU T&E.

[16] NRC medical license reviewers estimate that up to 90 percent of their time is spent on reviewing T&E for AUs.

[17] See OAS's comments at ADAMS Accession No. ML19184A590, North Carolina's comments at ML19170A073, Wisconsin's comments at ML19184A593, and Colorado's comments at ML19177A330.

Cons:

- The medical communities could view these options, particularly 1a and 1b, as an abdication of the NRC's regulatory responsibilities.
- Options 1a and 1b could create large disparities in AU T&E across licensees.
- For Option 1b, licensees may object to the resources required to develop their own policies, procedures, and training programs.
- Without additional requirements, Approach 1, and in particular Options 1a and 1b, could reduce assurance regarding the appropriateness of radiation safety training for radiopharmaceutical procedures.
- Option 1c would remove the alternate pathway, leaving only the board certification pathway; new physicians that have not been board certified would need to work under the supervision of another AU.
- For Option 1c, newly recognized board programs would not provide a pathway for their existing certified physicians to become AUs.

Approach 2. Maintain or Enhance the Existing T&E Framework

Option 2a, "Status Quo," would make no changes to the NRC's T&E requirements.

Pros:

- Supported by the ACMUI, some Agreement States, and the nuclear medicine and radiation oncology medical communities.
- The NRC, Agreement States, and licensees have experience applying the existing T&E regulations and accompanying guidance, and they are well-understood by the medical community.
- Radionuclide categories in § 35.300 can accommodate most future radiopharmaceuticals.
- Would not require rulemaking resources.

Cons:

- Is not fully risk informed—current T&E requirements may not be right-sized for certain radiopharmaceuticals.
- May not be adequate for complex emerging radiopharmaceuticals.
- Current T&E regulatory framework is not closely aligned with the Medical Policy Statement.
- The OAS Executive Board and some Agreement States do not support status quo.

Option 2b, "Tailored Requirements," would tailor and reduce T&E to create additional AU pathways for administration of specific categories of radiopharmaceuticals; the existing AU pathways would remain unchanged. The staff considered the following examples of tailored AU categories: patient-specific, unit-dose non-radioligand alpha-emitters; *any* patient-specific, unit dose radiopharmaceutical; or *any one* parenteral radiopharmaceutical.

Pros:

- Would risk-inform the T&E requirements for certain radiopharmaceuticals.
- Provides additional, more flexible pathways for non-traditional physicians to become AUs for specific radiopharmaceuticals.

Cons:

- Strongly opposed by the ACMUI, Agreement States, and the nuclear medicine and radiation oncology medical communities.
- May not consider safety-related characteristics such as energy level, dose, half-lives, and administration protocol.
- Categories may exclude emerging and future radiopharmaceuticals.

Option 2c, "Emerging Radiopharmaceuticals," would conduct individual reviews of each emerging radiopharmaceutical to determine drug-specific tailored T&E, and other requirements (e.g., physical presence) as necessary, similar to the current construct under § 35.1000, "Other Medical Uses of Byproduct Material or Radiation From Byproduct Material."

Pros:

- Addresses complexities and operating experience of emerging radiopharmaceuticals.
- Could create additional AU pathways for specific physicians and may address concerns regarding burdensome T&E.

Cons:

- No stakeholders supported Option 2c.
- Extensive licensing and inspection resources would be required for all stages of this option.
- Individual reviews could delay access to emerging radiopharmaceuticals and licensee resources would be required to train their staff on unique guidance.
- May create regulatory uncertainty for manufacturers, licensees, AUs.
- Would not address burdensome T&E concerns for existing radiopharmaceuticals.

Option 2d, "**Team-Based Requirements,"** would create an additional alternate pathway in which T&E requirements for AUs would be reduced based on pairing AUs with other individuals with radiation safety T&E. These approaches could include pairing AUs with ANPs or an "authorized administrator," or requiring a "nuclear medicine team" for administration of therapeutic radiopharmaceuticals (minimally consisting of an AU, a technologist, and a radiation safety officer).

Pros:

- The presence of more trained professionals may provide an additional measure of radiation safety while permitting flexibility in the T&E requirements for AUs.

Cons:

- Minimal stakeholder support for team-based approaches, and there was strong opposition to pairing AUs with ANPs because the T&E for ANPs does not address patient care nor does it fully cover radiation safety aspects of administration.
- May be impractical or infeasible due to legal, clinical, financial, and other professional issues outside the purview of the NRC.
- Very complex to inspect and license.

Enclosure

Background Information on the U.S. Nuclear Regulatory Commission Staff's Evaluation of Training and Experience Requirements for Radiopharmaceuticals Requiring a Written Directive

Introduction

The training and experience (T&E) requirements in Title 10 of the *Code of Federal Regulations* (CFR) Part 35, "Medical Use of Byproduct Material," Subpart E, "Unsealed Byproduct Material—Written Directive Required" cover:

(1) The use of unsealed byproduct material for which a written directive is required (10 CFR 35.390);
(2) The oral administration of sodium iodide I-131 requiring a written directive in quantities less than or equal to 1.22 gigabecquerels (33 millicuries) (§ 35.392);
(3) The oral administration of sodium iodide I-131 requiring a written directive in quantities greater than 1.22 gigabecquerels (33 millicuries) (§ 35.394); and
(4) The parenteral administration of unsealed byproduct material requiring a written directive (§ 35.396).

Table 1 provides a high-level summary of the different pathways for a physician to become an authorized user (AU) for radiopharmaceuticals under § 35.300, "Use of unsealed byproduct material for which a written directive is required":

Table 1. Authorized User Pathways in 10 CFR 35.300

10 CFR 35.390	**10 CFR 35.392**	**10 CFR 35.394**	**10 CFR 35.396**
Certified by a medical specialty board whose certification process has been recognized by the NRC or an Agreement State			Recognized medical specialty board + 80 hours of classroom and laboratory training + work experience under the supervision of an AU + preceptor attestation
OR			
	Is an AU under §§ 35.390 or 35.394	Is an AU under § 35.390	Is an AU under § 35.390
OR			
700 hours of T&E including a minimum of 200 hours of classroom and laboratory training + work experience under the supervision of an AU + preceptor attestation	80 hours of classroom and laboratory training + work experience under the supervision of an AU + preceptor attestation	80 hours of classroom and laboratory training + work experience under the supervision of an AU + preceptor attestation	Is an AU under §§ 35.490 or 35.690 + 80 hours of classroom and laboratory training + work experience under the supervision of an AU + preceptor attestation

Over the years, the NRC has received feedback from various stakeholders on its T&E requirements for radiopharmaceuticals under § 35.300, and the Advisory Committee on the Medical Uses of Isotopes (ACMUI) has also undertaken several efforts looking at T&E for radiopharmaceuticals. A summary of this feedback and those efforts is provided below to add context to the discussions provided in the main body of this paper.

Past Stakeholder Feedback on the Alternate Pathway and Related NRC Efforts

Since the T&E requirements were amended in 2002 (67 FR 62872; October 9, 2002) and subsequently in 2005 (70 FR 16336; March 30, 2005),[1] stakeholders have raised concerns about the effects of the T&E requirements in § 35.390, "Training for use of unsealed byproduct materials for which a written directive is required" on patient access to certain therapeutic radiopharmaceuticals.[2] Specifically, some stakeholders have asserted that the 700-hour requirement is overly burdensome for physicians who are not certified by an NRC-recognized medical specialty board and that the extensive requirements have resulted in a shortage of AUs for 10 CFR 35.300 materials.[3]

In a letter to the ACMUI dated October 28, 2015, Spectrum Pharmaceuticals (Spectrum), manufacturer of Zevalin® (rituximab + Yttrium-90), a beta-emitter radioimmunotherapy for treatment of non-Hodgkin's lymphoma, requested that the NRC re-evaluate the 700-hour requirement in the alternate pathway (§ 35.390(b)(1)) because "it is impacting patient and healthcare access to effective treatment options."[4] Spectrum went on to state:

> …[W]e believe 80 hours is the upper limit of the appropriate level of training for a limited license to administer pre-filled self-contained radiopharmaceuticals like Zevalin. Such an approach would eliminate the unnecessary regulatory barriers currently limiting cancer patient access to effective treatment options, while maintaining training requirements commensurate with the risks of handling Zevalin… …It is important to note that Zevalin involves limited physician preparation and handling. Zevalin is delivered to the AU as a patient-ready dose requiring only an acrylic shield and standard radiation

[1] From the inception of the Atomic Energy Commission's medical regulations in 1956 until about 1979, the T&E requirements for radiopharmaceuticals were general and performance-based—there were no hours-based requirements. Guidance issued in 1979 (Regulatory Guide 10.8, available at ADAMS Accession No. ML13350A208) recommended 80 hours of training in basic radioisotope handling techniques plus clinical experience that included a specified number of therapy procedures; these recommendations were codified in a 1987 rulemaking (51 FR 36932; October 16, 1986). The 700-hour requirement went into effect on October 24, 2002, as part of a broad rulemaking for 10 CFR Part 35 (67 FR 20250; April 24, 2002). More detailed information on the historical timeline of the T&E requirements for radiopharmaceuticals is available in "SECY-19-0XX Supplemental Information: Historical Background of the U.S. Nuclear Regulatory Commission's Training and Experience Requirements for Radiopharmaceuticals Requiring a Written Directive" (ADAMS Accession No. [redacted]).

[2] Stakeholders raised concerns in the petition for rulemaking submitted by William Stein III, M.D. (PRM-35-19) (71 FR 34285; June 14, 2006) and in comments on the proposed rule to amend the regulations related to the medical use of byproduct material (79 FR 42410; July 21, 2014). The NRC responded to those comments in the Denial of Petition for Rulemaking (72 FR 60285; October 24, 2007) and in the final rule (83 FR 33046; July 16, 2018), respectively.

[3] These concerns were raised by stakeholders during the ACMUI meetings held on March 10, 2016 (transcript can be found in ADAMS at Accession No. ML16109A042) and on October 7, 2016 (transcript can be found in ADAMS at Accession No. ML16357A688).

[4] The October 28, 2015 letter from Spectrum can be found on page 77 of the March 10, 2016 ACMUI public teleconference meeting transcript (ADAMS Accession No. ML16109A042).

precautions. A "hot lab" is not required and patients do not need to be assessed for radiation exposure. Due to the preparation of the patient-ready dose by the radiopharmacy before reaching the administering physician, training requirements for the physician on dose preparation and the safe handling of radiopharmaceuticals can be more limited. Board certified Hematologists/Oncologists are accustomed to using cytotoxic agents that require specific handling tailored to their risks, and are customarily trained on standard radiation precautions. Limited additional training on the proper handling and disposal of Zevalin should enable them to safely use this product.

Spectrum pointed out that an 80-hour T&E requirement would mirror the T&E requirements for administering sodium iodide I-131 in § 35.392 and 35.394 and that Zevalin® had a comparable or even more favorable safety profile than I-131. Spectrum stated that doctors wishing to offer Zevalin® to their patients were having a difficult time finding AUs who administer Zevalin® within a reasonable commuting distance for their patients, noting that in 2010, the number of AUs offering Zevalin® was greater than 400, but by 2015, that number had decreased to about 145. In their October 8, 2015 public teleconference meeting[5] the ACMUI discussed that the decrease in AUs offering Zevalin® could be attributed to an increase in competing therapies, and not a lack of AUs authorized to administer the radiopharmaceutical.

Additional stakeholders echoed similar concerns regarding patient access to alpha- and beta-emitters, including patients, patient advocacy organizations (the American Society of Hematology, Patients Against Lymphoma, the Lymphoma Research Foundation, Community Oncology Alliance), healthcare administrators, hematologists and medical oncologists, and former Nevada Congressman Joe Heck.[6]

In response to the feedback, the NRC staff reviewed the T&E requirements for the medical uses authorized under § 35.300 in 2015 and 2016. Specifically, the NRC staff reviewed the regulatory basis and comments received on past rulemakings related to the medical use of byproduct material and did not identify any new information that would call into question the basis of the existing requirements.[7] As a result, the NRC staff did not propose any changes to the regulations at the time.

In April 2018, as part of its initial evaluation of T&E requirements for administering different categories of radiopharmaceuticals in response to SRM-M170817,[8] the NRC staff conducted outreach with various medical and regulatory stakeholders. The outreach consisted of a questionnaire that covered four main areas: (1) the fundamental knowledge necessary for administering any radiopharmaceutical under § 35.390, (2) the additional specific knowledge necessary for administering specific types of radiopharmaceuticals, (3) how best to acquire this knowledge, and (4) how this knowledge and ability to function independently should be best evaluated. The NRC staff sent this questionnaire (ADAMS Accession No. ML18108A266) to

[5] The discussion of competing therapies can be found on page 70 of the October 8, 2015 ACMUI public teleconference meeting transcript (ADAMS Accession No. ML15294A421).
[6] Congressman Heck's letter dated January 5, 2016 can be found on page 89 of the March 10, 2016 ACMUI public teleconference meeting transcript (ADAMS Accession No. ML16109A042).
[7] The T&E requirements in 10 CFR Part 35 related to radiopharmaceutical therapies were amended in 1998 (63 FR 43516; August 13, 1998), 2002 (67 FR 20249; April 24, 2002), 2005 (70 FR 16336; March 30, 2005), and 2018 (83 FR 33046; July 16, 2018). Comments were received and reviewed in response to these rulemaking efforts.
[8] SRM-M170817, "Staff Requirements – Affirmation Session, 10:30 A.M., Thursday, August 17, 2017, Commissioners' Conference Room, One White Flint North, Rockville, Maryland (Open to Public Attendance)," dated August 16, 2017 (ADAMS Accession No. ML17229B283).

nine non-Federal stakeholders and seven Federal licensees in the medical community. The staff received responses from six of the non-Federal medical stakeholders and three Federal licensee stakeholders. Regarding the fundamental and specific knowledge for administering radiopharmaceuticals, most stakeholders responded that the list of knowledge topics included in the questionnaire was appropriate and that most of these topics are covered in sufficient depth during a physician's residency program for a specialty board certification.[9] Regarding how to best acquire this knowledge, the responses by stakeholders were more varied. Some stakeholders indicated that the knowledge would mostly be acquired in a physician's residency or fellowship program or through a combination of classroom and laboratory training and hands-on experience. Other stakeholders suggested eliminating the alternate pathway while one stakeholder stated that the alternate pathway should be maintained to provide flexibility due to the length of the board certification process. Regarding how knowledge, skills, and abilities should be evaluated, the responses by stakeholders were also varied. Some stakeholders suggested that the medical specialty boards create and administer an examination to test competency while another stakeholder was not sure if a written examination was a reliable evaluation by itself. One stakeholder suggested that the professional medical societies may be able to administer an examination while another stakeholder suggested that the NRC could administer such an examination. The overarching comment made by most of the stakeholders was that the NRC should collaborate with knowledgeable external entities to determine how the knowledge and ability to function independently as an AU should best be evaluated.

In addition to the questionnaire, the NRC staff solicited and received feedback from the Agreement States and the Organization of Agreement States (OAS) Executive Board. The OAS Executive Board and majority of Agreement States that provided feedback to the NRC did not support the idea of creating another subcategory of AUs because it would likely add another layer of complication when approving AUs. They also indicated that the focus of the NRC and Agreement States as regulators should be on radiation safety and protection and that the regulatory agencies should not allow their oversight approach to impinge on the practice of medicine.

Past ACMUI Evaluations

Separate from the NRC staff's review in 2015 and 2016, the ACMUI independently reviewed the T&E requirements for the medical uses authorized under § 35.300. The ACMUI, in its final report, "Sub-Committee Final Report on Training & Experience for Authorized Users of Alpha and Beta Emitters under § 35.390," dated March 16, 2016 (ADAMS Accession No. ML16089A271) concluded that no change to the T&E requirements was warranted and that the current requirement of 700 hours for AUs does not adversely affect patient access to therapeutic radiopharmaceuticals. Moreover, the ACMUI noted in that report that even in large metropolitan areas and at large medical centers, both of which have large numbers of AUs, certain therapeutic radiopharmaceuticals were used infrequently, indicating that factors other than the availability of AUs were dictating choices of treatment. In that report, the ACMUI recommended that a subcommittee be formed with the specific charge of periodically reviewing the T&E requirements currently in effect and making recommendations for changes as warranted.

[9] The general knowledge topics included radiation physics, instrumentation, radiation protection, mathematics pertaining to the use and measurement of radioactivity, general patient release determination, chemistry of byproduct material for medical use, radiation biology, medical events, and NRC requirements. The subtopics and additional topics based on specific categories of radiopharmaceuticals can be found in the questionnaire at ADAMS Accession No. ML18108A266.

In 2016, the ACMUI formed a subcommittee to periodically review the T&E requirements for all medical modalities (unsealed and sealed byproduct material) in Part 35, beginning with the review of § 35.300, and determine if changes are needed. As noted in its status report dated September 16, 2016 (ADAMS Accession No. ML17066A442), this subcommittee was formed in response to: (1) continued concerns raised by stakeholders regarding patient access to radiopharmaceuticals, (2) development of new radiopharmaceuticals since the current T&E requirements went into effect in 2002, and (3) a shift in the educational paradigm in the medical specialty training infrastructure from hours and experience to one that is more competency-based.

The ACMUI subcommittee provided the NRC staff with its draft interim report (ADAMS Accession No. ML18051A725) dated February 19, 2018 and discussed the report with the full committee in a public teleconference on March 1, 2018.[10] In its report, the subcommittee expressed concerns about the decrease in the number of nuclear medicine physicians in recent years,[11] noting that this could be a problem in the future. The subcommittee also indicated that while it is difficult to judge the effect of this decline on patient access, there is no data to suggest that "there is a surplus [of AUs], nor have future needs been addressed." Therefore, the subcommittee concluded that the creation of a new alternative approach for AUs under § 35.390 should be reconsidered, and the subcommittee committed to continue its work in this area.

The ACMUI reviewed the staff's preliminary evaluation of T&E requirements and in its final report, "Comments on the Draft SECY Paper Entitled Staff Evaluation of Training and Experience Requirements for Administering Radiopharmaceuticals," dated July 16, 2018 (ADAMS Accession No. ML18201A417), agreed with the NRC staff's conclusion in SECY-18-0084[12] that a limited AU status for radionuclide therapy is possible, but that there must be a clear outline for the individual's scope of practice. The ACMUI also agreed that additional stakeholder outreach is needed. The ACMUI recommended that the NRC staff conduct ongoing monitoring for the potential incidence of an AU shortage for the medical uses authorized under § 35.300.

Just prior to the staff's submission of final SECY-18-0084, Bayer HealthCare submitted a July 11, 2018 letter[13] to the ACMUI requesting that the NRC consider a proposal to enable medical oncologists and urologists to attain AU status for administration of their radiopharmaceutical, Xofigo® (radium Ra-223 dichloride) with 80 hours of T&E. (Xofigo® is an alpha-emitter approved for treatment of prostate cancer with symptomatic bone metastases.) Bayer HealthCare pointed to Xofigo's® "unit-dose and patient-ready form, uncomplicated administration, and minimal administered activity that enables patient release without instructions"[14] as the justification for reduced T&E. In their letter, Bayer HealthCare also provided market data to illustrate that

[10] Meeting summary can be found in ADAMS at Accession No. ML18092B615.
[11] The American Board of Nuclear Medicine (ABNM) provided a comment letter (ADAMS Accession No. ML18221A170) in response to the March 1, 2018, ACMUI public meeting. In that letter, ABNM indicated that the number of certificates issued each year had been relatively constant from 1977 to 2015. The average number of certificates issued each year was 72 during that time (range 50 - 107). The ABNM noted that it had issued 43 initial certificates in 2016, and 49 certificates in 2017.
[12] SECY-18-0084, "Staff Evaluation of Training and Experience Requirements for Administering Different Categories of Radiopharmaceuticals in Response to SRM-M170817," dated August 28, 2018, available in ADAMS at Accession No. ML18135A276.
[13] The July 11, 2018 letter from Bayer Healthcare can be found on page 58 of the July 11, 2018 ACMUI public teleconference meeting transcript (ADAMS Accession No. ML18221A170).
[14] Per the NRC's patient release criteria in 10 CFR 35.75(b).

“diminishing numbers of AUs” and the geographic distribution of AUs were factors that contributed to patients not receiving Xofigo® treatment.