**TRAINING AND EXPERIENCE REQUIREMENTS FOR UNSEALED BYPRODUCT MATERIAL: BACKGROUND INFORMATION**

Introduction

The U.S. Nuclear Regulatory Commission's (NRC's) 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 the following four uses of radiopharmaceuticals:

(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) (10 CFR 35.392)

(3) the oral administration of sodium iodide I-131 requiring a written directive in quantities greater than 1.22 gigabecquerels (33 millicuries) (10 CFR 35.394)

(4) the parenteral administration of unsealed byproduct material requiring a written directive (10 CFR 35.396)

Table 1 provides a summary of the different pathways for a physician to become an authorized user (AU) for radiopharmaceuticals under 10 CFR 35.300, "Use of unsealed byproduct material for which a written directive is required."

**Table 1. AU Pathways in 10 CFR 35.300**

<table>
<tr><th>10 CFR 35.390</th><th>10 CFR 35.392</th><th>10 CFR 35.394</th><th>10 CFR 35.396</th></tr>
<tr><td colspan="3">Certified by a medical specialty board whose certification process has been recognized by the NRC or an Agreement State</td><td>Recognized medical specialty board + 80 hours of classroom and laboratory training + work experience (including casework) under the supervision of an AU + preceptor attestation</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td></td><td>Is an AU under 10 CFR 35.390 or 10 CFR 35.394</td><td>Is an AU under 10 CFR 35.390</td><td>Is an AU under 10 CFR 35.390</td></tr>
<tr><td colspan="4">OR</td></tr>
<tr><td>700 hours of T&E, including a minimum of 200 hours of classroom and laboratory training + work experience (including casework) under the supervision of an AU + preceptor attestation</td><td>80 hours of classroom and laboratory training + work experience (including casework) under the supervision of an AU + preceptor attestation</td><td>80 hours of classroom and laboratory training + work experience (including casework) under the supervision of an AU + preceptor attestation</td><td>Is an AU under 10 CFR 35.490 or 10 CFR 35.690 + 80 hours of classroom and laboratory training + work experience (including casework) under the supervision of an AU + preceptor attestation</td></tr>
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Over the years, the NRC has received feedback from stakeholders on its T&E requirements for radiopharmaceuticals under 10 CFR 35.300, and both the staff and the Advisory Committee on the Medical Uses of Isotopes (ACMUI) have undertaken several efforts looking at the T&E requirements. The staff summarizes this feedback and those efforts below to add context to the discussions in the rulemaking plan SECY.

Stakeholder Feedback on the Alternate Pathway

Since the NRC amended the T&E requirements in 2002 (67 FR 20250; April 24, 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 10 CFR 35.390, "Training for use of unsealed byproduct material 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,[4] Spectrum Pharmaceuticals (Spectrum), requested that the NRC reevaluate the 700-hour requirement in the alternate pathway because "it is impacting patient and healthcare access to effective treatment options." Spectrum is the manufacturer of Zevalin® (rituximab + yttrium-90), a beta emitter radioimmunotherapy for treatment of non-Hodgkin's lymphoma. Spectrum's letter 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 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

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[1] From the inception of the Atomic Energy Commission's medical regulations in 1956 until about 1979, the T&E requirements for therapeutic radiopharmaceuticals were general and performance based—there were no hours-based requirements. Guidance issued in January 1979 (Regulatory Guide 10.8, "Guide for the Preparation of Applications for Medical Programs" (Agencywide Documents Access and Management System (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). The staff provides more detailed information on the historical timeline of the T&E requirements for radiopharmaceuticals in "Historical Background of the U.S. Nuclear Regulatory Commission's Training and Experience Requirements for Radiopharmaceuticals Requiring a Written Directive" (ADAMS Accession No. ML19176A455).

[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 the petition for rulemaking (72 FR 60285; October 24, 2007), and in the final rule (83 FR 33046; July 16, 2018), respectively.

[3] Stakeholders raised these concerns during the ACMUI meetings held on March 10, 2016 (ADAMS Accession No. ML16109A042), and October 7, 2016 (ADAMS Accession No. ML16357A688).

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

> 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 noted that an 80-hour T&E requirement would mirror the T&E requirements for administering sodium iodide I-131 in 10 CFR 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® and who are located within a reasonable commuting distance for their patients. Specifically, in 2010, the number of AUs offering Zevalin® was greater than 400, but by 2015, that number had decreased to about 145. During its public teleconference on October 8, 2015,[5] the ACMUI discussed that the decrease in AUs offering Zevalin® could be attributed to an increase in competing therapies and not to a lack of AUs authorized to administer the radiopharmaceutical.

Around this time, other stakeholders echoed similar concerns about patient access to alpha and beta emitters, including patients, patient advocacy organizations (American Society of Hematology, Patients Against Lymphoma, Lymphoma Research Foundation, Community Oncology Alliance), healthcare administrators, hematologists and medical oncologists, and former Nevada Congressman Joe Heck.[6] In July 2018, Bayer Healthcare submitted a letter[7] to the ACMUI requesting that the NRC consider a proposal to enable medical oncologists and urologists to attain AU status for administration of its radiopharmaceutical, Xofigo® (radium-223 dichloride)—an alpha emitter approved for treatment of prostate cancer with symptomatic bone metastases—with 80 hours of T&E. Bayer HealthCare pointed to Xofigo's® "unit-dose and patient-ready form, uncomplicated administration, and minimal administered activity that enables patient release without instructions" as the justification for reduced T&E. In its letter, Bayer HealthCare also provided market data to illustrate that "diminishing numbers of AUs" and the geographic distribution of AUs were factors that contributed to patients not receiving Xofigo® treatment.

Past NRC Efforts

In response to the alternate pathway feedback, in 2015 and 2016 the staff reviewed the T&E requirements under 10 CFR 35.300. The staff reviewed the regulatory basis and comments received on all 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.[8] As a result, the staff did not propose any changes to the regulations at the time.

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[5] The discussion of competing therapies can be found on page 70 of the transcript of the ACMUI public teleconference meeting on October 8, 2015 (ADAMS Accession No. ML15294A421).

[6] Congressman Heck's letter dated January 5, 2016, can be found on page 89 of the transcript for the ACMUI public teleconference meeting on March 10, 2016 (ADAMS Accession No. ML16109A042).

[7] The letter dated July 11, 2018, from Bayer HealthCare can be found on page 58 of the transcript of the ACMUI public teleconference meeting on July 16, 2018 (ADAMS Accession No. ML18221A170).

[8] The NRC amended the T&E requirements in 10 CFR Part 35 related to radiopharmaceutical therapies in 1998 (63 FR 43516; August 13, 1998), 2002 (67 FR 20249; April 24, 2002), and 2005 (70 FR 16336; March 30, 2005). The staff received and reviewed comments in response to these rulemaking efforts.

In the August 17, 2017, staff requirements memorandum (SRM) approving the final rule for medical use of byproduct material,[9] the Commission directed the staff to evaluate tailored T&E requirements for different categories of radiopharmaceuticals. In response to the SRM, the staff conducted initial outreach with various medical and regulatory stakeholders in April 2018. The outreach consisted of a questionnaire (ADAMS Accession No. ML18108A266) that covered four main areas: (1) the fundamental knowledge necessary for administering any radiopharmaceutical under 10 CFR 35.390, (2) the additional specific knowledge necessary for administering particular types of radiopharmaceuticals, (3) how best to acquire this knowledge, and (4) how this knowledge and ability to function independently should best be evaluated. The staff sent this questionnaire to a small sample of non-Federal stakeholders and Federal licensees in the medical community.

Stakeholder views varied widely, but, 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.[10] With regard to how to best acquire this knowledge, stakeholder responses 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 given the length of the board certification process. Stakeholder responses also varied with regard to how knowledge, skills, and abilities should be evaluated. Some stakeholders suggested that the medical specialty boards create and administer an examination to test competency, while another stakeholder was not sure whether 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 stakeholder questionnaire, the staff received feedback from the Agreement States and the Organization of Agreement States (OAS) Executive Board. The OAS Executive Board and a majority of Agreement States that provided feedback to the NRC did not support the idea of creating another subcategory of AUs because this would likely add another layer of complication when approving AUs. OAS and the Agreement States also indicated that, as regulators, the NRC and Agreement States should focus on radiation safety and protection and that the regulatory agencies should not allow their oversight approach to impinge on the practice of medicine.

The staff documented the initial results, status, and next steps of the evaluation of tailored T&E in SECY-18-0084, "Staff Evaluation of Training and Experience Requirements for Administering

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[9] 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 17, 2017 (ADAMS Accession No. ML17229B283).

[10] 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 (ADAMS Accession No. ML18108A266).

Different Categories of Radiopharmaceuticals in Response to SRM-M170817," dated August 28, 2018 (ADAMS Accession No. ML18135A276). The staff concluded that it may be feasible to establish tailored T&E requirements for different categories of radiopharmaceuticals and to create a means of authorizing the administration of these categories (i.e., a limited AU status); however, more extensive outreach with the medical community was needed to move forward with these efforts. This rulemaking plan SECY documents the staff's additional outreach efforts and evaluation of T&E for radiopharmaceuticals requiring a written directive.

Past Evaluations by the Advisory Committee on the Medical Uses of Isotopes

Separate from the staff's review in 2015 and 2016, the ACMUI independently reviewed the T&E requirements for the medical uses authorized under 10 CFR 35.300. In the "ACMUI Sub-Committee Final Report on Training & Experience for Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390," dated March 16, 2016 (ADAMS Accession No. ML16089A271), the ACMUI 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 certain therapeutic radiopharmaceuticals were used infrequently even in large metropolitan areas and at large medical centers, both of which have large numbers of AUs, indicating that factors other than the availability of AUs were dictating choices of treatment. In that report, the ACMUI recommended forming a subcommittee with the specific charge of periodically reviewing the T&E requirements currently in effect and making recommendations for changes as warranted.

In 2016, the ACMUI formed a subcommittee to periodically review the T&E requirements for all medical modalities (unsealed and sealed byproduct material) in 10 CFR Part 35, beginning with the review of 10 CFR 35.300, and to determine whether 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 about 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 staff with its draft interim report dated February 19, 2018 (ADAMS Accession No. ML18051A725), and discussed the report with the full committee in a public teleconference on March 1, 2018 (ADAMS Accession No. ML18092B615). 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 are 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 10 CFR 35.390 should be reconsidered, and the subcommittee committed to continue its work in this area.

[11] The American Board of Nuclear Medicine (ABNM) provided a comment letter (page 74 of ADAMS Accession No. ML18221A170) in response to the ACMUI public meeting on March 1, 2018. In that letter, the ABNM indicated that the number of certificates issued each year had been relatively constant from 1977 to 2015, with an annual average of 72 during that time (range 50–107). The ABNM noted that it had issued 43 initial certificates in 2016 and 49 certificates in 2017.

The ACMUI reviewed the staff's preliminary evaluation of T&E requirements and, in its final report, "Comments on the Draft NRC SECY Paper Entitled 'Staff Evaluation of Training and Experience Requirements for Administering Radiopharmaceuticals,'" dated July 16, 2018 (ADAMS Accession No. ML18201A417), agreed with the staff's conclusion that was later documented in SECY-18-0084. This conclusion was that a limited AU status for radionuclide therapy is possible, but that there must be a clear outline for the physician's scope of practice. The ACMUI also agreed that additional stakeholder outreach was needed. The ACMUI also recommended that the staff conduct ongoing monitoring for the potential incidence of an AU shortage for the medical uses authorized under 10 CFR 35.300.