SUNSI Review Complete
Template = ADM-013
E-RIDS=ADM-03
ADD=Sarah Lopas, Carrie Crawford

COMMENT (57)
PUBLICATION DATE: 5/2/2019
CITATION: 84 FR 18874

PUBLIC SUBMISSION

As of: 7/3/19 3:46 PM
Received: July 03, 2019
Status: Pending_Post
Tracking No. 1k3-9att-wp9j
Comments Due: July 03, 2019
Submission Type: Web

Docket: NRC-2018-0230
Training and Experience Requirements for Different Categories of Radiopharmaceuticals

Comment On: NRC-2018-0230-0162
Draft Approaches for Addressing Training and Experience Requirements for Radiopharmaceuticals Requiring a Written Directive

Document: NRC-2018-0230-DRAFT-0212
Comment on FR Doc # 2019-10760

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General Comment

See attached file(s)

Attachments

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July 3, 2019

Daniel S. Collins
Director, Division of Materials Safety, Security, State, and Tribal Programs
Office of Nuclear Materials Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: ACMUI Training and Experience (T&E) Report regarding the requirements for authorized users under Title 10 Code of Federal Regulations (10 CFR) 35.300, "Use of unsealed byproduct material for which a written directive is required."

Docket ID NRC-2018-0230

Dear Commissioners,

I am writing on behalf of United Pharmacy Partners, Inc. (UPPI)[1] to thank you for your commitment to move forward to consider alternative pathways for Training and Experience ("T&E") for radiopharmaceutical therapies.[2]

UPPI sincerely appreciates the time and attention that the Commission has provided to this issue. Finding an alternative pathway to safely increase the ability for patients across the country to have more readily available access to the benefits of radiopharmaceuticals is an important component of the NRC's responsibility in this space, and we are proud and honored to assist.

[1] Established in 1998, UPPI is an alliance of independent commercial radiopharmacies and leading non-profit academic medical center radiopharmacies, which are focused on delivering prepared radiopharmaceuticals for diagnostic molecular imaging and therapeutic patient care needs. UPPI national reach provides daily and on-call radiopharmaceuticals in metropolitan, secondary, tertiary, and rural market places. Every day UPPI member and affiliate pharmacies provide over twenty percent (20%) of unit dose prescriptions for diagnostic imaging and radiotherapy to nuclear medicine physicians, radiologists, nuclear cardiologists and oncologists. The UPPI network includes 73 radiopharmacies and academic radiopharmacies and 10 cyclotrons for the production of Positron Emission Tomography (PET) radiopharmaceuticals.

[2] https://www.federalregister.gov/documents/2019/05/02/2019-08996/draft-approaches-for-addressing-training-and-experience-requirements-for-radiopharmaceuticals

We are pleased to offer our thoughts and concerns about these important issues. UPPI looks forward to working with the Commission to help provide feedback and ideas and ultimately help implement any changes that the Commission seeks to make to the licensing and T&E required for Authorized Users and Authorized Nuclear Pharmacists and any alternative pathways.

The Commission's Notice in the Federal Register (NFR) lays out several questions and potential alternative pathways. UPPI will address these questions below.

Thank you very much for your consideration.

DRAFT APPROACHES FOR COMMENT

A) <u>Status Quo:</u> No changes to current T&E requirements

Question 1: If the "Status Quo" is maintained, how should the NRC ready itself for the expected increase in number and complexity of future radiopharmaceuticals?

UPPI commends the NRC for recognizing that there is indeed "an expected increase in the number and complexity of future radiopharmaceuticals." These advances will not only increase the demand for these treatments, but because of their complexity may require more time and attention from Authorized Users (AUs).

There is strong evidence that a number of alpha and beta radiotherapeutics will successfully receive FDA approval and will enter the market in the near future. For example, the FDA has already approved Lu-177 NETSPOT radiotherapy, which will be an early test of AU coverage, especially for the treatment of candidates from rural areas. The 2019 Society of Nuclear Medicine and Molecular Imaging (SNMMI) meeting, just concluded June 25th, also showcased many presentations, poster exhibits, and new commercial entities focused on new potential radiotherapeutic agents that are and expect to be released to the public.

In addition to these exciting commercial opportunities that will strain the already taxed availability of AUs, there are a significant number of treatments that are still in the research and development stage that are will most likely be approved by the FDA, as potential radiotherapeutics for cancer and related diseases. For example, at the SNMMI meeting, the National Isotopes Development Center, managed by the Department of Energy Isotope program, held isotope specific user group meetings for Ac-225, At-211and Pb-212., . In May 2019, the National Isotope and Development Center, made available to researchers Y-86, a PET imaging agent which can be pared with Y-90 in radiotherapeutics. Copper-67 has recently gained interest and Re-188, from the W-188/Re-188 generator is a promising beta emitter with application in the treatment of non-melanoma cancers of the face.

Beyond Ra-223, Sr-89, Y-90, Lu-177, I-131 and Sm-153, which are already FDA approved radiotherapeutics in certain forms, another cadre of expanded radioisotope candidates for therapy is in development for the future. Also, recent investigations of combined therapies using radio-sensitizing agents and chemotherapies will bring the nuclear medicine/molecular imaging and therapy physicians together with the specialists in medical oncology and hematologic oncology in the campaign of cancer and disease treatment.

As a result, the number of eligible candidates for such therapies will continue to grow, especially in prostate, breast and other cancers and/or therapies such as synovial injection to care for joint inflammation.[3]

Such a growth in radiotherapeutics will require more AUs, straining the already overburdened AU community. If this looming shortage of AUs is not addressed proactively, thousands of patients are at risk to receive less than ideal treatments.

However, as discussed further below, there *already appears to be a shortage of AUs* that is reducing patient availability to potential life-saving treatments.

For example, Ms. Nicki Hilliard Pharm D., MHSA, BCNP, FAPhA Professor of Nuclear Pharmacy, University of Arkansas for Medical Sciences stated:

> *"It is discouraging to see radiopharmaceuticals with documented clinical impact not used because they are not readily available in physician treatment regimens. For example, Zevalin (Ibritumomab tiuxetan) has been approved for first line therapy against Non-Hodgkin's lymphoma, the seventh most common type of cancer. Xofigo (Radium-223 dichloride) was fast-tracked by the FDA after demonstrating an increased patient life span and pain control in prostate cancer patients. However, the regulatory restrictions on access drive oncologists to use less effective chemotherapy regimens associated with significant side effects and diminished patient outcomes.*
> *These current alpha and beta emitting radiopharmaceuticals, and others under development, are delivered to licensed healthcare sites as patient ready doses with no additional manipulations needed before patient administration. The needed training and experience for safe handling of these specific drugs does not appear to warrant the full 200 hours of didactic training and 500 hours handling experience.[4]"(Emphasis added)*

However, because the pipeline for additional AUs to handle the burgeoning use of alpha and beta radiotherapeutics is long and is difficult to adjust without advanced planning, we believe that the Commission is taking the right steps to consider whether there is or is likely to be a shortage of AUs, and if there is how that could be addressed. Therefore, UPPI commends the Commission for engaging in efforts to safely and effectively address this looming shortage before it happens.

While we do not undertake to criticize the ACMUI lightly, we are forced to contrast the foresight that the Commission is engaging on this issue with the "head in the sand" approach taken by the ACMUI in assuming that there are a sufficient number of AUs both now and in the future.

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4967977/

[4] ML16119A158, NRC ADAMS released document, dated 02/09/2016

First, the ACMUI did not seek to conduct any sort of mapping or investigation into the numbers of AUs and locations -metro versus suburban and tertiary areas of the country. Because of this lack of engagement, we agree with ACMUI Chairman Palestro and strongly disagree with the ACMUI's Feb. 26th conclusion[5] that there is an adequate supply of AUs and that no further action to increase the number is required.

In this instance we believe that the ACMUI did not fully exercise their advisory role to the Commission. Specifically, the ACMUI failed to obtain all information necessary to make a factual, informed determination about the number and distribution of AUs and future demand for AUs. Instead, the ACMUI relied on conjecture, anecdotal evidence and incomplete information to support their conclusion, which led Chairman Palestro to dissent from the Report.

Further, even if the number of AUs coming into the system is steady or even increasing, that does not adequately measure the future demand for AU services. Instead, the ACMUI appears to simply assume that if the number of AUs is adequate today then it will be adequate in the future. A number of commentators to this Federal Register Notice make the same false assumption.

As Laura Weil, the Consumer Advocate for the ACMUI suggested, "the raw number of Authorized Users does not necessarily ensure patient access."[6] While the subcommittee Report did acknowledge that "the demand for [therapeutic therapies] will increase," it did not attempt to quantify the rate or level of increase and determine the anticipated number of AUs that will be required to meet that increased demand.[7]

In addition to the concern about the failure to measure the number of AUs that will be necessary in the future, the ACMUI did not engage in any effort to measure the geographic distribution of AUs, and whether the number of AUs is sufficient in all areas. That assumption requires an evaluation of the factors that would prevent patients from traveling to regional centers of care, including treatments that require multiple visits for successive radiotherapeutic treatments, such as Ra-233 dichloride (Xofigo® -the first-in-class alpha therapy used in the prostate cancer treatment armamentarium). Further, the ACMUI did not engage in any attempt to determine if there may be opportunities to alleviate some of the challenges facing rural communities. Instead, as will be discussed further below, the ACMUI members dismissed these rural challenges.

UPPI appreciates that the Commission recognizes that the need for additional access is coming and is proactively seeking to identify ways to address that future need.

In his dissent to the ACMUI's report, Dr. Palestro touched on this question,[8] asking the Subcommittee chair "how did you come to that conclusion… what data did you use? Did you attempt to determine the number of AUs throughout the United States and then look at the number per 100,000 people and determine if that's sufficient or insufficient? Exactly how did you arrive at that conclusion?" Dr. Metter, the Subcommittee Chair, replied that "those are the numbers that we have… there is no objective data regarding your question." Dr. Palestro: "So this was sort of I guess an intuitive approach or an intuitive conclusion? What are the trends over time if we look at the specialties? Have the number of individuals being certified, are they

[5] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf
[6] https://www.nrc.gov/docs/ML1808/ML18082A687.pdf, P. 68
[7] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf, P. 20

[8] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf, P. 49

increasing or decreasing?... Did you do any sort of calculations… to see whether or not the number of new graduates or newly certified individuals are compensating for retirees?" [9]

Dr. Metter's response demonstrates the "rush to judgement" that the ACMUI engaged in on reaching its conclusion that there is no shortage of AUs: "*It would be my desire to have that [data]available… But at this point in time, the data is not available… [Y]our data is something we need to look at."*[10] In other words, while that data may be forthcoming, the ACMUI did not wait on it in order to make a determination, even though the Subcommittee Chair indicated that it would be helpful.

In other words, maintaining the status quo will result in reduced patient care and access to radiopharmaceutical therapeutic treatment. The limited number of existing AUs, not accounting for those that enter commercial entities and leave the patient care arena or retire, is already straining patient care, resulting in reduced access to care. Failing to address this challenge as we see a coming increased demand for AUs will exacerbate this problem.

Should the training and education for AU, the 700 hours, remain as status quo? We believe the growth of radiotherapeutic radioisotopes therapies will necessitate a revision to the AU to allow a limited-trained AU and/or the emphasize a radiotherapeutic team to provide quality patient care.

A citation from the 2007 The National Academies of Sciences, Engineering and Medicine, The National Academies Press entitled: Advancing Nuclear Medicine Through Innovation stated:

"The training of physicians involved in research and the clinical practice of nuclear medicine will require substantial changes with the evolution of the field. One broad division within nuclear medicine can be found between nuclear medicine physicians who are predominantly involved in diagnostic imaging and those involved in targeted radionuclide therapy."[11]

It was recognized then that AU training and education ought to evolve with the field as targeted radionuclide therapy moves to the development, clinical trials and approvals of new products and applications.

Question 2: Is there a challenge with the current T&E requirements – such as concerns regarding patient access to radiopharmaceuticals – that should be addressed through a rulemaking?

a) There are indications that the distribution of AUs has created a geographic shortage in rural areas.

Regardless of future demand for radiopharmaceuticals, there appears to already be a shortage of Authorized Users in rural areas that is adversely impacting patient access to radiopharmaceuticals.

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[9] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf, p 50-52

[10] Transcript, P. 52-53

[11] Advancing Nuclear Medicine Through Innovation (2007). The National Academies Press, Committee on the State of the Science of Nuclear Medicine, Washington DC. 500 Fifth Street, N.W., Washington DC. 20001, page 125.

For example, as discussed in the National Rural Healthcare Association (NRHA) comment, rural access to these treatments is severely limited.[12]

> "These concerns were echoed in the ACMUI's discussion of whether there are "enough" AUs. Ms. Laura Weil, the Consumer Advocate of the ACMUI, stated that "[W]hile the Subcommittee's research found no evidence of shortage of Authorized Users, I think it would be a mistake to state that we found that there was demonstrable adequate numbers of Authorized Users in all healthcare settings and in all areas of the United States. We saw no evidence that there is shortage, *but we can't say affirmatively that there are enough Authorized Users in all places… The geographic distribution of those Authorized Users has to be taken into account…* when we try to make the argument that there's no need to look for an alternate pathway because there are plenty of Authorized Users already available, we have to be careful how we use the word 'available' because, then, it's a fallacy to say that every patient in the United States has access to an Authorized User, where there might be another way." CITE (Emphasis added)

b) Various research is being conducted to help ascertain whether there is such a rural disparity and if so how severe it is.

According to the ACMUI subcommittee discussion, various parties are working on seeking to ascertain whether there is a geographic shortage. The NRC staff has indicated that they are in the process of examining AU licenses to determine the geographic distribution of AUs,[13] which Dr. Martin, ACMUI Committee member, asserted during the ACMUI's discussion: "I know the NRC is working on collecting the data for where the authorized users are located."[14] While it is our understanding that that information will not provide the level of detail necessary to draw any firm conclusions, that data is available should give the Commission a better idea about the geographic distribution of AUs.

Dr. Ennis, another a member of the ACMUI, stated that "ASTRO is actually putting together a heat map of distribution [of AUs] across the country."[15] While UPPI does not have any independent knowledge of whether such an investigation is actually taking place and what the timing may be for the release of such data, this information would be very useful to the NRC in determining what the distribution of AUs is across the country and whether it is adequate.

In other words, rather than force a decision based on incomplete information, we believe that the NRC would have been better served if the ACMUI had followed the lead of Chairman Palestro and put off a final recommendation until they had more information available.

c) The Commission should undertake to raise the number of AUs regardless of future demand or a geographic disparity

Regardless of whether or not there is a current or future shortage of AUs, the NRC should seek to increase the number of AUs if it is feasible to do so in a way that is cost effective, ensures radiation safety for the administration of the radiopharmaceutical and protects patients and the environment. There are no reasons to artificially limit the number of AUs or to avoid creating an

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[12] https://www.nrc.gov/docs/ML1835/ML18354A678.pdf

[13] Nuclear Regulatory Commission Public Comment period.

[14] https://www.nrc.gov/docs/ML1835/ML18354A678.pdf

[15] Feb. 26th Transcript of ACMUI meeting, P. 55.

alternative pathway, such as a limited-trained AU or team, to expand future access and increase availability if it can be done in a manner to provide quality patient care and to ensure radiation safety and its inherent safety to the occupational exposed worker, the patient, the public and the environment.

Specifically, as ACMUI Consumer Advocate Weil pointed out, "[I]f there's an alternate pathway, there might be a way to have people in the community who are perfectly competent and well trained and able to offer those services to people in different geographic locations." "The primary role of regulation is to ensure safety. And it's true that the -- that regulation can limit access to some people who can't travel for care, and that is a legitimate barrier. However, it's not a question of whether those barriers exist. It's more a question of whether the regulatory standards that create those barriers are unnecessarily restrictive, out of current practice or ethically responsible -- or nor is it the role of the regulator to attempt to increase access by compromising necessary safeguards that protect patients, their families, health care providers, and the public." [16]

In other words, the question should not be whether there are "enough" AUs, but whether there is a way for the NRC to safely increase the number of AUs. If there is a way to do so, the NRC should attempt to do so.

Question 3: How should the complexity of the radiopharmaceutical administration protocol be considered in establishing the T&E requirements for limited approaches described in Sections B.1 and B.2 below?

The complexity should be taken into consideration, and considerations on to implement training and other requirements should be developed by stakeholders using today's existing and emerging standards. For example, the UPPI proposal suggests that only alpha and beta emitters should be included in the ANP teaming approach[17] to ensure that the type of training and specialization that should be implemented is appropriate.

UPPI further suggests that emergent alpha and beta therapies will have to be considered individually for radiation safety, radiation exposure and patient care purposes. Further, training should account for different uses and treatments. For example, the training required for an administration of a radiotherapy for pain palliation (i.e. Metastron™, Quadramet® or Xofigo® or Iodine-131) for hyperthyroid therapy, may be different than the requirements for the administration of the same radiopharmaceutical administered for a residual cancer therapy.

One example of how this training could be developed and implemented has been demonstrated by the approval process developed for the NorthStar RadioGenix™ System, a non-HEU Mo-99/Tc-99m generator system. This system introduced complexities for the elution of the most commonly used diagnostic imaging radiopharmaceutical, Tc-99m, and specific AU requirements

[16] https://www.nrc.gov/docs/ML1835/ML18354A678.pdf
[17] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf

were put in place to ensure safety handling and the appropriate radiation safety requirements.[18,19,20]

Breaking training into different requirements based on the complexity of the treatment and the risk is not at all unprecedented. For example, as the Council on Radionuclides and Radiopharmaceuticals (CORAR) pointed out in their January 24, 2019 submission to the NRC:

> "[A]n important point from the 2002 final rule in the fact that the NRC retained in its regulations a pathway under which, with 80 hours of training and experience, a 'limited authorization' could be achieved for the oral administration of Iodine-131 (cites omitted). The NRC noted the impeccable safety record of the product, the low risk of therapeutic misadministration, and the burden placed on patients who might have to travel long distances… In addition, NRC noted that and additional hours would be inconsistent with NRC Medical Policy to minimize intrusion into medical hours since additional hours were not justified by radiation risk."

The NRC has a history of designing different standards for different types of risk. For example, the administration of a manufacturer or nuclear pharmacy prepared dose may have relatively low risk compared to the administration of an ablation therapy, which could use high levels of radiation and could present risk to the administrator, patient and others in the area.

That is not to say, however, that a 700-hour trained Authorized User/ANP should not be present at the time the dose is administered. In fact, UPPI's proposal suggests that a 700 hour trained Authorized Nuclear Pharmacist (ANP), with the requisite levels of radiation and patient safety training should be present at the time the dose is administered, regardless of the relative risk of the therapy.

Why not? The ANP is trained for and involved in many aspects of the receipt and dispensing on prescription of radiopharmaceuticals for therapy, including:

- recording the radioactivity;
- participated in the development of measurements of alpha and beta radionuclides;
- retrieved the allowable waste to be returned to the nuclear pharmacy;
- performed the radiation surveys and wipe tests for detection of contamination;
- made appropriate actions for any measurements outside of allowable limits;
- worked within the guidance of ALARA
- dispensing under the FDA approved package insert with an understanding of: product description, physical characteristics, clinical pharmacology, indication(s) and uses, contraindications, adverse reactions, warnings, precautions including information regarding carcinogenesis, mutagenesis and impairment of fertility, dosage and administration, radiation dosimetry, receipt criteria and disposal.

In other words, UPPI believes it is possible to distinguish between the complexity and safety of various procedures, and the T&E requirements could be tailored to reflect that.

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[18] ML16305A409, NRC ADAMS released document dated 11/1/2016

[19] ML17293A249, NRC ADAMS released document dated 9/8/2016

[20] ML17338A449, NRC ADAMS released document dated 2/28/2018 entitled: NorthStar Medical Isotopes LLC., RadioGenix™ Molybdenum-99/Technetium-99m Generator System Licensing Guidance for Medical Use Licensees, Medical Use Permittees and Commercial Nuclear Pharmacies

The ACMUI has raised concerns that "it would be too cumbersome to develop and provide oversight for specific training and experience requirements within the regulations to fit each radionuclide therapy."[21]

However, each therapy contains a package insert that provides safety and handling instructions *that are specific to that therapy*, and radiation safety guidance can be developed and written, as shown for the RadioGenix System described above.

1. Limited AU for Alpha- or Beta- Emitting Radiopharmaceuticals

- "[A]ny physician could complete at least 400 hours of T&E to be authorized to administer any alpha- or beta- emitting radiopharmaceutical."

While CORAR has suggested that in certain instances the 700 hour T&E requirements are "excessive,"[22] UPPI has suggested that at least one person with the full 700 hours of training should be present when these doses are administered to fulfill the radiation safety aspects of the use of the product. As discussed further below, UPPI does not believe that that person needs to be a 700 hour-trained AU, but that requirement could also be satisfied by an Authorized Nuclear Pharmacist with at least 700 hours of T&E -who could be an Authorized Individual in the medical setting. For further clarification, ANPs are available to come on-site where a radiotherapy would be appropriately licensed for the radioactive materials and use. The ANP as an Authorized Individual could work with the physician having 400 hours training for the express purpose of conducting the appropriate radiation safety monitoring as required and to take the necessary corrective actions. The guidance for all radiation safety activities on-site by the Authorized Individual would be under the direction of a Radiation Safety Officer (RSO), such as a medical physicist, who would be accessible. The ANP would not be the RSO at the licensed medical site.

We also recognize that nuclear medicine technologists work-with patients for imaging and radiotherapeutics and play an important role. But the fact remains that AUs and Radiation Safety Officers (RSO) are still to be present or accessible in the conduction of patient imaging and therapeutic dosing in order to assure quality patient care and safety to the public.

Even though the ANP can be a RSO at a nuclear pharmacy, that individual would be an Authorized Individual, but cannot be the RSO at the licensed site of administration. However, based on the training and experience (700 hours), the ANP can perform radiation safety surveys, contamination wipes and other radiation related functions. The radiopharmaceutical handling experience of the ANP would complement the training and experience of the 400 hours trained physician, and they would work in consultation with the RSO in matters of radiation safety.

While specific training would have to be established, there are several industry examples to pull from. For example, Nicki Hilliard Pharm D., MHSA, BCNP, FAPhA Professor of Nuclear Pharmacy, University of Arkansas for Medical Sciences, et.al. submitted an outline for an 80-hour didactic training for medical oncologists and urologists "in basics of radioactive materials handling suitable to alpha/beta emitting products to which access will be granted" regarding

[21] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf, P. 22.
[22] CORAR comment to NRC.

NRC Training and Experience Requirements for Alpha and Beta Emitters to potentially handle Zevalin (Y-90 Ibritumomab tiuexetan).[23]

UPPI believes that Authorized User training and experience criteria should be developed for any or all categories under consideration: Limited AU for Alpha and Beta Radiopharmaceuticals, Limited AU for Unit Dose, Patient-Ready Radiopharmaceuticals, Limited AU for Any One Parenteral Radiopharmaceutical, Team Approaches and an ANP as an Authorized Individual under the advisement of an RSO.

As an example, and with the full understanding that Y-90 microspheres are classified as a brachytherapy and medical device, and not a therapeutic radiopharmaceutical, NRC guidances are in place to govern its use, and could be a model for the type of training that UPPI envisions. This training may be revised and includes: training and experience pathway for AU; License Commitments which includes Written Directives, Inventory, Patient Release, Labeling and Adverse Event Reporting; addresses Team Approach; Notification for AUs; Radiation Safety Programs including Waste Disposal.[24]

UPPI believes similar protocols can be put in place and vetted for new categories of limited-trained AUs and teams.

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Question 4: How should the NRC categorize radiopharmaceuticals with mixed emissions

UPPI suggests the NRC separately review each radiotherapeutic radiopharmaceutical as mixed emissions (beta and gamma), as long-lived decay products can have an effect on the handling, waste decay, radiation safety handling and patient release criteria.

2. **Limited AU for Unit-Dose, Patient-Ready Radiopharmaceuticals**
    - "Any physician could complete at least 400 hours of T&E to be authorized to administer any patient-ready dose."

Similarly, UPPI believes that having a physician with limited 400 hours of training should be required to "team" with an ANP that has completed the full 700 hours of training, and have access to a RSO, such as a medical physicist as explained under #1.

Question 5: Under what conditions should a radiopharmaceutical be considered "patient ready" such that the T&E requirements could be tailored?

Patient-ready radiopharmaceuticals would be classified as unit dose or single use vial. The T&E requirements should be tailored based on the risk posed by the nuclide and whether the treatment is an alpha- or beta, not whether it is "patient-ready."

3. Limited AU for Any One Parenteral Radiopharmaceutical

[23] ML16119A158, NRC ADAMS released document, dated 02/09/2016

[24] ML082450268, NRC ADAMS released document, dated 09/10/2008 entitled: Microsphere Brachytherapy Sources and Devices.

While UPPI believes that this approach could be better for patients in that it would require specific training for each type of therapy that a limited-trained physician would administer, we still believe that having a physician with limited 400 hours of training should be required to "team" with an AU and/or ANP that has completed the full 700 hours of training.

4. Emerging Radiopharmaceuticals

- NRC would conduct an assessment of each new emerging radiopharmaceutical to determine the T&E required.

UPPI believes that such a specific investigation or training is necessary for each new radiopharmaceutical. Such a requirement would not appreciably delay treatment for patients.

C. Performance Based

1. Competency-Based Evaluation

- Remove the 700 hour requirement and instead focus on performance-based metrics.

Performance-based metrics would be appropriate for any level of hours training of an AU such as the limited-trained AU or the 700 hour AU.

Question 6: How could a competency-based evaluation ensure appropriate training and experience for AUs administering radiopharmaceuticals?

Competency-based evaluation provides a means for peer review and updating the evaluations to be more contemporaneous to current practices and new entrants to alpha and beta radiotherapeutics.

2. Credentialing of Authorized Users

This is an intriguing idea, though UPPI urges the NRC to include Authorized Nuclear Pharmacists in this consideration.

Speaking solely for UPPI members and not for physicians or nuclear pharmacists that are not part of UPPI, UPPI believes that we could work with the Purdue Pharmacy school and other appropriate disinterested third parties to develop and apply a credentialing standard that ensured a high level of competency for UPPI members for radiotherapeutic applications.

Question 7: How could physicians in small practices be credentialed (e.g. physicians not associated with hospitals of other large institutions and their credentialing board.

UPPI believes that this potential concern could be addressed by making such credentialing mandatory (for example, an AU or limited-trained AU cannot renew their license without credentialing.), essentially a Continuing Education program.

Team-Based Approaches

UPPI agrees that team-based approaches could increase the availability of treatments for patients in a way that insures safety and training. For example, the ANP/limited trained AU proposal

drafted by UPPI was called "novel," "well-intentioned" and "worthy of consideration," by the ACMUI[25].

The Federal Register Notice has suggested that the team approach could have the following potential benefits:

- "Team-based approaches could remove prescriptive T&E requirements for AUs…"

  UPPI agrees with this and believes that ultimately it is the only pathway that ensures patient safety and expands availability of AUs in sufficient numbers to ensure that patients have availability of these treatments.

  UPPI agrees that the teaming approach could create an alternative pathway for limited-trained AUs who would not have to complete the full 700 T&E to ensure patient and radiation safety. However, we also believe that when these therapies are administered an ANP or Authorized Individual with 700 hours of T&E should be present for radiation safety purposes.

- "focus training requirements on the competency of the entire team…"

  While different proposed teaming approaches could enable different team training, UPPI believes that in our proposal each team member has specific responsibilities, and that the training of each individual to do his or her job to the best of their ability is what makes this program work. Further, focusing on the "entire team" implies that the "team" will work together multiple times.

- "or revise the current 700 hour T&E requirement for AUs based on pairing the AU with another individual with expertise in administering radiopharmaceuticals."

  UPPI agrees that the ANP/limited trained AU teaming approach that we have proposed would enable a physician to reduce their T&E, enabling them to spend more time with patients and less time in a class-room, without sacrificing safety.

  UPPI believes that another advantage of the teaming approach is that it would dramatically expand access for patients, particularly in rural areas by enabling the ANP/limited trained AU *to come to them*, as opposed to forcing rural patients to travel significant distances for their treatment.

  Question 8: How should the AU's radiation safety responsibilities be clearly distinguished from other members of the team?

  UPPI believes that a RSO should be accessible when these therapies are administered. However, because many ANPs are also RSOs at the nuclear pharmacy, we believe that a RSOs, such as a medical physicist, should be accessible and should be distinguished from other members of the team with explicit responsibilities to the licensed site.

  We have read reportable evidence where a person assigned the responsibility for a radiotherapeutic injection by an AU and RSO had not adhered to policies, procedures and practices when neither the AU and RSO was not in the building. If accurate, we believe that such activity should be remedied as soon as possible. Any alternative pathways should have an RSO

[25] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf

accessible to play a very important role in protecting the occupationally exposed individual, the patient and public.

1. **Radiopharmaceutical Team:** A team-based approach that utilizes a "AU, a radiation safety officer and a nuclear medicine technologist," and other specialists could join the team, as well.

   UPPI does not have an objection to this basic plan but does not believe that this will increase the availability of these services since a 700-hour-trained AU would still be required to participate in this process.

   In other words, this does not appear to address the status quo question that was raised earlier.

2. **Team AUs with Authorized Administrators:** "[B]oth an AU and an authorized administrator (AA) [would be required] to administer radiopharmaceuticals"

   UPPI has several concerns about this proposal.

   First, like the example above, this proposal does not alleviate the challenge of having too few AUs in too few places. However, this proposal has potential if the ANP in a team could be the AA. Like that offered by UPPI, the proposal needs clarification.

   While many new and existing therapies are complex and will require additional training, we have not seen any evidence that the current requirements and reliance on manufacturer training and the package insert has led to or is likely to lead to any problems in administering the therapeutic radiopharmaceutical.

   However, if the NRC has information related to the complexity of *particular* radiopharmaceuticals, perhaps the NRC could reserve the right to impose this requirement on radiopharmaceuticals that are deemed to be very difficult to administer, or very high dose and/or where there is concern for different types of radiation safety actions or training. As mentioned before the RadioGenix System required new guidance on training and qualification before operation and continued inspection of the training compliances.

   In other words, while it is very important to ensure that at least one member of the team is trained in administering particular radiopharmaceuticals, particularly if they are challenging, that can be accomplished in other, less time consuming and complex ways.

3. **Partner Limited-Trained AUs with Authorized Nuclear Pharmacists**

   The ACMUI called this proposal a "novel" approach that is "well intended" and "should be carefully considered."[26]

   This concept has the benefit that it advances patient safety and treatment availability. There may be some down-sides to this approach, but we do not think that the ACMUI draft report's objections and concerns are sufficient to derail this opportunity because they did not raise any insurmountable concerns or objections.

[26] Transcript, Page 23, Dr. Darlene Metter, Chair of the Subcommittee for Training and Experience for All Modalities.

This approach has several benefits, including:

- Physician AUs and Authorized Nuclear Pharmacists receive the same 700 hours of T&E in radiation safety, exposure control, etc., and so from an NRC perspective that focuses on radiation safety, the ANP is practically indistinguishable from the physician AU in the aspects of receipt, preparation, dose calibration, dispensing, radiation monitoring and radioactive waste disposal;
- ANPs likely have *more* experience handling radiopharmaceutical on a day-to-day basis than physician AUs: ANPs operate the Mo-99/Tc-99m generators that produce the nuclides that form the labeled radiopharmaceuticals, and they mix the nuclides with manufacture-provided cold kits to create an individual patient-based dose. They handle these radiopharmaceuticals hundreds of times a week.
- Generally, a radiopharmacist combines the radionuclides and cold-kits in one central location and ships the radiopharmaceuticals to locations generally within 2-4 hours away. This means that the nuclear pharmacy has a broader footprint and can provide therapeutic doses outside of a central location, unlike most AUs, who operate in a central location (i.e. hospital nuclear medicine department).
- Providing a limited-training pathway for physicians will likely lead to additional physicians taking advantage of this opportunity, expanding the availability of these treatments not only in terms of geography, but also creating a bigger pipeline of incoming limited AUs.
- The physician would be the person administering the radiopharmaceutical, but the limited trained physician would have less training than a 700 hour trained AU.

Further, with a strict training and preceptor attestation requirements, the NRC could be confident that the limited trained physician has the necessary training and skill to administer the radiopharmaceutical.

Because this alternative offers a shorter pathway to becoming licensed to administer radiopharmaceuticals, more physicians would presumably undertake this opportunity to become a limited-trained AU. This, in turn, would not only help alleviate the shortage in AUs that additional procedures in the pipeline will create, but would also help to alleviate the rural shortages that currently exist with regards to AUs.

Therefore, this model not only creates more limited trained AUs that could operate in rural and other settings, and the ANP could *deliver the radiopharmaceutical* to the licensed location, the ANP could be *physically present while the radiopharmaceutical is administered to address the radiation safety.*

We applaud the NRC for including this proposal in the list of ideas being considered as ways to increase the reach of radiopharmaceutical treatments without sacrificing the 700 hour training requirements.

As the NRC continues to develop how this proposal could work, including what type of training would be required and how it would be administered, and what type of licensing and attestation may be required, we look forward to working with you to help develop and refine this proposal.

In the meantime, however, we would also like to take this opportunity to address the concerns about this proposal that were raised by the ACMUI at its Feb. 26th Meeting.

Specifically, while suggesting that this proposal merited consideration, ACMUI members offered criticisms of the UPPI ANP/limited-trained AU proposal.

Therefore, UPPI would like to take this opportunity to address the questions and concerns that were raised about this proposal at the ACMUI's Feb. 26th, meeting based upon the comments in the transcript of that meeting.[27] Specifically, UPPI has laid out these concerns and objections raised at the ACMUI meeting on Feb. 26th below, and has provided responses to these concerns.

Many of these responses to ACMUI concerns were provided to the ACMUI and NRC in a submission to the ACMUI for their Feb. 26th meeting, but these do not appear to have been reviewed by the ACMUI.

There are several themes that run through the concerns raised by ACMUI members in their discussion of the UPPI proposal:

a) What type of training would or should be required

Some members of the ACMUI appear to have the expectation that he UPPI proposal would be fully formed and comprehensive, as opposed to the outline that we suggested to the NRC. As discussed further below, UPPI has the expectation that the medical community and the NRC would continue to refine this idea and would jointly develop the types of requirements that a limited trained AU would need to satisfy.

Dr. Palestro summarized UPPI's expectation well: "If and when a limited AU program is developed, to develop and create a curriculum, if you will, with all of the competencies that need to be met, and then after that go back and determine the hours [and training] that would be required to complete it."[28]

b) Only an AU with "comprehensive" knowledge of the entire procedure should be able to play this role

UPPI believes that the comprehensive 700 hours of T&E that the ANP receives, which is practically the same as the training that an AU receives with regards to radiation safety requirements, positions the ANP to serve this role. Additional standards and delineation of roles may be required, but that does not undermine the opportunity for this proposal to succeed.

c) 'There are enough AUs" and no need for more ANPs

As discussed elsewhere, there has been no demonstration that there is an adequate number of AUs or that there will be a sufficient number in the future, and even if there is, that is not a reason to restrict that number from growing as long as the team approach meets the safety requirements and care requirements for the patient.

<u>Responding to ACMUI Concerns</u>

Because it was the only specific alternative pathway that had been presented prior to the ACMUI meeting on Feb. 26th, this "novel" proposal became the center of a lot of attention from ACMUI members, including the Subcommittee.

[27] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf
[28] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf P.44

This provides UPPI with a significant number of thoughts about the proposal and enables us to respond to those concerns to ensure that the NRC can fully evaluate the viability of this proposal and whether the concerns that have been raised about it are justified.

Therefore, as you can see from the discussion that follows, we have attempted to collect and respond to all of the concerns and objections that have been raised by ACMUI members during their discussion of this issue.[29] While we hope to address any additional comments and concerns that are raised in this NFR process, we believe that the ACMUI concerns demonstrate a strong sample of the types of objections that may be raised to this proposal. We believe that all of them can be adequately addressed.

Finally, we believe that many of the concerns that were raised by ACMUI critics of the UPPI outline are actually included in the UPPI proposal. This is an indication to us that had the ACMUI members actually studied the proposal, they might have supported it. We hope that highlighting those areas of agreement will force those critics to reconsider their opposition to this proposal.

1) This approach could "have the unintended consequence of making things worse."

Response:

The ACMUI Subcommittee report cites to an American Psychological Association (APA) website for "The Standards for Educational and Psychological Testing," https://www.apa.org/science/programs/testing/standards , as the sole basis for the claim that there could be unintended consequences that could "make things worse." While we assume that this is the incorrect cite, neither the subcommittee nor the full ACMUI bothered to clarify or correct the citation even when UPPI highlighted it in our submission to the ACMUI that was included in the Committee Report.

Disregarding the incorrect citation, however, still does not yield a valid complaint or concern about this approach. Specifically, simply asserting that there may be unintended consequences without any discussion of what those may be, how they might be caused or corrected, and how significant they may be does not rise to the level of a realistic criticism.

Instead, UPPI would argue that if there are indeed any potential adverse consequences, which have not been alleged, those potential problems should be specifically spelled out so that they can be considered and addressed. Otherwise, simply suggesting that there are problems without articulating them gives the Commission no opportunity to seek to minimize or address them.

In other areas, the NRC and the ACMUI routinely monitor any challenges or problems that arise as 'medical events'and seek to develop ways to address those concerns and determine if changes are necessary to refine the program. Such recommendations and action items are reported in the

[29] These are taken in chronological order from the transcript of the Feb. 26th ACMUI meeting. If there are any concerns that we missed or failed to adequately respond to, UPPI would appreciate the opportunity to do so to ensure that the Commission has a full understanding of all of challenges this proposal could pose, and so that the Commission has a "roadmap" to minimizing these risks should the NRC move in this direction.

Advisory Committee on the Medical Use of Isotopes Recommendation and Action Chart for a given year.[30]

While any specific concerns can be addressed as the program is developed, the NRC and ACMUI will continue to monitor and tweak the program to address any additional problems that may arise, just as they do in other settings.

2) "Radionuclide therapy possess the highest risk and highest impact of all nuclear medicine procedures. And if doses are not properly handled or administered, these therapies can cause unintentional, serious organ or tissue injury. The newer therapeutic radionuclides have become increasingly more complex administrations. And with the potential for multi-organ or tissue toxicities, and, hence, this requires a basic competency in radiation therapy and radiation safety."[31]

Response:

This statement does not appear to raise a substantive or specific concern or objection, but UPPI agrees that there are risks, and hence we support having an ANP with 700 hours of training team with a limited trained AU with at least 400 hours of training. Likewise, the ANP is very likely the person that has taken receipt, prepared and dispensed the radiotherapeutic since most licensed facilities do not have hot labs and many that do are not designed for newly revised USP Chapter <795> Sterility and the new to be released December 2019 USP Chapter <825> Radiopharmaceuticals. Radiopharmacies have been operational under USP Chapter <797> and are adopting USP Chapter <825>.

Further, while we agree that new therapies may be more complex, as discussed above, with additional training, vetted protocols, SOPs and carefully following package inserts, those risks can be minimized.

In other words, let's do what we can to address the risk, rather than be paralyzed into inaction by the risk.

3) "A potential limited scope AU pathway for radionuclide therapy must ensure that the basic knowledge topics in 10 CFR 35.390 are obtained thereby obtaining an equivalent level of therapeutic competency and competency in radiation safety."[32]

Response:

UPPI agrees that at least one team member should have the requisite 700 hours of T&E, including radiation safety training, and the physician should demonstrate therapeutic competency as demonstrated by their 400+ hours of T&E.

It should be noted that a Limited AU designation does not mean that all medical oncologists and all hematology oncologists would seek the approval. UPPI has not proposed that such a program should blanket potential candidates. However, UPPI believes there is expertise in medical oncology and hematologic oncology, physicians with immense experience in treating cancer

[30] ML18099A351, NRC ADAMS released document dated -4/09/2018

[31] Transcript, p. 20

[32] Transcript, P. 20-21

patients, including understanding the cancer process in non-radiological treatments, that can be specifically licensed as a Limited AU

4) "[T]he subcommittee does not recommend a limited scope AU pathway for radionuclide therapy requiring a written directive [because] the emerging radionuclide therapies have multiple contraindications and more toxicities…"[33]

   Response:

   UPPI fails to see how the ACMUI makes the leap from saying that these therapies require extensive training to saying that someone with the requisite training (e.g. a Limited trained AU) should not be able to administer these products. Further, the ACMUI's assertion that these therapies are complex could be addressed by additional training and following the specific guidances.

5) "[A] novel team approach was proposed where an onsite authorized nuclear pharmacist, or ANP, who had prepared the radionuclide for therapy and handled the radiation safety components, while the limited scope authorized user would administer the patient-ready dose and manage patient care…The perceived benefits of a [well intended] AU partnership should be carefully reviewed."[34]

   Response:

   UPPI appreciates the acknowledgement by the ACMUI that our proposal is "novel" and "well intended," and appreciate the NRC including this proposal in the Federal Register Notice so that the aspects, benefits and risks associated with this approach can be carefully and fully reviewed, and any potential shortcomings can be addressed.

6) "A fragmented approach to a therapeutic procedure can have the unintended consequence of making things worse."

   Response:

   While we agree that there may be unintended consequences, simply stating a conclusion with no citations or discussion of what those may be and if there are ways to better anticipate them and minimize any potential unintended consequences, is not the "careful review" that the ACMUI suggests that this proposal needs and deserves.

   Further, UPPI does not believe that a "fragmented approach," where each member of the team plays a different role as part of the whole team, necessarily raises any risks at all. All physicians work with other doctors and other providers who have different specialties, including in emergency room operations and other high-pressure situations where everyone has their job to do. Therefore, the burden should be on the ACMUI and others who have concerns about this teaming approach to come forward to describe how a teaming approach could be harmful. Simply stating that it could be is not a sufficient argument.

[33] P. 21-22

[34] https://www.nrc.gov/docs/ML1906/ML19067A254.pdf, emphasis added.

7) "[I]f an onsite ANP or authorized nuclear pharmacist is available, a fully trained authorized user is also likely available for the entire radionuclide therapies, which are generally not on an emergent [sic] basis."

Response:

There are several problems with this statement.

First, an ANP receives the same 700 hours of T&E as a "fully trained authorized user." So in effect, a "fully trained authorized user" would be available in either case, only one would be an Authorized Nuclear Pharmacist and one would be an Authorized User. UPPI intended that the ANP would handle the aspects of radiation safety, and have access to a medical RSO for guidance, and the Limited trained AU would be responsible for the radiotherapeutic product administration and patient care.

Second, even if that is the case, whether other AUs may be available is not relevant to this inquiry. The Federal Register Notice seeks to determine "how should the NRC ready itself for the expected increase in number and complexity of future radiopharmaceuticals?" Relying on the current crop of AUs does not increase the number of and pipeline for additional AUs, while this proposal would *increase the number of AUs/ANPs available* to provide therapies to patients. The fact that they may be geographically located close to each other is not a relevant consideration.

Third, this response demonstrates a fundamental misunderstanding of the UPPI proposal and how UPPI members and ANPs operate. While some larger hospitals may have their own ANPs and facilities on site, for the most part ANPs operate in a central location and deliver radiopharmaceuticals to off-site locations. For example, one of UPPI's members operates a central nuclear pharmacy in Tampa, Florida, and delivers radiopharmaceutical up and down the Florida coast, from Tallahassee to Fort Myers. Other radiopharmacies in Tampa cover similar distances. This means that every hospital and imaging center, or new licensed sites could have access to radiopharmaceutical if there is a partially trained AU available. We have seen where ANPs are available and would be willing to travel to licensed sites on a regular, scheduled basis to assist in a local team for dose administration.

In other words, the ACMUI does not only fail to present *any* evidence to support this claim, but their failure to investigate even the basic operation of the ANP system renders much of their criticism suspect.

This objection also implies that there is no need to change the rules because a physician could handle the cases and an ANP is not necessary. That ignores the fact that a physician can only handle a limited number of cases at one time, so even if true, the UPPI proposal would still expand treatment opportunities for patients.

This statement also implies that a physician AU would be better able to provide services to the patient than the "teaming" approach suggested by UPPI, by implying that if both an AU and ANP are available, the AU would be preferable. Not only is this not necessarily true, but there is no evidence to support this claim. Further, it also ignores evidence that patients often choose physician extenders to provide services even when a fully trained physician is available.

8) "There are also far fewer ANPs than AUs."

Response:

While it is unclear if this assertion is true or not, even if it is accurate, this does not make the case for why this proposal should not move forward. If part of the NRC's goal is to consider how to expand access to these services without sacrificing safety, this proposal satisfies that need, even if there were only a handful of ANPs. However, there are approximately 1200 ANPs, and so enabling them to provide these services in a team with a Limited trained AU would significantly increase patient access.

9) "[AU]s are generally concentrated… in urban and not rural areas."

Response:

The anecdotal evidence that has been amassed, including the statement from the National Rural Healthcare Association (NRHA), and the statement from Congressman Joseph Heck, [ADAMS Cite] supports this assertion.

10) "[A]uthorized nuclear pharmacists are generally concentrated… in urban and not-rural areas."

As discussed above, this assertion demonstrates a fundamental misunderstanding of how ANPs practice and how this proposal would work, and therefore fundamentally undermines the critique of this proposal by the ACMUI, since they do not even appear to have taken the time to understand it.

Further, as discussed elsewhere, over-lap of ANPs and AUs is not a problem with this proposal but will help make additional therapies available to rural and urban patients.

11) "The safe and effective administration of radionuclide therapy is best accomplished by a comprehensively trained *physician* who is responsible for the entire therapeutic procedure and who has thorough knowledge and understanding of the therapy, to include the various factors and potential toxicities and serious hazards that can occur to the patient, the personnel, and the public."[35]

As discussed above, the UPPI proposal would have the therapy administered by a 400-hour trained *physician.*

Second, both the AU and the ANP have had the same 700 hours of T&E with regards to the safe handling of radiopharmaceuticals. In fact, the ANP likely has had more experience with nuclides and radiopharmaceuticals than the physician has.

Further, modern medicine is defined by specialties and teams of doctors, nurses and other providers who all work together to achieve a common goal of caring for the patient. This is not a unique situation in medicine.

Let's unpack this statement:

• "A comprehensively trained AU"

An AU under 35.59 receives the same training and requirements as a Authorized Nuclear Pharmacist under 35.55(a) – the same 700 hours of training in the same issues. UPPI is not suggesting that the ACMUI consider reducing those vigorous standards.

[35] P. 23-24

• "who is responsible for the entire therapeutic procedure"

UPPI is not suggesting that the ANP perform the specific procedure – that would be performed by the accompanying limited trained AU physician who would administer the entire therapeutic procedure to the patient.

• "who has thorough knowledge and understanding of the therapy to include the various factors and potential toxicities and serious hazards that can occur to the patient, personnel and the public."

The limited trained AU physician would have detailed knowledge and understanding of the therapy, including the possible problems and side effects that may arise. The ANP would provide the overall understanding of the larger risks that could occur. While the ACMUI implies that sharing this responsibility is somehow risky, there has clearly been no investigation of this question, which is what we are seeking by raising this issue. Simply stating that there are risks without undertaking even an elementary exploration or explanation of what those risks are, how they might be addressed or minimized, and whether the potential risks outweigh the benefits strikes us as an arbitrary decision that does not meet the requirements of the NRC in assessing the use of radiotherapies. Any therapy could be called high risk. We think some therapies do not carry the same risk and could be handled by limited trained AU.

12) "[T]he higher likelihood that the infrequent performance for radionuclide therapy in rural areas would make it difficult for physicians to retain basic AU competency in radionuclide therapy."[36]

Response:

As discussed above, ANPs handle hundreds of radiopharmaceuticals every week, and likely have more experience with them than AUs. This is more of an argument for continued competency evaluations rather than an argument against having a ANP and limited trained AU team up to provide a service to a patient.

13) "[T]he subcommittee strongly recommends an initial formal competency assessment and competency reassessment to ongoing longitudinal reassessment with specific emphasis on radiation safety."[37]

Response:

UPPI does not object to continued competency assessments, but we urge the Commission to consider that in the context of overall T&E requirements must consider the nature of the radiotherapeutic application(s) as opposed to taking a piece-meal approach.

14) "If the NRC moves forward in pursuing an alternative limited scope authorized user pathway, the subcommittee strongly recommends that the limited scope authorized user must successfully acquire the knowledge topics in 10 C.F.R. 35.390 [Training for use of unsealed byproduct material for which a written directive is required], which would be a minimum requirement for all authorized users involved in radionuclide therapy... [T]he authorized user candidate must acquire the basic knowledge topics in 10 C.F.R. 35.390 and satisfactorily complete a formal

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And satisfactorily complete [36] P. 26 [cite to who said it]

[37] P. 26

competency assessment... Furthermore, the individual's continued status as a limited scope authorized user is dependent upon maintaining a formal periodic reassessment of competency."[38]

Response:

10 CFR Part 35.390 knowledge topics, less the requirement of 200 hours didactic and 500 hours clinical, is agreeable to UPPI as a basis for a limited trained AU knowledge base to include radiation safety as part of their training, but UPPI believes that the NRC should consider what the pathway is going to look like how it will be administered, what roles each participant will play as a team approach, and what the safety and risk requirements are before determining specifically what training the limited-AU must obtain. Competency testing and periodic reassessment of competency should be established. Further, we urge the NRC to look at examples like nuclear cardiologists to determine what an appropriate level of training may be appropriate.

15) ACMUI Member Sheetz

"[I]n consideration of the limited scope AU/ANP partnership, while the ANP could help as an RSO, we feel that the AU must have a comprehensive knowledge and understanding of the entire therapeutic procedure. This includes all of the radiation safety issues associated with the procedure from package receipt, dose assay surveys, radioactive waste disposal, instrument Q&A, radiation safety training, personal monitoring and others. In the United Pharmacy Partners proposal, there is no delineation of tasks of who would be responsible for the aspects of the therapy. You know, would the ANP be physically present during the administration of the procedure? Would they be onsite for a person to do special surveys and waste disposal?"

Response:

Dr. Sheetz appears to be calling for a fully-formed plan, as opposed to the out-line that UPPI submitted for initial review and that the Commission is seeking comments on in this preceding. While we have thoughts on how these issues should be implemented, we look forward to working with the ACMUI and the NRC and other specialists to determine the specific outlines of how this partnership would work. In other words, questioning its feasibility because all of details have not yet been filled in is putting the cart before the horse – the better question to ask is could this work if all of these responsibilities are delineated and training is focused to address each person's responsibilities. UPPI would like to stress that the ANP would not be the medical site RSO and would consult with a medical physicist RSO named for the location who is accessible. It appears from Dr. Sheetz question that there is indeed a way to resolve those questions in a way that he might support.

16) ACMUI Member Sheetz;

[38] P. 27-28

"I believe [based on experience at UPMC] the core program on availability is really the extremely high cost of these drugs and not the availability of AUs.[39]"

Response:

While that may hold true for Lutathera and some of the other treatments in the pipeline, there are a lot of additional therapies that will be available, and not all of them will come with such high costs. Further, additional availability of ANPs/limited-trained AUs could spur more investment in facilities. This is a rhetorical statement that physicians and insurers will weigh the value (risks and benefits) versus the cost of the radionuclide therapy and has little to do with any AU.

17) ACMUI Member Dr. Ennis:

"I see a very lack of the understanding of the biological issues surrounding radiotherapy and the complications thereof. There seems to be some kind of implicit understanding or – that these are trivial drugs that anyone can learn to do, and it's just a technical application and a technical issue of this injection rather than understanding the complex biology and how radiation interacts with a variety of tissues…"[40]

Response:

UPPI certainly understands and appreciates the complexity and challenges that these treatments can pose. We are not seeking to minimize the level of training necessary, and deeply respect the training and expertise that physicians put into working with these radiopharmaceuticals. Medical oncologists and hematological oncologists understand the complex biology of cancers and the effect of radiation interactions since the patient is cared for during and after radiotherapeutic use.

That is part of the reason that UPPI has not proposed, as some others have, of reducing the 700 hours of training – we believe that having 700 hour trained ANP or AU is still important in administering these drugs but alternative pathways with lesser hours for an appropriate radiotherapeutic product can be applied18) ACMUI Consumer Advocate Ms. Laura Weil:

"Regulation can limit access to some people who can't travel for care, and that is a legitimate barrier. However, its not a question of whether those barriers exist. It's more a question of whether the regulatory standards that create those barriers are unnecessarily restrictive… nor is it the role of the regulator to attempt to increase access by compromising necessary safeguards that protect patients, their families, health care providers and the public."[41]

Response:

[39] P.33-34
[40] P. 34-35
[41] P 35-36

UPPI agrees that there are barriers to access to care, and that the regulator should not compromise safety to increase access. However, we believe that this proposal would increase access without compromising safety.

We also agree that the question should be whether the regulations create barriers that are unnecessarily restrictive, and in this case we believe that the NRC should continue to explore that question.

19) ACMUI Member Melissa Martin:

"In the letter from UPPI, they suggested that there would be a better geographic distribution of nuclear pharmacists than there would be of authorized users. Again, there has been no data submitted to support that statement. I think we need to see some kind of data that shows where the nuclear pharmacist would be distributed. I know the NRC is working on collecting the data for where the authorized users are located. But, again, if we have 4,000 authorized users, I think that there is a better geographic distribution already. I think –my impression is most of those authorized users are connected to relatively moderate to large size cities – the ones that live in the rural areas are used to travelling and getting accommodations to get their therapy. So I don't see that this has been a big -- I don't think that this is the impediment to receiving some of these treatments. The proposal is that it would increase access to the rural [areas], but there has been no proposed limitation on these procedures being performed by the team approach, limited to the rural areas. So it would assume that a lot of these procedures would be performed in the same geographic mid-to-large sized cities that is currently being performed. So I don't see that that would – I don't understand how that would be restricted to rural access."[42]

Response:

Ms. Martin weaves several points together, but to respond we have broken them out into separate points:

- No data about the distribution of ANPs, and how that would provide better coverage to rural areas:

  Response: The NRC and other groups are collecting data on the distribution of AUs, but we do not have that data to compare to yet.

  However, Purdue University does have a map which shows the distribution of ANPs, and many of them are spread across rural areas, not just large and mid-sized cities.[43] Second, her statement ignores one of the fundamental benefits of this proposal, in that it does *not limit where an ANP can provide these services by location*. As discussed above, radiopharmacy personnel regularly travel 2-4 hours from their primary facility to deliver radiopharmaceutical to the facilities that

[42] P 36-37

[43] https://nuclear.pharmacy.purdue.edu/nukeinus

need them, and in those travels place many areas where services *could be scheduled and provided* if there were a limited trained AU available.

- Patients that live in rural areas "are used to travelling and getting accommodations to get their therapy."

  Response:

  Just because patients in rural areas often do travel to obtain medical care does not mean that the NRC should not attempt to make it easier for them to do so, as her statement implies.

  Further, radiopharmaceutical treatments may often require several trips or multiple-day stays, which can be more taxing than one-off medical visits. According to Resio, et.al. survey, hardships like travel can dramatically reduce a rural patient's desire to travel to receive medical care, and so that concern and hardship should not be summarily dismissed. [44] Instead, we believe that the NRC should look at that hardship and see if there are ways to make it better.

- "[A] lot of these procedures would be performed in the same geographic mid-to-large sized cities that is currently being performed. [So] I don't understand how [the UPPI proposal] would be restricted to rural areas."

  Response:

  While UPPI believes that this proposal would increase access to these services in rural areas, we also believe that it will increase access across the board. Such an increase in access will benefit all patients, particularly as new treatments come on line increasing demand for these services. If there is no increase in the number of AUs in urban areas, these new treatments will be more difficult to obtain without an increase in the number of AUs,

18) ACMUI Member Ms. Martin:

"[W]hat is meant by minimally trained physician that would be administering the isotope in the proposed team approach?"

Response:

As discussed earlier, there are several examples of physicians with less than 700 hours of training, such as nuclear cardiologists. UPPI does not presume at this point in the discussion to lay out specifically what the requirements for training would be – we assume that a collaborative process could devise that type of detail. Instead, at this point, we are simply exploring whether such a concept is viable.

[44] Benjamin J. Resio, et.al., Motivators, Barriers, and Facilitators to Traveling to the Safest Hospitals in the United States for Complex Cancer Surgery. JAMA Network Open 2018;1(7):e184595. doi:10.1001/jamanetworkopen.2018.4595

19) ACMUI Chairman Dr. Palestro

"[I]f and when a limited AU program is in fact developed, to develop and create a curriculum, if you will, with all of the competencies that need to be met, and then after that go back and determine hours that would be required to complete it"[45]

Response:

This is indeed the concept that UPPI is relying on in determining how the limited trained physician would be trained and what they would need to be trained in.

The fact that it would take time to develop a concept like this should not be a reason to stop considering it.

20) Discussion between Dr. Palestro and Dr. Metter, ACMUI Subcommittee Chair:

Dr. Palestro: "The subcommittee concluded that there are no objective data to support an AU shortage at the present time… How did you come to that conclusion? [W]hat data did you use? Did you attempt to determine the number of AUs throughout the United States and then look at the number per 100,000 people and determine that's sufficient or insufficient? Exactly how did you arrive at that conclusion?"

Dr. Metter: "[T]hose are the numbers we have. [M]ost of [the AUs] are concentrated in urban areas… and there is really no objective data for that."

Response:

We know that ASTRO and the NRC are collecting information on the number and distribution of AUs to the extent that data is available, but it is clear that the ACMUI Subcommittee did not undertake a comprehensive look at the number of AUs nor of future needs and demand, and therefore have no objective basis to conclude that there is a "sufficient" number of AUs, even in urban areas.

23) Chair Palestro:

"It takes a long time to effect changes in rules and regulations. I would much prefer to be proactive rather than reactive. And by that I mean I would not like to find out two or three or four years from now that, in fact, there is a shortage, and now we need to something about it."[46]

Response:

We agree and commend the NRC for pushing forward in seeking to determine and alleviate the need for AUs proactively, rather than waiting to see what will happen.

[45] P.44
[46] P 52

24) Dr. Metter:

"[T]here is, unfortunately, a perhaps geographic barrier regarding the accessibility of certain therapies and treatments, but that's not [only related to] nuclear medicine. It's for any medical and health therapy."[47]

Response:

Rather than in effect throwing your hands up, we urge the NRC and the ACMUI to proactively seek to find ways to address this problem.

25) Dr. Metter:

"[P]rotecting the public is to have a confident individual who understands the entire therapy to be the one that is going to be responsible for the patient."[48]

Response:

As discussed above, modern medicine is characterized by team approaches to care which can include a design for radiation protection of the occupationally exposed worker, the patient, the public and the environment.

26) ACMUI Member Dr. Ennis:

[R]adiation oncology practices that involves the external radiation and treatments, those are, as you might imagine, even more challenging in the sense that patients have to come for daily treatments as opposed to a single or a periodic injection, and yet we not seeing [] and groundswell of concern of [] tremendous shortages in rural areas. Although there are challenges to practices in radiation oncology in rural areas, there is no overwhelming sense of a lack of access."

Response:

Surveys have shown that some patients, particularly in rural areas, will forgo medical treatment if there are significant burdens to obtaining that treatment, like travelling a long distance to obtain treatment.

Further, there have been a number of comments posted in this proceeding that highlight the concerns of rural areas, including the National Rural Healthcare Association. We cannot speak for what constitutes a "groundswell" of concern, but certainly the comments in this proceeding should constitute some alarm.

27) ACMUI Member Mr. Green:

[47] P. 53
[48] P 53-54

"I am involved in seven radionuclide therapy investigational agents that are across the gambit from AML to two for prostate cancer, non-Hodgkin's lymphoma… So there is a high likelihood that we're going to see multiple radionuclide therapies coming out for a multitude of different targets, cancers, in the next two to three years."

Response:

This is the concern that we have raised – with all of these therapies i reaching approval the ACMUI has not attempted to determine what the future demand is going to be, and even if the future supply of AUs will be enough to meet this demand.

28) Dr. Ouhib:

"[C]an you imagine having 1,000 users doing one case every six months versus having [] 500 qualified authorized users that will do multiple cases regularly? Their expertise, their skills, and all of that, will be much, much better, and []will most likely have less issues and complications."

Response:

This speaks to the concern about competence and regular training and should be addressed in that context. Further, if the number of therapies increase, the amount of engagement by AUs and ANPs could increase for everyone.

29) ACMUI Member Mr. Sheetz:

"The issue is the number of institutions or licensees, and so one of the questions would be, is the current number of institutions or licensees [] insufficient to provide these therapies? These new targeted therapies [is] not something that can be set up at every clinic. It's going to be set up at existing hospitals that have nuclear medicine and radiation oncology programs, for which I assume there will be a *sufficient* number of AUs."[49]

Response:

This statement, based upon no research or factual evaluation, may be true in the short term, but assumes that more clinics will not be developed and that AUs will not be sharing facilities with ANPs.

Other questions and concerns were raised by callers into the ACMUI meeting:

30) Dr. Carol Marcus:

"[T]he NRC, which has no medical competence whatsoever, would go against the unanimous opinion the medically competent groups involved."[50]

[49] P 57
[50] P 62

Response:

The role of the NRC is NOT to regulate medical competency, but to focus on radiation safety.

31) Dr. Carol Marcus:

"[M]ost of these therapies require sophisticated imaging studies ahead of time to ascertain whether the patients are good candidates for the therapies. And this kind of sophisticated imaging is found in urban areas… Since the patients are going to have sophisticated imaging procedures in urban areas, they certainly might as well get their therapy there."

Response:

This comment summarily dismisses the serious concerns of rural families. As discussed above, the goal should be to attempt to minimize the harm to rural patients, not dismiss it.

32) Dr. Wallner (on behalf of the American College of Radiology)

"We strongly agree with the subcommittee recommendation against adoption of a limited scope AU pathway mechanism that would fail to provide reasonable assurance of the adequate protections of health and safety.[51]"

Response:

UPPI agrees that we do not want to see an alternative pathway that does not provide adequate health and safety protections. We believe that the ANP/limited AU proposal that we have put forth could be tailored to ensure that health and safety could be protected. If so, we would urge Dr. Wallner to support this proposal.

33) Dr. Bennett Greenspan:

"[I]n rural areas with people with limited abilities that's not really sufficient, and I think patients would not be protected being treated by physicians who don't really understand what they are dealing with."[52]

Response:

UPPI agrees that training curriculum and standards should be set so that physicians that are certified as limited trained AUs "understand what they are doing." Assuming that that standard is met, we hope that Dr. Greenspan would support this effort.

34) Dr. Aria Razmaria:

[51] P 65
[52] P. 66

"If the NRC decides to pursue the creation of new pathways with limited training requirements, as physicians we cannot share in the responsibility for any consequences a physician have, the health of the patients, and NRC has to be the sole bearer if responsibility of the public for any competencies this rulemaking may have.[53]

Response:

Dr. Razmaria is in effect stating that if the NRC moves forward to create an alternative pathway, physicians will bear no responsibility to protecting patients or working with the NRC to ensure that any such pathway is as safe and effective for patients as it can be. Instead, he would suggest that doctors walk away for their responsibility to protect patients.

35) Dr. George Segall, American Board of Nuclear Medicine

"[The UPPI proposal is] interesting [but] wouldn't work. The authorized nuclear pharmacist would not be onsite and could not provide the level of coordination necessary of all of the personnel that is required in handling a spill of radioactive materials that do occur. And the coordination of these personnel involve physicians, technologists, as well as physicists. So the authorized user responsible for the radiation safety must be physically present in the department."

Response:

UPPI is not suggesting any different standards regarding whether the ANP is physically present at the site than current AUs have. Further, as the NRC develops standards, this could be incorporated in to the requirements. The ANP has knowledge of radiation safety, monitoring, contamination control, actions to handling a spill and waste disposal as any of these actions would happen in the nuclear pharmacy. The UPPI proposal is to have the ANP work with an accessible RSO.

Assuming that the ANP were physically present, would that alleviate Dr. Segall's concerns?

36) Finally, there is one concern that the ACMUI did NOT raise that this proposal addresses: the harm that will come to patients if there are not enough AUs, and patients are forced to forgo the optimum treatments that radiotherapy may provide.

As discussed above, the demand for AUs is going to grow as the number and complexity of treatments grows. If there are not enough AUs to administer these treatments, thousands of patients may be forced into taking suboptimum treatments, putting their lives at risk.

We all want to ensure the maximum safety for patients, but that calculus MUST include patients who otherwise would forgo these treatments. That is why UPPI developed this "novel" approach – to help ensure that the number of physicians that can administer these treatments will grow.

[53] P 67-69

- *Question 9:* How should the radiation safety responsibilities be divided between the AU and ANP?

  The ANP should have the primary responsibility for all radiation safety requirements that are not patient specific, while the AU should have responsibility for administration of the radiotherapeutic dose and medical care of the patient.

IV. Additional Questions for Consideration

The NRC is requesting input on the following questions as they relate to the draft approaches discussed above.

- *Question 10: What are the advantages and disadvantages of the draft approaches?*

  The advantages of the ANP/limited AU proposal, as discussed above, are that this proposal enables the expansion of treatment options and opportunities for patients without reducing the need for the presence of a 700 hour Authorized Individual.

- *Question 11: Are there significant costs or benefits associated with any of the approaches?*

  The main costs, as described by Dr. Palestrro, Chairman of the ACMUI in his objection to the ACMUI's recommendations, is that if there turns out to be a shortage of AUs in the coming years, patients will suffer from a lack of access to these vital treatments, the medical community will have to scramble to address these shortcomings, and the Commission will come under fire for failing to proactively address these challenges.

  The costs for the ANP proposal are expected to be the time and effort spent to create an appropriate licensing and training curriculum for ANP teaming with a limited trained AUs, and implementing that system.

  The benefits of this system, however as discussed above, are increased treatment opportunities for patients with no reduction in safety.

- *Question 12: Would any of the draft approaches impact patient access to radiopharmaceuticals or address stakeholder concerns of overly burdensome (regulatory) requirements?*

  As discussed above, the only teaming proposal that would increase the patient access to radiopharmaceuticals while maintaining the 700 hour T&E requirement is the ANP/limited trained AU proposal.

  UPPI does not believe that the problems with the current requirements are overly burdensome regulations, but rather a restriction on similarly situated individuals – 700 hour trained ANPs, who cannot perform the same functions as their 700 hour trained AU brethren, but undergo the same training and experience requirements.

- *Question 13: For the draft approaches that consider tailored hours of T&E, what are the appropriate numbers of hours and what radiation safety topics should comprise the limited T&E?*

  While UPPI believes that the current 700 hours of T&E is appropriate for an Authorized Individual, an ANP on-site, for radiation safety purposes, a curriculum will have to be developed to ensure adequate training of limited-trained AUs.

- *Question 14: Should the NRC consider inclusion of a formal radiation safety competency assessment and periodic reassessments for any of the draft approaches above? If so, who should establish and administer these assessments?*

  UPPI does not have an objection to a competency assessment and periodic reexaminations, but believes that AUs, ANPs and limited AUs should all be subject to the same criteria.

- *Question 15: How would the draft approaches impact the medical organizations that use the NRC's T&E requirements as a basis for establishing their training programs?*

  UPPI believes that this process could encourage medical oncology and hematology oncology specialist that could become limited trained Authorized Users to develop their own professional organization and become affiliated with the Society of Nuclear Medicine and Molecular Imaging. This was the outcome in the nuclear cardiology community – the profession moved forward to establish Board Certification and a specialty organization: American Society of Nuclear Cardiology.

- *Question 16: Are there concerns regarding implementation and/or viability for any of the approaches discussed above?*

  As discussed above, at the ACMUI meeting on Feb. 26th several concerns and objections were raised to the ANP/limited trained AU proposal. UPPI has attempted to address those concerns and believes that none of them are insurmountable. In fact, we believe that many of the concerns/objections are already addressed by the ANP proposal. (For example, see the concerns raised by Dr. Segal, who stated that the ANP must be physically present when the radiopharmaceutical is administered. We assume that if that were part of the requirement that he would end up supporting the proposal.

- *Question 17: Are there any unintended consequences of the draft approaches*?

  While several commentators indicated that the ANP proposal would have unintended consequences, none of them articulated what those concerns might be. This makes it difficult for anyone to assess whether these objections are serious problems that could have untoward consequences; or concerns that could be addressed by modifying the proposal; or simply convenient objections that do not have any real substance behind them.

In UPPI's analysis of the concerns raised by the ACMUI and public participants, none of the concerns or objections fell into the no-go category, and the others could be easily addressed through the creation and implementations of this program.

- *Question 18: Which of the draft approaches best positions the NRC to effectively regulate future radiopharmaceuticals?*

  None of them create a situation where the NRC control over radiopharmaceuticals and its responsibility to radiation safety would be put at risk.

- *Question 19: Should the NRC continue to play a role in the review and approval of AUs?*

  UPPI does not have an objection to a continued role at the NRC.

  However, Dr. Razmaria at the ACMUI meeting on Feb. 26th appeared to state that if the NRC creates an alternative pathway, then physicians will bear no responsibility to protecting patients. Instead, he would suggest that doctors walk away for their responsibility to protect patients.

  "If the NRC decides to pursue the creation of new pathways with limited training requirements, as physicians we cannot share in the responsibility for any consequences a physician have, the health of the patients, and NRC has to be the sole bearer if responsibility of the public for any competencies this rulemaking may have.[54]

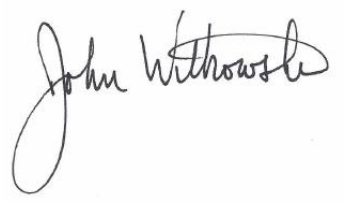
  UPPI assumes that this is an extremely minority position among physicians.

CONCLUSION

The NRC should be commended for your commitment to seeking to proactively address looming shortages of AUs without sacrificing patient safety.

We look forward to continuing to work with the NRC to help implement a program that expands access and maintains patient safety.

Sincerely,



President, UPPI LLC

[54] P 67-69