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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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TELECONFERENCE

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MONDAY,

JULY 16, 2018

The meeting was convened via teleconference at 2:00 p.m., Christopher Palestro, ACMUI Chairman, presiding.

MEMBERS PRESENT:

CHRISTOPHER J. PALESTRO, M.D., Chairman

DARLENE F. METTER, M.D., Vice Chairman

PHILIP ALDERSON, M.D., Member

VASKEN DILSIZIAN, M.D., Member

RONALD D. ENNIS, M.D., Member

RICHARD L. GREEN, Member

MICHAEL D. O'HARA, Ph.D., Member

ZOUBIR OUHIB, Member

MICHAEL SHEETZ, Member

MEGAN L. SHOBER, Member

JOHN H. SUH, M.D., Member

LAURA M. WEIL, Member

NON-VOTING MEMBERS:

MELISSA MARTIN

DESIGNATED FEDERAL OFFICIALS:

DOUG BOLLOCK, DFO

LISA DIMMICK, Alternate DFO

NRC STAFF PRESENT:

MARYANN AYOADE

VINCE HOLAHAN

SOPHIE HOLIDAY

ESTHER HOUSEMAN

KATIE TAPP

IRENE WU

P R O C E E D I N G S

2:00 p.m.

CHAIRMAN PALESTRO: All right, thank you. Good afternoon and welcome to the Advisory Committee on Medical Uses of Isotopes for the comments on the draft SECY paper. My name is Dr. Christopher Palestro, and I am the Chair of the ACMUI.

Thank you all for attending the meeting. And now I would like to turn it over to Mr. Doug Bollock, the Designated Federal Officer.

MR. BOLLOCK: Thank you, Dr. Palestro. Good afternoon, everyone. As the Designated Federal Officer for this meeting, I'm pleased to welcome you to this public meeting of the Advisory Committee on the Medical Uses of Isotopes, or ACMUI.

My name is Doug Bollock, I'm Chief of the Medical Safety and Events Assessment Branch. I have been designated as the Federal Officer for this Advisory committee in accordance with 10 CFR Part 7.11. Present today is the Alternate Designated Federal Officer, Lisa Dimmick, who is also our Medical Radiation Safety Team Leader.

This is an announced meeting of the Committee being held in accordance with the rules and regulations of the Federal Advisory Committee Act and

the Nuclear Regulatory Commission. This meeting is being transcribed by the NRC, and it may also be transcribed or recorded by others.

The meeting was announced in the June 7, 2018 edition of the Federal Register, volume 83, page 26503.

The function of the Committee is to advise the staff on issues and questions that arise on the medical use of byproduct materials. The Committee provides counsel to staff, but does not determine or direct the actual decisions of the staff or the Commission. The NRC solicits the views of the Committee and values their opinions.

I request that whenever possible, we try to reach a consensus on the various issues that we'll discuss today. And also recognize that there may be minority or dissenting opinions. If you have such opinions, please allow them to be read into the record.

At this point, I'd like perform a roll call of the ACMUI members participating today.

Dr. Christopher Palestro, Chairman.

CHAIRMAN PALESTRO: Here.

MR. BOLLOCK: Thank you. Dr. Darlene Metter, Vice Chairman.

VICE CHAIRMAN METTER: Here.

MR. BOLLOCK: Thank you. Dr. Philip Alderson, Health Care Administrator.

MEMBER ALDERSON: Here.

MR. BOLLOCK: Thank you. Dr. Vasken Dilsizian, Nuclear Cardiologist.

MEMBER DILSIZIAN: Yeah.

MR. BOLLOCK: Thank you. Dr. Ronald Ennis, Radiation Oncology.

MEMBER ENNIS: Here.

MR. BOLLOCK: Mr. Richard Green, our Nuclear Pharmacist.

MEMBER GREEN: Here.

MR. BOLLOCK: Thank you. Dr. Michael O'Hara, our FDA Representative.

MEMBER O'HARA: Here.

MR. BOLLOCK: Thank you. Zouhir Ouhib, our Therapy Medical Physicist.

MEMBER OUHIB: Here.

MR. BOLLOCK: Thank you. Mr. Michael Sheetz, Radiation Safety Officer. Ms. Megan Shober, our Agreement State Representative.

MEMBER SHOBER: Here.

MR. BOLLOCK: Thank you. Dr. John Suh, Radiation Oncologist.

MEMBER SUH: Here.

MR. BOLLOCK: Thank you. And Ms. Laura Weil, our Patients' Rights Advocate.

MEMBER WEIL: Here.

MR. BOLLOCK: Thank you. I confirm that we have quorum of over six members. On the phone, did we also have Ms. Melissa Martin?

MS. MARTIN: Yes, here.

MR. BOLLOCK: Thank you. And Mr. Robert Schleipman. Okay. Ms. Martin has been selected as the ACMUI Nuclear Medicine Physicist Representative. And Robert Schleipman has been selected as the ACMUI Health Care Administrator Representative. They are both pending security clearances, but may assist in the meeting. However, they do not have voting rights at this time.

I now ask the NRC staff members who are present to identify themselves. I'll start with the individuals who are in the room with me.

MS. WU: Irene Wu.

MS. TAPP: Katie Tapp.

MS. DIMMICK: Lisa Dimmick.

MS. HOUSEMAN: Esther Houseman.

MR. HOLAHAN: Vince Holahan.

MR. BOLLOCK: Okay, thank you. Now I'll

go to NRC Headquarters employees who are on the phone.

MS. AYOADE: Maryann Ayoade.

MS. HOLIDAY: Sophie Holiday.

MR. BOLLOCK: Okay, thank you. Do we have any NRC regional employees on the phone? Okay. Members of the public who notified Ms. Ayoade that they would be participating in the teleconference will be captured in the transcripts.

Those of you who did not provide prior notification, please contact Ms. Ayoade at maryann.ayoade@nrc.gov. That's M-A-R-Y-A-N-N dot A-Y-O-A-D-E at nrc.gov. Or (301)415-0862.

We have a bridge line available, and that phone number is (888)677-2595. The passcode to access the bridge line is 9887521, followed by the pound sign. This meeting is also using the GoTo webinar application to view presentation handouts real time.

You can access this by going to www.gotowebinar.com, that's www dot G-O-T-O-W-E-B-I-N-A-R dot C-O-M, and search in the meeting ID 419-602-667.

The purpose of this meeting is to discuss the draft report of the ACMUI Subcommittee on Training and Experience Required for All Modalities.

This report includes the Subcommittee's comments and recommendations on the NRC staff's evaluation of the training and experience requirements for different categories of radiopharmaceuticals in Title 10 of the Code of Federal Regulations, Part 35, medical use of byproduct materials, Subpart E unsealed byproduct material, written directive required.

Individuals who'd like to ask a question or make a comment regarding a specific issue the Committee has discussed should request permission to be recognized by the ACMUI Chairperson, Dr. Christopher Palestro. Dr. Palestro, at his option, may entertain comments or questions from the members of the public who are participating with us today.

Comments and questions are usually addressed by the Committee at the end of the presentation, after the Committee has fully discussed the topic. We ask that one person speak at a time, as this meeting is also close-captioned.

I would also like to add that handouts and the agenda for this meeting are available on the NRC's public website. At this time, I ask that everyone on the call who is not speaking place their phones on mute. If you do not have the capability

to mute your phone, please press star six to utilize the conference line mute and unmute functions.

I would ask everyone to exercise extreme care to make sure that the background noise is kept at a minimum, as any stray background sounds can be very disruptive on a conference call this large.

At this point, I would like to turn the meeting back over to Dr. Palestro.

MR. BOLLOCK: All right, thank you, Mr. Bollock. And at this point, I would like to turn the meeting over to Dr. Darlene Metter, who is the Chair of the Subcommittee on Training and Experience for All Modalities, and she will present the Subcommittee's evaluation of the draft SECY paper. Dr. Metter.

VICE CHAIRMAN METTER: Thank you, Dr. Palestro. And thank you for the introduction. Before I start, I'd like to thank my Subcommittee members, Dr. Philip Alderson, Dr. John Suh, Ms. Megan Shober, and Ms. Laura Weil for their contribution to this paper.

I'd also like to thank the opportunity to review and provide recommendations for the draft SECY paper entitled Staff Evaluation of Training and Experience Requirements for Administering

Radiopharmaceuticals.

Now, as an introduction, I'd like to give the following. In June of 2015, because of stakeholder concerns that a shortage of AUs caused by the 700 hours of training and experience required to become an authorized user under Title 10, Code of Federal Regulations, 35.300, specifically 35.390, training for use of unsealed byproduct material, for which a written directive is required, was limiting patient access to therapeutic radiopharmaceuticals.

The ACMUI at that time formed a subcommittee to look into this matter. The charge of the subcommittee was to determine if the 700-hour training and experience requirement placed a hardship on patient access to alpha- and beta-emitting therapeutic radiopharmaceuticals.

And if necessary, to make recommendations for potential changes and establish recommendations for the total number of hours of training and experience for use of unsealed byproduct material for which a written directive is required.

The Subcommittee concluded that the current requirement of 700 hours' training and experience for authorized users did not adversely affect patient access to these radiopharmaceuticals,

and that no change in the training and experience requirements was warranted.

The Subcommittee also noted that the current training and experience requirements had not been updated in nearly 15 years and recommended that in the future, periodic training and experience reviews be conducted.

This recommendation led to the creation of the Subcommittee on Training and Experience for All Modalities. This Subcommittee created a standardized template for training and experience reviews, which was completed for 10 CFR 35.100. However, due to ongoing patient access concerns, the Subcommittee was directed to expedite the review of 10 CFR 35.300, specifically 10 CFR 35.390.

During the March 1, 2018 ACMUI teleconference meeting, the Training and Experience Subcommittee reported that two recent developments identified potential future problems with patient access to 10 CFR 35.300 for radiopharmaceuticals.

The first was a potential increase in therapeutic procedures related to the recent U.S. FDA approval for broad use of the therapeutic radiopharmaceutical lutetium-177 dotatate. The second was a continued decrease in the number of

nuclear medicine physicians in training and sitting for the American Board of Nuclear Medicine initial certification exam.

Due to the potential future increase in the number of procedures and the concomitant decrease in AUs, the Subcommittee recommended that an alternate AU pathway should be reconsidered.

From this resulted a draft SECY paper, which I will summarize. This draft paper addresses the NRC staff initial recommendations based on limited stakeholder outreach for training and experience requirements for different categories of radiopharmaceuticals, with a specific focus on 10 CFR part 35 on the medical use of byproduct material, Subpart E, unsealed byproduct material, written directive required.

After the final re-revision of 10 CFR Part 35 in August 2017, the Commission tasked the NRC staff to evaluate the possibility of a limited AU training and experience pathway addressing the following. One, its feasibility for certain categories of radiopharmaceuticals.

Two, how to develop such categories. Three, the appropriate training and experience requirements for such categories. And four, whether

the training and experience requirements should be based on hours or competency.

Under 10 CFR Part 35, Subpart E, the staff considered the possibility of an alternate limited AU pathway with tailored training and experience requirements for certain categories of radiopharmaceuticals. Options for such categories were considered, along with appropriate corresponding training and experience and the documentation of training competency.

More extensive stakeholder outreach is planned to address the feasibility of a limited AU status for training and experience requirements and competency assessment.

To evaluate the feasibility of a limited AU pathway, the NRC staff first determined the knowledge topic for a training and experience curriculum. The curriculum included the current training and experience categories in 10 CFR 35.390, which would then be tailored to the specific category of radiopharmaceuticals, with additional knowledge topics as needed.

The staff then solicited stakeholder input on three other topics. First, the fundamental and specific radiopharmaceutical knowledge required

in 10 CFR 35.390 to safely administer the radiopharmaceuticals. The stakeholder response was overall support of the proposed knowledge topics.

The second was how to obtain this knowledge. The stakeholder response on this question was varied and ranged from maintaining the current training and experience, saying that only American Board of Radiology or American Board Nuclear Medicine certifications, competency assessments, and perhaps even radiopharmaceutical administration requirements.

The third question was how to evaluate the acquisition and independent application of this knowledge. The stakeholder response was varied but will likely require NRC and stakeholder collaboration to determine this assessment.

Other concerns were, one, categorizing radiopharmaceuticals, which had various stakeholder and NRC responses. Two, how to administer the training and experience requirements. And the staff was considering using the Reactor Operator Licensing Program as a, rather than a benchmark, but more as a guide to administer these requirements.

Three, NRC staff estimated that the required training experience would be up to 300

classroom hours. Four, competency assessment method or methods would be an examination developed by the medical community, whether it be a written exam or a hybrid exam, with or without preceptor attestation, and potentially also forming a new specialty board.

The final conclusion that the staff made was it may be feasible to develop a limited AU pathway for certain categories of radiopharmaceuticals with a competency-based approach for tailored training and experience requirements and knowledge of skills assessment.

The ACMUI Subcommittee had several comments on the SECY paper. The first was that the ACMUI Training and Experience Subcommittee recommended that the development of an alternate pathway be reconsidered.

Two, the stakeholder outreach has been limited and was likely related to time constraints. Staff should consider a broader stakeholder outreach. But this outreach could assist in defining the categories for radiopharmaceutical for limited AU status, tailoring the limited T&E requirements, and assessing the success of the knowledge and skills obtained.

Third, collaboration with the medical

community and other stakeholders to develop a competency-based assessment tool, mostly likely in advance, is commendable. Four, minimizing the training and experience requirements and thus one's knowledge and skills, potentially jeopardizes patients, personnel, and public safety.

Five, the initial projection of authorized users was underestimated in that only nuclear medicine physicians were considered. For the 2017-2018 academic year, the total number of residents who could potentially meet the AU training and experience requirements in 10 CFR 35.390 is nearly 900.

And this is a number that's all residents in training. And these are in radiation oncology, nuclear medicine, nuclear radiology, and the redesigned emerging Board of Radiology pathway.

The data on osteopathic AUs and on AUs leaving the workforce, however, is currently not available. Although this revised estimate of that total number of future AUs is encouraging, the Subcommittee still recommends reconsideration of an alternate AU pathway.

Number six. The Subcommittee is concerned about estimating the required training and

experience classroom hours for an alternate pathway. Given that the curriculum for limited status AU has not been established, the Subcommittee feels that it's premature to address the issue of hours.

The Subcommittee feels strongly that should a decision be made to proceed with a limited AU status, the training and experience requirements must be based on the knowledge and skills necessary to maintain patient, personnel, and public safety, and not based on a predefined number of hours.

Given these comments, the Subcommittee has five recommendations. The first is that the ACMUI Training and Experience Subcommittee recommends reconsideration of the existing pathways to AU status.

This reconsideration should have the goals of first maintaining maximal safety for the patient, personnel, and the public. Second, maximize patient access to current and future radiopharmaceuticals. And thirdly, to clearly define the AU's scope of practice.

Second, the educational program must be all-inclusive for the limited AU status. The didactic component necessary to obtain limited AU status under 10 35.390 must comprehensively cover the

knowledge topics required for all AUs involved in 10 CFR 35.300, thereby ensuring the safe use of radiopharmaceuticals for the patient, personnel, and the public.

Third, the assessment method or methods to assess AU competency must be objective and document both initial and continuing maintenance of competency for the limited AU status.

Fourthly, there should be greater and broader stakeholder input. And lastly, the NRC staff should conduct ongoing monitoring for potential AU shortages for 10 CFR 35.300. Data on the geographic distribution and practice patterns of AUs should be included in this surveillance.

So that's the end of our subcommittee report. Do I have any comments from the Subcommittee? Okay, hearing none, do I have any comments from the ACMUI Committee itself?

CHAIRMAN PALESTRO: Dr. Metter, this is Dr. Palestro. I have a question for you. First, the Subcommittee is to be commended for doing a more thorough investigation of the anticipated AUs that would be, quote unquote, graduating on a yearly basis. I think that's important information.

The Subcommittee's report says

approximately 900 potentially could meet the requirements. How does that compare historically? What numbers have been meeting those requirements and obtaining AU status in the past? Is that, do you have that information?

VICE CHAIRMAN METTER: No, I don't have that information. I just looked at the current group of individuals that are in training at this point. We can look at that, you know, the past, though.

CHAIRMAN PALESTRO: Okay, that might help to give a better picture of what we potentially could expect in the future.

MEMBER SUH: Dr. Palestro, this is John Suh, I just want to make a quick comment regarding your question.

CHAIRMAN PALESTRO: Yes.

MEMBER SUH: So if you look at the historic data which is provided from the American Board of Radiology, in terms of radiation oncology residents, if you look at the year 2006-2007, there were 585 slots, and the vast majority of those being filled. And if you look at 2016-2017, there were 808 slots, with the vast majority of those positions being filled.

So in the ten-year period, there is an

increase of about 220 potential authorized users who would be radiation oncologists.

CHAIRMAN PALESTRO: Okay, thank you. But the numbers you give are the total enrolled in the program, which is, if I'm not mistaken, four years. So the number of graduates then would be, or new AUs, would be approximately 25% of that on an annual basis. Am I correct?

MEMBER SUH: Yes, it would be about 200. And the number of programs for that ten-year period has increased from 79 programs to 92 programs. So an increase of 13 programs over that decade.

CHAIRMAN PALESTRO: Do you anticipate any further increases in the number of programs?

MEMBER SUH: I do know some programs that will be applying for residency. I couldn't give you an exact number in terms of what that number would be.

CHAIRMAN PALESTRO: Thank you.

VICE CHAIRMAN METTER: Also there's a small number also in radiology with the increased number of individuals in the nuclear radiology and the new Board pathway for being an AU. And I have a number, this past or this year, I think there were 11 graduates. And I think there's, that's just for this

year.

Any other comments from the Committee?

MEMBER GREEN: Dr. Metter, this is Richard Green. I wish we had more clarity on the number of authorized users, the number of licensees. I mean, that's just something we don't have.

But I think it's a great opportunity to, although the historical hours and assessments of competency based on hours has been in place for 15 years, no one can really say, you know, it's written in stone in a CFR.

But no one can really say what that was based upon, or whether those hour levels are appropriate today in today's modern modes of learning, computer-based training or web training. So I just think it's valuable that there's now a standing committee that you chair that looks at what is the current, really, the appropriate way to assess competency.

And I just think it's great that this is being refreshed now. So we can make comments relative to the request from the Commissioners and address the draft recommendations made by staff.

But to do that, we really take a look and see what it would take to adequately train a physician

to safely administrate radiopharmaceuticals. Until that's done, we are looking at history, but not really knowing where it came from.

VICE CHAIRMAN METTER: Thank you. Are there any other comments from the Committee?

MEMBER OUHIB: Yes, Dr. Metter, this is Zoubir Ouhib. I think to answer Mr. Green's comment is that my understanding is really this is based on all the education that was basically required from an authorized user, you know.

And I guess if you go back and take a look at what these authorized users had to complete and so on, I think that it will be a reasonable estimate of that kind of a number, in my opinion.

VICE CHAIRMAN METTER: Okay, thank you.

MEMBER SHOBER: This is Megan Shober, I also have a comment about the hours.

VICE CHAIRMAN METTER: Yes.

MEMBER SHOBER: So when the 10 CFR 35 had its major revision the last time, the final rule was in 2002, the proposed rule was issued in 1998. And as part of that, and with the proposed rule, there's a pretty extensive discussion on where the number, the training and experience hours comes from.

There's about five pages of discussion

about where that 700 hours comes from. So I encourage people to take a look at that original proposed rule from August 13, 1998. And it informs a lot of this discussion that we've been having over where the hours come from.

VICE CHAIRMAN METTER: Okay, thank you. Okay, are there any more comments from the ACMUI Committee members?

CHAIRMAN PALESTRO: Dr. Metter, this is Dr. Palestro again. In your summary of the draft SECY paper, you said it addresses the NRC staff's initial recommendations based on limited stakeholder outreach. Could you elaborate on what constituted the limited stakeholder outreach and what was the basis of selection of those stakeholders?

VICE CHAIRMAN METTER: As far as the stakeholders, I believe it was in the report. Maryann, or is there an NRC staff that can help with that?

MR. BOLLOCK: Yes, this is Doug Bollock, I can address that. So we had, I think, based on that paper, we had a limited time frame to get a limited amount of stakeholder outreach. And we are also limited by our burden requirements under OMB. So we can only reach out to nine non-federal agencies

or non-federal entities.

So we made the determination of the nine. We wanted to get as broad of a spectrum as we could, so we asked a number of licensees, picked a couple of licensees from different parts of the country trying to get a large institution and maybe a smaller size institution that's represented.

We asked one of the, a professional society. We asked CORAR for, I guess manufacturing, I'm trying to think what the proper term is. But we asked one board, the American Board of Nuclear Medicine, and we also reached out to one of our co-regulators, we reached out to Virginia.

And then we did reach out to a number of federal facilities, Navy, the Army hospitals to get, to kind of increase the stakeholder, from licensees or from users of the radiopharmaceuticals.

We tried to get as broad of a, with the limits of only being able to ask nine non-federal entities, we tried to get as broad of a spectrum as we could with that limit. So with licensees, our board, professional organizations, and one state regulator.

VICE CHAIRMAN METTER: Thank you.

CHAIRMAN PALESTRO: Yeah, thank you, Mr.

Bollock. That answers my question. I appreciate that.

VICE CHAIRMAN METTER: Are there any other questions from the ACMUI Committee or comments?

MEMBER OUHIB: Doctor Metter, this is Zoubir Ouhib again. I do have a comment, if you could go up a little bit on your document. Move to page one or two. There was a statement made regarding, let me just see that. I think this is relating to the FDA on the new isotope.

My question is that the, you know, there was a statement that says there's a potential increase of users or something. I'm just curious, that potential future increase is based on what, exactly? What data is used to actually make such a statement?

VICE CHAIRMAN METTER: Well, the dotatate has, it's going to be used for neuroendocrine tumors, and can be used for several of them. Most of the treatments right now with radiotherapy is limited, let's say for specific use. But this can be a broader use for neuroendocrine tumors.

Dr. Palestro, I believe you had looked into that in your report.

CHAIRMAN PALESTRO: Yes. The answer is that the previous radiopharmaceuticals that have been

approved were approved with a, had very narrow approval. Typically, they were for patients who had failed all sorts of previous therapies and very specifically defined criteria.

Lutetium 177 dotatate, however, had a much broader approval, a much more general approval, and could be used conceivably at virtually any point during the patient's treatment. It could be used as a first line, it could be used a second line, it could be used as an endline treatment. Really up to the discretion of the individuals managing the patients.

And then in addition to that, these tumors, these gastro, entero, pancreatic, neuroendocrine tumors, which were once thought to be relatively uncommon, are now recognized to be the second most common GI tract malignancy. So that's how we came to the conclusion that the potential exists for a broader use of this agent than previous similar agents.

MEMBER OUHIB: And this is simply just an estimate here, is that correct?

CHAIRMAN PALESTRO: Correct.

MEMBER GREEN: Dr. Palestro, it's also an additional fact that a single patient with a gastro-entero-hepatic tumor would undergo multiple

courses of radionuclide therapy also weighs into that consideration.

CHAIRMAN PALESTRO: To a lesser degree because patients who are being treated with radium dichloride also undergo multiple courses.

VICE CHAIRMAN METTER: Okay. Are there any additional comments from the ACMUI Committee members? Okay, I'd like to open the commentary then to the public.

OPERATOR: Thank you. Participants on the phone, if you have a comment at this time, press star one and record your name. One moment to see if we have any comments.

We have a comment from Sue, your line is now open.

MS. LANGHORST: Hi, this Sue Langhorst. Hi there. I had a few questions for the ACMUI and the NRC staff to consider.

My first question is will the NRC plan to track information on the kinds of physicians who utilize the specialty T&E training and experience tracks, as I'm terming them, and report back to the ACMUI the regulatory results and issues that come from this change, that is, how effective the training is for their regulatory compliance? That's my first

question.

My next question is if new licenses are issued for this specialty track training and experience, who will function as the RSO?

And my third question is will authorized users with specialty track approval be able to be appointed as an RSO, and if so, what additional training will they be required to obtain? I thank you all for considering the questions.

MR. BOLLOCK: Thanks, Dr. Langhorst. This is Doug Bollock, I'm going to go kind of in reverse order to answer your questions. It's a little bit easier. So these are just the, so this is nothing set in stone yet, but we just thought of what are some other ways, what are possible ways to allow for expanded authorized users.

And one way is to have a limited authorized user, potentially, who would be limited to whatever drug that they were going to use. But a limited authorized user, we have not had any thought or taken into consideration of changing the requirements for an RSO.

Therefore, if we had an authorized, a limited authorized user and is just right now, again, we're just, we haven't planned on anything yet. But

if they're I guess lesser requirements than a full, authorized user, it's unlikely that they would be, that they would meet the requirements for an RSO. Okay, so that likely they would not.

Your second question of who would function as an RSO, someone who is, meets the requirements for 35.50 and all the requirements in the license to be an RSO at whatever facility, or yeah, at a licensed facility. So those requirements are not, we're not considering any changes to the RSOs.

And then for your first question, I think we did, I don't think we quite understood your first question, and what. Were you asking if we, through our outreach, if we're going to get more information on the, on current AUs and their training or how they got training? I'm not, we're not sure we understand your first question, could you please repeat it?

MS. LANGHORST: Absolutely, absolutely.

MR. BOLLOCK: Thank you.

MS. LANGHORST: So really what, so Doug what I'm talking about is if the NRC and the ACMUI recommend that there be a specialty track, let's say like there is for 35.392 or 35.394 for I-131 therapies. If there are different kinds of

positions, then nuclear medicine and radiation oncology positions utilizing that track, will NRC be considering some way of reporting back any regulatory issues as far as what type of physician are having these issues?

And if that the training that's set for that level, is it adequate to meet all the regulatory compliance requirements? Not that I'm asking you to answer that question now, that's a question I'm suggesting you consider.

MR. BOLLOCK: Okay, thank you for the comment. We'll consider that.

MS. LANGHORST: Thank you all.

OPERATOR: Once again, if you have a question or comment, please press star one and record your name. Speakers, let me know whenever you're ready for the next question. And it looks like we have a question from Cindy Tomlinson. Your line is open.

MS. TOMLINSON: Thank you. Chairman Palestro and members of the ACMUI and NRC staff, thank you for allowing me to provide this statement on behalf of the American Society for Radiation Oncology.

In response to the ACMUI's comments on

the draft SECY paper entitled Staff Evaluation of Training and Experience Requirements for Administering Radiopharmaceuticals being discussed today, because the draft SECY paper is not public, our comments reflect only on the ACMUI draft and report and recommendations.

As we have commented in past statements to the ACMUI, we strongly oppose any reduction in the training experience requirements found in 10 CFR 35.390, training for use of unsealed byproduct material, for which a written directive is required.

ASTRO believes that the requirements found in this section are appropriate to protect the safety of patients, public, and practitioners and should not be changed. Radiopharmaceuticals are highly effective in treating cancer, with possible harmful effects to both the patient and the public if not used correctly and under the supervision of a highly trained physician.

The rigorous T&E requirement contributes to the excellent safety record of radiopharmaceuticals. We believe that it is important that the person administering the radiopharmaceutical is appropriately trained in the safe handling, exposure risks, and the management of

side effects of radiation.

In general, ASTRO is comfortable with the broad recommendations made by ACMUI and believes that a thorough and comprehensive review of current T&E requirements is reasonable.

Additionally, we fully support the ACMUI's recommendation that the NRC conduct a thorough examination of geographic distribution and practice patterns of current AUs under 10 CFR 35.390 and 300, as well as taking greater stakeholder input.

The American Board of Radiology estimates that between 2007 and 2017, approximately 1650 radiation oncologists were certified by the ABR with an authorized user eligibility designation and may become AUs.

In addition, we estimate that there are approximately 2200 radiation oncology facilities in the US. Together with current radiation oncology AUs, the 773 radiation oncology residents currently in residency programs and nuclear medicine-trained AUs nationwide, there are likely enough AUs to administer radiopharmaceuticals.

We caution a change in the current requirements without a comprehensive investigation could result in unintended harm to patients,

personnel, and the public. ASTRO looks forward to continuing to work with both the ACMUI and the NRC as we continue deliberations and review on this very important topic. Thank you.

VICE CHAIRMAN METTER: Thank you.

OPERATOR: Once again, if you have a question or comment, please press star one and record your name. It looks like we have a comment from Paul Wallner, your line is open.

MR. WALLNER: Thank you, good afternoon. My name is Dr. Paul Wallner, I'm a radiation oncologist who is separately Board-certified in radiation oncology and diagnostic radiology in nuclear medicine. I previously served as Chief of the Clinical Radiation Oncology Branch of the National Cancer Institute, when my research interest was in targeted radiopharmaceuticals.

I'm speaking today on behalf of the American College of Radiology, ACR. The ACR represents over 35,000 diagnostic radiologists, interventional radiologists, radiation oncologists, nuclear medicine physicians, and medical physicists.

The ACR understands the tight deadline and external pressures prompting the staff's draft paper. However, we strongly urge more extensive

public engagement of the medical stakeholder community before the NRC takes any significant action on the issues covered by the draft paper.

Forward movement on this topic seems to be predicated on the presumption that the 700-hour training and experience requirements in 10 CFR 35.390 is no longer appropriate, particularly for individuals without NRC-recognized Board certification.

But the underlying concerns have yet to be substantiated in a quantitative, impartial, and apolitical fashion. Before there is any serious movement towards modifying T&E content or hours, there should be a fact-driven assessment of the external criticisms regarding 35.390.

After all, 35.390 has a track record of success in providing NRC with a reasonable assurance of the adequate protection of public health and safety. To help substantiate or disprove AU population concerns, it's most important for NRC to gather trustworthy data on the active AU population providing various therapies under 35.390.

The collective data should enable exploration of AU numbers and coverage over a multi-year period of time. This suggestion has been made

previously, and we understand that such an activity would be labor-intensive and require collaboration with agreement states and broad scope licensees.

However, without confirmation by NRC of a problem, there is a questionable technical basis for any rulemaking to modify 35.390 or the other subparts of Part 35.

Moreover, any presumption of a future AU shortage informed solely by ABNM trends neglects the radiation oncology and new nuclear radiology pathways, which we understand to be stable, or in the case of nuclear radiology, expanding in size and distribution.

While prescriptive, the 700-hour training and experience prerequisite in 35.390 was fundamentally intended to ensure prospective AUs, without certification from the NRC-recognized board, have an adequate base of knowledge and radiation safety to supervise the proper use of these therapeutical medical nuclear materials, including medical event prevention, identification, and mitigation.

If NRC determines, based on data, that a rulemaking to overhaul 35.390 T&E requirements is ultimately necessary, any future regulatory

modification must reasonably ensure that clinicians who do not possess the expertise obtained via their residency programs and fellowships can appropriately fulfill AU responsibilities and protect their patients, staff, and other members of the public.

In conclusion, the ACR supports more extensive engagement of medical stakeholders on issues discussed in the draft paper. We look forward to seeing the final product at the end of summer and hope it reflects both the needs for more public engagement, as well as the need for an NRC assessment of AU members to justify any further action.

The ACR also hopes to provide input to the ACMUI on its own efforts related to these issues. Thank you for your time.

VICE CHAIRMAN METTER: Thank you, Dr. Wallner. Are there any other --

OPERATOR: We have a question. Yes, we do have an additional question. It comes from Bennett Greenspan. Your line is open.

MR. GREENSPAN: Hello, thank you. I'm Dr. Bennett Greenspan, I'm a nuclear medicine physician and radiologist and the immediate past President of the Society of Nuclear Medicine and Molecular Imaging. And I have a few brief comments.

I pretty much agree with, I shouldn't say pretty much, I agree with the ACMUI's Subcommittee report. I did want to point out that physicians who don't know what they're doing could create severe harm to patients, and even personnel in the public, if they're not careful and so on.

And so physicians completing an alternate pathway must have the knowledge and basic science and clinical information to the same degree as those people trained in nuclear medicine, radiology, or radiation oncology.

And it also turns out that to do these therapies properly, these physicians need to have some background in understanding the imaging related to these therapies for optimal patient care.

And one other point I'd like to mention is that physicians in nuclear medicine, nuclear radiology, and radiation oncology training programs are now, it's supposed to be related information but it immersed it during their training. They're basically involved in this for several years during their training.

And other physicians such as medical oncologists do not have this training at all. And so they would, they were just totally deficient in

anything related to radiation physics, radiation safety, and so on. So you know, if they wish to do these therapies, they really need to have the same kind of knowledge and skills that nuclear medicine, nuclear radiology, and radiation oncology physicians have.

I did want to point out that the number trainees in nuclear medicine appears to have stabilized over the last couple of years.

And one other comment, the future of these therapies I think will probably include combinations of various alpha and beta emitters. And so it's going to get much more complicated, and it's going to take some real expertise in the physicians providing these therapies. Thank you very much.

OPERATOR: Back to you, speakers. I'm showing no other comments at this time.

VICE CHAIRMAN METTER: Okay. So if there are no other comments, the Subcommittee, this committee, or its public, I turn this over back to Dr. Palestro.

CHAIRMAN PALESTRO: All right, thank you, Dr. Metter. I do have one final comment. I do want to point out that no one on the ACMUI, the Subcommittee, or staff has suggested anything about

minimizing or fast-tracking or limiting training and experience requirements. And that's certainly not the intention of, and I'll take the liberty of the speaking for the Subcommittee, the ACMUI and the staff.

And in fact, I would call your attention to the last page of the Subcommittee's report. At the top of the page, item number four, minimizing the training and experience requirements and thus one's knowledge and skill potentially jeopardizes patient, personnel, and public safety. And that deserves re-emphasis. And I will conclude my comments there.

Any other comments from the Subcommittee, or the ACMUI?

OPERATOR: Excuse me, speakers, it looks like we have a few additional questions queueing up. Would you like to take those questions?

CHAIRMAN PALESTRO: Yes.

OPERATOR: Thank you. And it looks like we have a question from Michael Guastella. Your line is open.

MR. GUASTELLA: Thank you, and I'm sorry for signaling in there a little bit late, I apologize. I'm Michael Guastella, I'm the Executive Director of CORAR. Mr. Bollock mentioned a little bit earlier

that we were one of the organizations that provided feedback.

And I'd just like to say that first of all, CORAR supports the ACMUI recommendation for the reconsideration of the existing pathways for AU status. And the goal, maintaining maximal safety for the patient, personnel, and the public, maximizing patient access to current and future radiopharmaceuticals, and clearly delineating the AU's scope of practice.

We've also supported in the past an alternative pathway and an alternative to the current 700 hours' training and experience requirements under 35.390. We have recommended a very specific scope of training requirements for radioisotope handling and radiation safety.

For specialists, like Hem/Oncs and medical oncologists, who wish to administer IV therapeutic radiopharmaceuticals, alpha- and beta-emitting radioisotopes, as has been mentioned, which have been prepared by a licensed nuclear pharmacist in a state-licensed radiopharmacy and dispensed to physicians as patient-ready doses.

In determining the appropriate amount of time and scope of content for radioisotope handling

and radiation safety training that physician must have to safely administer these types of therapeutic drugs, CORAR has offered the following for ACMUI consideration.

And I reiterate, the limited role in handling these radio-labeled therapeutic drugs that are dispensed and delivered to physicians in patient-ready doses from licensed radio pharmacies. The radiological safety profiles and radiopharmaceuticals containing alpha- and beta-emitting isotopes. And physician experience in training and handling toxic non-radioactive therapies, such as cytotoxic chemotherapy agents.

In closing, I'd like to say the goal of the training experience requirements under an alternate pathway is to provide licensed medical specialists with competency and cognitive and psychomotor skills necessary to effectively and safely prescribe and administer specific radiopharmaceuticals. Thank you.

OPERATOR: It looks like we have two additional comments. The next one comes from Shaemus Gleason. Your line is open.

MR. GLEASON: Hi, and thanks for taking my question today. I'm Shaemus Gleason with Bayer

Healthcare.

And in support of the ACMUI findings, we actually presented a petition of sorts to the degree of outlining some of the research that was missing around access to our drugs, particularly Xofigo.

And what you'll see is after five years on the market, 20,000 patients treated, 1400 sites up and running, we still notice significant patient falloff based on availability, both regionally and just generally.

And in addition to that, we see a number that exist that shows patients unwilling to travel that results in them not receiving the therapy. So once again, you know, we are very supportive of the ACMUI's recent attention to these issues, and look forward to engaging in further conversation. Thank you.

OPERATOR: We have a question from Bennett Greenspan. Your line is open.

MR. GREENSPAN: Thank you. This is Bennett Greenspan again. Again, I'm a nuclear medicine physician and radiologist. I'm the immediate past President of the Society of Nuclear Medicine and Molecular Imaging.

We were, we the Society of Nuclear

Medicine and Molecular Imaging, were expecting to have a statement, and that hasn't been presented. So if you don't mind, I'd like to present it on behalf of the Chair of the Government Relations Committee. I am a member of that committee, and we the Society, appreciate the opportunity to address the ACMUI on this topic.

SNMMI, together with representatives from the American College of Nuclear Medicine, the ACNM, and the American Society of Radiation Oncology, ASTRO --

VICE CHAIRMAN METTER: Did we lose Dr. Greenspan?

CHAIRMAN PALESTRO: I don't hear him on the line.

OPERATOR: He'll need to redial back in, or press star and one. It looks like we've lost him.

CHAIRMAN PALESTRO: All right, let's give him a couple of moments, see if he can rejoin the meeting.

MR. BOLLOCK: And this is Doug Bollock. We did receive, as you know we received a letter from SNMMI, ACNM, and ASTRO combined. We also received one from Bayer. Yeah, those will be publically available when we post the transcripts for this

meeting.

So Dr. Greenspan, if you hear us, your, the combined statement from SNMMI, ASTRO, and ACNM will be publically available. It has been received by ACMUI and the NRC, so we do have that, we are aware. And the rest of the public will be able to see it when the transcripts and everything else from this meeting are shared.

CHAIRMAN PALESTRO: All right, thank you, Mr. Bollock. Are there any other comments or questions from the Subcommittee, the ACMUI, or the public?

OPERATOR: We do have an additional question from the public. We have a follow-up question from Michael. Your line is open, Michael.

MR. GUASTELLA: Thank you. This is Michael Guastella again. And I guess my question is more of a process question. So I realize that the draft report has been presented the ACMUI. It's been reviewed. Maybe Mr. Bollock can speak to what the next step would be. I believe he said in March that the final report, the NRC staff report, is due to the Commission late summer.

I may have, my recollection may not be accurate. I'm just kind of curious if he could

comment or anyone can comment on that. And will this require changes to rulemaking, or are there other pathways that an alternate pathway could be considered? Thank you.

MR. BOLLOCK: Thanks for that question, this is Doug Bollock again. So we owe the Commission a, or we owe a product to the Commission on August 31, and so it'll be delivered to the Commission August 31 and made public within a few days of that.

So it will be available to the public I would say probably the first week in September. Yeah, subject to Commission, they get a chance to look at it and then it is made public after that point.

OPERATOR: Thank you, speakers. Once again, if you'd like to ask a question or a comment, please press star then one. We have a question from Carol Marcus. Your line is open.

MS. MARCUS: Thank you very much, Dr. Palestro and members of the ACMUI. I am opposed to an alternate pathway. I urge the ACMUI to follow the money here. The radiopharmaceutical companies want to sell more drugs. The medical oncologists who would not order Zevalin on their patients because they couldn't make money on it now want to get

licenses so they can make money on it.

This patient access issue I think is really a nonexistent issue. I think it's more a money issue.

The NRC is jumping on this because by selling more licenses, it's going to make a lot more user fee money to support its medical program bureaucracy. And so I think that you really have to look at the money.

If somebody living in Podunk, USA needs a triple CABG, he's not going to get it at his little 25-bed community hospital or county hospital where he lives. He is going to have to travel. Because complex medical procedures are not available all over the United States anywhere you live. And people are used to that fact.

Now, there's no limit to how low the quality of medicine can get, but that doesn't mean it's a good idea. I think these people who need specialized nuclear medicine therapy, which is combined with imaging, as I think Bennett Greenspan mentioned, or somebody mentioned, more and more combined. The whole reason lutetium is used for therapy is that it allows imaging as well as the therapy of the beta particle.

So you need even more qualified and competent and experienced and knowledgeable physicians for these therapies than you used to. This is no time to degrade the training and experience. We need the highly skilled practitioners.

Back in 1994, the ACMUI unanimously voted to get rid of the 80-hour program for endocrinology, on the basis that they simply do not get the education and training in all the aspects of physics, radiation safety, and more modern nuclear medicine requirements than they did back in 1946 when that 80-hour program started.

But the NRC ignored the ACMUI completely. This was the recommendation for the 1995, 1997 I guess it was, redo of all of Part 35. So when physicians in non-nuclear medicine or radiology practices say they want an 80-hour program as well, I think we should say that doesn't work. Albert Einstein couldn't learn this stuff in 80 hours, let alone somebody with no basic training in radiology or nuclear medicine.

And just bear in mind follow the money and let's stick with the qualifications that we've got. And I would add I would like to see the NRC

enforce them. I have seen the NRC examine residency training programs to see where the 200 and 500 hours are. And I think a lot of people's programs really don't reflect that. And I think it needs enforcement.

I got a letter from the head of NMSS a few weeks ago commenting on a letter I had sent, who insisted that the NRC does examine this. And I had to write back and tell him you're really under a misconception. NRC does not look at these hourly trainings.

And the preceptor statement has nothing to do with ascertaining those training hours either. And in this morning's Federal Register the NRC has announced among other things that the preceptor requirement is gone as of, you know, mid-January.

So without that last-ditch preceptor attestation of confidence, you really better make sure that the hourly and content requirements of the residency training programs are being met. And I really think that in many residency training programs they are not. Thank you very much.

VICE CHAIRMAN METTER: Thank you. Did Dr. Greenspan get back on?

OPERATOR: Again, Michael, if you're on

the line, please press star one to ask a question or finish your statement. One moment to see if he joins.

VICE CHAIRMAN METTER: Thank you.

MR. BOLLOCK: Dr. Palestro, this is Doug Bollock, and if I may, we appreciate the comments from everyone, including Dr. Marcus. I just want to clarify, one clarification to Dr. Marcus's statements to the Part 35 rule that went out. The preceptor attestation removal was only for Board-certified AUs. That's just a clarification.

CHAIRMAN PALESTRO: Thank you, Mr. Bollock. Any additional questions or comments?

MS. MARTIN: This is Melissa Martin. I am the incoming nuclear medicine member of the ACMUI.

Having served as Radiation Safety Officer at multiple medical centers in Southern California, I think one area that has not been considered that I'm not sure how we go about it, but when you raise the possibility that isotopes are going to come into medical facilities being sold or delivered directly to physicians, that will violate most of the hospital's radioactive materials licenses. Because right now, everything has to be delivered to a designated point.

I think the other thing we have to figure

out is if they are now going to be delivered to a nuclear medicine department or a radiation oncology department, that staff's time is now going to be spent taking care of a physician for which they will re-coop none of the cost of their time to receive the isotope, prep the isotope, potentially clean up the mess of the isotope.

I just want those points to be considered, because I think the practical end of opening the range of users could be quite significant.

CHAIRMAN PALESTRO: Thank you for that comment. Any other comments?

OPERATOR: No questions from the phone.

CHAIRMAN PALESTRO: All right. In view of that, I'm going to ask if there is a motion to endorse the Subcommittee's report as written.

MEMBER ALDERSON: So moved. This is Alderson, so moved.

CHAIRMAN PALESTRO: Okay, thank you, Dr. Alderson. Second?

MEMBER SHEETZ: Second from Sheetz.

CHAIRMAN PALESTRO: Thank you. All in favor?

(Chorus of ayes.)

CHAIRMAN PALESTRO: Any opposed? All

right, then the motion to endorse the report as written is unanimously passed. And at this point, I thank all of the participants, the Subcommittee for their work, the staff, the ACMUI, as well as the individuals who took time out of their day to comment on the bridge line.

And at this point, I will turn the meeting over to Mr. Doug Bollock.

MR. BOLLOCK: Thank you, Dr. Palestro. Just as a reminder to you all, the next ACMUI public meeting is our fall meeting here in NRC Headquarters in Rockville, MD, September 20 and 21.

And I'd like to thank ACMUI, the Subcommittee for reviewing our paper and providing us your comments and recommendations for full Committee, for your time today reviewing it and giving comments and considering it.

And also I'd like to thank all the public members who listened in today and gave comments. We appreciate it greatly.

OPERATOR: Thanks for your participation and you may disconnect at this time.

CHAIRMAN PALESTRO: Thanks a lot.

(Whereupon, the above-entitled matter went off the record at 3:08 p.m.)

July 10, 2018

Douglas Bollock
U.S. Nuclear Regulatory Commission
Mail Stop 0-16G4
Washington, DC 20555-0001

Re: Statement on training and experience for authorized users: Guidance for the Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Use of Isotopes (ACMUI)

Dear Mr. Bollock:

The leadership of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), together with representatives from the American College of Nuclear Medicine (ACNM) and American Society of Radiation Oncology (ASTRO) formed an ad-hoc committee to offer their collective recommendation for potential updates to the 10 CFR 35.390, *Training for use of unsealed byproduct material for which a written directive is required*. We are offering suggestions specifically regarding the basic and clinical knowledge and skills needed for those seeking authorized user status through the "alternate pathway" (10 CFR 35.390(b)) to utilize radioisotopes to provide safe and effective clinical diagnostic and therapeutic results to patients.

With regard to training and experience requirements and the initial determination of competency, it is our opinion that mastery of the curriculum listed below will ensure high quality practice of radionuclide therapy. This didactic instruction and laboratory training is important for safe and effective therapies and should not be minimized. The use of unsealed sources for therapeutic applications is complex and has serious medical and safety risk associated with it, not only for the patient but for their family, and the public at large. As such, we feel it is important to maintain this high quality of training and experience.

Furthermore, we do not have evidence of an authorized user shortage, and there is no hard data to support a potential shortage. Because of broad licensing by the NRC, exact numbers of authorized users across various disciplines is difficult, if not impossible to obtain. While the number of nuclear medicine trainees have declined over the past few years, combined diagnostic radiology and nuclear medicine residencies have developed and are rapidly gaining in popularity, balancing the decline of nuclear medicine residency trainees. Furthermore, thousands of radiation oncologists are authorized users of unsealed source radiotherapies or have an authorized user eligibility specified on their American Board of Radiology (ABR) diploma. In addition, the pipeline of radiation oncologists is strong with 773 currently in residency programs. Of note, this is the same conclusion that was reached in the Statement by the American Society for Radiation Oncology (ASTRO) to the Advisory Committee on the Medical Use of Isotopes (ACMUI) on 3/1/2018.

Given the many authorized users currently available to perform these therapies, it is not surprising that delay in availability of these therapies to patients is rare. This can be seen across many types of radioisotope therapies such as I-131, Ra-223, I-131 ibritumomab, and Strontium-89. It is possible that there is a patient access issue to certain radioisotope therapies, which could be as a result of physician preferences or multiple other causes, but a shortage of authorized users does not appear to be one of them. An example of this is the current availability of Lu-177-Dotatate. Long wait lists at most institutions are due to the ramping up of this therapy at hospitals around the country, primarily due to the complexity of providing the therapy, availability of infusion spaces, and nursing support, but not due to a lack of authorized users available to administer the therapy.

As such, the availability of authorized treating physicians is not a valid reason to consider shortening the training and experience requirements for unsealed radioisotope therapy under 10 CFR 35.390(b). And, indeed, the complexity of the Lu-177-Dotatate therapy further highlights the need for rigorous training.

Detailed in the addendum to this letter is a description of the basic science and clinical training requirements that are necessary for the proper training of an authorized user. It also fully describes the initial certification of competency as well as maintenance of certification. We would like to stress that these training requirements/hours alone are not sufficient. For example, the three mandated experiences for a given therapy are not sufficient by themselves, but rather should be the culmination of many more such experiences in residency and in practice over several years.

Based on the above points, we oppose lowering the training requirements as currently stated in 10 CFR 35.390(b). We thank the ACMUI for the opportunity to provide input and look forward to future discussions.

Sincerely,

Bennett S. Greenspan, MD, M.S.

Bennett Greenspan, MD
SNMMI Immediate Past-President

Alan K. Klitzke, MD

Alan Klitzke, MD, FACNM
ACNM President

Laura Thevenot

Laura I. Thevenot
CEO, ASTRO

Cc: Christopher Palestro, MD, Chair, ACMUI
Darlene Metter, MD, Vice Chair, ACMUI

Addendum to SNMMI statement on training and experience for authorized users: Guidance for the NRC's ACMUI.

The following are the basic science and clinical training and experience we feel are necessary to have as part of the total training designated in 10 CFR 35.390(b). Below that are the initial competency and maintenance of competency methods we feel are valid.

Basic Science

- Basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material and radionuclides requiring a written directive. Ordering and receiving radiopharmaceuticals.
- Radiation physics: structure of matter, modes of radioactive decay, particle and photon emissions, half-lives and energies. Calculations of radioactive decay. Interactions of radiation with matter, principles of radiation detection, radiation units.
- Mathematics pertaining to the use and measurement of radioactivity, including decay calculations and calculations of organ and whole body dose. Statistics and medical decision making.
- Biochemistry, molecular biology and pharmacology.
- Chemistry of radioactive material for medical use, including: reactor, cyclotron and generator production of radionuclides, radiochemistry, formulation of radiopharmaceuticals.
- Radiation biology: biological effects of ionizing radiation. RBE. Radiation exposure. Radiation biochemistry. Radiation syndromes - Classification of radiation damage. Factors affecting radiation injury. Late effects. Low dose and low dose rate effects. Comparison of risk.
- Instrumentation: Principles of instrumentation used in detection, measurement, and imaging of radioactivity with special emphasis on gamma cameras, including single photon emission computed tomography (SPECT), SPECT/computed tomography (CT), positron emission tomography (PET), and PET/CT systems, and associated electronic instrumentation and computers employed in image production and display. Dose calibrators and survey instruments, including personnel monitoring equipment. Dosage and dose measurements. Quality control of instrumentation – QI, QA, QC, acceptance testing. Artifacts.
- Radionuclide production and quality control. Radiopharmaceutical QC. Radiopharmacology. Radiopharmacy. Surveys and monitoring techniques.
- Radiopharmaceuticals involved in radionuclide therapy and related imaging – biodistribution, mechanisms of localization, potential toxicity. I-131 sodium, Ra-223 dichloride, Sr-89 chloride, Sm-153 EDTMP, Y-90 microspheres, labeled antibodies, Lu-177 Dotatate, Lu-177 PSMA, other alpha and beta-emitting agents.
- Radiation protection, including units, means of reducing radiation exposure, Occupational and public radiation dose limits, shielding and personnel protective equipment (e.g., eye protection, syringe shields). Management of contamination, including spills. Evaluation of patients exposed to potentially dangerous levels of radiation, assisting in the medical management of persons exposed to ionizing radiation, management and disposal of radioactive substances, radiation accident management, and management of radiation safety programs in accordance with federal and state regulations.
- Demonstrate compliance with radiation safety rules and regulations, including Nuclear Regulatory Commission (NRC) or agreement state rules, local regulations, and the ALARA (as low as reasonably

achievable) principle for radiation protection. NRC – 10 CFR 19, 20, 35, especially 10 CFR 35.390. Requirements for training and record keeping. National and international agencies. Restricted and non-restricted areas. Radionuclide therapy written directive. Patient release criteria.
- Medical events – determination of occurrence, evaluation of cause(s) and consequences. Prevention.
- Internal radiation dosimetry, MIRD calculations. Dose calculations – calculations of absorbed doses, therapeutic targets; tumor doses required for effective treatment.

Clinical requirements for radionuclide therapy

- Qualifications of physicians: competence in: patient evaluation - to include: pertinent patient information relevant to the requested procedure using clinical request form, patient interview; chart and computer data base review; Review of relevant imaging studies. Focused physical examination as indicated; and communication with the referring physician if necessary.
- Patient care and procedural skills. History and physical exam.
- Certification in NM, NR, RO, BLS. ACLS desirable.
- Patient selection – Verification of patient identity; Explanation of procedure to the patient. Informed consent. Determination and documentation of pregnancy states. Discussion of risks and benefits of the procedure, including patient education and counseling of expected benefits, possible adverse side effects, radiation safety. Determination of clinical indication. Evaluation of findings – clinical (e.g. operative), pathology, lab values (ex. FT4, TSH, thyroglobulin, WBC, platelets), relevant imaging studies - oncologic studies, including as appropriate studies of sentinel node localization, fluorodeoxyglucose (FDG) imaging, Meta-Iodo-Benzyl-Guanidine (MIBG), somatostatin-receptor imaging, and other agents as they become available. PET, PET/CT, and other hybrid molecular imaging studies for both oncologic and non-oncologic indications.
- Patient preparation: determine desired administered activity, route of administration. Determine required dosimetry. Understand risks specific to each therapeutic radiopharmaceutical, including types of emissions.
- Patient management (along with other physicians as needed) of post-therapy complications.
- Supervision of administration of therapeutic radiopharmaceutical(s) to patient. Radiation protection specific to each therapeutic radiopharmaceutical. Dosimetry.
- Patient release – timing and conditions, provision of radiation precautions, verbal and written.
- Prepare a complete but concise nuclear medicine procedure report.
- Post-therapy follow up. Follow up scintigraphy as necessary.
- Assessment of treatment response.
- Recommend, plan, conduct, supervise, interpret, and report diagnostic and therapeutic nuclear medicine procedures appropriate for the clinical problem or condition.
- Therapeutic administration of radioiodine for both malignant and benign thyroid disease. When appropriate, thyroid studies must include measurement of iodine uptake and dosimetry calculations for radio-iodine therapy.
- Therapeutic administration of other unsealed radiopharmaceuticals for malignant and benign diseases.
- Evaluate radionuclide uptake, biodistribution, metabolism, retention and clearance with quantitative imaging to determine tumor dosimetry and therefore treatment planning.

- Understand fundamentals of imaging molecular targets, processes and events, and existing and emerging molecular imaging techniques, particularly as they relate to current clinical practice of radiopharmaceutical therapy.
- Radiopharmaceutical and/or Clinical Indications (including but not limited to):
  - Hyperthyroidism – I-131 sodium iodide
  - Differentiated thyroid cancer – I-131 sodium iodide
  - Bone pain palliation – Sr-89 chloride, Sm-153 EDTMP
  - Radioembolization for hepatocellular cancer or liver metastases – Y-90 Theraspheres or SIRSpheres
  - Neuroendocrine tumors – I-131 MIBG, Lu-177 Dotatate and other potential PRRT therapies
  - Radiolabeled antibodies
  - Bone metastases - Ra-223 dichloride
  - Prostate cancer – Lu-177 PSMA, (Ac-225 PSMA – currently under active investigation in Europe)
  - Other therapeutic radiopharmaceuticals as they become available for clinical practice.
  - Other potential therapeutic radionuclides currently under investigation:
    - Beta-emitters: Cu-67, Re-186, Re-188, Ho-166
    - Alpha-emitters: Bi-212, Bi-213, At-211, Tb-149, Ac-225

Please note that much of the training delineated above would be obtained within the context of nuclear medicine training programs in Nuclear Medicine or Nuclear Radiology, or training programs in Radiation Oncology. For those physicians who have not had formal training in Nuclear Medicine/Nuclear Radiology or Radiation Oncology and wish to provide radionuclide therapy, the above information is considered essential for competent practice of radionuclide therapy.

Recommendations for initial and maintenance of competency under 35.390(b):

1) Certification process for physicians performing radiopharmaceutical therapy as is already recognized under 10 CFR 35.390 (a) – ABNM or ABR NR or RO certification is sufficient.
2) Participation in Maintenance of Certification for those who became an authorized user through the alternate pathway, similar to 35.390(a).
3) Accreditation of the Nuclear Medicine laboratory. This should include a proficiency testing program that will assess performance of the technologists and physicians.

Future possible evaluation of competency under 35.390(b):

Certification of physicians who have completed a Fellowship in radiopharmaceutical therapy and have passed a certification exam by an accredited medical specialty board.

Dr. Christopher Palestro, Chairman
Advisory Committee on the Medical Uses of Isotopes
The U.S. Nuclear Regulatory Commission

RE: Written Statement to the Advisory Committee on the Medical Uses of Isotopes, the Nuclear Regulatory Commission; Training & Experience Requirements

11 July 2018

Bayer HealthCare
Pharmaceuticals Inc.
Regulatory Affairs
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Whippany, NJ 07981-0915

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Dear Dr. Palestro and the Advisory Committee,

In response to the topics discussed during the Advisory Committee on the Medical Uses of Isotopes (ACMUI) meeting regarding Training & Experience (T&E) hours for AUs under 10 CFR 35.300 on March 1, 2018, Bayer HealthCare Pharmaceuticals Inc. would like to share both the real world operational safety history of Xofigo and the knowledge gained after 5 years of commercial availability to help inform the Nuclear Regulatory Commission (NRC). Bayer is requesting the NRC to consider a proposal to enable a class of physicians, notably medical oncologists and urologists, to attain Authorized User (AU) status under the limited authorization of parenteral administration of ^{223}Ra dichloride (Xofigo) with 80 hours of classroom and laboratory training, as well as appropriate work experience (under the supervision of an AU for Xofigo or a Xofigo manufacturer) and written attestation. Xofigo is an FDA-approved and commercially available therapeutic agent in the United States.

As the NRC is aware, our distribution model limits unintended exposure and reduces the risk of misadministration since it limits the handling requirements at end user facilities to an absolute minimum.

With this demonstrably safe model of distribution along with the previously discussed reality of decreasing numbers of AUs limiting patient access to effective Xofigo treatments, Bayer is interested in identifying a path forward for other physicians to attain AU status for limited authorization to administer Xofigo to patients under their care.

Xofigo

Xofigo ($^{223}RaCl_2$) is an alpha emitting radiopharmaceutical which is concentrated in areas of osteoblastic activity. Xofigo is currently FDA-approved for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. This approval was based on showing a 2.8-month survival benefit (3.6-month survival benefit at the updated analysis) over placebo during the pivotal phase III trial, ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer).

Since the launch of Xofigo in 2013 over 90,000 doses have been delivered and administered to patients at more than 1,000 sites located across the United States (Bayer internal database). During this time there have been very few cases of medication errors reported with the administration of Xofigo Patient Ready Doses in the US.

In our Phase III ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial, there was a higher incidence of Grade 3/4 thrombocytopenia and neutropenia in the radium arm compared to placebo. Overall, there was a higher incidence of Grade 3 and 4 adverse events and more patients discontinuing treatment on the placebo arm than the active Ra-223 arm.

Treatment-emergent AE	Radium (N=509)	Placebo (N=253)
CTC Grade 3 or 4*, n (%)	339 (56)	188 (62)
Serious adverse events, n (%)	281 (47)	181 (60)
Leading to discontinuation of study treatment, n (%)	99 (16)	62 (21)

*CTC toxicity grade: 1 = mild; 2 = moderate; 3 = severe, 4 = life-threatening; and 5 = death.

Per ALSYMPCA: "The number of patients who had adverse events after they received the study drug was consistently lower in the radium-223 group than in the placebo group for all adverse events (558 of 600 patients [93%] vs. 290 of 301 patients [96%]), grade 3 or 4 adverse events (339 patients [56%] vs. 188 patients [62%]), serious adverse events (281 patients [47%] vs. 181 patients [60%]), and study drug discontinuation because of adverse events (99 patients [16%] vs. 62 patients [21%])."

US Distribution/Administration Model of Xofigo

During the development of our distribution model for Xofigo in the United States, an unprecedented level of detail and attention was focused on ensuring that whenever possible, potential routes of exposure and contamination to end users were removed. This resulted in an operational model that provides patient-specific unit dosages in 10 mL syringes which carry both NIST traceability and a high degree of certainty that there is no external contamination.

Before the syringe containing the appropriate unit dosage of Xofigo arrives at the customer, there is an extensive amount of training and education provided by Bayer to all end users to ensure they handle and administer the unit dosage in a safe manner. Bayer has an entire team comprised of ten health physics/nuclear medicine trained individuals, called radiotherapy specialists, to assist in clinical site setup and maintenance activities as needed.

Xofigo injection does not require long infusions, pumps, or pre-meds; no significant injection site reactions have been observed with this radiopharmaceutical in the post-approval setting. An IV line is first established with saline to ensure patency, then the Xofigo-containing unit dosage syringe is connected via a three way stopcock (or similar) followed by a slow bolus injection over one minute. After another saline flush, all potentially contaminated materials are segregated and bagged for decay-in-storage. Due to the decay characteristics of the alpha-emitting radiopharmaceutical, external exposure is not an operational concern and internal contamination is effectively managed by using standard universal precautions. The patient is also immediately releaseable without instructions per 10 CFR 35.75(b). The dose associated with a Xofigo patient (1.6 mrem per NUREG-1556) to members of the public is less than 2% of the NRC limit for which instructions are required; for scale this is roughly the equivalent to the radiation dose experienced on a two hour plane flight.r. This treatment process is then repeated up to 5 more times separated in time by 4 weeks (8 weeks maximum).

NRC AU Licensing of Xofigo

In the fall of 2012, Bayer Healthcare along with the product inventor Algeta were asked to provide some background to the NRC on the health physics considerations of Xofigo usage, a first in class drug, to help inform the licensing decision. Subsequently in January 2013, the NRC announced that Xofigo would be licensed under 10 CFR 35.300, with T&E requirements pursuant to either 10 CFR 35.390 or 35.396, allowing nuclear medicine physicians/radiologists and radiation oncologists to be AUs for the administration of Xofigo (an alternate pathway involving the completion of 700 hours of T&E was available for any other physician to attain such AU status).

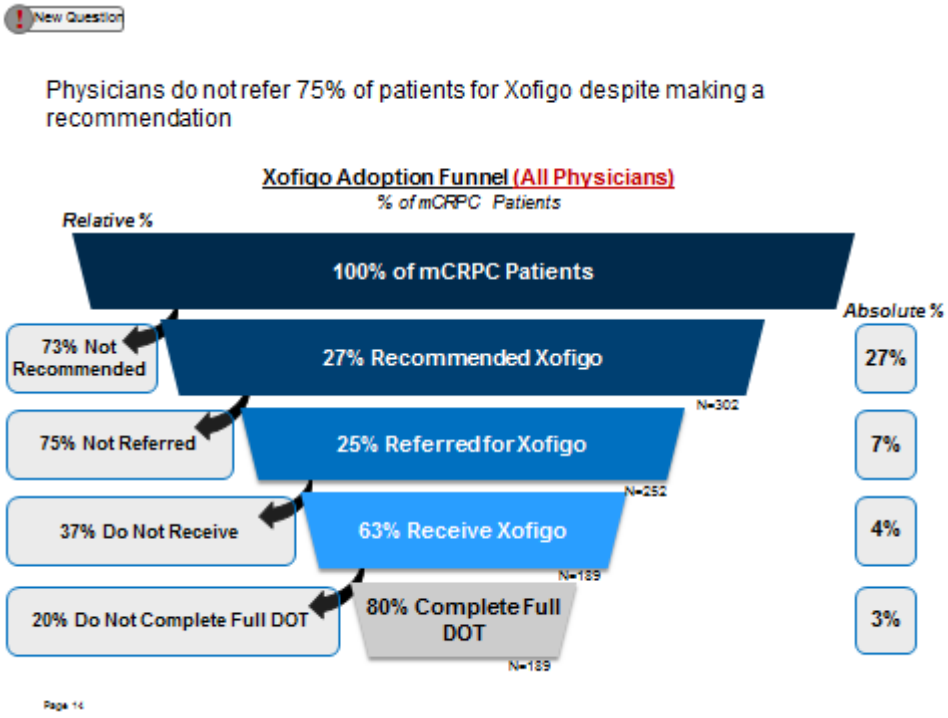
Issues with the current T&E requirements

While this model has worked well in the past, issues have now surfaced that limit patient access, despite the fact that these patients are indicated and eligible for Xofigo treatment. Some of the most prevalent issues are:

- Diminishing numbers of AUs
- Geographic distribution of Authorized Users
- Extraordinary interest within the referring physicians community to administer Xofigo themselves allowing for simplification and optimization of patient experience.
    - These physicians are also in many cases the most appropriately aligned with the clinical and safety benefits of Xofigo and the continuum of patient care.
- Logistical and financial burdens for patients being forced to visit different offices at different times during the course of treatment
- The referring physicians, instead of the administering physicians, historically manages the treatment of adverse events related to Xofigo and other systemic therapies

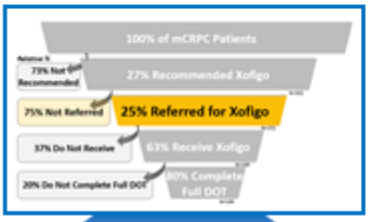
These considerations and hurdles do limit the access of patients to Xofigo as discussed immediately below (additional information can be provided as needed). Xofigo is a product which carries a NCCN Category I recommendation.

Below are diagrams illustrating this access limitation:



New Question

Patient health deterioration is a key reason for loss of referral

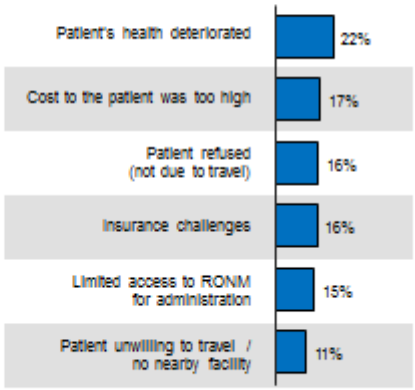


75%

of mCRPC patients ***recommended*** for Xofigo are ***NOT referred*** for Xofigo (among All Physicians)

Reasons for Not Referring Patients for Xofigo Despite Recommendation (Aided)

% mCRPC Patients



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All MDs 278

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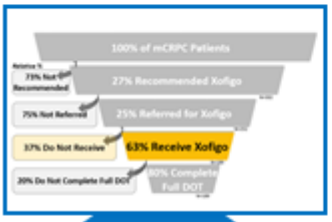
New Question

When Xofigo is not received despite a referral, this is most often because of lack of eligibility or cost/ reimbursement issues

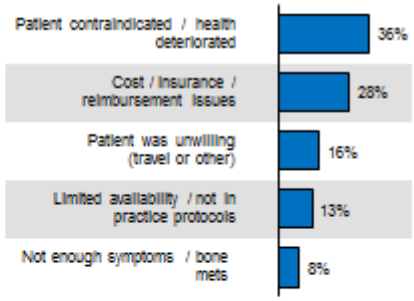


37%

of mCRPC patients ***referred*** for Xofigo do ***NOT receive*** Xofigo (among All Physicians)

Reasons for Not Receiving Xofigo Despite Referral

% mCRPC Patients



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All MDs 136

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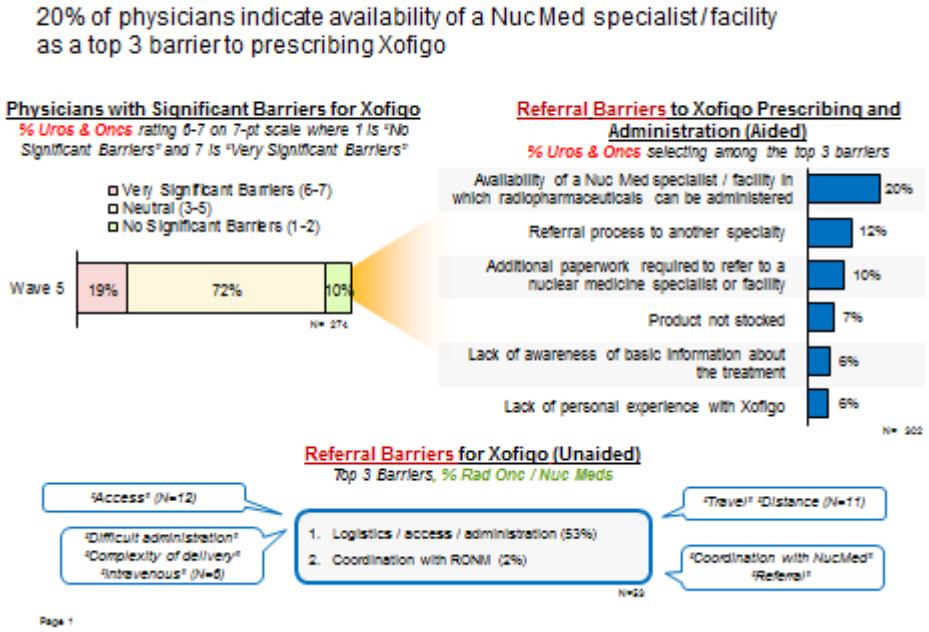
These diagrams indicate that of the 27% of patients who physicians recommend for Xofigo, only 25% are referred to a neighboring clinic for treatment. Even after a referral, 37% of patients don't end up getting Xofigo.

In addition, this patient-access limitation was also confirmed in additional market research:



Proposed path forward

These issues were discussed during the March 1, 2018 ACMUI meeting. It is recognized that an environment is being created in which not all the patients prescribed Xofigo treatment during the course of their disease are actually getting it.

Of importance to the regulatory scope of the NRC are the unique radiation safety considerations that make Xofigo a safe and easy to use product based both on emission characteristics, ease of administration and minimal administered activity. A considerable investment was made to ensure the product is both received and eventually dispensed in a fashion where operational risk is mitigated by engineering controls and in those areas where this is not possible, appropriate expert training is provided by Bayer.

Therefore, Bayer respectfully requests that the NRC allows for the licensers of physicians *vis a vis* T&E under the current distribution model after the completion of training/experience/competency requirements provided by the manufacturer OR other appropriately-trained Authorized Users.

If there are any questions regarding this statement, please contact me at yuan.xue@bayer.com or at 862-404-4057.

Respectfully yours,

Yuan Xue, PhD
Global Regulatory Strategist
Regulatory Affairs – Oncology
Bayer HealthCare Pharmaceuticals

References:

1. Xofigo US Packaging Insert.

2. Bayer internal database.
3. Bayer Responses to NRC Questions: Radium-223 dichloride; dated 8-November-2012.

The American Board of Nuclear Medicine

A Member Board of the American Board of Medical Specialties

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July 31, 2018

Christopher Palestro, M.D.
Chair, Advisory Committee on the Medical Uses of Isotopes
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Dr. Palestro:

The ABNM has reviewed the February 19, 2018 draft report of the ACMUI Subcommittee on Training and Experience Requirements for All Modalities regarding the current NRC requirements for 700 hours of supervised training and experience for Authorized Users (AUs) of radioactive materials under 10 CFR 35.390 – Training for use of unsealed byproduct material for which a written directive is required. The Subcommittee is considering whether the 700 hour training requirement decreases patient access to alpha and beta emitting therapeutic radiopharmaceuticals, and whether it should recommend changes for the total number of hours of training & experience that is required.

The Subcommittee draft interim report states there are two reasons for reasonable concern for a near-future decline in patient access to care: (1) U.S. Food and Drug Administration's approval of ^{177}Lu dotatate for treatment of certain neuroendocrine tumors, and (2) the decrease in the number of first-time candidates sitting for the Certification Examination of the American Board of Nuclear Medicine.

The ABNM welcomes the FDA-approval mentioned above and supports efforts to bring more targeted radionuclide therapies to patients in the U.S.; however, the ABNM strongly believes that the current requirement for 700 hours of supervised training and experience should not be changed and that reducing the *minimum* requirement for 700 hours of supervised training and experience for unsealed radioisotope therapy raises concern for patient safety. The decrease in the number of nuclear medicine or nuclear radiology qualified AUs is likely overestimated in the Subcommittee draft interim report. The need for fact-driven evaluation before any action was also endorsed by the American College of Radiology (ACR) in comments to the NRC ACMUI sent on July 16. The ABNM fully supports the ACR statement.

The number of initial ABNM certificates issued each year has been relatively constant from 1977 – 2015. The average number of certificates issued each year was 72 during this time (range 50 – 107). The ABNM issued 43 initial certificates in 2016, and 49 certificates in 2017. No data is available for 2018 since the certification examination will not be given until October.

The ABNM has issued a total of 5,744 certificates since the board was incorporated in 1971. There are at least 3,591 active diplomates (not deceased or retired) at the present time.

The Subcommittee draft interim report noted a decrease in the number of ACGME accredited Nuclear Medicine training programs and residents from 57 programs with 161 residents in academic year 2007 – 2008, to 41 programs with 75 residents in 2017 – 2018.

The decrease in the number of programs and trainees is partly due to an increase in the number of Nuclear Medicine physicians who are also certified in Diagnostic Radiology by the American Board of Radiology (ABR). Certification by the ABR decreases the duration of Nuclear Medicine training required for ABNM certification from 36 months to 16 months, creating the appearance of decreasing numbers of residents, when it is the duration of training that is decreasing. Contributing to this trend is the increasing availability of dual training pathways where residents training in Nuclear Medicine are counted as Diagnostic Radiology residents rather than Nuclear Medicine residents, due to the requirements of the ACGME and the ABR. At a recent professional meeting, the ABNM learned that there are at least 35 additional radiology residents engaged in a new program through the ABR aimed at additional qualification in nuclear radiology during the usual length of their diagnostic radiology residency.

The ABNM believes that dual training will result in better-trained physicians to meet the needs of patients in the era of molecular imaging and therapy. The ABNM sees no evidence that workforce issues have decreased patient access to care, and concern for potential future issues has not considered recent positive changes in Nuclear Medicine training. The popularity of the dual training pathways in Nuclear Medicine and Diagnostic Radiology is one of the reasons for the decline in the number of ACGME accredited Nuclear Medicine programs; however total number of residents is not reflected in a similar decline in number of ABNM certificates.

The ABNM urges the subcommittee to re-evaluate the initial estimates of AUs available and those in training to provide the needed services. We also request a re-review of the number of radiation oncology physicians in training as numbers quoted in the draft interim report were erroneously low.

In addition, targeted radionuclide therapies frequently require management by experts in multiple disciplines (surgery, radiation oncology, medical oncology, radiology, nuclear medicine) at centers of excellence; no shortage of AUs has been reported at such institutions. Finally, if the current number of AUs proves to be insufficient to make radionuclides widely available, we believe pursuing approaches to increase the number of properly trained nuclear medicine physicians, nuclear radiologists and radiation oncologists will be better for patient care than lowering the standards for administering radionuclide therapies.

Although the NRC does not oversee the insurance industry, we feel that a larger threat to patient access as compared to the number of AUs in the United States is insurance coverage.
Reducing the *minimum* requirement for 700 hours of supervised training and experience for unsealed radioisotope therapy further jeopardizes patient safety because there is no standardized

assessment of the knowledge, skill and judgment of these physicians who are not certified by the ABNM, or certified by the ABR in the subspecialty of Nuclear Radiology.

In summary, the ABNM strongly believes that the current requirement for 700 hours of supervised training and experience should not be changed and asks the NRC correct the errors in the number of trainees, which we would expect could reduce or end the concern on the number of AUs available to provide these services.

Sincerely,

George M. Segall, M.D.
Executive Director

Daniel A. Pryma, MD
Chair

GMS/DAP/mrf

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August 22, 2018

Christopher Palestro, MD
Chair, Advisory Committee on the Medical Uses of Isotopes
US Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Dr Palestro,

The leadership of the ABR reviewed the February 19, 2018 and July 5, 2018 draft reports of the ACMUI Subcommittee on Training and Experience Requirements for All Modalities regarding the current NRC requirements of 700 hours of supervised training and experience for Authorized Users (AUs) of radioactive materials under 10 CFR 35.390*, Training for use of unsealed byproduct material for which a written directive is required.* The subcommittee has suggested that the 700-hour training requirement might be reduced, partly because of a perceived decrease in patient access to care with alpha and beta emitting therapeutic radiopharmaceuticals.

The ABR board strongly opposes a reduction in the current training requirements or development of a "limited status AU". This is a patient safety and quality-of-care issue. As this field becomes more complex, it is important to maintain strong training requirements.

The subcommittee mentions shortages in the number of AUs in the United States. We are not aware of any shortage. The ABR and ABNM have not seen decreases in the number of candidates seeking certification in nuclear medicine or nuclear radiology (nuclear radiology is the term used by the ABR for our candidates and diplomates, whereas nuclear medicine is usually practiced by non-ABR certified individuals who are certified only by ABNM). It is true that there has been a decline in the number of "Nuclear Medicine Residency Programs", largely because of the increasingly limited job market for individuals without strong diagnostic radiology (DR) training in this era of hybrid imaging (PET/CT, SPECT/CT, PET/MR), which requires substantial knowledge of all aspects of DR modalities. However, in DR, there has been increased interest in nuclear radiology *because* of hybrid imaging and new therapeutic radioisotopes. DR residency programs are *not* closing and there are increased opportunities for nuclear radiology training in DR programs. The number of radiation oncology (RO) residents and candidates for ABR RO certification has been stable for many years. Most ABR DR and RO diplomates are AU Eligible at the time of certification, and most go on to become AUs.

In summary, the ABR strongly opposes a reduction in the number of hours of supervised training and experience for AUs under 10 CFR 35.390. We feel that maintenance of the current 700 hours is necessary to protect the public.

Sincerely,

Lisa A Kachnic, MD
President

Valerie P Jackson, MD
Executive Director

ACR®
AMERICAN COLLEGE OF RADIOLOGY

QUALITY IS OUR IMAGE

August 27, 2018

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

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

Dear NRC Chairman Kristine Svinicki:

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

Concerns Regarding NRC Activities Related to 10 CFR 35.390

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

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

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

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

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

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

Lack of Data Indicating AU Shortage

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

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

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

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

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

Other Factors Driving Utilization of Radiopharmaceutical Therapy Unrelated to NRC Regulations

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

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

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

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

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

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

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

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

Prepackaged Unit Dose Distribution Does Not Eliminate Need for Expertise

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

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

Alpha- and Beta-Emitters

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

Chemotherapy Drugs Are Not Radioactive

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

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

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

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

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

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

Summary of ACR Recommendations

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

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

Respectfully Submitted,

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