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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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THURSDAY, MARCH 10, 2016

The meeting was convened by Teleconference at 1:30 p.m. Eastern Standard Time, Philip O. Alderson, M.D., ACMUI Chairman, presiding.

MEMBERS PRESENT:

PHILIP O. ALDERSON, M.D., Chairman

FRANCIS M. COSTELLO, Agreement State Representative

VASKEN DILSIZIAN, M.D., Nuclear Cardiologist

RONALD D. ENNIS, M.D., Radiation Oncologist

STEVEN R. MATTMULLER, Nuclear Pharmacist

DARLENE F. METTER, M.D., Diagnostic Radiologist

MICHAEL O'HARA, Ph.D., FDA Representative

CHRISTOPHER J. PALESTRO, M.D., Nuclear Medicine Physician

JOHN J. SUH, M.D., Radiation Oncologist

LAURA M. WEIL, Patients' Rights Advocate

PAT B. ZANZONICO, Ph.D., Vice-Chairman

Non-Voting: ZOUBIR OUHIB

NRC STAFF PRESENT:

PAMELA HENDERSON, Deputy Director, Division of Material Safety, State, Tribal and Rulemaking Programs

DOUGLAS BOLLOCK, ACMUI Designated Federal Officer

SOPHIE HOLIDAY, ACMUI Alternate Designated Federal Officer and ACMUI Coordinator

LUIS BENEVIDES, Ph.D., RES/DSA/RPB

HECTOR BERMUDEZ, R-I/DNMS/MB

JENNIFER BISHOP, R-III/DNMS/MLB

TAMMY BLOOMER, COMM/OCMWO

COLLEEN CASEY, R-III/DNMS/MLB

JACKIE COOK, R-IV/DNMS/NMSB-B

SARA FORSTER, R-III/DNMS/MLB

ALAN FRAZIER, COMM/OCMKS

CASSANDRA FRAZIER, R-III/DNMS/MLB

MICHAEL FULLER, NMSS/MSTR/MSEB

GINA DAVIS, NMSS/DSFM/RMB

ROBERT GALLAGHAR, R-I/DNMS/MB

VINCENT HOLAHAN, Ph.D., NMSS/MSTR

ESTHER R. HOUSEMAN, OGC/GCLR/RMR

DONNA-BETH HOWE, Ph.D., NMSS/MSTR/MSEB

JAN NGUYEN, R-I/DNMS/MB

PATTY PELKE, R-III/DNMS/MLB

GRETCHEN RIVERA-CAPELLA, NMSS/MSTR/MSEB

VERED SCHAFFER, R-III/DNMS/MLB

TOYE SIMMONS, R-III/DNMS/MLB

KATHERINE TAPP, Ph.D., NMSS/MSTR/MSEB

TORRE TAYLOR, NMSS/MSTR/MSEB

LESTER TRIPP, R-I/DNMS/MB

ALSO PRESENT:

KATHI BENSON, Cardinal Health

NATHANIEL BOESCH, Spectrum Pharmaceuticals, Inc.; Foley Haag LLP

Sue Bunning, Society of Nuclear Medicine and Molecular Imaging

Jennifer Cultrera, Spectrum Pharmaceuticals, Inc.; Florida Cancer Specialists & Research Institute

AL DEJESUS, Spectrum Pharmaceuticals, Inc.

GARY DILLEHAY, Northwestern University

BRYAN EDWARDS, Fox Chase Cancer Center

DIERDRE ELDER, University of Colorado Health

HUGH EVANS, Eckert & Ziegler Radiopharma, Inc.

SANDRA GABRIEL, *unaffiliated*

MUNIR GHESANI, New York University School of Medicine

BENNETT GREENSPAN, Medical College of Georgia

MICHAEL DE LA GUARDIA, Cook Children's Health Care System

MICHAEL GUASTELLA, Council on Radionuclides and Radiopharmaceuticals

SHERRIE FLAHERTY, Organization of Agreement States Board

GREGG FRANKLIN, American Society for Radiation Oncology

STAN HAMPTON, Eli Lilly and Company

NICKI HILLIARD, University of Arkansas for Medical Sciences

KENDALL HORVATH, Society of Nuclear Medicine and Molecular Imaging

STEVE HOWARD, University of Kansas Medical Center

CLARE JENNINGS, Bayer

CLINT JOFFRION, *unaffiliated*

YUNGMI KIM, Spectrum Pharmaceutical

CAITLIN KUBLER, Society of Nuclear Medicine and Molecular Imaging

RALPH LEITO, St. Joseph Hospital

CRAIG LITTLE, Health Physics Society

GARY LUNGER, Bayer

STEVE MACK, Arkansas Department of Health

RICHARD MARTIN, American Association of Physicists in Medicine

GENE MENENDEZ, Spectrum Pharmaceuticals, Inc.

MICHAEL MILLER, Spectrum Pharmaceuticals, Inc.

CLARINE NARDI RIDDLE, Spectrum Pharmaceuticals, Inc.; Kasowitz, Benson, Torres & Friedman LLP

JEFFREY NORENBERG, University of New Mexico College of Pharmacy

AVI OLER, Spectrum Pharmaceuticals, Inc.

VIRGINIA PAPPAS, Society of Nuclear Medicine and Molecular Imaging

MICHAEL PETERS, American College of Radiology

JUSTIN QUINN, University of Michigan Health System

GLORIA ROMANELLI, American College of Radiology

KARL SCHWARTZ, Patients Against Lymphoma

KAREN SHEEHAN, Fox Chase Cancer Center

MICHAEL SHEETZ, University of Pittsburgh

PHILLIP STEVENS, Spectrum Pharmaceuticals, Inc.

MICHAEL TOMBLYN, *unaffiliated*

CINDY TOMLINSON, American Society of Radiation Oncology

ALLEN YANG, Spectrum Pharmaceuticals, Inc.

C O N T E N T S

P-R-O-C-E-E-D-I-N-G-S

1:34 p.m.

CHAIRMAN ALDERSON: Thank you. All right, good afternoon. Welcome to the ACMUI Teleconference to discuss the ACMUI's draft Subcommittee Report on the Training and Experience for Authorized Users of Alpha, Beta and Gamma Emitters under 10 CFR 35.390.

At this time I'd like to turn the meeting over to Mr. Bollock for opening remarks.

MR. BOLLOCK: Thank you, Dr. Alderson. As the Designated Federal Officer for this meeting, I am pleased to welcome you to this public meeting of the Advisory Committee on the Medical Uses of Isotopes. My name is Doug Bollock.

I'm the branch chief of the Medical Safety and Events Assessment Branch where I'm the Designated Officer for the Advisory Committee in accordance with 10 CFR Part 7.11. Present today is the alternate Designated Federal Officer is Sophie Holiday, ACMUI Coordinator.

An announced meeting of the Committee is 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 February 8th, 2016 edition of the Federal Register Volume 81 Page 6551.

The folks on the Committee advise the staff on issues and questions that arise on the medical use of byproduct material. The Committee provides counsel for the staff but does not determine or direct the actual decisions of the (telephonic interference). The NRC solicits the views of the Committee and values their opinion.

I request that whenever possible we try to reach consensus on the issues that we will discuss today. I also recognize 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 to perform a roll call of the ACMUI members participating today, starting off with Dr. Philip Alderson, our health care administrator and Chairman.

CHAIRMAN ALDERSON: Here.

MR. BOLLOCK: Thank you.

Dr. Pat Zanzonico, our nuclear medicine physicist and Vice Chairman.

VICE CHAIRMAN ZANZONICO: Here.

MR. BOLLOCK: Thank you.

Mr. Frank Costello, the Agreement States representative.

MEMBER COSTELLO: Here.

MR. BOLLOCK: Thank you.

Dr. Vasken Dilsizian, nuclear cardiologist.

MEMBER DILSIZIAN: Here.

MR. BOLLOCK: Thank you.

Dr. Ronald Ennis, radiation oncologist.

MEMBER ENNIS: Here.

MR. BOLLOCK: Thank you.

Dr. Sue Langhorst, radiation safety officer.

MEMBER LANGHORST: Here.

MR. BOLLOCK: Thank you.

Mr. Steve Mattmuller, our nuclear pharmacist.

MEMBER MATTMULLER: Here.

MR. BOLLOCK: Thank you.

Dr. Darlene Metter, diagnostic radiologist.

Okay, moving on. Dr. Michael O'Hara, our FDA representative.

MEMBER O'HARA: Here.

MR. BOLLOCK: Thank you.

Dr. Christopher Palestro, nuclear medicine physician.

MEMBER PALESTRO: 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.

All right. I determine we have over seven members present and we do have a quorum. Also on the phone we have Mr. Zoubir Ouhib. Mr. Ouhib has been selected as the ACMUI therapy medical physicist. He is pending security clearance but may participate in the meeting, however, he does not have voting rights at this time.

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

MS. HENDERSON: Pam Henderson, deputy director of Material Safety, State, Tribal, and Rulemaking Programs.

DR. HOWE: Donna-Beth Howe, medical team.

MR. FULLER: Mike Fuller, medical team.

MS. HOLIDAY: Sophie Holiday, medical team.

DR. TAPP: Dr. Katie Tapp, medical team.

MS. HOUSEMAN: Esther Houseman, attorney in the Office of the General Counsel.

DR. HOLAHAN: Dr. Vincent Holahan, senior level advisor.

MS. TAYLOR: My name is Torre Taylor. I'm in the Rulemaking Branch.

MR. BOLLOCK: Thank you all. Okay, now we'll go to the headquarters employees who are on the phone. Any NRC headquarters employees that are on the phone?

All right. Hearing none, I'll move on to the NRC regional offices. Do we have anyone on the call from Region I? Okay. Do we have anyone on the call from Region III? None. Do we have anyone on the call from Region IV? Okay.

Members of the public who notified Ms. Holiday that they would be participating in the teleconference today will be captured in the transcript. Those of you who did not provide prior notification, please contact Ms. Holiday at

sophieholiday@nrc.gov. That's sophieholiday@nrc.gov, or calling her at area code 301-415-7865. We have a bridge line available and the phone number is 1-800-593-7215. The passcode to access the bridge line is 1316655 followed by the pound sign.

This meeting is also used in the GoToWebinar application to view the presentation handouts in real time. You can access this by going to www.gotowebinar.com, www.gotowebinar.com and search for meeting ID number 107-511-939.

The purpose of this meeting is to discuss the ACMUI subcommittee's report on the training and experience requirements for authorized users of alpha, beta and gamma emitters under 10 CFR 35.390.

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

Comments and questions are usually addressed by the Committee near the end of the meeting after the Committee has fully discussed the topic. I would also like to add that the handouts and the agenda

of this meeting are available on the NRC's public website.

At this time I would ask that everyone on the call who is not speaking to place their phones on mute. If you do not have the capability to mute your phone, please press star 6 to utilize the conference line mute and unmute function. I would ask everyone to exercise extreme care to ensure that background noise is kept at a minimum as any sort of background sounds can be very disruptive on a conference call this large.

At this point I'd like to turn the meeting back over to Dr. Alderson.

CHAIRMAN ALDERSON: Thank you, Mr. Bollock. So at this time I will turn the meeting over Dr. Christopher Palestro who is chair of this subcommittee.

MEMBER PALESTRO: Okay. Thank you, Dr. Alderson. Before I begin, I'd like to acknowledge and thank the subcommittee members including Vasken Dilsizian, Ronald Ennis, Sue Langhorst, Laura Weil and Pat Zanzonico for their time and efforts and discussions to address the tasks with which we have been charged.

I'd also like to acknowledge the subcommittee has received numerous letters from stakeholders including professional organizations and

patients, and to acknowledge that our subcommittee has read and in fact considered all of the letters and comments while developing our recommendations.

That being said I would like to review for everyone our draft report. The subcommittee on training and experience for authorized users was charged with two tasks.

Number one, to determine if the current requirements of 700 hours for training and experience for authorized users of alpha and beta emitters in 10 CFR 35.390, which is the training for use of unsealed byproduct material for which a written directive is required, places hardship on the patient community, and to make recommendations for ACMUI action.

A second task with which we were charged was to establish a recommendation for the total number of hours of training and experience for authorized users of such emitters that appropriately balances safety with reasonable patient access to these agents.

With respect to the first charge, I'd like to provide some background. And just to review, radiolabeled antibody treatment of lymphoma with beta emitters was approved by the U.S. FDA approximately 14 years ago. Two agents initially were available -- yittrium-90 ibritumomab tiuexetan, Zevalin, and

iodine-131 tositumomab, Bexxar.

Use of both of these agents, which peaked a few years after introduction, has in fact, despite extremely favorable clinical results, steadily declined since that time. I call your attention to a Figure 1, which is adapted from a slide that was presented by Spectrum Pharmaceuticals after the ACMUI Fall meeting in October 2015.

You can see that use peaked in approximately 2005 and has for the most part followed a steadily downward trend since that time. Bexxar, in fact, was withdrawn from the market about two years ago because of a lack of use. At the time it was withdrawn, fewer than 75 patients had been treated in that year.

So the subcommittee examined various factors that could potentially or possibly account for the decrease in the use of these agents. One of the comments that was made at the 2015 Fall ACMUI meeting was a lack of knowledge.

And according to Dr. Cultrera's presentation at that meeting, she noted the hematology/oncology fellows are not exposed to these agents during their training so they may not be aware that these agents are available and consequently, since they're not aware of them, they do not prescribe them.

That is an educational, though unfortunate, that's really an educational, not a regulatory issue.

What about competition? That's another potential factor. Since these agents were introduced about 14 years ago, new effective therapies that do not involve radiation have been developed, and it is likely that some of the decrease in use is related to the availability of these newer agents.

And there's nothing unique about this, the radiolabeled antibodies. This really is a fact of life. It's common to all drugs, all therapies, and to even diagnostic approaches. As newer, equally or more efficacious, more effective agents or tools become available the use of older agents typically declines.

Another potential factor and issue that has been raised is the shortage of authorized users. It has been suggested that the infrequent and declining use of these agents is a direct result of the requirement for 700 hours of training and experience to obtain Authorized User, or AU, status that went into effect shortly after these agents were introduced.

In his letter of January 25th, 2016, to the ACMUI, Dr. Joseph Mace stated that to his knowledge, quote, no oncologist has been able to receive AU status under the alternate pathway, since the regulations went

into effect.

That in fact may be a true statement. However, without knowledge of how many oncologists sought AU status prior to the rule change, it's really not possible for us to assess the significance of this statement.

The only way that we can really assess the significance of the statement and the magnitude of it would be to determine the impact on AUs that the change in training and education requirements had, and we'd have to have aggregate data on AUs over time, data which unfortunately simply are not available.

The assertion that a shortage of AUs is the cause of the decline in the use of these agents is undermined by the fact that even at many large medical centers, even those with an abundance of clinicians and authorized users who work closely together, these radiopharmaceuticals are used infrequently.

And this you can see Figure 2 which was adapted from my presentation at the fall 2015 meeting how relatively infrequently these agents are used.

So according to his January 2016 letter, Dr. Mace who receives consultations from, quote, across the state of Florida, close quotes, has administered beta emitters including Zevalin to more than 40 patients

over the past decade. That amounts to only about four patients per year.

Safety. The exceptional safety record that has accompanied beta and more recently alpha emitting radiopharmaceuticals is indisputable. Therefore, given that they're safe, why not simply reduce the training and experience requirements anyway, regardless of whether or not there is a shortage of AUs?

Well, that's certainly an interesting question and it deserves some thought, but it is important to note that the excellent safety records achieved with these agents have been attained in the majority of cases. Not in all cases, but in the clear cut majority of cases by or in conjunction with AUs who have successfully completed the rigorous, the 700-hour training and experience requirements.

So in summary then, after reviewing all of the facts and all of the data that were available to us, the ramifications of a change in training and experience potentially are significant.

In terms of safety, as already noted, the excellent safety records that have been achieved with these agents had been attained for the most part by or in conjunction with AUs who have successfully completed the rigorous training and experience requirements.

Whether or not the safety records would be comparable in the hands of AUs with considerably less training and experience is a matter of conjecture.

It has been suggested that 80 hours of training and experience is sufficient for administration of these agents, and this is based on the concept that if 80 hours is sufficient for radioactive iodine administration, which has been asserted is far more complex and hazardous, then a comparable amount of training and experience is sufficient for administration of alpha and beta emitters.

It is important to note that the field of nuclear medicine, including therapy, originated to a great extent in endocrinology because of the role of radioactive iodine in both the diagnosis and treatment of thyroid diseases. Thus, endocrinologists have a long history of familiarity with the use of radioactive materials.

Virtually all of the letters in support of a change in training and experience support this change for oncologists. Surely there are other individuals in other specialties who are capable of administering these agents. Should they also be included?

Finally, should satisfactory completion of training and experience allow an individual to

administer all of these agents, or should use be restricted to specific radiopharmaceuticals as was suggested in the February 2016 letter of Hilliard et al. to the ACMUI?

Since it's not possible to conclude that the current training and experience requirements are the only or even the principal cause of the decreased use of radiopharmaceuticals like Zevalin and Bexxar, and because of the potential issues raised by the proposed changes in training and experience, the subcommittee recommends against the reduction in the number of hours of training and experience required for 10 CFR 35.390 use.

Our second charge was to establish a recommendation for the total number of hours of training and experience for authorized users of alpha and beta emitters to ensure safety. While for the reasons stated the subcommittee opposes the reduction in the number of hours of training and experience, we also recognize the need for a thorough review of the current requirements.

One important reason for this review is it has been nearly 15 years since the current requirements were established. Since that time, new radiopharmaceuticals have been introduced and this is

a trend that likely will continue. Appropriate training and experience requirements for these agents need to be established.

There's another equally important reason to undertake this review. The educational paradigm has changed over time. There has been a shift away from prescriptive curricula, i.e., specific number of classroom hours to competency-based education. The time really has come to reevaluate our approach to training and experience with an emphasis on competency, not just on experience/hours.

This is a complicated undertaking and simply cannot be completed in weeks or even months. It requires input from many stakeholders if it is to be successful, and once established the training and experience requirements need regular, periodic review to ensure that they maintain current or that they are current.

Therefore, the subcommittee recommends that the ACMUI establish a standing subcommittee with the specific charge of periodically reviewing training and experience requirements that are currently in effect and making recommendations for changes as warranted.

This report was unanimously approved by the

subcommittee. However, a differing opinion with respect to the barriers to access was presented by Ms. Laura Weil. And at this point I would like to turn the floor over to Ms. Weil to ask her to please voice her differing opinion.

MEMBER WEIL: Well, thank you, Dr. Palestro. I felt it was very important to acknowledge the testimony that we have heard regarding logistical barriers to access to alpha emitters and beta emitters in the community setting.

Had the charge of the subcommittee been to determine if there was unnecessary hardship created in the 700-hour training and experience requirements, I wouldn't have felt quite the need to state this slightly differing opinion or caveat, if you will.

But given that the word unnecessary was not included, I thought it was really important that we simply acknowledge that there appear to be barriers, necessary or not, in the community setting, and that is really the gist of my dissenting comments.

MEMBER PALESTRO: Okay, Ms. Weil, anything else you want to say?

MEMBER WEIL: No, I just wanted to add to our report that we acknowledge that there does appear to be some rationale, so why it may be difficult for some

patients in the community setting to have access to these particular radiopharmaceuticals due to the fact that the medical oncologists in the community are not able to administer it.

But I agree with the subcommittee statement that we need to move forward with an ongoing reassessment of all training and experience requirements for radiopharmaceuticals.

MEMBER PALESTRO: All right, thank you. At this time I'd like to welcome and invite any comments from the subcommittee members. I would just ask that you please be sure to state your name for the court reporter. Any comments from the subcommittee?

MEMBER DILSIZIAN: I could. All right, Vasken here. Does someone else want to speak or --

VICE CHAIRMAN ZANZONICO: Well, this is Pat Zanzonico. But Vasken, why don't you go ahead first, please.

MEMBER DILSIZIAN: Chris, first of all, I want to congratulate you for the excellent leadership position that you've taken in your presentation.

I do agree that the training has moved to the competency based educational examination, but I would like to remind everyone that having already been the chair of the training of the nuclear cardiology

program that competency based does not mean less number of training pre-specified period, whether it's years or hours.

For example, if the surgery program is three years, just because you're competent in doing appendectomies in two months you don't reduce the overall training period for surgery and that applies to cardiology and other things.

So I just want to emphasize that competency is important. We have to determine that the physician in some sort of examination or verification of safety is competent beyond the hours or the training period, but that doesn't necessarily mean that you have to shorten the period just because they learn it faster than other colleagues.

MEMBER PALESTRO: Okay. Thank you, Vasken. I just want to echo your comments. You're absolutely correct. It doesn't necessarily mean that the training period or the requirements are shortened. In some cases they may actually, in certain circumstances, be lengthened for individuals who are unable to achieve competency with a specific number of hours of training, or as you mentioned in the case of x number of surgeries that might be required.

So the focus is not so much on hours and such

like that. It's really on developing the competency.

Any other comments from the subcommittee?

VICE CHAIRMAN ZANZONICO: Yes. Dr. Palestro, this is Pat Zanzonico. And there were two points that I wanted to make, if I may. The first is, as all of us on the ACMUI have come to learn, the rulemaking process is by necessity a very lengthy one extending over a number of years at least.

And to at this point introduce an additional component to the ongoing rulemaking, which already includes some very important issues that need to be addressed in a timely manner such as definition of medical events and so forth, would inevitably delay the finalization of the current rulemaking significantly, probably of the order of additional years unless one were to rush to some sort of decision regarding the appropriate length of training whether it was competency based or prescriptive.

Not that that should be the driver of whether the current training requirements are maintained or not, it should be based on the merits. But I think it's a point that should not be ignored.

And the second point that I wanted to make is that in a number of the submissions, at least one of the submissions from a stakeholder recommending the

change of the training requirements from the current 700 hours to 80 hours was the observation, or the assertion rather that already, as you alluded to, endocrinologists can use I-131 therapeutically in the management of thyroid diseases and that I-131 is more hazardous than, for example, between 90 and other pure beta emitters and alpha emitters and so forth.

And I really take some issue with that statement. In some respects it is less hazardous, but in other respects these pure particle emitters are more challenging to deal with.

In the instance of contamination and possible contamination of the public they are more challenging to detect and to assay, and in some respects would require more training to recognize the subtlety of using those sorts of radionuclides and the hazards they present than I-131. So I take issue again with the assertion that I-131, which is used with message framing under some circumstances, actually represents a more hazardous or potentially more hazardous situation than the alpha or beta emitters that are actually being discussed at the moment.

So those are two points I wanted to make, and thank you.

MEMBER PALESTRO: Okay. Thank you, Dr.

Zanzonico. Any other comments from members of the subcommittee?

MEMBER ENNIS: This is Ron Ennis.

MEMBER PALESTRO: Yes, Ron.

MEMBER ENNIS: Thank you. I do want to thank the petitioners for raising this issue because it is pretty clear that this issue needs to be looked at carefully in an overarching kind of way.

I think it's clear to all that we need a regulatory language that speaks to the current situations and all their aspects in ensuring safety, but use and access in appropriate ways, but also that we not have rules that are individualized for one isotope at a time as that would be completely unworkable.

It's also very clear, I think, to me and I believe to the rest of our subcommittee that this is going to appropriately take some time for us to think through each of the scenarios and what would be appropriate and to design it more carefully.

And while that's important it necessarily takes time. There's no doubt that the rest of the rulemaking process that is near completion has taken a very long time and those rules are sorely needed.

Any delay in that would really have significant impacts in medical care, brachytherapy in particular,

and delaying that for us to now tackle a brand new issue just does not seem to be appropriate. I look forward to us tackling the issue carefully.

On the last point of a comparison to I-131 and its purported safety, in thinking about that I recognize that our committee in other contexts has been discussing improving the education available for I-131 as there are apparently many instances of problems with radiation safety precautions and patients having been treated. For example, radioactive material showing up at landfills in Pennsylvania on a consistent basis is one example of that.

And it strikes me that the notion that everything is great in I-131 with 80 hours may actually be completely incorrect. And it could very well be that NRC's response to these problems by enhancing education material on its website is really not the problem and not really the solution, but the problem may be in the T&E of the authorized users who are treating patients with I-131.

So I wonder about this and look forward to us or a subcommittee evaluating the entire spectrum of T&E requirements for all radiopharmaceutical isotopes. Thank you.

MEMBER PALESTRO: Thank you, Dr. Ennis.

Any other comments from subcommittee members?

MEMBER LANGHORST: This is Sue Langhorst. I appreciate all the hard work that Dr. Palestro did on this report, and I don't have anything other to add that everyone else has already addressed. Thank you.

MEMBER PALESTRO: Thank you, Dr. Langhorst.

Other comments from members of the subcommittee? Hearing none, at this time I'd like to welcome any comments from the committee members. And again, please make sure to state your name for the court reporter.

MEMBER METTER: This is Darlene Metter.

MEMBER PALESTRO: Yes, Dr. Metter.

MEMBER METTER: Thank you. I'm sorry I came in a little late. I was just chairing an RDRC meeting, and actually I was talking to our current radiation safety officer regarding the training requirements.

And her concern, which I also have concerns about reducing the hours, is that even though even our Y-90 microspheres that we do many therapies on these patients, the persons that the radiologist, the radiologist that administers it even though people didn't know what to do when they actually had

contamination of the field and they had not put the stop clock completely tight so there was a spill in the room and they didn't know what to do. So I think the training experience is very important, because if everything goes well there's not a problem but when things go wrong you have to know what to do when you have a mishap that is not expected.

So I think keeping the 700 hours is very important for safety for not only the individual, but the patient and the other health care professionals involved in the therapy.

MEMBER PALESTRO: Thank you, Dr. Metter. Other comments from members of the committee?

MEMBER COSTELLO: Yes, this is Frank Costello.

MEMBER PALESTRO: Yes, Mr. Costello.

MEMBER COSTELLO: Yes, a couple things. I would very much agree that nothing in this effort should delay the progress of the new Part 35 being issued and this should be treated as a separate matter. We've gone too far in Part 35 to drop back a couple of years.

However, I do have a question, this comparison of the alpha and beta emitters to the I-131 training. I think as a requirement, you know, the 80 hour required is not limited to endocrinologists. It

would be any doctor who had the 80 hours and other things that could be approved.

I don't, unless I'm wrong that the only people who use the iodine in the 35.300, are they all endocrinologists or do other doctors come in?

MEMBER METTER: Yes. This is Darlene Metter.

MEMBER COSTELLO: Yes.

MEMBER METTER: And the radiologists use 80 hours because they don't do the 700 -- oh, I'm sorry, they actually -- no, I'm sorry. They use these 80 hours. I believe our radiologists can do that.

MEMBER COSTELLO: Yes.

MEMBER METTER: Or is that correct, Chris? Is that what you all do too or --

MEMBER PALESTRO: No. All our radiology residents go through the full 700 hours as part of their training. But in answer to Mr. Costello's question, and this is Dr. Palestro speaking, Sophie, correct me if I'm wrong, but I believe that the 80-hour requirement is not limited to endocrinologists.

DR. HOWE: That is correct. Yes, we do have some like foreign medical international graduates who haven't gone through the diagnostic radiology and they may request the 80 hours plus three therapies.

MEMBER COSTELLO: So if the 80 hours are sufficient to get any physician approved and not just endocrinologists who already know a lot about this field, I still don't understand why for a treatment like Zevalin, why you would need so much more, almost ten times more training.

That said, I'll certainly vote for the report, but simply might mention that endocrinologists who already know a lot about the field, would presume that all the people who are being approved with the 80 hours are already endocrinologists and know a lot about the field that may not necessarily be true.

MEMBER PALESTRO: This is Dr. Palestro again. Mr. Costello, you're right. There may not be. I think it's probably reasonable to assume that the majority of these individuals are endocrinologists.

And I think it's also worth pointing out at this point is that the American Board of Endocrinology, about ten years ago, established a certification board in nuclear endocrinology that has achieved deemed status from the NRC.

And I can't give you the details because I'm not a hundred percent familiar with them, but I know there is extensive training in the use of radioactive iodine with a certification examination and so forth.

MEMBER COSTELLO: Okay. I present in support of the report, but while we may, you know, seem like we're just talking about Zevalin, we're not just talking about Zevalin. We could be talking about any potential alpha and beta emitter with quantities greater than they use with Zevalin and with radiological causes that are different than Zevalin and they won't always necessarily be unit doses.

So I like that just setting up the standing committee. It was just that when the report talked about endocrinologists, there's nothing in the rules that say that the 80 hours is only limited to endocrinologists. That's all. Thank you.

MEMBER PALESTRO: You're absolutely correct and I thank you for clarifying that and bringing it to everyone's attention. Any other comments from the Committee?

MEMBER ENNIS: Ron Ennis. Just one. I think that Frank, just to follow up on your comment, I think the subcommittee that we're proposing to deal with this, or standing committee, will have to look at 80 hours and decide whether that is appropriate in this day and age. I think the assumption that that's okay for iodine needs to be evaluated. It could very well be that that's inadequate at this point.

MEMBER PALESTRO: This is Dr. Palestro. Ron and Frank, in response to your comments, I absolutely agree with you. And it would be my concept, my plan that we approach training and education with no fixed mind set on hours but rather develop what we feel is competency and then sort of work backwards to determine what it takes to achieve the competency, rather than being fixated on 80 hours or 700 hours or whatever.

MEMBER COSTELLO: This is Frank, if I could.

MEMBER PALESTRO: Yes.

MEMBER COSTELLO: I think a challenge for this, for the standing subcommittee, is that we do not want to regulate on an isotope by isotope basis because that would be kind of impossible.

That said, I think a challenge would be for, and we just talked about alpha and beta emitters, you know, that that could encompass a wide variety of isotopes with a wide variety of hazards. And to come up with a single training and experience requirement for them, I think will be a challenge for the Committee to do. Thank you.

MEMBER PALESTRO: Thank you, Mr. Costello. I think again you're absolutely correct, and those are

issues that can't be addressed in a one-hour conference call or in emails over the course of several days.

I don't have an answer and I don't have a preconceived notion about whether one size fits all or we need to adjust it for various radiopharmaceuticals and so forth and so on. And that's why, and I think the subcommittee agrees that this is a complex issue that needs to be looked at and studied and worked on over time.

MEMBER METTER: This is Darlene Metter. Can I say something about the --

MEMBER PALESTRO: Yes.

MEMBER METTER: -- alpha and beta? So my question would be, would these alpha and beta emitters be unsealed or would they be sealed sources or do we need to parse that out? I'm just asking.

MEMBER PALESTRO: This is Dr. Palestro. In response to your question, right now the only alpha and beta emitters that we're using for therapy, really, are unsealed sources, although I know that the yttrium-90 microspheres are sort of flowing through a somewhat nebulous area.

I don't know what the future holds and that's the purpose of forming, establishing a standing subcommittee.

MEMBER COSTELLO: This is Frank. I think we're really talking about a therapy on the 35.300. I think that only encompasses unsealed material.

MEMBER PALESTRO: Okay. Thank you, Mr. Costello. Any other comments from the committee?

MEMBER MATTMULLER: Yes, this is Steve Mattmuller.

MEMBER PALESTRO: Yes, Mr. Mattmuller.

MEMBER MATTMULLER: Yes. In looking at your table that shows the relatively small number of Zevalin procedures performed at the various institutions in large metropolitan areas, I was curious as to what the overall incidence of new Hodgkin's lymphoma was for these areas. And I went to the NIH website, and actually there's about 20 new cases per 100,000 people in an area.

And so for New York City's metropolitan area that's close to 2,000 new patients a year, and yet between the two major institutions in your table there is only 37 procedures being done per year. And so it's clearly not because of a lack of authorized users in the city of New York. I mean -- and so I suppose this is, that's my comment.

So my question really is to yourself and/or to, I assume, representatives from the different groups

who are listening in, what would account for this low usage of this valuable therapy in an area such as New York City? Thank you.

MEMBER COSTELLO: This is Frank, if I may. Is this drug used for all -- I thought this drug was only used for a small subcategory of Hodgkin's lymphoma, non-Hodgkin's lymphoma, not all non-Hodgkin's lymphoma.

MEMBER MATTMULLER: And yes, I don't know the exact number. So right, it would not be all 2,000 of these patients that need it, but clearly a significant percentage of them would be eligible or this therapy would be appropriate for them.

MEMBER PALESTRO: You know, I can't speak for the other institutions, but as far as North Shore LIJ or what's now known as Northwell Health, I really don't have an explanation.

It's certainly not because of a lack of authorized users or the ability to get these treatments done quickly. You know, we've been doing this for a long time. The oncologists, we simply don't see the referrals. They use other agents.

And as to why to be honest with you, we haven't sat down and gone into detail with them about why. We just don't see and never did see a lot of

referrals.

MS. HOLIDAY: While we have a quick pause, this is Sophie Holiday. I just want to remind everyone that's speaking to identify yourself for the operator. While I may recognize your voice, the operator will not. Thanks.

MEMBER PALESTRO: Okay. This is Dr. Palestro again. I need more comments from the Committee members.

MEMBER COSTELLO: This is Frank Costello, just one more time, I think, if I may. I did a recent inspection at a facility and I spoke, where they do use Zevalin, and I spoke to the radiation oncologist there who is the authorized user and I asked him about it. And he says they had a lot of success with it, but he gets very, very few referrals as we've heard here. But the referrals would be coming of course from medical oncologists.

And I asked him, well, why do you get so few referrals and he said he didn't know, but he remembered who the referrals are coming from, you know, the -- so, but he did say they had a lot of success but he did say they had very, very, very few referrals. That's all.

MEMBER PALESTRO: Thank you, Mr. Costello. Again, this is Dr. Palestro. I think that is the

general consensus that it is a very useful therapeutic agent, but there are a dearth of referrals. Any additional comments from members of the committee?

MR. OUHIB: Yes, hi. This is Zoubir Ouhib. Mine is more of a general comment and this is based on the work that I had done looking at the data on medical events for about ten or twelve years, and that was from 2000 to 2012 or '13. And I'm just looking at my raw data here. I apologize for not having the final draft.

But there were several medical events reported with the yttrium-90, and the point I'm making here is that by lowering the standard I think we are going to affect that number significantly.

And I would have to agree with Dr. Ennis and others that just maybe that we need to look at the iodine-131 down the road and realize that what's in place might not quite be enough. Thank you.

MEMBER PALESTRO: Thank you. Any other comments from members of the committee?

MEMBER O'HARA: Hi. This is Michael O'Hara. I was wondering, is there any alternative that or any help that NRC or, could give that area of central Florida other than reduce the training necessary to become an authorized user? Is there any way that

another authorized user could be identified?

MEMBER PALESTRO: I think I would defer to the staff to respond.

MR. BOLLOCK: Hi, Dr. Palestro. This is Doug Bollock, NRC. Yes, there's not really anything we can do to direct that. Yes, and the Agreement States, they have their authorized users. Yes, it's not, for this there's not much we can do to promote or -- right. Yes, we cannot promote. We're not allowed to do that and so there's not really much we can do in that aspect.

MEMBER O'HARA: Again, Michael O'Hara. I'm not saying promote the use of one agent over another, but potentially identify an authorized user. That's what I was thinking. I was just thinking off the top of my head.

MEMBER PALESTRO: Thank you, Dr. O'Hara. Any other comments from the committee?

MEMBER SUH: Hi, this is John Suh. I just want to commend the work of the subcommittee on this report. I agree that in terms of the hours that are being specified, the 700 hours versus the 80 hours, I think that we do need to move to more of a competency based rather than actually an hour based type of metric in terms of considering whether or not an authorized user is capable of using these unsealed sources. And

so I favor the movement to actually have a subcommittee address this in the future.

MEMBER PALESTRO: Thank you, Dr. Suh. Any other comments from the committee?

All right. Hearing none, at this time I'd like to welcome any comments from members of the public including those who submitted letters in advance of the meeting to be captured in the record. And again, please be sure to state your name for the court reporter.

MS. HOLIDAY: Operator, can you please let members of the public know how they can signal that they would like to speak.

OPERATOR: Certainly. If you'd like to speak, please press star 1, please unmute your phone and record your name clearly when prompted. One moment, please.

I do have a question or comment from Gary. Sir, your line is open.

DR. DILLEHAY: Thank you. Can everyone hear me?

MS. HOLIDAY: Yes.

DR. DILLEHAY: Yes, okay. Good afternoon. My name is Gary Dillehay. I'm a practicing physician at Northwestern Memorial Hospital in Chicago, board certified in both radiology and nuclear medicine,

and I'm speaking today as a past president of the Society of Nuclear Medicine and Molecular Imaging, the SNMMI. We appreciate the opportunity to address the ACMUI on this topic or training and experience for authorized users of alpha and beta emitters. The SNMMI commends the ACMUI subcommittee for addressing these important issues and supports the report you've just been discussing.

A couple of years ago the SNMMI hosted two joint workshops with the National Cancer Institute. Both workshops were held at the NIH, and the purpose was to find the most productive strategies to ensure that potential benefits of targeted radionuclide therapy, which includes the drugs we've been talking about Zevalin, Bexxar and Xofigo, there was a recognition of the need to discuss the challenges related to the availability supporting technology and training and research required for this. The results of both workshops were published in two journal articles in the Journal of Nuclear Medicine, one in February of 2014 and one in July of 2015.

Many of the recommendations made at the workshop were in direct response to the barriers listed by the industry representatives who attended. The number of authorized users, however, was not listed

among the barriers to adoption.

I can assure you that the SNMMI and its members have worked hard to ensure that patients have the access to this particular treatment if they need it. We think it's essential that the NRC understand the full range of activities performed by multiple personnel in the delivery of these radioactive therapeutics.

Alpha emitters are a totally different class of therapeutic radionuclides from beta emitters like I-131 due to the potential for extreme toxicity from internal contamination and the difficulty of detecting alpha particle contamination for those who have inappropriate training.

For example, we're concerned about what processes are in place to deal with the cleaning of spills, handling of accidental contamination, the comprehension and ability to use a Geiger counter to detect spills.

Beta and alpha spills are more complicated as I mentioned. What kind of treatment preparation, discerning the legal limits of dose variation, do these places all have a dose calibrator? Most of us check the dose no matter what it comes from to make sure we're administering exactly what we think we are.

Disposal of the tubing, flushing the IV, disposal

of syringes and the competent supervision of ancillary staff, as noted, the process of delivery really is not as simple as just pushing a button.

In conclusion, the SNMMI agrees with the ACMUI Subcommittee Draft Report and does not support training and experience modifications for authorized users for alpha and beta emitters. A reduction to 80 hours would establish requirements at an inappropriate, we think, level for an entire class of current and more importantly future therapeutics. Again, thank you for allowing us to address the ACMUI today and I'm happy to answer any questions you might have.

MEMBER PALESTRO: Thank you, Dr. Dillehay, for your comments. Any additional comments from members of the public?

OPERATOR: Our next comment is from Karl Schwartz.

MR. SCHWARTZ: Yes, hello. Can you hear me?

MEMBER PALESTRO: Yes.

MR. SCHWARTZ: Yes. This is Karl Schwartz. I'm president of Patients Against Lymphoma. And we first would like to thank the committee for having this discussion and including the patient perspective.

I'm a research advocate and a member of the

NCI and Lymphoma Steering Committee. I also serve on the CIRB for the -- also I'm a caregiver to my spouse who's a 20-year survivor of follicular lymphoma.

I want to comment briefly on the low use of, what might explain the low usage in the metropolitan areas that came up earlier, Zevalin is for indolent lymphomas which is less than half of the types of non-Hodgkin's.

So to me I've had trouble appreciating why an unequal increase in the time is required. I don't know when that took effect, but it seems that 70 or 80 hours at one time seemed to work out well.

I think there is an important aspect of being an authorized user contributing to low usage, excuse me. The recognition is needed that radioimmunotherapy is not a me-too drug. There is something unique about it.

My spouse, for example, had only a six-month response to CHOP in 1997. She had treatments for eight years which impacted her quality of life. It gave her some time. It was, today she's free of the disease. She had consolidation with radioimmunotherapy in 2004. So I don't think that there was any other approach that could have had that result.

Also, the competing drugs listed by NCCN

for indolent lymphoma are all palliative in character. They have to be given continuously to avoid relapse, and resistance is pretty much inevitable.

So radioimmunotherapy seems to be the only approach that has the potential for durable remissions for patients who cannot tolerate chemotherapy. This includes the elderly and the frail.

You'll excuse my voice. I sort of become emotional listening to this testimony which seems overly focused on one perspective and that is understandably how to make training efficient.

I think the cost to the proposed solutions will be division between oncologists in the use of radiopharmaceuticals. Few patients tend to go to oncologists. And if they cannot, if it's not feasible for them to get training they may very well not be aware of the potential of those agents, and of course they have a financial disincentive to refer their patients to someone else to get treatment.

So I think, finally, again thanks for your patience with my voice. I think from the Belmont Report they said justice requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research.

So to my mind there is a problem with

awareness and assume that many oncologists are not trained, therefore not knowledgeable and not authorized to use it. We must look for ways to make this possible. The competency criterias make sense for training on the ability to demonstrate that. I thank you for your time.

MEMBER PALESTRO: Thank you for your comments.

MS. HOLIDAY: Dr. Palestro, before we go to the next comment, if you are not speaking put your phone on mute. I'm hearing a lot of background noise at the time. Thank you.

OPERATOR: The next comment is from Nicki Hilliard.

DR. HILLIARD: Hello. I'm Nicki Hilliard. I'm at the University of Arkansas for Medical Sciences, and I submitted a letter with my colleagues, Dr. Kristina Wittstrom from the University of New Mexico and Dr. Kara Weatherman at Purdue University. And I appreciate you reading over our comments.

I just wanted to comment on the subcommittee report and basically just say that just as our last speaker was speaking it is a risk-benefit. With all of medical imaging we have a risk-benefit ratio and the risk of radiation is balanced with the benefits

from the information that we get.

And I think it's very, very important to keep that in mind when we talk about the training requirements for this, because it is very true that if we do not give these life-saving radiopharmaceuticals for immunotherapy in the hands of the right physicians they're not being used, and therefore our patients are not benefiting from those.

And so I think with the risk-benefit ratio with these patient-ready doses, you know, there's a lot of manipulations involved, I don't think it's a big risk, and I think just reducing the training requirements to an 80-hour training requirement at the current time would be sufficient to address the safety issues that would accompany these drugs.

And we did submit an outline of training requirements that we thought would be acceptable. We've been training authorized users, each one of us have been training authorized users for 20 to 30 years. And we feel like that the training programs that can be put together, both didactic and experiential, can be adequate to maintain safety and also increase access to these life-saving and palliative care drugs that are so needed by our patients.

So I would ask that the subcommittee look

at specifically addressing these patient-ready doses, I mean, patient-ready radiopharmaceuticals in the regulations. So I appreciate you allowing me to make my comments. Thank you.

MEMBER PALESTRO: Thank you. Again, this is Dr. Palestro. And yes, thank you for your letter as well as a suggested training and experience program. The subcommittee did in fact look at it in detail and we are most appreciative of your efforts.

Other comments from the public?

OPERATOR: Our next comment is from Gregg Franklin.

DR. FRANKLIN: Hello. Can everybody hear me?

MS. HOLIDAY: Yes.

MEMBER PALESTRO: Yes.

DR. FRANKLIN: Hello? Okay, great. Chairman Alderson, I don't know if you're on or not.

CHAIRMAN ALDERSON: I am.

DR. FRANKLIN: Dr. Palestro? Great.

MEMBER PALESTRO: Yes.

DR. FRANKLIN: Members of the ACMUI and the NRC staff, I'd like to thank you for allowing me to provide this statement on training and experience requirements for the administration of

radiopharmaceuticals on behalf of the American Society of Radiation Oncology, or ASTRO.

My name's Gregg Franklin. I'm a radiation oncologist with the New Mexico Cancer Center in Albuquerque, New Mexico. As part of my community based practice, I administer radiopharmaceuticals such as I-131 for thyroid cancer, radium-223 for prostate cancer, yttrium-90, or Zevalin, as we've been talking about for lymphoma as well as other pharmaceuticals.

As an authorized radiation oncologist in New Mexico giving these radiopharmaceuticals, I have a lot of experience with their delivery, side effects, as well as the challenges inherent in their utilization.

I'm also a member of ASTRO, the largest radiation oncology society in the world with more than 10,000 members who specialize in treating patients with radiation therapies.

Radiopharmaceuticals including Zevalin are highly effective in treating cancer and are also potentially hazardous drugs and with possible harmful effects for the patient and the public if not used correctly and under the supervision of a highly trained physician.

ASTRO strongly opposes any reduction in the training and education 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 in this section are appropriate to protect the safety of patients, the public and practitioners and should not be changed.

Recently ASTRO has become aware of renewed push to reduce these training and education requirements for radiopharmaceuticals based on concerns about the shortage of authorized users for the administration of Zevalin in particular.

NRC intentionally designed the training and education requirements allowing new agents to come to market, but the NRC does not have to have the burden of writing different regulations for every new drug that is developed.

The classroom and clinical experiences encompassed by radiation oncology and nuclear medicine training programs provide appropriate levels of knowledge and skill for any current and future radioactive agents.

ASTRO supports the NRC's intent to craft a generally applicable rule rather than one that necessitates a specific review of each new radionuclide that becomes commercially available.

The rigorous training and education

requirements contribute to the excellent safety record of radiopharmaceuticals generally. We believe that it is important that the person administering the radiopharmaceutical is appropriately trained in the safe handling, exposure risks and management of side effects of the radiation.

We don't believe that an 80-hour course will adequately cover these topics. Administering radiopharmaceuticals is not as simple as ordering a patient-ready dose from a radiopharmacy and just injecting it into a patient.

Ultimately, it is the authorized user who is responsible for the safety of the patient, the providers and the public. It would be irresponsible to leave this to someone with inadequate training and experience.

And without proper and extensive training, will the authorized users be able to set up policies, procedures, radiation safety precautions, handling of radioactive spills and also make appropriate, sometimes quick decision making based on radiobiology and the effects of multiple prior therapies on the patients as well such as prior radiation external beam therapy?

In addition to ensuring patient safety, ASTRO is unaware of the data that suggests a shortage

of authorized users. ASTRO asked the NRC staff for the number of authorized users licensed in the 35.390 to assess whether there's a shortage of authorized users, but learned that the NRC only tracks authorized users licensed under 35.300.

Without being able to identify which authorized users are licensed under those two subsections, it is not possible to confirm whether there is an actual authorized user shortage or a perceived one.

Additionally, ASTRO has not heard what would be an ideal number of authorized users. ASTRO estimates there are approximately 2,200 radiation oncology facilities in the United States, which means aside from the many nuclear medicine trained authorized users nationwide there are likely enough authorized users just among the radiation oncologists nationwide.

Indeed, ASTRO is not aware of perceived shortage of radiation oncologists anywhere in the country. We do not believe the available data on authorized users supports a change in the T&E requirements. Instead, we believe other factors are influencing the use of Zevalin, most likely and notably the availability of alternative treatments including chemotherapy agents such as maintenance rituximab.

Unlikely that a change in the T&E requirements will impact the use of Zevalin, including instead having unintended consequences of exposing patients, providers and the public to risks that could otherwise be avoided.

There is no underlying public need for expansion of authorized users of which should not be placed in a position of heightened and unnecessary risk and therefore the T&E requirements should remain as written. ASTRO agrees with the ACMUI subcommittee's recommendation against the reduction of the number of hours.

ASTRO also agrees with the subcommittee's recommendation for establishment of a standing committee who periodically review the current training requirements and make recommendations for changes as warranted.

ASTRO is concerned that if the NRC decides to make changes to the T&E requirements that doing so within the Part 35 rulemaking will cause significant delays in the publication of the final rule. Part 35 final rule will add a much needed and appropriate activity based definition for medical events for permanent implant brachytherapy.

ASTRO also strongly opposes any further

delays in the Part 35 rulemaking, because without this definition there will continue to be much confusion surrounding medical events for permanent implant brachytherapy.

So in conclusion, for the numerous reasons stated above, ASTRO opposes a reduction in the T&E requirements of 10 CFR 35.390, supports the ACMUI subcommittee's recommendations to form a permanent committee to look at the requirements and to make suggestions as warranted.

We have submitted a written statement for the ACMUI's consideration. Thank you.

MEMBER PALESTRO: Thank you for your comments. Additional comments from the public?

OPERATOR: Our next comment is from Michael.

MR. GUASTELLA: Hi. This is Michael Guastella. Can you hear me?

MEMBER PALESTRO: Yes.

MR. GUASTELLA: Great. I'm the executive director of the Council on Radionuclides and Radiopharmaceuticals, and I want to, first of all, thank Dr. Palestro and the ACMUI subcommittee for the draft report.

And we appreciate, certainly, their

consideration to update the training and experience regulations, particularly to ensure patient access and to support technological advances and changes in medical procedures in the future.

However, we do remain concerned that the current 700-hour training and experience framework is excessive for patient-ready doses of alpha and beta emitters and that this does limit patient access.

I believe that the draft report, after review, fails to consider the limited role of physicians in handling these radiolabeled therapeutics which are prepared, as we've discussed, they are prepared at licensed radiopharmacies by licensed nuclear pharmacists, dispensed and delivered to the physician as a patient-ready dose.

The physician is not responsible for mixing, admixing or for preparing the radiopharmaceutical drugs. The radiological safety profiles of patient-ready doses of alpha and beta-emitting isotopes are in commensurate with the requirement of 700 hours of training and experience that are currently required.

Also, and we heard from Nicki a little bit earlier, the ACMUI has received training statements from experts in radiation safety education which

supports a 70- to 80-hour training and experience framework. I will say that it is encouraging that the ACMUI subcommittee recognizes that updates to the training and experience framework is appropriate and necessary moving forward.

CORAR does recommend that the didactic training required to adequately prepare physicians to safely administer patient-ready doses of alpha and beta emitting drugs should entail about 70 to 80 hours of classroom and laboratory time.

We are disappointed that the ACMUI subcommittee's decision to oppose a modification to the current training and experience framework and establish a standing committee to address appropriate requirements in the future does not meet the charge given to the subcommittee and the current needs of patients.

So in conclusion, I'd like to say the CORAR continues to believe that it is critical that the NRC address the appropriate level of training and experience requirements for authorized users of alpha and beta emitters in the current rulemaking on the medical use of byproduct material. Thank you.

MEMBER PALESTRO: Thank you for your comments. Additional comments from the public?

OPERATOR: Our next comment is from Bennett Greenspan.

DR. GREENSPAN: Hello, I'm Bennett Greenspan. Can you hear me?

MEMBER PALESTRO: Yes.

DR. GREENSPAN: Hi. Good. Good afternoon. I am a physician at the Medical College of Georgia, trained and board certified in radiology and nuclear medicine with 30 years of experience in those fields.

First, I'd like to say that I agree with the ACMUI report and I agree with the comments from Dr. Gary Dillehay from the Society of Nuclear Medicine and Molecular Imaging of which I am a member also, and I agree for the most part with the ASTRO comments, and I thoroughly disagree with CORAR.

I think 80 hours is grossly insufficient for clinicians, and particularly those who don't have backgrounds in radiology or radiation oncology. Those physicians have training in physics, but medical oncologists have no such training in radiation safety or medical physics and 80 hours will leave them clueless. I think they'll be totally inadequate to handle these products, and particularly alpha emitters with severe potential complications if they're

administered improperly.

But I think even beta emitters. In fact, I think 80 hours is insufficient for iodine-131. And many endocrinologists who are familiar with I-131 in terms of administration are not really very familiar with radiation safety aspects at least in my clinical experience over 30 years.

I think, I'm aware of two legal cases of major malpractice with I-131 and both of these involved major mistakes by endocrinologists.

I think the major problem regarding Zevalin usage is the lack of referral from medical oncologists, and I think part of that is they would prefer to give it themselves and have the income from it, and without adequate training and experience I'm very concerned that patient safety will be compromised.

So again I support the ACMUI report and I concur with the SNMMI comments and for the most part the ASTRO comments, and I thoroughly disagree with CORAR, and thank you very much.

MEMBER PALESTRO: Thank you for your comments. Any additional comments from the public?

OPERATOR: Our next comment is from Allen Yang.

DR. YANG: Hello. Can you hear me?

MEMBER PALESTRO: Yes.

DR. YANG: Thank you. Hi. My name's Allen Yang and I'm from Spectrum Pharmaceuticals. I'm previously a board certified oncologist, and I appreciate that the NRC and the ACMUI have reviewed this issue over the last year and a half.

And I wanted to point out that the 700-hour requirement is excessive for patient-ready doses. Going back to Michael Guastella's comment that 700 hours is excessive, we believe that it is excessive for patient ready-to-use doses for alpha and beta emitters.

And I understand the last speaker's comments about safety issues occurring over spills and radiation safety, but let's be realistic here about what are the safety issues with these agents.

So, you know, if we look at our own safety database in terms of preparation and handling and administration of these products, the safety issues are not related to spills. The reports that we get on mishandling are actually from radiopharmacists in which the preparation was not ideal and the labeling of it was not correct and therefore it's not really a physician matter.

The physicians who administer the product, the authorized users, really receive a patient

ready-to-use dose which is a single injection. And granted, as another person said it's not as easy as pushing a button, but it's fairly straightforward.

It comes in a protective box, it's administered IV to the patient, and then all the materials are turned back to the radiopharmacy which is equipped to handle those radioisotopes.

I would say that oncologists are trained to handle toxic and mutagenic materials, chemotherapy, mustard gases, et cetera, and when you look at patients who administer these agents, or excuse me, patients who receive these agents, the major complications and the risks to safety are not spills or accidental, you know, overdoses, but the complications of receiving the therapy. Myelosuppression, thrombocytopenia, neutropenia, and what's well known to be prescribed with Zevalin, myelodysplastic syndrome.

And I would argue that for the safety of the patient, it's best managed by physicians who are trained in managing those types of complications which are oncologists predominantly.

I would say that, you know, the 700 hours, I agree with the committee that maybe it shouldn't be hour based, but currently since it's 700 hours this is approximately five months of training. And what you've

done is effectively relegated this to people who do residency training in either nuclear medicine or radiation oncology.

And, you know, to comment on a couple things that were said by previous is the lack of referrals may be because of incentives of who keeps the patient and who treats the patient, but it may be due to a lack of confidence of are the physicians who are administering this, can they manage the clinical toxicities and the complications from that rather than the complications of spills or inadvertent exposure to alpha and beta emitters which should be very, very low for these pre-filled syringes.

Finally, I disagree that there's no lack of authorized users. I think, you know, there is a lack of authorized users and that is reflective of, you know, the amount of the product that is used and how many patients are getting it.

Going back to comments that were said by Dr. Palestro, there's approximately 70,000 cases of non-Hodgkin's lymphoma in the United States. You are correct in that most of the patients do not qualify for Zevalin. The indication is for a subset of lymphoma, something called follicular lymphoma.

However, if you look, and you made the comment

that there are other sort of better agents, you know, traditionally we define better as being demonstrated in a randomized clinical study.

Now in a randomized clinical study you can test one agent versus the other. And if you look at the NCCN guidelines there are very few randomized studies looking at follicular lymphoma. But there is, or excuse me, comparing different agents for follicular lymphoma.

But the one agent that is approved as a single agent and it has category I, which is the best data, is Zevalin not rituximab. In fact, if you look at the agents that are approved as single agents, Zevalin was compared to rituximab in a randomized clinical trial and Zevalin was shown to be superior.

However, as correctly stated, rituximab is more used than Zevalin and we have to think that it's due to access from patients and oncologists. That you're correct, they have more access to rituximab and they do not have access to Zevalin, and I believe that it's the access or lack thereof is because of this excessive training requirement.

Now we're not asking for you to put the whole public at risk. We're asking for specific isotopes, alpha and beta emitters, where pre-filled,

ready-to-use syringes that are handled by nuclear pharmacists, predominantly, and administered by oncologists who are trained to manage the toxicity as well as the long term sequela of these agents. Thank you.

MEMBER PALESTRO: Okay. Thank you for your comments. I just wanted to make a comment. This is Dr. Palestro again.

If I said more effective agents, then I misspoke. Just go back, I said newer, equally more effective agents become available and I was talking in generalities. My point was that as newer agents in general become available, agents that are currently available tend to suffer a decrease in their use, and I hope that clarifies it.

Other comments from the public?

OPERATOR: As a reminder, to state a comment please press star 1. Our next comment is from Jennifer Cultrera.

DR. CULTRERA: Hello. Can you hear me?

MEMBER PALESTRO: Yes.

DR. CULTRERA: Okay. Yes, I'm Jennifer Cultrera. I'm a medical oncologist/hematologist from Florida Cancer Specialists and Research Institute. We are a large community based practice all across the

state of Florida with approximately about 190 physicians.

I'm speaking today on behalf of those physicians and including Dr. Joe Mace who was planning to present at the March 17th conference and couldn't participate today. He had become an authorized user after completing a 100-hour course before the NRC changed its regulation to require the current 700 hours of training and experience.

Contrary to the statements in the draft subcommittee report that it would be conjecture to say that an 80-hour program would be safe, Dr. Mace has been administering Zevalin and more recently Xofigo since he achieved his authorized user license in 2006, so for approximately ten years without a safety incident.

The draft report also did not adequately address the fact that physicians seeking to administer patient-ready doses of alpha and beta emitters do not need to undergo the full 700-hours which includes material relevant for other radiolabeled materials.

He did submit an expert statement to the ACMUI expressing that even his 100-hour course contained material that was superfluous to hematologists and medical oncologists that were seeking only to administer these patient-ready doses for alpha

and beta emitters.

I would also like to include that in regards to the toxicity of the agents, as Dr. Yang mentioned, the majority of the adverse effects which occur from these agents are hematologic toxicities which I and my other medical oncologists are more than adequately trained to address and we do this on an everyday basis.

I also want to address some of the comments that were initially stated in this conversation regarding the natural history and the decline of use of agents when newer therapies come out.

So in this era of personalized medicine, we don't want to take useful agents out of the hands cancer patients just because they are older. And everyday use, I still use agents such as chlorambucil for chronic lymphocytic leukemia which has been around for decades, even though there at least five newer agents which have been approved in the last few years. We want to be able to tailor our therapies to our patients that even with diseases who are relatively rare such as follicular lymphoma.

As well as to address the issue of the educational bloc for medical oncologists I understand that this is not in the governing body for the NRC, but according to the American Society of Hematologists, the

American Society for Clinical Oncologists and the American Board of Internal Medicine, there will be no training for radiopharmaceuticals to medical oncologists and hematologists unless they are capable of administering these agents directly.

So there won't be a way to lift this educational bloc if we're not given that access to these agents to be able to administer these agents.

And I would also like to address the statement made that endocrinologists partner with radiation oncologists and nuclear medicine physicians and they are able to administer the I-131 and have more experience.

Hem-oncs have a very strong partnership with our radiation oncologists and nuclear medicine doctors. I partner with them every day to give concurrent chemotherapy and radiation. In my practice we actually help our radiation oncologists deal with some of the sequelae from the radiation toxicity to the patients and help manage these patients with them.

So to better serve my cancer patients and all of our patients I would like to become an AU to be able to administer these alpha and beta emitters, and I'm unable to spend 700 hours away from my practice.

And based on the experts' statements, it should

be clear the hematologists and medical oncologists can safely administer these patient-ready doses with the proper training which can be achieved in something to an 80- to 100-hour course.

I believe based on my years of training and experience and my familiarity with beta emitters that I could be competent after this training in administering drugs such Zevalin and Xofigo without the 700 hours of training.

And I welcome the opportunity to demonstrate this competency through a pathway other than those 700 hours, such as my colleague Dr. Joe Mace who has been competent again for up to ten years now and never went through those 700 hours.

And I would also like to add that I'd like to pursue throughout this time a regulatory exemption to be an AU to be able to offer that to some of our patients, if that is something that is possible while the new training paradigm is being established.

And I appreciate you allowing us to express our comments. Thank you.

MEMBER PALESTRO: Thank you, Dr. Cultrera. This is Dr. Palestro. Just one comment.

The subcommittee, and I speak on behalf of the subcommittee, has no questions or concerns about Dr.

Mace's competency. We weren't addressing a particular individual at all. We are merely looking at the overall picture. And whether or not you can extrapolate any one individual's competency or lack thereof to and entire group based on one individual, I still think is really a matter of conjecture.

But I do want to make clear that we weren't questioning Dr. Mace's capabilities. Thank you.

Additional comments from the public?

OPERATOR: Our next comment is from Karl Schwartz.

MR. SCHWARTZ: Yes, thank you. It's a great discussion. I wanted to address a few comments that were made and add some additional information I think that points to the unique qualities of radioimmunotherapy for lymphoma patients.

It's the only type of treatment that can be completed in a week and for some patients that's critical. And the course of therapy is short but can lead to very durable remissions measured in years.

No other approach other than chemoimmunotherapy has an equivalent potential, but not everyone can tolerate chemotherapy. So there's a sub-population with an unmet need, and if the course requirements limits access then that's a very tragic

outcome. Thank you.

MEMBER PALESTRO: Thank you. Additional comments from the public?

OPERATOR: I'm showing no further comments, sir.

MEMBER PALESTRO: All right. At this point then if there are no further comments, I would like to turn the meeting back to Dr. Alderson.

CHAIRMAN ALDERSON: Thank you. Thank you, Chris. Excellent discussion. Would the subcommittee like to make a motion for a vote on their report?

VICE CHAIRMAN ZANZONICO: It's Pat Zanzonico. I'm making a motion to approve the subcommittee report.

CHAIRMAN ALDERSON: Thank you. I would remind everyone that no second is needed since it's coming from a subcommittee, so we will now ask for the votes. So how many are in favor, please say aye.

All right, now how many are opposed? I hear none. Are there any opposition? Any abstentions? There are none. Is there a discussion on this vote? Is there a discussion?

Hearing none, if there is no discussion then this will be a unanimous vote by the subcommittee

to accept this report.

Thank you, Chris. If there are no other issues to come before this call, this will then conclude our meeting.

I want to thank you to the subcommittee members for their work on this report, thank you to the committee members for their engagement and thanks to all the members of the public who made comments and have participated in these discussions.

Mr. Bollock, does the NRC have any closing remarks that they would like to add?

MR. BOLLOCK: I don't believe we have -- Doug Bollock. We have no closing remarks, just to thank you all and everyone from the public for calling in and having this discussion. And we will see the ACMUI next week.

CHAIRMAN ALDERSON: Yes, thank you. Thank you, Mr. Bollock. Indeed, remind everyone that we will be holding our Spring 2016 meeting at NRC headquarters next week.

Hearing no other business then, we are officially adjourned. Thank you all very much.

(Whereupon, the above-entitled matter went off the record at 3:04 p.m.)

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October 28, 2015

Advisory Committee on the Medical Use of Isotopes
Subcommittee on Training and Experience for Alpha and Beta Emitters
c/o Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: Training and Experience Requirements for Beta-emitter Radiopharmaceuticals

Dear Members of the ACMUI Subcommittee:

We are writing to follow up on the meeting of the Advisory Committee on the Medical Use of Isotopes (ACMUI) held on October 8, 2015. At the meeting, stakeholders presented on the impact of the current training and experience requirements for beta-emitters on patient access to innovative lifesaving therapies. Additionally, stakeholders stated that the 700 hours of training and experience requirements for Authorized Users (AUs) needs to be re-evaluated by the Nuclear Regulatory Commission (NRC) because it is impacting patient and healthcare access to effective treatment options. We appreciate that the Subcommittee has expanded its charge to evaluate whether the 700 hour requirement is the appropriate level of training for the Alternate Pathway for beta emitters. We believe that the current NRC rulemaking provides the opportunity to modify the existing requirements and to alleviate an adverse impact the regulations have created on patient access to certain radioimmunotherapies. We urge ACMUI to take definitive action and make recommendations for potential changes to the regulations for the benefit of patients.

In response to questions and statements at the ACMUI meeting, Spectrum would like to provide the ACMUI Subcommittee with additional background and information on Zevalin as well as our proposal to modify to 700 hours required to become an AU to at most 80 hours. As set out below, we believe 80 hours is the upper limit of the appropriate level of training for a limited license to administer pre-filled self-contained radiopharmaceuticals like Zevalin. Such an approach would eliminate the unnecessary regulatory barriers currently limiting cancer patient access to effective treatment options, while maintaining training requirements commensurate with the risks of handling Zevalin.

Clinical Background on Zevalin

The topic of AU requirements has been of interest to Spectrum Pharmaceuticals, whose product ZEVALIN® (ibritumomab tiuxetan) is a radioimmunotherapy treatment for non-Hodgkin's lymphoma (NHL) patients. Zevalin was approved by the Food and Drug Administration (FDA) in 2002 for the treatment of patients with relapsed or refractory indolent non-Hodgkin's lymphoma. More recently, in 2009, FDA approved the use of

Zevalin for the treatment of patients with previously untreated follicular non-Hodgkin's lymphoma as consolidation therapy immediately after first-line chemotherapy.

In the Subcommittee report and at the meeting, there were numerous comments regarding the declining utilization of Zevalin due to new competing therapies. However, this in reality is only part of the story. While it is true that there are numerous new therapies for NHL, it is also important to understand that indolent NHL is not a curable disease, and therefore patients will typically require many treatments as they fail available therapies. A typical patient will receive induction chemotherapy and upon relapse will receive a salvage therapy that will hopefully induce another remission and disease-free period. However, it is known that the disease will ultimately relapse again and yet another salvage therapy will be needed. A patient with indolent lymphoma may live many years with their disease, but unfortunately they will need access to different treatment options to induce disease-free remission periods after relapse that typically become shorter with each line of therapy. It is critical, therefore, that all approved, effective treatment options be available and accessible for these patients. In addition, it is essential that multiple therapies with different mechanisms of action be available to help overcome resistance to standard therapies and provide these patients with various effective treatment options.

Currently, only one radioimmunotherapy for NHL remains commercially available, Zevalin. The drug uses the monoclonal mouse IgG1 antibody ibritumomab in conjunction with the chelator tiuxetan, to which a radioactive isotope (yttrium-90) is added. Zevalin is a unique and effective radioimmunotherapy therapy approved by FDA for patients with indolent lymphoma, which has proven safety and efficacy in multiple randomized clinical trials with a long duration of study follow-up. Although it is known to be safe and effective treatment, its clinical use has definitely been markedly limited due to the hurdles resulting from administration logistics, ie, the inability of treating oncologists to administer it. Importantly, unlike many of the newer therapies, Zevalin can maintain NHL patients in remissions lasting many years with only a single course of therapy that consists of just one dose. The National Comprehensive Cancer Network (NCCN) clinical treatment guidelines list Zevalin as one of the few Category 1 options for patients with relapsed or refractory follicular lymphoma, which by definition is only for treatments that, "based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;" the only other Category 1 NCCN recommendation for these patients is intensive combination chemotherapy with FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (NCCN v2.2015). Unlike Zevalin, which is a novel radioimmunotherapy targeting CD20, newer targeted therapies are small molecules that target tyrosine kinase signaling pathways. While these small molecule therapies have the convenience of being oral, they target a different mechanism of action and require continuous treatment that can be associated with chronic side-effects.

It is important to note that Zevalin involves limited physician preparation and handling. Zevalin is delivered to the AU as a patient-ready dose requiring only an acrylic shield and standard radiation precautions. A "hot lab" is not required and patients do not need to be assessed for radiation exposure. Due to the preparation of the patient-ready dose by the radiopharmacy before reaching the administering physician, training requirements for the

physician on dose preparation and the safe handling of radiopharmaceuticals can be more limited. Board certified Hematologists/Oncologists are accustomed to using cytotoxic agents that require specific handling tailored to their risks, and are customarily trained on standard radiation precautions. Limited additional training on the proper handling and disposal of Zevalin should enable them to safely use this product.

Not All AUs Can Administer Zevalin

At the ACMUI meeting, several ACMUI members asked whether the 700-hour requirement has caused a lack of AUs who can administer Zevalin. Dr. Cultrera spoke to the difficulty she has faced finding Authorized Users able to administer Zevalin to her patients outside of the major metropolitan areas with academic medical centers, and based on our discussions with multiple clinical practioners, this is not an isolated instance. In speaking with patient advocates and practitioners across the country, we have found the problem to actually be nationwide. Hematologists and oncologists who wish to offer Zevalin as an appropriate treatment option for their patients outside of major cities are often unable to locate AUs who can administer Zevalin within a reasonable commuting distance for these patients.

Board-certified radiation oncologists and nuclear medicine practitioners, who can achieve Authorized User status through the certification pathway, have also noted that the proctored case requirement is also difficult to meet. Because the use of the treatment option is limited outside of major academic medical centers, it is difficult for practitioners in these areas to locate and participate in the required three case administrations. So while it is possible to find Authorized Users in some areas, these AUs may not be eligible to administer Zevalin specifically, due to a lack of exposure to this treatment option.

Some panel members stated that residency requirements include training and licensure for therapeutic radiopharmaceuticals, so all AUs should be able to administer Zevalin. However, this is not the case. Most nuclear medicine practitioners are AUs, but not all are authorized users under the NRC or equivalent Agreement State Regulations. In addition, not all radiologists or radiation oncologists are listed as AUs on many radioactive material licenses for therapeutics under NRC 35.300 or equivalent Agreement State regulations.

When Zevalin received FDA approval in 2002, the therapy regimen included an Indium -111 Bio-scan, which did require nuclear medicine practitioners to image Zevalin patients. At that time, numerous nuclear medicine, radiation oncologist and radiologists/nuclear practitioners had received education about Zevalin that included low-grade and follicular non-Hodgkin's Lymphoma Disease, Handling, Administration and Radiation Safety. ~~With this said, the actual number of AUs had been estimated as greater than 400.~~ However, since the FDA removed the requirement for an Indium -111 Bio-scan in 2011, nuclear medicine practitioners have shown a lack of interest in offering Zevalin as a therapy option in their departments, resulting in a decrease of radiation oncologist AUs providing Zevalin and other therapeutic radiopharmaceuticals to patients. The lack of AUs in the community setting has decreased in non-metropolitan areas and has created an obstacle to cancer patient access to this effective radiopharmaceutical.

While hospitals and/or academic institutions located in metropolitan cities have AUs, these centers are focused on drug development and clinical trials and do not provide adequate, convenient cancer patient access to radiopharmaceuticals like Zevalin. In 2010, the number of AUs was greater than 400, while today, the number is only about 145 who are willing and working with medical/hematology oncologists to offer Zevalin as a therapeutic option to patients.

#1 Number of known AUs treating Zevalin patients has decreased from >400 AUs to 145 AUs since 2010.

#2 Number of Cities with Known AUs for Zevalin Administration

Hematologists/Oncologists Should Have Access to Appropriate Training Requirements that Enable them to Safely Administer Zevalin

The many hematology and oncology practitioners with whom we have spoken across the country have identified the AU training and experience requirements as the primary hurdle in preventing access of their patients to Zevalin as an effective treatment option. Board certified hematologists and oncologists cannot realistically devote 700 hours of time away from their clinical practices to achieve AU status through the Alternate Pathway for Zevalin, particularly since it is the only radioimmunotherapy used in their practice for a specific group of patients.

As Dr. Cultrera noted in her comments, she does work with nuclear medicine and radiation oncologists at academic medical centers whenever possible. However in her experience, not all patients are located near centers with nuclear medicine AUs to allow for the administration of a radiopharmaceutical product such as Zevalin. The point of the Alternate Pathway is to allow interested oncologists like Dr. Cultrera to be trained and become able to provide Zevalin as a feasible treatment option, which they then can administer to their patients as they routinely do with cytotoxic therapies. Dr. Cultrera mentioned that her colleague Dr. Mace underwent training similar to that proposed in the Alternate Pathway for beta-emitting radiopharmaceuticals before the current requirements went into effect, and he has now been safely administering these products for over a decade.

700 Hours is Not The Appropriate Level of Training for the Risk Associated with Beta-emitter Radiopharmaecuticals

At the meeting several panel members asked how the 700 hours of training and experience was developed. NRC staff explained that the number is set in regulation in § 35.390, but they were not clear on how the number was actually determined. It is our understanding that this number was set to reflect the complete course work that a physician would undertake to specifically become board certified in nuclear medicine, which is a dedicated medical imaging specialty involving the broad use of various radioactive substances in the diagnosis and treatment of disease. As such, the 700 hours include training for all aspects of medical use and safe handling of various radioactive byproduct materials used clinically (nearly 100), including alpha, beta and gamma emitters. As described in the attached chart, Spectrum believes there is ample support that 80 hours of training or less is sufficient and a more appropriate level of training and experience for the risks associated with the administration of a beta-emitter like Zevalin in the hematologist / oncologist setting.

Prior to the 2002 rulemaking, hematologists and oncologists could be licensed as AUs able to administer beta-emitting radiopharmaceuticals such as Zevalin with 80 hours of classroom and laboratory training. A number of the current AUs for Zevalin received AU status under the prior regulations with 80 hours of training and have grandfathered status. These physicians have had an excellent safety record in handling this radioimmunopharmaceutical, like Dr. Cultrera's colleague Dr. Mace.

The proposed Alternate Pathway, requiring at most 80 hours of training and experience for beta-emitters, would mirror the training and experience requirements for those physicians seeking to administer sodium iodide I-131 under the current regulations at § 35.392 and § 35.394. The safety profile of Zevalin is comparable to and in some ways even more favorable than that of sodium iodide I-131. The excellent safety record associated with Zevalin has been recognized by the FDA, which requires only minimal precautionary labelling on the product. Gamma-emitting radiopharmaceuticals such as I-131, in contrast, require more precautionary measures during administration, such as isolation and Geiger counter measurement. Zevalin's safety profile is further enhanced by its unique process of preparation, wherein it is radiolabeled and packaged by a licensed radiopharmacy and then delivered to healthcare providers as a patient-ready dose. Therefore, the physician administering Zevalin is not required to perform the typical radionucleotide handling operations associated with other radiopharmaceuticals, and only has to administer the pre-packaged product to the patient.

There was discussion at the meeting regarding whether a modification to the 700-hour requirement may be included in the final rule. NRC staff indicated that because the proposed rule did not specifically address reducing the 700-hour requirement, it was not subject to public comment. However, the proposed rule did seek public comment on whether the training and experience requirements were having an adverse impact on patient care. Additionally, the proposed rule makes specific revisions to § 35.390. NRC did receive numerous comments from stakeholders advocating for lowering the 700-hour training requirement for AUs to 80 hours or less, and held a public meeting on this issue in February 2015. As such, the changes can be

viewed as a logical outgrowth of the proposed rule. If the Agency determines that an additional comment period must be provided, the Agency rules allow for a post-promulgation comment period. Under 10 CFR § 2.804(d)(2), the NRC can provide a thirty-day post-promulgation comment period. Thus, the NRC has the authority to adopt a training and experience requirement of 80 hours or less at this time.

Emerging Technology Regulation Under 35.1000

One panel member suggested the use of § 35.1000 to address training requirements for beta-emitter radiopharmaceuticals. The NRC's regulations are designed to provide flexibility for emerging technologies, and changes to the regulations would reflect a policy interest in encouraging innovation in alpha- and beta-emitters, a relatively new class of therapeutic radiopharmaceutical products. Alternatively, if the Agency does not pursue a regulatory change in the Final Rule, we request that the NRC pursue licensing Zevalin pursuant to 10 CFR § 35.1000, which gives the NRC broad discretion to regulate emerging technologies. Pursuant to § 35.1000, the NRC could approve Zevalin as an emerging technology as its use is not "specifically addressed" elsewhere in the regulations.

Licensure of Zevalin as an emerging technology pursuant to § 35.1000 would allow applicants to provide materials and seek written approval from the Commission that a requirement of at most 80 hours of training and experience is sufficient for the safe and proper handling and administration of Zevalin.

Regulatory Exemption under 35.19

If ACMUI and the NRC do not believe that the current rulemaking provides an opportunity to address training and experience requirements for Zevalin, Spectrum would like to seek a regulatory exemption for AUs for Zevalin. The NRC has the authority, upon application of any interested person or upon its own authority, to specifically exempt Zevalin from the requirements of 10 CFR § 35.390. Based on the materials presented at both the NRC public meeting in February and ACMUI meetings in June and October, the Commission can determine that such an exemption will not endanger life or the public interest. 10 CFR § 35.19.[1] The Commission has precedent for applying exemptions for new technologies. For example, at the October ACMUI meeting, ACMUI recommended that Ge-68/Ga-68 generators be granted license-specific exemptions from certain DFP requirements until a regulatory solution is reached through a subsequent rulemaking. There, ACMUI found that such an exemption would ensure public health and safety by allowing greater access to needed radiopharmaceuticals. A similar situation is presented here.

[1] *See also* Consolidated Guidance About Materials Licenses: Program-Specific Guidance About Medical Use Licenses, NUREG-1559, 10-1, NRC (Jan. 2008).

Recommendation

Stakeholders at the ACMUI meeting and during the rulemaking comment period have proposed that an alternate training and experience requirement that consists of at most 80 hours would be both commensurate with the actual safety risk for the focused handling of beta-emitter radiophamaceuticals, and also clinically appropriate and achievable for practicing hematologists and oncologists who wish to offer Zevalin as a viable treatment option to their cancer patients; this would eliminate the adverse impact the current regulations have created on patient access to these radioimmunotherapies. Spectrum strongly supports this more focused and appropriate training and experience requirement of no more than 80 hours for beta-emitter products. Spectrum would also support any other revision to the training and experience requirements that would reduce the shortage of AUs by ensuring that training requirements are commensurate with the actual risks, and improve patient access to Zevalin. ACMUI may be aware of alternative requirements that would either reduce training and experience requirements to a reasonable amount and/or reduce the proctored case requirement to a single case for Zevalin or a combination of alpha and beta emitters.

We appreciate the time and attention the ACMUI Subcommittee has devoted to considering these issues, and urge the ACMUI to take definitive action and make recommendations for changes to the regulations for the benefit of patients. We would be pleased to speak with the Subcommittee further, and provide any additional information that the Subcommittee might find helpful as it completes its review. We remain optimistic that the ACMUI will take immediate action in both the interest of cancer patients, and in alignment with the intent to not discourage the use of certain therapeutic options or adversely impact clinical practice.

Sincerely,

Lee F. Allen, M.D., Ph.D.

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Authorized User
Training and Experience Requirements

Alternate Pathway 35.300 700 Hours	Proposed Alpha and Beta Emitting Pathway At Most 80 Hours
Description of Training Nuclear Medicine residency program provides a broad understanding of general nuclear medicine, as well as advanced subspecialties in nuclear oncology, nuclear cardiology, and molecular imaging. Teaching sessions during service readouts, including emphasis on: • Physics and instrumentation • Radiopharmacy • Clinical technique • Computer applications • Quantitative and semi-quantitative analysis of images • Literature reviews • Correlative imaging • Formulation of differential diagnosis • General Nuclear Medicine • Nuclear Cardiology • PET CT • Rotations in cross sectional imaging including CT and MRI • Research rotations	**Description of Training** • Radiation physics and instrumentation • Radiation protection • Mathematics pertaining to the use and measurement of radioactivity • Chemistry of radioactive material for medical use • Radiation biology **Description of Experience** • Ordering, receiving, and unpacking radioactive material safely and performing the related radiation surveys • Performing quality control procedures on instruments used to determine the activity of dosages and performing checks for proper operation of survey meters • Calculating, measuring and safely preparing patient or human research subject dosages • Using administrative controls to prevent a misadministration involving the use of unsealed radioactive material • Using procedures to contain spilled radioactive material safely and using proper decontamination procedures. • Parenteral administration of any alpha or beta emitter, for which a written directive is required

AMERICAN SOCIETY OF HEMATOLOGY
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December 29, 2015

Advisory Committee on the Medical Use of Isotopes
Subcommittee on Training and Experience for Alpha and Beta Emitters
c/o Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: Alpha and Beta Emitters Training and Experience Requirements

Dear Subcommittee Members:

I write on behalf of the American Society of Hematology (ASH) to request that the Nuclear Regulatory Commission (NRC) set appropriate training and experience requirements for hematologists who wish to administer alpha- and beta-emitters to patients as part of an anti-cancer regimen. Our Society believes that your Agency has the opportunity to set a more appropriate requirement in its forthcoming rulemaking relating to the medical use of byproduct material.

ASH represents over 15,000 clinicians and scientists who are committed to the study of blood and blood-related diseases. These diseases encompass malignant hematologic disorders, such as leukemia, lymphoma, and myeloma; non-malignant conditions, including anemia and hemophilia; and congenital disorders, such as sickle cell anemia and thalassemia. In addition, hematologists have been pioneers in the fields of stem cell biology, regenerative medicine, bone marrow transplantation, transfusion medicine, gene therapy, and the development of many drugs for the prevention and treatment of heart attacks and strokes.

ASH's membership, which includes basic scientists, physician scientists, PhD researchers, as well as, physicians working in universities, hospitals, and community practices, is concerned that the current 700-hour training requirement as applied to alpha- and beta-emitters is inappropriate and limits physician use of clinically appropriate therapeutics. Our Society believes that this requirement is excessive and unduly restrictive of patient access to a valuable treatment option for non-Hodgkin lymphoma. ASH is pleased that the NRC formed a Subcommittee on Training and Experience for Alpha and Beta Emitters to further explore these issues. Our Society would like to take this opportunity to provide comments on this issue.

The Current 700-Hour Training and Experience Requirements are Not Appropriate

The current 700-hour requirement is aimed at training and certifying physicians in the use of an array of radioactive substances in the diagnosis and treatment of disease. While this may be appropriate for clinicians who seek to be certified for all uses of radioactive materials, it is not appropriate for a limited authorization for hematologists who seek to administer a limited set of products. We believe a reduced training and experience requirement is appropriate for alpha- and beta-emitters, such as Zevalin, which are prepared and packaged in a licensed radiopharmacy

and easily administered as a patient-ready dose in the hematologist/oncologist office setting. Such emitters present fewer risks than other radiopharmaceuticals, such as I-131, which requires more precautionary measures during administration, but is authorized after 80 hours of training and experience. Therefore, there is no reason why a similar pathway should not be provided here.

Furthermore, prior to a 2002 rulemaking, 80 hours of classroom and laboratory training was deemed sufficient for purposes of licensing Authorized Users to administer beta-emitting radiopharmaceuticals. And indeed, Authorized Users licensed under this training regimen have since been safely administering such products. To our knowledge, no hematologist has been so certified since the 700-hour licensing pathway was created in 2002.

The Current 700-Hour Training and Experience Requirements Restrict Patient Access to Effective Treatment Options

Since the implementation of the 700-hour requirement, it has become more difficult for patients in certain parts of the country to locate Authorized Users who are licensed to administer alpha- and beta-emitters outside of the academic medical center setting. We believe that the burdensome training and experience requirements are the primary impediment to providing greater patient access to these treatments. The additional 700 hours of training and experience is disproportionate and too onerous for the practicing community hematologist/oncologist to pursue. Without the ability to become an Authorized User or to locate an Authorized User within a reasonable distance, the rural hematology/oncology practitioner is unable to realistically offer this treatment as an option to their patients. This is a serious problem, given that alpha- and beta-emitters provide unique and effective treatment options for those suffering from non-Hodgkin lymphoma. Standard treatment options that offer excellent response rates should be available to all patients, whether those patients live near an academic medical center or in more rural areas of the country.

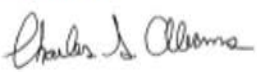
NRC Can Address the Training and Experience Requirements and Patient-Access Issue

With this current rulemaking, the NRC has the opportunity to improve access to these potentially life-saving anti-cancer treatments by addressing the shortage of Authorized Users able to administer them. Stakeholders have requested a change in the rules to permit a lesser training requirement of 80 hours of classroom and laboratory training, plus relevant work experience and case administrations for a limited authorization to administer alpha- and beta-emitters that are prepared at a licensed specialty pharmacy and delivered intravenously in a patient-ready dose. ASH supports this reasonable and limited proposed change in the regulations. Should the NRC decline to adopt this change via the ongoing rulemaking, ASH supports pursuing an exemption that would allow for more appropriate training and experience requirements with regard to alpha- and beta-emitters.

ASH urges the Advisory Committee on the Medical Use of Isotopes and its Subcommittee on Training and Experience for Alpha and Beta Emitters to consider a more proportionate training and experience requirement as applied to alpha- and beta-emitters and make appropriate recommendations to the NRC. This could significantly improve patient access to lifesaving treatments in the community hematology/oncology setting, while also addressing important safety considerations.

Thank you for considering our above comments, and please do not hesitate to contact Suzanne Leous, ASH Director of Government Relations and Practice at 202-292-0258, with any questions concerning this letter.

Sincerely,



Charles S. Abrams, MD
President

JOSEPH J. HECK
3RD DISTRICT, NEVADA

COMMITTEE ON
ARMED SERVICES

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THE WORKFORCE COMMITTEE

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ON INTELLIGENCE

Congress of the United States
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January 5, 2016

Ms. Sophie Holiday
Advisory Committee on the Medical Use of Isotopes
Subcommittee on Training and Experience for Alpha and Beta Emitters
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555-0001

Dear Subcommittee Members:

As you are aware, the Nuclear Regulatory Commission (NRC) regulates the medical use of radiolabeled products to treat cancer and other life threatening diseases. The NRC's regulations require that a physician treating patients with a therapeutic radiopharmaceutical must be licensed as an "Authorized User." My office has heard from patient advocates and physicians about the shortage of Authorized Users and the barriers to patient access to these life-saving cancer treatments such as Zevalin, a beta-emitter treatment for patients with non-Hodgkin's lymphoma.

The NRC's proposed rule on the "Medical Use of Byproduct Material—Medical Event Definitions, Training and Experience, and Clarifying Amendments" (RIN: 3150-AI63 [NRC-2008-0175]) intended to address related issues, including shortages of authorized users, the classification of radiopharmaceuticals and associated work experience requirements. In its rulemaking, the NRC specifically requested comments on whether its regulations "*discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how.*" On March 2, 2015, I offered my comments as a physician and as someone trained in the Medical Effects of Ionizing Radiation by the Armed Forces Radiobiology Research Institute. However, on December 29, 2015, the NRC released its draft final rule, which failed to include any changes to the training and experience requirements for authorized users of therapeutic radiopharmaceuticals.

I write today to restate my concerns with the burdensome Authorized User requirements and to request ACMUI work to establish a more equitable training requirement for physicians wishing to administer therapeutic radiopharmaceuticals, in order to ensure patient access to these drugs.

The NRC's current regulatory framework requires that most hematologists and oncologists who want to become Authorized Users must complete 700 hours of training and experience, including a minimum of 200 hours of classroom / laboratory training in radionuclide handling techniques. This training requirement has created a shortage of Authorized Users able to administer therapeutic radiopharmaceuticals, particularly in the community oncology setting. Outside of major academic medical centers, patients sometimes have to travel great distances in order to

find Authorized Users able to administer these products. For patients living in rural areas, especially elderly patients with mobility difficulties, these barriers can be insurmountable. The regulations have the effect of limiting the treatment options available to these cancer patients.

The Spring 2016 ACMUI Meeting on March 17th presents another opportunity for the NRC to address the current shortage of Authorized Users able to administer these anti-cancer therapies. By creating a training requirement commensurate with the precautions necessary to administer these products, the NRC can ensure that products are handled safely and appropriately, while ensuring all patients can access these treatment options. I understand that there is precedent in the NRC regulations for reduced training and experience requirements for products that pose minimal safety and handling risks prior to and after administration. For example, the regulations require only 80 hours of classroom and laboratory training in order to administer oral sodium iodide I-131.

As the Committee reviews the subcommittee report on Authorized User training and experience hour requirements for alpha- and beta- emitters, I strongly urge the you to seriously consider the information provided regarding the shortage of Authorized Users able to administer alpha- and beta-emitting products, and to make a recommendation to the NRC that reduces the training and experience requirements to a level appropriate for these lower risk products. This will increase access to critical, life-saving therapies without exposing patients or providers to any significant risk.

I appreciate your consideration and look forward to being updated as the process moves forward.

Sincerely,

Joe Heck, D.O.
MEMBER OF CONGRESS

cc: The Honorable Fred Upton, Chairman, House Committee on Energy and Commerce

Holiday, Sophie

From: Jan Waters <janwsyc@yahoo.com>
Sent: Friday, January 15, 2016 4:36 PM
To: Holiday, Sophie
Subject: [External_Sender] Zevalin

Janet Waters
675 Shore Drive
Columbus, OH 43229

Advisory Committee on the Medical Use of Isotopes
Subcommittee on Training and Experience for Alpha and Beta Emitters
% Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S.Nuclear Regulatory Commission
Washington, DC 20555-0001 January 15, 2016

Dear Members of the AGMUI:

My name is Jan Waters. I am 73 years old and I am alive today because of a treatment I had in 2004 with a drug named Zevalin. I was diagnosed with Smalll Cell Follicular Non Hodgkins Lymphoma in 1997 at age 55, just as I was looking forward to becoming a grandmother.

After a two year watch and wait program, I experienced pain and needed treatment. I was given CVP followed by Rituxin which had just been approved by the FDA. I was in remission a little over a year when I relapsed. I chose a clinical trial of Interleukin plus Rituxin. This treatment made me feel like I had the flu all the time and had no effect on my disease as evidenced by a CAT scan. In or about 2001 I was then given Fludarabine. I relapsed again in early 2004 and began reading about a treatment called Zevalin that looked good in clinical trials. My oncologist in Columbus said this treatment was new and hard on the bone marrow. I said, "Hasn't the chemo been hard on my bone marrow"? He replied, "Yes".

I read about Zevalin on an Internet support group where it posted the clinical trial showing the good results for Zevalin. I decided to get a second opinion from a doctor in Michigan who had given the drug. I had my records faxed to the second opinion doctor and went to see him. In the spring of 2004, the second opinion doctor said I was a good candidate for Zevalin. He didn't say why but I thought it was because I had relapsed several times and he had had good results with Zevalin at his hospital in Grand Rapids.

I took this information back to my oncologist, Dr. Eric Kraut, at the James Cancer Hospital in Columbus, Ohio and he said he could arrange for it to be given at the James. So in June of 2004 I had the treatment and in the following series of CAT scans I experienced the disease disappearing! I have been free of any observable disease since that time. I have my life back. I've watched my 8 grandchildren grow up. The baby that was born when I was diagnosed will graduate from high school this year. I was wearing out from chemotherapy. I would begin to get my strength back and would need another treatment again. The Zevalin treatment was much easier on me and was a one episode treatment.

Over the years I have been dealing with this disease. I have attended many workshops on Small Cell Follicular Lymphoma. I always ask the presenter, usually a doctor, why they aren't mentioning Zevalin as a treatment. The answers I have received always involve the fact that under current regulations, it takes two departments (oncology and nuclear medicine) to coordinate the treatment. Also many oncologists community practices do not have a nuclear medicine department and therefore cannot offer the therapy.

These reasons are unacceptable to me the patient. The primary focus should be whether the therapy is medically appropriate for the patient and is safe for the oncologist to administer it.

My hope is that all patients with my diagnosis will be told about Zevalin and have a chance to be treated with it. I think it would really help patients if the NCR would make it easier for doctors to obtain authorization to administer this drug,

Once I added up the cost of my three treatments before Zevalin I realized the total was more than the single Zevalin treatment. I wish my oncologist had been given the opportunity to start my treatment with Zevalin at the outset.

Thank you for reading this. Please forward to all commissioners.

Jan Waters

STATEMENT OF JOSEPH R. MACE, M.D.
Medical Oncologist and Licensed Authorized User
Florida Cancer Specialists
to the
Advisory Committee on the Medical Use of Isotopes Subcommittee on Training and Experience for Beta-emitters

I. Introduction

1. My name is Joseph Mace, and I am writing to provide the ACMUI Subcommittee with my opinion and recommendations as it reviews the appropriate level of training and experience requirements for hematologists and medical oncologists to safely administer beta-emitters under 10 CFR 35.390. As set out in my statement, I have been an Authorized User for over a decade and have safely administered beta emitters, including Zevalin (ibritumomab tiuxetan), to over 40 patients.

2. I have detailed my training and clinical experience for the Subcommittee. I believe that the information provided in my statement supports a modification to the training and experience requirements to provide a limited authorization for beta emitters prepared by a licensed radiopharmacy and delivered to the hematologist/ medical oncologist in a pre-filled syringe.

3. I strongly urge that the ACMUI Subcommittee consider a modified alternate pathway of requiring 80 hours of training and experience for hematologists/ medical oncologists seeking to administer beta-emitting therapeutic radiopharmaceuticals such as Zevalin.

II. Academic and Clinical Qualifications

4. I received a Bachelor of Arts with highest honors, from the State University of New York at Binghamton in 1989 and a Doctor of Medicine, *summa cum laude*, from the State University of New York Health Science Center at Syracuse in 1993.

5. I served as a Diagnostic Radiology Resident at the Hospital of the University of Pennsylvania between 1994 and 1996, an Internal Medicine Resident at the State University of New York Health Science Center at Syracuse between 1996 and 1998, and was a Hematology and Medical Oncology Fellow at the University of Michigan Medical Center from 1999 to 2002.

6. Starting in the summer of 2002, I practiced as an Attending Physician at Gulfcoast Oncology Associates in St. Petersburg, FL. I founded both the Gulfcoast Oncology Associates' Clinical Research, and Radioimmunotherapy Programs, and served as director until our merger with Florida Cancer Specialists in February of 2011. I continue to serve as an Authorized User (AU) of radioimmunotherapy agents, treating patients at our St. Petersburg office location. In addition, I travel to several additional Florida Cancer Specialists office locations to administer radioimunitherapy agents, in an effort to expand patient access to these important and effective therapies. I also serve as a Thought Leader for Lymphoma, Leukemia, bone marrow disorders, as well as benign hematology within Florida Cancer Specialists' Clinical Research Program .

III. Authorized User Training and Experience

7. I obtained my AU license from the Nuclear Regulatory Commission in 2006, after completing an on-site, eight-day, 100-hour radiation safety and handling course offered through the University of Chicago.[1]

8. This course consisted of didactic lectures and two daily written examinations. Course topics included radiation physics, instrumentation, protection, and biology, as well as mathematics pertaining to radioactivity; and radiopharmaceutical chemistry. Specific characteristics and aspects of use surrounding those radioisotopes that are commonly in use for both medical diagnostic and therapeutic indications, across all medical subspecialities, were reviewed in detail. In part owing to this, and as I explain in greater detail below, the 100-hour course I attended did cover a notable volume of material that was/ is superfluous for those physicians seeking to use/ administer solely beta emitters.

9. I have been safely administering Zevalin at multiple office locations in Florida since I received an AU license in 2006, as discussed above.

IV. Medical Experience with Beta Emitters

11. During my fellowship training at the University of Michigan Medical Center, I had the unique opportunity to work closely with Dr. Mark Kaminski in the Lymphoma clinic from 1999 through 2002. During this three year period, the use of radioimmunotherapy was commonplace, and as a result I obtained significant experience with their pharmacology, safe handling, and administration. Upon completing my

[1] Until the regulations were changed in 2002 to require 700 hours of training, one could become an AU with 80 hours of training and experience. Because Florida did not implement the rule until 2006, the 80-horu requirements were grandfathered.

Hematology and Medical Oncology fellowship, and joining Gulfcoast Oncology Associates in St. Petersburg, I was uniquely positioned to enhance the services our practice provided. I felt then, as I do now, that Zevalin offers many advantages for our Non-Hodgkin Lymphoma (NHL) patient population.

12. As compared to conventional chemotherapy regimens, beta emitters such as Zevalin provide an invaluable treatment option for patients NHL. For one, treatment with beta emitters is far less intrusive and cumbersome for patients; It can be completed in approximately one week and involves the administration of one dose of radiolabeled antibodies. In addition, antibody-bound beta emitters target NHL cells highly selectively, which translates into mild and generally well tolerated side effects. Patients do not need to be admitted to a hospital for treatment, and beta emitters such as Zevalin typically do not result in significant adverse impact on patients' quality of life, functional capacity, or their other medical problems. Taken in total, it is the clinical features of Zevalin that make it so appealing to those of us who treat Lymphoma patients on a regular basis, particularly where a large proportion of patents are elderly, and unable to tolerate conventional cytotoxic therapy.

13. Beta emitters are employed at many stages of a NHL patient's clinical course. Their tolerability and efficacy are well established in the setting of indolent NHL, which comprises a large percentage of new NHL diagnoses and, unfortunately, is a non-curable disease. This being said, indolent NHL typically runs a very long clinical course thats can be measured in years to decades, with intermittent treatments required over time. This fact highlights the importance of having as many effective agents in our arsenal as possible. In essence, it is crucial that proven agents, such as the antibody-

bound Beta emitters be readily available to patients with indolent NHL, as optimal improvements in life span and survival will be achieved by employing many different treatments over the course of their disease. The antibody-bound Beta emitters have well established efficacy particularly in those patients who have received many prior conventional chemotherapy agents, where responses to subsequent conventional chemotherapeutic agents is less frequent and of shorter duration.

14. Recognizing this, after I received my AU license I worked to establish a "hot lab" as well as an administration area at our practice location. It soon became clear that the ability to provide Zevalin locally, thereby precluding the need for outside referrals to either radiation oncology or a regional academic center, was of tremendous benefit to our patients. While it might be unusual for a hematologist/ medical oncologist to obtain an AU license for RIT administration, there are clear advantages to doing so. We have a unique understanding of chemotherapy, including its administration, potential short- and long-term side effects, as well as the requisite monitoring both during and after treatment. In addition, a hematologist/ medical oncologist is ideally suited to manage patients who receive Zevalin, and the ability to actually administer this agent (as opposed to referring a patient elsewhere to do so) improves convenience, access, and provides for optimal continuity of patient care.

15. As a result, I received consultations for Zevalin therapy, not only from within Gulfcoast Oncology, but also from physicians outside our practice across the state of Florida. Patients clearly appreciated seeing the same physician for their consultation to review and discuss Zevalin therapy, for the administration of the agent, and for the requisite monitoring over the subsequent two to three months thereafter.

16. I have been administering Zevalin for approximately ten years now and have not had a single safety event. I strongly believe that completing an intensive 100-hour course provided me with more than sufficient training to administer this safe and straight forward therapy.

V. Shortage of AUs

17. Since the introduction of the 700-hour training and experience requirements, I have observed an immediate and dramatic impact on access to beta emitters. In my own practice at Florida Cancer Specialists, there are many oncologists who would like to administer beta emitters, however it is not logistically feasible or realistic for them to pursue the 700-hour training requirement. It is difficult to fathom a practicing hematologist/ medical oncologist being able to take an aggregate 700 hours away from patient care, in order to attend a radiation safety and handling course, be it at a brick and mortar facility, or online. In fact, to my knowledge, no oncologist has been able to receive AU status under the alternate pathway of 700 hours, since the regulations went into effect.

18. Accordingly, there is in my opinion, a marked shortage of physician "champions" in any given community who are willing to undertake what is now an extensive number of hours to obtain an AU license. In turn, this decreases patient access to this important and effective therapy.

19. The lack of access to beta emitters is an especially acute problem for the elderly, for whom Zevalin is an especially advantageous treatment option. St. Petersburg has a particularly large population of elderly cancer patients, and owing to this, the incidence of low-grade lymphoma occurs with greater frequency than the national average. Not unexpectedly, a majority of elderly patients are not only less able tolerate

conventional chemotherapy, but are also less mobile, and thus typically cannot manage the rigorous clinic visit schedules associated with these chemotherapies.

20. The problem is severe enough that in order to provide patients with access to beta emitters, I initiated a "traveling AU" program, wherein I see patients in consultation, and for administration of Zevalin at multiple office locations throughout Florida. While the program has been effective in modestly increasing access to beta emitters, increasing the number of oncologist AUs in a given community would be far more impactful. This could be accomplished by lowering the training and experience requirements to a more appropriate level.

VII. 80 Hours of Training is Sufficient

21. Based on my own experience with the course, 80 hours of training and experience would sufficiently prepare AUs to administer beta emitters such as Zevalin, which is delivered to the AU as a treatment-ready dose prepared by a licensed radiopharmacy. Its administration is not complex, requiring only an acrylic shield and adherence to standard radiation precautions. It does not even require patient isolation or exposure measurements

22. Zevalin has an excellent safety profile, particularly when compared to cytotoxic chemotherapeutic agents. Rates of nausea, vomiting, alopecia, hepatorenal injury and dysfunction, cardiopulmonary toxicity, neuropathy, and constitutional decline, are all less frequent with Zevalin. Like many cytotoxic chemotherapeutic agents, Zevalin does produce myelosuppression, and once again, it is the medical oncologist/ hematologist who is best prepared to manage this common and expected side effect of NHL therapy.

23. By contrast, the administration of sodium iodide I-131 based therapies is a much more involved process requiring a greater degree of precautionary measures. The patient must be isolated, and anyone handling the patient's fluids must wear protective clothing, including eye protection and a mask. In addition, the patient is not permitted to share toothbrushes, towels, or even a bed with another person. Yet currently, this therapy only requires 80 hours of training to administer.

24. The currently required 700 hours of training is vastly disproportionate to Zevalin's safety profile. Indeed, the requirements contained in 10 CFR 35.390 appear to be aimed at physicians seeking to become board certified in nuclear medicine. Board-certified nuclear medicine practitioners handle an array of radioactive substances in diagnosing and treating a variety of diseases. The course that I completed in 2005 covered topics ranging from diagnostic medical imaging, non-medical radiation uses, historical radiation events, to therapeutic thyroid I-131 administration—all superfluous from the standpoint of radionuclide management and safe handling of Beta emitters. That course was 100 hours, and while I am a strong proponent of general knowledge and academic pursuit, this highlights that 700 hours of training is unnecessarily prohibitive for hematologists/ medical oncologists seeking specifically to administer a limited class of beta-emitting products.

25. By reducing the requirements, practicing hematologists/ medical oncologists who either specialize in, or have an interest in NHL, can feasibly complete the required coursework and have an immediate impact on access within their community. In addition, with less onerous requirements in place, improvement in the

degree of familiarity and comfort with using Zevalin would undoubtedly follow, which in turn would translate into even greater access to these important therapies.

26. I believe the current training and experience requirements should be modified with respect to beta emitters. The course content can be appropriately focused on issues related to the administration and handling of beta emitters in order to lessen the time burden, while still resulting in proficiency on the part of the individual physician.

27. Based on my experience, the relevant components of the 700 hours of training for beta emitters can be successfully encompassed by focused study within an 80 hour course/ pathway. Topics essential to this should include training on:

(a) Radiation physicsand biology

(b) Radiation instrumentation, with particular attention to those used and setting appropriate for beta emitter therapy

(c) Radiation protection

(d) Mathematics pertaining to the use and measurement of radioactivity

(e) Pharmacology and chemistry of radioactive materials in the context of medical use.

(f) Safe handling practices for radioactive material and instrumentation

(g) Performance of standard quality-control procedures on instrumentation (those used to determine the activity of dosage, survey meters, etc.), and on received dose packaging, as well as reviews of personnel badges/ rings, and periodic radiation exposure reports.

(h) Calculation, measurement, and safe preparation of patient or human research subject doses (despite the fact this is performed by a licensed radiopharmacy).

(i) Review of the standard administration practices for specific Beta emitters.

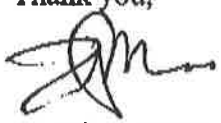
28. In such an 80-hour program, prospective AUs would gain ample experience with the logistics, medical and scientific, as well as administrative aspects and requirements of therapy. This would successfully serve to prevent and/or address adverse events associated with drug misadministration, personnel exposures and decontamination procedures, as well as with procedures for containing spilled radioactive material.

29. The above recommendations can be encompassed and successfully covered with a dedicated 80-hour training and experience requirement. A 700-hour requirement is unnecessary and deprives NHL patients of a valuable treatment option that is needed in many communities.

30. Stakeholders have proposed requiring 80 hours of training and experience to obtain an AU license as part of the current NRC rulemaking on radiolabeled materials, and I fully support this proposal.

31. I appreciate that the ACMUI is taking the opportunity to consider the appropriate training and experience requirements for beta emitters. I urge the ACMUI to consider my experience and recommendations as you prepare your Subcommittee report. I would welcome the opportunity to provide the ACMUI Subcommittee with any additional information that might prove helpful. Please feel free to contact me with any questions.

Thank you,



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February 9, 2016

Ms. Sophie Holiday
Health Physicist / ACMUI Coordinator
U.S. Nuclear Regulatory Commission (NRC)
Washington, DC 20555-0001

Re: NRC Training and Experience Requirements for Alpha and Beta Emitters

Dear Members of the Advisory Committee on the Medical Use of Isotopes,

As experienced nuclear pharmacists and experts in the field of radiation safety education and training, we appreciate the opportunity to submit our comments on the training and experience requirements for authorized users of alpha and beta emitters.

It is discouraging to see radiopharmaceuticals with documented clinical impact not used because they are not readily available in physician treatment regimens. For example, Zevalin (Ibritumomab tiuxetan) has been approved for first line therapy against Non-Hodgkin's lymphoma, the seventh most common type of cancer. Xofigo (Radium-223 dichloride) was fast-tracked by the FDA after demonstrating an increased patient life span and pain control in prostate cancer patients. However, the regulatory restrictions on access drive oncologists to use less effective chemotherapy regimens associated with significant side effects and diminished patient outcomes.

These current alpha and beta emitting radiopharmaceuticals, and others under development, are delivered to licensed healthcare sites as patient-ready doses with no additional manipulations needed before patient administration. The needed training and experience for safe handling of these specific drugs does not appear to warrant the full 200 hours of didactic training and 500 hours handling experience.

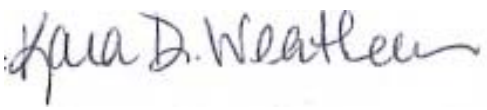
We recommend that NRC, as part of the current rulemaking, modify the training & experience requirements for authorized users for patient ready alpha and beta emitters to a didactic program which consists of 80 hours of educational material. This will provide a strong foundation for practitioners who wish to become involved in the administration of alpha and beta emitting radiopharmaceuticals. A program such as this would also include enhancements to the distance based didactic education, including specific

requirements for experiential radiation safety hands-on exercises as well as supplemental handling experience for each specific radiopharmaceutical. A representative outline of our consensus for a training program is included as an addendum to this letter.

An addition to the user training requirements, each facility is mandated to have a radioactive materials license and radiation safety officer. With adequate training, radiation safety procedures and guidance documents in place, the risks should be minimal while providing the maximum benefit in patient care.

Sincerely,

Nicki L. Hilliard, Pharm.D, MHSA, BCNP, FAPhA
Professor of Nuclear Pharmacy
University of Arkansas for Medical Sciences
NLHilliard@uams.edu



Kara D. Weatherman, PharmD, BCNP, FAPhA
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Authorized User Training for Alpha & Beta Patient Ready Radiopharmaceuticals

Recommendation for ACMUI Subcommittee Report

Developed by:

Kristina Wittstrom, PhD, RPh, BCNP, FAPhA
University of New Mexico

Kara Weatherman, PharmD, BCNP, FAPhA
Purdue University

Nicki Hilliard, PharmD, MHSA, BCNP, FAPhA
University of Arkansas for Medical Sciences

Summary of Needs

In that patient access to clinically meaningful therapeutics for treatment of oncologic conditions can be enhanced through better access, it is proposed that individual medical oncologists or urologists be licensed by the NRC or Agreement States for the isotope-specific radiopharmaceutical products. The licensure would consist of

1. Completion of an 80-hour didactic program in basics of radioactive materials handling suitable to alpha/beta emitting products to which access will be granted;

2. Completion of not less than 10 hours of experiential training in radiation safety techniques, protocols, and procedures;

3. Observe/participate in the administration of the specific radiopharmaceutical to not less than 3 patients.

4. Completion of not less than 4 hours of product–specific handling and patient administration techniques including record-keeping and patient counseling as provided by the radiopharmaceutical manufacturer; and

5. Addition to an existent or pending radioactive materials license with restriction in access and use to isotope, form and maximum activity.

Instructional Notes

a. *Suggest restriction to specific radiopharmaceuticals rather than a classification to maximize considerations of patient safety. For example, safe use of Ra-223 is different from safe use of Y-90.*
b. *There is no need for instruction on radiochemistry if use is restricted to patient-ready doses and there is no need for radiolabeling, reconstitution, or preparation of radiopharmaceuticals. Product quality control testing is also not needed.*
c. *Increased didactic and experiential training in radiation safety is recommended to maximize safety of patient and the general public.*
d. *As therapeutic uses do not involve imaging, training on imaging equipment is not needed. Testing and quality assurance of imaging equipment is not needed.*
e. *The requirement of dose calibrators will be variable dependent upon state requirements. Training is included. Instrumentation for contamination wipes and area surveys is included – function, testing, calculations, etc.*
f. *This training does NOT address issues specific to the use and handling of radioiodine products.*

Authorized User Didactic Training to Administer

Patient- Ready Alpha / Beta Emitting Radiopharmaceuticals

Block I: Nuclear Physics & Instrumentation: 25 hours

I. Structure and Properties of Atoms
II. Radiation and Radioactive Decay
III. Production of Radionuclides
IV. Interaction of Radiation with Matter
V. Gas-Filled Detectors
VI. Scintillation Counters
VII. Personnel Monitoring Devices

Block II: Radiation Biology: 20 hours

I. Physical Effects of Radiation
II. Chemical effects of Radiation
III. Cellular Effects of Radiation
IV. Biological Effects of High Dose Radiation
V. Biological Effects of Low Dose Radiation
VI. Therapeutic Application of Particulate Radiation

Block III: Regulations and Radiation Protection: 25 hours

I. Characteristics of Ionizing Radiation
II. Definitions of Radiation Measurement
III. Principles of Radiation Protection
IV. Personnel Monitoring & Safety Precautions
V. Regulatory Agencies
VI. Documentation and Regulatory Reporting
VII. Sealed Reference Sources
VIII. Area Monitoring
IX. Waste Management & Disposal
X. Packages containing Radioactivity

Block IV: Mathematics Pertaining to Use & Measurement of Radioactivity: 10 hours

Includes fundamental calculations: decay equation, half-value layers, exposure calculations, instrumentation needs.

Note: The traditional Radiochemistry material is not included here as the intended Authorized User will not be mixing, radiolabeling, or preparing patient doses. All radiopharmaceuticals will be received in patient-specific, ready-to-inject unit dose form.

Name of Trainee (Please print)

Assignments

	Operator	Supervisor
1. Use basic operational functions of GM meters.	_____	_____
2. Use basic operational functions of dose calibrator.	_____	_____
3. Perform area wipe test for contamination.	_____	_____
4. Perform regulatory performance checks of SCA / MCA	_____	_____
5. Perform area-monitoring (surveys) for contamination.	_____	_____
6. Perform decontamination procedure in a contaminated area.	_____	_____
7. Dispose of radioactive waste and radioactive labels.	_____	_____
8. Radioactive materials package check-in procedure.	_____	_____
9. Determine appropriate patient-specific dose/ dose volume for ordering and administering radiopharmaceutical doses.	_____	_____
10. Know regulatory requirements for, and how to arrange for, calibration of survey meters.	_____	_____
11. Perform regulatory requirements for dose calibrator performance. (If applicable)	_____	_____
12. Take appropriate steps to ensure that the right patient receives	_____	_____
the right drug, in the right dosage, at the right time, via the right route of administration	_____	_____
13. Interpret radioactive material license, applications, amendments.	_____	_____
14. Locate applicable state/federal regulations for handling radioactive materials	_____	_____
15. Demonstrate the proper selection, placement and handling of radiation dosimetry devices.	_____	_____
16. Compile and maintain appropriate documentation to meet regulatory requirements	_____	_____

Name of Supervisor *Signature* *Date*

_____

Licensed Facility Name

_____

Mailing Address

_____

City, State Zip

Date(s) of Training

Biographical Information

Nicki L. Hilliard, PharmD, MHSA, BCNP, FAPhA

Dr. Hilliard was the manager and radiation safety officer in a nuclear pharmacy for 7 years before coming to UAMS to start a nuclear pharmacy education program. In the past 30 years she has taught thousands of authorized users both at the University and through the Nuclear Education Online program. Among her numerous awards she has received the William H. Briner Distinguished Achievement in Nuclear Pharmacy Practice and the American College of Nuclear Medicine Personal Mentor of the Year.

Kara D. Weatherman, PharmD, BCNP, FAPhA

Dr. Weatherman is a Board Certified Nuclear Pharmacist, with experience in both operational and clinical aspects of nuclear pharmacy practice prior to moving to academia as a member of the nuclear pharmacy program at Purdue University College of Pharmacy in 1998. Through her faculty appointment and as Director of Nuclear Pharmacy Programs at the College, she has focused on the development and implementation of various authorized user training programs, both via live and distance based education. In addition, she coordinates Purdue's continuing education program in nuclear pharmacy and maintains a research program in areas relating to nuclear pharmacy practice.

Kristina Wittstrom PhD, RPh, BCNP, FAPhA

As a Board Certified Nuclear Pharmacist since 1983, Dr. Wittstrom has extensive experience in operating a nuclear pharmacy both as manager and RSO. Her nuclear experience combined with a doctorate in adult education supports nuclear science education at the University of New Mexico in the classroom, the dispensing pharmacy and in the online environment.

Patients Against Lymphoma

Non-Profit | Independent | Evidence-based

Founded in 2002 by patients, for patients

EIN: 51-0426732

February 16, 2016

Advisory Committee on the Medical Use of Isotopes (ACMUI)
Subcommittee on Training and Experience for Alpha and Beta Emitters

Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission (NCR)
Washington, DC 20555-0001

Re: Radioimmunotherapy Training and Experience Requirements

To whom it may concern:

Patients Against Lymphoma (PAL) is a non-profit group founded by patients and loved ones who are afflicted by lymphoma. We are an evidence-based source of information on lymphoma that is independent of health industry funding and therefore our perspectives are not influenced by funding sources.

We are writing to urge the ACMUI and NCR to amend the ruling that substantially increases the required time needed to be certified to administer ibritumomab tiuxetan (Zevalin) a type of radioimmunotherapy (RIT). It's our understanding that the required time for training has increased **from 80 hours to 700 hours.** It is very difficult to understand the rationale of an 8-fold increase in the time needed to receive accreditation to administer RIT.

We have been informed that 700 hours of training is not required for similar therapeutics, such as for sodium iodide I-131, which is considered more complicated than the administration of RIT. It is also our understanding that RIT products are provided to oncologists in "patient-ready doses prepared at licensed radiopharmacies."

PAL agrees with the medical authorities such as the American Society of Hematology that have submitted letters opposing the additional time for training, specific to the administration of RIT. We urge the ACMUI and NCR to instead focus on the redesign of the course work so that it trains physicians in an efficient way -- in a time frame that makes it feasible for community oncologists and hematologist to take part and acquire the necessary skills to meet the needs of their patients.

Our major concern is an important one. The rule change will make it virtually impossible for oncologists in the community setting to receive the training needed to offer this important FDA-approved therapeutic to patients, a treatment that demands less of the patient in terms of time – taking about one week to administer, compared to months of treatment with cytotoxic chemotherapy.

RIT is an important class of treatment that can induce very durable remissions with side effects that can be easier for patients to tolerate. This aspect of RIT can be especially important to elderly patients or patients with a

preference to avoid the side effects of cytotoxic agents, such as nausea, hair loss, neuropathy, and gastric and oral complications.

We remind that many insurance policies do not support receiving therapies out of network; and that travel to nuclear medical facilities will not be feasible for many patients due to their age, secondary medical conditions, frailty, and their income status.

We appreciate the critical role of the ACMUI and NCR in protecting patient safety. We urge you to reconsider the rule change based on the anticipated and serious impact on patient access to RIT in the community setting. We urge the committees to focus on redesign of the course work so that the necessary skills can be delivered in a time frame that has been used previously – and so the training is applicable to the skills that are needed by hematologists and oncologists who treat lymphoma.

We thank you for your attention to this matter.

Sincerely,

Karl Schwartz
President, Patients Against Lymphoma
Approved by PAL's Board of Directors

CORAR

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Michael J. Guastella, MS, MBA
Executive Director

Via email February 23, 2016

Advisory Committee on the Medical Use of Isotopes (ACMUI)
Subcommittee on Training and Experience for Alpha and Beta Emitters
c/o Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: NRC Training and Experience Requirements for Alpha- and Beta- Emitters

Dear ACMUI Committee Members:

The Council on Radionuclides and Radiopharmaceuticals (CORAR) would like to provide the Advisory Committee on the Medical Use of Isotopes (ACMUI) with additional comments about the training and experience requirements for physicians to safely administer alpha- and beta-emitters that are delivered to them in patient ready doses.

As you know, CORAR's members include the manufacturers and distributors of both FDA approved radiopharmaceuticals, as well as other therapeutic products that are still undergoing research and development. CORAR continues to support the NRC's efforts to update the training and experience regulations, particularly to ensure access and to support technological advances and changes in medical procedures.

As we've noted previously, we continue to hear from providers, patient groups, and our members that the current regulatory framework requiring 700 hours of training before hematologists and oncologists who can become Authorized Users licensed to administer alpha- or beta- emitting radiopharmaceuticals is limiting access to medicines such as Xofigo® (Radium Ra 223 dichloride) and Zevalin® (ibritumomab tiuxetan), as well as raising concerns about the future development of radiopharmaceuticals designed to treat or cure cancers - often in a very precision way.

This letter is about the specific scope of training requirements for Radioisotope Handling and Radiation Safety for physicians wishing to administer intravenous therapeutic radiopharmaceuticals containing alpha- or beta- emitting radioisotopes, which have been prepared by a licensed nuclear pharmacist in a state-licensed radiopharmacy and dispensed to physicians as patient-ready doses. Surely the Advisory Committee members will agree, that as the Advisory Committee and the NRC are evaluating the appropriate level of training and experience for these physicians for their limited use of radionuclide therapies, that the Committee and the NRC consider not only the current state of radiological science, but also how biomedical advancements have produced new valuable drugs for patients and their physicians.

In determining the appropriate amount of time (and scope of content) for Radioisotope Handling and Radiation Safety training that physicians, such as medical oncologists and hematologists, should receive to enable them to safely administer these types of therapeutic drugs, the following factors need to be considered:

- Their limited role in handling these radiolabeled drugs (which would be dispensed and delivered to them in patient-ready doses from a licensed radiopharmacy);
- The radiological safety profiles of radiopharmaceuticals containing alpha- and beta-emitting isotopes; and
- Physician's experience and training in handling toxic non-radioactive chemical therapies, e.g., cytotoxic chemotherapy agents.

CORAR believes that the didactic training required to adequately prepare physicians to safely administer patient-ready doses of alpha- and beta- emitting radiopharmaceuticals would entail about 70-80 hours of classroom and laboratory time, as described in more detail below.

In considering what information should be covered in this training, it should be noted that the didactic training for cardiologists wishing to be added to a radioactive materials (RAM) license as an Authorized User of Diagnostic Radiopharmaceuticals/Radionuclides and/or to be Board Certified in Nuclear Cardiology emphasizes primarily Instrumentation and Physics, Radiopharmacy, and Radiation Safety along with a reasonable amount of Radiobiology and Mathematics Associated with Use of Radioactivity.

For physicians who wish to be added on to a RAM license as an Authorized User of Therapeutic Radionuclides for administering alpha- and beta- emitters as described above, however, the emphasis should change significantly. Emphasis on Instrumentation can be reduced since it historically has covered Imaging Instrumentation, Principles of Scintillation Detection, cameras and scanners, and related topics. That information is not relevant to the administration of non-imageable therapeutic isotopes, but learning about dose calibrator operation and quality control should be on top of the list of important instrumentation topics, along with survey meter operation and quality control and other radiation detection equipment.

Additionally, it is more important to concentrate on Radiation Safety and Radiation Biology, the basics of Radiopharmacy, and in particular, Radionuclide Therapy (basic principles, administration procedures, risks and benefits, radiation safety considerations). Also, the mathematics associated

with use of radioactivity in humans is important since it can help in dose calibration and adjustment, when necessary.

As for the specific areas to cover in this training, considering the didactic lectures and lab training required by the NRC and Agreement States, a course that covers the following areas would be appropriate for physicians who would be administering the therapies described above:

1. Radiopharmacy:

The basics of radiopharmacy, including a comprehensive review of the mechanisms of localization of the drugs, internal radiation dosimetry, waste disposal, radiopharmacology, sterility and apyrogenicity, aseptic technique, quality control procedures, and properties of the ideal therapeutic radiopharmaceutical, as well as an in-depth understanding of the interrelationship between physical, biological, and effective half-lives; it is also valuable to learn the basic operation of a central radiopharmacy and know what to expect when a patient-ready dose of a therapeutic radiopharmaceutical has been received.

2. Radiobiology and Mathematics Associated with Using of Radioactive Materials:

It is very important to understand the biological effects of ionizing radiation in humans, especially when administering therapeutic radiopharmaceuticals. In addition, physicians should be able to perform calculations related to the mathematics associated with the use of radioactivity, including radioactive decay calculations as well as radiation shielding. As part of this understanding, physicians must also know how to convert between the units of the US and SI systems since there is a growing trend now toward reporting doses in the SI System and some radiopharmaceuticals, particularly therapeutic ones, only mention GBq and not mCi.

3. Radiation Safety:

Since these radionuclide therapies will be utilizing only alpha- and beta- emitters, safety issues focusing on particulate-emitting radioisotopes should be emphasized along with safety issues for photon emitters since all particulate emitters have associated X-ray (and sometimes gamma ray) production. Safety discussions should cover detailed information about maximum permissible doses to radiation workers (whole body, extremities, eyes, gonads, internal; organs, etc); definition of a reportable event and a recordable event, and to whom the report should be sent and how soon; discussion of the Declared Pregnant Worker and its associated regulations; radioactive waste disposal limits and procedures as well as reporting requirements in the case of an accidental overdose or underdose of a prescribed therapeutic; how to deal with spills of radioactive materials and decision-making regarding reportability; and relevance of the interrelationship between the physical, biological and effective half-lives.

And of course, it would also be important to include drug administration procedures since there are procedural differences between administering radioactive and non-radioactive drugs, and there is a significant risk related to extravasation of a dose of any cellular toxic medicine designed to be delivered intravenously. Other relevant NRC regulations not included in this paragraph should also

be covered; including a discussion of the various shielding materials appropriate for use with particle emitters, which are typically very different from those used with photon emitters.

4. Instrumentation and Physics:

As noted above, the emphasis for this section should be appropriate for physicians delivering radionuclide therapies rather than conducting diagnostic exams, (e.g. understanding the design and function, and QC for gamma cameras would be of little to no use for these physicians). However, the course should include an extensive review of dose calibrators, including description of mandatory quality control tests, their required frequency, performance of the tests, specifications for determining if the test is a "Pass" or a "Fail"; what to do if there is a failure, and whether or not there is a reporting requirement in the case of a failure. Dose calibrators are much more difficult to use in the case of particle emitters than gamma ray emitters due to the poor penetrability of alpha and beta particles and also due to a dependence on sample geometry. There should also be a comprehensive review of all relevant radiation detection equipment used for monitoring the environment to locate spills; what tests must be performed on the equipment; regulatory requirements for quality control for each type of equipment;

5. Radionuclide Therapy, Including Drug Preparation and Quality Control:

The basics of these areas are important. Even though all dose preparation and quality control procedures will be performed at the central radiopharmacy and the patient-ready dose will be delivered to the healthcare facility, the physician should understand the operation of the central radiopharmacy. An understanding of the inner workings of the central radiopharmacy would enable a physician to communicate effectively with the nuclear pharmacists about their patients and the radiopharmaceutical/radionuclide drugs being prepared and dispensed to them.

In addition, it would be important for physicians to observe the "start-to-finish" performance of 3-4 therapies performed by an authorized user on a RAM license who has had experience in administering these therapies. And (in compliance with current NRC Regulations), the physician wishing to become an AU on a RAM license should perform at least three dose administrations of each radiopharmaceutical under the direct supervision of an authorized user on a RAM license who has had experience in administering these therapies.

Overall, successful completion of a high-quality course including 70 - 80 total classroom hours of didactic and laboratory training covering this material - combined with hands-on experience with dose calibrators and other equipment that these physicians should know how to use, and supervised administrations of alpha- and beta- emitter therapies - would provide adequate training for medical oncologists and hematologists to enable them to safely administer these types of alpha and beta therapies. And since some information in the five areas described above potentially could be covered under more than one area, rather than quantify the numbers of hours that should be dedicated for each topic, it would be better to provide course director flexibility in how they cover the required course material.

In addition, although outside the direct scope of the Committee's and the NRC's role - but appropriate for you to consider as individuals engaged in making public policy - CORAR hopes

that the Committee would also recognize how NRC's current regulations encompass public health and policy factors in the training requirements for physicians administering therapeutic I-131, and apply those same principles to radiotherapies for cancer, so that the number and geographic distribution of physicians who could administer alpha- and beta- emitters as described above - and patient access and treatment options - would expand dramatically.

Thank you for your consideration of this letter.

Sincerely,

Michael J. Guastella
Executive Director

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February 24, 2016

Re: Administration of Ibritumomab tiuxetan (Zevalin) by Physicians other than Radiation Oncologists and Nuclear Medicine Physicians

Members of the Board of ACMUI:

In late 2002 I was diagnosed with non-Hodgkin's lymphoma (later deemed to be related to my Agent Orange exposure in Vietnam) and, rather quickly, was given the unnerving news that I had Stage IV, incurable disease.

Based upon my background and creed I would not accept standard therapy if standard therapy had no chance of curing me. Therefore, I sought something new, an experimental clinical trial that might offer me a better prognosis.

It was my good fortune that my son is a physician; together, we searched and found a National Cancer Institute-sponsored clinical trial in which Zevalin would be administered after a very short course of CHOP chemotherapy and rituximab. I learned much about Zevalin from professors who were leading figures in the emerging and exciting discipline of radioimmunotherapy.

I was, particularly, impressed with what I like to call the specificity and punch of Zevalin, as its tagged antibodies attack the antigens on my tumor cells without killing my normal tissues. I applied for this clinical trial and was pleased to have been accepted as a patient. (I believe I was the 6th patient in the trial.)

In May 2003 I received a single dose of intravenous Zevalin in an examination room of a radiation oncologist. I was clearly aware that no special protective garments needed to be worn by myself or the administering clinician; no radioactive monitoring devices surrounded me; I was not enveloped within thickened walls in order to prevent radiation exposure to the unsuspecting public.

The painless intravenous infusion, as I recall, took 2 or 3 minutes. A small adhesive bandage was applied. I shook everyone's hand and left with my wife. That evening I had dinner with my wife, my son, and my daughter-in-law.

My hematologic response to the Zevalin was superb and, to my delight, I did not miss a single day of work as a university professor. I did continue to communicate with professors who were experienced in radioimmunotherapy and I was terribly dismayed when they informed me that many prospective patients who could benefit from Zevalin were unable, for several reasons, to receive it.

I trust that the members of the Advisory Committee on Medical Uses of Isotopes (ADMUI) to be aware of this unfortunate situation. Patients who could receive a single dose of radioimmunotherapy are consigned to prolonged chemotherapy and multiple, serial infusions of monoclonal antibodies.

Respectfully,

Morton A. Diamond, MD

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March 3, 2016

Advisory Committee on the Medical Use of Isotopes
c/o Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: Draft Report on Training & Experience for Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390

Dear Members of ACMUI:

We are writing in advance of the March 10th Advisory Committee on the Medical Use of Isotopes (ACMUI) teleconference to provide our response to the Subcommittee Draft Report on Training and Experience for Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390. While we appreciate the time and attention that the NRC and ACMUI have devoted to this important issue over the past 18 months, we are concerned that the Subcommittee fails to justify why the currently required 700 hours of training and experience is appropriate for an oncologist or hematologist seeking to administer a patient-ready dose of an alpha or beta emitter. Additionally, while the Draft Report acknowledges that the education paradigm has shifted since the 700-hour requirement was established in 2002, the Subcommittee does not recommend a sufficient level of training and experience for Authorized Users (AUs) of patient-ready dose therapies. As discussed in greater detail below, we agree with the Subcommittee's finding that the current requirements are outdated, and urge the Full Committee to make specific recommendations for training and experience for a patient-ready dose.

The Subcommittee Failed to Justify Why 700 Hours of Training and Experience is Appropriate

The Subcommittee was charged with developing a recommendation for the appropriate number of hours of training and experience for a patient-ready dose of alpha and beta emitters. Instead, the Draft Report only notes that "[a]ppropriate T&E requirements for these agents need to be established" and recommends the issue for further study. In particular, the Subcommittee did not address the stakeholder expert commentary regarding appropriate training for AUs for a patient-ready dose. This is a critical distinction because a patient-ready dose does not involve handling or preparation of the radioactive isotopes. Rather, the biological product is prepared by a fully licensed radiopharmacy and delivered to the physician on the day of the scheduled patient appointment.

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It is our understanding that the 700-hour requirement was set to reflect the complete coursework that a physician would undertake to specifically become board certified in nuclear medicine, which is a dedicated *medical* imaging specialty involving the broad use of various radioactive substances in the diagnosis and treatment of disease. As such, the 700 hours include training for all aspects of medical use and safe handling of various radioactive byproduct materials used clinically (nearly 100), including alpha, beta, and gamma emitters. We believes there is ample support that 80 hours of training or less is sufficient and is a more appropriate level of training and experience for the risks associated with the administration of a beta emitter like Zevalin in the hematologist / oncologist setting.

The Subcommittee Found No Safety Issues with Alpha and Beta Emitter Therapies

We agree with the Subcommittee finding of an "exceptional" and "excellent" safety record of alpha and beta emitters. Indeed, the Subcommittee made no mention of any safety incidents or risks associated with the administration of such therapies. However, we disagree with the Subcommittee that the safety record is attributed to AUs "who have successfully completed the rigorous T&E requirements." Notably, at no point in its report did the Subcommittee find that 700 hours of training and experience is necessary to ensure that alpha and beta emitter therapies are safely administered. In particular, the regulations previously required 80 hours of training and experience prior to the 2002 NRC rulemaking, and we are not aware of a single safety event during that time period. Moreover, oncologists who became an AU under the 80-hour alternate pathway continue to administer alpha and beta emitters today without any safety events. This means that physicians who became AUs under the 80 hour requirements have since been administering beta emitters wholly without any safety issue or incident. Contrary to the statement in the Draft Report, "[w]hether or not the safety records would be comparable in the hands of AU's with considerably less T&E [than 700 hours]" is *not* "a matter of conjecture."

The Subcommittee Recognized That the Current Training Paradigm Is Outdated

We agree with the Subcommittee's conclusion that, since it has been "nearly 15 years since the current requirements were established," they are now outdated. It is clear from the Subcommittee's acknowledgement that the training paradigm has shifted that 700 hours is not appropriate and a new training program is needed.

However, we disagree with the Subcommittee's conclusion that establishing a more appropriate educational approach based on competency "is complicated and cannot be completed in weeks or even months." Given the significant involvement of and input from the NRC, ACMUI, the Subcommittee, and numerous stakeholders throughout this process, further delay is unwarranted. Stakeholder input has already demonstrated that competency could be established through programs imposing much less of a burden on practicing physicians.

For example, Kristina Wittstrom, Kara Weatherman, and Nicki Hilliard are experienced nuclear pharmacists and experts in the field of radiation safety education and training. They represent academic training programs that have trained thousands of AUs over the past decades and submitted detailed recommendation to the NRC to "modify the training & experience requirements for authorized users for patient ready alpha and beta emitters to a didactic program which consists of 80 hours of educational material." Course material would be tailored to issues involving the administration of specific patient-ready alpha and beta emitters, and would include a didactic program consisting of 25 hours on Nuclear Physics & Instrumentation; 20 hours on Radiation Biology, 25 hours on Regulations and Radiation Protection, and 10 hours Mathematics Pertaining to Use & Measurement of Radioactivity.

Based on the expert stakeholder commentary, we have prepared the attached proposed regulatory text for a new training and experience paradigm for patient ready doses of alpha and beta emitters.

The Subcommittee Continues to Ignore Patient Access to Needed Therapies

The NRC as well as ACMUI have heard extensive testimony regarding the impact of the current 700-hour training and experience on access to care in certain patient communities. No one maintains that no patients have access. However, the Subcommittee continues to take the position that "it is not possible to conclude that the current T&E requirements are the only, or even the principal, cause of the decreased use of radiopharmaceuticals . . .". ACMUI continues to ignore the letters and expert statements that are contrary to this conclusion. In fact, ACMUI has received letters from, among others, the Leukemia and Lymphoma Society, the Lymphoma Research Foundation, the Community Oncology Alliance, the American Society of Hematology, the Council of Radionuclides and Radiopharmaceuticals, Inc., and Florida Cancer Specialists.

We were pleased to see that Subcommittee Member Laura Weil correctly observed that "[t]he 700 hour T&E requirement effectively limits AUs to those medical specialties that cover the requirements in residency training. Those specialists may simply not be available in the community setting, creating a real barrier to access for those patients who are unable to seek treatment in a larger medical center." In fact, the data displayed in the Subcommittee's report about the decline in the use of Zevalin since 2002 can also be interpreted as evidence that there is an access problem for patients, which is partially caused by the lack of AUs for alpha and beta patient-ready dose therapies outside of major medical centers.

In addition, we noted that NRC Commissioner Svinicki raised concerns about the NRC's actions potentially restricting patient access to medical therapies at a February 25th meeting of the Commission, by stating, "I think we want to just be nuclear geeks, but I just, I don't know that that's practical going forward and it may be that we're just going to have to enmesh ourselves in a community

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of regulators that is grappling with these issues to make sure that patients have access to things that could be beneficial and that we don't artificially suppress the use."[1]

Furthermore, the report's generalization that the use of older medicines declines "as newer, equally or more effective, agents becomes available" does not apply to Zevalin since the development of new therapies has not replaced the need for alpha and beta emitter therapies. As Dr. Mace noted in his expert statement, because indolent non-Hodgkin's lymphoma (NHL) is a non-curable disease, "it is crucial that proven agents, such as the antibody-bound Beta emitters, be readily available to patients. . . , as optimal improvements in life span and survival will be achieved by employing many different treatments over the course of their disease." Ms. Weil also observed that "NHL patients often live with the disease for many years, and require a varied armamentarium of therapies to address each subsequent recurrence." Supporting those statements about the importance of access to multiple medicines for treating NHL is the **National Comprehensive Cancer Network's** recommendations for radioimmunotherapies as 1st line therapy for the follicular lymphoma form on NHL - particularly for elderly or infirmed patients who may not tolerate other treatment options.[2]
We thank ACMUI for its attention to these issues, and we again request that the ACMUI full committee consider our concerns relating to the Draft Report in advance of the March 10 teleconference. We urge the NRC and ACMUI, in the interest of cancer patients, to act quickly to establish a more appropriate training and experience requirement for becoming an AU able to administer beta emitter therapies in patient-ready doses, and we believe that there is ample information and rationale for establishing an 80 hour didactic course-based requirement for these medicines.

Sincerely,

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[1] NRC's "Briefing on the Strategic Programmatic Overview of the Fuel Facilities and the Nuclear Material Users Business Lines (Public)". Transcript, p. 105. [http://pbadupws.nrc.gov/docs/ML1606/ML16060A375.pdf]
[2] NCCN "Clinical Practice Guidelines in Oncology, Non-Hodgkins Lymphoma, v 4.2014 (8/22/2014)" page 37. [Accessed at http://www.nccn.org/about/nhl.pdf on 3/1/2016]

"Attachment: Proposed Regulatory Text for New Training and Experience for Patient-Ready Doses of Alpha and Beta Emitters."

Training for the Administration of Alpha- and Beta-Emitting Radiopharmaceuticals Prepared as Patient-Ready Doses by Licensed Nuclear Pharmacists at Licensed Radiopharmacies

Except as provided in 35.57, the licensee shall require an authorized user for the administration of pre-prepared patient-ready doses of alpha- and beta-emitting radiopharmaceuticals requiring a written directive to be a physician who--

(a) Is certified by a medical specialty board whose certification process has been recognized by the Commission or an Agreement State and who meets the requirements in paragraphs (c)(1) and (c)(2) of this section. (Specialty boards whose certification processes have been recognized by the Commission or an Agreement State will be posted on the NRC's Web page.); or

(b) Is an authorized user under § 35.390 for uses listed in § 35.390(b)(1)(ii)(G)(2) or equivalent Agreement State requirements; or

(c)(1) Has successfully completed 80 hours of classroom and laboratory training, applicable to the medical use of alpha- and beta-emitting radiopharmaceuticals administered as pre-prepared patient-ready doses for procedures requiring a written directive. The training must include—

(i) Nuclear physics and instrumentation;

(ii) Radiation biology;

(iii) Regulations and radiation protection; and

(iv) Mathematics pertaining to the use and measurement of radioactivity; and

(2) Has completed experiential training exercises, under the supervision of an authorized user who meets the requirements in §§ 35.57, 35.390, [this regulation], or equivalent Agreement State requirements. A supervising authorized user, who meets the requirements in § 35.390(b), must also have experience in administering dosages as specified in § 35.390(b)(1)(ii)(G)(2). The experiential training exercises must involve—

(i) Completion of not less than 10 hours of experiential training in radiation safety techniques, protocols, and procedures;

(ii) Participation in or observation of the administration of the specific radiopharmaceutical to not less than 3 patients; and

(3) Has obtained written attestation that the individual has satisfactorily completed the requirements in paragraphs (c)(1) and (c)(2) of this section, and has achieved a level of competency sufficient to function independently as an authorized user for medical uses authorized under § 35.300. The written attestation must be signed by a preceptor authorized user who meets the requirements in §§ 35.57, 35.390, [this regulation], or equivalent Agreement State requirements. A preceptor authorized user, who meets the requirements in § 35.390(b), must also have experience in administering dosages as specified in § 35.390(b)(1)(ii)(G)(2).

Via Electronic Submission

March 8, 2016

Advisory Committee on the Medical Use of Isotopes (ACMUI)
Subcommittee on Training and Experience for Alpha and Beta Emitters
c/o Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: ACMUI Report on Training & Experience For Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390

Dear ACMUI Committee Members:

Bayer Corporation LLC ("Bayer") appreciates the opportunity provided by the NRC's Advisory Committee on the Medical Use of Isotopes (ACMUI) to submit comments on your Draft Report on Training & Experience for Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390. Bayer has more than 12,000 employees across the United States and is a world-class innovation company with more than 150 years of experience researching and developing new pharmaceuticals and medical devices. We focus our efforts where we can have the most beneficial impact on the lives of those who depend on our innovative products. Our mission is to discover and manufacture products that will improve human health worldwide by diagnosing, preventing and treating diseases.

Christopher Leahy
Vice President
Head of Government Relations & Policy

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On the basis of this long experience, Bayer wishes to share its perspective on your report.

In brief, we remain concerned that the requirement of 700 hours of Training and Experience for medical oncologists and urologists to become an authorized user of alpha and beta emitters is excessive and may have a detrimental impact on patient access to treatment in the community setting. In the case of our alpha-emitting product, Xofigo® (radium Ra 223 dichloride injection), is prepared by a centralized radiopharmacy, CardinalHealth Nuclear Pharmacy Service, and shipped to hospitals , physician offices and other treatment facilities as a patient-ready dose, personalized to individual patients and the expected treatment date and time of administration. Xofigo is administered by slow intravenous injection over one minute.

Given the relative safety of alpha and beta- emitting radiopharmaceuticals from a handling perspective on the part of the physician, we support a more focused approach to training. As such, we are supportive of recommendations submitted by the Council on Radionuclides and Radiopharmaceuticals, Inc. (CORAR).[1]

As noted in the dissenting opinion of your report, we are also concerned about the logistical barriers that may exist for rural and community-based physicians that may see benefit in using an alpha- product for the treatment of their patients.[2] While patients may technically have access to treatment at major medical centers, the distance that patients must travel to reach an authorized treatment facility may impose an undue hardship on patients with severe and painful medical conditions making the journey difficult if not impossible. Thus, efforts to help improve access to these types of therapies are essential for ensuring adequate access for appropriate patient care, particularly when a more efficient training and experience approach for providers will achieve the desired outcomes for the necessary handling of alpha- and beta- emitting radiopharmaceuticals.

*****

Bayer appreciates NRC's ACMUI's consideration of our input and looks forward to working with ACMUI in the future to improve access to quality, affordable healthcare coverage.

Sincerely,

Christopher Leahy
Vice President
Head of Government Relations
and Policy
Bayer Corporation

[1] Guastella MJ. Letter to the ACMUI "Re: NRC Training and Experience Requirements for Alph- and Beta- Emitters." February 23, 2016.
[2] ACMUI Sub-Committee Draft Report on Training & Experience for Authorized Users of Alpha and Beta Emitters under 1- CFR 35.390. Submitted on March 10, 2016.

CORAR

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Via email March 8, 2016

Advisory Committee on the Medical Use of Isotopes (ACMUI)
Subcommittee on Training and Experience for Alpha and Beta Emitters
c/o Sophie Holiday
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission (NRC)
Washington, DC 20555-0001

Re: Draft Report on Training & Experience for Authorized Users of Alpha and Beta Emitters Under 10 CFR 35.390

Dear ACMUI Committee Members:

The members of the Council on Radionuclides and Radiopharmaceuticals (CORAR) have reviewed the Draft Report on Training & Experience for Authorized Users of Alpha and Beta Emitters Under 10 CFR 35.390 and are providing these comments in response. CORAR members include the manufacturers and distributors of both FDA approved Xofigo® (Radium Ra 223 dichloride) and Zevalin® (ibritumomab tiuxetan), as well as other therapeutic products that are still undergoing research and development. CORAR appreciates the ACMUI's and NRC's efforts to update the training and experience regulations, particularly to ensure patient access and to support technological advances and changes in medical procedures.

CORAR continues to believe that the current regulatory framework requiring 700 hours of training to become an Authorized User licensed to administer alpha- or beta- emitting radiopharmaceuticals is excessive and limiting patient access to radiopharmaceutical drugs such as Xofigo and Zevalin, as well as raising concerns about the future development of radiopharmaceuticals designed to treat or cure cancers. As such, we are concerned that the draft report (referenced above) does not address the important issues the ACMUI "Subcommittee on Training and Experience for Alpha and Beta Emitters" was charged to review. Specifically, their failure to recommend a modification to the excessive 700-hour Training and Experience

requirement within the current rule-making period will continue to place hardship on the patient community and restrict patient access to important therapeutic drugs.

The ACMUI subcommittee's draft report fails to adequately explain why the 700-hour Training and Experience requirement is necessary for patient-ready doses of alpha- and beta-emitters. As an alternative, CORAR recently provided comments to the ACMUI recommending a specific scope of training requirements for Radioisotope Handling and Radiation Safety for physicians wishing to administer intravenous therapeutic radiopharmaceuticals containing alpha- or beta- emitting radioisotopes, 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 physicians, such as medical oncologists and hematologists, should receive to enable them to safely administer these types of therapeutic drugs, we provided the following factors for the ACMUI to consider:

- The limited role in handling these radiolabeled drugs (which would be dispensed and delivered to them in patient-ready doses from a licensed radiopharmacy);
- The radiological safety profiles of radiopharmaceuticals containing alpha- and beta-emitting isotopes; and
- Physician's experience and training in handling toxic non-radioactive chemical therapies, e.g., cytotoxic chemotherapy agents.

CORAR continues to believe that the didactic training required to adequately prepare physicians to safely administer patient-ready doses of alpha- and beta- emitting drugs would entail about 70-80 hours of classroom and laboratory time. The ACMUI has received training statements from experts in radiation safety education which is consistent with this 70-80 hour recommendation. Also, the ACMUI subcommittee's draft report concluded that it has been "...nearly 15 years since the current requirements were established." The report continues by stating that, "Since that time new radiopharmaceuticals have been introduced and this is a trend that likely will continue. Appropriate T&E requirements for these agents need to be established."

It is encouraging that the subcommittee recognizes that a new Training and Experience framework is necessary and needs to be established, ostensibly for patient-ready doses of alpha- and beta- emitters like Xofigo and Zevalin, both of which have been launched over the last 15 years. However, we believe that the ACMUI subcommittee's decision to oppose reductions in the current Training and Experience framework and establish a standing subcommittee to address appropriate requirements in the future does not meet the charge given to the subcommittee and the current need of patients. Specifically, we believe the subcommittee failed to:

1. Explain why 700 hours of Training and Experience is necessary for patient-ready doses of alpha- and beta- emitters;
2. Offer specific safety concerns that would preclude the ACMUI from recommending modifications to the Training and Experience requirements for patient-ready doses of alpha- and beta- emitters;

3. Consider Training and Experience expert statements to safely administer alpha- and beta-emitting radiopharmaceuticals. For example, Nicki Hilliard, Kara Weatherman, and Kristina Wittstrom provided a tailored 80-hour didactic program recommendation to modify the Training and Experience requirements for Authorized Users who administer patient-ready alpha- and beta- emitter doses. Their recommendations included 25 hours on Nuclear Physics & Instrumentation, 20 hours on Radiation Biology, 25 hours on Regulations and Radiation Protection, and 10 hours on Mathematics Pertaining to Use & Measurement of Radioactivity;
4. Recognize that patient access to alpha- and beta- emitters in the community and rural settings remains problematic. In addition to CORAR, this has been communicated through testimony and comments to the ACMUI and NRC staff by organizations such as Leukemia and Lymphoma Society, Lymphoma Research Foundation, Community Oncology Alliance, American Society of Hematology, and Florida Cancer Specialists;
5. To establish a specific recommendation for the number of T&E hours for Authorized Users of alpha- and beta- emitters that appropriately balances safety with reasonable patient access.

In conclusion, CORAR believes it is critical that the NRC address the appropriate level of Training and Experience Requirements for Authorized Users of alpha- and beta-emitters in the current rulemaking on the ***Medical Use of Byproduct Material: Medical Event Definitions, Training and Experience***. Improved access to alpha- and beta- emitting drugs will improve the quality of life of cancer patients and support the continued innovation and development of new targeted anti-cancer therapies.

Thank you for your consideration of this letter and comments.

Sincerely,

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Statement of
The American Society for Radiation Oncology (ASTRO)
Before the Nuclear Regulatory Commission's Advisory Committee on the Medical Use of Isotopes
March 10, 2016

Chairman Alderson, members of the ACMUI and NRC staff, thank you for allowing me to provide this statement on training and experience (T&E) requirements for the administration of radiopharmaceuticals on behalf of the American Society for Radiation Oncology (ASTRO).

My name is Gregg Franklin and I am a radiation oncologist with the New Mexico Cancer Center. As part of my practice, I administer radiopharmaceuticals such as I-131 for thyroid cancer, Ra-223 (Xofigo) for prostate cancer, Y-90 (Zevalin) for lymphoma as well as many others. As an authorized radiation oncologist in NM giving radiopharmaceuticals, I have a lot of experience with their delivery and side effects, as well as the challenges inherent in their utilization.

I am also a member of ASTRO - the largest radiation oncology society in the world, with more than 10,000 members who specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, biology and physics, the Society is dedicated to improving patient care through education, clinical practice, advancement of science and advocacy. ASTRO's highest priority has always been ensuring patients receive the safest, most effective treatments.

Radiopharmaceuticals
Radiopharmaceuticals, including Zevalin, are highly effective in treating cancer, but also potentially hazardous drugs with possible harmful effects to both the patient and the public if not used correctly and under the supervision of a highly trained physician. ASTRO strongly opposes any reduction in the training and education (T&E) requirements found in 10 CFR 35.390, *Training for use of unsealed byproduct material for which a written directive is required*. Under this section, the NRC requires an authorized user (AU) to be certified by a medical specialty board recognized by either the NRC or an agreement state, or has completed 700 hours of T&E in "basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material requiring a written directive." ASTRO believes that these requirements are appropriate, protect the safety of patients, the public, and practitioners, and should not be changed.

On March 20, 2006, William Stein, III, MD filed a petition for rulemaking requesting "the codification of the 80-hour training and experience requirement as appropriate and sufficient for physicians desiring to attain AU status limited to therapeutic administrations of ^{153}Sm-lexidronam (Quadramet), ^{131}I-tositumomab (Bexxar) and ^{90}Y-ibritumomab tiuxetan (Zevalin), all FDA-approved parenterally-administered therapeutic agents." ASTRO submitted comments opposing the petition for rulemaking on August 28, 2006 stating that "Decreasing the training required for physicians to administer radiopharmaceuticals places the patient at risk for higher rates of misadministration and treatment-related toxicities. Significant knowledge regarding radiation dose distribution, radiation dose tolerance of normal tissues, and the safe use and handling of radiopharmaceuticals cannot be imparted with limited training." The NRC subsequently denied this petition for rulemaking on October 27, 2007, stating that "the current NRC regulations at 10 CFR 35.390 and 35.396 establish the appropriate amount of training and experience for a physician to become an authorized user for the parenteral administration of unsealed byproduct material requiring a written directive, including Quadramet, Bexxar and Zevalin." Bexxar was ultimately pulled from the market in 2014 because of lack of use. Quadramet and Zevalin are still in use.

Recently, we have become aware of a renewed push to reduce the T&E requirements for radiopharmaceuticals based on concerns about a shortage of AUs for the administration of Zevalin. ASTRO continues to object to a reduction in the T&E requirements based on a threat to the safety of patients and the public and a lack of data to support a shortage of AUs. The NRC's focus on patient safety and the safety of the general public as it develops T&E requirements is appropriate. With this in mind, the NRC determined that the level of training required to administer these treatments must include either board certification or 700 hours of training and experience. The NRC intentionally designed these requirements to allow new agents to come to market, so the NRC does not have the burden of writing different regulations for every new drug that is developed. The rule was intended to classify agents by their similar properties and particular risk profiles. The classroom and clinical experiences encompassed by radiation oncology and nuclear medicine training programs provide appropriate levels of knowledge and skill for any current and future radioactive agents. ASTRO supports the NRC's intent to craft a generally applicable rule rather than one that necessitates a specific review of each new radionuclide that becomes commercially available.

The rigorous T&E requirements contribute 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. We do not believe that an 80 hour course will adequately cover these topics.

Administering radiopharmaceuticals is not as simple as ordering a patient-ready dose from a radiopharmacy and injecting it into a patient. In general, clinics administering radiopharmaceuticals follow these steps:

1. The AU develops the general policies, the standard operating procedures, and the quality assurance checks for their radiopharmaceutical program.
2. The AU ensures that good radiation protection procedures are followed throughout the procedure.
3. The AU determines whether or not it is appropriate for the patient to receive the radiopharmaceutical.
4. The patient receives any required pre-treatment laboratory and/or imaging studies.
5. The AU must determine the required dose and will enter the dose into the written directive.
6. The AU orders any additional medications and or drugs prior to delivery of the radiopharmaceutical.
7. The radiopharmaceutical is received from the radiopharmacy in either the nuclear medicine, radiology, or radiation oncology department. (This is determined by the facility, and may vary from site to site.)
8. The receiving department checks that the dose from the radiopharmacy is correct and accurate.
9. The AU confirms that the dose is correct and accurate. If there is an error to the dose, the AU will need to make a decision on how to proceed.
10. The AU administers the radiopharmaceutical, or will supervise the administration by appropriately trained personnel.
11. The AU monitors adverse reactions of the patient and handles any radioactive spills that may have occurred.

The above description assumes that the ordering, receiving, administration, and clean up goes as planned. However, without proper and extensive training, how will the AU know how to clean spills? How will the AU understand limits of dose variation? Will the AU know how to use a dose calibrator to assess the dose, and change it if necessary? Will the AU know how to dispose of tubing and syringes? What about flushing the IV? Will the AU know how to use a Geiger counter to detect a spill? Will the AU know how to handle a person who is accidentally contaminated? Will the AU be able to appropriately and competently supervise ancillary staff? Will an AU know how to handle the accidental delivery into the interstitial tissues of the body (i.e. "IV infiltration") or into an artery? Will the AU be able to make appropriate decisions based on radiobiology and the effects of multiple prior therapies on the patient (ie., external beam therapy)?

Ultimately, it is the AU who is responsible for the safety of the patient, the providers, and the public. It would be irresponsible to leave this to someone with inadequate training and experience.

In addition to ensuring patient safety, ASTRO is unaware of data that suggests a shortage of AUs. ASTRO asked NRC staff for the number of AUs licensed under 35.390 to assess whether there is a shortage of AUs, but learned that the NRC only tracks AUs licensed under 35.300. Without being able to identify which AUs are licensed under 35.390 and 35.300, it is not possible to confirm whether there is an actual AU shortage or a perceived one. Additionally, ASTRO has not heard what would be an ideal number of AUs. ASTRO estimates that there are approximately 2,200 radiation oncology facilities in the United States, which means aside from the many nuclear medicine trained AUs nationwide, there are likely enough AUs just among the radiation oncologists nationwide. Indeed, ASTRO is not aware of a perceived shortage of radiation oncologists anywhere in the country. ASTROs members are ready to care for patients needing any radiopharmaceutical.

We do not believe the available data on AUs supports a change in the T&E requirements. Instead, we believe other factors are influencing the use of Zevalin, most notably the availability of alternative treatments, including chemotherapy agents such as maintenance Rituximab. It is unlikely that a change in the T&E requirements will impact use of Zevalin, but could instead have the unintended consequence of exposing patients, providers, and the public to risks that could otherwise be avoided. Since there is no underlying public need for expansion of authorized users, the public should not be placed in a position of heightened and unnecessary risk, and therefore the T&E requirements should remain as written.

In addition, the NRC's Advisory Committee on the Medical Use of Isotopes (ACMUI) tasked a subcommittee to determine "if the current requirement of 700 hours for training and experience for authorized users … places hardship on the patient community." In its March 10, 2016 report, the subcommittee notes that even in "many large medical centers with an abundance of clinicians and AUs who work closely together, these radiopharmaceuticals are used infrequently." Further, the subcommittee was unable to conclude that the current T&E requirements have caused the decreased use of radiopharmaceuticals, including Zevalin, and "because of the potential issues raised by the proposed changes in T&E, the subcommittee recommends against the reduction in the number of hours of T&E required for 10 CFR 35.396 use." ASTRO agrees with this recommendation. ASTRO also agrees with the subcommittee's recommendation for the establishment of a standing committee to periodically review the current T&E requirements currently in effect and make recommendations for changes as warranted.

Part 35 Rulemaking

ASTRO is concerned that if the NRC decides to make changes to the T&E requirements, that doing so within the current Part 35 rulemaking will cause significant delays in the publication of the final rule. The Part 35 final rule will add a much needed and appropriate activity-based definition for medical events for permanent implant brachytherapy. ASTRO strongly opposes any further delays in the Part 35 rulemaking because without this definition there will continue to be much confusion surrounding medical events for permanent implant brachytherapy.

Conclusion

In conclusion, for the numerous reasons stated above, ASTRO opposes a reduction in the T&E requirements for 10 CFR 35.390, and supports the ACMUI subcommittee's recommendations to form a permanent committee to look at the requirements and make suggestions for changes as warranted.