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UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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PUBLIC TELECONFERENCE

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TUESDAY,

JUNE 16, 2015

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The meeting was convened at 2:00 p.m. Eastern Daylight Time, Bruce R. Thomadsen, Ph.D., ACMUI Chairman, presiding.

MEMBERS PRESENT:

BRUCE R. THOMADSEN, Ph.D., Chairman

PHILIP O. ALDERSON, M.D., Vice Chairman

FRANCIS M. COSTELLO, Agreement State Representative

VASKEN DILSIZIAN, M.D., Nuclear Cardiologist

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

SUSAN M. LANGHORST, Ph.D., Radiation Safety Officer

STEVEN R. MATTMULLER, Nuclear Pharmacist

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

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

Physician

LAURA M. WEIL, Patients' Rights Advocate

PAT B. ZANZONICO, Ph.D., Nuclear Medicine Physicist

NRC STAFF PRESENT:

JOSEPHINE M. PICCONE, Ph.D., Director, Division of Material Safety, State, Tribal and Rulemaking Programs

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

DOUGLAS BOLLOCK, Designated Federal Officer

SOPHIE HOLIDAY, Alternate Designated Federal Officer, ACMUI Coordinator

MARYANN O. ABOGUNDE, NMSS/MSTR/MSEB

NEELAM BHALLA, NMSS/MSTR/RPMB

MARCIA CARPENTIER, OGC/GCHEA/AGCNRP

JACKIE COOK, RIV/DNMS/NMSB-B

GINA R. DAVIS, NMSS/DSFM/RMB

MICHAEL L. FULLER, NMSS/MSTR/MSEB

SANDRA GABRIEL, Ph.D., NMSS/MSTR/MSEB

ROBERT GALLAGHAR, RI/DNMS/MB

ESTHER HOUSEMAN, OGC/GCLR/RMR

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

PENNY LANZISERA, RI/DNMS/MB

NRC STAFF PRESENT CONT'D

JOHARI MOORE, COMM/OCM

JAN NGUYEN, RI/DNMS/MB

DIANE RENDER, Ph.D., NMSS/MSTR/MSEB

GRETCHEN J. RIVERA-CAPELLA, NMSS/MSTR/MSEB

MICHELLE SMETHERS, NMSS/MSTR/SMPB

TARA WEIDNER, RI/DNMS/MB

ALSO PRESENT

LEE ALLEN – Spectrum Pharmaceuticals, Inc.

ILHAM ALMAHAMID – New York State Department of Health

KATHLEEN BRILL – Foley Hoag LLP

BRIAN CAREY – Foley Hoag LLP

CHARLES COLEMAN – Virginia Department of Health

JENNIFER CULTERA – Florida Cancer Specialists & Research Institute

ROBERT DANSEREAU – New York State Department of Health

AL DEJESUS – Spectrum Pharmaceuticals, Inc.

HUGH EVANS – Eckert & Ziegler Radiopharma, Inc.

NEBEYOU FEKADU – Cedar-Sinai Medical Center

ASFOU FENTA – Virginia Department of Health

KAREN FLANIGAN – New Jersey Department of Environmental Protection

ALSO PRESENT CONT'D

PHILIP GRIFFIN – Utah Division of Radiation Control

MICHAEL GUASTELLA – Council on Radionuclides and Radiopharmaceuticals (CORAR)

GEORGIA HEARN – American Society of Nuclear Cardiology (ASNC)

AMANDA JOHNSEN – The Pennsylvania State University

YUNGMI KIM – Spectrum Pharmaceuticals, Inc.

CAITLIN KUBLER – Society of Nuclear Medicine and Molecular Imaging (SNMMI)

KAREN LANGLEY – University of Utah

ANGELIQUE LEE-ROWLEY – Spectrum Pharmaceuticals, Inc.

ROBIN LEVY – Lymphoma Cancer Foundation

RALPH LIETO – St. Joseph Mercy Health System

GARY LUNGER – Bayer

RICHARD MARTIN – American Association of Physicists in Medicine (AAPM)

GENE MENENDEZ – Spectrum Pharmaceuticals, Inc.

MICHAEL PETERS – American College of Radiology (ACR)

ANDREA RAVARD – Cedar Sinai Medical Center

CLARINE NARDI RIDDLE – Kasowitz

ALSO PRESENT CONT'D

JOSEPH RODGERS – Theragenics Corporation

JAMES SCHUH – Council on Radionuclides and Radiopharmaceuticals (CORAR)

KAREN SHEEHAN – Fox Chase Cancer Center

MICHAEL SHEETZ – University of Pittsburgh

CINDY TOMLINSON – American Society for Radiation Oncology (ASTRO)

JEFFREY VACIRCA – Community Oncology Alliance

T-A-B-L-E O-F C-O-N-T-E-N-T-S

P R O C E E D I N G S

2:07 p.m.

MR. BOLLOCK: As the designated federal officer for this meeting, I am pleased to welcome you to this public meeting of the Advisory Committee today. My name is Doug Bullock. I'm the Branch Chief of the Medical Safety and Advanced Assessment Branch and I have been designated as the federal officer for this Advisory Committee in the course of 10 CFR Part 7.11. Present today is the alternate designated federal officer, on the phone, is Sophie Holiday, our ACMUI Coordinator.

This is an announced meeting of the Committee and it's being held in the accordance of the rules and regulations of the Federal Advisory Committee Act and the Nuclear Regulatory Commission. This meeting is being transcribed under the NRC and it may also be transcribed or recorded by others. The meeting was announced in the April 7, 2015 Edition of the Federal Register, Volume 80, Page 18655.

The function of the Committee is to advise the staff on issues and questions that arise in the medical use of byproduct material. The Committee provides counsel to staff, but does not determine or direct the actual decisions of the staff or the

Commission. The NRC solicits the views of the Committee and values their opinion.

I request that whenever possible, we try to reach a consensus on the procedural issue that we'll discuss today. There may be minority or dissenting opinions. If you have such opinions, please allow them to be read into the record.

At this point, would like to perform a roll call of ACMUI members participating today. Starting with Dr. Bruce Thomadsen, our therapy medical physicist and Chairman.

CHAIRMAN THOMADSEN: Here.

MR. BOLLOCK: Okay. Next, Dr. Philip Alderson, our health care administrator and Vice-Chairman. Okay. Moving on. Mr. Frank Costello, our agreement state representative. Okay. Moving on. Dr. Vasken Dilsizian, our nuclear cardiologist.

MEMBER DILSIZIAN: Present.

MR. BOLLOCK: Okay. Thank you, Dr. Dilsizian. Dr. Ronald Ennis, our radiation oncologist.

MEMBER ENNIS: Here.

MR. BOLLOCK: Thank you, Dr. Ennis. Dr. Sue Langhorst, radiation safety officer.

MEMBER LANGHORST: Present.

MR. BOLLOCK: Mr. Steve Mattmuller, our nuclear pharmacist.

MEMBER MATTMULLER: I'm here.

MR. BOLLOCK: Thank you. Dr. Michael O'Hara, our FDA representative. Moving on. Dr. Christopher Palestro, our nuclear medicine physician.

MEMBER PALESTRO: Present.

MR. BOLLOCK: Thank you, Dr. Palestro. Dr. John Suh, radiation oncologist.

MS. HOLIDAY: He will not be joining us.

MR. BOLLOCK: Okay. And Ms. Laura Weil, our patient's rights advocate.

MEMBER WEIL: I'm here.

MR. BOLLOCK: Thank you. And Dr. Pat Zanzonico, our nuclear medicine physicist. Okay. Well, we do have a quorum with at least seven members. I now ask the NRC staff members who are present to identify themselves. I'll start with the individuals in the room here and we can go around the room.

MR. FULLER: This is Mike Fuller, medical radiation safety team leader.

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

MS. DAVIS: Gina Davis, NMSS.

MS. HENDERSON: Pam Henderson, Deputy

Division Director, MSTR, NMSS.

MS. ABOGUNDE: Maryann Abogunde, medical radiation team.

MR. BOLLOCK: Okay. Thank you. Now I'll also go to the NRC Headquarters employees on the phone.

MS. RIVERA-CAPELLA: Gretchen Rivera-Capella, medical team.

MR. BOLLOCK: Okay. I heard Gretchen. Thank you.

MS. RIVERA-CAPELLA: You're welcome.

MS. HOLIDAY: I'm Sophie Holiday, ACMUI Coordinator.

MR. BOLLOCK: Okay. Any other Headquarters employees on the phone? All right. Thank you. And next we'll go to our regional offices. Who do we have on the call from Region I? I'm getting a little bit of feedback, I couldn't hear anybody from Region I. Do we have anyone from Region I?

MS. HOLIDAY: I'm sorry, I can hear a lot of background discussion. If you could mute your phone, please. Please mute your phone.

MR. BOLLOCK: Okay. We're still getting a lot of background. Okay. All right. So no one from Region I? Who do we have on the call from Region III? All right. Hey, Sophie?

MS. HOLIDAY: Yes.

MR. BOLLOCK: Did you hear what Mike said?

MS. HOLIDAY: I did not.

MR. BOLLOCK: Just go ahead and mute everybody. We'll get attendance at the end.

MS. HOLIDAY: Okay.

MR. BOLLOCK: We can't have it go on like this. We've got to mute everyone but the ACMUI members so we can continue on.

MS. HOLIDAY: Sure.

MR. BOLLOCK: Okay. All right. So we'll go through the rest of the roll call. We do have a number of members of the public who have emailed Sophie and should be calling in.

We have a bridge line available, and that phone number is 415-655-0059. The pass code to access the bridge line is 944-664-243.

We are also using the GoToWebinar application to view presentation handouts real time. You can access this by going to www.gotomeeting.com and searching for Meeting ID 126-126-243. You'll need to register for the GoToMeeting to receive an audio PIN to interact with any of the presenters.

The purpose of this meeting is to hear presentations from representatives of Spectrum

Pharmaceuticals relating to the training experience for authorized users of alpha and beta emitters, as well as to discuss the Committee's comments on the existing 10 CFR 35.1000 licensing guide for iodine-125 palladium-103, low dose brachytherapy seeds used for localization of non-palpable lesions.

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

Comments and questions are usually addressed by the Committee near the end of the meeting after the Committee has fully discussed the topic. I'd also like to add that handouts and agenda for this meeting are available on the NRC's public website.

At this time, I would ask 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 stray background noises can be very

disruptive on a conference call this large, as we've already discovered.

At this point, I'd like to turn the meeting over to Pamela Henderson, our Deputy Director Division of Materials Safety State Travel and Rulemaking Programs from the Office of Nuclear Material Safety and Safeguards for some opening remarks.

MS. HENDERSON: Good afternoon, everyone. I would like to welcome you to this meeting. Josephine Piccone, who is our new Director will be joining us sometime a little later. But could not be here for the opening remarks. And with that, I would like to hand it over to Dr. Thomadsen. Thank you.

CHAIRMAN THOMADSEN: Thank you very much. And our first order of business is the request to address the Committee by Spectrum Pharmaceuticals. Is a representative there?

DR. CULTRERA: Yes, I'm here. Can you hear me?

CHAIRMAN THOMADSEN: Barely. Can you speak a little bit louder?

DR. CULTRERA: Yes. This is Dr. Jennifer Cultrera. Is this a little bit better?

CHAIRMAN THOMADSEN: That's better, yes. Thank you. And please proceed.

DR. CULTRERA: Okay. Thank you. I would like to thank everybody on the conference call and with ACMUI for hearing us today. And I'd like to present my experiences.

My name is Jennifer Cultrera. I'm a physician with Florida Cancer Specialists. And my colleague's experience, Dr. Joe Mace, who was unable to be here today due to a family emergency. Florida Cancer Specialists is actually one of the largest community oncology practices and we're centered here in Florida with over 90 practices.

And I'd like to -- if you can maneuver the slides a little bit to Slide Number 3 that would be great. Thanks. And we'd like to talk to you today about approving certain intravenous radiopharmaceuticals to be administered by hematologists and medical oncologists through an 80 hour course rather than the 700 hours of training which is currently necessary.

And this addresses the NRC rulemaking, which states that its regulations discourage licenses from using certain therapy options or otherwise adversely impact clinical practice and if so, how. With these slides today, I would hope that we're going to educate you on the medical oncologist experience and

the patient care and how the restrictions placed on these medications are now limiting the use of vitally necessary cancer medications. And if you could proceed to Slide 4?

So the clinical benefit of therapeutic radiopharmaceuticals are that they produce a less intensive treatment schedule, they're very efficacious, as well as producing less constitutional and somatic toxicity, such as chemotherapy, traditional chemotherapy, and even some of the newer targeted agents that are available both intravenous and PO.

And this is especially beneficial for elderly cancer patients who have limited access. They really don't have the capability of going to academic centers that maybe 50 to 100 to even 150 miles away. Slide 5 please.

So I'm going to use Zevalin as a representative of this class of agents. And Zevalin is used to treat follicular non-Hodgkins lymphoma patients. And 80 percent of these patients are managed by medical oncologists such as myself or hematologist oncologists in the community.

Zevalin as a treatment is given traditionally through authorized user, which are

traditionally radiation oncologists or nuclear medicine physicians. And there has been a shortage of AUs in the rural setting or settings that are outside of academic institutions, which severally limit the use of Zevalin and other radiopharmaceuticals for these certain patient populations.

I'm going to present in subsequent slides that beta emitter anti-cancer therapies have declined since the imposition of the 700 hour training rule in 2002. And, actually, there is one RIT treatment at this time which is unavailable due to lack of use, specifically Bexxar. Next slide.

And this just points out that as a hematologist oncologist, I'm responsible for basically diagnosing my patients, treating them prior to getting their radiopharmaceutical with traditional chemotherapeutic agents or other targeted therapies. We basically follow them on their cancer journey and are side-by-side with them.

And it's very difficult sometimes to refer them on to a secondary healthcare provider which may not be local to us and have the patients unable to really have this continuity of care where we're able to order the agent, administer the agent, and deal with the follow-up and side effects.

And you can see here that outside of actually administering the radiopharmaceutical, we are responsible as the hematologist oncologist for the rest of the patient's care. Next slide.

So, Dr. Mace is one of my colleagues. He's also a practicing hematologist oncologist in Southern Florida. And he's one of the few AUs that gained AU status before the 700 training requirement was imposed. I believe there's only five other AUs in his position in the country.

He completed a radiation safety and handling course that met this 80 hour requirement and I would like to tell his quote here, "After my course experience, I felt fully prepared to administer Zevalin, with all of the attendant radiation safety and handling issues."

He has administered Zevalin and Xofigo, the other FDA approved radiopharmaceutical, for over ten years with no safety incidents at our institution. And I believe he has proven that these radiopharmaceuticals can be given in the community oncology setting without having the need to travel and providing the best patient care close to home for them. Next slide.

This is a small diagram to show that the

radiation safety in alpha and beta emitters is definitely feasible for use for a practicing medical oncologist. As you can see here, gamma emission is extremely dangerous. We're not asking to utilize that type of radiation. We're asking for alpha emission, which can be blocked by human skin, and beta emission, which can be blocked by plastic. Next slide.

Alpha emitters, of which Xofigo is a representative of, are listed here and some of the properties of Xofigo. I am not going to belabor the point to this very knowledgeable community. However, these drugs are very safe and efficacious and limiting their use will actually limit the development of drugs and clinical trials. Next slide.

And beta emitters, of which we're going to use Zevalin as a representative, you can notice here, they have a very short half-life of 2.67 days and a short pathlength of 5.3 millimeters. As well as a maximum dose, which is given of Zevalin, of 30 millicuries.

The elimination of this agent in the body is based on its parent molecule Rituxan, which also does not remain in the body over 18 to 24 hours. So the actual exposure that the patient is getting is very low. As well as no exposure to their surroundings or their loved ones. Next slide.

So there's a demonstrated safety record for Zevalin. It's been approved since 2002. There's over 30 published studies with radiation safety with this agent. And all of these studies have concluded that the risks are minimal to negligible to both physician and patient.

Over 10,000 administrations, only three reports to the NRC for radiation safety issues. And all of these three reports were during compounding. And I want to stress that this drug is delivered as a patient-ready dose, so there is no issues with exposure for neither the patient nor the physician or their families.

I would also like to stress that the FDA removed a requirement for the indium-111 biodistribution scan based on its safety profile. And despite these risks of Zevalin, now there's a disproportionate burden for us to prescribe it because of the restrictions that have been placed on the AUs. Next slide please.

We're also concerned because of the impact that may occur on new radiopharmaceuticals and, unfortunately, if you're not exposed to an agent during fellowship or a class of agents during fellowship and training, it's very difficult to allow the new doctors

to begin to learn how to prescribe it and they won't be using it.

And this is something that we're seeing with radiopharmaceuticals at this time. The training and experience requirements are discouraging current clinicians from recommending Zevalin to patients. There's a lack of exposure. I myself am seeing fellows graduating right now and they have no idea what a radiopharmaceutical is.

And as we have seen, the regulatory barriers have contributed to the removal of one of these agents from the market already. And there are several in development which are threatened. Next slide.

So in my career, I actually was a lymphoma specialist at Moffitt Cancer Center for several years. And I was able to have access to radiopharmaceuticals through our radiation oncology department. And I was able to order these medications and have my radiation oncologist prescribe them and have my patients benefit greatly.

However, when I transitioned into the community and moved about 100 miles away from my local academic center, I find that I am unable to have access to this agent to provide care for my patients. Unfortunately, as a medical oncologist in a 80 hour work

week, I'm unable to undergo 700 hours of additional training and experience to be able to become an AU so that this could be provided to my community. Next slide.

So I'd like to talk about the two pathways which are available right now to become an AU. And the first pathway is the certification pathway. And these are available for physicians who are board certified in radiology or nuclear medicine. And this would traditionally be who we would contact in an academic center to be able to provide the care for our patients.

I, myself, moving to a more rural community, even though I have access to a radiation oncologist, actually several of them in the area, I am unable to provide Zevalin for my patients because none of them have chosen to become authorized users.

They feel that there is a burden to becoming an AU where they need several proctored cases, three proctored cases, from a current AU, as well as they sometimes don't want to deal with the side effects of these agents. The side effects are more hematologic in response and the medical oncologist is a lot better equipped to handle them.

The second pathway, the alternative pathway, requires an additional 700 hours of training

and experience. And, again, this would be completely -- I would be completely unable to do this as a practicing medical oncologist or hematologist as it would entail basically a second fellowship for me and limit my time to be able to care for patients. Next slide.

So this is a map of the area of the current authorized users just in Florida alone. And if you notice, they're all basically lumped up in these large cities, Tampa, Miami, Orlando, and Jacksonville, and anybody in between is basically in a gap area where they're unable to have access to radiopharmaceuticals.

And just in my area alone where I'm an hour north of Orlando, that represents an 80 -- or, I'm sorry, an hour and a half from Orlando, an 80 mile to 100 mile drive for my frail, elderly patients in the villages that they're unable to take. So they are not able to obtain the benefits of this class of agents. Next slide.

And this graph demonstrates how Zevalin came to market in 2002 and then when the 700 hour training restrictions were initiated in 2006, there was a dramatic decline in the amount of Zevalin that was prescribed. And, again, demonstrating that we're losing a vital component of personalized medicine.

Next slide.

I'd like to talk a little bit to the recommendation that we're asking for the rule making. Next slide.

And our need is that patient access is severely limited and it's declining outside of the academic medical centers. And in the places where the patients need the care, where the patients are debilitated because of their disease, they're frail, they are not mobile, we are unable to provide the medications that they need. These are drugs that are very safe and very efficacious.

I have had over ten years of experience also following these patients and am very comfortable dealing with the hematologic toxicities and other toxicities that these agents may incur. They're low-risk alpha and beta emitters and the 80 hours of training and relevant work experience is appropriate for hematologist oncologists who are seeking only to administer the low-risk beta and alpha emitting radiopharmaceuticals.

And there is precedent in that there is an 80 hour training that was required of clinicians prior to 2005, which is available to clinicians to administer the oral I-131. Next slide.

Zevalin, in particular, is produced as a patient-ready dose. It has a very low level of radiation. And some states do require dose verification, but this can be covered in the 80 hour training requirement. It's delivered intravenously and only universal radiation precautions are necessary, which we all are familiar with who are working in a healthcare setting and in a hospital setting.

The administration side effects I'd like to point out are not related to the radiation exposure. They're actually related to the parent compound, which is rituximab, which is a monoclonal antibody that we use every day in oncology. Next slide.

And the precedent for using the 80 hour training is that in 2005, hematologists and oncologists could become AUs, as Joe Mace is an example. And he's been doing this for over ten years and he's been helping our patients out. But one man for over 90 practices is very difficult. And unfortunately, we can't get him out to everywhere he's needed. So we do need that need for increasing the authorized users.

The rulemaking created an alternative pathway for 700 hours of training and experience. However, it's all inclusive and what we'd like is for

a rule to be made for the alpha and beta emitters so that medical oncologists and hematologists and other clinicians could be allowed to administer these agents when their patients are in need. Next slide.

And I'd like to talk a little bit about the precedence for the oral administration of I-131, we are asking for a similar requirement. The limited scope of the license, it doesn't authorize the preparation of radioactive drugs, but again, this comes as a patient-ready dose. And it is a drug with a low radiation and good safety record. So next slide.

And I'd just like to compare and contrast. Right now the training requirements to administer Zevalin require 700 hours. And according to the patient release instructions, there is no need for a hospital stay after receiving Zevalin. There is no need to limit contact with your loved ones or others.

There's no effective radiation within your body or bodily fluids. And after the first three days, the only issues are universal precautions, which are necessary for any type of either chemotherapy or medications or any of day-to-day living. And of course, wash your hands after using the toilet.

As well as -- then for iodine-131, that is under the 80 hour training, you do have significant

restrictions where you need to be at least six feet away from other people, you're avoiding crowds and places, you're avoiding handling of any of your bodily fluids, and you're not sharing a bed or bathroom with another person. You're not sharing drinking glasses, plates, or silverware.

So, as you can read here, there are several more restrictions for an agent that has much less training requirements at this time. Next slide.

So what we're asking in the recommendation is to allow an 80 hour course for authorized users for alpha and beta emitters. We are not asking -- in the end, I don't think that all medical oncologists or hematologists will want to be authorized users. But at least those that are in gap areas may have the opportunity to be able to offer these agents to their patients.

Because right now in cancer medicine, any personalized therapy is our goal to be able to keep these patients living longer with a better quality of life. And radiopharmaceuticals may help us get to that goal quicker. And that's all I have for slides. I think if you'd like to open it up for questions from Committee.

CHAIRMAN THOMADSEN: Yes. Thank you very

much. Do we have questions for the presenter? Can you speak loudly and give your name?

MEMBER DILSIZIAN: Yes. Vasken Dilsizian. Great presentation. Just to let you know, I'm a cardiologist in training. And in nuclear cardiology by doing additional fellowship in nuclear medicine. Very similar to your training.

The reason there's a sub-specialty like nuclear medicine that exists is specifically to administer these registrations. I found it very interesting in your discussions that you kept mentioning radiation oncology, but not nuclear medicine. You also know very well that every community hospital has to have a nuclear medicine program for spec imagining and nuclear medicine physician.

So I find it disingenuous, if you will, of you not presenting the real fact that the Zevalin decrease in the number of patients is not related to lack of access. It's lack of referral of patients. As you pointed out, Zevalin's only being used in very limited number of patients.

DR. CULTRERA: I appreciate your comments and, yes, I did mention radiation oncologists. Unfortunately, in my community and from what I can see from the authorized users, even in nuclear medicine,

I don't see that there are any nuclear medicine doctors even in my community that will administer radiopharmaceuticals.

I think that there are others on the line that may be able to speak to that better in a little bit. But in my experience, I have not had the capability of referring to a nuclear medicine doctor that's an AU.

MEMBER DILSIZIAN: By definition, all nuclear medicine physicians are AU and all nuclear medicine physicians are trained and will welcome additional therapeutics. It's just that there's no referring physicians. So what I would like to suggest is really not limit your discussion to radiation oncology.

DR. CULTRERA: Okay.

MEMBER DILSIZIAN: All nuclear medicine physicians will be happy to administer it. And they will and they'll be happy to. It's just that the opportunity hasn't been there because the referral hasn't been there.

CHAIRMAN THOMADSEN: Thank you very much. Other comments or questions? Hearing none, I think that while there is a lot of potential discussion surrounding the issues that have come up, I would like

to establish a subcommittee to evaluate if the 700 hour requirements in the alternative pathway places a hardship on the patient community. And I would ask Dr. Palestro to chair that committee. Dr. Palestro, are you there?

MEMBER PALESTRO: Yes, I am.

CHAIRMAN THOMADSEN: Would you be willing to chair that committee?

MEMBER PALESTRO: Yes, I will.

CHAIRMAN THOMADSEN: And I would like Dr. Dilsizian, Dr. Ennis, Dr. Zanzonico, and Dr. Langhorst to sit on that. I think that all of those are on the line right now. Is that correct?

MEMBER DILSIZIAN: Yes.

MEMBER ZANZONICO: Yes.

MEMBER LANGHORST: Yes, I'm here. And might I make a suggestion? This is Sue --

CHAIRMAN THOMADSEN: Yes.

MEMBER LANGHORST: -- Langhorst.

CHAIRMAN THOMADSEN: Yes.

MEMBER LANGHORST: Because of the patient access question --

CHAIRMAN THOMADSEN: Yes.

MEMBER LANGHORST: -- would it be appropriate to have Ms. Weil serve on this

subcommittee?

CHAIRMAN THOMADSEN: I think it would be very appropriate. Ms. Weil, would you be willing to sit on that committee? The subcommittee?

MEMBER WEIL: Indeed, I would.

CHAIRMAN THOMADSEN: Very fine.

MS. HOLIDAY: Dr. Thomadsen, can you tell me --

CHAIRMAN THOMADSEN: Doctor --

MS. HOLIDAY: -- this subcommittee --

CHAIRMAN THOMADSEN: I'm sorry. Can you speak a little bit louder, Ms. Holiday?

MS. HOLIDAY: Yes. Can you repeat what the charge of this subcommittee is?

CHAIRMAN THOMADSEN: Yes. To evaluate if the 700 hour training requirement places a hardship on the patient community and to make recommendations for potential changes if they feel that would be appropriate.

MS. HOLIDAY: Excellent. And I have Dr. Palestro as the chair, Dr. Dilsizian, Dr. Zanzonico, Dr. Langhorst, and Ms. Weil?

CHAIRMAN THOMADSEN: And Dr. Ennis.

MS. HOLIDAY: And Dr. Ennis. Thank you.

MEMBER MATTMULLER: Dr. Thomadsen, can you

hear me?

CHAIRMAN THOMADSEN: I can barely hear you, but I can.

MEMBER MATTMULLER: Yes. This is Steve Mattmuller. And I'd like to ask a question if I may.

CHAIRMAN THOMADSEN: Please do.

MEMBER MATTMULLER: Yes. I'm the nuclear pharmacist on the Committee. And we all agree that these are terrific therapeutic radiopharmaceuticals that are horribly underutilized.

And ourselves at Kettering Medical Center, Kettering, Ohio and in caring for -- excuse me, Dayton. We have in the metropolitan area a population of about one million. Yet, for the past nine years, we've only done three studies.

And so, I'm curious, I guess this follows somewhat Dr. Dilsizian asked as to why there's a reluctance on medical oncologists to refer patients to us for these valuable drugs. And I also noticed, along that same effort or question line, you showed on your one slide that there was a lack of authorized users in the Orlando area.

And we happen to be sponsored by the Seventh Day Adventists and there's a large hospital in Orlando called the Florida Hospital with well over

1,000 beds. And they too are sponsored by the Seventh Day Adventists and we share personnel at times.

So, when I spoke to them recently, they mentioned that for the past nine years, with a much larger metropolitan area, they too have only done three patients. So, again, they're ready and willing as we are to treat these patients, but we're not getting the referrals from the medical oncologists. Would you be able to explain why that is?

DR. CULTRERA: Yes. To answer your second point first, about the Orlando area, actually I am about an hour and a half north of the Orlando area. And I'm very familiar with the Adventists system. We actually have one that's about 45 minutes from my main practice location in Tavares, Florida.

And they do not offer radiopharmaceuticals there. They actually have to -- you have to travel to Orlando. And my patients, many of them cannot. That's the issue. Orlando does have AUs. Tampa does have AUs. And Jacksonville, I believe, does have AUs.

But, outside of that, Florida ranges from tip to tip about 400 miles and it's almost impossible to get my 65 plus patient who may only have a golf cart to be able to commute to and from his or her visits to be able to get to these areas. So, yes, I mean, I would

love to be able to utilize those AUs in Orlando. And I do for certain cases or patients that are able to get out there.

Now, as to your first point as to why medical oncologists are not referring, and this is, I of course cannot speak for all medical oncologists, but what I believe is -- number one, they may not have the experience with using Zevalin. For many of them, they left their fellowship and went straight into the community and didn't have access to using the drug.

So they went to the next best agent that they could use or not even, sometimes in the front line setting, not even using any follow-up agents. I think a lot of it is that they're just very unfamiliar with the drugs and, hopefully, with Xofigo and other agents that are hopefully going to be approved for other malignancies in the solid tumor area, they're going to start to be able to be utilized further and become more knowledgeable.

And I think as well, when I was an academician at Moffitt Cancer Center, I found that the fellows weren't even being trained in the use of radiopharmaceuticals. And we were actually using them in a significant amount at Moffitt Cancer Center. So I think if they don't learn it in their training, if

they don't see it being used by their colleagues, they're just -- we're not going to know to refer the patients out.

So that's my theory on why the medical oncologists are not referring out. And, unfortunately, sometimes even our local hospitals won't be able to use these agents just because of cost and contracting. So they might not have access through the hospital base on the nuclear medicine side of things.

CHAIRMAN THOMADSEN: Thank you. Other questions?

MEMBER DILSIZIAN: Yes. Vasken Dilsizian again.

CHAIRMAN THOMADSEN: Yes.

MEMBER DILSIZIAN: I guess it would be similar to say that the oncologist may not have training in MRI or CT, but they do understand what the role of MRI and CT is in their patient management in their training.

So, lack of training does not necessarily mean that the technique is not available by other sub-specialties that the oncologist should be treating patients with radiation. That's why sub-specialties exist. And so, to me, that's not a very good argument

that the teaching has to be incorporated just like any other modality.

MEMBER WEIL: Dr. Thomadsen?

CHAIRMAN THOMADSEN: Yes.

MEMBER WEIL: Laura Weil.

CHAIRMAN THOMADSEN: Who's speaking? Oh, yes.

MEMBER WEIL: I'd like to --

CHAIRMAN THOMADSEN: Ms. Weil.

MEMBER WEIL: I would just like a clarification. Florida Cancer Specialists are physician practices, non-hospital based. Correct?

DR. CULTRERA: Correct.

MEMBER WEIL: They're community based, non-hospital. You must have affiliations with some hospitals, but you're basically community practices?

DR. CULTRERA: Correct.

MEMBER WEIL: Thank you.

CHAIRMAN THOMADSEN: Other questions?

MEMBER MATTMULLER: Yes. I had a quick -- this is Mattmuller again.

CHAIRMAN THOMADSEN: I'm hearing two here.

MEMBER MATTMULLER: Steve Mattmuller again.

CHAIRMAN THOMADSEN: Yes. Mr. Mattmuller.

MEMBER MATTMULLER: Just to point out, on the Bexxar and quite possibly -- Bexxar compared to Zevalin was much, much more difficult to use and to prepare and much more complicated. And, in fact, most people I believe would agree that its demise was precipitated when Zevalin went from a two dose program to a single dose program. And thus, was much, much simpler to use versus the Bexxar.

So, from our perspective, it wasn't the lack of AUs, I mean, it was really the added complexity of Bexxar versus Zevalin that really led to its downfall. Thank you.

CHAIRMAN THOMADSEN: Thank you. Was there somebody else that wanted to comment that was vying with him?

MEMBER ENNIS: Yes. Ron Ennis.

CHAIRMAN THOMADSEN: Dr. Ennis.

MEMBER ENNIS: Yes. Just, again, it sounds difficult for me to understand how if there is such a demand and utility for these drugs that the nuclear medicine physicians and the radiation oncology physicians in the communities with whom you work, your practices clearly work for a wide variety of care patients, why there's a barrier to making that part of that collaboration.

CHAIRMAN THOMADSEN: There seems to be a conversation going on in the background. Can people mute their phone please? Or microphone. Did the speaker want to address the question?

DR. CULTRERA: Yes. So, of course, I can't speak for why -- I can only speak for the radiation oncologists and I personally have not spoken to nuclear medicine physicians. But why they haven't become AUs in my area, I was generally told that it was a very cumbersome process to become an AU and it wouldn't benefit them.

Even assured, because I had told them that I would like to be able to refer patients, that they would have that patient referral base. So I can't speak as to why they're not becoming AUs.

I know my current affiliations with the hospitals that are in my area, including Florida Hospital, Waterman, The Villages Regional Hospital, and Leesburg Regional Hospital, which cover probably about a 60 to 70 mile radius, the nuclear medicine departments in those three hospitals do not administer any of the radiopharmaceuticals. Because we have discussed this with them and there are no plans to in the future.

So that's -- and I know that there are other

oncologists in my practice that are in the rural setting that don't have that -- their local hospitals as well, they're not administering even some of the targeted therapies that are intravenous that are not radiopharmaceuticals.

MEMBER ENNIS: So is the problem that the reimbursement is not commensurate with the work. And if so --

DR. CULTRERA: I think --

MEMBER ENNIS: -- it's not a regulatory question, but a CMS, financial insurance question.

DR. CULTRERA: I can't speak to that. I am not knowledgeable on that front. There may be a component of that happening in the hospital based setting. I don't know about the community physicians or the current community physicians that are able to be AUs.

I do know as well that they also don't want to have to deal with the follow-up of some of these patients who do need to have regular hematologic toxicity evaluations, basically a complete blood count done every week for 10 to 12 weeks after they receive the drug. And they don't want to have to deal with most of the toxicity from the drug, which is basically hematologic and not radiologic in nature.

CHAIRMAN THOMADSEN: I'll just ask the question. That seems a bit strange because that is what radiation oncologists generally have to deal with is hematological complications of treatments. It seems strange that this would be different from that.

DR. CULTRERA: I can only speak to what my local radiation oncologists have discussed with me. And those are my experiences.

CHAIRMAN THOMADSEN: Other questions from the Committee?

MEMBER LANGHORST: Yes. Dr. Thomadsen, this is Sue Langhorst.

CHAIRMAN THOMADSEN: Yes, Dr. Langhorst?

MEMBER LANGHORST: Dr. Cultrera, I wondered if you have looked at this beyond Florida or are you primarily looking at this strictly from your state basis?

DR. CULTRERA: In my experience, I'm only speaking based on Florida. However, there are other members on the line that can speak after we're done to better answer that question. And I know, basically, other members from Spectrum, and I think CORAR, is here that may be able to speak to the national issues that are ongoing.

MEMBER LANGHORST: Okay. I just wondered

if there might be some special situations with the Florida regulatory requirements.

DR. CULTRERA: From what I understand, no. I think this is -- from what I see from the data that Spectrum has presented to me, it's nationwide.

MEMBER LANGHORST: Okay. Thank you very much.

CHAIRMAN THOMADSEN: Other questions from the Committee? Otherwise --

MEMBER ENNIS: Is Florida an agreement state?

DR. CULTRERA: I'm sorry, can you repeat that?

MEMBER ENNIS: Is Florida an agreement state?

MS. HOLIDAY: Yes. This is Sophie. Florida is an agreement state.

MEMBER ENNIS: Thank you.

CHAIRMAN THOMADSEN: Let me open up the floor to others on the line if they have questions or comments they would like to make.

DR. ALLEN: Yes. Lee Allen, Chief Medical Officer at Spectrum Pharmaceuticals. Can I make a few comments?

CHAIRMAN THOMADSEN: Dr. Allen.

DR. ALLEN: Yes. The questions that the NRC raised was this question of are the regulations discouraging the use of current therapeutic options and adversely impacting clinical practice. And I think as the subcommittee investigates the use of this product, I think they will see that indeed it is.

And I think as Dr. Cultrera mentioned, these patients are managed pretty much in totality in terms of their clinical care and follow-up through the hematologist oncologists. And in terms of -- the issue that's being recommended here is the question of allowing those physicians to manage the administration of a relatively low risk beta emitter, alpha emitter products to make them part of their clinical armamentarium.

And we think that, that will certainly enable the patients to have access to this more easily. Again, I think there -- like everything else, there are multiple reasons for the challenge in why patients aren't referred.

But the reality is that this is a modality that is very effective, particularly for elderly patients. Because, again, unlike chemotherapy which requires multiple rounds of treatment, this is a one shot deal. One and done is the expression that's used.

So it would be very convenient for that patient population who can't really handle the toxicity of the repeated cycles of chemotherapy. So, again, I think, back to the question on the table, I think the current regulations do limit the use of this product and do impact clinical care.

And I think that a reasonable solution is to match the training requirement with the risk and safety of managing alpha and beta emitters. And I think the Committee has an opportunity to make a recommendation on that and the subcommittee has an opportunity to evaluate that more comprehensively. Thank you.

CHAIRMAN THOMADSEN: Thank you, Dr. Allen. Are there others on the line that --

DR. VACIRCA: Yes.

CHAIRMAN THOMADSEN: -- would like to comment? Who is that?

DR. VACIRCA: Hi, this is Jeffrey Vacirca. I'm the CEO of North Shore Hematology Oncology in New York. I'm a medical oncologist. But I'm also the Vice President of Community Oncology Alliance. We prepared a brief statement if that would okay to be read in?

CHAIRMAN THOMADSEN: Please. Yes.

DR. VACIRCA: So, Community Oncology

Alliance or COA is a non-profit organization. We're dedicated to cancer patients and providers in the community oncology setting. We currently represent over 7,000 community oncologists and are deeply concerned about any barriers to patients having access to lifesaving treatments.

As part of this rulemaking, the NRC has specifically requested comments on whether its regulations discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how? Our members support the NRC's efforts to update its regulations to reflect changes in clinical practice, as well as advantages in medical technology.

This rulemaking presents an opportunity for the NRC to improve access to potentially lifesaving anti-cancer treatments by addressing a shortage of authorized users able to administer these treatments. COA has been following the NRC's current rule making process and has submitted a comment letter to the NRC last fall.

In February, we attended and spoke at the public meeting held by the NRC on alpha and beta emitters training, as well as the experience requirements. COA is pleased to share its thoughts

with ACMUI on this topic today.

The NRC's regulations create a shortage of authorized users able to administer therapeutic radiopharmaceuticals. Under current regulations, as a drug administered parenterally and used primarily for its beta radiation characteristics, therapeutic radiopharmaceuticals can only be administered by an authorized user who has met the training and experience requirements set forth in 10 CFR 35.396.

These requirements involve either board certification or 700 hours of training and experience specifically in radionuclide handling. The hematologists and oncologists who typically prescribe therapeutic radiopharmaceuticals outside of the hospital setting often do not have the training and experience required to meet the AU requirements and do not work at facilities that have such AUs.

They have extensive training and experience and are frequently board certified, but in different specialized field. The effect of the regulation is to severely limit patient access to a very safe and effective treatment.

Certain patient populations are particularly negatively affected by a lack of AUs for therapeutic radiopharmaceuticals. Access is

particularly difficult in rural geographies or in other areas where patients must travel great distances to their primary oncologist, and even further to a specialized facility with an authorized user.

Standard treatment options that offer excellent response rates should be available to all patients, whether these patients live near an academic medical center or in a more rural area of the country. The experience of Doctors Mace and Cultrera, and many other community oncologists, demonstrate the burden that current regulations place on practitioners seeking to provide patients with these treatment options.

Dr. Mace, with 80 hours of training and experience in the safe handling of radionuclides acquired before the current regulations went into effect, has been safely administering these treatments to patients in need for a decade. Dr. Cultrera has worked with Dr. Mace and is unable to administer these treatments because she cannot realistically complete 700 hours of additional training and experience with the high demands of her practice.

Even though these treatments might be the best option for some of her patients, she feels that the burden placed on patients requiring them to travel

great distances to reach an authorized user is too high. These patients are frequently frail and elderly and traveling such distances can be taxing.

Doctors Mace and Cultrera have proposed a change to the rules to permit a lesser training requirement of 80 hours of classroom and laboratory training, plus relevant work experience and case administration, for a limited authorization to administer alpha and beta emitters that are prepared in a licensed specialty pharmacy and delivered intravenously in a patient-ready dose.

COA would support this reasonable and limited proposed change in the regulation. We do recognize the difficulty of balancing safety considerations with preserving patient access to medical care and we encourage ACMUI to consider this proposal that could significantly improve patient access to lifesaving treatments in the community oncology setting. Thank you.

CHAIRMAN THOMADSEN: Thank you, Dr. Allen. Other comments?

MS. LEVY: This is Robin Levy calling from the Lymphoma Research Foundation. May I --

CHAIRMAN THOMADSEN: Yes.

MS. LEVY: May I address the Committee now?

CHAIRMAN THOMADSEN: Yes. Please.

MS. LEVY: Thank you very much. Like I said, my name is Robin Levy. I'm the Director of Public Policy and Advocacy for the Lymphoma Research Foundation. The Foundation has submitted a letter to the Committee and I just wanted to speak today.

First, I'd like to say thank you for addressing the issue and I appreciate the subcommittee that you've just formed to evaluate the patient access question. Because that is very important to the Lymphoma Research Foundation and to our community.

The LRF is the nation's largest non-profit organization devoted exclusively to funding innovative lymphoma research and providing people with lymphoma and healthcare professionals with up-to-date information about this type of cancer. We appreciate the opportunity to respond to this Commission and the Foundation supports the NRC's efforts to update its regulations and to reflect changes in the clinical practice and advances in medical technology.

What we are concerned about is that we do not want to see any changes that will affect -- any regulation that will prove too burdensome for practitioners and result in limited access to safe and effective pharmaceuticals among the lymphoma

population.

We acknowledge the importance of training and experience requirements when dealing with therapeutic radiopharmaceuticals and we respectfully request the NRC consider regulatory framework that balances the importance of training and safety while not creating undue hardship on hematologists and oncologists who wish to administer these therapies.

A lymphoma patient faces a difficult and complex process as it relates to their diagnosis and treatment. And lymphoma is unique in that there are more than 67 subtypes of the disease and each are considered to be rare and complex diagnosis, which is notorious for recurrence. And a lymphoma patient needs access to every tool in the arsenal for the management of their disease.

So we believe the Commission must find balance between ensuring public safety during the administration of radiopharmaceuticals, while not hindering access to potentially lifesaving treatment. And we thank you for the opportunity to address you.

CHAIRMAN THOMADSEN: Thank you for your comment. Others on line?

MEMBER MATTMULLER: Yes.

CHAIRMAN THOMADSEN: Hearing none -- oh,

yes?

MEMBER MATTMULLER: Yes. Steve Mattmuller again.

CHAIRMAN THOMADSEN: Mr. Mattmuller.

MEMBER MATTMULLER: Yes. I think Dr. Cultrera has really mentioned a much simpler solution to all of this. Because in the Dayton area, there is ready access at our facility. And I know in the Orlando area, while it may not be convenient to her patients, but with -- and she's outside of the Orlando metropolitan area, and they're ready.

And yet, both facilities between the two of them, have done six patients in the past nine years. Even though we're ready to go, we're just not getting the referrals.

And she suggested that it was possibly that the medical oncologists and the hematologists are unaware of these radiopharmaceuticals and unaware that they are available and ready to go. That through the professional organizations, they need to educate their members that, to use these valuable drugs to give the best care to their patients, they need to refer them to departments that are ready to go right now. Thank you.

CHAIRMAN THOMADSEN: Thank you.

MEMBER DILSIZIAN: Vasken Dilsizian here.

CHAIRMAN THOMADSEN: Dr. Dilsizian.

MEMBER DILSIZIAN: Yes. I would like to echo that the University of Maryland Medical Center is an NCI sponsored oncology center and I've been here for 14 years. We have a great relationship with the oncologists and radiation oncologists. And we've had several meetings and dialogues about use of Zevalin by the oncologists.

And I would like to report that we've probably done only two patients over 14 years, despite having 13 system hospitals in the Baltimore area. If I could have one question, Dr. Allen, did you say you're from North Shore, New York? Dr. Allen? Okay. That's fine if he's not on --

CHAIRMAN THOMADSEN: Ms. Holiday, is Dr. Allen's microphone live?

MS. HOLIDAY: Yes. But I think he just dropped off the call.

CHAIRMAN THOMADSEN: Oh, okay.

MEMBER DILSIZIAN: My question was actually directed at Dr. Vacirca. Sorry. I just wanted to know if Dr. Allen represents North Shore New York Oncology Group, and I know Dr. Palestro is at North Shore Hospital.

I was wondering how many patients has he referred to North Shore Hospital given that Dr. Palestro is a very competent authorized user, nuclear medicine physician. That's what I thought. Thank you.

CHAIRMAN THOMADSEN: Okay. Thank you very much. And with that, I think that we'll come to an end of this part -- oh, am I hearing somebody?

MEMBER PALESTRO: Yes. Bruce, Chris Palestro. Hello?

CHAIRMAN THOMADSEN: Dr. Palestro.

MEMBER PALESTRO: Yes. Can you hear me?

CHAIRMAN THOMADSEN: Yes.

MEMBER PALESTRO: Couple of comments that I'd like to make listening to the discourse. Number one, to respond to the question that was just asked. If I remember correctly, over the past year, we may have done two Zevalin administrations. And I would say over the past decade, we've averaged one to two per year.

In terms of unsealed source, if you will, or intravenously administered, parenterally administered radiopharmaceuticals, there doesn't seem to be anything unique to me about Zevalin. They have all, for whatever reason in the past, started out being very popular with fairly large numbers of patients

receiving these treatments and then gradually it has diminished over time for whatever reason. So it's not unique to Zevalin.

In addition to that, in an area like the New York metropolitan area where, if anything, we have a surplus, an overabundance of authorized users who are capable and willing to administer this sort of treatment like Zevalin, the numbers just aren't there. So I think it's more than just a barrier put up by regulations. There are other reasons and I'm not sure what all they are.

But if you look at the New York City area and think about how many large academic institutions there are with innumerable authorized users, all of whom are experienced in radiopharmaceutical therapy of one sort or another, it's more than regulations that account for the lack of use.

CHAIRMAN THOMADSEN: Thank you very much. Now I think we're ready to move on to the next agenda item. Which is the report on the radionuclide localization procedures. Dr. Ennis, are you ready to present the Committee's report?

MEMBER ENNIS: I am, Mr. Chairman. Thank you.

CHAIRMAN THOMADSEN: Then I will turn the

chair over to you. I have to step out for just about a minute and a half. I'll be right back. But please start, I've looked at the beginning of this.

MEMBER ENNIS: Okay. Very good. So thank you, everyone. And behalf on Dr. Alderson, Mr. Costello, and Dr. Zanzonico, I will be presenting the results of the subcommittee's deliberations that we had on the radioactive seed localization for mostly non-palpable breast lesions. Next slide please.

So, as most on the call are probably aware, the use of a radioactive seed to localize non-palpable breast tumors began in the early 2000s. The NRC's first guidance was issued in 2006.

This review on which I'm reporting now was stimulated by a request from users to reanalyze the guidelines and the ACMUI at large and the subcommittee particularly thought this was an appropriate time given the evolution in the procedure and the time elapsed since the prior guidance. Next slide please.

The use of radioactive seed localization has increased significantly since it started being used. Oops, somehow my slide has jumped back to the first one. Okay. So anyway. We reviewed the guidance again. Next slide please. Okay, there we go. Please, back one slide. All right.

So, it's interestingly and potentially has already been started to be applied to other parts of the body beyond the breast itself and particularly the axilla. Which makes some sense given that the same physicians are involved in that as part of the breast treatment. But we can envision and some articles have and the medical literature has, indeed, suggested the possibility of using this for other similar procedures in other parts of the body. So we bore that in mind.

The typical procedure's done with the I-125 seed with low activity of about 2.2 millicuries. And this is low, but not that much lower than the low activity seeds used in some brachytherapy procedures. And the dose delivered with this to surrounding tissue, as the whole idea of brachytherapy, is going to be very low, particularly if the source is removed in a timely manner.

Of course, very close to the source there are some significant doses, but that will in general be a non-issue. Next slide please.

Getting into the specifics of the guidance and the questions raised by the users. Our subcommittee did not feel that a change in the authorized user guidance would be appropriate in balancing the safety concerns. We do agree that the

work experience aspect regarding removal of seeds is unnecessary, as that is done by someone else.

And similarly, other radiation safety training for the surgeon who is doing the lumpectomy should not include preparing the sources for placement, as that is something they are never going to be involved in. Next slide please.

Regarding the Written Directive, the subcommittee believes this continues to be an important part of the safe use of these isotopes and the safe execution of this procedure. We did agree to some modifications that had been suggested as I will detail in a moment.

Specifically, the Written Directive needs to indicate the name of the patient and before the procedure is done, the site of the body that's to be implanted, left breast, right breast for example, the isotope being used, iodine or palladium, and the activity of the source that will be implanted.

And then after the procedure, but before full completion of the procedure, documentation that, that's what has happened, that the radionuclide has been implanted, the site it was implanted, number of sources used, the total activity of the sources, and the time of exposure, i.e., time until surgery is

planned. Next slide.

Okay. And medical events would kind of follow as a consequence of a Written Directive, if you will, in a straightforward manner. A medical event would have been considered to have occurred if the radioactive source was placed into the wrong patient or it was the wrong isotope or it was put into the wrong part of the body, opposite breast for example, if the activity placed was more than 20 percent longer than anticipated, so the surgery did not happen in a timely manner, or that it was 20 percent higher activity than planned, these 20 percent numbers are consistent with other regulatory guidelines in this space, if you will, and obviously, a leaking source.

Exception of course is if this is due to patient intervention, then this is not a medical event. However, it is if it is expected that this would lead to unintended permanent functional damage, as noted in Part B. Next slide.

Regarding safety issues, there are a number that were raised by our subcommittee or by the users. And we will briefly review each of those. We do think it continues to be important to have safety concerns for ruptured seeds. And although they are rare events, we know that there have been such events,

so this is not something that does not happen and, therefore, concern for it needs to be continued.

We have felt that independent verification of seed activity is an important part of quality and safety. We agree that the preference stated in the guidance for sodium iodide meters over Geiger meters is really not necessary in this setting.

And we do advise -- specifically that patients be advised not to breastfeed with the breast into which a radioactive seed has been implanted until that seed has been removed. Next slide.

In addition, we do believe written policies need to be developed for a variety of scenarios where things don't go as planned, such as loss of seed, implantation of seed into the wrong location or wrong patient, inability to locate a seed at the time of surgery or at the time or pathological processing, and if a patient who has had a radioactive seed implanted does not show up. Next slide please.

Continuing on with some other points, we do agree that all notions and comments about therapy in the guidance are not relevant. And similarly dose not relevant as we are not trying to deliver a dose in the therapy. And recommend the guidance language be modified to reflect these clarifications.

And also to clarify or to correct prior guidance and allow seeds to be returned to the supplier as being an acceptable form of taking care of the seeds rather than needing to keep it to decay. Next slide.

In addition, we agreed that requiring staff training to know how to deal with a patient who cannot be discharged is unnecessary, as this would never occur with this type of procedure being such low activity. So that really is unnecessary. Reflect in the language of the guidance that this could be used outside of the breast, as is already occurring apparently.

And lastly, clarifying or changing the language of the guidance in the 'Change in Physical Conditions of Use' section to reflect the fact that the sources are indeed now approved by FDA for this use, which was not the case when the guidance was first put into effect. Next slide. I think that may be the last slide.

MS. HOLIDAY: That's the end of the slide deck, Dr. Ennis.

MEMBER ENNIS: Okay. That's what I thought. Okay. Thank you.

CHAIRMAN THOMADSEN: And Dr. Ennis, would you now want to take comments from the Committee on the

report itself? Which is --

MEMBER ENNIS: Sure. I'd be happy --

CHAIRMAN THOMADSEN: -- extensive.

MEMBER ENNIS: -- to do that.

CHAIRMAN THOMADSEN: I'll let you chair that discussion too.

MEMBER ENNIS: Okay. Great. Are there any members of the Committee that would like to bring up any issues before we open up the floor to outside?

MEMBER WEIL: Dr. Ennis, this is Laura Weil.

MEMBER ENNIS: Hi Laura. Go ahead.

MEMBER WEIL: In the text of your detailed report, you provide figures for the anticipated low risks of exposure to any members of the public from patients with implanted seeds. But you provide the figures only for a single implanted seed.

And, yet, earlier in the report, you mentioned that from one to four seeds may be used. For clarity's sake, I would suggest that the report be amended to include that range of exposures. Which are certainly nothing to be concerned about. But just for accuracy's sake.

MEMBER ENNIS: Sure. That's a good point. Absolutely. Thank you. Okay. I'll make a note of that.

CHAIRMAN THOMADSEN: This is Bruce Thomadsen again. Sophie? I'm sorry, Ms. Holiday?

MS. HOLIDAY: Yes.

CHAIRMAN THOMADSEN: Would we be able to get that report up on the screen so we could go to places people might talk about?

MS. HOLIDAY: Sure.

CHAIRMAN THOMADSEN: There we go. Thank you. Now I had -- Dr. Ennis?

MEMBER ENNIS: Yes, please.

CHAIRMAN THOMADSEN: I have some comments.

MEMBER ENNIS: Yes, please.

CHAIRMAN THOMADSEN: If you go to Page 2, where it discusses OLINDA, which is -- let me get there on mine. It's the second paragraph at the top of --

MEMBER ENNIS: Okay.

CHAIRMAN THOMADSEN: -- Page 2. It talks about how the dose could be calculated with OLINDA, but in this case, the doses would be overestimates due to the lack of backscatter from a breast in the algorithm used. And it just might be -- the statement that we could use OLINDA to calculate it may be qualified, just recognizing it'll be an overestimate.

MEMBER ENNIS: All right. I think we could certainly do that. Do you feel strongly that we should

use some other software to model the dose rather than OLINDA?

CHAIRMAN THOMADSEN: No. No, just, I think, just recognizing that the doses calculated are overestimates is quite sufficient.

MEMBER ENNIS: Okay. That's quite reasonable. We'll have to modify the report accordingly.

CHAIRMAN THOMADSEN: And then, later in that paragraph, when it talks about the dose to the breast from the seed, if the seed were removed seven days post-implantation and you're talking about the mean dose to the breast, does that account for the volume of the breast that surrounds the seed that is removed?

MEMBER ENNIS: So you're saying, is the dose, when we say that are we saying the dose that remains in the breast? Or does that mean the dose to the breast, which includes some dose absorbed into the tissue that's been removed?

CHAIRMAN THOMADSEN: That's --

MEMBER ENNIS: Is that your questions?

CHAIRMAN THOMADSEN: The question is, if you're calculating the mean dose to the breast, is the breast that's included in that mean also include the

tissue around the source which is being removed? If so --

MEMBER ENNIS: Right. Yes.

CHAIRMAN THOMADSEN: -- then it actually --

MEMBER ENNIS: I do.

CHAIRMAN THOMADSEN: What's that?

MEMBER ENNIS: I'm sorry. Continue.

CHAIRMAN THOMADSEN: If that's the case, then the mean dose to the breast is going to be considerably lower than the dose if you calculate it with the tylectomy sample in situ.

MEMBER ENNIS: Right. Correct. I understand. So, is Dr. Zanzonico on the call?

CHAIRMAN THOMADSEN: He was not earlier.

MS. HOLIDAY: Can you all hear him?

CHAIRMAN THOMADSEN: No. Is he there?

MEMBER ZANZONICO: Yes. Hello?

MEMBER ENNIS: Hi. Speak a little louder please.

MEMBER ZANZONICO: Yes. Hello?

CHAIRMAN THOMADSEN: Hello.

MEMBER ZANZONICO: Hello?

MEMBER ENNIS: Hi.

MEMBER ZANZONICO: Can you hear me?

MEMBER ENNIS: Yes.

MEMBER ZANZONICO: I've been on the call since the beginning. For some reason, I haven't been heard, though I didn't take it personally when my questions and comments were removed.

(Laughter.)

MEMBER ZANZONICO: Is there a question coming my way?

MEMBER ENNIS: Yes.

CHAIRMAN THOMADSEN: Yes. Can you hear us?

MEMBER ZANZONICO: Yes.

CHAIRMAN THOMADSEN: The question is on Page 2 of the report. And it deals with the calculation of the mean breast dose from the seed that's in place for seven days.

MEMBER ZANZONICO: Yes.

CHAIRMAN THOMADSEN: And the question is, does that mean dose include the dose to the breast tissue that will be removed during the tylectomy?

MEMBER ZANZONICO: Yes. But it is the mean dose, so it doesn't account for the fact that there will be a much higher dose to the local tissue and a lower dose to the more distal tissue. But it does incorporate in the mean the tissue that will be removed.

CHAIRMAN THOMADSEN: So the effect of mean dose would, again, be much lower? Since --

MEMBER ZANZONICO: Yes.

CHAIRMAN THOMADSEN: -- the tissue would be removed?

MEMBER ZANZONICO: Are you talking about the effective dose now?

CHAIRMAN THOMADSEN: No. No, the effective dose isn't going to change much. But the mean dose to the breast, effectively, would be a lot less --

MEMBER ZANZONICO: You're correct.

CHAIRMAN THOMADSEN: -- because the high --

MEMBER ZANZONICO: That's correct.

CHAIRMAN THOMADSEN: -- highest doses will be gone?

MEMBER ZANZONICO: Yes. That's correct.

CHAIRMAN THOMADSEN: There might be some note to that in the report. Just to recognize that.

MEMBER ZANZONICO: Understood. That sounds reasonable.

CHAIRMAN THOMADSEN: The next comment is on Page 3, under Changes to Guidance Considered by the Subcommittee in Its Recommendations. In the first paragraph there, it mentions palladium-103 and says the subcommittee sees no reason to exclude this isotope and, therefore, recommends retaining the reference to

it in the title.

But by doing so, you're not recognizing the possibility of other radionuclides, such as cesium-131, which would give a much lower dose to the patient for similar activity implanted at the beginning.

MEMBER ENNIS: So I suppose, although the short half-life, I think, would make that source an unlikely candidate.

CHAIRMAN THOMADSEN: Well, the short half-life is nine days.

MEMBER ENNIS: Right.

CHAIRMAN THOMADSEN: If you talk about the source being implanted for, at the most, seven days, you still have a considerable activity at the end of the seven days.

MEMBER ENNIS: Right. So are you --

CHAIRMAN THOMADSEN: Definitely -

MEMBER ENNIS: -- suggesting that we remove --

CHAIRMAN THOMADSEN: That would weakly --

MEMBER ENNIS: Are you suggesting that the title ought not mention any particular isotope?

CHAIRMAN THOMADSEN: Correct.

MEMBER ENNIS: I see.

CHAIRMAN THOMADSEN: That would --

MEMBER ENNIS: We can certainly --

CHAIRMAN THOMADSEN: -- be my suggestion.

MEMBER ENNIS: -- consider that.

CHAIRMAN THOMADSEN: Just refer to them as brachytherapy sources.

MEMBER ENNIS: Okay.

CHAIRMAN THOMADSEN: And next one is on Page Number 5. And it's -- the comment is on the Medical Event Reporting B. And the question I would have is the question of whether you need in the event reporting a paragraph talking about unintended permanent functional damage. This sounds more like an OA than a medical event.

MEMBER ENNIS: And OA is a --

MS. HOLIDAY: AO?

CHAIRMAN THOMADSEN: AO. Sorry, yes. AO. Abnormal occurrence.

MEMBER ENNIS: I see.

CHAIRMAN THOMADSEN: Which are automatically reported. Is that right? Ms. Holiday?

MS. HOLIDAY: I'm sorry. What did you say, Dr. Thomadsen?

CHAIRMAN THOMADSEN: In that paragraph, which is the B in here, that would fall into the category

of an abnormal occurrence, would it not?

MS. HOLIDAY: I think that was proposed language for the abnormal occurrence criteria.

CHAIRMAN THOMADSEN: At one point, yes.

DR. HOWE: Dr. Thomadsen? This particular --

CHAIRMAN THOMADSEN: Yes.

DR. HOWE: This particular -- this is --

CHAIRMAN THOMADSEN: Who is speaking right now?

DR. HOWE: -- Dr. Howe. This is Dr. Howe at the NRC. This particular language in Section B parallels the language in medical event reporting if there's patient intervention. It has nothing to do with the abnormal occurrence.

It has to do with if there's patient intervention, it would only be reported -- and it was a medical event, then you would only report it if you have permanent functional damage. So that's where that particular language comes from.

CHAIRMAN THOMADSEN: Very fine. Thank you. And the next one is in the last line of that page. The verification of source activity and the question I have is --

MEMBER ENNIS: Do we have a question? I

think there's a question.

MEMBER ZANZONICO: Yes. While we're on -- this is Pat Zanzonico. While we're on that section, if you look at the second line of Item A, it appears that there's some text missing, doesn't there? At the very end of the line?

MEMBER ENNIS: That's just how the slides are projecting. It's cut off. The end of the lines are cut off on my screen as well, but I think that is just how the text is projecting on our webinar.

CHAIRMAN THOMADSEN: Actually, I'm looking at the Acrobat, the PDF, and indeed, that line does end exactly like on the screen.

VICE CHAIRMAN ALDERSON: Yes. This is Phil Alderson. Can you hear me?

CHAIRMAN THOMADSEN: Yes.

MEMBER ENNIS: Phil. Go ahead.

VICE CHAIRMAN ALDERSON: Yes. Good. That's great. Because like Pat Zanzonico, I've been on listen-only most of the time, ever since it began. I'm looking at a piece of paper, I hate to be so out of touch with reality of the current day. But it's the full sentence is there. It's as it's appropriately written and material results in dash and then it goes through all the subsets. So, it's a computer problem.

CHAIRMAN THOMADSEN: Okay.

MEMBER LANGHORST: Hi. This is Sue Langhorst. May I offer something in this section?

MEMBER ENNIS: Sure, Sue. Go ahead.

MEMBER LANGHORST: I just -- Dr. Ennis is there anything different here than is in medical event reporting? And might it be easier to just reference medical event reporting and any differences that you may be recommending? And I couldn't tell that there were any differences that you all were recommending.

MEMBER ENNIS: I'd have to bring up those --- it parallels it. All dose issues are removed and I think that's probably the main difference.

MS. HOLIDAY: Dr. Ennis, this is Sophie.

MEMBER ENNIS: Yes, Sophie.

MS. HOLIDAY: I just wanted to point out that one of the biggest differences in this section is that the subcommittee put language in there about administration of radioactive byproduct material for more than 20 percent longer than planned.

MEMBER ENNIS: Correct.

MS. HOLIDAY: And administration of the radioactive byproduct material activity of more than 20 percent of the intended activity.

MEMBER ENNIS: Correct. Thank you.

MEMBER LANGHORST: This is Sue Langhorst again. I think it might be better if you, just my personal opinion, if you only discuss what the differences are rather than trying to figure out are you saying something different for all these other items that are exactly the same as in the regulations.

MEMBER ENNIS: Okay.

MEMBER LANGHORST: That's just my thought.

MEMBER ENNIS: Right. I guess the alternative thought is to put the whole thing in one place so that users have one place to look to know rather than, oh God, I've got to look here for part of the regulation and here for another part.

MEMBER LANGHORST: This is Sue. Okay, I understand.

MEMBER ENNIS: I think, Dr. Thomadsen --

CHAIRMAN THOMADSEN: Yes.

MEMBER ENNIS: -- you had more comments.

CHAIRMAN THOMADSEN: Yes. On the last line on that page, Verification of Source Activity, since these all come sterile, what is the recommendation of the subcommittee to perform that verification?

MEMBER ENNIS: So this may be something we have to reconsider actually, based on Mr. Sheetz's follow-up comments.

VICE CHAIRMAN ALDERSON: I'm sorry, Bruce, could you --- this is Phil. Would you restate your question? I didn't understand your question in relation to this sentence.

CHAIRMAN THOMADSEN: The current practice in brachytherapy to evaluate source activity or source strength rather than activity is to measure seeds in a well chamber. If the seeds are sterile, that makes it very difficult to do.

Some places have come up with procedures, but they aren't universally accepted. So the question here is, since these sources come loaded and sterile, how is the committee expecting the users to make this determination of activity?

VICE CHAIRMAN ALDERSON: Thank you.

MEMBER ZANZONICO: Dr. Thomadsen? This is Pat Zanzonico.

CHAIRMAN THOMADSEN: Yes.

MEMBER ZANZONICO: When you're referring to a well chamber in the context of assaying seeds for brachytherapy, are you referring to something other than a dose calibrator?

CHAIRMAN THOMADSEN: A well chamber used for brachytherapy usually is designed slightly differently than the typical nuclear medicine well

chamber, although they have many features in common. But, yes, you could potentially use a nuclear medicine well chamber if it were calibrated.

MEMBER ZANZONICO: Right. This is Pat Zanzonico again. I think as Dr. Ennis said, there's probably something we need to reconsider. But I would think a standard nuclear medicine dose calibrator could easily be calibrated with the source from the manufacturer initially to calibrate the dose calibrator to allow it to give an accurate reading of the seed in the whole assembly, in the whole sterile assembly.

CHAIRMAN THOMADSEN: And that's a question too. Some people have suggested that the varying thickness in a needle can markedly affect the reading in a brachytherapy seed of that energy.

MEMBER ZANZONICO: Agreed. That's why there would have to be some initial calibration to account for that and that calibration would subsequently be used for actual patient seeds after that.

CHAIRMAN THOMADSEN: The variation was needle-to-needle as opposed to manufacturer-to-manufacturer.

MEMBER ZANZONICO: Understood.

MEMBER LANGHORST: Dr. Ennis, this is Sue Langhorst.

MEMBER ENNIS: Yes, Sue?

MEMBER LANGHORST: I would recommend that you drop that recommendation. Because in 10 CFR 35.432 in Paragraph D, that allows licensees to use instead of their own measurement, measurements provided by the source manufacturer or a calibration laboratory that's accredited. And so, the recommendation that the subcommittee has put forward on measuring the seed strength, it goes beyond what the current regulations have for regular brachytherapy seeds.

MEMBER ENNIS: Yes. I agree. We will definitely reconsider this particular point.

MEMBER ZANZONICO: This is Pat Zanzonico again. While I initially thought it was good idea to retain the end-user calibration, just based on this discussion and given the low energies of the I-125 emissions, it may actually be more problematic. As Dr. Langhorst is suggesting, it may be more problematic to retain that requirement. It brings more problems than it potentially solves. But we should reconsider it.

VICE CHAIRMAN ALDERSON: Yes. This is Alderson. I agree.

MEMBER ENNIS: Very good.

CHAIRMAN THOMADSEN: Okay. I only have two more.

MEMBER ENNIS: Go ahead, please.

CHAIRMAN THOMADSEN: On the next page, under Training. The first three words are "the subcommittee agrees" and it's not clear with whom it's agreeing.

MEMBER ENNIS: With the user presentation.

CHAIRMAN THOMADSEN: Yes. But I don't think the report is in response to any --

MEMBER ENNIS: Fair enough.

CHAIRMAN THOMADSEN: -- user presentation.

MEMBER ENNIS: We will change that language. Correct. Thank you.

CHAIRMAN THOMADSEN: And I think it's also used down under Procedures also.

MEMBER ENNIS: Okay.

CHAIRMAN THOMADSEN: And my --

MEMBER ENNIS: Thank you.

CHAIRMAN THOMADSEN: My last point is on the next paragraph, Survey Instruments and Radiation Survey Requirements. I do not see why you need to designate either sodium iodide or Geiger-Mueller counters, rather than just saying detector with demonstrated capability to detect the radiation from

the sources at the radiation levels anticipated. There are diode detectors that can do just as well, along with other scintillator detectors and it just seems that you don't need to restrict it to those detectors.

VICE CHAIRMAN ALDERSON: If you don't want to restrict it to those, I think you should just show on a sentence or a phrase that says, or other detectors that provide acceptable readings. I think that many people who read this will actually be guided by the fact that some of these detectors are named rather than just talking about ones that are only acceptable.

They'll say, well what are they and how do we find out? So I accept your recommendation, but think this should be an addendum to what's already here.

MEMBER ENNIS: Are there specifics that we would need to stipulate in what is considered an acceptable?

CHAIRMAN THOMADSEN: Well, and that's a good question for both of those detectors too. Because you can have a sodium iodide meter that has a thick enough shield around the detector that it won't measure the radiation from the iodine. And likewise, the GM counter.

So even with those, you would need to

specify that the detectors have demonstrated the capability to detect the radiation from the sources at the radiation level. Which is usually probably with that same source.

MEMBER ENNIS: So are we going to be requiring people to demonstrate ex vivo and how are we going to -- are we going to now have a whole kind of requirement and documentation before using whatever detector -- is that what we're talking about?

CHAIRMAN THOMADSEN: Well, it doesn't sound like a bad idea. If you're going to parallel, for example, with a prostate implant, for looking for lost seeds in the operating room, you have to check that the radiation detector is capable of detecting the seeds.

MEMBER LANGHORST: This is Sue Langhorst.

MEMBER ENNIS: Yes, Sue?

MEMBER LANGHORST: When a licensee requests approval to do such things, that's part of what the regulators review is whether they have adequate equipment to perform surveys and so on. So I think -- I agree with Dr. Thomadsen that we should probably just say that it's a survey meter capable of detecting the seed activity. And you might say, for example, and you may list a few of these things.

But I think it doesn't have to go beyond

that. We may want to include in there caution about being able to see the seeds in light of other nuclear medicine procedures that may be impacting a given patient. Mr. Sheetz has that in one of his comments --

MEMBER ENNIS: Yes.

MEMBER LANGHORST: -- on the report. Thank you.

MEMBER ENNIS: Thank you, Sue.

MEMBER ZANZONICO: This is Pat Zanzonico. Yes. I think we could easily revise this paragraph to incorporate all these concerns. But we may not be able to do the word-smithing in real time.

CHAIRMAN THOMADSEN: Oh, I wouldn't think you'd want to.

MEMBER ENNIS: Yes.

MEMBER ZANZONICO: Okay.

CHAIRMAN THOMADSEN: That would be difficult, yes.

MEMBER ENNIS: Very well. Any other comments on this topic? Dr. Thomadsen, do you have any more?

CHAIRMAN THOMADSEN: No. I'm done. Thank you.

MEMBER ENNIS: Thank you very much. Any

other Committee members have any other questions or comments?

MEMBER LANGHORST: Dr. Ennis, this is Sue Langhorst again.

MEMBER ENNIS: Yes.

MEMBER LANGHORST: I wanted to ask about whether the subcommittee might want to consider including -- and I've lost my place as to exactly where that should be. But as far as patient intervention goes, defining if the patient is not able to have surgery when scheduled, would that be -- like the patient doesn't come back or something to that effect, would that be considered patient intervention?

MEMBER ENNIS: That was our thinking and understanding in our committee discussions, yes.

MEMBER LANGHORST: This is Sue again. We may want to specify that a little bit more clearly. Because I didn't get that out of what I read.

MEMBER ENNIS: Thoughts from any other Committee members on that particular issue? Okay. We will consider that as well. Any other comments or questions?

MEMBER PALESTRO: Yes. Chris Palestro. I have one question. On your presentation, Slide Number 7, addressing breast-feeding and a recommendation that

it be deferred until such time as the seed or seeds are removed. What happens in the case of a ruptured or transected seed?

MEMBER ENNIS: Well, I guess this would come under the recommendation that guidelines be put into place -- I don't know that we are going to mandate those guidelines. We talked elsewhere about putting into place guidelines should a seed rupture, and I guess this would fall under that.

I don't know that we would as a guidance go beyond that. I'm certainly interested in what other people have to say. Wearing my medical hat, I would say that the patient would be advised not to breast-feed until X number of half-lives have passed. Probably many.

MEMBER PALESTRO: Thank you.

MEMBER ZANZONICO: This is Pat Zanzonico. Yes. I mean, it would obviously be unfortunate and hopefully very rare, but I think to be internally consistent, if the seed were ruptured and the activity were not retrievable, the only logical course of action would be to have the patient discontinue breast-feeding until physical decay has effectively eliminated the activity.

MEMBER ENNIS: Well, I guess the question

on the table though is, is this something that ought to be written into guidance language?

CHAIRMAN THOMADSEN: This is Bruce Thomadsen. It actually sounds reasonable to have it in there. I hadn't thought of it.

MEMBER WEIL: This is Laura Weil. May I suggest something?

MEMBER ENNIS: Please.

MEMBER WEIL: In that bullet point, perhaps what needs to be communicated is that the patient should be advised not to breast-feed with the breast into which an intact seed has been implanted and successfully removed. And all those other unfortunately situations would then default to a different set of precautions.

VICE CHAIRMAN ALDERSON: This is Phil Alderson. I was thinking of an example of how could this possibly happen. And the one thing I could come up with is that the person who has the seed implanted and also is breast-feeding, which is, again, probably unlikely, but in any case, is in a modest automobile accident where they are pushed forward into a steering wheel or something. And that blunt impact on the anterior chest wall ruptures the seed while it's actually in their breast and before they have everything done and the seed's removed.

So this could happen. And in that sense, I would agree with whoever it was that stated that perhaps we should include some language that the public would easily understand in that regard.

MEMBER ENNIS: Okay. Then we should come up with some language accordingly. And I guess the key thing really would be how many half-lives.

VICE CHAIRMAN ALDERSON: Ten.

MEMBER ENNIS: Very good.

MEMBER LANGHORST: Hi, this is -- Dr. Ennis, this is Sue Langhorst again.

MEMBER ENNIS: Yes, please.

MEMBER LANGHORST: I had a question on training for authorized users. Because the subcommittee's not suggesting any changes in the training requirements, does that mean that an authorized user who is not a 490 authorized user, they cannot train anyone else?

MEMBER ENNIS: So, are you asking that someone who is a 290 who has already been trained, can he or she subsequently train someone else?

MEMBER LANGHORST: Yes. Because I think that was one of the questions of whether a new person being trained -- they couldn't be trained by a 290 authorized user who's been approved for this procedure,

because that person is not a 490 trained authorized user.

MEMBER ENNIS: Right. Yes, that was raised by the comments from the users. Other members of the Committee can obviously speak as well. Becoming an authorized user for RSL, I don't know, is there a way in regulatory space that, that person has a designation of some type? That can -- I don't know. This is more of a regulatory language and process question, I think, that I'm a little less familiar on being new to the Committee.

MEMBER LANGHORST: I think the regulatory language, and NRC staff can help me on this, is on the -- when it talks about getting training from an individual, it talks about someone who's approved in that procedure. I don't have that pulled up in front of me. But I think --

MS. HOLIDAY: It's on the screen, Dr. Langhorst.

MEMBER LANGHORST: This is from the report or this is the regulations?

MS. HOLIDAY: This is from the current 35.1000 guidance.

MEMBER LANGHORST: Okay. Sorry, I'm going to have to read it. I can't speak and read at the same

time.

MS. HOLIDAY: Sure.

MEMBER LANGHORST: I take it back.

DR. HOWE: This is Dr. Howe. In partial response to, I believe, your question or statement. When someone is authorized for a 35.1000 use, at least on an NRC license, then they are authorized for that particular NRC 35.1000 use. And so that authorized user would be listed for radioseed localization.

One of the concerns for having training from the 35.490 is that many of the requirements for keeping an inventory and accounting for seeds are significantly different from what an authorized user is normally doing in 35.200 uses.

MEMBER ENNIS: Right. That is --

CHAIRMAN THOMADSEN: It seems like --

MEMBER ENNIS: -- the advantage --

CHAIRMAN THOMADSEN: -- the question might be, though, that if somebody has trained under Part 1000 for this procedure, could they then act as a preceptor and trainer for somebody else for this procedure?

MEMBER ENNIS: Right. That is exactly the question on the table right now.

MEMBER LANGHORST: This is Sue Langhorst again. I think they would be the best ones to be giving

that training specific for this 35.1000 use.

VICE CHAIRMAN ALDERSON: This is Alderson. I think they would be good trainers also.

CHAIRMAN THOMADSEN: And this is Bruce. I agree.

MEMBER LANGHORST: So this is Sue again. I would recommend that the subcommittee maybe work on that wording just to make sure to clarify that, that's what they're meaning. That a person who may have originally the 290 training, that once they become an authorized user for this seed localization under 35.1000, that they may act as a trainer and preceptor for other authorized users or other 290 users who want to become seed localization authorized users.

MEMBER ENNIS: Right. And again, this would not be a generalizable thing. This can be made to be a specific that they're trained in this specific one and they can precept in this specific one. Dr. Howe, am I understanding that correct?

DR. HOWE: Could you repeat?

MEMBER ENNIS: Just clarifying your comments. I think I understood it correctly, but we could stipulate that a 290 who is specifically approved in the 35.1000 RSL, very specifically could then be a preceptor and that would not be generalizable to other

35.1000 or other things. It could be made that specific.

DR. HOWE: Yes. It would not extend to any other 35.1000 use.

MEMBER ENNIS: Thank you. All right. The subcommittee will consider this as well.

MEMBER LANGHORST: This is Sue Langhorst again, Dr. Ennis. And one thing I just want to say is, I really appreciate the subcommittee's work on all this. I think you guys did a marvelous job on this and appreciate all your thoughts and discussions in this request to update a very old guidance document that was much needed.

MEMBER ENNIS: On behalf of the committee, we accept your compliments.

(Laughter.)

MEMBER ENNIS: Any other questions or comments from the Committee? Okay. I guess we will now open the floor for comments or questions from the public.

MR. LIETO: Question.

MEMBER ENNIS: Yes. Is there a question?

MR. LIETO: This is Ralph Lieto from St. Joseph Mercy Hospital in Ann Arbor. Can you hear me?

MEMBER ENNIS: Yes, we can. Please go

ahead.

MR. LIETO: I had just a couple questions. On your Written Directive recommendations, your subpart II for after implantation. The very last criteria there where it says total activity implanted and exposure time/time planned before surgery. Is the exposure time and the time planned before surgery supposed to be both a criteria of the Written Directive? Or is it one --

MEMBER ENNIS: So --

MR. LIETO: -- or the other?

MEMBER ENNIS: I suppose we should clarify that language. Exposure time seems to be an older phrase from more of a therapeutic type of concept. And what we really meant was time from the implantation until it's supposed to be removed at surgery. Perhaps we should take out the exposure time phrase completely.

MR. LIETO: I take it that the intent was sort of like the old cesium implant sources that were --

MEMBER ENNIS: Correct.

MR. LIETO: -- specified by you were going to take it out at a certain time.

MEMBER ENNIS: Yes. Correct. It's coming from that language base. That's correct.

MR. LIETO: Okay. Related to that is the -- in terms of activity implanted, did the subcommittee give any consideration to the activity being a range with the seeds? I think --

MEMBER ENNIS: Make a case --

MR. LIETO: I just think that things are being -

MEMBER ENNIS: Make a case why that would be --

MR. LIETO: Well, I --

MEMBER ENNIS: -- a situation.

MR. LIETO: Well, I'm just thinking that a Written Directive would allow -- if it was more than one seed, rather than specifying the activity per seed, you would say X seeds, say 3 seeds between 0.2 and 0.3 millicuries. Because the sense of the report is that it's written as if you're doing a -- that dose is the priority here. Absorbed dose is the priority in consideration of these implants, when really whether you're using 0.2 or 0.3 millicurie seed is really immaterial for, at least, the purposes of the study.

And I think you might want to consider some flexibility to permit a range or so forth, a range of activity of seeds that could be used and not get into where you could potentially then fall into a Written

Directive -- or excuse me, a medical event, from the way the Written Directive is done.

MEMBER ENNIS: It seems that, other Committee members can certainly speak, but it seems to me that when you're putting a particular seed in a particular patient, you know which seed it is and you ought to know which seed it is and not just be fishing them out from a bucket. I don't really quite get how this is really, from a practical point of view, a concern.

MR. LIETO: Well, all right. Well, just like I said, I just thought it might be a consideration for how these seeds are, how the prescription is written for the Written Directive. Because I could see that there could be a facility that would be using spent brachytherapy seeds where they would have a range of seeds of availability for this type of purpose. And just give that type of flexibility rather than overly prescriptive nature for what's being prescribed. My next question had to do --

CHAIRMAN THOMADSEN: Could I just make a suggestion on that though?

MEMBER ENNIS: Please.

CHAIRMAN THOMADSEN: In that type of situation --- this is Bruce Thomadsen. In that type

of a situation, if they have a brachytherapy program, they should be able to measure the activity and know the actual activity of that given seed, no?

MR. LIETO: Agreed.

MEMBER ENNIS: Yes.

CHAIRMAN THOMADSEN: It's still good to hear from you, Ralph.

MR. LIETO: Thank you. It's good to participate. My next question had to do with the medical event recommendations. I wasn't sure, are you recommending that this be the changes to the Part 35 definition?

MEMBER ENNIS: No. This is for this particular guidance only.

MR. LIETO: Well, I guess, might not be able to be answered now, but I'd like to understand from NRC staff how you can change an ME definition in guidance space. I could understand that there might be designations that you would want maybe some follow-up action on, such as if the source had to be in there, say, 20 percent longer in time, which might be due to some event that's beyond the licensee's control.

But I guess I'd be really concerned about the precedent that would be set in changing an ME definition in guidance space. Because I could see a

number of other applications where there might be the interest to do this for other Part 1000 uses --

CHAIRMAN THOMADSEN: This is --

MR. LIETO: -- which --

CHAIRMAN THOMADSEN: This is Bruce. And you already have that going on with the microspheres.

DR. HOWE: Correct. Dr. Thomadsen, if I could answer that? This is Dr. Howe. When we look at 35.1000 guidance, we are looking at the unique characteristics of the particular device or use and if it has a unique characteristic that would prevent it from meeting part of the requirement, we can modify the guidance so that it meets kind of the standard of what the guidance is looking for, but may be particular to this use.

And as you stated, in the yttrium-90 microspheres, we recognize that stasis would always lead to a medical event. And so we said that you could write stasis in the Written Directive and if you reach stasis, that would not be a medical event. And we have other 35.1000 guidance where we've manipulated the medical event reporting requirements to fit the unique properties of that particular medical use. So this not a precedent.

MR. LIETO: But this is not a unique source,

unlike the Y-90 brachytherapy. Okay. This is a low dose sealed source used in brachytherapy applications. I mean, I guess I'm trying to understand why this unique for this type of application, yet iodine, palladium, whatever that's applied to prostate or lung or so forth, would not have the potential for having these same types of applications.

CHAIRMAN THOMADSEN: This is Bruce Thomadsen again. You could also look at capsules with iodine-131, sodium iodide used for imaging and for therapy, the same capsule with the same radionuclide, just with different activities, would be used for each. That's the procedure that's defining whether you would fall under medical event reporting in one way or another that way.

MR. LIETO: I'm sorry, Bruce. I'm not sure if I'm following your -- the capsules are not considered sealed sources.

CHAIRMAN THOMADSEN: No. I'm just saying, we have an analogous situation where we have the same radionuclide delivered in the same way, but used in one case for diagnosis and for another case for therapy. And yet if we have a difference of 20 percent in dose in one case, with the therapy, it's an event. Whereas, if it's a 20 percent difference in the imaging, it's

not an event.

So, the procedure itself can be demarcating the rules for medical event reporting. And in this case, you have the same source and in the same form, yet the procedure itself is very different. In this case, it's much more like an imaging study. Whereas, in brachytherapy, it's therapy.

MR. LIETO: No. I guess I would disagree. The analogy you're using with I-131 would not -- I mean, they're both capsules given orally, it's just the difference in activity that's administered. That's the only criteria difference. And the physical form difference is the same. I mean, physical form is the same. There's not a difference.

I mean, you're adding a medical event definition for a diagnostic procedure based on time that the source is left in the patient. I mean, you're creating some unique medical event definitions for a diagnostic procedure. I just think that there's going to be some real difficulty with these added restrictions or prescriptive definition of a medical event. Because I'm assuming these do encompass the current definition, you're adding other specific criteria.

MEMBER ENNIS: Anyone have any comments?

MEMBER ZANZONICO: Well, this is Pat. I mean, I appreciate the importance of precedence, but apparently, even though this is an existing source, it is a distinct application. And as was pointed out, there is a precedence for defining medical events in guidance space. So I think given that it's specific for this application, I think the potential for abuse of this practice is avoided. And I personally --

MR. LIETO: What is --

MEMBER ZANZONICO: -- don't have any real concern with defining a medical event for the radioactive seed localization as it's been recommended in the subcommittee's report.

MR. LIETO: Dr. Ennis, what is the problem that you're trying to solve that the current definition does not address?

MEMBER ENNIS: The main issue has to do with removing any issues of dose, since dose is not really relevant. But keeping the spirit of making sure the source is safely implanted and explanted and the exposure to patient's surrounding tissues is aligned, is what was intended.

MR. LIETO: So the current definition is an activity-based, and that's what you're trying to demonstrate here, correct?

MEMBER ENNIS: This is an activity-based definition, correct.

MR. LIETO: Well, I guess why then the time issue being entered into the definition? If the right activity is put in and so forth, it still seems like you've got this dose characteristic associated with it indirectly.

MEMBER ENNIS: Right. Well, I guess there -- I mean, there certainly is an exposure element here. There's no doubt that the reason this can be regulated this way as opposed to like a permanent seed implant is because, one of the elements is because of the short time it's expected to be in the breast. There is no doubt that's part of why regulations can be a little different. And this is a way of assuring that, that's happening.

MR. LIETO: I appreciate that and I guess I respectfully will just, I guess, have to agree to disagree on that issue.

MR. FULLER: Dr. Ennis, this is Mike Fuller with the NRC. If I may?

MEMBER ENNIS: Sure. Please, Mike.

MR. FULLER: Mr. Lieto, this is Mike Fuller, as I said. To allow this to go ahead and proceed, I think there's a lot of information that we could provide

you offline.

If you wanted to contact me after this meeting, I'd be happy to walk you through a lot of the things that are in the existing 35.1000 guidance right after seed localization studies. And then, maybe help that way. But rather than take the time in this meeting, maybe I could help you offline.

MR. LIETO: Fair enough. Thank you.

MEMBER ENNIS: Are there any other comments from the public?

MEMBER MATTMULLER: Yes. Well, actually from the Committee. This is Steve Mattmuller. And I just noticed in our package, there was a letter from Michael Sheetz and Jeffrey Brunette, both health physicists, in regards to this topic. And it seems they have some differing opinions to what the Committee came up with. So I guess my real question is, had you had a chance to read this and to evaluate their comments in formulating your --

MEMBER ENNIS: So we had their presentation that they made to our Committee a couple months ago. We only recently received their response. As a subcommittee, we have not met or decided whether to meet to discuss their response to our posted guidance. Most of what's in there has either been addressed, actually,

in this conversation or is just, frankly, a repeat of a position they had already presented once that we may have not agreed with.

MEMBER MATTMULLER: Okay. That's fine. I just thought as a public meeting, since their comments had been submitted, we should acknowledge that. So, thank you.

MEMBER ENNIS: Sure. Thank you.

MR. SHEETZ: This is Mike Sheetz. I guess I would like to make comments.

MEMBER ENNIS: Sure. Please go ahead.

MR. SHEETZ: -- Appropriate time. We have submitted written comments. Both Jeff Brunette and I have active programs. Ms. Holiday, I'm not sure if it's possible to bring up our document? It may be easier if somebody can see the responses or our comments.

MS. HOLIDAY: Sure. Let me pull them up.

MR. SHEETZ: Okay. And I wish to thank the ACMUI for establishing a subcommittee to review the NRC's guidance document on RSL and presenting recommendations and the draft report. And while we support most of the recommendations from the subcommittee, there are a couple areas where we think there could be some alternatives made to make the

guidance more relevant to the way the procedure's performed. And to be able to increase patient access and still maintain a high level of safety.

MEMBER ENNIS: Mr. Sheetz, I would just ask you if you would in this conversation, to make clear how this is different than what you presented already. Since we certainly have heard your previous presentation and taken that into consideration.

MR. SHEETZ: Okay. The one comment was already, with respect to the qualifications for the authorized user has already been discussed. With respect to an authorized user being approved for RSL through the 290 pathway, that they be allowed to be the preceptor for another 290 authorized user in the process to become approved. And so once --

MEMBER ENNIS: Yes. We discussed --

MR. SHEETZ: -- an authorized user is approved -- we discussed that. The main point on the authorized user is that both the current NRC guidance document and the ACMUI's subcommittee report states or implies that only an authorized user may implant a seed for RSL.

In 10 CFR 35.27, use of radioactive materials by individuals working under the supervision of an AU is permitted under certain conditions. And

so obviously, the RSL procedure involves implanting a seed, removing a seed, and extracting the seed from the specimen, where the last two procedures are performed by individuals working under the supervision of the AU.

And so, I don't see why a radiologist trained in the procedure cannot implant a seed under the supervision of an AU. There's no other precedent in the current regulations or in Part 35 that requires the use of the radioactive material to only be performed by the AU. So it's unprecedented.

And this is not a therapeutic procedure. It's very similar to radiologists administering, injecting technetium sulfur colloid for sentinel node biopsy procedures. They're not authorized users. They're not nuclear medicine physicians. They're radiologists. And so this is a very similar situation. And radiologists by training --

MEMBER ENNIS: Well, again, the first -- if you just clarify how this is different than what you discussed at the prior presentation.

MR. SHEETZ: Well, I guess I'm trying to clarify and make sure that it was understood on --

MEMBER ENNIS: Okay.

MR. SHEETZ: -- how this procedure was performed. That this procedure is performed by

radiologists who routinely implant clips to mark biopsy sites and wires to localize lesions. And so implanting the seed is a very equivalent procedure. But the radiologist may not qualify as an authorized user under 290, due to when their training occurred and so forth.

MEMBER ENNIS: There are pathways to deal with that.

MEMBER LANGHORST: Hi, this is Sue Langhorst.

MEMBER ENNIS: Yes, Sue.

MEMBER LANGHORST: May I ask a quick question on that? So, the subcommittee believes that the authorized user is the only individual who can implant the seed? No radiation worker or other worker can work under their supervision to do so? Is that your intent?

MEMBER ENNIS: Yes.

MEMBER LANGHORST: Okay. I disagree with that. I agree with Mr. Sheetz on -- we have other individuals who work under the supervision of the authorized user and I think that could happen in this case. Thank you.

CHAIRMAN THOMADSEN: Yes. A common example is, once again, the microspheres. Where the microspheres are usually administered by an

interventional radiologist while the authorized user may be the radiation oncologist or a nuclear medicine physician.

MR. LIETO: Comment please? Not from the Committee.

MEMBER ENNIS: Yes.

MR. LIETO: This is Ralph Lieto again. I would endorse both Sue and Mr. Sheetz also. I mean, your nuclear medicine technologists are not AUs and they're administering activities orders of magnitude greater than this per patient multiple times a day. And they're not an AU.

And at our institution, actually the technologists are the ones that do inject activity for sentinel lymph node studies. They've been trained and they do it under the supervision of an AU, but the AU is not standing next to them when they do it. I think this is just almost a total analogy to those types of situations.

MEMBER ENNIS: I guess the subcommittee will reconsider this issue.

MR. SHEETZ: This is Mike Sheetz again. With respect to the Written Directive, a couple of comments. That I think that the Written Directive should be able to be signed by the individual working

under the supervision of the AU. Should that come to be. I also think that it should be the prescribed activity or activity range per source that's identified under I.

MEMBER ENNIS: Prescribed activity --

MR. SHEETZ: And on top of what --

MEMBER ENNIS: -- as opposed to what?

MR. SHEETZ: As opposed to just activity.

MEMBER ENNIS: And what's the difference?

MR. SHEETZ: Because there are protocols for diagnostic studies that state that this is the activity or this is the activity range that is intended to be administered for the procedure. Again, this is not therapy. And I would contend that the activity range should be allowed as is done in other diagnostic studies.

And the reason for that is we order many seeds and store them for use. And so we don't know what the exact activity is going to be on that day. Well, we can look it up and that's not necessarily what was prescribed. And as stated earlier, we would accept any activity from 50 microcuries to 200 microcuries.

So the exact activity is really irrelevant. And so from a procedural standpoint, it would be more convenient to be able to prescribe this

activity range as is permitted elsewhere.

And then with respect to after implantation, instead of exposure time and time planned for surgery, I would simply say the scheduled surgery date. Since, again, exposure time is not pertinent. It's really when the surgery is scheduled.

MEMBER ENNIS: Any comments for Mr. Sheetz?

MEMBER ZANZONICO: This is Pat Zanzonico, a member of the subcommittee. I think there have been a lot of good points raised in Mr. Sheetz's document and being discussed here. And I think as Dr. Ennis said, they need to be considered carefully and perhaps that best would be done offline rather than trying to make any sort of decision at this time.

VICE CHAIRMAN ALDERSON: Yes. This is Alderson, also a member of the subcommittee. I agree with Dr. Zanzonico.

MEMBER ENNIS: Very good then. Our subcommittee will schedule a follow-up meeting to discuss the issues raised.

CHAIRMAN THOMADSEN: I have -- this is Bruce Thomadsen. And I have one more that I forgot about, but it came out just with what's on the screen right now. And that is, since these are brachytherapy sources, rather than activity, it should be source

[strength].

MEMBER ENNIS: I'm sorry. Bruce?

CHAIRMAN THOMADSEN: Rather than activity or activity range or whatever you end up with with that, it should be source strength.

MR. SHEETZ: Well, again, these are not used for therapy and so we're going to use the manufacturer's rated activity.

CHAIRMAN THOMADSEN: I understand that and the professional organizations are trying to move the manufacturers away from activity altogether and it seems counterproductive to have that written into regulatory guidance here when the activity itself can't really be specified for these sources meaningfully. Just like in the brachytherapy Written Directive, it's not activity, it's source strength actually.

MEMBER ENNIS: That is good. Are there any other comments for discussion?

MR. SHEETZ: I'm not sure if you wanted me to continue through for the other items in the document or you were going to look at them and then evaluate.

MEMBER ENNIS: I mean, if there's something new, I'm happy for you to discuss it please.

MR. SHEETZ: Well, there is in the medical event since you included some sieverts criteria. I

would recommend that under A, IV, and V, or Four and Five, that the medical event definition for RSL included a dose threshold of 0.5 sieverts to tissue at one centimeter so that we bring this back to a dose threshold base, which all other medical events are conditional on.

So this goes back to the previous discussion on modifying the definition of a medical event, which I think is certainly appropriate. Because it's a different procedure and it's covered under 35.1000. But I think --

MEMBER ENNIS: It strikes me as a little --

MR. SHEETZ: -- those criteria --

MEMBER ENNIS: Go ahead.

MR. SHEETZ: But I think the criteria under IV and IV(1) is the administration of the byproduct materials more than 20 percent longer than planned or administration of the byproduct material of more than 20 percent of what's intended.

I think there should be a dose threshold tied to that, i.e. greater than 0.5 sieverts, 20 percent longer than planned if the surgery is scheduled that same day and it goes for more than five hours from what the time was scheduled, it becomes a medical event. So 20 percent is approximately five hours per day.

MEMBER ENNIS: Right. So, but the whole point of this, of course, is not have to do it the same day because it's more convenient. So I don't know that it's a realistic scenario and I do find it a little ironic that we spent a lot of time talking about how there's very little dose and it's not a dose, we're not delivering dose, and yet we want to yet include those now.

MR. SHEETZ: I want to include a dose threshold. I have no problem with the criteria where surgery was delayed or scheduled or the activity implanted was outside of what was prescribed range or outside of plus/minus 20 percent prescribed. But there should be a dose threshold tied to it as there is with any other procedure under medical event.

MEMBER ZANZONICO: This Pat Zanzonico. I just think a dose threshold as a criteria for medical event, not matter how it's parsed, just becomes very problematic in practice. And I think the criteria for medical event are designed to identify where something, for lack of a better term, incorrect was done on the part of the care giver. Like the seed was left in place longer than intended, other than patient intervention. And it just strikes me that a dose threshold just becomes very problematic in practice.

MEMBER LANGHORST: Dr. Ennis, this is Sue Langhorst.

MEMBER ENNIS: Yes, Sue?

MEMBER LANGHORST: In 10 CFR 35.3045, that's report and notification of medical event, I think what Mr. Sheetz is asking for is that the subcommittee include that first statement that all medical events there is a dose threshold that has to be met before it's a medical event. And so it's in the regulations right now and I think that's all Mr. Sheetz is asking is if you're going to include the whole medical event, that you include that part also.

MEMBER ENNIS: Yes. No, I understand that. Although there is, as you, I think, well know, a move to move away from dose when it comes to the definition of medical events in permanent brachytherapy. So I don't know that it's true going forward that all medical events are defined by dose.

As Pat was alluding to, it sounds to me it would be challenging for the team, who doesn't think in dose and has argued so strongly that they don't need to or want to think in dose, to then have to think in dose to decide whether or not something was a medical event and not having the tools to estimate dose potentially. It seems like it's creating problems

that is much cleaner if we avoid.

MR. SHEETZ: But the dose threshold is already there for, say, diagnostic procedures. And so if the dose left in the seed, the 0.5 sieverts or effect dose equivalent dose threshold, then it doesn't rise to the level of a medical event, does not need to be reported.

And so that's all I'm asking for here is that if a certain dose threshold, i.e. 0.5 sieverts to tissue at one centimeter, which is a look-up table. So there's no calculation really on the part of the licensee. It depends on the seed activity and the length of time implanted. So it's a very simply look-up table type of calculation.

MR. LIETO: Comment, please?

MEMBER ENNIS: Yes, please comment.

MR. LIETO: This is Ralph Lieto. I think the problematic part of the medical event definition is IV there which -- because all the other ones are pretty much, I think, very prescriptive in terms of it either happened or it didn't or the activity is what it is or it isn't. It's that time factor that gets into that 20 percent longer.

Is there something that maybe could be done by the subcommittee in addressing maybe events that

might cause delays, therefore the dose would be higher than that 20 percent? Mr. Sheetz alluded to the fact that a surgical schedule delay could put things back several hours or maybe even until the next morning.

Is there some way to maybe address that specific issue? Which gets to, I think, the only part of that definition that gets to a dose issue where you'd need to be concerned about a threshold.

MEMBER ENNIS: In the subcommittee's future meeting, we will certainly discuss this issue. Does anyone have any comments for the moment?

MR. SHEETZ: If I can also state with respect to the source activity verification previously discussed. It's really impractical. Most everybody is using the pre-loaded seeds and needles, coming in a sterile package.

It is impractical to assay this in a dose calibrator or any other type of equipment without breaking sterility. There's always a stainless steel or lead sleeve shielding it, so you'd have to take that off to put it into the dose calibrator or other instrument.

Again, would compromise sterility. Again, in 35.4323B for brachytherapy sources, you're allowed to reference the manufacturer's source

strength or activity. So, why not for RSL?

MEMBER ENNIS: Yes. And of course, then you have a very specific activity, not an activity range.

MR. SHEETZ: Right. I previously presented as far as imagining being able to substitute for the survey. I see the Committee feels strong that the survey be performed and the imaging should not be able to substitute for that.

I would still contend that there's not going to be confusion in interpreting the image with respect to a seed or a clip. Radiologists are trained and very adept at identifying a seed and can certainly differentiate between the two.

And in fact, if you use a sodium iodide or GM meter in the OR environment, where there is technetium, you would be confused because you couldn't tell whether it was activity coming from technetium or from the iodine-125 seed. So I would ask you reconsider also that the imaging may be satisfactory to replace the survey.

And then also with respect to the instrumentation, the instrument that is used in the operating environment by the surgeon is a gamma probe. Which does have the capability to window and

discriminate between different energies and different isotopes. And that's the instrument really of choice for doing the survey in the OR environment as far as identifying the seed and make sure it's in the tissue specimen and not in the cavity.

And then this instrument that does not fit the standard annual calibration procedures. And so in my previous presentation, it was the gamma probe that I was looking to have exempt from an annual calibration because it really doesn't get calibrated. It has its own self-check every time you turn it on. I think the sodium iodide or GM detector should still be subject to annual calibration requirements. And that concludes my comments.

MEMBER ENNIS: Thank you, Mr. Sheetz. Any comments from anyone else? Okay. Hearing none, Chairman Thomadsen?

CHAIRMAN THOMADSEN: Yes. Right

MEMBER ENNIS: Our subcommittee report appears to be done.

CHAIRMAN THOMADSEN: Thank you very much. And I would hope that your committee could report back at the fall meeting. Does that seem reasonable?

MEMBER ENNIS: Yes.

CHAIRMAN THOMADSEN: Very good. Do we have

other items of business that anybody wishes to bring up? Hearing none, thank you very much for your report. Thank you very much for everybody's participation. And we will see you in the fall.

(Whereupon, the above-entitled matter went off the record at 4:37 p.m.)

Community Oncology Alliance

Statement to be read at the Teleconference of the Nuclear Regulatory Commission - Advisory Committee on the Medical Use of Isotopes (ACMUI) on June 16, 2015 at 2:00 pm

The Community Oncology Alliance (COA) is non-profit organization dedicated to cancer patients and providers in the community oncology setting. COA represents over 7,000 community oncologists and is deeply concerned about barriers to patient access to lifesaving treatments. As part of this rulemaking, the NRC has specifically requested comments on whether its regulations "***discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how***." Our members support the NRC's efforts to update its regulations to reflect changes in clinical practice and advances in medical technology.

This rulemaking presents an opportunity for the NRC to improve access to potentially life-saving anti-cancer treatments, by addressing a shortage of Authorized Users (AUs) able to administer these treatments. COA has been following the NRC's current rulemaking process and submitted a comment letter to the NRC last fall. In February, COA attended and spoke at the public meeting held by the NRC on alpha- and beta- emitters training and experience requirements. COA is pleased to share its thoughts with ACMUI on this topic today.

The NRC's regulations create a shortage of authorized users able to administer therapeutic radiopharmaceuticals. Under current regulations, as a drug administered parenterally and used primarily for its beta radiation characteristics, therapeutic radiopharmaceuticals can only be administered by an Authorized User who has met the training and experience requirements set forth in 10 CFR 35.396. These requirements involve either board certification or 700 hours of training and experience specifically in radionuclide handling.

The hematologists and oncologists who typically prescribe therapeutic radiopharmaceuticals outside of the hospital setting often do not have the training and experience required to meet the AU requirements and do not work at facilities that have such AUs. They have extensive training and experience, and are frequently board certified, but in different specialized fields.

The effect of the regulations is to severely limit patient access to a very safe and effective treatment. Certain patient populations are particularly negatively affected by a lack of AUs for therapeutic radiopharmaceuticals. Access is particularly difficult in rural geographies or other areas where patients must travel great distances to their primary oncologist, and even farther to a specialized facility with an AU.

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. The experience of Drs. Mace and Cultrera, and many other community oncologists, demonstrate the burden that the current regulations place on practitioners seeking to provide patients with these treatment options. Dr. Mace, with 80 hours of training and experience in the safe handling of radionuclides acquired before the current regulations went into effect, has been safely administering these treatments to patients in need for a decade. Dr. Cultrera, who has worked with Dr. Mace, is unable to administer these treatments because she cannot realistically complete 700 hours of additional training and experience given the demands of her practice. Even though

these treatments might be the best option for some of her patients, she feels that the burden placed on patients requiring them to travel great distances to reach an Authorized User is too high. These patients are frequently frail and elderly, and traveling such distances can be taxing.

Drs. Mace and Cultrera have proposed 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. COA would support this reasonable and limited proposed change in the regulations.

COA recognizes the difficulty of balancing safety considerations with preserving patient access to medical care and encourages ACMUI to consider this proposal that could significantly improve patient access to lifesaving treatments in the community oncology setting.

CORAR

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Michael J. Guastella, MS, MBA
Executive Director

Via email June 11, 2015

Ms. Sophie Holiday
Health Physicist/ACMUI Coordinator
U.S. Nuclear Regulatory Commission (NRC)

Written Statement of
The Council on Radionuclides and Radiopharmaceuticals
Advisory Committee on the Medical Use of Isotopes (ACMUI) - June 16, 2015 - 2:00 pm

The Council on Radionuclides and Radiopharmaceuticals (CORAR) is an organization whose members include manufacturers and distributors of diagnostic and therapeutic radiopharmaceuticals regulated by the Nuclear Regulatory Commission (NRC). Our members support the NRC's efforts to update the training and experience regulations as part of the Medical Use of Byproduct Material—Medical Event Definitions, Training and Experience, and Clarifying Amendments Final Rule. The proposed regulation states that "***the NRC is proposing changes to update its regulations to address technological advances and changes in medical procedures***."

CORAR has participated in the NRC's rulemaking process by submitting a written comment letter last fall and participating in the NRC's public meeting in February on the topic of the training and experience requirements for alpha- and beta- emitters. CORAR appreciates the opportunity to provide comments to ACMUI on this topic.

CORAR's members include the manufacturers and distributors of the currently marketed products Xofigo® (Radium Ra 223 dichloride) and Zevalin® (ibritumomab tiuxetan), as well as other therapeutic products in the research and development stage. We have heard from our members, as well as providers, that the current regulatory framework has limited the number of hematologists and oncologists who can become Authorized Users licensed to administer alpha-or beta-emitting radiopharmaceuticals like Xofigo and Zevalin. Before the 2002 rulemaking went into effect, hematologists and oncologists who sought to administer beta-emitting radiopharmaceuticals such as Zevalin could become licensed to do so after completing 80 hours of classroom and laboratory training. Under the current framework, the NRC created a licensure pathway under which, with 700 hours of training and experience, physicians would be "authorized to elute generators and prepare radioactive drugs, as well as to administer a wide variety of radionuclides requiring written directives." As the presenters have demonstrated in their materials, the additional training and experience requirements have severely limited patient access to these treatments.

In their comment letters and presentations at the February public meeting, Doctors Mace and Cultrera and Spectrum Pharmaceuticals have proposed that the NRC finalize a training and experience requirement of 80 hours for a limited scope authorization to administer alpha- and

beta-emitters that are parenteral injections prepared at a licensed commercial or institutional radiopharmacy. The training and experience requirement would also include relevant work experience and case administration.

CORAR would support a modification to the NRC's regulations that would set the training and experience requirement at an appropriate level for this limited class of products. These products are prepared in a licensed commercial or institutional radiopharmacy, delivered in a patient-ready dose, can easily be administered in the hematologist/oncologist physician office setting, have an excellent safety record, and present relatively few risks.

CORAR believes that agency precedent exists for the 80 hour requirement, which was available to physicians prior to the 2002 rulemaking and is currently available to physicians seeking to administer I-131, a gamma-emitting product with a similarly low risk of misadministration and solid safety profile.

CORAR recommends that ACMUI consider whether this or a similar limited authorization could be incorporated into the NRC rulemaking process to address the shortage of authorized users able to administer these products and the burden on patient access to treatments. We believe it is important not only for access to current products like Zevalin and Xofigo, but also for continued innovation and development of new targeted anti-cancer therapies. Based on advances in drug development and clinical practice over the past decade, we believe it is appropriate that the training and experience requirements for alpha- and beta- emitters should be modified.

Sincerely,

Michael J. Guastella, MS, MBA
Executive Director

SPECTRUM™
PHARMACEUTICALS
Redefining Cancer Care

Statement of
Lee Allen, M.D., Chief Medical Officer, Spectrum Pharmaceuticals
Advisory Committee on the Medical Use of Isotopes - June 16, 2015 - 2:00 pm

Introduction

Spectrum Pharmaceuticals appreciates the opportunity to present to the Advisory Committee on the Medical Use of Isotopes on the appropriate training and experience requirements for alpha- and beta-emitters. Spectrum submitted a comment letter on the NRC's proposed rule last November and presented at the February public meeting on this topic.

Spectrum Pharmaceuticals is a company whose mission is to develop biopharmaceutical therapies for patients with unmet medical needs, with a focus on oncology/hematology products. Our product Zevalin is a safe and effective radioimmunotherapy treatment for non-Hodgkin's lymphoma (NHL) patients.

The current NRC rulemaking presents an opportunity for the Commission to update the training and experience requirements for physicians that administer potentially life-saving anti-cancer beta emitter products such as Zevalin.

Patient Access to Beta-Emitter Therapies is Limited

As part of this rulemaking, the NRC has specifically requested comments on whether its regulations "*discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how*." The NRC's current regulations have had the unintended consequence of severely limiting patient access to Zevalin and a prior radioimmunotherapy that has been withdrawn from the market due to a lack of Authorized Users to administer the treatment.

There is an urgent need to address the shortage of Authorized Users able to administer Zevalin. Since the 2002 rulemaking went into effect, the number of patients treated with Zevalin has declined dramatically. Current annual treatments in the U.S. are less than half than when initially approved in 2002 and only 25% of the peak usage in 2005, when the training requirement increases went into effect. Spectrum is the third company to offer Zevalin as a treatment option, and it may soon become financially unsustainable to continue to market the product if the access issues are not resolved.

NHL is typically treated by hematologists and oncologists in the hospital outpatient or physician office setting. While these hematologists and oncologists are board certified physicians, the demands of their practice do not permit them the time to complete an additional 700 hours of training and experience in order to administer Zevalin. Spectrum knows of only 5 hematologists or oncologists who are Zevalin AUs, all of whom were trained prior to the increased training requirements of the 2002 rulemaking. In the academic medical

center setting the burden on patients is minimized, as a hematologist or oncologist can still recommend the treatment, sending the patient to an Authorized User located at the same facility to receive the treatment. But in the community oncology setting, a hematologist or oncologist might have to send a patient a great distance to an unfamiliar setting in order to reach an Authorized User willing and able to administer the treatment. This is particularly difficult for a patient population that is often older and disabled. The burden can be so great in rural areas that physicians are discouraged from recommending the treatment.

Recommendation

Spectrum has requested that the NRC address this shortage in its final rule by establishing an appropriate training and experience requirement for a limited authorization to administer alpha- and beta-emitters that are delivered intravenously in a patient-ready dose prepared at a licensed radiopharmacy.

The proposed training and experience requirement would include 80 hours of classroom and laboratory training along with relevant case administrations and work experience similar to the requirements for clinicians prior to the 2002 final rule. This alternate pathway would provide hematologists and oncologists with the necessary training to safely administer this product. Spectrum believes this pathway is appropriate based on the excellent safety record of the product, the low risk of therapeutic misadministration, and the burden placed on patients who have to travel far distances to unfamiliar settings if their primary treating hematologist or oncologist is unable to administer the treatment. The proposed limited authorization would be solely for the administration of this limited class of low risk alpha- and beta-emitters; it would not include the broader authorization to elute generators, prepare radioactive drugs and administer the wide variety of radionuclides requiring written directives for which 700 hours of training and experience is currently required.

A reduced training and experience requirement is appropriate for products like Zevalin that present few risks due to their excellent safety records, straightforward application procedures, and low exposure levels. Compounding and preparation of Zevalin is conducted at a licensed specialty radiopharrnacy for the individual patient and delivered to the prescribing physician as a patient-ready dose in a pre-filled syringe. The product has a short half-life and is administered to the patient within 8 hours of radiolabeling. The maximum dose of Y -90 permitted per the product's label is 32 mCi (1184 MBq). Zevalin is administered in an intravenous injection, as part of a therapeutic regimen that has three parts over 7-9 days: two infusions of rituximab and one injection of Yttrium-90 (Y-90) Zevalin, which must be given within 4 hours of the second dose of rituximab. Rituximab is used to reduce the number of B-cells in the blood and Y-90 Zevalin is given to treat NHL. The safety record of Zevalin is impeccable. Over the course of more than 10,000 administration, there have been only three reports to the NRC of radiation safety issues, none of which occurred at the time of administration or resulted in patient harm.

There is precedent for the NRC permitting a reduced training and experience requirement for products with excellent safety records and low risks of misadministration. Prior to the 2002 rulemaking, hematologists and oncologists could became authorized users able to administer beta-emitting radiopharmaceuticals such as Zevalin with 80 hours of classroom and laboratory training. Physicians such as Dr. Joseph Mace, who achieved authorized user status prior to that time, have been safely administering Zevalin for years.

Additionally, as part of the 2002 rulemaking, the NRC retained an alternate pathway of 80 hours of training and experience for the oral administration of I-131. The NRC noted this was appropriate for a limited scope authorization, one which did not encompass the preparation of radioactive drugs using generators and reagent kits. Spectrum believes a similar pathway is appropriate for the administration of Zevalin, a product with an excellent safety record and even fewer post-administration considerations than I-131.

Conclusion

Spectrum strongly urges ACMUI to consider whether a limited scope authorization could be incorporated into the NRC's final rulemaking that would address the authorized user shortage and the patient access issues by creating a more appropriate training and experience requirement for the administration of alpha- and beta-emitters that are delivered intravenously in a patient-ready dose prepared at a licensed specialty pharmacy.

Comments to the ACMUI Sub-Committee Report on Radioactive Seed Localization Guidance for Non-Palpable Lesions

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Introduction

A presentation was given at the March 19, 2015 ACMUI meeting on the "Radiation Safety and Regulatory Issues for Radioactive Seed Localization (RSL) of Non-Palpable Lesions" to recommend certain revisions to the current NRC licensing guidance document on RSL in order to make it more relevant to the way the procedure is performed, make it less burdensome for licensees to establish an RSL program, and to allow for increased access to this beneficial procedure to patients. We wish to thank the ACMUI for promptly establishing a sub-committee to review the NRC guidance document and for its recommendations presented in its draft report submitted on May 29, 2015. While I support most of the recommendations contained in the sub-committee draft report, the following comments and recommendations are provide to identify areas where alternative revisions could be made to make the guidance more relevant to the way the procedure is generally being performed, and increase patient access while still maintaining a high level of safety.

Qualifications for Authorized User

1. In the current guidance, an individual who meets the criteria in 35.290 must also have work experience under the supervision of an individual who meets the criteria in 35.490. This required work experience should be able to be obtained under the supervision of a preceptor who is already approved as an AU through the 35.290 pathway and not just the 35.490 pathway, since this procedure is not typically performed by a radiation oncologist. The following language is recommended:

    > An Authorized User (AU) for RSL should meet the following training and experience requirements:
    >
    > Criteria in 10 CFR 35.490 or equivalent Agreement State regulations; or
    >
    > Criteria in 10 CFR 35.290, or equivalent Agreement State regulations, including supervised work experience under the supervision of an AU and preceptor **approved for RSL** on an NRC or Agreement State license. Training and supervised work experience should include the following: ……"

2. Both the current NRC guidance and the ACMUI sub-committee report state or imply that only an AU may implant a seed for RSL. In 10 CFR 35.27, the use of radioactive material by individuals working under the "supervision" of an AU is permitted under certain conditions. The RSL procedure involves three different components:
    a. Implanting the radioactive seed in a patient under mammographic or ultrasonic guidance by a radiologist,
    b. Surgically removing the target lesion/tissue and seed from the patient by a surgeon, and
    c. Removing the seed from the tissue specimen by a pathologist or pathology assistant.

Therefore, many, if not all, of the procedures involved with RSL are performed by individuals working under the "supervision" of the AU. This should also include a radiologist who is not an AU, but has the appropriate training and experience to implant seeds under the supervision of an AU. Radiologists by training routinely implant clips to mark biopsy sites and wires to localize lesions for surgery using needles under mammographic or ultrasonic guidance. Implanting a radioactive seed with a needle is an equivalent procedure. This is similar to a radiologist performing a sentinel node injection of Tc-99m sulfur colloid under the "supervision" of the nuclear medicine AU. It is also similar to a thoracic surgeon implanting an I-125 seed vicryl mesh in the lung or an ophthalmologist implanting an I-125 seed eye plaque under the "supervision" of a radiation oncologist. There is no other precedent in the current regulations or 35.1000 licensing guidance that requires a procedure involving the use of radioactive material to only be performed by the AU. Therefore, there is no justification in requiring this for RSL based on the level of risk associated with this procedure. It is recommended that the wording "the radioactive seed will be implanted by or under the supervision of an AU" be used.

Written Directive

We still contend that this procedure does not meet the requirements for a written directive as identified in 35.40(a), as the dose to tissue from the seed(s) will not reach therapeutic levels unless it is left in for several weeks. However, working with the subcommittee's new definition of written directive for RSL and not the defined under 35.40(b)(6) for manual brachytherapy, the following revisions are recommended:

> A WD must be dated and signed by an AU **or individual working under the supervision of the AU** before the administration of I-125 or Pd-103 for seed localization. The WD must contain the patient or human research subject's name and the following information:
>
> (i) Before implantation: implantation site, the radionuclide, and **prescribed** activity **or activity range** per source; and
>
> (ii) After implantation, but before completion of the procedure: the radionuclide, implantation site, number of sources, ~~and~~ total activity implanted, and ~~exposure time/time planned before~~ **scheduled** surgery **date**.

Medical Event

It is recommended that the criteria under (a) (iv) and (v) from the subcommittees definition of Medical Event for RSL include a dose threshold of 0.5 Sv (50 rem) to tissue at 1 cm from the seed to be consistent

with the current dose threshold for medical events defined under 35.3045. Note that the distance of 1 cm was chosen because the tissue being removed from the patient will be the 1 cm or more sphere of tissue surrounding the implanted see and dose to that tissue is irrelevant.

Safety Precautions

1. Verification of Source Activity

   The subcommittee states that independent verification of source activity by the recipient is important. If a licensee uses the prepackaged sterile seeds in needles, then source activity verification using a dose calibrator is impractical, as it will compromise sterility and the needle and shielding sleeve will interfere with the direct measurement. It is recommended that the requirement be worded to read: "The activity of sealed sources will be determined prior to each patient implant, either through direct measurement or based on manufacturer's indicated activity after correcting for decay". This is similar to the allowance to use the source manufacturer's measurements for brachytherapy source activity in 35.432(3)(b).

2. Surveys

   The subcommittee states that a survey using a NaI or GM meter is required to verify seed removal and that a specimen radiograph is not acceptable to substitute for the survey because of the potential confusion if the patient also had placement of surgical clips in the same area where the seed was implanted. Seeds are routinely placed next to a clip that was implanted during the biopsy to localize the lesion. Radiologists by training are very adept at differentiating a clip from a seed on a radiographic image. There is more likely to be confusion from a survey performed with a NaI or GM meter in the OR following seed removal when the procedure also involves a sentinel node biopsy using Tc-99m Sulfur Colloid, as these instruments cannot discriminate between the photon energies of I-125 and Tc-99m. It is recommended that a radiographic image taken of the specimen after it has been surgically removed from the patient (which is routinely performed to confirm the seed location and tissue margins) be allowed to substitute for a radiation survey. Similarly, a confirmatory mammographic or ultrasonic image should be allowed to substitute for a radiation survey using a GM or NaI meter following seed implant as it will visually confirm the seed, its location, and if it was damaged.

Survey Instrumentation

It should be recognized that a gamma probe (e.g. Neoprobe Gamma Detection System) is used by the surgeon to guide the excision of the seed and surrounding tissue. This instrument has windowing capabilities and can discriminate between the photon energies of I-125, Tc-99m, and several other radionuclides. These intraoperative probes are a far superior device for determining if the implanted I-125 or Pd-103 seed has been removed from the patient and remain within the removed specimen as compared to any portable NaI or GM meter. The excised tissue is routinely surveyed by the surgeon with the gamma

probe to confirm the presence of the radioactive seed, and the surgical site (cavity) where the tissue was removed is surveyed to confirm the absence of the radioactive seed. It is also used by the pathologist to locate the seed in the tissue specimen and confirm its removal. Most gamma probes do not require any routine (annual) calibration. There is only a system check when the instrument is turned on for use. If the ACMUI strongly believes that a post-surgical removal survey is required and that a specimen radiograph is not adequate proof of removal, then we would recommend acceptance of the gamma probe as an acceptable instrument for post removal surveys and should discourage the use of a NaI or GM detector. As such, the exemption for an annual calibration recommended by the subcommittee should only apply to this instrument and not a NaI or GM meter.