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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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FALL 2016 MEETING

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FRIDAY, OCTOBER 7, 2016

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The meeting was convened in Room T-02B3 of Two White Flint North, 11545 Rockville Pike, Rockville, Maryland, at 8:00 a.m., Philip O. Alderson, M.D., ACMUI Chairman, presiding.

MEMBERS PRESENT:

PHILIP O. ALDERSON, M.D., Chairman

PAT B. ZANZONICO, Ph.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

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

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

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

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

LAURA M. WEIL, Patients' Rights Advocate

NON-VOTING: RICHARD GREEN

NON-VOTING: ZOUBIR OUHIB*

*via telephone

NRC STAFF PRESENT:

DANIEL COLLINS, Director, Division of Material Safety, State, Tribal and Rulemaking Programs

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

DOUGLAS BOLLOCK, ACMUI Designated Federal Officer

SOPHIE HOLIDAY, ACMUI Alternate Designated Federal Officer and ACMUI Coordinator

MARYANN ABOGUNDE, NMSS/MSTR/MSEB

SAID DAIBES, Ph.D., NMSS/MSTR/MSEB

CLIFF DOUTT, NRR/DLR/RASB

MICHAEL FULLER, NMSS/MSTR/MSEB

VINCENT HOLAHAN, Ph.D., NMSS/MSTR

ESTHER HOUSEMAN, OGC/GCLR/RMR

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

ANGELA MCINTOSH, NMSS/MSTR/MSEB

TANYA PALMATEER OXENBERG, Ph.D., RES/DSA/RPB

GRETCHEN RIVERA-CAPELLA, NMSS/MSTR/MSEB

REANN SHANE, COMM/OCMJB

MICHELLE SMETHERS, NMSS/MSTR/MSEB

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

TORRE TAYLOR, NMSS/MSTR/RPMB

JENNY WEIL, OCA

MEMBERS OF THE PUBLIC PRESENT:

BETTE BLANKENSHIP, American Association of Physicists in Medicine (AAPM)

KATHLEEN BRILL, Spectrum Pharmaceuticals

SUE BUNNING, Society of Nuclear Medicine and Molecular Imaging (SNMMI)

BRIAN CAREY, Spectrum Pharmaceuticals

ASHLEY COCKERHAM, Sirtex

JENNIFER CULTRERA, Florida Cancer Specialists

ROBERT DANSEREAU, New York State Department of Health

WILLIAM DAVIDSON, University of Pennsylvania

ALBERTO DEJESUS, Spectrum Pharmaceuticals

MORTON DIAMOND, NSU Physician Assistant Program

JENNIFER ELEE, Conference of Radiation Control Program Directors (CRCPD)

BRIAN ERASMUS, BTG

FRANK FACCHINI, BTG

LYNNE FAIROBENT, American Association of Physicists in Medicine (AAPM)

STEVEN FEIN, Miami Cancer Institute, Member of American Society of Hematology

SANDRA GABRIEL, International Atomic Energy Agency

WENDY GALBRAITH, University of Oklahoma College of Pharmacy

MUNIR GHESANI, NYU Medical Center

IRA GOLDMAN, Lantheus Medical Imaging

MICHAEL GUASTELLA, Council on Radionuclides and Radiopharmaceuticals, Inc (CORAR)

BONNIE HAMILTON, BTG

JAMES HARVEY, NorthStar Medical Radioisotopes, LLC

GEORGIA HEARN, American Society of Nuclear Cardiology (ASNC)

NICKI HILLIARD, University of Arkansas for Medical Sciences

CLARE JENNINGS, Bayer Healthcare

JASON KELLY, Texas Department of State Health Services

KSENIJA KAPETANOVIC, American Society for Radiation Oncology (ASTRO)

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

JOSEPH MACE, Florida Cancer Specialists

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

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SHAHIN NASSIR KHANI, Walter Reed National Military Medical Center

ABRAHAM OLER, Spectrum Pharmaceuticals

MARK PAULSON, Wisconsin Department of Health Services

ERIC PERRY, Kentucky Department for Public Health

MICHAEL PETERS, American College of Radiology

KAREN SHEEHAN, Fox Chase Cancer Center

DEVON REED, United States Army

GLORIA ROMANELLI, American College of Radiology ACR)

RIAD SALEM, BTG

KARL SCHWARTZ, Patients Against Lymphoma

MICHAEL SHEETZ, University of Pittsburgh

RAJESH SHROTRIYA, Spectrum Pharmaceuticals

DAVID SMITH, Medstar Georgetown University Hospital

BRUCE THOMADSEN, Center for the Assessment of Radiological Sciences (CARS)

CINDY TOMLINSON, American Society for Radiation Oncology

KARL VON AHN, Texas Department of State Health Services

KARA WEATHERMAN, Purdue University

KRISTINA WITTSTROM, University of New Mexico

ANDREW ZACH, House Committee on Energy and Commerce

C-O-N-T-E-N-T-S

P R O C E E D I N G S

8:03 a.m.

CHAIRMAN ALDERSON: Thank you. All right, we're ready to open the Friday, October 7th session of the ACMUI, and the first item on the agenda today is Discussion of Yttrium-90 Microspheres Brachytherapy Licensing Guidance. It will be presented by Katie Tapp and Darlene Metter.

DR. TAPP: Thank you, Dr. Alderson. Good morning.

This morning, I'm going to start with a discussion on a draft revision to the Yttrium-90 Microspheres Brachytherapy Licensing Guidance, Revision 10. This is a revision that we sent over -- this is a draft revision that we sent over to the ACMUI for their consideration and recommendations. I want to stress that this document sent over to the Working Group -- or to the ACMUI, is a draft, and its sole purpose is for the NRC to solicit comments from the ACMUI and their recommendations.

This is not a final document at this time. It is not used for licensing at this time at the NRC. Therefore, the NRC has not issued this document as a publically available document, but I'd like to discuss some of the elements of this document today to kick off

what the ACMUI is going to be discussing here.

First, I would like to start off with the Agreement State and NRC Working Group members. I am the co-chair of this Working Group, and Bob Dansereau from New York State is my Agreement State co-chair. Penny Lanzisera is from Region I of the NRC. Victor Diaz is from New Mexico, and Sara Forster is from Region III.

The Working Group task that we considered during this draft revision to the document was the training and experience pathway, specifically related to the manufacturer-provided training pathway, known as Pathway 2. We looked at the waste disposal section, and then potentially adding information regarding autopsy and cremation. I am going to go over each of these topics one at a time.

First, I wanted to start with the training experience. The current and proposed revision to the licensing guidance has two components to training. First, it has a radiation safety training and experience. This is including the classroom training, the didactic training, basic training during residency, and other experience outside of specific Y-90 hands-on training.

Then there is an additional component on

specific clinical experience to yttrium-90 microsphere therapy, including the operation of the delivery system, safety procedures, and the clinical use. In this component, there are -- the applicant should have three supervised in vivo cases. These three supervised in vivo cases can be done in two different ways.

The first is if the applicant could have these cases done before they apply to be added on the license, and the supervision coming from an authorized user already on a license. This pathway is known as Pathway 1. The second pathway is the applicant completes all their training, and then they be asked to be added to a license. They are added to a license, and then they receive the three in vivo cases from a manufacturer representative. This is the current training experience guidance in the document.

Pathway 2 was introduced when there was limited numbers of authorized users that could provide supervision. This manufacturer supervision is a unique pathway specific to yttrium-90 microspheres and is not found in other 10 CFR 35 modalities.

The Working Group wanted to, in the draft revision, to ask the ACMUI to consider the potential to remove Pathway 2 following two years of issuance of

Revision 10. The reasoning that the Working Group was considering this was after 10 years of licensing authorized users for these microspheres, there's more AUs available today, and we believe they would have enough to provide the supervision.

With this, we wanted to make sure there was adequate time for the industry to adapt. We know this would be a substantial change, so we are recommending a two-year grace period where the Pathway 2 would still be in the guidance and available, specifically spelled out in the guidance document.

During the grace period and another recommendation from the group was to recommend a six-month limit for those applicants who got added to a license using Pathway 2, a six-month limit for them to complete their three supervised in vivo cases after being added. This would avoid substantial time difference between their training, their in vitro training before they would have their first hands-on case in a clinic. We understand that there may be cases where patient load wouldn't allow for this, so we want to highlight in the document that there should be -- that this should really be reviewed by the license reviewers, and the six-month limit is a recommendation, but should specifically be reviewed on a case-by-case

basis.

The second topic that the Working Group was considering was long-lived contaminants in the waste and disposal section. In 2007, the NRC was notified that there's long-lived impurities in the microspheres. We issued an information notice at that time that gave information regarding these impurities. The Working Group considered updates that were provided and new information and added that into the licensing guidance for ACMUI recommendation.

Finally, we looked at the addition of autopsy and cremation, if we wanted to add additional information. The current draft, we were looking at adding just a reference to NUREG-1556, Volume 9 and NCRP Report Number 155 because we believe there was no substantial safety issue beyond -- specific to the yttrium-90 beyond what would be found in permanent implants, so we're referencing reports that have this or are also in the draft process, that are adding information on the autopsy and cremation. We didn't believe there were specific safety issues that would be unique to yttrium-90 that it should be spelled out separately.

I now would like to turn it over to Dr. Metter to hear the recommendations and the ACMUI

subcommittee's thoughts.

MEMBER METTER: Well, good morning, and this morning, I will be presenting the ACMUI Subcommittee Report on three draft guidance issues in the Draft Y-90 Microsphere Brachytherapy Licensing Guidance, Revision 10.

But before I start, I would like to thank the work of my subcommittee members Mr. Frank Costello, Dr. Susan Langhorst, and Dr. Christopher Palestro.

So we know that the liver is a common site of primary and secondary malignancies that are traditionally managed by surgery or various routes of chemotherapy. In the last several years, the introduction of intra-arterial brachytherapy implants, specifically radioembolization of yttrium-90 impregnated resin or glass microspheres, have been used to treat these primary and secondary malignancies and really has emerged as a very important therapy in the management of these patients.

Y-90 microspheres are regulated under 10 CFR 35.1000, Other Medical Uses of Byproduct Material or Material from Byproducts. The NRC licensing guidance on Y-90 microspheres brachytherapy sources and devices draft revision is near complete. As you heard, the ACMUI was tasked to comment on three draft

guidance issues that Katie Tapp nicely reviewed, and these are: one, to consider the elimination of Pathway 2, the manufacturer AU training; second, update the waste and disposal section; and third, review the Y-90 radiation safety issues in autopsy and cremation.

So let's look at issue one, the authorized user training and experience. The draft guidance delineates first an update of the AU qualifications for Y-90 microtherapy; second, the didactic clinical and the clinical work experience, specifically, the three hands-on in vivo cases which can be accomplished in one of two pathways. The first pathway is supervision by an authorized user, and the second pathway is supervision by a manufacturer representative or proctor.

So again, to review, Pathway 1, the AU training pathway, where one or more physician AUs for a specific Y-90 microsphere therapy supervises an individual for the training and clinical experience of three hands-on in vivo cases for which the specific Y-90 microtherapy is being sought. After completion of the third case, the training is complete. The individual can then be listed on their license and perform this therapy on patients for this specific therapy on their own.

The manufacturer training, Pathway 2: a Y-90 microsphere manufacturer supervises three in vitro simulated Y-90 therapies for the specific AU therapy being sought. They also provide certain uniform didactic content, and it is very standardized, very thorough review of the therapy.

The individual then goes back to their home institution and is placed on the radioactive license for that specific therapy, and then the individual also commits that the first three in vivo-specific Y-90 therapy cases for which the approval is being sought must be supervised by the manufacturer proctor, or representative and completed within six months after the date of license amendment. The individual then can perform the therapy on their own.

So as you heard with Katie the history of Pathway 2, in 2004, the NRC licensed AU for Y-90 brachytherapy, but there were few AUs available to provide the clinical supervision. So in 2008, Pathway 2 was created.

So as you all know, the current issue is elimination of Pathway 2, and there are pros and cons for this. So let's review the rationale for eliminating the pathway. So after over 10 years, or over a decade of authorizing authorized users via

Pathway 1 and Pathway 2, there are sufficient AUs to meet the clinical demand and provide the required clinical experience to train future authorized users.

Licensees that list AU on their license do not differentiate AUs who have completed the three clinical cases through Pathway 1 or Pathway 2 from those AUs in Pathway 2 who have not. Tracking AUs in Pathway 2 who have or have not completed the clinical experience is difficult and at times impossible, and if you look at the NRC state regulatory authority of the licensees, you see there is far less NRC licensees than there are agreements.

Manufacturer AU proctors are not physicians. There are some physicians, but they may or may not be physicians, and Pathway 1 AU training will be more clinically based on the AU physician proctor's direct clinical experience. And when these three cases are complete, the physician seeking the AU status is then listed on the radioactive license and then can perform these cases on their own.

The NRC is proposing a multi-year delayed removal of Pathway 2 with a subsequent deadline date. Individuals may enter Pathway 2 up until this deadline, which, as you heard, is a two-year grace period.

The rationale for not eliminating Pathway

2: how do we know we have sufficient AUs? Are there enough AUs to provide the training, clinical experience, and to provide the resources to train future AUs? What about access? Are there enough AUs, particularly in the rural communities without AUs? Could this have a negative effect on patient safety and access to care?

Pathway 2 provides a uniform standard of training, and with the Pathway 2 elimination, there may be no uniform training standard and potential gaps in training for future authorized users. Patients may not receive timely care, and there may be a potential lack of cooperation between networks and institutions to train authorized users. And in fact, authorized users may say, look, I am too busy; I can't supervise you for the clinical cases.

So the subcommittee reviewed the pros and cons of rationales for eliminating Pathway 2 and came up with the following comments: if there is a sufficient need for Y-90 microsphere therapy, sites performing a large number of therapies might offer mini-fellowships, and this includes didactic and the clinical training experience, and they may also even partner up with the manufacturer current uniform training standard.

If a current AU for Y-90 microspheres joins a new site, their prior training and experience will apply to that site, and they won't need further training. The subcommittee also encourages current AUs for Y-90 microsphere therapy to drive the proctoring experience in their community.

Issue two, waste and disposal: the production of Y-90 varies, being it generator- or reactor-produced, and with that, it results in the mixture of impurities with varying half-lives. The current guidelines are as follows: for disposal of byproduct material with the half-lives less than 120 days, that is short-lived, and you are allowed to decay these in storage. The concern, however, is for the long-lived half-life agents, such as greater than 120 days, and these cannot be decayed in storage, and these would be byproduct materials such as europium-152, -154, cobalt-60, and strontium-90.

Licensees need to be aware of these long-lived impurities, which can increase with partially used or unused vials. Long-lived impurities do present disposal issues, and the subcommittee supports -- although impurities may not be listed on an NRC license, licensees are responsible to ensure the microspheres are handled and disposed of in accordance

with 10 CFR Part 20 and 35 requirements.

So the waste and disposal options are two: if your impurities are short-lived, you are allowed to decay this in storage. If they are long-lived, they need to be returned, used or unused vials, to the manufacturer if the manufacturer is authorized to receive them. If the manufacturer is not authorized to receive them, you need to transfer it to a recipient authorized to receive the Y-90 microsphere vials.

So in the end, if you have measurable long-lived impurities, you need to return the vial or transfer it to an authorized recipient. However, the good news is that most licensees are not detecting these impurities, and measurable long-lived impurities is an uncommon problem. Therefore, the majority of material can be decayed in storage. The subcommittee supports the NRC draft and this additional guidance on waste disposal.

Issue three, autopsy and cremation: we know that Y-90 microspheres is a unique device. It's the implantation of millions of permanent brachytherapy implants, and these are not biodegradable. Yttrium-90 has a half-life of 64 hours. It's a pure beta emitter. It has a maximum energy of 2.27 MeV, maximum tissue reach of 11

millimeters, and it is very small in size, depending on whether it is glass or resin.

So the current guidelines are really related to the autopsy personnel. Radiation exposure can be increased with the handling of radioactive autopsy material that is impregnated with Y-90 microspheres. On the death of a Y-90 therapy patient, the RSO and the patient's authorized users need to be notified upon the death, and if an autopsy is requested, the RSO must approve the autopsy. During the autopsy, ALARA principles need to be adhered to and assessed and directed by the RSO.

So, the subcommittee agrees with the current guidelines with the additional comment. Deceased Y-90 microsphere patients do not generally present a radiation hazard to those individuals handling the deceased body. However, if the autopsy is performed within two to four weeks after the Y-90 therapy, this may call for additional precautions to manage the autopsy radiation workers' exposure. Additionally, if cremation occurs within two to four weeks after the Y-90 therapy, we may also require additional precautions, and potentially beyond that, due to long-lived contaminants.

So in summary, the ACMUI Subcommittee

recommendations are the following: considering the elimination of Pathway 2 of the manufacturer authorized user training, we recently received several stakeholder comments, and the committee could come to no consensus. So, we would like to present this to the full ACMUI Board for discussion and a vote.

Second, update the waste and disposal section. We think it is adequate, and the subcommittee supports the current guidance.

And three, review the Y-90 radiation safety issues in autopsy and cremation. We currently support, however, as a comment, to edit on autopsy or cremation timing, with addition of potential precautions. Thank you.

CHAIRMAN ALDERSON: All right. Thank you, Dr. Kapp, Dr. Metter. We will open this particular session up to the ACMUI for questions and comments. Director Ennis?

MEMBER ENNIS: I heard some theoretical arguments regarding the possible change to remove company representatives as the trainers for new authorized user applicants, and I heard some arguments from you presented about why maybe we should not do that, but I did not hear any substance behind those theoretical arguments. In other words, are those

theoretical arguments actually a problem in the country right now: rural access, not having authorized users available, those were arguments that were raised, and my question is, well, what is the reality? What is people's experience nationally? Do we have any information that would support those theoretical arguments, or are they only just theoretical answers?

MEMBER METTER: Well, I spoke to Frank Costello, who, as you know, is on our committee, and he said that as a regulator, he sees a lot of the Pathway 2 still being utilized.

MEMBER COSTELLO: Yes, this is Frank, can I comment on that?

CHAIRMAN ALDERSON: Yes, Frank, please go ahead.

MEMBER COSTELLO: Yes, I would turn that question around. I don't know that there is any data to indicate that there are a sufficient number of authorized users because, I'll tell you, in southeastern Pennsylvania, which is not really a rural area, I see mostly Pathway 2 being used, and I think it is partly because I don't know that authorized users really want to be the ones doing this.

In addition to that, we may recall from our discussions on medical events yesterday that many of

these medical events occur because of problems with the administration set, and the manufacturers' representatives often are more familiar with the problems of a current administration set because they've seen so many of these issues.

So the two reasons I am thinking I would like to retain it is I don't see a pressing need to eliminate it. I don't know that there are enough authorized users everywhere that are willing to do this, and finally, I see that most of these, currently, institutions are choosing manufacturers' representatives when they could be choosing authorized users, so right now, I am not -- I don't find the evidence compelling to eliminate that option.

CHAIRMAN ALDERSON: Dr. Ennis, did that satisfy your question?

MEMBER ENNIS: Yes.

CHAIRMAN ALDERSON: Yes, Dr. --

MEMBER LANGHORST: This --

CHAIRMAN ALDERSON: -- Langhorst?

MEMBER LANGHORST: -- is Sue Langhorst. Can we go to Dr. Metter's tenth slide, I think? These -- mine are not numbered, and I think it is number ten. Yes. And I wanted to discuss the point on -- the second point, and ask Dr. Tapp this: licensees do not put what

category their AUs are in. It's the NRC and Agreement States who are issuing those licenses that put in that designation.

And so I understand that one of the difficulties that there are is that the Pathway 2 authorized users are put on the license before they have their three cases, and that has to be, especially if it's a new license for them, or a new type of use under that license, but you all are frustrated by not knowing when they have their three cases and would like to put a time frame on that to have them get done. And in fact, I think we have heard anecdotally that there are some AUs that just never did do their -- or maybe not all their three cases.

So I wanted to ask Dr. Tapp as far as the Working Group goes if you discussed, were there other ways to fix that problem, such as putting on the license that they are required to do these three cases within six months of the date of -- or put the date on, because maybe the license changes in the meantime?

DR. TAPP: This has been discussed in the past. The way the NRC licenses, to put something on a license and call it like a limited scope or a temporary authorized user, we don't have that ability to do it. Now, I do know some Agreement States do have that

ability, but in the past, we have looked at that, and we were told we could not put provisional status, I believe was the term that was looked at, on our licenses. So --

MEMBER LANGHORST: So it is an issue?

DR. TAPP: -- it is evaluated during inspection space at the NRC.

MEMBER LANGHORST: Yes. Did you explore what it would take to do that? I mean, that sounds like another problem to fix, short of getting rid of the whole pathway.

DR. TAPP: Yes. Our reasoning for looking at getting rid of the pathway, just evaluating, was to see if we could bring it back closer in line with the other modalities. It was not on -- specifically on the difficulty in tracking it, but bringing it back into like 10 CFR 35 modalities, if it was a possibility, and that is why we went up to ACMUI with those recommendations. If that's the recommendations, we could look at that further.

MEMBER LANGHORST: Well, I am in agreement with Frank that I don't think elimination of Pathway 2 is -- it's worth discussing, but I don't agree that it is worth getting rid of at this point in time. I will have a couple other questions when we go to the

other parts, but I think we need to talk through this topic.

CHAIRMAN ALDERSON: Ms. Weil?

MEMBER WEIL: Is there any way to know, since there are so many -- thank you. Is it possible to determine, because there's so many medical events involving microspheres, which pathway the authorized users were approved under?

DR. TAPP: Yes, the Working Group actually asked that question, and unfortunately, when we track medical events, we do not track which pathway they fall under, as well as some of these are under broad scope licenses, and they have the ability to approve their authorized users in different pathways as well, so we do not have that ability at this time.

We have -- one thing I would mention was the Agreement State representatives have issued a survey to the Agreement States asking them if they have any information in their state level to see if we have that, so we are gathering a survey with our Agreement State representatives to look into that.

CHAIRMAN ALDERSON: So what is -- this is Dr. Alderson -- what is implicit in this, and I have not heard anyone say it yet, so I just want to state this and then have you confirm it. No one has really

commented on the equality of the educational experience during the training by the manufacturer representative. It's in vitro simulation and then followed by the manufacturer being present; that's how the slides describe it. Do we know that the outcomes of that educational experience in practice are generally the same as the person trained with live patients by an AU?

So do we know that it is an equivalent experience? Do we know that the outcomes are the same? Do we have any idea whether it's a good experience at all, or what the outcomes are? Yes, Sue?

MEMBER LANGHORST: This is Sue Langhorst. I would say at my license, more than likely, we have our own AUs training new AUs.

CHAIRMAN ALDERSON: Right.

MEMBER LANGHORST: But if the manufacturer comes in and trains, that is okay with us too. I mean --

CHAIRMAN ALDERSON: Yes.

MEMBER LANGHORST: -- we have not seen the difference. I can only talk from experience.

CHAIRMAN ALDERSON: So, subjectively in your local experience, you haven't noticed a --

MEMBER LANGHORST: Yes.

CHAIRMAN ALDERSON: -- difference in those trainees.

MEMBER LANGHORST: And it's a good training for -- I think as some of the letters that we've received, for the whole team because it is really a team administration.

CHAIRMAN ALDERSON: All right. Yes, we have two more comments. Dr. Ennis?

MEMBER ENNIS: Since we don't have information, this is more I guess speculative, but nevertheless, just extrapolating if you will from the types of brachytherapy procedures that I do, which is not these, but to the degree that they may be similar, and interacting with manufacturer representatives and physicians to do this, I cannot -- I feel fairly strongly that the depth of the training, at least for the authorized user himself, maybe not the team, is very different if a physician who is actually doing the procedure is training you.

The depth of the understanding of what you are trying to do and the subtleties and the problems that can develop in the procedure itself and the proper handling of the radioactive materials, I think the depth that you're going to get from a physician who is actually doing it is much, much deeper, richer, and

valuable than from a drug company or, you know, a representative.

I share -- and I hear what Sue was saying about maybe the team as a whole and maybe the tubing issues and things like that -- but on the medical and proper handling of the isotope by the authorized user, I don't think there is a comparison. I guess this is all opinion, but I don't think there is a comparison in the information and the depth of the training.

Adding that to the notion that it is possible that they get trained only in vitro and then go out and never -- and we don't know if they are getting that three or not, it makes me very uncomfortable with Pathway 2.

CHAIRMAN ALDERSON: Mr. Green, you had the next statement. Then we'll let Dr. Metter speak.

MR. GREEN: Follow-up on Dr. Ennis's comments: with the in vitro training from a sales consultant representing their manufacturer's product, is that going to be specific only to that product and not generally applicable to the other manufacturers' products, so we have an individual who is doing three simulated cases of Brand A, and really won't understand the nuances and the clinical issues that might come up if they happen to acquire the product from Brand B?

And with Ms. Weil's comment about can we attribute this medical event to an authorized user who was a Pathway 1 trainee or a Pathway 2 trainee, is that applying to the preceptor or the student? I don't know.

DR. TAPP: Can I --

CHAIRMAN ALDERSON: I think --

DR. TAPP: -- answer --

CHAIRMAN ALDERSON: -- Dr. Metter had the next comment, but Dr. Tapp would like to respond? Yes.

DR. TAPP: Yes, there is -- when added to a license or added for one type of specific manufacturer, so if they were to switch the manufacturer and use the other, they would have to do, retrain specific to the type.

MR. GREEN: And once they're on the license, do you think if they do trade vendors, they are doing three new case studies?

DR. TAPP: We have no indications or violations that they have never received their training.

CHAIRMAN ALDERSON: Dr. Metter is next, and then we have a comment from the audience.

MEMBER METTER: Well, I agree with Dr. Ennis's comment regarding the subtleties of a direct

AU with their supervision and their clinical experience. The manufacturer training program, however, is very standardized and encompasses the -- since 2008, all their experience, and they actually do, like what Sue said, regarding the team approach, the nuclear medicine, the radiopharmacist, the whole team approach, and then they give -- the in vitro simulated cases also, I believe, apply to, like what happens if the hub came undone, or the different scenarios so that you know how to approach the problem issues.

But again, I still think that the direct clinical training with the authorized user is very important, and that is why my first thing is that as far as if you provide mini fellowships, that you may hopefully incorporate the manufacturer's didactic training and then provide the direct training with the authorized user.

CHAIRMAN ALDERSON: Next comments from the audience here, and then we'll go to Dr. Palestro.

DR. FACCHINI: Good morning, and I appreciate the ability. My name is Frank Facchini, and I'm in interventional radiologist, but I am actually also the Head of Medical Affairs for BTG, which is one of the manufacturers of Y-90. I am a product of the -- I am an authorized user, a product of the second

pathway about ten years ago.

I will make a point that the medical events are extremely low: when we at BTG looked at this, over the last five years, on the order of 0.14 percent, and so it's an incredibly low rate of medical events.

The second point I will make is we have done that survey. We have reached out to products of the training courses, the physicians that have gone through it, and it is overwhelmingly positive, overwhelmingly positive. In fact, the amount of people that responded is above the average you would expect in any other survey, so people giving us feedback that they want to keep it, they appreciate it, and that the quality of education is excellent.

I will take some exception to the point of they're not sales representatives that are doing this. These are actually medically educated people that are under me, personally, as a physician, as an interventional radiologist, and as an AU, so they fall directly in line. They are not sales-compensated whatsoever.

And the depth of education, sir, is incredibly deep because, remember, they have the ability to harvest the pharmaco-vigilance that we do and the device vigilance feedback that we do and get

incorporated. A regular AU that sits out there that might have done three, and by the way, an AU is qualified as three cases, that depth of experience, then, if they have done four cases, they can proctor someone that has done none. That does not represent depth of experience in any way, shape, or form.

So with great respect, I appreciate everybody's comments, but I wanted to give you the perspective from a user and from someone that has the responsibility of overseeing these educational programs.

CHAIRMAN ALDERSON: Very good, thank you, good comment. Dr. Palestro is next.

MEMBER PALESTRO: Yes, I think I come at it from a slightly different perspective. Putting the quality of the training aside and so forth, the rules governing the relationship between medicine and industry today I think are so incredibly strict and well-defined that there is a clear separation between the two, that I find it somewhat incongruous that the training for microsphere administration is given by a vendor or vendors, that -- and clearly, that is not to impugn the quality of the training.

But to a disinterested observer, you have to wonder why it is being done, and clearly, it could

be construed as being self-serving. And I understand that at the beginning, there are no alternatives, and I suspect looking ahead to new generators for technetium, clearly, it's going to have to be industry-sponsored training because they are the only individuals or only group who is familiar with it, but at some point down the road, that training should move on to other groups, other organizations, and I would think this agent or these agents have been available now for about a decade, that there should be an alternative to company- or industry-sponsored training, so that is my concern.

CHAIRMAN ALDERSON: Good, thank you. Excellent comment. The spectrum of the training is a key issue, and the previous speaker gave some good examples of the depth and the quality of the training provided on the manufacturer side, but the presentation itself and the rules and -- the rules that we saw don't make that distinction. It could go all the way the other way.

We have another comment from the audience.

DR. SALEM: Thank you, sir. My name is Riad Salem. I am also an interventional radiologist, and actually, I was here, what, 12 years ago when these pathways were devised.

So when you're referencing vendor training on this on the BTG side, I am a trainer. So I have trained about 1,000 people now who have come through the course over a decade, and there is no doubt that there are sort of multiple pathways that are beneficial, but I too would take exception that at least high-level MSLs or highly trained sort of vendors aren't able to assist with the administration.

What we do in our course, which is a whole-day course, eight, ten hours or so, people come to Chicago, is go through the entire clinical scenario, the patient selection criteria.

We learned from our early experiences, and I think that has translated into a very low sort of mod reporting and sort of adverse event rate, and for those of you that have radiologists, nuke med, rad oncs that have come to Chicago, if you see, the evaluations themselves are pretty high. And so I think there are multiple things that we have learned over a decade, and the fact that you can teach physicians sort of the patient selection and all of these things, the medical aspect, I would argue that the MSL or the vendor representative that has now done 500 cases, 1,000 cases, he is much better-versed to manipulate and help with administration, the kit, et cetera, than a

physician who has done, theoretically, three based on AU to AU.

So I just think there are multiple pathways that we need to consider, and this has certainly been something that we developed ten years ago with this committee. It has worked extremely well, and the evaluations are good, and it is really sort of, in my opinion, parallel to sort of stent grafting; you really need a lot of expertise onsite to help you do these things safely.

CHAIRMAN ALDERSON: Thank you. Yes?

MR. OUHIB: Hello, this is Zoubir.

CHAIRMAN ALDERSON: Yes, Zoubir, please, go ahead.

MR. OUHIB: Yes. I just thought I'll throw out a question: should the manufacturer representative be defined, so that way we understand all these comments that have been submitted?

CHAIRMAN ALDERSON: Yes, should it be further defined? I think that is a good point. I'll expand on that in a moment. Dr. Ennis has a comment.

MEMBER ENNIS: I was thinking something similar. Perhaps to satisfy my, for example, anxieties about level 2, if we were to continue it, we'd need to be much more prescriptive about what that means,

along the lines of what we have been talking about in training experience in general, that we need to have more defined, not just company representative coming, but -- and, you know, what we have heard from some of the companies sounds quite good, but maybe we can't just leave it up to the company, but it needs -- if Pathway 2 continues, it needs to be defined, and I'm not going into details of what that might be, but something very robust, and then maybe we could be comfortable with it.

But without that definition, although a company may be doing a wonderful job, this really allows someone with modest education coming in and watching you do a couple cases, and the NRC and I and ACMUI have no idea that that is not happening, so those are my thoughts.

CHAIRMAN ALDERSON: Another comment from the audience.

MS. COCKERHAM: This is Ashley Cockerham with Sirtex Medical. Just for the committee's clarification, we have approximately 30 proctors. They are all physicians. They have about 159 years' combined experience, and they do up to about 400 cases per year, so all of our in vivo cases are supervised by physician proctors. Yes, Sue?

CHAIRMAN ALDERSON: Sue Langhorst.

MEMBER LANGHORST: At our institution, radiation oncologists serve as the authorized users, and our interventional radiologists are what we term approved physicians. I know several of our physician -- our interventional radiologists have served as those representatives for some of the manufacturers to go and do training elsewhere and to proctor elsewhere, so those interventional radiologists at our site are not AUs, but they could be. It is just that is not the model that we use at our institution.

So I am very comfortable with the training and the physician-level oversight of those training proctoring sessions.

MS. COCKERHAM: This is Ashley again, one more quick comment. All of our physician proctors are interventional radiologists.

CHAIRMAN ALDERSON: Well, yes, Dr. Zanzonico?

DR. ZANZONICO: You know, all these points are very well-taken. I think one thing we need to recognize is these procedures are very labor-intensive, labor- and time-intensive, and I think while in principle, peer-to-peer training, in this case, physician-to-physician, AU-to-AU training, is always preferred, I am just not sure how receptive

busy IR, busy interventional radiologists and other attending physicians will be in terms of providing the amount of training.

So just because there is a growing number of qualified individuals who could provide this training in principle, physicians who could provide this training, I don't necessarily think that translates into the number of physicians who would be willing and able to do it on the basis of time and logistics, and so eliminating Pathway 2 at this point may compromise at some point in the near future the pool of individuals qualified to perform these procedures just because of the inability of those users to dedicate the time and effort to do so.

CHAIRMAN ALDERSON: All right. Well so it was the lack of definition in the current presentation and regulations, I presume, that led to my question, which resulted in the recent exchange, and I am very pleased at the attestations of quality that we've heard from several manufacturers. I think when you combine that with the low level of complications in the field over time, I think we can say that it is probable that things are working out reasonably well.

But I think the comments that have been made by Dr. Palestro and Dr. Ennis about better defining

this type of training in the future, particularly such training of the type, this may become more common in the future for certain reasons, that better definitions, at least in guidance, if not in regulation, I think would be very helpful to letting all people know that high quality education was being provided. Thank you.

Next question: any other comments on this presentation? Yes, Dr. Langhorst?

MEMBER LANGHORST: And, have others -- if we're going to move away from the pathway to discussion.

CHAIRMAN ALDERSON: Yes.

MEMBER LANGHORST: Okay. I think it's on Dr. Metter's slide 22 with regard to autopsy and cremation and what you labeled as current guidelines.

This is recommendations from the NCRP report. It's not any recommendations from NRC guidance. And, in fact, I have no authority over patients who pass away after the leave our hospital and are released under 35.75.

So, these are not what are in the guidance document. I mean, you reference that, but it's not something that the NRC is saying you have to do.

I'll yield to Dr. Tapp.

DR. TAPP: You're correct. It's not a

requirement specific to autopsy or cremations. The requirements are, as you stated, in 10 CFR 35.75 regarding patient release and keeping it to a 100 millirem or the 500 millirem as the maximum.

So that requirement does encompass autopsy and cremation of some -- if you knew there's a situation where someone could be exposed to 500 millirem, you could then fall under 35.75 and need a license.

But, we are not recommending at this time new rules for autopsy and cremation. It's just a reference for information for RSOs to use.

MEMBER LANGHORST: I just wanted to clarify that point. And, as far as the waste disposal section goes, this really isn't anything new to how people are doing waste disposal of microspheres. The NRC, I think very rightly, is trying to be consistent in their RAD waste disposal guidance, and especially on their 35.1000 licensing guidances. So, it's nothing new. It just states what us RSOs have had to do all along. So, we were -- I was happy with how that was stated.

CHAIRMAN ALDERSON: Yes, Dr. Dilsizian.

MEMBER DILSIZIAN: So, regarding the waste and disposal issues, I am -- I was curious to know why you listed a number of long decaying isotopes. You

also said that most licensees are not detecting these impurities. Do we know what the cause of variability is? I mean why is there like very little, and then at times there are long-term impurities.

DR. TAPP: The very small amount of activity that falls -- that is in the -- that comes from the manufacturing process, it is so small that it would require very sophisticated detection instruments to see it. So, manufactures or licensees are not seeing it.

The times where they possibly could detect it is if they had a vial that wasn't used at all. So, there's more long-lived impurities in it. It is possible in those situations that they could detect it because you have a -- more amount. But, a used vial is --

MEMBER DILSIZIAN: So, is it possible that they are not detecting; is that what you're saying? I mean, it's difficult to detect, in essence, it exists and that we not --

DR. TAPP: Yes.

MEMBER DILSIZIAN: -- actually keep it for a long time?

DR. TAPP: Yes, it's below the detection limits.

MEMBER DILSIZIAN: Okay.

MEMBER LANGHORST: It's in very small amounts. It's very small amounts, if at all.

MEMBER DILSIZIAN: So, what is then -- why are we even discussing it, I guess?

MEMBER LANGHORST: Because they have been observed, and it's just an alert that if you still have activity that you're measuring, that you can't decay and storage it.

More than likely, we would ship it with our radioactive waste shipments.

MEMBER DILSIZIAN: Okay.

CHAIRMAN ALDERSON: Mr. Green?

MR. GREEN: For Dr. Dilsizian, there may be two things. One is the partially unused vial may be more detectable because normally it's infused in the patient and you don't have much leftovers.

It also may be in a certain production cycle of that batch, whether they had a longer bombardment time in the reactor where you could actually make europium. We see the same thing with samarium-153 lexidronam, or Quadramet, where we get europium-154.

On slide 19, which is the waste issue, too, waste and disposal. I just have a -- I don't know the

answer, but since both manufacturers are outside the U.S., if we were to ship unused vials back to the manufacturer, would the licensee have to be licensed for export of such materials to use that pathway for disposal?

DR. TAPP: If they were to ship it to their outside locations. I believe that, and Sue could answer this, a lot of times, it goes through an authorized recipient, but it is an option that we wanted to remain in the licensing guidance in case, if manufacturers would like to do that in the future.

MEMBER LANGHORST: I may be wrong, but isn't there a level that you have to reach as far as activity goes? And, I don't think this would be anywhere near, but it's -- I guess it's waste. If you'd count it as waste. But, if it's unused material, presentation is everything.

CHAIRMAN ALDERSON: We have another comment from Ms. Cockerham.

MS. COCKERHAM: This is Ashley Cockerham with Sirtex Medical.

Our manufacturing facility is here in the U.S.

CHAIRMAN ALDERSON: Dr. Langhorst?

MEMBER LANGHORST: I have one final

comment, I think.

And, I know that the NRC has explained this, but it is very frustrating not to have these draft licensing guidance made publically available so that all can look at them well ahead of time and know what they say, rather than inferring it from just our review of their -- of the draft.

That's very frustrating. If NRC can figure out a way to be able to let the public see these draft licensing guidances, I think it would be very helpful. Thank you.

CHAIRMAN ALDERSON: Thank you. And, Dr. Zanzonico?

VICE CHAIR ZANZONICO: I agree. The long-lived contamination is a non-issue. Having said that, in terms of cremation, there have been estimates that range from completely insignificant to fairly significant radiation doses to members of the general public from the effluents from crematoria. And, they're fairly well established models, plume models and so forth and so on for making those dose estimates.

So, has the NRC done those calculations to verify with conservative assumptions of the amount of radio contaminates, long-lived contaminates if a patient were to undergo or the deceased would undergo

cremation, that, in fact, the dose to the general public would be well below regulatory limits?

DR. TAPP: I believe you presented on this a few -- a year ago.

VICE CHAIR ZANZONICO: Right, that was more -- yes.

DR. TAPP: And, there was a paper in that presentation. I did look at that paper. I have more data on the impurity levels. And, I used their plume models, which was very conservative, in that.

And, we did do some evaluations and some numbers. I don't have that available with me today, but I -- the NRC has looked at that.

VICE CHAIR ZANZONICO: And, so, everyone's comfortable that the dose limits are below like 100 millirem --

DR. TAPP: Yes.

VICE CHAIR ZANZONICO: -- a year. Okay, that's fine. Thank you.

CHAIRMAN ALDERSON: Do we have further comments on this area? I think to summarize it, and I'll say this a little more directly than I did a few moments ago, it seems that there's virtually a consensus around the table that Training Pathway 2 should be maintained at this time. And that better

definitions through guidance of what comprises manufacturer-based training would be useful in the future. Other comments on this issue? Dr. Tapp?

DR. TAPP: Can I ask, you said at this time. I didn't know if the ACMUI would want to continue to look into this, if there'd be some time where it could be brought back in, or is your recommendation that it remains as is? I was just trying to follow up and make sure I understand the recommendation.

CHAIRMAN ALDERSON: Dr. Ennis?

MEMBER ENNIS: My opinion would be I would not want to maintain Pathway 2 unless it is better defined. So, I would like to see that process happen and then be able to support maintaining Pathway 2.

CHAIRMAN ALDERSON: Dr. Palestro?

MEMBER PALESTRO: I also would, under the current structure being company- or vendor-sponsored would be opposed to a continuation of Pathway 2.

CHAIRMAN ALDERSON: All right. Well, it seems then that perhaps we should actually take a vote on this issue just so we can show the NRC what's really here. I had assumed that we had sort of a consensus given that we would better define training and that the training that seems to be provided now is high quality, but that -- but your issues are reasonable issues.

So, given what we know today, among the members here, how many believe that we should maintain Pathway 2?

MEMBER COSTELLO: This is Frank, I do.

CHAIRMAN ALDERSON: Okay.

MEMBER COSTELLO: But only -- I do with proviso that we better define who a manufacturer's representative can be.

CHAIRMAN ALDERSON: Okay, with the proviso that it's better defined, all right. So, but, without that proviso, there's still -- we have five people, I believe, who have suggested one, two, three, four and Frank.

MEMBER COSTELLO: Oh, include me in that group, too.

CHAIRMAN ALDERSON: Right, right, right. So, we have five. This is just generally for your advice, it's not a binding -- we're not doing a binding referendum here, it's just for your advice.

I think we have five people who support that idea and, if the manufacturing standards are -- the training by manufacturers are made more precise and more rigorous, then how many would support the idea that Pathway 2 would be maintained?

MEMBER COSTELLO: That would be me, too.

CHAIRMAN ALDERSON: Then a couple of the people who opposed would now agree, although one would not. So, just as general advice, at the moment, Pathway 2 stands, but we do need to take these models that we've heard about today of really high quality training and do whatever we can to promulgate that throughout the industry and, in the future, to be more prescriptive about what that training should entail. Yes?

MEMBER LANGHORST: I would be prepared to make a motion so that this can be a little more formal for --

CHAIRMAN ALDERSON: All right.

MEMBER LANGHORST: So, I would move that Pathway 2 remain and that we recommend that the working group evaluate what additional definition can be put or requirements be put on the proctoring of those cases --

CHAIRMAN ALDERSON: By the manufacturers.

MEMBER LANGHORST: -- of the three manufacturers.

CHAIRMAN ALDERSON: Yes.

Okay, so that's a motion. Is there a second on that motion?

MEMBER ENNIS: I second that.

MR. COSTELLO: I second.

CHAIRMAN ALDERSON: All right, it's seconded, and we've had a fair amount of discussion already. Is there further discussion? People --

Yes, Ms. Weil?

MS. WEIL: Just a quick question. Would we want to specify that the training, the industry training be performed by physicians?

MEMBER LANGHORST: This is Sue Langhorst. I would say that is something to be evaluated by the working group and to be brought back.

CHAIRMAN ALDERSON: I agree, yes, that's part of the work to be done. Further questions or comments before we take a vote on this issue? All right, all those in favor of Dr. Langhorst's motion, please say aye or raise your hand.

(Chorus of aye.)

CHAIRMAN ALDERSON: Opposed? One. Abstaining?

So, it carries. So, the group is in favor of this approach.

MS. HOLIDAY: I'm sorry, I just need to clarify how many abstained and how many dissented?

Is Dr. Metter abstained?

DR. METTER: Abstain.

MS. HOLIDAY: And Dr. Palestro dissented?

CHAIRMAN ALDERSON: Yes, that's correct, very good. All right, thank you. Well, excellent report and I think this led to good knowledge and --

MEMBER LANGHORST: Dr. Alderson?

CHAIRMAN ALDERSON: Yes?

MEMBER LANGHORST: I'd like to move that we support the recommendations of the subcommittee on the waste disposal and the autopsy and cremation recommendations.

CHAIRMAN ALDERSON: Okay. Is there a second to that?

MEMBER DILSIZIAN: Second.

CHAIRMAN ALDERSON: Any further discussion? All in favor?

(Chorus of aye.)

CHAIRMAN ALDERSON: Are any opposed? Any abstaining? That's unanimous. Thank you very much.

All right, our next report is on Abnormal Occurrence Criteria and Policies Update and it's to be given by Ms. Oxenberg of the NRC.

DR. OXENBERG: Good morning. I'm filling the position intermittently as the Abnormal Occurrence Coordinator. I started on a rotation in May, and I'm in the Radiation Protection Branch permanently, but I'm

not a medical health physicist. So, we're going to be hiring -- we've hired a medical health physicist that'll be starting later in the month.

So, I'm here to give an update, as you may know, an abnormal occurrence is on the schedule of incident or event which the Commission determines is significant from the standpoint of health and safety to the -- health or safety, it's not necessarily both, required by the Energy Reorganization Act of 1974.

The first policy was in place in 1977. And, we've periodically updated the policy; the last was in 2006. The current proposed change, which you were briefed on in 2015, was proposed to the Commission, and it was actually a work in progress since about 2011.

The Commission proposed the changes with minor edits. But, they directed the staff to go back to the public and specifically ask on comments on whether exposures to embryo and fetuses or a nursing child as an AO should be as it is now under criterion 1.A.2 or under criterion III.C as a medical event as a result of treatment to a pregnant patient.

It was published in the Federal Register in the summer of 2015, and the comments were received from the Advisory Committee, Organization of Agreement States, the State of Washington and the Commonwealth

of Virginia.

And, basically, with criterion 1, the original footnote had just said that medical patients were excluded from consideration of criterion 1. The Commission had added that specifically those, the criteria that did not apply as defined in Part 35.3045, which of course are medical events under criterion III.C. But, in response to comments from the public, we added medical patients and human research subjects.

As far as criteria 1.A and III.C, the staff did not agree -- are not making a recommendation for a change. We're recommending that it remain and applicable to all licensees under 1.A.2 as it is. And, the basis for this is that the staff felt that the embryo/fetus dose of 50 millisieverts or 5 rem is 50 times what the public dose is allowed, and it's intended for all licensees.

And, we really didn't want to have two thresholds: one for an, unintended for anything else but medical; and then one for, as a result of treating a pregnant patient.

Under III.A, events at facilities other than nuclear power plants and all transportation events, the Commission just deleted "of licensed facilities or regulated materials." They thought it

was redundant.

Under criterion III.B, fuel cycle facilities, the Commission added -- they replaced the second bullet with the first. And, basically, they're saying any high consequence events for facilities licensed under Part 70 are those that seriously could harm a worker or a member of the public in accordance with 70.61.

And, basically, 70.61 are performance requirements, and here, it should be stressed that these are physical engineering controls that you have to prevent an exposure. And, for an abnormal occurrence here, doesn't necessarily have to result in an exposure. But, if those engineering controls fail, then that, under Part 61, could then be an abnormal occurrence.

Under III.C, the only change that the Commission recommended was in the first criterion 1, they added which results in a dose, and they spelled out the word gray.

Under criterion III.C.2, they added a medical event as defined in Part 35.3045. They did not add Paragraph (iii) that pertained to the independent physician; they crossed that out.

And, so, currently, we've received

comments; we've staffed the changes with the offices and the regions. We've received those comments. We're now incorporating them and prepared to go up to the EDO and to the Commission with the recommendations. If those recommendations, if they approve it, then it will be incorporated in the next fiscal year's 2016 Abnormal Occurrence Report to Congress.

MEMBER LANGHORST: Dr. Alderson, thank you.

CHAIRMAN ALDERSON: Dr. Langhorst?

MEMBER LANGHORST: For those of you new on the committee, and maybe those of you who are just a year or two on the committee, probably abnormal occurrences, you've never heard of them before, never aware that they went up to Congress, and this is all brand new. It was brand new to me, too.

It is very disappointing that the recognition of medical use being different is applied -- is not applied to the criteria for an embryo/fetus of a pregnant, especially I-131 therapy patient, who is in this initial throws of pregnancy that no one could recognize. That is an abnormal occurrence.

And, whenever a 35.3047 occurrence happens, or excuse me, event happens and a licensee reports that, that is automatically an abnormal

occurrence; that just puts it right in that category. There have been since 2007, like, maybe one to three a year that show up in abnormal occurrences.

So, our recommendation of what that should be was not in what was published for the proposed change to AO criteria. But, the question was asked as the Commission directed.

I should say, let me get to this here, Commissioner Ostendorff said there may be unintended consequences of using the medical use criteria. However, I do not think that it's reasonable for the NRC to offer less protection to the embryo/fetus or nursing child of a patient than that afforded the embryo/fetus of a declared pregnant worker.

That had nothing to do with this AO criteria. And, so, there is confusion over what an AO criteria is and what it's supposed to do.

I looked at the comments from the ones that I could find from the proposed AO change. And there were two I could see, and I know there was one -- one was from the State of Washington; one was State of Virginia; one was from the OAS, and I could not find that document, so I don't know what their comments were; and then our comments. That was the public response.

And, it wasn't clear to me that the two

states didn't agree with us, it was kind of unclear because I think the question was unclear being asked.

So, I did want to tell the committee what Dr. Svinicki said. And, I'd like to, if you would, allow me to read this here.

She said in her vote on the proposed change of AO criteria, "I regretfully observe that the staff's proposed revision of criterion III.C.3, that's the embryo/fetus, does not appear to have garnered the support of the" -- or excuse me, that was the, sorry, that was the additional paragraph to the criteria -- did not support -- or garner "the support of a Commission majority."

"I agree wholeheartedly with the NRC staff and the Advisory Committee on the Medical Uses of Isotopes that reporting medical events each year to the Congress have not resulted and are not forecast to result in any significant adverse effect or permanent medical harm that is inappropriate.

"As I have reviewed these reports year to year during my service on this Commission, noting that most of the descriptions of the abnormal occurrence events reported to this Agency conclude with a statement to the effect that no adverse health effects from the misadministration of radiation are expected,

I can only imagine the anguish created for patients and family knowing that their medical treatments are labeled abnormal by a federal government agency and, yet, their medical care provider has concluded that no harm will follow."

"This is made all the more confusing when the policy statement clearly states that the criteria use a high reporting threshold so that only those events considered significant from the standpoint of public health and safety are reported."

"Clearly, the circumstance should be corrected. The staff's proposed revision to this criterion would have moved in that direction. I hope the staff and the Advisory Committee will continue to bring thought and attention to this issue in spite of the Commission's actions here."

So, we're not going to change it at this point in time, but I just encourage the ACMUI to fight the good fight the next time it's up for revision.

Thank you.

CHAIRMAN ALDERSON: So, this issue of a high reporting threshold does, in fact, seem to be one of the key things that we should discuss at this time.

I'll just make an opening comment that will follow what Dr. Langhorst just commented. And, it has

to do with criterion III.C, which is slides 8 and 9, which, again, confused me a bit. So, slide 8, it talks about a medical event, and then it talks about 100 rads to the bone marrow; it talks about 250 rads to the gonads; a 1,000 rads to -- high doses that clearly represent a high threshold. And, if something like that happens, however it happened, perhaps Congress should know about that.

But, then on the very next slide it says that a medical event using the same terminology again and then just goes through the same definition that we've used for clinical events in the field, the wrong -- a route of administration for an otherwise appropriate dose -- that is not a high threshold. That happens frequently in regular practice. That criteria, this part on slide 9 should not be part of an AO; this should not be reported to Congress. And, so, I, too, have a problem with how this is all rolled out.

MEMBER LANGHORST: I think the paragraph that was dropped --

CHAIRMAN ALDERSON: Yes.

MEMBER LANGHORST: -- took that into account. And, there had to be certain criteria that were met.

DR. OXENBERG: And the staff proposed it.

MEMBER LANGHORST: Right.

DR. OXENBERG: The Commission did not accept it. And, they dropped -- and that was the paragraph that specifically stated results in one or more of the following as determined by an independent physician deemed qualified by the NRC and/or Agreement State, unintended or unexpected permanent functional damage to an organ or physiological system, a significant unexpected adverse health effect, or death. That's what you wanted; they didn't accept it.

CHAIRMAN ALDERSON: They didn't accept. Yes, we have Dr. Howe who hasn't spoken on this. Let her speak on this.

DR. HOWE: This is just for clarification. If you look at the slide, you'll see that C.1 ends with an "and". And, then, you go to C.2. So, C.2 does not stand alone. It has to meet the very high dose criteria that you see in C.1.

CHAIRMAN ALDERSON: No, I didn't follow that. So --

DR. OXENBERG: It's C.1, okay, the one slide, in addition to, "and", and the next slide, paragraph two.

CHAIRMAN ALDERSON: I see.

DR. OXENBERG: It's both. You have to have both conditions to have an abnormal occurrence.

CHAIRMAN ALDERSON: I see. So, if a radiopharmaceutical were given the wrong route of administration and resulted in a 100 rad exposure to --

DR. OXENBERG: Yes, sir.

CHAIRMAN ALDERSON: -- the bone marrow, that would be an abnormal occurrence? Is that what is being said?

DR. OXENBERG: Yes, sir.

CHAIRMAN ALDERSON: I see.

MEMBER LANGHORST: But -- this is Sue Langhorst again.

CHAIRMAN ALDERSON: Yes.

MEMBER LANGHORST: But, if you meet the criteria of 35.3047 of an event dealing with an embryo/fetus or a nursing child, that automatically becomes an AO event because it is included in the group as if a power plant releases radioactive material and all these pregnant women are exposed.

CHAIRMAN ALDERSON: Okay.

MEMBER LANGHORST: Now, I will remind the committee that with -- since 2007 through 2015, we've had, like I said, one to three of these embryo/fetus

doses that have been I-131 pregnant patients.

There have been 7 to 19 medical events that reached the current criteria. And, only in 2012 and 2011 have there been any other AO events. So, they're all medical. And, so, that's what Congress sees are all these medical problems out there. And, so, that's what we were trying to help fix.

CHAIRMAN ALDERSON: Dr. Howe would like to comment again.

DR. HOWE: This is just for a historical perspective. With the 2000 Part 35 Rule, this is the first time that the embryo/fetus from a medical event was added to the regulations.

And, when they were trying to decide on what level of reporting there should be, they set the reporting level at the AO criteria so that medical events which are set at a much lower dose level, you wouldn't trigger. You'd only trigger at the abnormal occurrence level. And, that's why you see those two numbers matching up.

CHAIRMAN ALDERSON: So, Dr. Tapp's going to comment in a moment. So, I've got to still clarify this. I think maybe everyone else is very clear about this; I am not.

So, if we have the sort of thing that

happens frequently in the clinic where a patient who is pregnant is there and doesn't know they're pregnant, and they get a bone scan and then the next week, they turn up and say, well, I was pregnant then. Now, we have just exposed the fetus during a normal situation, but with the regular dose given in the regular way and so on. Does that become an abnormal occurrence?

DR. HOWE: It's not a medical event, but, if the dose to the fetus exceeds the levels put in 30.47, which is not a medical event, then it meets the criteria of an abnormal occurrence and would be reported.

CHAIRMAN ALDERSON: Only if those levels of exposure are very high?

DR. HOWE: Yes.

CHAIRMAN ALDERSON: Thank you.

MEMBER LANGHORST: Which is 5 rem to the embryo/fetus.

CHAIRMAN ALDERSON: 5 rem?

MR. BOLLOCK: Right, so, in that case, they would have to -- the licensee would have determine the 5 -- that the fetus got 5 rem from the bone scanner or whatever it was.

CHAIRMAN ALDERSON: Yes, right. All right. And, Katie Tapp had the next comment, then we'll go to Ron Ennis.

DR. TAPP: I was going to go back to the medical events themselves. You said there were 7 to --

MEMBER LANGHORST: 19.

DR. TAPP: -- 19 for a year. There is a change, though, in this III.C criteria that will reduce it slightly, where it is in the -- on the screen right now, it's C.1(b) that, in the past, it was exceeds 5 -- exceeds 10 Gray to another organ or tissue not listed in A.

But, now it is, exceeds 10 Gray above what you had defined in a written directive.

So, this would deal with, if it's something happened, and they exceed the dose very closely to the written directive, but it was with the wrong patient, if they switched the vials but they're similar, that used to be reported. That will no longer report. It has to exceed the prescription by 10 Gray or the written directive by 10 Gray.

CHAIRMAN ALDERSON: Okay.

DR. TAPP: It will drop some.

CHAIRMAN ALDERSON: And, now, Dr. Ennis?

MEMBER ENNIS: So, for people on this side of the table who haven't had that much experience with this, just so I'm understanding, so, it's like a bit

of a question for Sue to make sure I'm summarizing this correctly. The definition of AO is supposed to be something of big health and safety that, to the level that Congress ought to be notified?

MEMBER LANGHORST: I will say public health and safety. I think it's very important to put public --

MEMBER ENNIS: Thank you.

MEMBER LANGHORST: -- because that doesn't mean individual.

MEMBER ENNIS: Yes, very good. Right.

MEMBER LANGHORST: But, they assume it's individual, that should be --

MEMBER ENNIS: And, the vast majority of these actually turned out to be medical, and the medical community at least as represented by ACMUI has weighed in, and that the criteria that are being used right now do not match that definition of a serious public health and safety issue in the vast majority of cases.

Despite all that, what I'm hearing is that the regulation has decided to remain the same.

DR. OXENBERG: But, the key is what's significant as determined by the Commission. That's the definition.

MEMBER ENNIS: So, back to the Commission

--

DR. OXENBERG: So, the Commission says this is what we determined.

MEMBER ENNIS: Right. So, the Commissioners decided to ignore the advice of the medical community on medical issues where basically all the authorized -- to keep things consistent when, the fact is, that the vast majority of the AOs are medical, but we still have the medical to be consistent with the minority of other situations. I don't understand that logic.

CHAIRMAN ALDERSON: We have a comment from the audience.

MS. MCINTOSH: Yes, I'm actually an NRC employee. My name is Angela McIntosh. I just wanted to make a clarification that, with the AO criteria in general, there does not have to be a safety consequence in order for it to be considered a reduction to the degree of the public health and safety.

We did try to introduce the concept of a safety consequence in the medical arena only because we agreed with the committee that there were an awful lot of medical events that were easily making the AO criteria and, perhaps, misrepresenting the medical community in that regard.

And, so, as Dr. Oxenberg pointed out, we forwarded ACMUI's recommendation to the Commission to have these very high safety consequence criteria to include death and the Commission didn't agree.

So, the criteria largely have stayed in the medical area of AO criteria as they are except for, as Dr. Tapp mentioned, now, for the C.1(b), it has to exceed by 10 Gray rather than just meet 10 Gray.

So, we did -- we were able to get that piece through, but it's remained largely as it has because the Commission just didn't agree that, even in the medical area, that a safety consequence has to be adjusted.

MEMBER ENNIS: And, do we have an articulation from the Commission of their rationale?

MR. BOLLOCK: I could say a little, because that was actually Angela, Katie and myself that briefed the Commission on this two years ago or so. I can't speak for the Commission; I can't say verbatim what their reasoning was, but, essentially, in that briefing, the Commission -- the majority of the Commission, they just felt that the more reporting -- the general understanding is that the more reporting, the better.

They just wanted to know what is going on

in the medical field and they felt, because the reporting had been coming in, it should kind of maintain what we've had in the past. So, just, that was the general understanding that we got following our briefing of the Commission. We tried -- we argued the same points that you did. You know, we agree with you that, without serious medical consequence, we didn't believe it was necessary to report to Congress.

But, you know, the Commission, that's their prerogative. They felt that they wanted to maintain the similar reporting to what we've had.

CHAIRMAN ALDERSON: And, would it then, and I ask this as a question, is it then -- would it be reasonable for the next time that this group, the ACMUI, meets with the Commission to once again bring up this AO issue? Because, right now, it seems like that many people in the ACMUI remain frustrated by the way this is being done.

MR. BOLLOCK: And, that would be your prerogative.

CHAIRMAN ALDERSON: That would be our prerogative?

MR. BOLLOCK: Yes.

CHAIRMAN ALDERSON: Good, thank you.

Yes, Dr. Langhorst?

MEMBER LANGHORST: This is Sue Langhorst.

I don't think it'd do any good. Well, and, let me explain why, and nothing against -- the Commission wouldn't want to hear it and whatever, but I think this is pretty much a done deal. This what it's going to be. They're not going to re-review it for a time, and there'll be whole new set of Commissioners by the time it does make any difference.

And so I would just as the ACMUI to keep it in mind and fight the good fight next time and try to inch it down the road again.

CHAIRMAN ALDERSON: Right.

So, I think that it's not unreasonable for us to consider putting it on our proposed agenda for our next meeting. And I, in fact, in the time that I've been on the ACMUI, that the Commissioners have changed dramatically, in fact.

So, this is a much different group now, and they might feel about it a different way. But, we will have to -- the ACMUI will have to be extremely careful about how it words what it has to say and so that it makes a specific, precise point without getting global.

Because, if it gets at all diffuse, I understand why the Commission will say, no change. All right, there are -- would anyone have more comments on

this?

Dr. Zanzonico?

VICE CHAIR ZANZONICO: I have a question. What happens to these reports when they go to Congress? Is it -- I mean, I haven't even heard Senator Markey have a press conference about it.

MR. COLLINS: Yes, so, I would say that -- and this is Dan Collins -- we rarely get any congressional questions about the abnormal occurrence reports that we send. Every once in a while, we may get a question from a particular member of Congress who wants some additional detail about what the circumstances of a specific case were. And, we provide that back and usually that kind of answers the mail, if you will.

If I might make another point, though, Dr. Ennis had a thought about the small numbers of actual events in totality when you compare it to all of the medical uses or actually any uses of radioactive materials that occur in any given year.

In our annual report, we do try to provide context to highlight the fact that this is a very, very small percentage of the actual total numbers.

So, if you go and look, you'll find language that says, you know, something along the lines

of there are more than a million uses of radioactive material in any given year and that the five or six or seven events represent a very small percentage of it.

So, and, sometimes, we actually put the decimal points in there, but we do provide -- try to provide that context.

MR. OUHIB: Hello, this is Zoubir.

CHAIRMAN ALDERSON: Yes, Zoubir?

MR. OUHIB: Yes, I'm just thinking here, because I recall reviewing some of these cases over periods of 12 years.

I recall running into a case where a patient, well-educated in the medical field, was asked for a pregnancy test. And, that patient literally refused the test.

Well, what happened, after the injection, it turned out a couple weeks later, that that patient was actually pregnant.

The point that I'm making here is that, the institution might very well find themselves with such implications that they might decide that, if a patient is not willing to have a pregnancy test prior to the injection, they might simply say that we cannot do it and you'll have to find another institution. Perhaps that's what they need to do here.

I guess it's -- we need to think about the patient and the implications a little bit more about this.

CHAIRMAN ALDERSON: Yes, I wonder whether that's an issue of regulation of clinical practice?

MEMBER LANGHORST: It has nothing to do with the AO criteria.

CHAIRMAN ALDERSON: I agree.

MEMBER LANGHORST: It's --

CHAIRMAN ALDERSON: I agree.

MEMBER LANGHORST: Yes.

CHAIRMAN ALDERSON: I mean, it's a true statement but it's unrelated.

All right, are there any other comments about AO criteria?

Hearing none, thank you, Dr. Oxenberg.

And, now, we'll move on to another uncontroversial subject with Dr. Palestro, training and experience for all modalities.

MEMBER PALESTRO: All right, I'm going to present the report of the standing subcommittee on training and experience requirements.

And, I would like to acknowledge and thank the members of the subcommittee Dr. Sue Langhorst, Darlene Metter, John Suh and Ms. Laura Weil for their

invaluable contributions and patience with me.

This is a newly formed standing subcommittee and our charge is to periodically review the training and experience requirements that are currently in effect, making recommendations for changes as warranted.

It would probably behoove us to review once again some background to the formation of the subcommittee.

Beginning about two years ago in 2014, stakeholders expressed concerns that the 10 CFR 35.396 training and experience requirements currently in effect, which is 700 hours in total, adversely affects patient care by limiting use of parenterally administered Alpha and Beta emitting radiopharmaceuticals to physicians who complete the requisite 10 CFR 35.390 training and experience requirements, the end result being a shortage of authorized users.

At that time, the subcommittee of the ACMUI, which was charged with looking into the situation provided a report in March of 2016 and could not find evidence to support these concerns.

Therefore, the subcommittee recommended against changing the training and experience

requirements that are currently in effect.

However, as a corollary to that or as an outcome of our work, the subcommittee also noted that over the nearly 15 years since these requirements went into effect, new radiopharmaceuticals, both diagnostic and therapeutic, have been developed.

Furthermore, the educational paradigm has evolved from experience-based to competency-based.

Consequently, the subcommittee recommended, and the ACMUI approved, your creation of a standing subcommittee to periodically review and, when warranted, recommend changes to the training and experience requirements.

So, what's the focus of the standing subcommittee? Part 35 of the Code of Federal Regulations pertains to the medical use of byproduct material.

And, the specific parts of Part 35 that will be the initial focus of the subcommittee includes Subpart D, unsealed byproduct material, a written directive not required, 35.190, training for update dilution and excretion studies, 35.290, training for imaging and localization studies and Subpart E, the unsealed byproduct material for which a written directive is required.

35.390, training for use of unsealed byproduct material for which a written is required, 35.392, training for the oral administration of sodium iodide I-131 requiring a written directive in quantities less than or equal to 1.22 gigabecquerels or 33 millicuries.

35.394, training for the oral administration of sodium iodide I-131 requiring a written directive in quantities greater than 1.22 gigabecquerels or 33 millicuries.

35.396, training for parenteral administration of unsealed byproduct material requiring a written directive.

So, the subcommittee is charged with the responsibility to, quote, unquote, periodically review the training and experience requirements.

However, what constitutes a reasonable periodic review, a reasonable length of time? Well, it's been 15 years since the regulations were revised and it seems to the subcommittee that 15 years is too long an interval.

At the other extreme, one year probably is neither a practical nor a useful interview -- interval, excuse me.

The subcommittee believes that the

training and experience requirements should be reviewed at least once every five years and more frequently if warranted.

The subcommittee also is not certain, and it's really unclear to us how training and experience changes in once section of Part 35 will affect training and experience requirements in other sections.

Could there be an implication of changing say, 35.390 on 35.290? And, the answer is we don't know for sure.

The subcommittee is also uncertain, given the time needed to make changes to Part 35 and the status of the most recent changes to Part 35, how quickly any proposed changes to Part 35 training and experience requirements can be considered and instituted.

An important issue that the subcommittee will need to address is competency. In other words, what constitutes satisfactory completion of training and experience requirements?

Is merely completing a predetermined number of hours of training and experience equal to competency or can it be equated with competency?

At the present time, this really is not an issue because the vast majority of physicians seeking authorized user status satisfy the training and

experience requirements by obtaining certification through a medical specialty board whose certification process is recognized by the NRC or by an Agreement State.

The situation becomes different, however, for individuals or for physicians seeking authorized user status through an alternate pathway.

For example, it's been suggested that 80 hours of training and experience is sufficient for hematologists to administer one or perhaps two different parenterally administered therapeutic radiopharmaceuticals to patients with malignant diseases.

Other than number of hours assigned, how will a consistency and quality of the training and experience be assured and how can competency be determined?

Would a medical specialty board or boards assume the responsibility for establishing a curriculum and administering a, quote, unquote, certification examination? If so, what criteria would the NRC use to recognize this board?

How many different categories of therapeutic radiopharmaceuticals can the NRC and Agreement States manage for medical licenses?

So, what's the plan for our subcommittee, for the standing subcommittee?

First and foremost, we recognize that any recommendation for or against changes in training and experience should be made to ensure that the requirements and provisions in Part 35 which, quote, provide for the radiation safety of workers, general public, patients and human research subjects are satisfied, end quote, while simultaneously ensuring that patient access to these procedures is not unnecessarily compromised.

So, the subcommittee intends to begin a thorough a review of the training and experience requirements and the CFR Subparts D and E and to make recommendations for or against changes in these training and experience requirements for presentation at the spring 2017 meeting.

However, I want to make it abundantly clear that we don't anticipate being able to make recommendations for all of these Subparts at the spring meeting. We're going to take it one step at a time, so I don't want any misunderstanding there.

In addition, the subcommittee welcomes, and we've already received letters and comments, stakeholder and NRC input throughout the process. We

clearly cannot accomplish our task operating in a vacuum.

We also, along that vein, ask the full ACMUI for suggestions on how to improve our considerations and our plans.

And, finally, we request that the medical team appoint an NRC contact or resource to assist us in our work.

Thank you.

CHAIRMAN ALDERSON: Thank you, Dr. Palestro.

All right, this report is now open for discussion by the ACMUI. Do we have comments? Comments or questions? Apparently, this very thorough report has not resulted in any initial comments or questions.

I'll turn to the audience and ask if there are any comments there?

Oh, yes, Mr. Green?

MR. GREEN: Yes, just for Dr. Palestro, it's quite a large task that you had in front of you to look at this whole spectrum of all of the Subpart D and Subpart E uses.

It seems like, from what I've seen on the agenda, that it's probably 35.396 is the most interest.

Is that one that you'll take up first?

MEMBER PALESTRO: Yes, it's certainly been the lightning rod for the controversy that has gone on. I'm not sure if that's going to be the one we take up first, because I think we need to figure out how to approach the matter. And, I'm not sure we've solved that yet.

And, then, taking up any one of these particular categories, we also need to think about the ramifications on another category.

For example, on 35.390, if we suddenly decide to come up with say, a reduced number, X of hours, well, what about 35.290? Does that then become applicable to that? Is that appropriate to consider that? I'm just not sure.

CHAIRMAN ALDERSON: Good.

Yes, we have a comment from the audience. Ms. Fairobent?

MS. FAIROBENT: Thank you, Dr. Alderson. Lynne Fairobent with the American Association of Physicists in Medicine.

Dr. Palestro, I applaud you all for attempting to tackle this initiative. However, I think I might make a different suggestion and step back and take a look and start with a clean sheet of paper

and look at T&E from a high level perspective.

And, if we started with a clean sheet of paper today, how would we write T&E requirements for all of the medical sections rather than looking at individual subparts?

We have had a number of issues that have surfaced since, I believe we started the drafting of the revision to Part 35 in 1998.

There has been a lot that we've learned over the history of the various discussions and debates and changes that have occurred. We are still awaiting final changes to the T&E sections that are included in the major revision right now at the Commission.

And, I think maybe it's time that we all stood back and just say, with a blank sheet of paper, if we started from square one today, what would we draft T&E without any preconceived notions of what's currently there? I think it might be a very different outcome than what we would have in the current regulation.

And, AAPM would be happy to have any discussions that are applicable or able to happen with the ACMUI subcommittee.

CHAIRMAN ALDERSON: Thank you.

We have another comment from the audience.

DR. DIAMOND: Thank you, Dr. Alderson. My name is Dr. Morton A. Diamond from Fort Lauderdale, Florida.

I was planning to speak later, but Dr. Palestro's comments have prompted me to address you at this time in very brief fashion.

I speak from a perspective afforded to very few, a physician forced to leave medical practice because of multiple serious medical issues including some Stage IV Non-Hodgkin's Lymphoma all attributed to my military service in Vietnam.

I was a patient in a clinical trial, who, I am told, I am the sixth person ever to receive Zevalin therapy as first line therapy for incurable lymphoma. So, please understand my hoarseness and breathlessness are part of my medical issues.

I respect the goal of this committee, safe administration of radioisotopes in order to protect the patient, the caregiver and the public citizen.

With 80 hours of required instruction, endocrinologists are safely administering radioactive iodine. But for a medical oncologist to administer Zevalin, as you know, 700 hours are required.

It is clear that a radioisotope can be given safely without onerous educational requirements.

I live in South Florida. Though I did not feel a single raindrop or a wisp of wind, I was battered leaving home by four cancelled flights and shuffling between two airports as a result of Hurricane Matthew.

My sole purpose in appearing today was to try to defend and save Zevalin. But, as I listen to the discussion, I realize that the issue is not Zevalin.

I am reminded of the infamous killer in Ancient Greece, Procrustes. Every victim had to fit perfectly into his bed. If the victim were too tall, the limbs were cut off. If the victim were too short, the body was stretched with ropes to fit into bed, not one-size-fits-all, all sizes fit one.

It seems that this honorable committee is trying to have a single Procrustean answer for all radioisotopes, alpha and beta emitters.

Indubitably, more and more radioisotopes will be developed for diagnosis and treatment. This must be addressed promptly. Patients are demanding new and better treatment. Payers are demanding cost-effective therapy.

As a result, I believe that legislatures and the media will be increasingly mindful of your decisions and your rules. Heavy-handed Procrustean regulations will no longer be accepted.

I urge you, I urge you to develop a system of required competencies for administration of radioisotopes.

I believe that this can be accomplished with dispatched. And, at the same time, the patient, caregiver and public citizen would be protected.

Patients cannot wait for another four or five years for new regulations to be promulgated.

I leave you with this thought, medications and humans have much in common. We are born, we live and we die. For a medicine to die because another affects a higher rate of cure or eases pain more safely or prolongs useful life is the essence of pharmaceutical progress.

But, for a medicine to die slowly and tortuously in the full flower of its efficacy because of overbearing regulatory restriction is a tragedy no less, a tragedy no less than the tragedy of human death in the full flower of life.

Thank you very much, Dr. Alderson.

CHAIRMAN ALDERSON: Thank you, sir.

All right, here's another comment from the audience.

MS. TOMLINSON: Cindy Tomlinson from ASTRO.

I'm just going to read this because, if I don't, it'll be terrible.

Chairman Alderson, members of the ACMUI, NRC staff, thank you for allowing me to provide this statement on training and experience requirements for the administration of radiopharmaceuticals on behalf of ASTRO.

ASTRO is the largest radiation oncology society in the world with more than 10,000 members who specialize in treating patients with radiation therapy.

As the leading organization on radiation oncology, biology and physics, the society is dedicated to improving patient care through education, clinical practice, advancement of science and advocacy.

ASTRO's highest priority has always been ensuring patients receive the safest, most effective treatments.

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

ASTRO strongly opposes any reduction in

the T&E requirements found in 10 CFR 35.390, training for the use of unsealed byproduct material for which a written directive is required.

Under this section, the NRC requires an authorized user to be certified by a medical specialty board recognized by either the NRC or an Agreement State or has completed 700 hours of T&E in, quote, basic radionuclide handling techniques applicable to the medical use of unsealed byproduct material requiring a written directive.

ASTRO believes that these requirements are appropriate, protect the safety of patients, the public, and practitioners and should not be changed.

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

In addition to ensuring patient safety, ASTRO is unaware of data that suggests a shortage of AUs. ASTRO asked NRC staff for the number of AUs licensed under 35.390 to assess whether there is a shortage of AUs, but learned that the NRC only tracks AUs license under 35.300.

Without being able to identify which AUs are licensed under 35.390 and 35.300, it is not possible to confirm whether there is an actual AU shortage or a perceived one.

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

Indeed, ASTRO is not aware of a perceived shortage of radiation oncologists anywhere in the country. ASTRO's members are ready to care for patients needing any radiopharmaceutical.

Results from the ASTRO 2016 membership survey show that those medical directors responding, over half reported current use or plans to use radiopharmaceuticals in the next 18 months.

When asked to indicate the reason or reasons radiopharmaceuticals are not being administered, 74 percent said that another department is responsible, 33 said that there were not enough patients to make it a viable part of their practice and 25 percent indicated that radiopharmaceuticals were

not a critical component of their practice. Only 9 percent said that they were not comfortable administering radiopharmaceuticals.

In conclusion, for the reasons stated above, ASTRO opposes a reduction in the training and experience requirements for 10 CFR 35.390 and supports the ACMUI's standing subcommittee on training and experience requirements plan to thoroughly review the current requirements and looks forward to providing input to the subcommittee as it begins its deliberations.

Thank you.

CHAIRMAN ALDERSON: Thank you.

And, we have another comment from the audience.

MS. BUNNING: Hi, Sue Bunning with the Society of Nuclear Medicine and Molecular Imaging. Thank you for allowing me to be here today.

Dr. Ghesani was to deliver a brief statement but he got called away on an urgent matter.

So, I don't have his written remarks, but we've talked about this before. We fully support the creation of this subcommittee and we look forward to the work that you're going to do.

The SNMMI Board of Directors met a couple

weeks ago and this was on the agenda. And, they believe that they could be useful, helpful. We want to be a resource. We are forming an internal work group for this and any way that this group deems appropriate will be willing to be helpful and support your work.

Thank you.

CHAIRMAN ALDERSON: There seem to be no other comments from the audience at this time.

Are there some comments from the ACMUI?

Dr. Zanzonico?

VICE CHAIR ZANZONICO: I just have a question for the NRC staff. So, a change in the training and education requirements, the number of hours, for example, that would be rulemaking, correct?

MR. BOLLOCK: Yes, correct.

VICE CHAIR ZANZONICO: And, so, the usual time frame for that?

MR. BOLLOCK: Right. Once, yes, once we have a basis for change and would work through the rulemaking process.

VICE CHAIR ZANZONICO: One other question, if I may?

CHAIRMAN ALDERSON: Please.

VICE CHAIR ZANZONICO: Could anyone sort of tell us the history or into where the 700 hours

originated from?

MR. BOLLOCK: Yes, we can -- we actually, our staff actually worked on that. I don't know, if Maryann, you want to speak on it or you want me to?

DR. ABOGUNDE: And, when you say 700 hours, are you referring to the 390 or just the hours in general? Because there is 80 hours for diagnostic -- or 200 hours for diagnostic and then 700 hours which includes the classroom and lab and the --

VICE CHAIR ZANZONICO: Yes, that is correct, the classroom.

DR. ABOGUNDE: The second one?

VICE CHAIR ZANZONICO: Yes.

DR. ABOGUNDE: So, what NRC --

CHAIRMAN ALDERSON: Please identify yourself.

DR. ABOGUNDE: I apologize, Maryann Abogunde from NRC.

So, when the medical regulations were initially included in 10 CFR, the T&E training requirements were specifically just with hours. And, they were -- well, before they were specifically with hours, but more of this in guidance documents.

In the regulations, however, they were more generic and performance-based and so, it

referenced words like -- yes, so they basically said for you to complete your -- for you to have training and experience, you should have significant experience in different therapeutic uses or diagnostic uses.

And, so, moving forward, after that, we had specifics in terms of hours in our guidance documents.

And, so, at about 1987, that's when we formalized our guidance documents that started to include board certificates. And, the board certificates were based on those hours that we had in our guidance documents, but they weren't formalized at the time in our regulations.

And, so, moving forward, by about 2000, that was when we formally included in our regulations the actual number of hours that we wanted for our training and experience for the different modalities.

And, so, for the therapeutic uses, we started out with the 700 hours from there. But, we don't have any evidence that showed how the number of hours came about from the beginning.

VICE CHAIR ZANZONICO: Just to follow up, I gather that they were originally based on some board requirement. So, was that figure from a board requirement specifically?

DR. ABOGUNDE: Can you repeat that

question?

VICE CHAIR ZANZONICO: Yes. I gathered from one of the things you said that that 700 hour requirement was based on a board requirement.

DR. ABOGUNDE: No.

VICE CHAIR ZANZONICO: So, you know, did I have a sense --

DR. ABOGUNDE: Initially --

VICE CHAIR ZANZONICO: Initially?

DR. ABOGUNDE: Yes, so the board certificates came in, you know, for approval for us to, you know, approve their different programs and they came in based on the hours that we had specified.

VICE CHAIR ZANZONICO: Oh, so you guys specified to the board what would satisfy your requirements --

DR. ABOGUNDE: Yes.

VICE CHAIR ZANZONICO: -- for recognition, so to speak?

DR. ABOGUNDE: Yes.

VICE CHAIR ZANZONICO: Okay. But, I'm still not understanding, that number seems critical in all of this because we're parsing numbers. So, I'm trying to understand what the origin, the rationale for that number of hours originated from.

MS. HOUSEMAN: Hi, my name is Esther Houseman with the NRC Office of the General Counsel.

In the proposed rule around 2000 that Maryann was referencing, the number of hours for therapeutic uses was much lower. And, you can see in the Statement of Considerations for the final rule that the NRC received several adverse comments on that much lower number.

There were some public commenters who stated that that number was too low and that number was changed to 700 in response to those adverse comments.

I apologize, I don't have the reference on me right now, the actual Federal Register cite for that, but that was discussed in the Federal Register notice for the final rule.

VICE CHAIR ZANZONICO: And, so, what I'm inferring is that that number of hours did not actually originate in the sense with the NRC, it was in response to comments to an NRC proposed lower number of hours?

MS. HOUSEMAN: Yes.

VICE CHAIR ZANZONICO: And, what was that lower number of hours at that time?

MS. HOUSEMAN: I believe it was 80, but I would have to double check the proposed rule.

VICE CHAIR ZANZONICO: I guess what I'm

trying to understand is, I mean, any number is arbitrary to a certain extent, but there should be, hopefully, a compelling logic in coming up with some number of hours. I'm just trying to understand what that logic was.

CHAIRMAN ALDERSON: Dr. Palestro, the chair of the committee?

MEMBER PALESTRO: Yes, we have had -- the subcommittee has had the same difficulty in trying to understand exactly how all of these numbers developed and it's not really clear. And, there's probably a certain amount of arbitrariness to it.

What we're trying to do and, admittedly, it's not easy, is we're trying to put hours aside for the moment and define competency. What does it take for an individual to be competent as an authorized user, didactic training and so forth and so on, experience, without categorizing or without classifying hours.

Ultimately, we'll have to come up with some sort of hours. But, hopefully, we'll be able to do a job of basing it in some sort of fact or some sort of reference that we can point to.

For example, and this is just off the top of my head, if we're talking about didactic lectures in radiation safety, we know the elements that we want

to be covered.

How many hours does it take? Well, I really don't know off the top of my head but, perhaps there is a medical physics course given at a university that covers these same topics and you look at it and you say it's 8 hours or 16 hours.

In that sense, I think it makes the hours a bit more logical, rational approach to it. So, as I say, at the moment, we're putting hours aside. The first step is to define competency and then try to determine how you achieve it.

VICE CHAIR ZANZONICO: Can I just follow up?

CHAIRMAN ALDERSON: Okay, follow up then I have --

VICE CHAIR ZANZONICO: So --

CHAIRMAN ALDERSON: -- Dr. Langhorst was next after.

VICE CHAIR ZANZONICO: I agree completely, there should be competency-based and less ad hoc and so forth.

But, when I think about 700 hours, that's a full year of matriculation at college. I mean, that's -- it's more -- it's actually more than that if you count up numbers of hours for typical courses for

full-time matriculated students.

It just strikes me as a lot of hours for any sort of thing. But, I agree, competency is the key.

DR. ALDERSON: Dr. Langhorst and then Dr. Ennis?

MEMBER LANGHORST: And, so it's not credit hours, it's hours, it's not credit hours? Heaven forbid we have to pay for that.

But, I think we are kind of, as Ms. Fairobent had suggested, trying to start from scratch. Because what -- I don't think we're going to find the rationale because it wasn't there, put down, it wasn't documented.

But, the number of hours will be helpful once we set the competency and I don't think we want to, okay, so rad safety has to be this many hours and this has --- we're not looking at that fine detail.

But, the number of hours helps be a measurable guide or measurable level of training and experience that NRC can use in their regulation and that we all can recognize.

And, this, then, also, not only impacts the alternate pathway, but it impacts what the boards are judged against, too. Because they are judged against whether they meet that criteria in providing their

training and experience.

Doesn't mean that the boards don't go well beyond it, but I just wanted to support Dr. Palestro in that. We're looking at competency, but we may come back to hours because it's a ready measure that we all can agree upon.

CHAIRMAN ALDERSON: Dr. Ennis?

MEMBER ENNIS: So, thinking about 700 hours, just since that's kind of out there, for a 40-hour work week, we're talking about less than 20 weeks, four months.

I think about the depth, the amount of time it took me to get the depth so that I feel confident and comfortable administering Xofigo and all the possible scenarios that could come up, and not just for the routine. I mean, I guess, this is a big part of it for me.

If everything goes well and it's a routine thing, much less training is necessary. But, what we're trying to do is protect the public and protect patients for essentially all possible variabilities and that requires a lot more depth of understanding than might be presented.

And, my thinking that four or five months seems very short, frankly, for the amount of depth

necessary to really know how to handle all radiopharmaceuticals properly in essentially all scenarios when you're out in practice on your own, whoever you might be.

CHAIRMAN ALDERSON: Yes, Dr. Dilsizian?

MEMBER DILSIZIAN: I just wanted to bring up the fact that we keep talking about competency versus hours. But, take any medical subspecialty training, competency comes after specific number of years of training.

For example, to become a competent internist, you have to spend three years of training. So, I think that we're making this assumption that competency can be defined with a short training.

For example, if you're going to become a good surgeon, you really need to do four years of surgery and then be competent.

In essence, you can't say, well, in six months, I learned to do all of the surgery. Let me take my competency test and pass it. There's no such thing, surgeons still have to do a certain number of years. Internists still have to do a certain number of years.

Just because you're competent in six months, it doesn't mean that, you know, you can take the test earlier.

So, I just wanted to -- so competency goes hand in hand, but there's a predefined training period for every subspecialty.

CHAIRMAN ALDERSON: So, seeing no other --

VICE CHAIR ZANZONICO: Yes, one --

CHAIRMAN ALDERSON: Certainly, Dr. Zanzonico?

VICE CHAIR ZANZONICO: The reason why I ask is, it's easy to be dismissive and critical at the number of hours because it appears so ad hoc. So, I'm just trying to understand, was there originally a logic and a thought process that rationally supported that that we're just not understanding?

But, I, you know, I fully appreciate that there is a sort of an in-residence requirement for experience in any field to become fully competent.

CHAIRMAN ALDERSON: So, Dr. Bollock?

MR. BOLLOCK: Yes, just to go into a little bit more detail and the 2002 rule, there was -- because I talked with staff that had worked on it back at the time, so in the late '90s, '97, '98 when this was coming out.

You know, prior to 2002, it was 80 hours for unsealed sources. But, a lot of the mindset, at least of the staff, was this was for P32 and iodine.

Note that there were other radiopharmaceuticals coming down and, you know, the therapeutic radioactive drugs coming down and the importance of those, that was one of the main reasons for getting into opening up the training and experience.

At the same time, the diagnostic training and experience alternative to board certifications was 1200 hours.

So, that was actually -- the initial thought was go to 1200 hours for therapeutic. And, this is in, again, this is like NRC going out talking to the communities and working out the details.

So, and in that process, they recognized in opening alternate experience for both diagnostic and therapeutic, they recognized there was a lot of the redundancies in the training, 500 hours of experience given for the diagnostic uses.

So, that is basically how the numbers got down from 1200 to 700. And, then, comparing diagnostic and therapeutic, I mean, these are, you know, it's -- I mean, you know better than I do, diagnostic, these are much, much lower doses of radiation than the therapeutic. There's different reasons, different things in the diagnostics with elations and certain

things you do with -- in the diagnostic practice.

But, those were the thoughts. So, there was a lot of thought in there. And, I think they did go back to, yes, there is some time frame of, you know, that experience. The majority of the 700 hours is the 500 hours of work experience, practical experience under an authorized user, that is the majority of the 700. The 200 hours is the classroom, just, you know, basic radiation safety use, safety that.

So, there, yes, it wasn't necessarily arbitrary. There was thought in that. It did go, you know, back and forth. But, there was a time that it was considered -- they were considering 1200 just because, again, diagnostic which was much, much lower, while you're injecting much, much lower levels of radiation to a patient for therapeutic. So, you know, maybe therapeutic should be 1200.

So, there -- all these things were discussed back then. And, it was worked out to come up with the 700 as an alternative to the board certifications which is much, much more in depth and, you know, yes, years, residencies.

You know, this is the alternative to going for doctors that want to prescribe this going to another residency and taking three-plus years. You know, this

was a -- it's the alternate pathway.

And, yes, one of the questions I may have for the -- for Dr. Palestro's subcommittee and the ACMUI, as we try to -- as the NRC tries to understand that going forward, if we're going to make, you know, to make changes, we want to stay in line with what the medical community does in educating. You know, we don't want to be -- we don't want to stay on the path of hours if the medical community has other means from their boards and everything to go for competencies.

And, so, we want to stay, you know, we don't want to go too far off that. We want to stay in line with, you know, general medical practice and what the boards do. So, that is something that we, as the NRC, you know, we rely on you for that input and the medical community as a whole for that input.

CHAIRMAN ALDERSON: Good. So, I'd like to compliment the subcommittee on getting this process started. And, I do want to emphasize that this process is getting started, it isn't over. It isn't probably going to be over extremely soon if the work that is done is thorough. And, I believe that Dr. Palestro and his subcommittee plan on doing thorough work.

I would also point out that all of the things that the boards do, those -- the ability that

people eventually demonstrate is the result of an educational process and then a learning outcome that is documented by an assessment.

And, so, ultimately, I think whatever we come up with is going to have to contain those elements. There's going to have to be a learning process and there's going to have to be an assessment.

And, in line with maintenance of certification, which, itself, is sometimes come into harder times these days because it wasn't administered by the boards in exactly perhaps the ideal way.

But, a maintenance of competence or certification is also going to be, I think, important. It's not just an initial amount of training and some sort of assessment, but the fact that people who want to continue without the board certification or a maintenance of certifications through that board that they are still capable, will have to find another way to be reassessed, to demonstrate, again, on a periodic basis that they know the safety and security principles.

So, it's a large and complex process and I, again, compliment the committee on starting with the concept that, as you just mentioned also, Dr. Bollock, that not all types of use of radionuclides are as

complicated as other types so that one size of education or type may not fit all of these processes.

On the same -- at the same time, we don't want to inhibit patient access to radionuclide therapies in an unreasonable way.

So, I also urge the committee to not sort of just start with the easy things and go slowly in time, but to grasp the issues that the public is asking us to grasp and try to get into what we can do to assess whether those are currently handled in the correct way through the current regulations or whether a new approach needs to be approached.

DR. DIAMOND: May I have 15 seconds?

CHAIRMAN ALDERSON: Yes, Doctor, you may speak again. Please identify yourself again, Doctor.

DR. DIAMOND: Morton Diamond.

I appreciate, as a patient, that this committee is addressing competencies. But, I wish to make one comment.

One can gain competency without having to know every potential complication. I recently saw a wonderful movie, Sully, and when Captain Sully ran into this problem in New York City in Manhattan, he didn't know and he asked his co-pilot to look up in the book how to deal with the problem. Unfortunately, the

answer wasn't in the book.

So, please, I ask you, respectfully, to reject the notion that competency means the individual must understand and address every single possible complication. It's not reasonable.

Thank you, Dr. Alderson, thank you, ladies and gentlemen.

CHAIRMAN ALDERSON: Fine, thank you.

And, thank you, Dr. Palestro, and the work of this committee. And, we look forward to hearing your reports on a regular basis.

All right, at this particular time, are there any comments on this subject from the people that are on the phone? Would we like to have -- are there any people who are not in the room here who would like to comment on this subject?

OPERATOR: If anyone on the audio lines does have a question, please press star followed by the number one at this time. You will be prompted to record your name and then announced into conference.

Sir, we've had no one queue up at this time. Thank you.

CHAIRMAN ALDERSON: No one wants to speak? Very good. Hearing that no one wants to speak on the line, I believe that this session has come to a close.

The schedule now shows a 15 minute break. So, we will reconvene at, that may actually be about 20 minutes from now, we will reconvene at 10:30.

Thank you very much. Session's closed.

(Whereupon, the above-entitled matter went off the record at 10:10 a.m. and resumed at 10:32 a.m.)

CHAIRMAN ALDERSON: We're ready to reconvene. And the next section will be given by people at Spectrum Pharmaceuticals who will discuss their proposal for training and experience requirements.

DR. SHROTRIYA: Chairman Alderson, thank you very much for inviting us this morning. I am Rejesh Shrotriya, a physician and have been involved with novel treatments for cancer for the last 30 years. And for the last 14 years I have been Chairman and CEO of Spectrum Pharmaceuticals.

Today's meeting is not about Spectrum and it's not about Zevalin as misquoted here. It's about the access to drugs that help treat cancer, all alpha- and beta-emitters. These are experts in radiation and it's surprising that nobody is talking about the differences between the different emitters, what risks do they propose?

Cancer is a killer. The moment we have the diagnosis of cancer, people are looking for help and the drugs that we give to treat cancer patients are killer drugs. Side effects of drugs cause hair loss, nausea, vomiting. So we, the oncologists, the hematologists are used to treating with very deadly drugs. Sometimes they say the drugs are worse than the disease itself.

So what I'll be talking about is better -- other drugs, Zevalin is supplied in this kit. It's a good emitter. Radiopharmacies make a patient-ready dose that is supplied in a container like this, all the physicians have to do is take it out. This is contained here in this syringe. No gowns, no lab, nothing and then they put in this device and it's a ten minute push to the patient. That's it. After that, the patient goes home. And this is put back in the kit and sent back to radiopharmacy. There is no manufacturing or making of the radioisotope at the site. Seven hundred hours of training. I looked into it after you asked the question.

NRC says that the increase from 80 hours of training under the existing 35.93 to 700 hours of training under the final rule is required because the

new rule would authorize physicians to elute generators and prepare radioactive drugs on site, as well as to administer a wide variety of nucleotides.

Zevalin isn't about any of this, and therefore -- and I have also been told, best of my knowledge, not a single in 15 years, not a single physician has gone through 700 hours of training. So if you say that rulemaking will be delayed for the next five years and we still have 700 hours, I'm sorry, I have to pull Zevalin out of the market. Bexxar has already been pulled out of the market. We can't support it. Period. People don't use it because they say hey, managing a cancer patient with lymphoma means these patients need continuity of care. The continuity of care is missing when you refer this patient to an authorized user. Authorized users don't want to manage a cancer patient because when you give any of these drugs, there's a fall in white blood count.

A hematologist knows how to manage the white blood count drop. A nuclear medicine doc doesn't have to manage that. So even if there are 2,200 or whatever the number I heard, this is wrong. This is a misnomer. They don't give Zevalin. They don't treat neutropenia of these patients. So I think

there's a real problem you're dealing with.

Today, I request you, make no mistake. The future of cancer patients is at stake. Future innovation is at stake.

Dr. Palestro, rightly said, that we should be looking at safety of the patients, patient access, and innovation. Two things are missing. Safety -- we can't just focus on safety when we're dealing with cancer. You have to also be looking at are we denying the access to these patients? And are we hampering innovation?

Zevalin has a safety record of 15 years of safety and efficacy. Eighty-three percent of patients, it's a single-dose treatment. How many people here in this room knew that Zevalin is given once. The time for second dose is eight years. For that one injection, you want someone to go to 700 hours of training? What are we talking about?

As I said, we are ready to pull this drug. This drug is now approved in 46 countries around the world. It's only the United States where we are required 700 hours of training.

I've got stakeholders. I've got all these doctors, Dr. Steven Fein, Dr. Cultrera is online and

Dr. Julius. They're all stakeholders. They're not employees of Spectrum. They are physicians who take care of these patients. And they've had it.

And they are here to appeal to your good judgment and say please, how can we keep this drug available to cancer patients?

Zevalin is a combination of monoclonal antibody called CD-20 and the radioisotope is Y-90 yttrium which is one of the safest radioisotopes I'm being told. I'm not a nuclear physician.

We would like to request today an expedited rulemaking. We don't have five years. Patients who are suffering from lymphoma, if anybody in this room who had cancer, they would know what I'm talking about. There's an urgency. There's death knocking at their door. These people want treatment today.

By pushing this, what has been a useless rule for the last 15 years, you want to continue for another 5 years before making a decision? I'm sorry, this is travesty. While educators and innovators are trying to discover new treatments for cancer, how do we treat these patients? In burdensome regulations. We want seven hundred hours to wait another five years. To me, that is disgusting, as disgusting as I could

hear.

I'm here, a physician just like many of you are in this room. And I'm just saddened to hear that this approach that is at least being proposed by the stakeholders here.

Please open your hearts and minds and let's call a spade a spade, in answering Dr. Zanzonico's comments to the prior panel. What you are hearing here is a shameful turf war that is hurting patient care. Seven hundred hours? That's like two years of fellowship. You think a practicing oncologist wants to go for a two-year fellowship to give Zevalin one dose, give a push? Doctors don't even give this push. It's given by a nurse.

And nobody here can justify why it changed from 80 to tantamount to forcing hematologists and oncologists to become nuclear medicine doctors or radiation oncologists, but they are not. And they're not going to bicker.

Ladies and gentlemen, it is beyond time to end this turf war. Mr. Green asked a good question about the steps in the subcommittee process. The first step of the subcommittee's work should not wait for next five years and I urge you, please. Think of the poor

patients. Don't think of Spectrum or Zevalin. We may not be there tomorrow, but these patients will be here forever. That does not balance safety record. It balances access of these patients. There is other responsibility, everybody's responsibility to make sure that the patients have access. And of course we want to protect the safety of these. These are board-certified hematologists and oncologists who do this every single day.

The request for ACMUI to vote and act now in advising NRC to deal with alpha- and beta-emitters now. In fact, Commissioner Christine Svinicki wrote very nicely in her report. I just happened to read it and she's talking about we don't want to kill innovation. We want to make sure that patients have access and we should revisit all these rules that have been in existence. I'm telling you, I was told, I've investigated how many people have gone through 700 hours of training. They could not find one person who has gone through 700 hours of training. And you want to continue with this rule?

We are focusing and asking -- for you to focus here not on all modalities as Dr. Palestro addressed, but on therapeutic patient-ready dose of

alpha- and beta-emitter radiopharmaceuticals, I repeat. Patient-ready dose just the way I demonstrated, please focus on that. What is needed so that a hematologist, oncologist in his office can give this drug and continue with the care of this patient.

We started this conversation five years ago. I have been to NRC. In five years, I have met all of the Commissioners of NRC and they all are very empathetic. They say you know, we are dealing with nuclear submarines, nuclear plants, we're worried about terrorist attacks on these. What in the hell are we doing here with a beta emitter in a cancer patient setting? I also need to point out that this section is misnamed the Spectrum Pharmaceuticals Proposal for training and experience requirement. That's not so.

Spectrum is sharing the time here today with ACMUI to hear from a broad group of experts including AU educators and interested parties about making a more reasonable and rational competency based on training pathways made possible for alpha- and beta-emitters.

The rest of the speakers are AU educators and CORAR, Council of Radionuclides and Radiopharmaceuticals. They have instructional

material which they have submitted with the committee.

In a moment, I will turn it over to these AU educators and ask them to introduce themselves. Professor Kristina who comes from the University of New Mexico; Professor Nicki Hilliard from the University of Arkansas; and Professor Kara Weatherman from Purdue University, are all on the call and at this time I will turn over the call to Professor Kristina Wittstrom and her colleagues. And I will come back with my concluding remarks after all the presentations.

Dr. Kristina.

DR. FEIN: I'm not sure is she on the phone, Dr. Wittstrom.

DR. SHROTRIYA: Dr. Wittstrom? Is she on the telephone?

DR. FEIN: We might have lost her.

DR. FEIN: Can we move on to Dr. Cultrera's remarks?

CHAIRMAN ALDERSON: Is the line muted?

MS. HOLIDAY: It is not muted.

DR. FEIN: Can we move on to Dr. Cultrera's remarks for the moment?

DR. SHROTRIYA: In that case for the benefit of time, let's move on to Dr. Cultrera's

comments, please?

DR. FEIN: Is Dr. Cultrera on the phone? Is the phone okay? Is anyone on the line?

I have a copy of Dr. Cultrera's planned remarks and I'm just going to start. If she joins us, then she can continue.

Dr. Cultrera and I are hematologists.

MS. SMETHERS: We can hear you now.

OPERATOR: The parties you have been asking have been on line and they do have open line.

DR. FEIN: Well, this is Dr. Cultrera and Dr. Joseph Mace. They were both planning to come today.

DR. CULTRERA: This is Dr. Cultrera, can you hear me?

DR. SHROTRIYA: Yes, we can hear you, Dr. Cultrera. Please continue.

DR. CULTRERA: Is Kathleen still on the line, because she should be able to hear -- you should be able to hear her as well.

DR. WITTSTROM: This is Kristina Wittstrom. Am I being heard?

DR. FEIN: Okay, let's go on with Kristina, please.

DR. SHROTRIYA: Kristina Wittstrom, will you please -- you start first, please.

DR. WITTSTROM: Okay, and everyone I'm trusting can hear me. I am here representing a group of us who provide authorized user training to physicians, pharmacists and nuclear medicine technologists. My background is approaching 40 years of experience in nuclear medicine, primarily in the education arena, as well as being a practitioner.

What we have to offer the group is a sample or an example, if you will, of a competency-based curriculum derived from the expectation of the Commission, the Nuclear Regulatory Commission, as well as some best guesses, if you will, on expectations of critical competency that an individual user would need to have strong working skills and abilities to safely handle these alpha and beta, patient specific radiopharmaceuticals.

And as you can see, they parallel and it's kind of structured very similar to what we're all familiar with in the hourly or the time-driven curriculum. But instead of specifying hours, the difference is that there's some kind of an assessment process by which the individual user demonstrates a

level of competency.

In the more knowledge-oriented aspects such as understanding basic physics or the theory behind operation of measurement and detection equipment, those would be by written examination. The other probably more important from a safety standpoint, operation and ability to perform specific tests.

MR. BOLLOCK: Professor Wittstrom, are you still with us? We can't hear you right now.

DR. FEIN: Summarize Dr. Wittstrom's -- is Dr. Cultrera still with us?

DR. WITTSTROM: I'm saying that I would be willing to entertain any questions. So anyone can give me -- or an example of a proposed curriculum.

MS. HOLIDAY: Dr. Wittstrom, I'm sorry. This is Sophie Holiday, and it appears that our phone line cut out maybe within the last few minutes of your discussion.

DR. WITTSTROM: Are there any questions?

DR. SHROTRIYA: Yes, so maybe I can just kind of summarize what her point was. Her point was that the training and competency training can be divided into five or six different headings where people would be given training, once again, are

physics, instrumentation, radiation, biology and there will be a written exam and then there will be a competency requirement.

I think basically she's giving a syllabus which again we can share with the subcommittee and with others. She has provided this in writing.

So basically what she has done is a target program that can be run anywhere within 20 hours to 80 hours.

As you heard from Professor Mort Diamond, he's a professor of cardiology at the University of Miami and he himself suffered with lymphoma and received one dose of Zevalin and he's been cancer free for the last seven years. And he came here on his own volition. He departed the storm and came here to talk about that how ridiculous it is to require 700 hours of training. We will support a training that's more reasonable that hematologists and oncologists would like to become authorized users. So that is the main purpose of her presentation.

So we finally ask Dr. Jennifer Cultrera if you are available now?

DR. CULTRERA: Yes, I'm on the line.

DR. SHROTRIYA: Please go ahead.

DR. CULTRERA: Good morning, ladies and gentlemen of the NRC and ACMUI Committee. As Dr. Rajesh has told you, my name is Dr. Jennifer Cultrera. I'm a Board-certified hematologist and medical oncologist with Florida Cancer Specialists. We are the largest-based community practice in the country at this time.

I had hoped to be there in person, but I appreciate you letting me call in. Our area is currently being hit by Hurricane Matthew, so any prayers and support you can send our way, thank you.

I appreciate your time and presence here today to further discuss the need for competency-based training and education for alpha- and beta-emitters. I was initially introduced to radiopharmaceuticals in my training at MD Anderson Cancer Center in Houston where I participated in the registration trials for the lymphoma-directed agents both Zevalin and Bexxar. I then became comfortable working with my radiation oncologist and managing lymphoma patients who were treated with Zevalin and Bexxar as a lymphoma specialist at Moffitt Cancer Center.

Upon moving my practice to Florida Cancer Specialists in The Villages, Florida which is a rural

community about one hour north of Orlando, I found myself unable to utilize these agents because of a lack of authorized users, despite the prevalence of those who were potentially qualified to administer it as we discussed this morning.

I do have nuclear medicine physicians and radiation oncologists that I work with every day to help treat my patients and give concurrent radioimmunotherapy, radiation therapy with chemotherapy, as well as several diagnostic nuclear medicine tests. But if they are not an authorized user or if they are not incentivized to become authorized users, we cannot partner to help these patients.

Upon inquiring to others in my practice of over 200 medical oncologists and hematologists, I found that this was the norm, rather than a rarity in the majority of the communities throughout Florida that did not have either large cancer centers or academic centers.

I have come before this committee several times and spoken with several NRC Commissioners before to express this unmet need that my patients are experiencing. And it is disappointing to see that the changes to the current training and education

requirements are not going to be in the proposed rule draft. But I do appreciate the hard work that everyone is doing to help make future changes.

As a medical oncologist, I work with highly toxic chemotherapeutic agents on a daily basis. We are trained for the safe handling and management of these agents, as well as for the serious, adverse events in our patients. Nobody can ever be trained for every single possibility that can occur, but I feel comfortable with the agents that I'm utilizing that I can react in a timely fashion to help keep my patients safe.

Unlike radiopharmaceuticals, chemotherapy is often prepared and administered in our own infusion centers. Alpha- and beta-emitters are provided to the authorized user as a patient-ready dose as you have seen, prepared at radiopharmacies. The administration is simple requiring little manipulation and preventing little safety risk.

Lymphoma is a disease of the elderly and most of my patients are very frail, debilitated, and have been treated with highly-toxic treatments prior to them receiving some of these drugs. They are unable to travel 80 to 100 miles which is the current issue

to the nearest authorized user.

In cancer care, where there is rarely a simple treatment, radiopharmaceuticals are a safe, efficacious, and minimally toxic treatment that is saving patient lives. I have co-managed over 25 patients who have received Zevalin and I am pleased to continue to follow the majority of them living their lives cancer free with an excellent quality of life.

How can deprive these patients that have such a devastating disease of any modality of treatment? Cancer is ever changing, ever mutating. Every day, we discover resistance to the established agents. I urge you to please not take away a piece of our ever-limited arsenal against cancer.

It is very imperative that a targeted competency based training and education framework be developed to allow medical oncologists such as myself and my colleagues to demonstrate competency and administer these therapeutic patient-ready doses to our patients.

Also, I am the primary physician for my cancer patients. They look to me to manage their disease, to manage their treatments and their toxicities. Patients having to travel miles to see an

authorized user face disruptions in both their continuity of care and further burden their needs.

Medical oncologists are well versed in all the toxicities of these agents, even though we aren't administering them because they are intravenous, systemic, and their main toxicity is systemic, bone marrow suppression. Administration is just one simple step in the complex management of a cancer patient. We, as medical oncologists and hematologists, are prepared and willing to use these agents if we have the designation to provide them. And we are asking only for limited authorization to administer patient-ready doses of alpha- and beta-emitters.

We do not see the need to train for hours to learn certain material that will not benefit the precaution and practice that is specific to the safe administration of this patient-ready dose. And due to the constraints of caring for patients in a community practice, competency versus time-based training and education is the only way a medical oncologist and hematologist will ever be able to deliver these vital therapeutics.

Dr. Joseph Mace, who couldn't be here with us today is one of my colleagues at FCS and he resides

in the Tampa Bay Area. He currently takes time away from his primary practice and his patients to travel across the state to administer radiopharmaceuticals. He was trained over ten years ago prior to the new requirements under a shortened course and he has had no safety events and successfully administered alpha- and beta-emitters for over these ten years throughout the state.

In conclusion, I just want to express that I and my fellow medical oncologists and hematologists are asking for a limited authorized user license that is currently not available to us and there's no feasible pathway to obtain. And as you deliberate, I look to you to assess for competency, not time-based training requirements that will still give us the skills and the knowledge to safely administer these patient-ready doses that have been prepared by a licensed radiopharmacy and to continue to allow us to provide cutting-edge care and the best care that our patients deserve and expect. Thank you very much and if there are any questions, I'd like to field them.

DR. FEIN: I'm the final hematologist/oncologist here with you. We all work -- coming from Florida, but I managed to escape the storm.

I'm Dr. Steven Fein.

I'm on faculty at the University of Miami School of Medicine. I trained at Johns Hopkins and I'm in the Miami Cancer Institute. We're affiliated with Sloan-Kettering and I'm the Chief of the Hematologic Malignancies Section of the Miami Cancer Institute and I've been a lymphoma expert for 15 years. I've been using radioimmunotherapy or I should say offering and prescribing radioimmunotherapy although I myself don't administer it, because I'm not trained.

Now I'm also here to represent the ASH, American Society of Hematology and I was invited and offered myself to come from the storm on behalf of American Society of Hematology. I'm a member of the Foundation and Development Committee of the American Society of Hematology. You probably know that ASH advocates and educates hematologists and oncologists about standards of care for treating hemalogic malignancy. And ASH, in conjunction with the NCCN are strong advocates of radioimmunotherapy for follicular lymphoma.

I'm here to discuss the ASH position and also the reality of being a lymphoma doctor and lymphoma expert in our era.

First, I'm just going to review a couple of comments made by the President of ASH last December in a letter to this committee or to the NRC. The President of ASH, Dr. Charles Abrams, wrote in the letter supporting the position that we're here to request. He said, "Since the implementation of the 700-hour requirement, it has become more difficult for patients in certain parts of the country to locate authorized users who are licensed to administer alpha- and beta-emitters outside of the academic medical center setting. With this current rulemaking, the NRC has the opportunity to improve access to these potentially life-saving, anti-cancer treatments by addressing the shortage of authorized users able to administer them." And he also commented, "This could significantly improve patient access to life-saving treatments in the community hematology/oncology setting."

Now I know we're short on time, but I want to make a few comments as a hematologist/oncologist who specialists in lymphoma. Probably everybody is aware that Non-Hodgkin's Lymphoma is one of the most common types of cancer and it affects young people and old people and all kinds of individuals, all equal

opportunity cancer. Fourteen thousand new patients a year, 100,000 people estimated to be living with lymphoma. Most eventually need anti-tumor therapy, radioimmunotherapy and right now Zevalin is the only one of these available. For the longest time all chemotherapy as you heard an average of eight years and sometimes even longer. There's no other treatment that we know for follicular lymphoma comparable in terms of duration of benefit and for quality of life.

Now hematologists and oncologists rarely prescribe and rarely refer for radioimmunotherapy. I want to make the plea to you --- speak to you that the reason for this is that there's a penumbra of inaccessibility of this agent and this class of innovative, and as I said very effective, safe and effective medications. And the penumbra of inaccessibility is something that I confront with my patient. So I'm there with a patient and I'm deciding with the patient whether or not it's time to refer you to a new face to give this treatment that I know is so beneficial and so safe and effective. And yes, it's on my radar. I'm a lymphoma expert, but it's not that easy for the other thousands of medical oncologists to have this on their radar.

There's a penumbra of inaccessibility related partly just to the fact that it's a referral to another provider. A cancer patient is my patient. I don't actually want another provider to be discussing life and death with this cancer patient who they've never met. I want to actually be the one to provide these treatments that as you hear are safe and effective and easy for us to be trained to administer.

So point number two, requires referral right now to another provider because I'm not trained and authorized to infuse this medication.

Each of us, point number three, each of us has -- a medical oncologist has anecdotes about incredible successes with this agent. There's no doubt that it's beneficial, but we're not using it because of this penumbra of inaccessibility.

The first point on this slide, the newer anti-tumor treatments we've been waiting for to supplant or improve upon, radioimmunotherapy, they're coming, slowly but surely, but they're just not as good. The only other one approved in the past probably 15 years I think for follicular lymphoma is idelalisib and this one is -- we're using this, it's targeted therapy. We're all excited and optimistic about it. But we're

talking about one or two years of benefit, not 8 or 12 years and we're talking about a treatment that has toxicities that are challenging. And in fact, most recently over the past few months this agent has been found to increase mortality for follicular lymphoma patients if it's given too early. So we're really not enthusiastic about different treatments.

At one time, radioimmunotherapy was looked at as too expensive, but in the modern era over the past 10 or 15 years, radioimmunotherapy is now extremely cost effective compared to almost everything we have to offer our patients. It's something we would like to be able to use.

In addition, radioimmunotherapy is a type of innovative treatment that we would like to see used for other radiopharmaceuticals in general for other cancers and right now, the fact that the door is possibly closing on radioimmunotherapy makes me fear that we won't have that kind of innovation.

So in closing, I'm just going to say I support the development of a limited authorization for hematologists and oncologists who seek to administer therapeutic patient-ready doses of alpha- and beta-emitters that we feel are not that challenging to

be trained upon. And I say that by enabling us hematologists and oncologists to get trained, more patients will have access to Zevalin and potentially other important radiopharmaceuticals that will be coming along. That's it for me. Closing comments?

DR. SHROTRIYA: Any questions you have to Dr. Fein?

CHAIRMAN ALDERSON: I would say thank you to Dr. Cultrera and to Dr. Fein for their presentations and yes, let's open up their presentations to questions. Do the members of the ACMUI have a question they'd like to ask?

VICE CHAIR ZANZONICO: Thank you very much. We empathize with you with your travel difficulties and making it here to present to us. We're all with you.

DR. FEIN: My heart's in this. Actually, it was so important for me to get out. Thank you.

VICE CHAIR ZANZONICO: I just have a question. It's not to be argumentative, but I'm trying to understand. I'm from Sloan-Kettering. We see a lot of lymphoma patients. We have many authorized users and obviously many hematologists and oncologists who are treating these patients. Yet, in the last

number of years, I would say in the last five years, probably fewer than 30 patients at Sloan-Kettering have been treated with Zevalin. And we have a very robust radionuclide therapy program and radioimmunotherapy program, in particular.

So I'm trying to understand as a non-specialist in this area trying to reconcile why in a center which has an ample number of authorized users, a large number of patients, the choice is to use therapies other than Zevalin.

DR. FEIN: I'd like to answer that question from the perspective of a lymphoma expert and now a Sloan-Kettering affiliate. My first thought is that Sloan-Kettering is a tertiary care center, probably getting referrals later and maybe in some of the ones that are getting have already received possibly. I would think that Sloan-Kettering has trials of newer agents and they're trying to use that more, although I don't know the spectrum of trials that they have, and that maybe this is maybe standard treatments like radioimmunotherapy aren't actually the main thrust of the medical oncology group.

But I still argue, my main argument and still stands with that idea of the Sloan-Kettering

issue is that the penumbra of inaccessibility may even pervade Sloan-Kettering. It may be there where the medical oncologist doesn't really want to hand off their patient to a different face to discuss life and death, to discuss the toxicities that the medical oncologist is going to be dealing with anyway. And even though they may all be friends on the same committee and the same meetings and where they have this colleague that's ready to give the drug, it may be challenging even for a tertiary care doctor to want to hand off their patient.

DR. CULTRERA: So if I could also comment, this is Dr. Cultrera.

CHAIRMAN ALDERSON: Yes, Dr. Cultrera, please.

DR. CULTRERA: Thank you. So I did actually have this conversation with some of my colleagues back at Moffitt and I have discussed it why was it so easy for us to be able to work in conjunction when I was down there. And ironically, Moffitt did experience a loss of a couple of their authorized users after I had left, and they were beginning to have issues and their usage of Zevalin did decrease as the authorized user was not present. And one of

the things that they started turning to also was stating that they had several clinical trials that they were utilizing with newer targeted agents that weren't available to the public. So yes, I think clinical trials is a main concern, as well as the fact that some of the younger physicians, they're not -- the younger medical oncologists are not even learning about this.

I had fellows that I go and do talks to at the University of South Florida and they come back and they tell me we've never heard of radiopharmaceuticals. And I try to explain to them these drugs have been around since 2005. You need to be able to know that they're there.

One of the things that I know ASH has made a statement of is that if we are not -- if medical oncologists are not able to administer the drugs, they're not going to include it in a training program, so one of the options that I do want the committee to understand is that by withholding our capability of being able to administer the drug, you're actually taking it away from our future physicians because out of sight is out of mind. Thank you.

CHAIRMAN ALDERSON: Dr. Langhorst.

MEMBER LANGHORST: Thank you. I just

wanted to echo Dr. Zanzonico's experience at Washington University and Siteman Cancer Center. It's our physicians' jobs to partner up to fight cancer and to treat patients in the best way they can. And our radiation oncologists are authorized users for these types of radiopharmaceutical administrations and they have partnered with interventional radiology to do hundreds of microsphere cases in a year. In the past, they partnered with cardiologists in doing beta-cath treatments that wasn't cancer, but again it was to treat patients.

And in the past several years, even though we work with our oncologists all the time, we've done one or two Zevalins a year. And so if it was so great I would think they would be prescribing it. I just don't understand that disconnect and I find it very hard to believe that our oncologists would not work with our radiation oncologists in order to give their patients the best care. So I'm confused by that.

CHAIRMAN ALDERSON: Dr. Fein.

DR. FEIN: Just my answer to that is I'm agreeing with Dr. Cultrera that it's actually not even on the radar of new oncologists being trained, and it could be that some of the training programs don't have

access and there's not even a way to hear or see this. So some of the reasons that there may not be referrals to Wash U or Sloan-Kettering might be that some of the newer oncologists may not even have this on their radar because it's already falling away. It's certainly not because of lack of efficacy and safety of the agent. In fact, I again argue it's probably the single most efficacious and safe anti-lymphoma treatment, but it has to do with this penumbra of inaccessibility and unawareness.

CHAIRMAN ALDERSON: Ms. Weil will be next.

MEMBER WEIL: Thank you. So you describe a penumbra of inaccessibility and I'm a little confused about your choice of that word because it sounds to me like this is more a penumbra of ignorance, that there's been a failure perhaps on the part of companies like Spectrum to market and make the appropriate practitioners aware of this particular agent and its availability. And I'm not quite sure why.

DR. FEIN: It could very well be both. You know a lot of times patients who are savvy and hear about it through patient support groups or online will approach us and say why haven't you prescribed this? Some of us might say well, it's not something I normally

prescribe. So it's not necessarily that we've never heard of it. It's just not on our radar. Maybe some of us haven't really heard of it or used it and these are patients that don't come so often because individual hematologists and oncologists have maybe a handful of these patients, so it's not all the time on our radar. So I'd say it's both lack of awareness and education.

CHAIRMAN ALDERSON: Dr. Dilsizian.

MEMBER DILSIZIAN: Thank you very much. Again, I would like to echo the comments made regarding major medical centers. As you know, being at Hopkins, I'm at the University of Maryland. I'm an internist, cardiologist, head of the Nuclear Medicine Division. And what I was bothered with your comment I have to be honest is that you don't trust your patients to be managed by someone like me.

We have a lot of oncologists that send patients for iodine-131 treatment, radium-223 treatment. To suggest that we are not a team of physicians with expertise, that we trust each other and refer patients to each other, I find that disingenuous, I must say.

CHAIRMAN ALDERSON: Dr. Ennis was next.

MEMBER ENNIS: So I had two comments. My first actually was similar to that and then maybe -- the notion that the hematologist doesn't want other physicians to discuss -- let me finish, life and death issues is -- it's not the reality, because I'm sure you are referring to radiation oncologists and surgeons all the time to manage other diseases, so in what way is a lymphoma patient not able to converse with other specialists? Or how would that ruin the patient's management is something I don't understand and I find disappointing. So that would be comment number one.

Comment number two would be I don't have actual numbers in front of me, but from what I hear, other radiopharmaceuticals like Xofigo, for example, is doing great. I understand they're setting up a new manufacturing plant. So what is the difference? Why is that company doing well with its agent when again a medical oncologist is presumed to be referring the vast majority of those patients to nuclear medicine or radiation oncologists for that. Why is that working out well? Why are those doctors able to work together? Why is that company making money? And Spectrum and this great drug are struggling?

CHAIRMAN ALDERSON: Dr. Cultrera.

DR. CULTRERA: This is Dr. Cultrera. So I'd like to comment to the latter point first. One of the issues is also the number of patients. Xofigo is indicated in the treatment of relapse refractory prostate cancer with bone disease which is a much larger population of patients than Non-Hodgkins' Lymphoma.

I will tell you just based on the numbers that I don't have in front of me, but I can see if I can provide from my large practice is that the numbers of Xofigo administrations in our communities without the AUs is also decreased in comparison when you see them as related to when there's an academic center locally or the AU is present locally. I have seen that need for both my prostate cancer patients and my lymphoma patients.

I'm a lymphoma specialist, even though I treat everything right now so that's what I'm focusing on here in this discussion.

For the first comment, in no way did I ever once mention and I don't think any of my colleagues did either that we don't partner and use a multi-disciplinary approach. Even though I'm practicing in the community, Florida Cancer is a hybrid practice and we have a very strong research focus. We

have a very strong multi-disciplinary approach. We have tumor boards that occurs across the state as well as with our local academic centers.

And like I said, I know my radiation oncologists. I partner with my nuclear med doctors and honestly, I sat down with the ones in my area in Lake County, Florida and they have all told me that they don't want to become authorized users because they don't feel the need. The nuclear medicine doctors, in particular, have told me they want to continue as a diagnostician and they don't want to have to deal with some of the side effect profiles or liabilities that some of these systemic medications can occur. I can't speak for them, but I will tell you what they have sat down and discussed with me. Thank you.

DR. FEIN: If I may, also -- I really didn't mean to imply that we don't partner and I appreciate that comment. I apologize for making that disingenuous comment.

The partnership that I'm talking about that isn't necessary is a single ten-minute infusion of a medicine that we think will potentially give somebody eight years of progression-free survival without needing an on-going relationship with a

radiation oncology provider. It could be a one-time infusion. And so I would think that they wouldn't really need a strong partnership or even a strong relationship with that doctor. If anything, I view it sometimes and I think the other radiation oncologists view it as not really a great investment of their time to sit down and explain all this and then see that patient once for the infusion and then refer back for the potential side effects to the medical oncologist. Really, it's not so much a partnership in that case. On the other hand, prostate cancer and everything else, certainly partnership we're taking about palliation closer to terminal disease.

CHAIRMAN ALDERSON: Dr. Palestro would like to comment.

MEMBER PALESTRO: Yes, I have to tell you at this point I'm a little bit confused about what exactly you said and I'm going to go back to the discussion on Sloan-Kettering. The way I understood it you said that there were one or two possible reasons why Zevalin is so infrequently used. One is the fact that there are large numbers of clinical trials and patients are being moved into those trials. And the other is perhaps a reluctance -- I'm not trying to put

words in your mouth, I'm just trying to understand -- a reluctance on the part of the hematologist/oncologist to turn the patient over for the Zevalin treatment, whether it's a nuclear medicine specialist or a radiation oncologist. Is that correct?

DR. FEIN: In terms of my ideas for why Sloan-Kettering doesn't have so many referrals for RIT, I would say that their patient group is different including patients that have already possibly even received radioimmunotherapy or those that are sent for potential clinical trials, more innovative ideas and maybe patients that have other reasons not to use RIT as a tertiary part in their care centers. So I just don't know all the reasons why they don't have so many patients.

I would say the reason is certainly not because of lack of efficacy and safety of the medication. And just to finish, in terms -- I still say the idea is it's not really so much on our radar that it's that the idea of referring to another provider for the one infusion it's just not something on the radar of the community of hem/oc doctors. Even if it's something that we think works and works well, the patient wants to stay with us. We want to keep the

patient. We want to keep giving them treatments. And so you see doctors continuing to give every two or three month treatments, rather than sending them to another doctor for a once in eight year treatment. And it's just not on the radar, maybe not even in their training to hear about it.

MEMBER PALESTRO: All right, and if I may, a couple of points. I'm the Chief of Nuclear Medicine & Molecular Imaging in what is now known as Northwell Health which used to be North Shore Long Island Jewish Health System. And we have a very large patient population, large number of lymphoma patients. We're certainly not Sloan-Kettering. And I think the likelihood of our patients being shepherded into a variety of clinical trials as an explanation for why we do two to three Zevalins a year probably doesn't hold up. I don't think that explains the reason.

If on the other hand, an important, perhaps not the only reason, but an important reason is a reluctance on the part of hematology/oncology to send that patient to the treatment for whatever reason, I'm not sure that that's a justification for shortening training because that doesn't say to me that there's a lack of availability. It says to me that there's a

resistance to sending the patient to another physician. And I'm only basing that on what I've understood you to say.

DR. FEIN: I'd say that as not just a lack of availability, it's also more than anything a lack of it being on our radar. So if we had this list of five possible options, we'd have the ones that we're capable of using ourselves and we feel closer to and then the one that's sort of distant from us is the one where we have to send them away.

MEMBER PALESTRO: Now if I could respond to that, I don't believe that education of your specialties is the responsibility of the NRC or the ACMUI. If the treatment, any treatment, any technique -- forget treatment -- procedure, is as efficacious as it is claimed, I would find it hard to believe and I speak as a past chair of a review committee for the ACGME Nuclear Medicine that it wouldn't be included in the training.

I'm sure, for example, hematologists and oncologists for the most part don't perform PET/CTs or CTs or MR. And yet, I'm sure you're all extremely well acquainted with the capabilities of these technologies and modalities. So again, I just don't quite

understand why you would not be equally familiar with something as efficacious as Zevalin, even if you're not administering it.

CHAIRMAN ALDERSON: So I will take the chair's prerogative to do a follow up on that question. And I'd like to indicate that despite the fact that Zevalin may be a case in point, the ACMUI's current reconsideration of training and experience requirements is not about Zevalin. It is a much more generic consideration of whether the current regulations are appropriate to current training and experience and on-going safety in the utilization of a wide variety of materials. In that sense, the comment was made earlier that the ACMUI was withholding access to Zevalin. And the ACMUI is not withholding access to Zevalin.

The ACMUI has agreed to reconsider this whole issue of training and experience, the rules of which were made long before anyone who sits before you today on this panel was involved in that decision. So we plan to continue that activity and look at a broad variety of things that relate to that activity, but I did just want to make the point that this is not about Zevalin. It is only one of the effects of what's going

on.

Mr. Green has a comment.

MR. GREEN: I appreciate those comments. I heard repeatedly the phrase used, "patient ready dose of alpha and beta". And this is not about Zevalin. And we do want to have the effective review of the T and E requirements for all modalities and all practitioners who potentially handle radiopharmaceuticals. But specifically, I'll use brand names because they're easier to pronounce and the stenographer can actually type them. Zevalin, Quadramet, Metastron, and Xofigo are the four available FDA approved radiopharmaceuticals. We've lost Bexxar. So those are the four that come out typically from a radiopharmacy on a unit dose basis that we perhaps should consider whether or not we can find a way to provide a training and education mechanism for limited scope use of unit dose of alphas and betas. Those are the four that I wanted to picture that we're not just focusing on Zevalin. It's those four.

DR. FEIN: If I may augment that we're also expecting new ones to come along and the idea of opening -- or figuring out how to do this in a way that's accessible to hematologists and oncologists and might

encourage development of new agents that are even better.

CHAIRMAN ALDERSON: Yes, fine. Yes, thank you. Who else would like to make a comment on this particular subject? Yes, Mr. Collins.

MR. COLLINS: Thank you, Dr. Alderson. So I guess one thing, just a thought for consideration. Dr. Ennis talked earlier today about the importance of a physician having the knowledge to deal with the off normal or abnormal situations rather than just the textbook when everything goes well. So wherever this ends up landing in terms of the number of hours or the training requirements, I would think we need to really focus on that.

And I would express, Dr. Fein, what you described as kind of an exclusive relationship that you would maintain with the patient would concern me if whatever training program doesn't provide adequate knowledge for those off norm moments. So something to be considered.

CHAIRMAN ALDERSON: Are there other comments on this particular discussion?

DR. HILLIARD: I'd like to --

CHAIRMAN ALDERSON: Yes, hello. Is there

someone online?

DR. HILLIARD: Hi, this is Nicki Hilliard at the University of Arkansas. I'm a professor teaching nuclear pharmacy and nuclear medicine.

One of my comments is that it's 700 hours of training, but historically, physicians have done 200 hours of didactic work and 500 hours of experiential work. And that's what most people do. But I can say in this case, I'm trying to -- how would you have these physicians do 500 hours of experiential work for a patient-ready dose? They don't need to learn how to interpret images. They don't need to learn all the things that you need to learn about nuclear medicine.

So I think that if you look at the training experience, look at it not on who's referring to whom, but on what does it take to administer these safely. And I think that it would behoove us to look at a competency-based education model. That's all my comments.

CHAIRMAN ALDERSON: Thank you.

DR. WEATHERMAN: I'd like to make a comment as well.

CHAIRMAN ALDERSON: Yes, and who is speaking now?

DR. WEATHERMAN: Kara Weatherman from Purdue.

CHAIRMAN ALDERSON: Yes, please.

DR. WEATHERMAN: So I agree entirely with Nicki's statement, but I also think we need to keep in mind that the technology that we're seeing from the education perspective is changing dramatically which allows us to do a lot more interactive and engaging type of assessments and evaluating the training of some of our folks when they actually go through training programs.

And so I think a lot of times we kind of started this discussion with paper, pencil, and taking a test and things like that and I think as we embrace the changes in technology that we see in education, I think we're seeing much better educational models and training methodologies that can be done in a lot shorter period of time. And that's only going to improve with time.

CHAIRMAN ALDERSON: Yes. Thank you for that comment. We certainly are aware of those educational changes and we'll take those into consideration.

Are there other comments from people on the

line?

MEMBER COSTELLO: Yes, this is Frank. Can you hear me?

CHAIRMAN ALDERSON: This is Frank. We hear you Frank. Speak up.

MEMBER COSTELLO: Okay, I think in some ways it's irrelevant at this point whether -- why medical oncologists do or do not refer patients to nuclear medicine or radiation oncologists. I think the question really is what is the appropriate amount of training necessary to administer alpha- and beta-emitters. And I think that's what our subcommittee is going to be looking into.

But I think the problem that comes from that is that the current Part 35 changes are too far down the line and they're not going to be held up for this. Whatever the subcommittee comes up with and whatever the full committee winds up approving, even if it were to say 80 hours is enough, people should recognize it's going to be years and years before that can come into effect. That's just the way the rulemaking process works.

So ultimately, I think, our subcommittee is going to look at it, what's the perfect number of

hours? And do you use competency-based training? But we should recognize that this is not going to be a fast process and I don't know anything that could improve that. Thank you.

CHAIRMAN ALDERSON: Thank you, Frank. Frank is a member of this committee, but he could not be here today, so he is speaking by phone from his home.

Are there any other calls from outside?

OPERATOR: Yes, sir. We have just one at this time. Karl Schwartz, your line is open.

CHAIRMAN ALDERSON: Very good.

MR. SCHWARTZ: Yes, thank you. My name is Karl Schwartz. I'm President and Founder of Patients Against Lymphoma. I've also served as a research advocate on the Alliance, the Cooperative Groups, and the NCI Steering Committee. I want to thank the committee for hearing the concerns of patients. I think many of the prior speakers have done that eloquently on behalf of the patients.

I'll limit my comments to what hasn't been discussed or what still appears to be an open question among the committee members. I want to point out that a study I've cited in my written statement shows that 80 percent of patients are diagnosed and treated in the

community setting. So I think the point made earlier that elderly patients and patients in the community with lower incomes may not be able to even be referred to a nuclear medicine center.

So as a member of the Alliance, I worked with Dr. Bruce Cheson, who was the chair at the time and he didn't say this then, but he has said that I could make this quote, "That oncologists must send their patients elsewhere to receive radioimmunotherapy is the major reason for the low usage of this effective treatment."

So I think we should not expect that research concepts will develop when there is this lack of access to a drug. Why put your resources into the study of a treatment that is not widely available to the patient?

So I also want to make a comment that -- about the Cancer Moonshot. The purpose of that is to foster treatment innovation, but it's also to ensure that innovations are accessible to the patients. Here, we have a new kind of drug that's half drug, half radiopharmaceutical, if you will. And I think it's a precedent-setting situation. It's a new type of therapy. It really is easy to administer and I know

that first hand.

My final point is it's not a me-too drug. It is perhaps the least burdensome treatment available to patients. It takes very little time to give it as described by the speakers. And it can lead to very durable remissions lasting many years. My spouse is in remission now for 12 years.

Finally, about conflict of interest. I think it's important to recognize that it exists, but it's not an inferred way. It is often unconscious -- it leads to unconscious decisions. We have many choices for lymphoma, but this drug is a unique choice. It has unique aspects that make it better suited for elderly patients who cannot tolerate chemotherapy. It's the only drug that can be given with so little burden to the patient that can achieve that goal. So I think it's important that we recognize that the patients are the primary stakeholders in the healthcare system, and we need to adapt and adjust our policy when new drugs come on the market for this drug and for future drugs. Thank you very much.

CHAIRMAN ALDERSON: You're welcome. Are there any other final comments on the phone?

OPERATOR: There are none, sir. Thank

you.

CHAIRMAN ALDERSON: There are none, so we're finished with those comments. And we'll turn our final comments here around the table.

Dr. Fein, do you have such comment?

DR. FEIN: Just, I'd just like to reiterate that it isn't just Zevalin. I'm here to talk about lymphoma and ASH's perspective which is focused on Zevalin for now. The bigger issue is this sort of practice for training and future access for hematologists/oncologists will enable, if we can find a path to get trained, it would enable and encourage companies to develop more radioimmunotherapy that will be part of the innovative treatments for the future. This is not just about what we have now. It's really focused on the future.

CHAIRMAN ALDERSON: Thank you. Thank you. Are there other comments?

DR. SHROTRIYA: I'd just like to make some final comments.

CHAIRMAN ALDERSON: One from the audience.

MR. SHEETZ: Mike Sheetz, University of Pittsburgh. I can understand your position to reduce

the training and experience requirements for Y-90 Zevalin, similar to what was done on I-131 sodium iodide. But I caution the committee on reducing the training and experience requirements for patient-ready doses as the FDA will likely approve lutetium-177, dotatate later this year, lutathera which is a 200 millicurie administration, slow infusion, concomitant with an amino acid cocktail that could have adverse reactions so the patient would have to be admitted and so there are other products that may come down later. Patient-ready doses require much more knowledge and effort on radiation safety and issues of administration.

CHAIRMAN ALDERSON: Thank you, Dr. Sheetz. I don't want to get off into a discussion of that comment because that comment is generically relevant to these discussions, but not otherwise.

Are there other comments? Yes, from the audience.

MR. GOLDMAN: Good morning. I'm Ira Goldman from Lantheus Medical Imaging. We're the manufacturer of Quadramet. Just speaking on behalf of CORAR which Spectrum is a member. CORAR which is the Council Radionuclides and Radiopharmaceuticals.

We're an industry group. We have corresponded with the committee.

We are supportive of a new look at these requirements. We do think that there needs to be a reduction in the requirements because as several people have noted, not only are there a number of radiopharmaceuticals on the market today which we believe are under utilized. There's a complex of reasons for that, but we do think these training requirements are excessive, but as noted, we do see new radiopharmaceuticals coming out in the market very soon which, you know, have a lot a promise for treating cancer and it would be a shame if some of these new drugs suffered some of the difficulties and under use that we've seen from some drugs that have been on the market for some time. Thank you.

CHAIRMAN ALDERSON: All right, any final comments? We're about to close the session. Yes. Dr. Shrotriya.

DR. SHROTRIYA: Chairman Alderson, thank you very much for giving me this opportunity to make some final comments. I'll make four points.

First of all, we didn't invent this drug. Biogen Idec did. And after 700 hours of training

killed their interest in this drug. And four years later, they walked away from it. Bayer Germany was the developer of this drug in Europe and they walked away from it. Spectrum came onto the scene about ten years ago. And we made this patient-ready dose. It was not a patient-ready dose at that time. In fact, when FDA approved this drug, it was only for a lapse of refractory indication for lymphoma. We dictated their trials and got approval from the FDA in 2007 as a first-line palliative treatment for lymphoma. And were really aggressive. We have 50 people transferred to educate physicians and to get this done. We were absolutely frustrated by 700 hours of training. Physicians dropped their hands. And keep in mind, the other treatment that the people use for this was given every three weeks for two years to these elderly patients and it cost them hundreds of thousands of dollars and inconvenience.

So FDA has been really kind to us that we have received now another indication for this drug and we have gotten rid of the requirement that first we have to give a dose and get a bioscan. So to do that, patients had to really be in a hospital setting.

The second point I want to make is that

innovation, if these drugs walk away like Bexxar has gone away and Zevalin will go away. I can assure you, I'm not investing and continuing to market this drug, but it's not about Zevalin.

I'm here to talk about the radioimmunotherapy. As a practicing physician, I want these drugs not to go away, as you heard from Dr. Mort Diamond. We want these drugs to be encouraged that they should be used. If physicians and oncologists, 80 percent of these patients are treated in community centers, not in major centers where they have access to authorized users. And their people want to be able to give this drug to their patients like they give other treatments. Right now, they cannot do it.

Third point is our safety and access, patients' access. And please, I urge this committee to make recommendations for a revised training, that I believe is somewhere between 20 to 80 hours, but certainly not 800 hours. And I would like to urge you, request you that we don't wait for the next five years. Please do this as soon as you can. Thank you very much for this time.

CHAIRMAN ALDERSON: So I am going to take the chairman's prerogative to call this session to

close. We're almost ten minutes over time. I think it's been a wonderful discussion from people on all sides, both in the room and on the phone, and clearly it's going to be an issue of great interest to the committee, the subcommittee, as the ACMUI moves forward. So with that, this session will conclude and we will reconvene at 1 p.m. Thank you very much.

(Whereupon, the above-entitled matter went off the record at 11:35 a.m. and resumed at 1:00 p.m.)

CHAIRMAN ALDERSON: All right. We're going to reconvene the meeting of the Advisory Committee on the Medical Uses Isotopes for the Friday afternoon session.

Before we begin this session and for the record, Esther Houseman would like to enter a numerical correction from the discussion of the last session.

MS. HOUSEMAN: Yes, thank you. I wanted to correct a number that I provided in response to Dr. Zanzonico's question of how many hours of training and experience the NRC proposed in its -- it was the 1998 proposed rule. And that's the training and experience requirement for therapeutic use of unsealed byproduct material.

I said that I thought it was 80 hours. It was actually 120 hours. That's 80 hours of didactic training and plus 40 hours of practical experience. And then as we all know in the final rule that changed to 700 hours. So I just wanted to be sure to correct that number for the record. Thank you.

CHAIRMAN ALDERSON: Thank you very much.

All right. We'll proceed now with the new session, which is the worldwide supply of molybdenum-99. And Mr. Richard Green will provide and update for us.

MR. GREEN: Good afternoon. Thank you, Dr. Alderson. It's kind of a horrific experience to try to summarize the worldwide supply, and I don't speak on behalf of any of the suppliers. In my position as a nuclear pharmacist I'm a consumer of molybdenum and technetium, so I'm going to give you my perspective as a purchaser and user of technetium. I'm pleased that we do have some representatives in the room today who are actually manufacturers in that supply chain and hope they'll be able to speak.

So we'll look at the supply chain, and it is a global supply chain. One thing we can say today, none of the moly is made in America. And that will be

changing I think in the near term. We'll look at how we might have a ripple in the supply chain with the later this month closure of the Canadian Chalk River reactor, the NRU reactor, the National Research reactor that's been the major supplier of worldwide molybdenum for the last 50-plus years.

Can't get away from this topic without throwing in some comments about how changes from highly enriched uranium to non-highly enriched uranium will also impact supply, and that's got to do with the Global Threat Reduction Initiative. And then we'll get into some bright aspects of potential new supplies that have not been on the map before that are actually domestically located in the U.S.

First of all, for those who may not know, we're talking about molybdenum, but I don't use molybdenum in patients. It's the decay product of moly-99, which is tech-99m, the six-hour half-life gamma emitter that we use in diagnostic imaging and nuclear medicine. And so from the worldwide standpoint the U.S. consumes approximately 44 percent of the worldwide supply of this isotope, but probably since the mid-'80s we've not manufactured any of this on our shores. It's all been sourced from outside the

United States. So we consume at least half of the world supply of moly-99.

What do we do with moly-99? It is used to prepare technetium-99m radiopharmaceuticals where we could attach a compound to the isotope that's going to take this radiopharmaceutical to a different organ system: hearts, lung, liver, gall bladder, whatever the physician would like to see. And today there are 14 tech-labeled radiopharmaceuticals where as you can see from the graph the vast majority of which are used in myocardial perfusion imaging, at over half of the entire volume. Coming in second would be the bone scan looking for metastatic spread of cancer.

But, so technetium is today the workhorse in nuclear medicine and it will continue to be so in the future. There's new compounds that are gallium labeled, gallium-68 that will be a topic for discussion again later this afternoon, which is new and upcoming, but tech is always going to be our workhorse as long as we have access to it.

So real briefly, today's supply of molybdenum-99 originates in a nuclear reactor. There are lots of reactors around the world that can produce fission and split atoms and make heat and make steam

and make turbines, go around to make power, but there are very few that are dedicated or available for radiopharmaceutical production. And today that is seven reactors in the entire world. Well, seven that produce moly commercial scale that are used in generators that are available in the United States. There are smaller reactors in Argentina, Russia, South Korea that can produce small-scale quantities that might serve local markets, but for U.S. use there are seven today.

And so it's when uranium-235 fissions are split by being hit by an incident neutron, we're going to break that atom into pieces. Six percent of fission byproducts are molybdenum-99, so they're going to sort through the pieces and pull out moly-99 and send it off. That sorting occurs at a processor. So you have the reactor that's going to take the target of clad uranium-235, put it in neutron flux, have it smashed into pieces, if you will, and then the processor is going to chemically dissolve that in a hot cell and purify bits and pieces.

We're specifically talking about moly-99, but also from this fission process we'd be getting iodine-131, xenon-133 and many other nuclides that are

useful in nuclear medicine. So there are five processors that are going to sort through the bits and pieces.

Here in the United States we have three commercial manufacturers that have FDA approval to provide molybdenum-99 generators. There are three depicted on the slide here. The first one, the upper left-hand corner is GE's product that is actually made in Amersham, United Kingdom and flown across the Atlantic in finished form. The Lantheus Medical Imaging is the white with the blue label. That comes out of Boston, Massachusetts, or -- what's the suburb? Anyway, Boston.

Billerica. Thank you. North Billerica. And Mallinckrodt Medical in St. Louis is the one depicted in the lowest picture. So there are three commercial manufacturers that can provide the industry, whether that be hospitals or radiopharmacies, moly generators today.

We need to have a little discussion about where the world is going. We talked about uranium-235, enriched uranium. We have to dig uranium ore in the earth to find the ore to make yellow cake to enrich. There's a threshold. Twenty percent or below is

considered low enriched uranium. Above 20 percent is called high enriched uranium. And as you get higher enrichment -- with low enriched uranium you can fuel the nuclear reactor, you can make pellets and put them in a reactor and have fission.

Well, when you get high enriched uranium, you have the potential to make a nuclear bomb, make a weapon out of it, to weaponize it. And so there have been efforts in the recent past to limit the use of highly enriched uranium to manufacture radionuclides and molybdenum-99. And there's a slide on that later.

So there are concerns going forward that will affect this whole dynamics of supply is what are you using to make the moly? Is your reactor fuel highly enriched? Is your target highly enriched? And when are you changing to low enriched, because that is the directive we received from Congress to link the threat of potential terrorism acts by limiting access to high enriched. So it is the reactor fuel and the targets that are both involved.

I've attempted to take this -- I apologize. There are some very small fonts in this slide, but it shows the complexity of the moly-99 supply chain. The top bar in blue is all in the reactor. And so it's

around nine days total time to take targets of clad uranium and put them down into the target chambers, the slots, and bombard them with neutrons for four to eight days to split uranium into pieces and then take out that very highly radioactive target and take it into a hot cell and chemically purify that, separate it out and come out with the pieces that you want. The rest gets relegated to radioactive waste. So it's got nine days on that first horizontal bar.

Middle bar in the yellow or orange is a transportation cycle to get that to the manufacturer, to Lantheus Medical Imaging or Mallinckrodt or GE where they have to put it into a form that's been approved by the FDA as a commercial drug product that comports with their license application package insert.

And then logistics, to get that to the point of use. So as you'll see in a minute as I pull up a worldwide map, we may be going from Central Europe to North America to San Antonio. So there's a lot of logistics that is behind the scenes that if pharmacists do their job, it's transparent to the physician, it's transparent to the patient. The stuff is just there. But there's a lot involved in this process.

The very last line, the line in greenish

tint is local. In your community, at your hospital, at Sloan Kettering or in your communities where the generator arrives Federal Express, where a pharmacist or technician can get access to that and extract short-lived technetium from that molybdenum generator and then finally prepare kits and get doses out to the patient.

In the U.S. today over 90 percent of all radiopharmaceuticals, not just technetium-labeled, but all pharmaceuticals originate from a centralized nuclear pharmacy. So that's why we have the unit dose led pig depicted in the car, because we're going to make that at one site and then transport those to the 15 or 20 hospitals in town and out-patient clinics that are there as well. So it's part of the logistics process.

If we go back to the beginning, to the reactors, let's look at a list of reactors and physically where they are and; although this is a little bit shocking, how old they are. The NRU is in Chalk River, Canada. It was commissioned in 1957 and it is closing 24 days from today. Okay? Halloween. That's a kind of scary day. But October 31st is when they will stop the commercial manufacture of radiopharmaceuticals. They're still going to be up

and running for other industrial purposes. It's a great source of neutrons, but they're not going to be manufacturing molybdenum.

So with that impending closure is that going to destabilize the market? Will there be no supply? If anyone lived through the 2009-2010 moly crisis, you're thinking, oh, my God, here we go again. Well, I can tell you the world is different. Back then we didn't have the collaboration between the Association of Imaging Producers and Equipment Suppliers or AIPES. We didn't have the Organization of Economic Cooperation and Development, or OECD, that coordinate between reactors so that they're not inadvertently all down at the same time for maintenance.

They coordinate their maintenance and say, okay, you go down this month. I'll stay up and I'll go down the next month. Because these guys, if you look at that list, there are many generators here that I can say are older than I am. And if my knees are rickety, I'm sure theirs are, too. The only one at the bottom, the Australian reactor in Lucas Heights, the ANSTO OPAL reactor, is new, 2007.

In addition to this list you can see the

fuel type. Many of the reactors are still using highly enriched uranium or HEU. That's no longer going to be available I believe this year or next. So they're going to have to convert over to using LEU as a fuel type. And then the targets will have to convert over from HEU to LEU.

Now, is that a big deal? Well, it affects the commercial scale of manufacturing. I don't know what enrichment they're using for their targets, but if we just simplify it, LEU is 20 percent or less. HEU could be as high as 100. So if you go from H to L, you may have to have five times as many targets to get the same amount of moly. You're also going to generate up to five times as much waste to get the same amount of moly. So that will affect the ability to produce and the cost to produce. So more on that later.

But as you can see they're old and none of them are in the United States.

Here's another way to depict the current supply chain maintenance. The HFR, which is closely associated with Mallinckrodt, is in the Netherlands. They're a large-scale producer. After the 2009-2010 moly crisis Mallinckrodt was able to pull up additional resources. I know that the Maria reactor in Poland was

an additional new entrant to the commercial marketplace. Same with the LVR-15 in the Czech Republic.

And very recent is the OPAL reactor in Australia. They've been producing for quite a while for domestic use in Australia, but they now can produce for the U.S. I know that Lantheus is sourcing some material from Australia and is able to provide not just moly, but on certain production cycles LEU generators that are entirely manufactured without any HEU product within them.

So those three commercial manufacturers of generators: Mallinckrodt, GE and Lantheus are connected, interconnected with multiple reactors and multiple processors. They don't put all their eggs in one basket. We've seen that have bad outcomes. So they've diversified their supply chain, which we in the industry are very appreciative of.

So the other thing is that the OPAL reactor has invested in the Australian Nuclear Medicine Project and they will be tripling their capacity. I made the business trip of a lifetime a year ago and flew to Australia to see that reactor. It's an amazing thing and they will play a more important role in domestic

supply of moly in the U.S.

Another way to look at it, geographically superimposed on a map. You can see that the only reactor in North America is that Canadian reactor, which was opened in 1954 and she will be closing Halloween of this year. Okay. Now that's -- depending on how you look at your numbers, that may have been 40 percent of the supply. So will we manage without them? It's my opinion that we will. Because of the coordination between the reactor producers, the processing plants that target the targets and the generator manufacturers I think we'll have very good supply going forward.

As I mentioned earlier the American Medical Isotopes Production Act of 2009 for the first time that I can recall put forth U.S. money to support the production of isotopes used in nuclear medicine. And I think that's great. At the same time they said let's reduce the risk of potential terrorists acts using highly enriched uranium. So let's keep that to ourselves and not send it out there to places where it may become vulnerable.

So seven years after enactment; so I guess that's 2016, right, we're not going to provide HEU to

a reactor that might be giving us moly. They need to convert over to LEU. So that will change their efficiencies and their number of targets and their waste. But I think that's a good thing going forward for stability of supply and for safety and the world. So as we talk about supply, this is a part of it, conversion to LEU from HEU. So the Global Threat Reduction Initiative was enacted to eliminate HEU as a source of medical isotopes. So GTRI is a worthwhile act and it's going to also play a role in supply.

Currently HEU is only sourced from the United States and from Russia. You can't buy it at a convenience store. There are very limited supplies and sellers that sell that. So you can see on the slide here that of the number of reactors; at that time it was 10, that only 3 have converted to LEU targetry. And that's a very small percentage.

Now there are lots of folks who can theorize in why this has been a slow conversion to non-HEU, and I think it's all based on economics. We have a large supplier to our north in Canada that's using highly enriched targets and highly enriched fuel, and they're economical. But once they're out of the mix I think we'll see a much more rapid adoption to the

LEU targetry and LEU fuel. But that does have to happen. That will be the case going forward.

So we've talked about supply of moly from reactors. There is a bright spot on the horizon. Oh, I got my slides mixed up.

So there may be disruptions. There's going to be unplanned shutdowns with old reactors. Hopefully they can schedule coordination of maintenance. There are permanent shutdowns coming in Canada. We've already had one French reactor, the OSIRIS, go down two years ago and is completely offline today. And the other large producer in the Netherlands, HFR, is targeted for replacement. So it has a finite life cycle as well.

Another thing that's on the horizon is what's called full-cost recovery. Where we've always thought that neutrons were cheap and they were available, we could just kind of use that reactor to make isotopes in addition to whatever else it's doing, that has undervalued the production of isotopes and made them perhaps artificially cheap. So now with full-cost recovery the OECD has said we've got to stand on our own two feet and we can't have government subsidizing that reactor. So we're going to see much

more transparent perhaps of costing of the production of isotopes. We have to pull our own freight.

But the light that I see is that there are some U.S. producers coming on the market. I think are blessed to have a presentation shortly from NorthStar Medical Isotopes. Oddly both of these folks are up in Wisconsin, but they are going back to an old technology. They were the very first nuclear moly generators that were made in the U.S. were made with irradiated moly-98.

And so it produces moly-99, but it's low specific activity. It takes a large column or other ways to concentrate the product. And NorthStar is submitting before the FDA, as you can see depicted here, a multi-unit computer-controlled generator. Today's generators are a giant chunk of lead or depleted uranium, no user service to the parts inside. You don't plug it in. It's very simple. You use a vacuum and you suck saline through and you withdraw the technetium from the mother isotope. It's very simple.

They're looking an innovative technology to separate and concentrate the technetium from this low specific activity moly. So their short-term use intention is to produce moly from moly-98. I believe this will be the MURR, the Missouri University Research

Reactor in Columbia, Missouri. And then longer term use a nuclear accelerator to take moly-100 with a P2N reaction to moly-99.

The second firm that I should mention is Shine Medical Technologies. They are looking at an innovative way to use -- to obtain neutrons, not from a reactor, but from an accelerator, where they accelerate protons to hit a target to generate neutrons to cause fission in a source of liquid uranium salts. They can colloquially open the tap, take some of it out, chemically purify the moly and put the leftovers back in. And so that will be again another domestic source of moly-99 that won't be using a traditional reactor.

Now just recently, it may have been the last week, there was the National Academy of Sciences publication that in my mind was Chicken Little. Is the world going to fall? Is the sky falling? Are we going to have a repeat of 2009-2010? It's my opinion that we won't see that. I think there's been great collaboration between the reactor managers and the producers.

The OECD has projected this out. And you can see the green line is the demand, current demand with a slight increase over time. We see nuclear

medicine getting slightly higher volumes as we recuperate and come back from that moly crisis in '09 and '10.

The blue line is the drop in processing capacity. Again with the departure of this Canadian reactor we're also losing one of our processors who used to dissolve targets and separate out the moly.

The yellow and red lines represent production capacity with outage reserve capacity. And this is where they planned. A reactor may have -- and I'm making up numbers in my head. A reactor may have 50 target slots where you could put something in there and bombard with neutrons. And because of the supply and demand the manufacturer of the generators rents out 16 slots and they put targets in those 16 slots, and that gives them enough moly to meet their demand.

Well, what they've done now is they don't rent out 16 slots. They may rent out 20 or 24 slots. They may not slip targets in all of the, but they've got reserved space, outage reserve capacity. So if a reactor goes down or has a maintenance issue, they can insert their targets into their reserved spots to produce moly.

So now; and knock on wood, we have the

ability to -- even with one less reactor and one less processing plant I think we'll have a fairly stable supply of moly going into the future. Again, in addition to this we have the opportunity to have some domestic supply and some innovative sources that we have not had in the past.

So in my mind; and this is my opinion, I don't think the sky is falling. I think we'll be able to serve our patients and look forward to some innovative ways to get the moly that we need. Thank you.

CHAIRMAN ALDERSON: Questions from the ACMUI? Dr. Zanzonico?

VICE-CHAIR ZANZONICO: It was my understanding at one time that I guess it was Medicare or one of the payers was paying incrementally higher reimbursement for using technetium from a low enriched uranium. Is that still in effect?

MR. GREEN: That's still the case. CMS does offer, if you ask for it, a $10 supplemental reimbursement for unit doses or patient doses of technetium-99m radiopharmaceuticals that were prepared; and I'm going to correct you slightly, with technetium obtained from non-HEU sources. Now we have

to call it non-HEU. It's so much simpler to say LEU, but as I just showed you on that last slide we have a couple processors here who'll be making moly that doesn't start from uranium. So it really is correct to say non-HEU.

So, yes, they're trying to realize that with the full-cost recovery, with using much less efficient low enriched uranium as targetry and a fuel the cost is going to go up. And so they said if you are going to get unit doses of tech-99m pharmaceuticals from sources that are 95 percent or greater non-HEU and you submit the request, we'll give you $10 per patient. I don't know exactly how long that will be, but there does need to be a little bit of a readjustment with reimbursement because the world is not going to be as cheap as it is today.

VICE-CHAIR ZANZONICO: Another question. So as we transition, at least in part, from international to domestic suppliers, I can't imagine shipping radioactive materials in general internationally is cheap. Could we anticipate a reduction in overall cost of technetium as it becomes more domestically produced and shipping costs presumably go down?

MR. GREEN: I'll let the manufacturers speak to actual -- I would think that transportation is probably one of the smallest cost variables. I mean, it's one flight out of Belgium, I mean from the IRE reactor, from the Netherlands reactor. We had a problem where there was terrorism in Belgium. We had problems when there was a volcano on Iceland. That shouldn't be a problem if we have a domestic source.

I think any domestic production puts more moly in the pie. So whether it's a U.S. producer or some produced in South Korea or Russia or Argentina, that's just more in the worldwide supply. So I think transportation of the bulk moly -- it's one cask on one flight, so I really don't think that will play much role.

CHAIRMAN ALDERSON: You describe, Mr. Green, that short term the reactor at the University of Missouri is going to come on line to fulfill an amount of the need. How much of that need and how long? I mean, you say "short term." What does that really mean?

MR. GREEN: Well, I think they're standing up a processing plant so that they can chemically separate out isotopes from their targetry. So that's

nice that we'll have a domestic processor. I know that -- and again, I won't speak for their; they're coming up shortly, but I think NorthStar has a short term -- with the unenriched moly-98 they can only make I think a generator that may be a six-curie generator.

Well, once they get the other processor using enriched moly-98, they can make a higher activity yield. Because right now as a nuclear pharmacist I can get my hands on and 18 or 19-curie generator. So having to have multiple six curies would be quite inconvenient and quite cumbersome. So their first out-of-the-gate is make some and then later make improvements and make it more available. So we'll have more.

Again, I don't know what market share they're targeting to acquire, but any moly produced in America I think is positive.

CHAIRMAN ALDERSON: Thank you.

Dr. Langhorst?

MEMBER LANGHORST: Just to clarify, University of Missouri Research Reactor is working with these companies, and NorthStar is one of them, to irradiate this, but MURR is not setting up their own processing plant. So they're working through some of these other companies that are trying to establish

domestic --

MR. GREEN: Good. Okay.

MEMBER LANGHORST: -- production.

MR. GREEN: Good. Thank you.

CHAIRMAN ALDERSON: Other questions?

(No audible response.)

CHAIRMAN ALDERSON: From the audience, anything?

(No audible response.)

CHAIRMAN ALDERSON: Yes?

OPERATOR: If anyone on the audio lines would like to press star, one to queue up for questions or comments.

CHAIRMAN ALDERSON: We'll take one question here in the audience.

OPERATOR: Thank you.

CHAIRMAN ALDERSON: Yes.

MR. GOLDMAN: Ira Goldman, Lantheus Medical Imaging. I'm also the co-chair of the CORAR Isotope Supply Committee and the vice-chair of the AIPES Reactor and Isotope Working Group.

I'd like to thank Rich. I think you made a very good concise presentation about the current state of supply and the perspective. A couple things

I would just add.

People are worried about the end of isotope production in the NRU, which is less than a month from now. As he noted the NRU will continue to operate even though they won't be producing moly-99 and the Canadian government has announced that they will have an arrangement in place that if there is some severe disruption of isotope supply up until the time of the end of March of 2018 when the reactor will close permanently, then they will be prepared to reenter the market to provide an emergency backup supply arrangement. So that's an important insurance policy.

At the same time, he mentioned, Rich mentioned, the Australian Nuclear Medicine Project, which is going to -- which is building a new processing facility. And they're currently hoping to be online by the middle of next year. But at the same time Australia has recently increased its capacity from its existing processing facility, whereas they were making about 1,000 curies a week and now they're up close to 2,000 curies per week.

So with the NRU and Nordion not supplying after the beginning of November of this year there has been already a step up in capacity from Australia.

Plus Belgium has been authorized to produce at a higher level. Mallinckrodt has announced that they're going to be producing moly at a higher level. So it looks like there is new capacity already coming into the system even before some of these new projects, including the U.S. projects, actually would produce moly-99.

So the only thing is, is that there will be fewer processors and fewer reactors even if there is equivalent capacity that does create some vulnerabilities and less overall spare capacity in the system.

So we do expect industry -- both AIPES and CORAR are confident that the industry because of the measures that have been taken over the past five years to further diversify supply, bring new reactors online, bring new capacity online, that there will be the ability to reliably supply sufficient moly to make technetium generators.

The one thing I would note is that without a local processing capacity here in North America, which provided us the ability sometimes to get last-minute moly when there was a disruption, even just a logistics disruption -- because the moly that does

come from overseas comes on commercial aircraft. And so there are sometimes problems with that. So we've had the luxury of being able to kind of call up Nordion at the last minute. And since, at least for Lantheus, it's only an hour flight away, they've been able to kind of ruffle out some short-term problems. That's not going to be available.

So we may see just a little bit more kind of fluctuation where you may have a problem on a day basis because of a transport problem or the like, which is inevitable in this far-flung supply chain.

But the message is we do feel that the situation is manageable. New capacity will further be coming online in the next year and beyond that. And we're pretty confident that barring some unforeseen disaster there will be a sufficient reliable supply over the next few years.

CHAIRMAN ALDERSON: Thank you. Are there other comments or questions? Yes?

MR. FULLER: I just had a question, and I think, Mr. Green, you should probably be able to help me out here, but others in the room might also as well.

Years ago, many years ago; I'm old enough to remember when, basically moly and technetium-99m was

the absolute workhorse when it came to nuclear imaging studies and so forth. But now we have other PET pharmaceuticals and so forth. Could you give us an idea of the mix now? If you talk about total imaging studies, how many are moly-based and how many are -- or what percentage -- just kind of like a big picture, please?

MR. GREEN: Eighty-five percent are still technetium-based. Xenon, thallium, gallium-67, gallium-68, all the fluorinated compounds, Y-90 compounds. But still 85 percent is technetium. They're still our workhorse and are going to be in the future.

CHAIRMAN ALDERSON: Thank you, Mr. Fuller. Any other questions?

(No audible response.)

CHAIRMAN ALDERSON: Seeing none, thank you very much, Mr. Green, for a fine report.

And that will carry us onto the next presentation. Dr. Howe and Dr. Dilsizian are going to talk to us about the NorthStar Generation Licensing Guidance.

DR. HOWE: Thank you, Dr. Alderson.

Let's see. Oh, let me back up a little

bit. The subject of my discussion is going to be the NorthStar and our licensing guidance. The first thing you're going to notice on the cover slide is it's not just medical use licensees. It is also for commercial nuclear pharmacies. This is one of the first guidance documents that has covered more than just 35.1000.

On my next slide I'm going to -- I'm showing you an image of the NorthStar generator. The first thing you notice is it's not your grandparents' moly generator. There's a little square over to the left-hand side that says, source vessel. That source vessel is roughly the size of a current big technetium moly generator. And Richard Green gave us a nice description of the current fission moly generators where you put liquid in the top, you elute the technetium off of the column. Then you have your technetium for your radiopharmaceuticals.

In this case you have a source vessel. The source vessel is a vial inside of a heavily-shielded transport container. And if you look at the diagram, you'll see four different doors that are labeled as transfer doors. And those are the locations that you put each one of these source vessels in. You have to connect it out to the rest of the device. And that's

where the moly is going to come from.

Now the source vessel goes into the transfer door, gets connected by tubing. It goes up into the service bay door. The service bay door is where the heart of the NorthStar generator is located. It's where the syringe pump is located. It's where the multi-barrel distribution point is. Because you're going to do a lot of -- you're going to do some chemical separation preparation here. And at the top right above the service bay door there's a white thing, and that white thing happens to be the chemicals that you're going to be processing through this device.

So what happens is you take the moly and you pull it out of the source vessel. You ship it up through the service bay door. You distribute it to where it needs to be at that particular point of the process. All of this is computer-run. And you see the computer screen over to the side. There are about six protocols. Each protocol is a step in the moly production or a step in changing out a source vessel or a step in changing out a waste area, and it's multi steps.

So now the moly goes from the service bay door into a column behind the PSC door. The PSC door

-- unlike the technetium moly generator that holds the moly and lets the technetium come off -- this particular device holds the technetium and lets the moly flow through.

So where does it flow? It flows down to the box between the four transfer doors, and that's the -- well, the four source doors -- and that's the transfer door. And it goes into a location there. And then later on, once the process is finished for that particular amount of moly, it is transferred back to the source vessel that it came from. Okay?

And so then you process further behind the PSC door and eventually you wash it with chemicals coming from the top of the device and it will come off in the product door. And that's where your technetium is produced.

Now, this particular device is regulated by both the NRC from a radiation safety perspective and also the FDA, because this particular device is the final step in the manufacturing of technetium. And because it's regulated by FDA, there are some considerations that FDA has that we're not concerned with, but they definitely affect radiation safety.

You're seeing a device with a lot of doors.

All of those doors are locked. A pharmacy will have to go in to almost every one of those doors at some part of the process to take out a component, to set up another component, to change out a chromatography column, to change the product door column, and everything has to be done in a sterile manner. So there's also an ozone sterilization process associated with this device, so that adds additional steps.

And each time you open one of those doors the source shield is highly shielded, the doors are shielded, the container -- the cabinet that you have the door connected to is shielded. You now are opening up a shielded area if you have a potential for high radiation levels depending on where the moly is in the process, because the moly is being moved throughout this device at various times in its processing. And so you end up with additional radiation safety concerns that you don't have with a regular generator.

The other thing I want to point out is the heart and soul of this device is the service bay door. It is locked. It has components that are specifically designed for NorthStar to be used with this moly that are not accessible or available or need to be accessible or available to the end user. So that door is

incredibly important and there's only one person at the facility that has a key to that door. And that door doesn't open without the direct -- I don't want to say supervision, but the direct correspondence with NorthStar. So as you're seeing from this description this is not your grandparents' generator.

So we were tasked -- we had a committee made up of NRC and Agreement State individuals to look at this generator and see whether it could be regulated under our current regulations or it would need to come under -- for the medical use, 35.1000.

Our committee is -- as co-chair we have Marc Paulson from the State of Wisconsin and myself from the NRC. We have three other Agreement State representatives, Elaine Crescenzi from Pennsylvania; Karl Von Ahn, who started out from and then transferred to Texas; and Jason Kelly, who is in Texas; and three more NRC employees, Lymari Sepulveda, who is a member of the Sealed Source and Device Registry Group, because we felt we needed to look at this device in the same level of detail that you would for a device in the Sealed Source and Device Registry; and Cassandra Frazier in Region III and Maryann Abogunde, who is here in headquarters.

So we looked at this device and we said it's a closed system. It contains, moves and shields all moly-99. And this moly-99 comes in as a mixture, because it's always decaying, of moly-99 and technetium. And it can either come from moly-98 or it can either come from moly-100. It is computer-driven, so that makes sure things are going in the right sequence, the right valves are opening, the right valves are closing, but there is a lot of human intervention in here to change out from one procedure -- from one protocol to the next.

The materials used in this generator and the components are engineered to maintain the device's integrity as a closed system, withstand high radiation fields for extended periods, and to maintain adequate shielding when all the doors and the excess shielding is in place. It's designed and constructed with components that differ significantly from conventional moly generators, fission moly generators.

It needs additional information and commitments in order to be used safely. And it needs additional training and experience for individuals and it needs additional components to address specific training and safety -- commitments to address specific

training and safety provisions. And for those reasons we put it in 35.1000.

You will see at this slide it says not only 35.1000, but 30.33. 30.33 is the general licensing regulation that we have for regulating all byproduct material. And we felt that in order to put this generator in a commercial nuclear pharmacy that the current commitments that a commercial nuclear pharmacy has made are not adequate and the current training and experience requirements for the commercial nuclear pharmacy are not adequate to safely use this device. And so we are addressing those issues in our guidance also.

So our guidance is pre-decisional at this point. The ACMUI has reviewed the guidance. The Agreement States are reviewing it. Our regions are reviewing it. They're providing comments back to us. Dr. Dilsizian will give you a summary of the ACMUI review of the document.

So in our licensing guidance we're going to have some of the things that you see in all licensing guidance. We're going to talk about radionuclides, possession limits and purpose. We're going to have posting requirements. We're going to have training

and experience for authorized individuals.

And why do we have authorized individuals? Because this could go into a medical facility and the authorized individual could be a physician AU. It could go into a big medical facility and the authorized individual that's running the device would actually be a nuclear pharmacist. And it goes into a commercial nuclear pharmacy, then the authorizing individual would be the authorized nuclear pharmacist.

We believe that the authorizing individuals need additional training and experience in using the RadioGenix and we believe that they need practical experience in running protocols and that they need an attestation that they have successfully completed that training.

We have a radiation safety officer and we believe this device is sufficiently different from anything else that the medical facility or commercial nuclear pharmacy has that he needs. He or she also needs specific training in the NorthStar RadioGenix system.

We have included training and experience for supervised individuals. We believe most people that are operating the unit on a day-to-day basis will

be supervised individuals, supervised by the authorized individuals. But because this device has a number of protocols that have highly specific steps and radiation safety concerns associated with them, that these supervised individuals need to have highly specific training with the NorthStar generator and they need to be approved for each protocol that they will be using before they can use it and that they also will be tested to make sure that they can do things safely.

We've got a new individual that you've never heard of before. It's a RadioGenix system administrator. This person is responsible for putting the people that can run the protocols into the computer system that allows them to run the protocols. They are also the person that has control of that one key that we were talking about earlier for an area that should not have any one at a licensee's facility going into it without direct NorthStar oversight.

And there's also -- we recognize that the system -- one system administrator isn't going to be present all the time, so we designated a system administrator designee, and that responsibility is the person that has responsibility for the key if the system administrator is not there.

So in licensing commitments we realize that this particular device may go on the market before our current new Part 35 takes effect, so we have incorporated the new moly-99 concentration limits into our guidance. We have put in for training in licensing procedures. And we've also given licensees freedom that if there are changes to the training resulting from -- changes to the system that affect safety, we're going to set up a procedure where they can go ahead and incorporate those changes and not have to get a license condition because they'll already be granted an authorization for it.

And then emergency procedures, we're also going to do the same thing with that, that if there are changes in the device that affect safety, if they've got a procedure that we've accepted, they can go ahead and make those changes without having to come in for us and special safety radiation.

We have notes to licensees. Many of these are general things that you've seen before. You cannot alter the RadioGenix without needing an amendment. You cannot use any other moly in the system without an amendment. You cannot use another generator with the NorthStar moly without needing an amendment. You

can't change the physical conditions.

We are going to allow flexibility just as we do in Part 35 about notification. If you've got a trained authorized user that's already listed for this device, they can go to another licensee without having to provide their training already. And they can start working within -- as long as the agency is notified within 30 days. And if we've got things that change because we change our guidance, we have a provision that allows the licensee to adopt those provisions without having to come in for an amendment. So those are typical types of boilerplate procedures that we see for other 1000 devices.

And I've only used two abbreviations, moly and technetium.

CHAIRMAN ALDERSON: Thank you, Dr. Howe.

Questions for Dr. Howe?

DR. HOWE: Yes, Dr. Zanzonico?

VICE-CHAIR ZANZONICO: I have a couple questions. This may be over-thinking this, but on your photograph of the system --

DR. HOWE: Yes.

VICE-CHAIR ZANZONICO: -- the radiation trefoil symbol is only on two of them. That's not to

imply that those are the only cabinets that contain radioactive material?

DR. HOWE: No, when they are using radioactive material in this device, we are going to require the trefoil on all places that have the material because the material will constantly be moving from one location to another location.

VICE-CHAIR ZANZONICO: And you also said that in these transfer doors the source -- so the source vessels are identical in terms of content? It's just for redundancy? So you don't have to change them that often?

DR. HOWE: It's part of what Mr. Green was talking about. In order to have enough technetium to us on say a commercial pharmacy they may have four of these source vessels. Right now it's going to be about six curies so that they can make moly from each one of these source vessels, take -- make technetium from each one of these source vessels so they have enough technetium for a day's workload.

VICE-CHAIR ZANZONICO: But I presume you could operate it if there was some catastrophic shortage. And then someone who has the generator could only get one or two source vessels. You could still

operate it under those circumstances? In other words, you don't have to have --

DR. HOWE: You do not have to have four. You can have one, two, three, any number. They've built it with four for the maximum.

VICE-CHAIR ZANZONICO: Yes. And --

CHAIRMAN ALDERSON: Mr. Green?

VICE-CHAIR ZANZONICO: Can I ask just one last question?

And I presume you still have to -- since there is radioactive modeling you still need to do some sort of moly breakthrough test with --

(Simultaneous speaking.)

DR. HOWE: Yes, I mentioned that because this generator may go on the market before the new Part 35 takes effect, that we have incorporated into the guidance the new moly breakthrough procedures.

CHAIRMAN ALDERSON: Mr. Green?

MR. GREEN: On slide 7 your second bullet, the note to licensees, you say there will most likely be a prohibition of using other moly or tech solutions or other generator systems. And I certainly do not want to advocate the combining or mixing, but I don't want that to be confused. If a pharmacy or hospital

has a RadioGenix system, they will likely have a Mallinckrodt or a Lantheus or a GE grandfather-style, grandparent-style unit as well in the same room where you could elute the new one or the old style. You just can't put solutions in from the unit. But I don't want it to be --

DR. HOWE: No, my --

MR. GREEN; -- misinterpreted as --

DR. HOWE: If --

MR. GREEN: -- mixing.

DR. HOWE: I'm giving a really quick overview of the guidance. This is intended to address only the fact that you cannot take another moly and run it through this generator. You cannot take the NorthStar moly and run it through some other generator other than RadioGenix. I am not saying that a pharmacy can not have both a Lantheus, Mallinckrodt, NorthStar moly supply and use those for all of those materials.

The other point to make is that this technetium is -- has to meet the same standards of all technetium, so there is really virtually no difference.

CHAIRMAN ALDERSON: Dr. Langhorst.

MEMBER LANGHORST: More than likely this will be a central nuclear pharmacy, I would guess, and

so more than likely the authorized individual will be an authorized nuclear pharmacist. But you talk about authorized users. Does that only mean an authorized user who's a physician, or can that authorized user be a non-physician authorized user and be responsible for this working also with -- perhaps with a pharmacist?

DR. HOWE: Currently our regulations are set up -- so for a medical use licensee an authorized individual would be the nuclear pharmacist or the physician. We would have to think about --

MEMBER LANGHORST: Yes, you might want to clarify that. I can't imagine it being a non-physician, but it could happen. And so I --

DR. HOWE: We --

(Simultaneous speaking.)

MEMBER LANGHORST: -- think you might want to clarify that.

DR. HOWE: We're having trouble imagining it being a non-physician and a non-commercial nuclear pharmacy.

MEMBER LANGHORST: Right.

DR. HOWE: And that's what you're talking about, having somebody that is either of those.

CHAIRMAN ALDERSON: Dr. Palestro?

MEMBER PALESTRO: Regarding the source vessel --

DR. HOWE: Yes.

MEMBER PALESTRO: -- which contains the molybdenum, with the conventional generator, molybdenum/technetium generators they expire after a certain date and they're shipped back to the manufacturer, to the processor. What happens here? I assume the molybdenum is in the source vessel. Where does that go?

DR. HOWE: The molybdenum will be sent back to the source vessel each time it's used. And so if it has gotten to a level that you really can't more technetium out for practicality, then that source vessel will be shipped back to NorthStar. And NorthStar will reprocess the source vessel and take the used moly out and then clean out the source vessel and the current -- as we understand, will send it off to MURR to have new moly put into it and then MURR will ship it to the end user.

MEMBER PALESTRO: One other question, if I may, a quick question.

CHAIRMAN ALDERSON: Yes.

MEMBER PALESTRO: It's hard looking at the

image or the photograph to get a sense of the dimensions or the size of the generator.

DR. HOWE: Well, that's why I included the source vessel. The source vessel is essentially the same size as a traditional moly/tech generator. So the manufacturer has said in many public meetings that this occupies a surface area that's about the same as four large generators. It's a big thing. You stand and look eye to eye with the computer screen.

MEMBER PALESTRO: Thank you.

CHAIRMAN ALDERSON: Mr. Green?

MR. GREEN: Dr. Palestro, I believe it's a four-foot left to right. Again, since it has the capacity for four source vessels, if you elect or need that much activity, it is -- it's about four feet left to right.

Dr. Langhorst, there are very -- there are much fewer nuclear pharmacists in hospital practice settings than there were and the market is predominantly centralized nuclear pharmacy. There are more places where generators are used under the direction of the authorized user physician, but the technical hands-on users are nuclear medicine technologists. So you want to make sure that the

regulations do not prohibit the nuclear medicine technologists from eluting this as they would a Lantheus or Mallinckrodt generator today.

DR. HOWE: Our current licensing scheme is to have -- in the case where you do not have a nuclear pharmacist and you are in a medical facility, the physician will be the responsible person. We are making sure they get adequate training. And then we are also recognizing that the supervised individual, which in your case that you're talking about would be the nuclear med tech, also has adequate training and authorization for each one of the protocols. So we think we have covered the spectrum.

CHAIRMAN ALDERSON: Dr. Langhorst?

MEMBER LANGHORST: I wanted to ask about the training and experience documentation. And I agree this needs a lot of training and that needs to be documented that you have experience with it. And I appreciate the radiation safety aspect of things, too.

But am I understanding that all of the authorized individuals will have to have a preceptor signatures in order to show they've done this --

DR. HOWE: Yes.

MEMBER LANGHORST: -- documentation?

DR. HOWE: Absolutely.

MEMBER LANGHORST: And then you say for the system administrator they're not going to be there 24/7. Well, the RSO's not going to be there 24/7 either. Will all of the radiation technologists have to be? I mean, will health physicist or rad techs have to go through that preceptor training, too?

DR. HOWE: What we have envisioned is that the radiation safety officers will get training from NorthStar on the radiation safety and emergency procedure aspects of this device, not on running the safety. Anybody that is going to run the device, if you're an authorized individual, will need a preceptor statement saying that they have done this. But also the supervised individual has to show they've -- they're proctored and they need to show they can successfully go through this before they're added to the system.

So they're -- but all the authorized individuals have to meet training and experience requirements to be on the license. The supervised individuals, that's the licensee's responsibility, but we explain what we think that responsibility is. And

then the system administrator, that's the licensee's responsibility, and we explain what we think that responsibility is.

MEMBER LANGHORST: And so the radiation safety officer you're just saying needs to be trained, but there's no experience I'd have to show, or --

DR. HOWE: No, you have to go --

MEMBER LANGHORST: -- I'm confused on why I need a preceptor statement. I mean, I agree I need training and experience. But we will have the vendor signing off as our preceptor, is that correct?

DR. HOWE: Initially because no one else knows this system but the vendor.

CHAIRMAN ALDERSON: As we go onto the detail we really should hear from Dr. Dilsizian --

DR. HOWE: I think so.

CHAIRMAN ALDERSON: -- who's going to talk a lot more about this generator. So let's let him speak and then we'll see where the questions are.

MEMBER DILSIZIAN: Thank you, Dr. Alderson, Dr. Howe, for that outstanding introduction to this topic already.

Dr. Alderson asked us as the Subcommittee members, which include Mr. Costello, Dr. Palestro, Dr.

Zanzonico, and of course Dr. Howe was a key member of the NRC staff facilitating the conversation, to provide comments to the licensing guidance that was just described on this RadioGenix NorthStar agenda.

And so the Subcommittee's charge were rather twofold. One is to particularly focus on the training and experience, all individuals interacting with the generator, and safety precautions to minimize the potential of radiation exposure for individuals running the protocols and others in the room.

So as a background, which was already stated, just briefly, as you know the conventional column-based generator utilizes exclusively fission-produced molybdenum. Since foreign reactors, according to Mr. Green, are aging and increasingly unreliable there is a welcome need for domestic supply of molybdenum-99. And the RadioGenix generator uses a linear-accelerator or neutrons from --- that's an accelerator, and thus should be addressing this unmet need for non-HEU molybdenum-99.

One thing the Subcommittee noticed as Dr. Howe was very elegantly going through all of these boxes this was very complicated for most of us. And we thought that despite putting labels and elegantly going

through it, even third time around it was very difficult for me. So we thought that perhaps the best way to go through this is to have a video quick of the generator that actually shows the movements of how things are done from each box to the next box. And that would be probably the first recommendation for those who are going to be trained with the system to familiar with it.

Regarding training requirements, again there are a number of individuals involved with this equipment. Those who actually operate it, those are called the training individuals. And all of the individuals would have to go through these individual protocols, which I'd rather call them, as you can see later, individual tasks. And then there's going to be the system administrator or designee, a radiation safety officer, and of course an authorized user or an authorized nuclear pharmacist.

And so what is the -- again, the company calls protocols, but these are in essence steps, individual tasks, if you will, within -- there's only one protocol producing tech-99 and one software. These are simply steps to get that accomplished. And you can see it's initializing the system, adding or

changing reagent kit, separating tech-99m, removing the source vessel, sterilizing and exchanged use reagent container.

The administrator, system administrator needs to make sure that the training individuals have actually gone through each of these individual tasks and signs off on it. And one individual obviously can't do all six, but you can imagine that several individuals can be doing several of these tasks at different times.

So the training and experience. So how shall we go about this? Well, it's a new system. And if you think about all of these individuals that need to be trained, it will be difficult to have this all started. So since there's going to be large number of individuals to be trained and it's impractical, we felt that it is appropriate for NorthStar to start training the AUs and ANPs first.

And we also noted that as was discuss here given the complexity of the system this is not going to be in units, hospitals. It's probably going to be mostly in large pharmacies. And again, we estimate that it's probably going to be less than 10 percent of all clinical imaging programs that may even go here.

So with that in mind, we felt that if the AUs or ANPs are trained first and then they go about and training each of these individuals that's probably much more practical than everybody going to NorthStar to be trained first.

And so what about the course itself? Should NRC be involved in deciding whether the course is appropriate or not? This was discussed. And given the unique design of the system and the operation of the NorthStar system, the Subcommittee agreed that NorthStar should probably have the sole responsibility for the content and the training course and certification because they really know the system best and better than the NRC Subcommittee members.

What about the system administrator or system administrator designee? It seems to be a unique position. As Dr. Howe very nicely described, this is a unique role to make sure that the operators are well trained and also has that key, specific key to so-call the brain of the system that only under unique situations that would be needed to open that box. But then we noted that perhaps given the unique role of the system administrator maybe this individual should be named on the license.

And we also noticed that it's was -- maybe there should be more than one designee, and that wasn't clarified. And perhaps it should be clarified whether it could be only one designee, several designees, and that's not very clear on the current guidance.

What about the changes? What if within six months or a year there's a new software or new changes that occur in the boxes? How will that be implemented? We feel that the changes should be the responsibility of the manufacturer, but there should be a specific time that should be specified from the change to how long will take to implement that change and how will this go about to introduce these changes to the AUs, RSOs and all those trainees. Again, this has not been defined well and we feel that there should be a time frame defined and perhaps -- again should the system be non-operational until all these occur or should it be continuing until everybody's trained? These have not been well defined and we felt that this was important to define in the document.

Again, the term "protocol, "software," when I read it first I was very confused. I thought that there were a number of software, different protocols. To me it's individual tasks, but I

understand that the way the company has written it each of those tasks is defined as protocols. To me a protocol has a multitude of tasks. But anyway, I thought that that should be clarified and the Subcommittee recommendation agreed on that.

Regarding safety precautions, which is our second main task, we felt that the licensing guidance was largely silent on the emergency response other than defer it to the procedures of the manufacturer. While the Subcommittee appreciates that NRC endeavors to be non-prescriptive, given the potential severity of the spill however with such large quantities of radioactivity in liquid form, perhaps the manufacturer's procedures should be reviewed and incorporated into the license guidance itself.

Regarding the surveys and survey meter and monitors, the guidance currently states that it is necessary for the licensee to routinely perform additional surveys to identify, "higher than expected radiation fields and system failures." Again, the Subcommittee recommendation was that the term "higher than expected" was rather vague. It should be defined in terms of maximum specific exposure or exposure-rate limit which a survey meter should be capable of

measuring.

In conclusion, we felt that the Draft Licensing Guidance overall was reasonable and not particularly onerous for prospective users. And given the new and novel features of the NorthStar generator systems, licensing under 10 CFR 35.1000 is reasonable. Thank you very much.

CHAIRMAN ALDERSON: Thank you, Dr. Dilsizian.

So to those who would like to continue the discussions we've been having about the generator or ask questions, the floor is open. Anyone from the ACMUI that would like to ask? Dr. Langhorst?

MEMBER LANGHORST: I would just suggest for the Subcommittee the first ones needing to be trained are AUs, ANP and RSO, because you need the RSO to be able to get it licensed.

MEMBER DILSIZIAN: That's a good point.

MEMBER LANGHORST: So you might want to add that.

MEMBER DILSIZIAN: Sure. That's a great point.

CHAIRMAN ALDERSON: Yes, Mr. Green?

MR. GREEN: Normally the preceptor is an

authorized user. If the preceptor is the corporate representative, are they an authorized user or authorized nuclear pharmacist?

DR. HOWE: In 35.1000 guidance many times when you have a brand new device coming in there is no one other than the manufacturer that knows how to operate the device. And so we tend to let the manufacturer be the preceptor, specifically under this guidance, for a period of time. And then once there are more authorized users or authorized individuals, then they can assume the responsibility. But we do allow the manufacturer. And they may not be an authorized nuclear pharmacist, but they know their device.

MR. GREEN: Similar to our discussion earlier today about medical science liaisons training individual authorized users on the Y-90 spheres products where they attest that those are primarily physicians conducting that, individually all just conducting that training, it might be something to consider that the training staff that proctor or precept will be nuclear pharmacists.

MEMBER DILSIZIAN: Well, yes, I mean, unlike the Y-90 case it's really physician-patient

relationship and a procedure that has complications and has implications about using it more frequently, in particular patients where industry's involvement may influence that. I think in this case we're talking about equipment that's complicated and we're talking about producing a product that's going to be used. And there's no real direct influence of that, if you will, by industry of utilizing technetium-99m, where in the Y-90 case I could understand the potential impact of influencing.

DR. HOWE: And let me add that we have built into our guidance that the training is provided either by NorthStar or someone that NorthStar certifies to provide the training. So when they feel comfortable that someone really understands what they're doing and how to train and certifies them to do the training, that person can start providing training. So that is the role I would see for your nuclear pharmacists down the road.

MR. GREEN: One question on the safety precautions, the higher than expected exposure rates. That may differ whether you've got one source vessel with six curies, for example, or four source vessels. So I'm not sure that the manufacturer can give you a

number. If you exceed so many MR per hour, it may be difficult to do.

DR. HOWE: And our intent with higher than normal was because everything is behind closed doors and you are required to open these doors at different times to perform different functions, that the survey be made, and if it looks like it's higher than you would normally expect, then that's a good indicator that maybe you don't want to open that door and you want to step back.

MEMBER DILSIZIAN: So for that particular case for example what is more than expected? Some range right, I mean, and we will be --

DR. HOWE: Yes.

CHAIRMAN ALDERSON: Other questions? Dr. Langhorst?

MEMBER LANGHORST: I'll just weigh in on answering that. When you have a new source container, it'll have a high dose rate to it. If you have a lower one but it's still in use, yes, it may be -- I don't think you need to define that number. I think that's part of what you learn in the training and so on and part of your experience. I would be nervous of having the NRC set a number, because it's very hard to do.

DR. HOWE: And the difficulty with this one at setting a specific number is that you have this material moving --

MEMBER LANGHORST: Right.

DR. HOWE: -- between the different cabinets. And so at any given time that number can change based on the time in the protocol or maybe what's happening behind the closed door that may or may not be good.

I would like to also mention that we do have Jim Harvey on the phone, and so he is the NorthStar person that's responsible for this device.

CHAIRMAN ALDERSON: All right. So, Mr. Harvey's on the phone.

Can you hear us, sir?

DR. HARVEY: Yes, I can hear you and I'd be happy to provide a couple of clarifications and supporting statements to what Dr. Howe has already said, if you would like to hear them.

CHAIRMAN ALDERSON: Why don't you do that, sir? Yes, we'd be pleased to hear from you.

DR. HARVEY: First of all, there was a question on the professional photograph of the instrument that we had provided. That was just a

professional photograph. The commercial units will go out with the radioactive materials label on all doors.

Secondly, all the training that Dr. Howe has described to you is the same that we are committed to the FDA. There were many questions about training that came up as part of the review of our new drug application and NorthStar had already made the same commitments to the agency as part of the NDA review.

The next item, the source size, the source vessel size of six curie was used. That is six curies at noon, next day of production. So if it arrives at a pharmacy a little bit before noon, it'll be a little bit higher than six curies. If it arrives a little after noon, it'll be lower than six curies just because of the decay.

Another question came up about moly breakthrough. The FDA still requires that technetium-99m produced by the RadioGenix to meet the definition of the U.S. Pharmacopeia for sodium pertechnetate technetium-99m. And of course the instrument does do that and we've shown that in the new drug application. But that requirement meeting the U.S. Pharmacopeia includes a moly breakthrough test.

The life of a source vessel is the same as

the current systems that are out there today, which is 14 days. Dr. Green was correct. It is 48 inches wide and it holds four of the source vessels, which is the equivalent of four -- face-wide four individual units in the pharmacy today.

As far as changes are concerned, we already have an understanding and an agreement with the FDA. There is a process through the FDA that we have to go through to notify the agency if we're making any changes. And we understand that we will follow the same process with the -- under our guidance from the working group. So that is not unexpected either.

And just as an additional piece of information, yes, NorthStar will be doing the training. Our people are well-versed in the instrument. And in addition to that we have four nuclear pharmacists on our staff.

I'll be happy to answer any other questions. Those are just some additions and clarifications that I thought might be useful.

CHAIRMAN ALDERSON: Good. Are there questions from members of the ACMUI? Dr. Zanzonico?

VICE-CHAIR ZANZONICO: I have a question. In the USP the -- for conventional moly generators there

is a requirement of course for alumina breakthrough. That doesn't apply to this instrument, but in terms of sort of -- in a bookkeeping sense has that requirement been appropriately eliminated for this system, or to comply with the USP requirements that need to be retained for some reason?

DR. HARVEY: Actually the alumina breakthrough does still apply because the way this system works the guard column, which is one of the last things that the product sees before it goes into the product vial is an alumina cartridge. It's changed with every elution so that it helps protect further against any unwanted moly breakthrough, but the alumina test does still apply. We do not have any exemptions so to speak under the U.S. Pharmacopeia other than the fact that because it is a non-fission process we don't make fission strontium and we don't make alpha emitters. So those tests are -- we've proven that that material is not there. And so those tests are typically not performed or required. But the basic tests, moly breakthrough, alumina, that's still required.

VICE-CHAIR ZANZONICO: Okay. Thank you.

DR. HOWE: And let me clarify. NRC does

not require an alumina test. We only require the moly-technetium breakthrough.

MEMBER DILSIZIAN: Right, that's a USP required test.

DR. HOWE: Yes. And so by meeting the USP, they're going to meet the NRC requirement.

CHAIRMAN ALDERSON: Do we have other questions from the ACMUI?

(No audible response.)

CHAIRMAN ALDERSON: Do we have questions from anyone here in the audience?

(No audible response.)

CHAIRMAN ALDERSON: Do we have questions from anyone who is on the phones, either for our current speak or for anyone who has spoken on this subject?

Operator, do we have any requests?

OPERATOR: Currently there are no requests, sir. I'll remind them it's star followed by the number one. If you wish to queue up, you will be prompted to record your name.

CHAIRMAN ALDERSON: We'll wait just a little bit and let you see if anyone comes on. Please tell us momentarily.

OPERATOR: All right, sir. Thank you. I

will do that.

(Pause.)

CHAIRMAN ALDERSON: Has anyone come on?

OPERATOR: No. Thank you.

CHAIRMAN ALDERSON: Very good.

DR. HOWE: And thank you, Dr. Harvey.

CHAIRMAN ALDERSON: Yes.

DR. HARVEY: Thank you.

CHAIRMAN ALDERSON: So seeing no more questions; and thank you all and thank you for the outside speaker. And that will conclude this particular --

MS. HOLIDAY: Dr. Alderson?

CHAIRMAN ALDERSON: Yes?

MS. HOLIDAY: May I request if the Committee will endorse the Subcommittee's report which contains all of those recommendations?

CHAIRMAN ALDERSON: I was afraid of that.

(Laughter.)

CHAIRMAN ALDERSON: Well, so that's the question. The question is does the Committee wish to endorse this report that had like six different recommendations on multiple different pages? And I really have to say that if the answer is no, if the

Committee is not ready to do an on-block endorsement, then we have one or two minutes left and we cannot really go through paragraph by paragraph in six different pages to decide what we want to endorse or not to endorse. So we could perhaps move to do this at another time, or there might be someone who says this is very straight forward and we'd like to move that we endorse the report on block.

Yes, Dr. Langhorst?

MEMBER LANGHORST: I would like to move to endorse the Subcommittee's report. I think we need to move it forward. I think the Subcommittee has looked at this very carefully. I think it's worth moving it forward.

CHAIRMAN ALDERSON: Very good. So that's the motion. Is there a second?

(No audible response.)

CHAIRMAN ALDERSON: Is there a second?

MEMBER O'HARA: Second.

CHAIRMAN ALDERSON: There's a second. Good. All right.

Now we're open for discussion. Would anyone like to discuss this motion on the ACMUI?

(No audible response.)

CHAIRMAN ALDERSON: Hearing none, is there a motion to approve? Well, all in favor, I should say.

(Laughter.)

(Chorus of aye.)

CHAIRMAN ALDERSON: Any opposed?

(No audible response.)

CHAIRMAN ALDERSON: No. Any abstaining?

(No audible response.)

CHAIRMAN ALDERSON: It's unanimous. The report is endorsed.

MS. HOLIDAY: Thank you.

CHAIRMAN ALDERSON: You're welcome. I think that that brings this session to a close. So we now are on break and we will reconvene at 3:00. 3:00 p.m. Thank you.

(Whereupon, the above-entitled matter went off the record at 2:25 p.m. and resumed at 3:00 p.m.)

CHAIRMAN ALDERSON: We'll reconvene the session. We are now going to hear from Katie Tapp about the Germanium/Gallium-68 Medical Use Generator Licensing Guidance.

DR. TAPP: Thank you, Dr. Alderson.

First, I would like to say that the Eckert and Ziegler GalliaPharm Germanium-68/Gallium-68 Generator Licensing Guidance has been published.

Final it is now available for use by our NRC regional offices for licensing. It was issued on September 28th and has now been posted to our medical toolkit website I believe on Thursday.

I would like to thank many groups for helping in the development and the review of this guidance. First, I would like to thank the Agreement States and NRC Working Group.

The Co-Chair is actually in the Region III office, it was Vered Shaffer. The Co-Chair for the Agreement States was Andy Halloran from Washington. We had another member from Agreement State North Carolina, which is Caleb Smith, our Region I representative, Jan Nguyen, and then myself, and then when I was unavailable Said has filled in my place to make sure this got issued in a timely manner.

Next, I would like to thank the ACMUI Subcommittee for their expedited review. I know you guys reviewed it quicker than the 60 days generally allotted and we really thank you for that, it helped us get it published in a timely fashion.

As well I would like thank a past ACMUI member, Steve Mattmuller, for his support as NRC consultant in the development of this and also when he was here at the ACMUI.

The ACMUI provided comments and endorsed a draft version of this licensing guidance on August 25th of this year. Based on the ACMUI comments the final licensing guidance tried to make it very clear that this guidance is for the use of the generator and not for the use of Gallium-68 radiopharmaceuticals.

We put a note at the top of the guidance before you would even get into the body of this report specifying that it's for the use of the generator itself and not for the radiopharmaceuticals. The radiopharmaceuticals are licensed under 35.200.

Additionally, like we heard from Dr. Howe earlier, this licensing guidance applies to both commercial and nuclear pharmacies and medical facilities if they are using this generator for medical use.

This guidance provides recommendations for breakthrough limits set to the manufacturer's stated limits for this generator in its drug master file.

Additionally, this guidance talks about the frequency of elution because the breakthrough could build up and that's set to manufacture-stated operating procedures.

As well as this guidance recommends the reporting of breakthrough similar to what is for the moly and technetium-99 generators in the proposed final rule of the 10 CFR 35.

And then, finally, this licensing guidance has a note to remind licensees that the Germanium-68 has a half-life of greater than 120 days so there is some waste disposal issues that they need to think about and go back to refer to Part 20 on that.

This licensing guidance as shown in the title is specific to the Eckert and Ziegler GalliaPharm Generator because the working group only evaluated the safety considerations for this generator as it has been approved with a -- as it has a drug master file.

But that does not mean that the NRC is recommending that this is the only generator that can be used. Generators that are used by broad scope licensees that are not this generator can be used in accordance with regulations.

The only reason that we are focusing on the

Eckert and Ziegler Generator is that was what the NRC was reviewing with this working group, that's what we had to work with at the time.

We can open up another working group in the future if manufacturers are notified that there are future generators coming down the pike as we are becoming aware.

I would like to turn it over now to Dr. Daibes for his talk about the financial assurance.

DR. DAIBES: First of all thank you for the opportunity. First of all let me express our gratitude to Steve Mattmuller for his support in making sure that information became available.

Thanks to ACMUI for your support in providing guidance and for the guidance and expedient review from OGC and making sure that we were able to deliver.

At our last meeting we said we were going to provide something and we have made something. We have provided progress and today we are going to provide you some information on it.

So do we need to provide background on gallium, I think everybody is pretty familiar on -- So do we not go there?

Okay, so let's go directly to the point. We in the past had an issue, people have raised concerns in the past with respect to the DFP requirement that we had and we still have in place.

We provided multiple options or regulatory options as potential options. One of them was this license specific exception that we -- oh, my apologies -- so that we in our last meeting provided as the plan forward and our progress towards that initiative is that we indeed have provided that exemption to the regions.

It was provided on July 29 and an SCC letter was provided to Agreement States as well on August 18th. So having that aligned and concurrent to that we were working on a direct final rule which the -- I was today provided a question on, well, why a direct final rule.

Well in order for the exemption to proceed we had to demonstrate that we had a rulemaking process aligned or in process in order to provide a path forward, and we went ahead and provided a direct final rule plan to OGC and as of today OGC is still reviewing that package.

And the intent of the direct final rule was to provide a potential footnote, I had to clarify this

that it was not to work on the actual table itself it was to provide a footnote in order to accommodate the isotope that we were pursuing, and another question was raised today on that same issue.

The DFP exemption basically was providing a short term option to licensees in order to provide access to the needed isotopes. Another question that has been raised is do we need financial assurance. I want to clarify this.

Indeed, we need financial assurance. In this case why do we need financial assurance? Well, the exemption, and I need to clarify, financial assurance if the exemption is requested. So why do we need financial assurance?

Well there has to be a guarantee that there is a mechanism in place to allow for if something that is not planned happens and we have a mechanism to accommodate that, right.

So that financial assurance is very explicit in that exemption in the enclosure and I am going to refer back to that enclosure to provide you more details on it, but the summary of that financial assurance is here on the screen and it's basically any licensee possessing one or two medical generators or

Germanium/Gallium-68 generators will need financial assurance in accordance to $225,000 minimum of financial assurance.

And licensees having or possessing more than two, up to 20, will need $1.125 million in financial assurance. I need to clarify that because, again, another question was raised.

So I am going to refer you back to that exemption, or the enclosure, that will provide you further information with respect to this. We can proceed. Do we have any questions?

CHAIRMAN ALDERSON: Questions for Dr. Daibes? Mr. Green?

MR. GREEN: The current strength, the size of the GalliaPharm generator is 50 millicuries of model activity, plus or minus 15 percent, so with the luck of the draw you can receive a unit that's 57-1/2 millicuries or 42-1/2, and that's today's strength.

They are looking at manufacturing and licensing a larger, more potent generator, so you may want to look at the one or two or look at the 50 to 100, because if you possess two brand new ones you may be at 114 millicuries. So just a caveat.

DR. DAIBES: Thank you. We spoke to the

company and we were provided that info, that there is a potential down the road for that to be implemented, but thank you for that.

CHAIRMAN ALDERSON: Other questions for either of our panelists? From the audience? No. Anyone on the phone would like to comment, operator?

OPERATOR: If you'd like to share a comment please press star 1.

MEMBER LANGHORST: While we are waiting --

CHAIRMAN ALDERSON: Yes?

MEMBER LANGHORST: -- I would just like to express gratitude to the NRC --

CHAIRMAN ALDERSON: In getting through it all.

MEMBER LANGHORST: -- in getting through all this and providing this exemption. It's not the way we like to regulate, I understand, but it is going to impact so many patients and make this available to them and it was based on a rule that's an old rule that didn't get updated when other parts of the regulations did and so thank you, thank you, thank you.

CHAIRMAN ALDERSON: Well said.

OPERATOR: And I am showing no comments from the phones.

CHAIRMAN ALDERSON: No comments, that ends this particular session. Thank you very much.

DR. DAIBES: Thank you.

DR. TAPP: Thank you.

CHAIRMAN ALDERSON: You can be the moderator.

VICE CHAIR ZANZONICO: Okay. So I'm just going to step into this last presentation to serve as moderator since our Chair, Dr. Alderson, will be making a presentation and he will be presenting on ongoing efforts and strategies for enhancing communication with the medical community. Dr. Alderson, the floor is yours.

CHAIRMAN ALDERSON: Yes, thank you, thank you. So this will be an update on the discussion we had at a previous meeting about the importance of establishing stronger and more regular communications between the ACMUI and the user community.

And so it was decided after a discussion that the most cost effective way to do this would be to have our members at the meetings that they typically attend and offer to their respective societies the opportunity to have a session with the representatives of the NRC and we have gone on in trying to set that

up and a number of the members of the ACMUI did agree at that time to approach their respective societies and to determine if there was interest in actually setting up such a session.

This was not the only thing that was recommended, there were some other recommendations that could foster a society outreach. Well, we talked about the first one just now, that is a regularly scheduled presentation by one of you, an ACMUI member, at the annual Society meeting.

There was also the suggestion that we should consider an NRC booth at these meetings in the exhibit area, that perhaps we would offer to write a regular NRC column in the respective Society newsletter, or that we would potentially pay to have other people travel to come to us, and that's what a reverse outreach means here.

The last note on this slide would be that one of the societies would be nominated at each particular meeting, the Society of Nuclear Medicine and Molecular Imaging at one, the American College of Radiology at another, to actually be here and sit at this table and make a presentation about their concerns.

But when it was all said and done we came around to the fact that the most cost effective and the most efficient way to get things going in a hurry was to have our respective members who are out in these Society meetings, because of their own professional interests, to actually make presentations on behalf of the ACMUI at those meetings.

So I am happy to say that in the last several months a number of you have actually done this and have set up meetings of this type, so I will go on down the last couple of slides to talk about that, the Ask the Regulator Q&A session.

Some sort of overview slides that sort of tell generally what the important issues are in front of the ACMUI and then a Q&A so that the audience can actually stand up and those people can say exactly what their concerns are so that we can get that communication and work on putting those things together.

Now we did find out in the course of these approaches to various Societies that a number of them believe that they have open communications and exchange with the NRC ACMUI already and that perhaps additional things weren't necessary and well that's fine.

The idea of the approach is to increase

communication and if communication is already fine and they are happy with it, and many of those are like people that you see frequently at these meetings in the audience who step up and make comments at the microphone. Well that's fine, no need to change something like that.

But here some ideas of some of the things that we hope will happen where these sorts of discussions have already led to tentative plans to have an ACMUI session.

So the American College of Radiology will consider holding such a session as part of the continuing medical education program in May of 2017, and that's Dr. Metter who has made that contact, is that correct?

(No audible response)

CHAIRMAN ALDERSON: Great, excellent. The Society of Nuclear Medicine and Molecular Imaging seems like they would like to hold such a session at their next meeting in June of '17. Was that you, Chris, who --

MEMBER PALESTRO: Yes.

CHAIRMAN ALDERSON: Chris Palestro made that particular contact. ASTRO, that's the Society

for Radiation Oncology, therapeutic and radiation oncology fields, that they have a good communication with us already, but they are talking about a formal session at the September meeting next year, is that right, John Suh?

MEMBER SUH: Yes, this is something Ron Ennis worked on.

CHAIRMAN ALDERSON: Right, Ron is the one who is working with ASTRO, and Ron had to leave early so Ron isn't here to make a comment on that.

And the Association of Residents in Radiation Oncology, ARRO, also seems to be supportive of this meeting, and was that you, John?

MEMBER SUH: Yes.

CHAIRMAN ALDERSON: Yes, very good. So you can see that a number of our people have reached out. The Association of Physicists in Medicine and the Brachytherapy Society are interested in maintaining efforts that are already existing in communication between our organizations.

And the Health Physics Society was receptive to an outreach program and their mid-year meeting is scheduled for January of '17 in North Bethesda, which is where we are now, this is North

Bethesda.

Obviously, they are not meeting here at the NRC, but they are meeting at a hotel nearby I presume, and they would like to invite an NRC representative to be the speaker.

Well, Sue, was it you who made that contact?

MEMBER LANGHORST: Well Pat and I have. We are going to be working with the medical committees, medical section on that, to I hope involve NRC staff that aren't necessarily medical team staff, but other NRC staff to kind of broaden the understanding and opportunity to learn that medical use is different.

I will also point out that I have been stomping for my replacement and so if you go to the Health Physics Society webpage you can look at the HPS Newsletter and my article is there, questions and answers of serving on ACMUI, and not only asking for people to consider being my replacement but to encourage people how they interact with ACMUI and how they can be part of the discussions.

CHAIRMAN ALDERSON: Well, we certainly appreciate that outreach and at the same time we appreciate the context that you are virtually

irreplaceable.

MEMBER LANGHORST: Thank you.

CHAIRMAN ALDERSON: Are there questions or comments about this? That was the end of my brief report and I thank everyone who has reached out to their respective societies and is starting to set up these communication links.

Questions or comments? I see none in the audience.

VICE CHAIR ZANZONICO: Any on the phone?

OPERATOR: Yes, we do have a question from the phone, it comes from Cindy Tomlinson, your line is open.

MS. TOMLINSON: Thank you. This is Cindy Tomlinson from ASTRO. I just wanted to let you know that we are trying to figure out how to engage with the NRC and the ACMUI at our annual meeting, but just know that nothing is firmly in place.

We just finished our last one at the 2016 annual meeting, so we are still trying to figure out how we can do some things in 2017.

CHAIRMAN ALDERSON: Well, thank you for that update.

VICE CHAIR ZANZONICO: Thank you. If

there is no one else on the phone then that brings this session to a -- well not this session, but this presentation to a close.

CHAIRMAN ALDERSON: All right. So that brings us to the administrative closing and Michelle Smethers will do that for us.

MS. SMETHERS: Thank you. As part of the administrative closing we are going to discuss possible potential future dates for our Spring ACMUI meeting.

This is typically in March or April and subject to the Commission's availability. We try and couple it with the Commission meetings.

I sent out a doodle a few weeks back and we got a number of dates that actually seem to work for the Committee, so we are just going to talk through those and make sure those still work.

It appeared that the first choice that worked for everyone was March 20th through 21st, that was a Monday/Tuesday. Please confirm if this still works for everyone, or let me know if that does not work for someone rather.

MEMBER LANGHORST: Dr. Alderson?

CHAIRMAN ALDERSON: Yes? Oh, I'm sorry.

MS. FAIROBENT: Dr. Alderson, Lynn

Fairobent with AAPM. I just want to note that the AAPM Spring meeting is that week.

MS. SMETHERS: Okay, thank you for letting us know.

CHAIRMAN ALDERSON: Other comments? No.

MS. SMETHERS: We did try and check the different professional organizations, but I appreciate the information. April 25th through 26th, that was a Tuesday/Wednesday, that seemed to work for all members. I believe there was a preference by one not to have that date.

VICE CHAIR ZANZONICO: I'm sorry, which date?

MS. SMETHERS: I'm sorry, say that --

VICE CHAIR ZANZONICO: The dates again you just said.

MS. SMETHERS: That was April 25th through 26th, that is a Tuesday/Wednesday. Dr. Palestro, I believe you had a preference not to do that date, is that still the case?

MEMBER PALESTRO: It's a preference, but I can certainly attend.

MS. SMETHERS: Okay, thank you. Okay, the second one for other backup dates was April 26th

through 27th, that will be a Wednesday/Thursday. Are there any conflicts for that date?

(No audible response)

MS. SMETHERS: Again, I think it was a preference by Dr. Palestro not to have that one if we can avoid it. Okay, a third choice was April 27th through 28th. That appeared to work for all members, is that still the case?

(No audible response)

MS. SMETHERS: Okay, is there anyone who it doesn't work for?

(No audible response)

MS. SMETHERS: Okay, I'll keep that one on there. And then the last one was April 20th through 21st, that was a Thursday/Friday. It appeared to work for all members. I believe there was a preference not to pick that date, but it seemed to work for everyone.

Okay, do we want to pick a first choice date, should we -- So our first choice date was March 20th through 21st, would we like to remove that as our first choice since that seems to be in conflict with the other meeting?

CHAIRMAN ALDERSON: Sure. Yes, if that seems reasonable. We have several other choices here

in April.

MS. SMETHERS: Okay.

MS. HOLIDAY: Dr. Alderson, this is Sophie. As Michelle stated earlier we try to have the Spring meeting in alignment with the Commission meeting. I can tell you that the Commission has tentatively held March 21st as a possible Commission Spring meeting date.

However, they have not started looking at their April calendars yet since that's another month in advance from that, but I just wanted to make you guys all aware that you are nailing down your first and second choice of dates that March 21st is something that they are holding.

CHAIRMAN ALDERSON: I think that -- Yes, Mr. Fuller?

MR. FULLER: I hate to be talking across the ACMUI but I would ask Sophie, Sophie based upon your experience with the Commission would you advise, in trying to get these States scheduled over the years, would you advise that we jump on this opportunity that the Commission has provided us so that we can sort of nail down, in other words what is your, why don't you just go ahead and tell us what you think we should do

with regards to that date.

MS. HOLIDAY: My advice would be for March 20th and 21st to be your first choice and then from there you can select your alternative second and third backup choices.

CHAIRMAN ALDERSON: So I think, to the ACMUI members, that we have felt it to be quite important to be in front of the Commission if we can get there on an annual basis.

So that would suggest that these two dates in March would be the first alternate, the first choice. Is anyone opposed to that?

MEMBER LANGHORST: Not opposed, my question is if there is a Commission date in April that coincides with these other ones that that could then become the first choice.

CHAIRMAN ALDERSON: Yes.

MEMBER LANGHORST: Okay. I would suggest that.

CHAIRMAN ALDERSON: Right. Yes, that's the idea.

MS. HOLIDAY: As you are aware the dates that you are planning now are tentative.

CHAIRMAN ALDERSON: Yes.

MS. HOLIDAY: We actually don't confirm it until possibly in December or January, so when this meeting ends we will alerting our technical assistant staff as well as the EEO and SECY staff to tell them what ACMUI choices are and after that they will come back to us and tell us which dates the Commission has chosen.

CHAIRMAN ALDERSON: Yes, all right. So I think we have just agreed that the first choice will certainly to be with the Commission and that will be these March dates at the current time.

MS. SMETHERS: Okay. And we can definitely let them know --

CHAIRMAN ALDERSON: Right.

MS. SMETHERS: -- our various choices.

CHAIRMAN ALDERSON: And it looks like the April options then we have no idea of what they might be considering in April, Sophie, we don't?

MS. HOLIDAY: No.

CHAIRMAN ALDERSON: We do not. Well there is a whole group of these that sort of run together in one particular week, running from Tuesday the 25th through Friday the 28th --

MS. SMETHERS: Right.

CHAIRMAN ALDERSON: -- so my suggestion would be sort of as a broad thing just kind of keep those dates as a reserve date, the dates that week, and then we'll -- if they decide to meet in late April, I think that would be unusual for them, then we would try to flex within whatever they decide so that we coincided with one of their days.

MS. SMETHERS: Okay. Do we want to pick a second choice from that group or should we let them know we have this range of dates available?

CHAIRMAN ALDERSON: That's what I just suggested, that we have the range of dates for the April second choice.

MS. SMETHERS: Okay, sorry.

CHAIRMAN ALDERSON: Now because we just discussed that and no one said I can't do any of them. Chris had some dates that he felt he could make, but weren't probably ideal, but none of the dates were excluded in that particular week.

MS. SMETHERS: Okay.

CHAIRMAN ALDERSON: If we missed someone who has an exclusion that week then please speak now.

(Off mic comment)

CHAIRMAN ALDERSON: My suggestion is that

we were just going to consider holding the 25th through the 28th, those dates, all in the same week the last week in April.

MS. SMETHERS: Okay. And then not to include the 20th and 21st?

CHAIRMAN ALDERSON: Not include the 20th and 21st, yes.

MS. SMETHERS: Okay.

CHAIRMAN ALDERSON: Obviously, if the Commission makes a decision that we don't expect we can reconsider all of this.

MS. SMETHERS: Okay, sounds good. Okay, so to confirm, we have our first choice as March 20th through 21st, which is a Monday and Tuesday, and our second choice would be to provide to the Commission the range of dates between April 25th through 28th, for availability.

CHAIRMAN ALDERSON: Yes.

MS. SMETHERS: Okay, excellent, thank you. At this time I would like to go over the new recommendations and actions, which are in red. Each member of the ACMUI should have the hard copy in front of them and we will be sending out an electronic version as well after this meeting.

Beginning with Item 38, Dr. Alderson requested that the ACMUI discuss the Nursing Mothers Guidelines during the Spring 2017 ACMUI meeting. Are there any updates to that item?

(No audible response)

MS. SMETHERS: Okay.

CHAIRMAN ALDERSON: I did make that suggestion.

MS. SMETHERS: Yes. Okay, Item 39, the Committee recommended that staff issue a generic communication in the form of an information notice regarding tubing issues, such as kinking, connection, hub, et cetera, during the administration of Y-90 microspheres brachytherapy.

Item 40, for the medical event reporting for all modalities, excluding Permanent Implant Brachytherapy Subcommittee, Dr. Alderson removed Dr. Pat Zanzonico and appointed Mr. Frank Costello.

The Subcommittee membership includes Mr. Costello, Dr. Dilsizian, Dr. Ennis, Dr. Palestro, and Dr. Suh as Chair. Mr. Ouhib will be added to the Subcommittee once he receives full voting rights and Dr. Katie Tapp is the NRC resource.

CHAIRMAN ALDERSON: I actually think that

it's more proper to say that Dr. Zanzonico agreed to step aside so that Frank Costello could be appointed. Otherwise, it sounds dictatorial, like saying you're out.

MS. SMETHERS: We can make that update of my -- excellent, okay. Item 41, Dr. Alderson reestablished the Patient Intervention Subcommittee. The Subcommittee's new charge is to make a recommendation on what the definition of what patient intervention should be.

Subcommittee membership includes Mr. Costello, Dr. Dilsizian as Chair, Dr. Ennis, Dr. Suh, and Ms. Weil. Ms. Maryann Abogunde is the NRC resource.

CHAIRMAN ALDERSON: Yes. So this was to resolve some ongoing lack of clarity. Thanks to the Committee for being willing to tackle this a little longer.

MS. SMETHERS: Item 42, the Committee recommended that the Pathway 2 remain. The NRC and OAS Working Group should determine what the requirements should be for the proctoring of cases by the manufacturer.

VICE CHAIR ZANZONICO: Just to clarify,

this is specifically for the Yttrium-90 microspheres?

MS. SMETHERS: Yes.

VICE CHAIR ZANZONICO: Okay.

CHAIRMAN ALDERSON: I think that should actually be in what's written.

VICE CHAIR ZANZONICO: In that, yes.

MS. SMETHERS: We will add that in. Item 43, the Committee recommended to support the update to the waste disposal section and the review of the Y-90 radiation safety issues in autopsy and cremation. Now -- yes, Mr. Green?

MR. GREEN: I think it's worth being specific, Y-90 could be broadly assumed to include Zevalin. We are really talking about the spheres here.

MS. SMETHERS: Just adding that word would make it --

PARTICIPANT: Yes, we're adding it.

CHAIRMAN ALDERSON: Yes.

MS. SMETHERS: Excellent. Oh, I am seeing it now, thank you, Ms. Holiday. Okay, for Items 44 through 52, so Item Numbers 44 through 52 are recommendations which were contained in the NorthStar Mo-99 Tc-99m Generator Licensing Guidance Subcommittee report and were endorsed by the Committee today as

stated in Item 53. Are there any questions, comments?

CHAIRMAN ALDERSON: Langhorst?

MEMBER LANGHORST: I know that this, this has bothered me with all of these lists, but actually if you could have a little something up there at the beginning that says exactly what you just said, that these numbers refer to that licensing guidance then you know what you are reading, you know, but each one you don't want to have to say oh, it's with the licensing guidance.

We all know it today, but when you go back and read it in 2020, whoever is still here, you may not remember that's what all those refer to, so I just, it's confusing sometimes.

So I don't know if there is anything to be done to help kind of clump those together so that you can say this is what these refer to.

MS. SMETHERS: I think we could put a simple note, like a little header on the paper, yes.

MR. GREEN: Yes, parentheses LG.

MS. SMETHERS: Yes.

MR. GREEN: We can do that.

MS. SMETHERS: Okay, so those are the items, the new items. Are there any other

questions/comments/updates?

MR. OUHIB: Sophie, this is Zoubir.

CHAIRMAN ALDERSON: Yes, speak up.

MR. OUHIB: Yes. I'm sorry, I was trying to communicate earlier but the whole afternoon I was unable to communicate with you, I was totally on a different line.

But at any rate, for the Spring meeting, April 20th through the 22nd is the American Brachytherapy Society Meeting, so just to note that for us.

MS. SMETHERS: Okay.

CHAIRMAN ALDERSON: Thank you.

MS. SMETHERS: Thank you.

(Off the record comments)

CHAIRMAN ALDERSON: Laura, did you have a question?

MEMBER WEIL: No.

CHAIRMAN ALDERSON: It's been resolved? Thank you. Other comments?

(No audible response)

CHAIRMAN ALDERSON: Hearing none, is there further business to be brought before the ACMUI?

MR. BOLLOCK: No. At this time we don't

have any other business unless there is anything that you or the Committee would like to discuss or bring up.

CHAIRMAN ALDERSON: Does anyone wish to make a final statement? Hearing none I --

MR. BOLLOCK: Or any questions for staff that I could answer?

CHAIRMAN ALDERSON: Yes. Comments/Questions?

(No audible response)

CHAIRMAN ALDERSON: Hearing none I think that we stand adjourned.

MR. BOLLOCK: Thank you.

(Whereupon, the above-entitled matter went off the record at 3:35 p.m.)

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BTG

September 22, 2016

Re: **BTG Position Statement on the NRC Proposal to Remove the Pathway 2 Training Option from the Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance**

Dear Dr. Philip Alderson (ACMUI chairman),

This letter outlines BTG's position on the NRC proposal to remove the Pathway 2 training option from the Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance. BTG believes that a well-trained clinician is essential to ensure that TheraSphere® is used in the safest manner possible. Moreover, we are committed to working with the US NRC to ensure that the training requirements for Authorized Users (AU) are appropriate, comprehensive and in the best interest of patients.

TheraSphere® is manufactured by Nordion (Canada) Inc. (named on the Sealed Source and Device Registry) for Biocompatibles UK Ltd, a BTG International group company. BTG is responsible for the TheraSphere® training program which has been intentionally designed to match the educational needs of the AU for licensing purposes as well as the needs of the treating team, while addressing the evolving use of TheraSphere® for its approved indication.

BTG believes that the removal of Pathway 2 in the experience and training section of the Y-90 Microsphere Brachytherapy Licensing guidance would not be in the best interests of physicians seeking AU designation for Y-90 Microsphere Brachytherapy and could have a negative effect on patient safety and access to quality of care. We further believe that eliminating Pathway 2 would create a hindrance and a gap in training for physicians seeking AU status. In addressing this concern, we have noted the following areas for your consideration:

Hindrance/Delay for physicians seeking AU status

Elimination of Pathway 2 would hinder physician AU training and patient access to TheraSphere® as follows:

- Liver oncology patients require immediate and timely access to Y-90 microsphere treatment which would be restricted if treating physicians have to first identify external AUs and rely on their availability to coordinate training and subsequent documentation-related requirements for a license amendment. Existing healthcare networks may limit identification or access to AUs from other healthcare networks. Hence, patient treatment may the unintended consequence of getting immediate treatment for their hepatic malignancy. Therefore, the patient may not get the best treatment available for their liver cancer.

- Existing AUs have active clinical practices and are managing a multitude of needs for their liver oncology patients. An AU with sufficient expertise and experience with TheraSphere providing high-quality training to candidate AUs would also be regularly treating patients. Taking time away from their own clinical practices to train candidate AUs would therefore reduce their ability to treat their current patients, further negatively impacting their patient access to radioembolization therapy. Treating fewer patients creates a hindrance for patients seeking the best clinical care. In the current training approach, BTG provides the candidate AU ample training to ensure TheraSphere® use is safe and effective. The BTG trainers are full-time trainers, primarily responsible for delivering high-quality training.

- Outsourcing external physicians to provide training to staff can be burdensome with internal barriers and political issues within hospital administrations. This can delay or restrict the ability of a candidate AU to receive Pathway 1 training. Training of additional AUs within a single institution is expected to be far easier than bringing in an external AU to provide training at an institution.

    - BTG has the flexibility to address the needs of various institutions and their teams in a timely manner, including the ability and willingness to train multiple AUs at the same time. If Pathway 2 is eliminated, physician access would be affected due to the limited availability of AUs for training.

- It is also important to recognize the difference in clinical indication and FDA approval status of the Y-90 microsphere products and how this might hinder the training of candidate AUs. In the US, TheraSphere® has specific FDA approval for hepatocellular carcinoma (HCC, a sub-set of liver cancer patients) under a Humanitarian Device Exemption (HDE). HDE approvals are reserved for devices that are intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year restricting its use. SIR-Spheres is approved for metastatic colorectal cancer (mCRC) which has a significantly higher incidence than HCC, and without limitation on the number of patients that can be treated. Consequently, there is currently a larger number of SIR-Spheres AUs compared to TheraSphere® AUs. Removal of Pathway 2 training would result in an imbalance due to the limited the availability of existing AUs with TheraSphere experience, which would hinder the training of candidate AUs. The difference in product indication and approval status creates a disadvantage for TheraSphere® with respect to the number of existing AUs, which then would cause a physician access hindrance to hospitals starting a TheraSphere® treatment program or replacing an AU who is no longer at that hospital.

Creating a gap in training for physicians seeking AU status

BTG is concerned the proposed change in training requirements could lead to a training gap in the following ways:

- The TheraSphere® administration system has been specifically engineered by BTG to safely and efficiently transfer the TheraSphere® dose to the treatment site. A major benefit of Pathway 2 is the three simulated (in-vitro) hands-on cases which include troubleshooting and mitigation measures unique to the administration system. BTG medical employees convey a comprehensive understanding of the administration system features, benefits and limitations at every training session.
    - Although AUs are familiar with the use of the TheraSphere® administration system, BTG medical employees engage in Quality System post-market surveillance activities (e.g. complaints, AEs, medical events) of the device use. BTG has the capability to adapt the training in a timely and standardized manner for continuous education and enhanced product knowledge.

- There is concern with the removal of Pathway 2 of BTG's ability to control the training information provided. Candidate AUs would need to rely on independent AUs to complete the three supervised hands-on cases. The training for both the supervised hands-on *in-vitro* simulated cases and the three supervised patient administrations is currently provided by BTG medical employees who present comprehensive, standardized information so all AUs receive the same information. The absence of this standardized training platform would create a gap in training.

- BTG is concerned that the absence of a standardized training platform could result in a risk of higher incidence of gastrointestinal ulcer adverse events. The gastrointestinal ulcer rate associated with TheraSphere® treatment has decreased since the implementation of BTG's comprehensive training program in 2004 (4% before 2004 vs. <0.5% currently) based on comprehensive published literature review of over 1600 hepatocellular carcinoma (HCC) patients.

- The comprehensive BTG training program is delivered in partnership with physicians in clinical practice as follows:

    - Clinical use experience and literature training is provided by multidisciplinary teams at the TheraSphere® Center of Excellence (CoE) and supported by field-based physician advisors. The multidisciplinary CoE training team typically includes representatives from radiation safety, nuclear medicine, interventional radiology, nursing, surgical and/or radiation oncology.

    - BTG has a medical team dedicated to supporting and training AUs and their medical teams including Radiation Safety Officers (RSO). BTG periodically adapts the training to integrate changes to TheraSphere® clinical practice nationally, with global awareness, versus independent institution-based AUs who may be unfamiliar with evolving clinical practice.

- Independent AUs who are currently providing training on Y-90 microspheres typically only train the prospective AU and not the entire multidisciplinary treatment team. This lack of comprehensive training for the whole treatment team would lead to a gap in knowledge for the safe and efficient handling of TheraSphere®.

- Brachytherapy medical training is standard curriculum in medical schools due to the prevalence of prostate cancer whereas TheraSphere® administration is provided to Interventional Radiology fellows in select institutions with existing TheraSphere® treatment programs. Alignment of the licensing guidance in keeping with brachytherapy medical training is premature relative to radioembolization training and a majority of institutions would not have the skills to deliver this product specific training resulting in a less robust training program.
    - In addition, brachytherapy treatment involves the selected placement of a 50-100 radioactive seeds with percutaneous needle placement into the prostate or other target tissue under imaging guidance. Whereas with TheraSphere®, millions of microspheres are implanted in the liver tumoral area while taking into consideration catheter navigation, hemodynamics, perfusion volume for dosing, non-target deposition, arteriovascular shunting and other relevant primary and secondary liver cancer treatment considerations to ensure fundamental liver function is maintained to sustain bodily functions. The absence of this standardized training currently stated within the Licensing Guidance for the administration of a unique, implanted radioactive device could create a negative impact to patients.

The robustness of BTG's AU Pathway-2 training program is described further in Appendix A.

BTG is committed to ensuring that the training requirements for Authorized Users (AU) are appropriate and comprehensive and in the best interests of patients. As stated above, BTG believes that eliminating Pathway 2 of the Y-90 Microsphere Brachytherapy training program could have a negative impact on patient safety and access to quality care, hinder/delay the training of AUs and leaving a gap in the training requirements of physicians seeking AU status.

We thank the ACMUI for their consideration and welcome further discussion on the matter.

Respectfully,

Francis Facchini, MD FSIR

Head, Medical Affairs

Frances E. Harrison, RAC

Senior VP, Global Regulatory Affairs

Appendix A

BTG Multidisciplinary Center of Excellence (CoE)

The BTG Center of Excellence program is a one day course that provides the multidisciplinary treatment team with information on implementing a TheraSphere® program. The Center of Excellence Program began in September 2004 and since that time has trained Authorized Users (AU) which include Interventional Radiologists (IR), Nuclear Medicine physicians and Radiation Oncologists.

The program agenda consists of the following:

- Y90 Physics, Nuclear Medicine, Radiation Safety, Regulatory Information
- Clinical Care of the Patient
- Angiography Considerations
- Hepatocellular Carcinoma and Treatment Considerations
- Comprehensive Review of TheraSphere® Clinical Data
- Administration Accessory Kit Set Up
- TheraSphere® Dosimetry with Practice Dosimetry Questions

The CoE course is held approximately every six weeks at one of three sites nationally: Northwestern Hospital in Chicago, Mt. Sinai Medical Center in New York and Banner University Medical Center in Phoenix.

On-site training

The BTG AU training program includes face to face training that takes place with the physician seeking AU status. During this training session the physician is trained on the TheraSphere® Y-90 Glass Microsphere System with three mock infusions, including reviewing issues that may be encountered during a TheraSphere® administration. At the conclusion of this training for IR's seeking AU status a) – g) training is covered as outlined below.

a) Ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys; (Includes ordering, receipt and storage of dose vial; removal of dose vial from box and using the TheraSphere® measurement template.)

b) Performing quality control procedures on instruments used to determine the activity of TheraSphere® and performing checks for proper operation of survey meters; (Includes demonstration of dose calibrator checks; discussion of reference standard and dose vial measurement; and performance checks on contamination detection equipment.)

c) Evaluation of each patient or human research subject for the dose/activity of TheraSphere® to be administered to each treatment site; (Includes discussion of recommended dose as per the Package Insert (80-150 Gy) and dose vial size options for perfused liver volumes.)

d) Calculating and measuring the activity and safely preparing TheraSphere® to be delivered to the patient or human research subject; (Includes demonstration of dose calculation to treatment volume and infusion system setup as per the Package Insert checklist.)

e) Using administrative controls to prevent a medical event involving the use of byproduct material; (Includes reviewing administration system assembly, infusion flow rate, dose vial preparation, and pinch clamp use; demonstration of percent delivery calculation.)

f) Using procedures to control and to contain spilled byproduct material, including TheraSphere®, safely and using proper decontamination procedures; (Includes identifying potential spill or contamination risks; how to mitigate risks; and decontamination principles and techniques for TheraSphere®.)

g) Follow up and review of each patient's or human research subject's case history for Y-90 microspheres; (Includes reviewing typical follow-up regimens; identifying typical treatment response periods, and typical and atypical adverse events, as per the Package Insert and TheraSphere® Reference Manual.)

On-Site Multidisciplinary Training

BTG provides a multidisciplinary Vendor Training session for each new site. This session typically includes the following staff: Interventional Radiology and Nuclear Medicine technologists; radiation safety; medical physics; nursing staff and AU's and IR's if not the AU. During this session a review of TheraSphere® takes place including dosimetry calculations, kit set up and roles and responsibilities of everyone involved in the Y-90 TheraSphere® treatment.

Supervised Cases

For at least the first three cases, prior to the treatment day, usually the day of or the day after the mapping angiogram, BTG medical employees consult with the physician seeking AU status to assist in proper patient selection and review the calculations. At this time the correct TheraSphere® dose vial for the patient treatment is identified and ordered.

On the treatment day BTG meets with Nuclear Medicine prior to the case and walks through all of the pre-treatment measurements necessary for the TheraSphere® Written Directive. During the case, BTG guides all staff so a safe administration takes place and all radiation safety monitoring is performed properly. Following the case BTG medical works with the AU/ nuclear medicine staff to complete the TheraSphere® written directive.

BTG Preceptor (Physician Advisor) Program

BTG also works closely with physicians seeking AU status through the TheraSphere® Preceptor Program. This program consists of two highly respected Interventional Radiologists with extensive Y-90 TheraSphere® experience who assist AUs with cases that are technically challenging or in cases that require a second opinion relating to clinical practice and appropriate use or constraints for Therasphere® use. Typically a phone call takes place where the case is discussed and a medical response is generated by the TheraSphere® Preceptor.

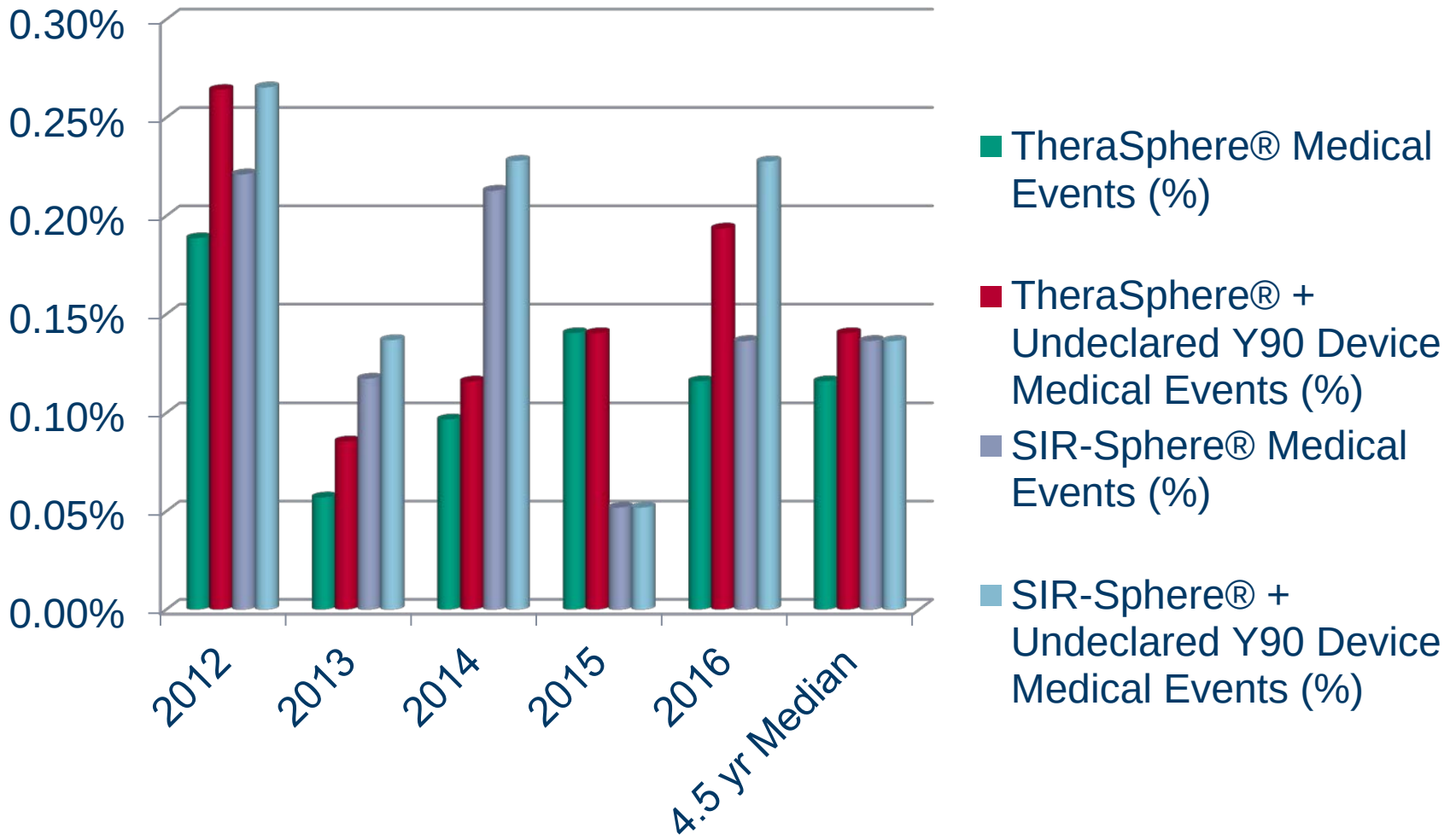
US NRC Yttrium-90 Microspheres Brachytherapy Licensing Guidance

BTG Training for TheraSphere® Yttrium-90 Microspheres

ACMUI Meeting October 7, 2016

Imagine where we can go.

US NRC Y90 Microspheres Reported Medical Events: Low



Source: US NRC Yttrium-90 Microsphere Medical Event http://www.nrc.gov/reading-rm/doc-collections/event-status/event/2016/s

TheraSphere® Training Program* Results: Positive

Input Source	Feedback Period	Results
Center of Excellence (CoE): feedback @ training day	16 CoE sessions since Dec 2014	65% provided feedback at CoE; on a scale of 1-5, with 5 being excellent, 98% rated the program as 4 or higher
Post training survey (CoE participants and treatment protocol Principal Investigators)	September 2016	94% of responders preferred licensing guidance remain the same; testimonials volunteered (see Appendix 1)
Global Adverse Event Rate (any grade) as reported to BTG	January 2015 – June 2016	0.3% (FDA audit July 2016)
Medical Event Rate (US) – 4.5 yr median	2012 – July 2016	0.12%

* BTG TheraSphere® Training Program established in 2004, operating worldwide.

Licensing Guidance: Vendor Training is effective

- Physicians and other healthcare workers value program
  - At training day session and post-training surveillance
  - Supported by testimonials

- Device training by vendors is standard practice in industry to account for unique device features and engineering
  - eg. Catheter use, implanted devices

- TheraSphere® global Adverse Event rate is 0.3 % (reviewed in recent FDA audit)
  - worldwide training program is effective

- 4.5 yr Median Medical Event rate is low:
  - TheraSphere® (0.12%) vs SIR-Spheres® (0.14%)

Conclusions

- BTG TheraSphere® Training Program has effective, proven track record since 2004:
  - Conveys valuable information to ensure patient safety is high priority
  - Ensures physicians and healthcare workers are better equipped to implement a Y90 microsphere treatment program

- Removal or modification of Pathway 2 from Yttrium-90 Microsphere Brachytherapy Sources and Devices Licensing Guidance is not warranted
  - Would be disservice to the medical community

Appendix 1

Post Training survey:

CoE participants and treatment protocol
Principal Investigators

Survey

Survey Dates: **Sept 23 – Sept 29, 2016**

Survey Audience: CoE participants and treatment protocol principal investigators

Circulation: **642**

Response Rate: **8%** (53)

Total Number of Survey Questions: **2**

Comments Received: **62%** (33 respondents included comments)

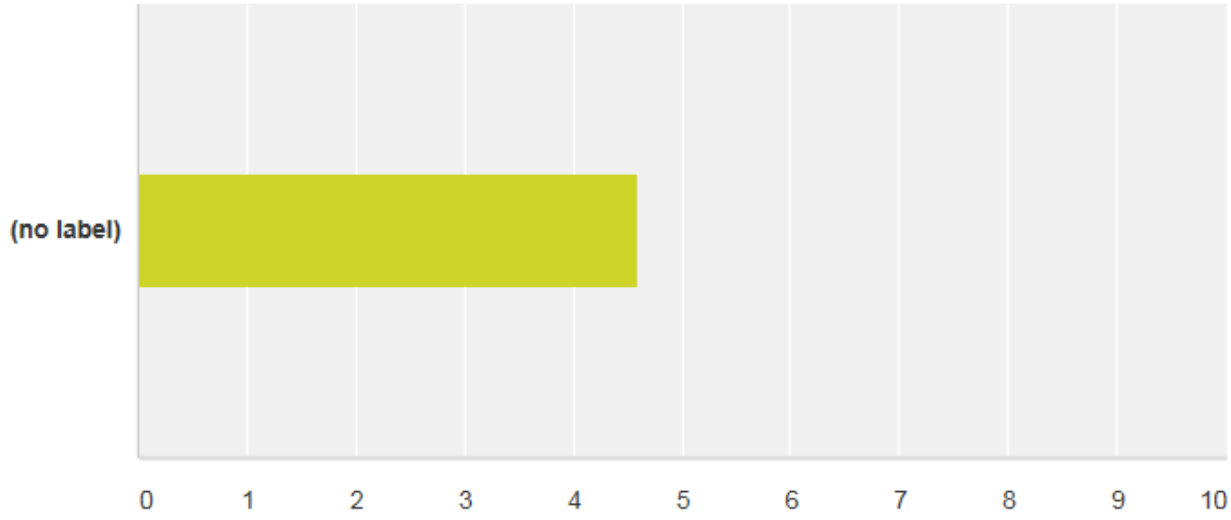
Respondents who self-identified:

19 - Interventional Radiology
4 - Radiation Oncology
2 - Nuclear Medicine
2 - Radiation Safety Officer
2 - Medical Physicist

Question #1

Please rate the value of the TheraSphere® Yttrium-90 Glass Microsphere training you have received from BTG:

Answered: 53 Skipped: 0

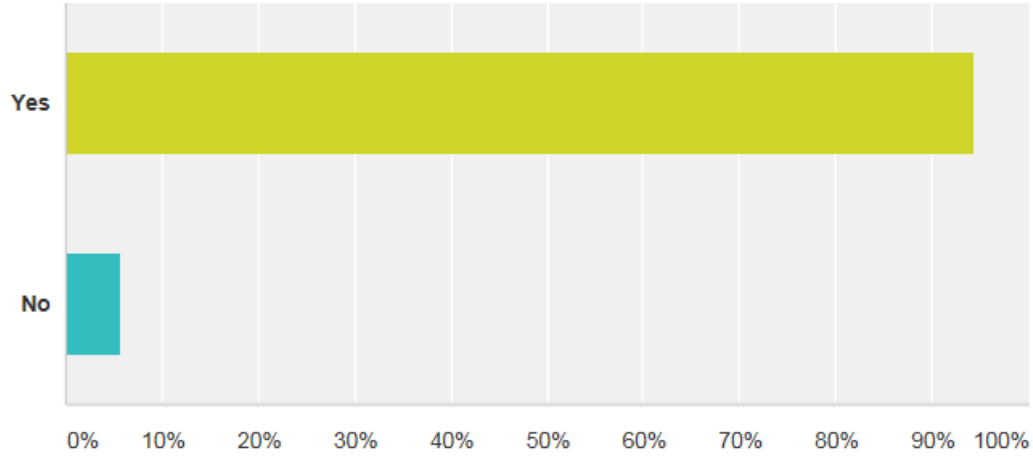


	Poor	Satisfactory	Good	Very Good	Excellent	Total	Weighted Average
(no label)	1.89% 1	3.77% 2	5.66% 3	9.43% 5	79.25% 42	53	4.60

Question #2

Would you prefer the Y90 Brachytherapy Licensing Guidance remain the same allowing BTG to provide a comprehensive training program for TheraSphere®?

Answered: 53 Skipped: 0



Answer Choices	Responses	
Yes	**94.34%**	50
No	**5.66%**	3
Total		53

Survey Testimonials

I believe that vendor provided training is essential to the optimal integration of Y-90 microspheres into our department's operations. While training by AUs is very helpful a well, there are many aspects of the administration of microspheres that are better done by non-physicians. This includes some aspects of technologist and radiation safety functions as well as other tasks usually handled directly by physicians. the Center of Excellence program greatly facilitates the overall organization's involvement in the technique. I question whether visiting AUs will have the time and interest to do this in-depth training.
Warren Moore, Nuclear Medicine

The BTG training that I received was outstanding. It comprehensively covered the technical aspects of patient selection, dosimetry and delivery technique. It gave me knowledge of and confidence with a complex procedure. I think that omitting this program would be a disservice to physicians and their patients.
Radiation Oncology

Treatment delivery is multidisciplinary team effort and the vendor training is able to adequately train all participants of that team. If this is stopped, I believe that could lead to safety deficiencies that would compromise patient care.
Radiation Oncology

The BTG training program was very helpful for understanding the procedures for using Theraspheres. Having the training away from the clinic allowed for uninterrupted time to learn and ask questions. The presenters were experts in the use of Theraspheres, having done hundreds of treatments. Learning what their experience showed to be best practices was very valuable. Methods for safely handling the radioactive materials were demonstrated and the extensive experience of the presenters was of great use.
Radiation Oncology

This training provides comprehensive teaching on the rational which should guide therapeutic decision. It is also a great opportunity to share with other future users about the challenges encountered when setting up a Y-90 program.
Radiation Oncology

Survey Testimonials

The BTG training I experienced for my facility was IMPERATIVE to our success in a very specialized treatment. Without this training and proctoring we would not be set up for the best possible patient outcomes.
Nuclear Medicine/Interventional Radiology

Off site training at the North Western site in Chicago was extremely helpful, I am a safer authorized user and safer procedural physician as a result. Anything done to reduce the ability of physicians to receive vendor sponsored training on or off site will certainly be deleterious to safety and outcomes. We as physicians do not have significant non-vendor resources to sponsor ourselves to obtain additional training, and without vendor support we will certainly be less well trained. Lastly, I received free training from BTG, and have not even used their product yet, rather I have a long standing program using the competitor vendor SIRTEX. Therefore, I can not see how an argument (if being made) against vendor bias can be substantiated. I am appreciative of the vendor sponsored experience, and use it to improve quality in a vendor neutral manner.
Interventional Radiologist

The BTG training is comprehensive, safety oriented, and patient oriented. It is invaluable to the treatment of a large cohort of patients who have very few good treatment options.
Interventional Radiologist

Our BTG team that trained us here at our site and at 2 of our sister facilities was instrumental in us getting our Y90 programs going. Hundreds of patients in our system have benefited from their work.
Interventional Radiologist

Excellent comprehensive training of significant value.
Interventional Radiologist

I believe BTGs presence helped tremendously in safe handling, set up and administration of Y90.
Interventional Radiologist

Survey Testimonials

1. Excellent technical review 2. Safety issues addressed 3. Helpful review of the pertinent literature.
Interventional Radiologist

Excellent, comprehensive training was provided with an emphasis on patient care and radiation safety.
Interventional Radiologist

The BTG training was comprehensive and important.
Interventional Radiologist

I thought the training by Dr. Salem at Northwestern was outstanding! No specific weaknesses.
Interventional Radiologist

Excellent didactic and hands on training through BTG, which was critical to the success of our program at the University of Utah.
Interventional Radiologist

It is extremely important for the training to come from the company. Having AUs be the only source will water everything down. It is similar to having a 10th generation photocopy. You get some of the information, its kinda blurry, the numbers are faded. When its given by the company, its like an original document.
Interventional Radiologist

Fantastic training that helps us better treat our patients in an effective and safe manner. It would be extremely detrimental if this were to be changed.
Interventional Radiologist

The training we received from BTG, particularly the Center of Excellence seminar, was hugely valuable to us. It would be a great loss if this opportunity was removed. We have observed that current users may have developed their own short cuts or other practices that, while not necessarily wrong, may not comport with BTG recommendations. It is essential that new users be trained according to manufacturer recommendations first.
Medical Physicist

Great Classes.
Medical Physicist

Survey Testimonials

The training our proposed AU and the whole team received was excellent. It also provide personal contact with excellent individual resources for follow-up.
Radiation Safety Officer

Both the onsite and COE training was great.
Radiation Safety Officer

Since I'm an RN and not involved with direct transfer of particles and not able to see much, it was great to be able to really see first hand what is actually going on.
Registered Nurse

The actual intention of the training seems to be tailored to removing the idea that Y90 is purely palliative. The written directive, dose calibrator, and room clearance training shown at the NYC center of excellence was subpar. Too much of a sales pitch and very little of safe administration, and room release as required of NRC oversight. Anyone who comes from a Nuc med background would be disappointed to the actual live training, simple things such as room prep, and dose calibrator review would have been far more important than explaining how y90 may improve the Milan score.
(no speciality given)

Our interventional radiographers and nuclear medicine tech attended the Center of Excellence. It was very comprehensive and as a radiation safety officer I felt better knowing they attended this training as well as having the proctor on site for our first three cases. I feel this should be required due to the complexity of these types of cases and the issues that can come into play.
(no speciality given)

This training provides comprehensive teaching on the rational which should guide therapeutic decision. It is also a great opportunity to share with other future users about the challenges encountered when setting up a Y-90 program
(no speciality given)

Survey Testimonials

BTG was outstanding in their training, meticulous to detail and inclusive of all required parties.
(no speciality given)

The training was comprehensive and covered all aspects of prescribing, dose calculation, and dose delivery. Currently certified authorized users may not be able to make the time commitment to individually train other authorized users over an 8 hours or so training session that involved a multidisciplinary team. As a radiation oncologist, I know that I would not have that amount of time available in a single block.
(no speciality given)

Excellent didactic and hands on training through BTG, which was critical to the success of our program at the University of Utah.
(no speciality given)

I had very good training course in NY. My knowledge about HCC and TheraSphere treatment was greatly updated.
(no speciality given)

I think it's an essential part of training. I'm afraid that without it there will be increase in complications given the importance of paying attention to detail. Additionally, even after completing my proctoring I've asked them to come on additional cases.
(no speciality given)

The training programs are excellent and provide me with the necessary tools to treat patients safely and effectively. The advanced courses are fantastic as well. Please do not change the training programs.
(no speciality given)

y90 brachytherapy vendor training and preceptor support are very important ancillary resources that have supplemented my training. I believe both the courses and preceptor support enhance user knowledge and contribute to patient safety and improved outcomes, particularly as practitioners are beginning their careers with these devices.
(no speciality given)

COMMUNITY ONCOLOGY ALLIANCE
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October 3, 2016

Philip O. Alderson, M.D.
Advisory Committee on the Medical Uses of Isotopes
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

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

Dear Philip O. Alderson, M.D.:

The Community Oncology Alliance (COA) appreciates the opportunity to provide input in advance of the October 7, 2016, meeting of the Advisory Committee on the Medical Use of Isotopes (ACMUI) regarding training and experience requirements for authorization to administer therapeutic patient-ready doses of alpha- and beta-emitters to cancer patients. COA is a non-profit organization dedicated to cancer patients and providers in the community oncology setting, representing over 7,000 community oncologists from across the country. The majority of Americans treated with cancer are treated in the community oncology setting. However, COA has tracked numerous barriers nationwide to patient access to lifesaving treatments and is deeply concerned about this unfolding crisis.

COA has participated in the Nuclear Regulatory Commission (NRC) rulemaking process on the *Medical Use of Byproduct Material: Medical Event Definitions, Training and Experience, and Clarifying Amendments* (RIN 3150-AI63), responding specifically to the NRC's request for comments on whether its regulations *"discourage licensees from using certain therapy options or otherwise adversely impact clinical practice, and if so, how."* COA submitted a comment letter in the fall of 2014, attended and spoke at the NRC's public meeting in February of 2015, spoke during the ACMUI teleconference in June of 2015, and submitted an additional comment letter in July of 2015, responding to questions raised during the ACMUI teleconference. COA is extremely disappointed that the NRC does not intend to address the training and experience requirements for authorized user status to administer alpha- and beta-emitters in that rulemaking. In order to address the issue raised and considered during the rulemaking process, COA encourages ACMUI to support proposals for an expedited standalone rulemaking to develop a competency-based alternative to these requirements.

Patient Access Barriers

From what I know from my practice (NSHOA Cancer Center) on Long Island, NY, and based on input from colleagues in community oncology from around the country, the current burdensome training and experience requirements are the primary impediment to providing greater patient access to alpha- and beta-emitter therapies. The 700 hours of training and experience required by the regulations includes many competencies not required to administer such therapies and the commitment required to complete the training and experience is too onerous for the practicing community oncologist to implement and is not needed. As a result, it is exceedingly difficult to find authorized users geographically accessible to patients in many rural and socioeconomically disadvantaged areas far from major academic medical centers. This is a particular problem because patients in need of alpha- and beta-emitters are often either elderly with limited mobility or facing disabilities as a result of their cancer or

treatment, making significant travel virtually impossible. For these reasons, community oncologists often are dissuaded from recommending alpha- and beta-emitter therapies even when they would otherwise be beneficial to their patients.

Targeted, Competency-Based Pathway Could Ease Access Problem

There would be significant interest from community oncologists in acquiring limited authorization to administer therapeutic, patient-ready doses of alpha- and beta-emitters if there were a practicable pathway to doing so. Fortunately, developing such a pathway is feasible and would not in any way compromise patient safety. The experience and training of oncologists in the provision of chemotherapy prepares them for the handling and intravenous administration of highly dangerous substances. Although certain targeted additional training is needed to learn the specifics of administering and safely handling therapeutic patient-ready doses of alpha- and beta-emitters, this training can be accomplished in a small fraction of the current 700-hour requirement.

Furthermore, such a pathway has existed successfully before. Prior to the 2002 rulemaking, practitioners could obtain authorized user status for the administration of beta-emitting radiopharmaceuticals through 80 hours of classroom and laboratory training. Dr. Joseph Mace, the director of the radioimmunotherapy program at Florida Cancer Specialists, was trained under those requirements, and he has been administering Zevalin for a decade and Xofigo for many years without safety incidents.

Stakeholders have proposed the creation of a targeted, competency-based training pathway to obtain 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. This pathway, designed by experts in the field of radiation safety education and training, involves classroom and laboratory training plus relevant work experience and case administrations. COA supports this reasonable and limited proposed regulatory change. Standard treatment options that offer excellent response rate should be available to all patients whether those patients live near an academic medical center or in more rural or socioeconomically disadvantaged areas of the country. COA urges ACMUI to consider this proposal that could significantly improve patient access to lifesaving treatments in the community oncology setting.

Conclusion

COA is concerned that the current 700-hour training and experience requirement for authorized user status to administer therapeutic patient-ready doses of alpha- and beta-emitters limits the number of authorized users and restricts access to these treatments among community oncology patients who live at a distance from large academic medical centers. We believe that this state of affairs is not necessary and that access to these therapies can be meaningfully enhanced by the development of an alternative, competency-based pathway to a limited authorized user status. We respectfully urge ACMUI to recommend that the NRC initiate a standalone rulemaking to create such a pathway. As the next NRC rulemaking cycle may not be until 2021, we encourage the NRC to act quickly to resolve these burdens on cancer patients.

Thank you for the opportunity to comment on behalf of the COA. Please let me know if you would like to follow up directly with me for any additional discussions.

Sincerely,

Jeffrey Vacirca, MD
Community Oncology Alliance
Vice President

LYMPHOMA
RESEARCH • FOUNDATION

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October 3, 2016

Advisory Committee on the Medical Uses of Isotopes
U.S. Nuclear Regulatory Commission
Attention: Michelle Smethers
Washington, DC 20555-0001

RE: Training and Experience Requirements for Alpha and Beta Emitter Therapies, Docket NRC-2016-0022

Dear Members of the Advisory Committee on the Medical Uses of Isotopes (ACMUI):

The Lymphoma Research Foundation (LRF) appreciates the opportunity to comment on the proposal to consider the training and experience requirements for alpha and beta therapies, specifically radioimmunotherapy, which is utilized in the treatment of patients with non-Hodgkin lymphoma (NHL). Radioimmunotherapy represents an important option for those with NHL, and all required professional training and security standards for this treatment must be clear, straightforward and adequate, to ensure that safe access to this therapy is not limited unnecessarily.

The burden of NHL in the United States is significant. More than 70,000 Americans are diagnosed with NHL annually and almost 20,000 will die from the disease this year alone. NHL is not a single disease but a group of several closely related cancers. Follicular lymphoma is the most common indolent form of NHL, accounting for approximately 20 percent to 30 percent of all NHL cases in the United States.

LRF offers broad and diverse programming aimed at meeting the needs of those with NHL and other forms of lymphoma. We support innovative research and provide up-to-date education about lymphoma and treatment options available to patients and healthcare providers. It is with this experience in mind that we express that those with lymphoma cannot afford to lose any element of their treatment armamentarium. Innovative therapies like radioimmunotherapy provide an option for patients for whom other treatments for the disease may not provide a therapeutic benefit. It is an effective, singular course of treatment that provides long-lasting results for many patients.

Training and delivery for radioimmunotherapy are important issues when considering patient access to this treatment. By convening expert stakeholders in a timely manner, the Commission can safely and systematically implement appropriate training, competency and safety standards which can facilitate patient access. By implementing an expedited process and not delaying until the next rulemaking process in 2021 to determine these standards, the Commission will also establish the importance of federal regulations keeping pace with new cancer treatment delivery methods, so that the fruits of the research system are available to patients in need of them the most, particularly those individuals within a small patient population.

LRF acknowledges the past efforts of the Nuclear Regulatory Commission to review and consider this important issue; we look forward to the continued willingness of the Commission to engage the patient and other stakeholder communities for a full resolution of the issues surrounding radiopharmaceutical training and experience requirements. Toward that end, the Foundation would be amendable to participating in the process and providing additional information about the patient experience and importance of access to the full range of available therapies for people with lymphoma.

Sincerely,

Meghan Gutierrez
Chief Executive Officer

September 30, 2016

Morton A. Diamond, MD

Philip Alderson, MD, Chair

Advisory Committee on the Medical Uses of Isotopes

US Nuclear Regulatory Commission

Two White Flint North Building (T2-B3)

Rockville, MD

Dr. Alderson and members of the committee:

I write from a perspective afforded to very few: a physician forced to leave medical practice because of multiple serious medical issues including stage IV non- Hodgkin's lymphoma, all attributed to military service in Viet Nam; a patient in a clinical trial who was the 6th person to receive Zevalin experimentally as first-line therapy; and one who has had a continuing interest in the utilization of this medication.

I respect the goal of this committee: safe administration of radioisotopes in order to protect the patient, care giver, and public citizen. The question this morning is straightforward: what is the appropriate training and experience physicians need for this safety?

I posit that the committee's effort to protect has, unwittingly, caused harm--- indeed, a strong word--- because the present 700 hours of education required for Zevalin administration has resulted in many lymphoma patients having been denied this efficacious and cost-effective therapy.

Admittedly, I am neither a radiation oncologist nor a nuclear medicine physician. However, I submit that I have important information that bears on the issue before you.

Allow me to present radioactive iodine I131 and Zevalin side-by-side to you.

The required educational training for an endocrinologist to administer I 131 is 80 hours. The required educational training for a medical oncologist to administer Zevalin is 700 hours.

The half-life of I 131, the gamma emitter, is 8 days. The half-life of yttrium, a beta emitter, in Zevalin is 2.6 days.

In advance of treatment, what is the patient told about <u>administration</u> of the 2 agents?

From the literature I have recently reviewed:

I 131 **80 hours of required education**

- I 131 is administered in a special room with radiation shielding on the walls and doors.
- The room will have paper on the floor.
- There will be plastic covers on furniture, doors, handles, and switches.
- You will eat with plastic dishes and utensils: after use, you will place them in a special trash container.
- You will flush your toilet 3 times after each use.
- Staff will limit time spent in your room.
- A radiation specialist will visit your room 1 to 2 times each day to measure radiation levels.
- You cannot have visitors in your room.

Zevalin **700 hours of required education**

- I was a "celebrity", for I was a patient in an experimental clinical trial. When I received the Zevalin I was sitting in a regular examination room surrounded by a nurse, two secretaries, radiation oncologist, radiation physicist, and my wife.

Later, the follow-up <u>instructions</u> for the patient after having received the two medications:

I 131 80 hours of required education

For 7 days:

- You will stay at least 6 feet away from children under age 16 years
- You will sleep alone
- You will separate and wash linens separately

Zevalin 700 hours of required education

For 3 days:

- You will wash hands thoroughly
- You will clean up spilled urine

For 7 days:

- You will employ sexual protection

Members of the Advisory Committee:

Something is awry; something is incongruous; something is wrong. There is a 9 times greater requirement for education in administering Zevalin than I 131; 700 hours versus 80 hours.

In March 2016 ACMUI concluded there is a sufficient number of authorized users to administer Zevalin. Respectfully, this number loses significance because, I believe, an overwhelming number of medical oncologists do not refer the lymphoma patient to the authorized user. This is not the forum to debate why

medical oncologists do not refer the patient. Clearly, the answer has nothing to do with efficacy and safety profile of Zevalin.

Medications and humans have much in common: we are born; we live; and we die.

For a medicine to die because another effects a higher rate of cure or eases pain more safely or prolongs useful life is the essence of pharmaceutical progress.

But, for a medicine to die, slowly and tortuously, in the full flower of its efficacy because of overbearing regulatory restriction is a tragedy no less than the tragedy of human death in the full flower of life.

Dr. Alderson and committee members, do not let Zevalin, a medicine whose effectiveness is supported by a body of data, die because of regulatory restriction.

Respectfully,

Morton A. Diamond MD FACP FAHA FACC(E)

October 1, 2016

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

Regarding access to radioimmunotherapy in the community setting

To whom it may concern:

I am Karl Schwartz, president and founder of Patients Against Lymphoma.

Thank you for listening to the concerns of patients on the matter of access to radioimmunotherapy and for considering the sponsor's recommendations. Here I am submitting a summary of patient concerns, and a longer detailed statement along with a petition from the patient community.

My summary statement:

- Current NRC policy requires oncologists to take a 700-hour course (on the full range of nuclear medicines) to give one medicine to their patients: prepackaged radioimmunotherapy. It's apparent that it's not feasible for oncologists to take the entire course to be authorized to offer this one treatment to their patients.

- As I understand it, a purpose of the Cancer Moonshot is to foster treatment innovation, but also to ensure that innovations are accessible to the patients.

  The current policy is significantly limiting access to a unique targeted therapeutic based on where the patients happen to live. As Dr. Cheson (Georgetown University) noted: that oncologists must send their patients elsewhere to receive radioimmunotherapy is a major reason for the low usage of this effective treatment.

  The current circumstance seems a disincentive to innovate further and test radiopharmaceuticals in combination with emerging targeted therapeutics for lymphoma and other cancers. (Why would clinical investigators champion study concepts for a therapeutic that is not available where most patients receive the diagnosis of cancer?)

- My final point is that radioimmunotherapy is not a me-too drug. It is perhaps the least burdensome treatment available to patients. It takes about 1 week to give, compared with many months of chemotherapy. It's the only non–chemotherapy-based approach with a high rate of durable remissions.

Again, I offer my sincere thanks to the committee for its continuing attention to this matter. I ask that the committee review also my written statement and the comments from the patient community that are attached to it.

Written Statement:

Present policy requires oncologists to take a 700-hour course (on the full range of nuclear medicines) to give one medicine to their patients: prepackaged radioimmunotherapy. It's apparent that it's just not feasible for oncologists to take the entire course to be authorized to offer this one treatment to their patients. The burdensome training requirement has contributed to the underutilization of radioimmunotherapy in the community setting—where 80% of patients receive the diagnosis of cancer and are treated.[1]

This is a classic "catch-22" situation: Most doctors who treat patients with lymphoma are not authorized by the NRC to give radioimmunotherapy. Those who are authorized (nuclear medicine physicians) do not see these patients. The sponsor of one remaining radioimmunotherapy drug, Zevalin [ibritumomab tiuxetan], is losing money and may discontinue it. Recently, Bexxar [tositumomab/iodine-131 tositumomab], a similar agent, was discontinued for lack of profitability.

Personal Experience: It's evident that lives are being lost, tragically. Here I can speak from personal experience. My loved one was diagnosed with lymphoma. She suffered a relapse after rigorous combination chemotherapy in 1997, just 6 months after her initial treatment. For 8 additional years, she endured one harsh treatment after another. Each time, the lymphoma was back and progressing even before her hair grew back.

In 2004, she received radioimmunotherapy after a short course of chemotherapy. She has had no sign of lymphoma since—enjoying 12 years of normal life for which we are profoundly grateful.

A Remedy Needed: A remedy seems feasible and necessary: Have the NRC work with the sponsor of the particular drug to develop a focused course on how to safely administer a prepackaged radiolabeled antibody (as was done when it was first approved)—a protocol similar to that for the nonlabeled rituximab (Rituxan) antibody that oncologists give routinely. It's especially important to consider the *unique* properties of a radioimmunotherapeutic drug and that the burdensome training requirement has negative implications for other types of cancer that may be treated with similar targeted radiotherapies.

Radioimmunotherapy is perhaps the least burdensome treatment available to patients. It takes about 1 week to give, compared with many months of chemotherapy. It's the only non–chemotherapy-based approach with a high rate of durable remissions. It's an important and *unique* choice for patients who must continue to work through or shortly after treatment; who cannot tolerate chemotherapy, because of advanced age or specific comorbidities; and who may prefer to avoid or substantially limit the on-treatment side effects of chemotherapy such as nausea, neuropathy, hair loss, as well as gastric and mucositis complications.

Durable Responses Reported: I recognize that not every patient who receives it will remain free of treatment for as long as my loved one. Yet, clearly, this is an important and easily tolerated therapy with high efficacy, particularly when given early in the disease course. It also has substantial potential for enhancement if combined with other targeted agents in clinical trials.

Larson and colleagues[2] have summarized outcomes with radioimmunotherapy as follows.

Seven phase II studies and two phase III studies have tested [radioimmunotherapy] in patients newly diagnosed with [non-Hodgkin lymphoma] who received front-line therapy either alone or as consolidation following chemotherapy. These studies have all demonstrated efficacy, with [overall response rates] of 90% to 100% and [complete response rates] of 60% to 100%. Also, the [complete response rates] induced by this approach have been very durable, with median remission durations exceeding 6 years in many studies.

Ensuring Access to These Agents: We need to honor the sacrifices made by the patients who enrolled in the trials that led to the U.S. Food and Drug Administration approvals of radioimmunotherapy agents by making sure that access to these agents is not limited by where a patient happens to live. And we need to ensure that future access to these agents is not eliminated entirely.

—***Karl Schwartz***
Riegelsville, Pennsylvania

Disclosure: Mr. Schwartz is the President and Cofounder of Patients Against Lymphoma (PAL).
Mr. Schwartz and PAL have no financial conflicts of interest in this matter.

References

1. Copur MS, Ramaekers R, Gönen M, et al: Impact of the National Cancer Institute community cancer centers program on clinical trial and related activities at a community cancer center in rural Nebraska. J Oncol Pract 12:67-68, 2016.

2. Larson SM, Carrasquillo JA, Cheung NK, et al: Radioimmunotherapy of human tumours. Nat Rev Cancer 15:347-360, 2015.

REDACTED petition from the online patient community

The persons within have expressed their support for a letter to the Senate HELP committee (available on request) and the written statement above.

NAME	COMMENT
Michael [REDACTED], Warwick, RI	
Richard [REDACTED], Columbus, OH 43229	Zevalin saved my wife's life. She has been in remission for 12 years.
Marilyn [REDACTED], Belleville, WI 53508	It is unconscionable for anyone to think or do anything or stop the availability of this drug to people that it can cure and let them live.
Dr. LInda [REDACTED]Pipersville, PA	As a lymphoma survivor, I urge you to also read the letters submitted to the ACMUI and NCR opposing the rule change ... letters submitted by qualified and informed stakeholders, such as by the president of the American Society of Hematology, Dr. Jeffery Vacirca - Community Oncology Alliance, Joseph R. Mace, MD, and by the Lymphoma Research Foundation. Please reconsider the training requirements
Ann [REDACTED], Columbus, Ohio	My good friend is alive and well many years after her treatment with Zevalin radioimmunotherapy. Please keep it available for others.
Carol [REDACTED], Clearwater, FL	People are dying!
Jan [REDACTED], Columbus, Ohio,	I received Zevalin in 2004. The three previous treatments provided short remissions. I am still in remission from Zevalin and living a normal life! I want others to be able to receive Zevalin if their doctors deem it a choice of treatment.
Michelle [REDACTED], Attleboro, MA	
Molly [REDACTED], Columbus, Ohio,	
Patti [REDACTED]. Westerville. Ohio	
Marilyn [REDACTED], Belleville, WI	I understand my first sign up may not have registered. Those who have the power to cause possible changes for eliminating these needed drugs for cancer patients, and do so, are abominable. It's a sin to take away the possibility of life when the whole world has been looking for a cure.
Deborah L [REDACTED], Columbus, Ohio,	Please make this drug easily available to lymphoma patients and easily prescribed by their oncologists, who don't need 700 hours of training for one drug administration.
Betty [REDACTED], Pebble Beach, CA	
Kathleen A [REDACTED]Columbus, Oh	
Stephanie [REDACTED], Columbus, OH	Zevalin gave my friend 10 years more life than she could ever have expected and she is still in remission. Please don't make it too difficult for others to get this treatment.
Michael [REDACTED], Columbus, Ohio,	Zevalin saved my mother and allowed my children to know their grandma. I support its use and prescription, and I oppose any restriction of said use and prescription due to increased regulation.
William [REDACTED], Dumfries, VA	Zevalin is important to me as my wife has progressed following four treatments for follicular lymphoma. Zevalin may well be her next treatment.
Leonhard [REDACTED], Jr. Jersey City, NJ	
Jane [REDACTED], Columbus. OH	Do it!
Robert [REDACTED], Hamden CT	
Andrew [REDACTED], Half Moon Bay, CA,	
Shannon [REDACTED]Michigan	Please help us we need this drug my wife got cancer in March of 2015 at the age of 44
Suzanne [REDACTED], Toms River, NJ	

Adele [REDACTED], Columbus, Ohio	I have a dear friend whose lymphoma was put into complete remission (over 10 years now) by Zevalin after two other chemotherapy treatments failed to work. It seems unconscionable to me that there is a single reason why this EFFECTIVE option should be removed as a choice for patients when it clearly saves lives. I urge you to do the right thing here. If this type of lymphoma strikes you or one of your loved ones, I am certain you would want to have access to ALL well-tested treatment options, especially one like Zevalin that is among the simplest for the patient to receive AND the most effective. Thank you for taking the time to consider your role in keeping patient options open and saving lives. Adele Stratton, 2154 Lytham Rd., Columbus, OH 43220 adelestratton@gmail.com
John E. [REDACTED], Jr., Marblehead, MA	I received Zevalin in May, 2007, one month after a four-month course of CHOP chemotherapy. I remain free of follicular lymphoma progression to date. In the almost nine years since Zevalin treatment my oncologist has failed to refer any other patient for Zevalin treatment!
john [REDACTED]overton, nv	Please look into this Senator!
Rebecca M. [REDACTED], Granger, IN	I have lymphoma, was diagnosed in 2000, and was treated with Zevalin in 2005. I achieved a complete remission (CR) for 5.5 years, the longest remission that I've had out of 4 treatments that I've received. Zevalin was a one-time treatment, and I experienced few side-effects, in complete contrast to the months-long, very expensive chemo treatments, with debilitating side effects. I urge you to continue to support radioimmunotherapy, both those currently available as well as financial support for much-needed research on newly emerging radioimmunotherapy treatment options.
Patti [REDACTED], Sherwood MI	I was diagnosed with non-Hogkin's lyphoma 13 years ago, and have received various treatments three times during that time. I am currently participating in a clinical trial (not Zevalin). Many of Mr. Schwartz's concerns speak for me as an individual patient. Since I live a significant distance from a major cancer center, this rule change will make Zevalin (and perhaps future similar radioimmunitherapies) an unlikely option. Please consider this rule change carefully.
Zane [REDACTED]	
Deb [REDACTED], Mesa, AZ	
J [REDACTED], Chincoteague Island, VA	As a survivor of 21 years post-diagnosis with b-cell non-Hodgkin's lymphoma and a moderator for a web-based patient group, I have witnessed many patients who seek unique treatments to find the special lock that will kill their malignant cancer cells. The struggle is overwhelming sometimes but worth the investigation. Among our "tools" has been Radioimmunotherapy (RIT) which has been very beneficial to life extension in numerous patients. The new rule of 700 hours of training for administration will, in effect, close the lid on RIT as the hours are excessive (80 hrs. to 700 hrs.) and will limit the number of technicians who are able to dedicate so much time to this new rule. I ask that common sense and logic be employed to review and adjust this requirement. Please give patient needs and options consideration - overregulation will harm many patients who have failed in other treatment protocols and wish to option RIT.
Daniel [REDACTED], Easton, PA,	As someone currently in remission for Stage IV non-Hodgkins Lymphoma I would hope that every option is available to extend my life once this cancer returns. Zevalin is one of those treatments that could save thousands of lives.
David [REDACTED], Chapel Hill, NC,	As a physician and as a patient with lymphoma, I urge you to use your power to roll back the rule change requiring increased training for administration of Zevalin. My lymphoma is highly likely to recur and I want to be able to have the option to have Zevalin for treatment. Thank you.

Chris [REDACTED], Belfast Northern Ireland, UK	Please consider generously and with compassion the information within this well written request. To Make this treatment unreachable is a kin to the theft of our hope.
Donna [REDACTED]Boise, ID	Please reconsider this unreasonable rule change.
Judy [REDACTED], St. Louis, MO	
Deborah [REDACTED], VA,	
Craig [REDACTED], Los Angeles, CA	
Judy [REDACTED], Bellaire, MI	This rule change will keep patients, like me that are not near large medical facilities from getting appropriate treatment. Lymphoma patients should not have the extra burden of traveling long distances for a treatment that could easily be done locally.
Scott [REDACTED], Mt. Sidney, VA	I have been a Lymphoma patient for 12 years. I have had various treatments in that time, ranging from Immunotherapy to chemotherapy. I would like to think that when these treatments fail to work any more, I can turn to radiotherapy. Bexxaar was taken away from us simply because it did not make enough money for big Pharma. I was still hopeful, though, because we still had Zevalin. Now a ridiculous rule change after so many years of providing relief with fewer side effects is going reduce our opportunity for longer life. I could understand doubling the training time for administering Zevalin, but 700 hours??? This sounds like a Republican ploy on the order of closing voting places in order to prevent citizens fro voting for liberal candidates. Please reconsider all the cancer patients out here and let us have access to Zevalin.
T. [REDACTED], Portland, Maine	I am a lymphoma patient. We need all the possibilities for treatment that are safe and affordable. This new rule is unreasonable and will make a promising therapy unavailable.
Elizabeth [REDACTED], Patterson NY	Training is important, but unreasonable "training" requirements don't save lives, rather the opposite.
Janice [REDACTED], Kansas City, MO	I hope you consider this important option for patients and those that are not close to a center of excellence and need to have more community oncologists who give this drug.
Aimee [REDACTED], Horse Shoe, NC	So important for all patients to have a chance to receive a treatment that could help them live longer
Patricia [REDACTED], Cinnaminson, Nj	
Gabe [REDACTED], palm beach Gardens, FL	After having had chemotherapy, radiation and oral medication for my non-Hopkins Lymphoma I believe that Zevalin will be an important regiment to control my cancer.
Linda [REDACTED], Worthington, Ohio,	I have a friend, of moderate middle-class income, who is 8 years cancer-free thanks to the Zevalin radioimmunotherapy. She traveled to another state to receive treatment. We were so sorry this was not available at the time in Ohio and now it is unbelievable that it may be even less available, or perhaps not at all.
Julian [REDACTED], Dallas TX	Allow
Lisa [REDACTED], Columbus, Ohio	This drug has saved a dear friend's life. While I understand that doctors need to be trained in order to administer it safely, the increased training hours are not supported by the data and would seriously limit the number doctors who provide this very effective treatment. Please keep the training to a reasonable number of hours so that more patients can continue to survive and thrive after this treatment.
M. [REDACTED]Feck Columbus, OH -	I have seen firsthand the life-saving effects of this simple therapy. What world do we live in where its use should be compromised or challenged?
Lesllie [REDACTED], Blacklick, Ohio	
Diane [REDACTED]Hilliard, Ohio	
Susan [REDACTED], Austin, TX	

Edmund [REDACTED], Buffalo Grove, IL.	I have received zevalin as a second therapy after my initial chemotherapy put me in remission. I relapsed about four years later and my oncologist recommended zevalin. which put me back in remission. I was fortunate to have received my care at a major teaching hospital in Chicago. Therefore, I simply went to the nuclear medicine dept. to receive my zevalin treatment. I strongly feel that this treatment should be available for patients like me with indolent lymphoma. The new training recommendations would make it impossible for community-based oncologists to administer this drug.
Susan [REDACTED] Rockville Centre, N.Y.	Please don't allow any of our treatment options to effectively be eliminated.
Barbara [REDACTED], Mason City, Iowa	I would like to see this treatment remain available if I need it in the future for relapse of my lymphoma treatment in 2002.
Gabrielle [REDACTED], Jersey City, NJ	
F. [REDACTED], PA	We are already limited by the effective treatment s available please don't let us lose this one, thanks.
W. [REDACTED], M.D., Oklahoma City, Oklahoma	
Neva [REDACTED], Chapel Hill, NC	
Jacqueline [REDACTED], Tulare, CA	There is no cure for lymphoma please consider this letter. Thank you!
Wendy [REDACTED], Macomb, Michigan	
Julie [REDACTED], Columbus, Ohio	Please don't limit patient access!
Lisa [REDACTED], Manchester, NH	I know of at least 3 people who were essentially cured of follicular Non-Hodgkins Lymphoma using either Bexxar (which is no longer available) or Zevalin. Please preserve this choice for the future of Lymphoma treatment and lymphoma patients in the U.S.A.
Tiffaney [REDACTED], Lansing, MI	Please consider the information in this letter. My aunt is alive and in remission because of access to taking Zevalin. This drug, proven effective, should not have stricter provisions which will limit access to cancer patients who could suffer greatly if Zevalin is not available.
Nadine [REDACTED], Suwanee, Georgia	As a Lymphoma survivor in Georgia, and recently diagnosed with a recurrence for the third time, please consider supporting our cause. Zevalin needs to be part of the fight against Lymphoma!
Marshall [REDACTED], Boa RATON, FL	I obtained a three-year remission with Zevalin and would hate to see it disappear as a viable option
Kathleen R [REDACTED], Santa Rosa, Ca	
Cynthia [REDACTED], Sierra Madre, CA	My wife was fortunate enough to receive RIT in 2011. Virtually no side effects compared to chemo. She's still in remission and going strong. A priceless gift.
Elizabeth [REDACTED], Patterson NY	Medicine is almost a living community, and needs our support in all areas to stay strong.
Barbara [REDACTED], Tampa, Florida	Thank you for your consideration.
Gaby [REDACTED], Omaha, NE	
Amy [REDACTED], Ca	
Erin [REDACTED], Plano, TX	
Michael [REDACTED], MA	
Reva [REDACTED], MI	
Mindy [REDACTED]St Charles IL	
Barbara [REDACTED]Asheville NC	My husband died from lymphoma, the best treatments must always be available asap Lymphoma is increasing in the US.
LuAnn [REDACTED], Smithfield, PA	Please consider. We need your help. My life could depend on this. God bless!
Tina [REDACTED], Sanford, FL,	9/97 Diagnosed with lymphoma. I'm 82 and have had many rituxan and chemo treatments.

Patricia [REDACTED], Cinnaminson, NJ,	
Razia [REDACTED]Phoenix AZ	I have been a recipient of this treatment and it was administered in the most safe and professional manner by a well trained medical professional. He walked me through the process and the details drug itself.
Mahedi [REDACTED]Phoenix AZ	My wife received the treatment and the doctor administering the drug could not be more professional in his delivery of the drug, care and in informing us on the drug benefits and effects. She has been feeling much better since she received Zevalin. It has been almost two years.
Michael [REDACTED], Mashpee, MA.	Cancer is hard on everyone, lets try to help make some things easier.
Dean [REDACTED]	Any protocol that can provide remission from lymphoma should never be dismissed
Peter [REDACTED], Frankfort, Il,	
Anthony [REDACTED]; Coon Rapids, MN.	I received a Zevalin treatment in 2005 at a time when my tumor burden was quite high. The Zevalin treatment shrunk the tumors completely away in a mater of weeks. I strongly feel this treatment should remain an option for patients without any unnecessary hindrances that may prevent a patient from receiving it.
Jim [REDACTED], Sanford, FL,	My wife has been in treatment for many years. Her age and conditions from past treatments leave only one alternative if more treatment is needed, Zevalin. The nearest center for that is in Tampa. We would prefer that a source be closer, such as Orlando, and are concerned that the excessive training requirement will prevent any oncologist from seeking training in our area.
A. [REDACTED]Revere, PA	The rule change would increase the training required for oncologists to be authorized to administer Zevalin radioimmunotherapy 8-fold, from 80 to 700 hours. I cannot understand why a treatment that has been already shown to save people's lives would require such a drastic change in additional training that would surely prevent many from participating. Dealing with the disease is difficult enough, let alone fighting for the cure on top of it.
M. [REDACTED], Lansing, Michigan	
Heather [REDACTED], Traverse City, MI	Please save access for this life-saving cancer treatment. It's saved people I love.
Joan [REDACTED], Scottsdale, AZ	I am hoping to get treatment with Zevalin in the future and hope that this new regulation will not cause Zevalin to become harder to obtain. I have a form of transformed lymphoma which is extremely hard to control. I am not able to get a stem cell transplant and have already had a large amount of chemo. Zevalin may be the only treatment option when the lymphoma gets out of control again. Please reconsider this onerous regulation.
Ronald [REDACTED], Upper Black Eddy, PA,	Immediate action would be appreciated.
Kathleen [REDACTED]. Callahan, FL	We need easier access to a choice of treatments that are effective in order to continue to be a survivor of NHL. I have read of many survivor success stories of people who underwent this form of treatment.
Joanne [REDACTED], Riegelsville, PA	My first treatment with aggressive chemotherapy in 1997 led to a good response, but that lasted only 6 months. For eight years I had treatments with chemotherapy with very short responses - the tumors were visible and growing before my hair grew back. In 2004 I had chemotherapy again followed by radioimmunotherapy. I have been without signs of the lymphoma since then for 12 years. I owe the return to normal life and probably my life as well to radioimmunotherapy. Please do what you can to influence the NRC to make sure that other patients will be able to make use of this important treatment when they need it.

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sirweb.org

Society of Interventional Radiology
The vision to heal

September 30, 2016

Michelle Smethers
U.S. Nuclear Regulatory Commission
One White Flint North
11555 Rockville Pike
Rockville, MD 20852-2738

Dear Ms. Smethers,

The Society of Interventional Radiology (SIR) is a physician association of over 6,100 members that represents the majority of practicing vascular and interventional radiologists in the United States. SIR appreciates the opportunity to comment on the proposed revisions to the Licensing Guidance for Yttrium-90 Microspheres.

The Society of Interventional Radiology strongly opposes the proposed changes to the "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere and SIR-Spheres Licensing Guidance" that would eliminate vendor involvement from the Interventional Radiology pathway to Authorized User (AU) status. The current process, updated earlier in 2016, has been in place since the concept evolved that interventional radiologists are the natural authorized users of the devices. For the procedure, interventional radiologists: perform the dosimetry necessary to deliver the appropriate activity to the patient; oversee the processes directly before the procedure to ensure appropriate handling and preparation of the device; directly deliver the device to the patient; and are primarily responsible for the longitudinal care of the patient following the procedure. This process includes collaboration of physicians and industry to ensure safe and comprehensive training in use of the Yttrium-90 microspheres.

The current guidelines have been tremendously successful in expanding the number of users of the Yttrium-90 products while maintaining impeccable safety. This has resulted in many tens of thousands of patients globally who have safely received such treatment for their liver malignancies. Manufacturer And User facility Device Experience (MAUDE) reports have remained at 10 or fewer for both devices since 2013. In addition, rather than being due to the device itself, the majority of the MAUDE reports focus on procedural complication and treatment toxicities seen with all types of hepatic embolization.

Changing the current arrangement, in which industry and physicians work together closely to allow for appropriate training of interventional radiologists in the safe use of these devices, will make it exceedingly difficult for Interventional Radiologists entering practice to perform radioembolization. Without the current direct training provided offsite by the device vendors, training for physicians will have to be performed by a proctoring process only. Securing physician proctors is a challenge as proctors already have challenges finding time away from their own practices, a factor that limits availability. Placing additional responsibilities on physician proctors may also have the untoward effect of limiting access to care, particularly for programs in underserved areas. **The unanticipated**

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Society of Interventional Radiology
The vision to heal

consequence of the proposed change is that training interventional radiologists in the safe and effective use of these devices will suffer greatly.

Interventional Radiologists deliver high quality care via imaging guidance using a variety of devices. Training with other devices, such as aortic stent grafts, frequently involves a combination of vendor and physician collaboration. The current NRC guidelines have allowed physicians to safely perform radioembolization in patients with devices currently on the market. Without evidence of a need for change, the current NRC guidelines provide for training in the safe and effective use of these devices, benefiting patients, physicians, and government.

Once again, SIR appreciates the opportunity to provide these comments on the proposed revisions. If you have any questions or need additional information, please contact Erica Holland, Assistant Executive Director, SIR at eholland@sirweb.org or (703) 460-5568.

Sincerely,

Charles E. Ray Jr., MD, PhD, FSIR
2016-2017 SIR President

Sirtex Response to Proposed Changes to the
Yttrium-90 Microsphere Brachytherapy Sources and Devices Licensing Guidance
Statement to the U.S. Nuclear Regulatory Commission
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
October 7, 2016

Proposed Policy Change

The Nuclear Regulatory Commission (NRC) is proposing removal of "Pathway 2" from the Authorized User (AU) Training and Experience section, Item B, in the February 12, 2016, *Yttrium-90 Microsphere Brachytherapy Sources and Devices Licensing Guidance*, hereafter referred to as the NRC guidance

Intended Consequence

The NRC is proposing that only an AU for yttrium-90 (Y-90) microsphere technology be allowed to oversee the training of a new physician for that particular Y-90 microsphere technology. Manufacturer representatives (i.e. Proctors and/or Sales Representatives) would not be allowed to supervise *in-vitro* or *in-vivo* cases for the purpose of a new physician becoming an AU for Y-90 microsphere technology.

Unintended Consequence

If Pathway 2 is removed in its entirety Y-90 manufacturers will not be able to open new accounts, thereby limiting patient access to this life extending technology.

Explanation

In general practice, Pathway 2 inherently provides "provisional" licensing authorization for physicians at sites that do not currently use Y-90 microspheres. Non-physician manufacturer representatives provide three (3) *in-vitro* simulated cases for a physician at a new site to be named as an AU on the license. The *in-vitro* training provides a working knowledge of Y-90 microspheres in accordance with NRC guidance Section A.3.iii. Following the "provisional" license amendment, the site is then allowed to order Y-90 microspheres from the manufacturer, which will subsequently be utilized via the first three (3) *in-vivo* patient cases. These *in-vivo* patient cases are supervised by a manufacturer representative for each type of Y-90 microsphere for which the physician is authorized.

Without the ability to "provisionally" amend a license naming an AU, it would be impossible to order and receive the Y-90 microspheres for the *in-vivo* supervised training at the facility in compliance with 10 CFR 35.11, "License Required." In other words, sites cannot order Y-90 microspheres, if they are not licensed to possess them, which require an AU on the license. The site cannot name an AU on the license until the site has possessed Y-90 microspheres for the AU to undergo the *in-vivo* supervised training. It is the proverbial "Chicken or the egg."

A majority of physicians coming out of a Fellowship program do not have the required hands-on experience to become an AU for SIR-Spheres Y-90 resin microspheres (i.e. not <u>every</u> program offers hands-on experience for fellows). This applies to Interventional Radiologists (IRs), Nuclear Medicine physicians, and Radiation Oncologists. SIR-Spheres Y-90 resin microspheres must be an integral part of all Fellowship programs and included in board certification processes before Pathway 2 can be removed in its entirety.

For Sirtex, removal of Pathway 2 would mean that all potential AU physicians must gain hands-on experience with SIR-Spheres Y-90 resin microspheres either during Fellowship or at an existing site previously authorized for the medical use of SIR-Spheres Y-90 resin microspheres. This was not possible in 2011 when the NRC guidance was originally revised to include a manufacturer pathway and is still not possible now for several reasons:

1. A physician without prior hands-on experience would be required to obtain the experience by going to another hospital that is currently using SIR-Spheres Y-90 resin microspheres. Unfortunately, a physician rarely has credentials or privileges to practice medicine at sites other than his or her own. A physician visiting another site would not be allowed to touch the patient or product; therefore negating the "hands-on experience."

2. Some sites use a "two-physician model" (e.g., Radiation Oncologist AU and IR as a non-AU team member). An IR who performs procedures would not likely receive a preceptor statement from a radiation oncologist AU in order for the IR to apply for AU status at a new facility and vice versa. This is evident when IRs try to obtain preceptor letters from fellowship when a non-IR served as the AU on the radioactive material license (RAML) at the fellowship facility. When a physician comes from a two-physician model site where they cannot receive sign-off for previous casework, another option must exist for that physician to become an AU at a new facility.

Sirtex Proposal

Sirtex recommends retaining Pathway 2. Pathway 2, as it currently stands, not only allows manufacturers to provide thorough and comprehensive training and clinical-use experience for new Y-90 microsphere users in the safe and effective use of the technology, but also allows

manufacturer representatives to satisfy the real-world need to provisionally train new AUs at sites without an existing Y-90/Selective Internal Radiation Therapy Program in a timely manner.

Additional Background on Sirtex Training Program

Sirtex received U.S. Food and Drug Administration (FDA) premarket approval with a requirement to only supply SIR-Spheres Y-90 resin microspheres to trained users. This is reflected in the Sirtex SIR-Spheres Y-90 resin microspheres labelling in that, "Only doctors qualified and licensed under Title 10 Code of Federal Regulations Part 35 (Nuclear Regulatory Commission) and trained under the Sirtex [Training, Education and Certification] TEC training program may order and implant SIR-Spheres microspheres." As a part of the TEC program, Sirtex provides a robust training program for all new physicians who wish to use SIR-Spheres Y-90 resin microspheres such as an Interventional Radiologist (IR). Noting that the IR plays a critical part in ensuring safe delivery of the product to the patient, the Sirtex TEC program utilizes Sirtex trained and board certified Interventional Radiologists to instruct all new physician users involved in the clinical use of SIR-Spheres Y-90 resin microspheres.

The Sirtex trained and certified Interventional Radiologist may or may not be an AU named on a RAML, depending on whether his/her site operates under a one-physician or two-physician model. Sirtex only utilizes Interventional Radiologists as proctors because a Radiation Oncologist or Nuclear Medicine physician would not be qualified to oversee all critical components of training, including mapping the patient's vascular anatomy or ensuring proper catheter placement. Sirtex proctors are able to provide training on radiation dosimetry and safe handling of SIR-Spheres Y-90 resin microspheres. Sirtex physician proctors are selected because they are active expert users of SIR-Spheres Y-90 resin microspheres with some 159 years combined experience performing up to 400 procedures per year. All new physician users are certified by a Sirtex Medical Director, based on feedback of successful training from Sirtex proctors. Sirtex proctors help an institution build a sustainable, high-quality program that is consistent with Sirtex standards and Federal and state regulatory requirements.

The Sirtex TEC program will continue irrespective of the NRC's AU training and experience requirements, as Sirtex has a training commitment to the FDA.

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