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NUCLEAR REGULATORY COMMISSION

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ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

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TELECONFERENCE

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WEDNESDAY,

AUGUST 12, 2015

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

MEMBERS PRESENT:

BRUCE R. THOMADSEN, Ph.D., Chairman

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

FRANCIS M. COSTELLO, Agreement State Representative

VASKEN DILSIZIAN, M.D., Nuclear Cardiologist

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

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

STEVEN R. MATTMULLER, Nuclear Pharmacist

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

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

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

LAURA M. WEIL, Patients' Rights Advocate

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

Non-Voting: DARLENE F. METTER, M.D.

Member-Elect: ZOUBIR OUHIB

NRC STAFF PRESENT:

DOUGLAS BOLLOCK, Designated Federal Officer

SOPHIE HOLIDAY, Alternate Designated Federal Officer, ACMUI Coordinator

MARYANN ABOGUNDE, NMSS/MSTR/MSEB

JENNIFER BISHOP, RIII/DNMS/MLB

MARCIA CARPENTIER, OGC/GCHEA/AGCNRP

COLLEEN CASEY, RIII/DNMS/MLB

ASHLEY COCKERHAM, NMSS/MSTR/MSEB

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

CASSANDRA FRAZIER, RIII/DNMS/MLB

MIKE FULLER, NMSS/MSTR/MSEB

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

PATRICIA PELKE, RIII/DNMS/MLB

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

GRETCHEN RIVERA-CAPELLA, NMSS/MSTR/MSEB

SHAWN SEELEY, RI/DNMS/MB

FRANK TRAN, RIII/DNMS/MLB

LESTER TRIPP, RI/DNMS/MB

ALSO PRESENT

BONNIE CLARKE, Society of Nuclear of Nuclear Medicine and Molecular Imaging

LYNNE FAIROBENT, American Association of Physicists in Medicine

CHUCK FLYNN, Texas Department of State Health Services

WENDY GALBRAITH, University of Oklahoma Health Sciences Center

MICHAEL GRAHAM, University of Iowa

FRED GRATTAS, Triad Isotopes

ANINE GRUMBLES, Washington Department of Health

GEORGIA HEARN, American Society of Nuclear Cardiology

CAITLIN KUBLER, Society of Nuclear Medicine and Molecular Imaging

SAM LEVERITT, Cardinal Health Nuclear Pharmacy

JOSH MAILMAN, NorCal CarciNet Community

RICHARD MARTIN, American Association of Physicists in Medicine

MICHAEL SHEETZ, University of Pittsburgh

MICHAEL WELLING, Organization of Agreement States

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

P-R-O-C-E-E-D-I-NG-S

2:05 p.m.

MR. BOLLOCK: Good afternoon, everyone. I'm going to start off this public meeting on our ACMUI Subcommittee meeting on Germanium/Gallium-68. So without any other delay, we'll begin.

As the Designated Federal Officer for this meeting I'm pleased to welcome you to this public meeting of the Advisory Committee on the Medical Use of Isotopes.

My name is Doug Bollock. I'm the Branch Chief of the Medical Safety and Events Assessment Branch and I have been designated as the federal officer for this Advisory Committee in accordance with 10 CFR Part 7.11.

Present today as the Alternate Designated Federal Officer is Ms. Sophie Holiday, our ACMUI Coordinator.

This is an announced meeting of the Committee. It is being held in accordance with the rules and regulations of the Federal Advisory Committee Act and the Nuclear Regulatory Commission. This meeting is being transcribed by the NRC and it may also be transcribed or recorded by others.

The meeting was announced in the April 17th, 2015 edition of the *Federal Register*, Volume 80, pages 21268 through 21269.

The function of the Committee is to advise the staff on issues and questions that arise on the medical use of byproduct materials. The Committee provides counsel to staff but does not determine or direct the actual decisions of the staff or the Commission. The NRC solicits the views of the Committee and values their opinions. As such, whenever possible we try to reach a consensus on the procedural issue that we'll discuss today, but also recognize there may be minority or dissenting opinions. If you have such opinions, please allow them to be read into the record.

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

Dr. Bruce Thomadsen, Chairman, therapy medical physicist?

CHAIRMAN THOMADSEN: Here.

MR. BOLLOCK: Thank you. Dr. Philip Alderson, Vice-Chairman, health care administrator?

VICE-CHAIR ALDERSON: Here.

MR. BOLLOCK: Thank you. Mr. Frank Costello, our Agreement State representative?

MEMBER COSTELLO: Here.

MR. BOLLOCK: Thank you. Dr. Vasken Dilsizian, our nuclear cardiologist?

MEMBER DILSIZIAN: Present.

MR. BOLLOCK: Thank you. Dr. Ronald Ennis, radiation oncologist?

MEMBER ENNIS: Here.

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

MEMBER LANGHORST: Here.

MR. BOLLOCK: Thank you. Mr. Steve Mattmuller, our nuclear pharmacist?

MEMBER MATTMULLER: Here.

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

MEMBER O'HARA: Here.

MR. BOLLOCK: Thank you. Dr. Christopher Palestro, nuclear medicine physician?

MEMBER PALESTRO: Here.

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

MEMBER SUH: Here.

MR. BOLLOCK: Thank you. Ms. Laura Weil, our patients' right advocate?

MEMBER WEIL: Here.

MR. BOLLOCK: Thank you. Dr. Pat Zanzonico, nuclear medicine physicist?

MEMBER ZANZONICO: Here.

MR. BOLLOCK: Thank you. We have a quorum of at least seven members. Also on the phone we also -- I've got to verify this -- we also have Dr. Darlene Metter and Mr. Zoubir Ouhib.

MR. Ouhib: Here.

MR. BOLLOCK: Are you both present?

MR. Ouhib: Here.

MR. BOLLOCK: Thank you. And, Dr. Metter, are you present with us today?

(No audible response)

MR. BOLLOCK: Okay. Dr. Metter, who has been selected as our ACMUI diagnostic radiologist, she's pending a security clearance, but if she joins us, she may participate in the meeting. However, at this time she doesn't have voting rights until she gets the security clearance. And Mr. Zoubir Ouhib has been selected as the next ACMUI therapy medical physicist, but will not begin his term until Dr. Thomadsen rotates off the Committee in mid-October.

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

MS. ABOGUNDE: Maryann Abogunde, medical team.

DR. RENDER: Diane Render, medical team.

DR. DAIBES: Said Daibes, medical team.

MR. FULLER: Mike Fuller, medical team.

MR. BOLLOCK: Okay. Do we have any NRC Headquarters employees on the phone?

MS. CARPENTIER: This is Marcia Carpentier, Office of General Counsel.

DR. GABRIEL: Sandy Gabriel, medical team.

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

MR. BOLLOCK: Thanks, Gretchen.

MS. COCKERHAM: Ashley Cockerham, medical team.

MR. BOLLOCK: Thanks, Ashley.

MS. HOLIDAY: And Sophie Holiday.

MR. BOLLOCK: Thank you. Do we have any other NRC Headquarters employees on the phone?

(No audible response)

MR. BOLLOCK: All right. Next we'll go to the NRC Regional Office. Do we have anyone from Region I on the phone?

(No audible response)

MR. BOLLOCK: Region I?

(No audible response)

MR. BOLLOCK: Okay. Moving on. Do we have anyone from Region III on the call?

MS. PELKE: This is Patty Pelke from Region III.

MR. BOLLOCK: Hi, Patty. All right. Anyone else from Region III?

MR. TRAN: This is Frank Tran, Region III.

MR. BOLLOCK: Thank you. Anyone else from Region III on the phone?

(No audible response)

MR. BOLLOCK: Okay. Thank you. Do we have anyone on the call from Region IV?

(No audible response)

MR. BOLLOCK: Anyone from Region IV?

MR. BOLLOCK: All right. Thank you. Now members of the public who have not pre-registered for this teleconference, please notify Ms. Sophie Holiday of your participation by either email or phone at Sophie.Holiday@nrc.gov. That's S-O-P-H-I-E, dot, H-O-L-I-D-A-Y at nrc.gov. Or she can be reached by phone at area code (404) 997-4691.

We have a bridge line available. That number is 1 (800) 369-3196. The pass code to access the bridge line is 3433756 followed by the pound sign.

The Committee is also using the GoToWebinar application to view the presentation handouts real time. You can access this by going to www.gotomeeting.com and searching for Meeting ID 135-961-131.

The purpose of this meeting is to hear from the patients from the ACMUI Germanium/Gallium-68 Subcommittee related to the decommissioning financial assurance requirements for this medical use generator.

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

I'd also like to add that the handouts and agenda for this meeting are available on the NRC's public web site.

At this time I'd ask that everyone on the call who is not speaking to place their phones on mute. If you do not have the capability to mute your phone,

please press star, six to utilize the conference line mute and un-mute functions.

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

DR. METTER: Hello, this is Darlene Metter. I just joined the conference.

MR. BOLLOCK: Hi, Dr. Metter.

DR. METTER: Hi.

MR. BOLLOCK: As I said earlier, Dr. Metter, you -- I did announce that you will be joining the Committee full term once you have a security clearance and you are able to participate in this meeting, however, you'll not be able to vote at this time until you've received your security clearance. And welcome to your first ACMUI public meeting.

DR. METTER: Thank you.

MR. BOLLOCK: And with that, I just welcome to the ACMUI and turn it over to Dr. Thomadsen.

CHAIRMAN THOMADSEN: Thank you very much, and I would like to thank everybody who's on the line for coming in and joining us for this discussion. And now I'm going to turn the chair over to the Subcommittee Chair, Mr. Mattmuller, to discuss the topic for today's

meeting.

Mr. Mattmuller?

MEMBER MATTMULLER: (No audible response)

CHAIRMAN THOMADSEN: Are you on mute?

MEMBER MATTMULLER: Possibly.

(Laughter)

MEMBER MATTMULLER: Good afternoon. We'll try this again un-muted. First of all, I'd like to thank my fellow Subcommittee members Frank Costello, Sue Langhorst, Chris Palestro and Pat Zanzonico who all contributed significantly to this report and this effort.

I would like to address first the highlights in our report, and to me the first is the challenges because of the restrictive aspects of a decommissioning funding plan for Germanium-68 that arise from the current Part 30 regulations as preventing and/or deterring the use of promising Gallium-68 diagnostic imaging agents for patients.

The charge for our Committee is: (1) Estimate the number of potential Gallium-68 generator licenses affected; and (2) Recommend to the Committee on which route of action it believes the NRC should pursue to address the decommissioning funding plan issue.

So a little background first: Neuroendocrine tumors, or NET tumors, present a very difficult diagnostic challenge. For NET patients, it currently takes an average of seven years for a proper diagnosis to be made and appropriate therapy prescribed.

There is a new class of radiopharmaceuticals using a positron emitter radionuclide, Gallium-68, that's nearing FDA approval. The advantages of these radiopharmaceuticals can be best demonstrated by a comparison of their images in the same patient in Figure 1 of the report. On the left is Indium-111 DTPA-Octreotide images, the current radiopharmaceutical in clinical use today. And on the right is the Gallium-68 DOTA-TOC image.

The advantages of the Gallium-68 images are readily apparent. The PET images leads to greater sensitivity and specificity resulting in superior accuracy for this diagnostic imaging procedure. There is also greater patient convenience as the Gallium-68 image only takes one day versus two days for the Indium-111 image. And finally, the radiation dosimetry burden to the patient is less for the Gallium-68 image versus the Indium-111 image.

Moving onto the background of the

regulatory DFP trigger for a Gallium-68 generator. The regulations require a licensee to submit decommissioning funding plans per 10 CFR 30.35. The trigger level, or a quantity of a given radionuclide for a DFP comes from a calculation using a labeling quantity for a radionuclide listed in the appendix entitled, "Quantities of Licensed Material Requiring Labeling." The calculation involves multiplying the labeling quantity by 10 to the 5th power to derive the trigger level. And at this time, however, Germanium-68 doesn't have a listing on this table, so a very small default quantity of only 0.1 microcuries is used in the calculation when it's multiplied by 10 to the 5th. The resulting trigger level is only 10 millicuries.

So the impact of a DFP medical licensees. For a medical licensee the foregoing regulatory considerations create a cascade effect leading to an extensive and expensive DFP as a DFP must cover not only one area where a Gallium-68 generator is used, but also all areas where radioactive materials are used under the same license.

Consider for example a mid-sized medical center in the Midwest and the various areas of use its license may include. And, yes, this is in the Midwest. And just to give you an idea, it's one of the States

that has a current candidate for the Republican presidential primary right now.

In this Midwest facility they have a nuclear medicine facility with SPECT imaging rooms and a radiopharmacy. They have a full PET center with a cyclotron, PET chemistry labs, PET imaging rooms, multiple satellite cardiac imaging suites throughout the surrounding area, a large radiation oncology department including Gamma Knife and brachytherapy, and also an affiliated separate hospital with its own nuclear medicine facility and radiopharmacy.

So without a Gallium-68 generator a DFP is not needed for this medical center. However, if they were to add a Gallium generator, they would have to develop a DFP not just for the one room that houses the generator, but for all the forgoing areas. A DFP thus becomes very extensive and expensive, perhaps prohibitively so for a licensee with numerous areas of use.

This scenario did in fact occur last year at a large university-based medical center on the East Coast, but they did not acquire the necessary financial assurances for a DFP and they were not able to conduct their research in patients. The restrictive aspects arising from the current Part 30 regulations are

preventing and/or deterring the use of promising Gallium-68 diagnostic imaging agents for patients due to the DFP burden for its parent radionuclide Germanium-68.

So to address our first charge to estimate the number of potential licenses affected. Given how extensive of an effort it is to prepare a DFP, this is actually a very complex and time-consuming effort for each licensee to consider to try and answer whether or not they would be affected by one as a DFP is unique to each license, and once prepared it's only applicable to that license and can't be used by another. So it's a difficult question to answer accurately, but we do know now it has deterred the use of Gallium-68 DOTA radiopharmaceuticals throughout the country.

And this quote in this box comes from Josh Mailman, who is the President of the NorCal CarciNet Community, which is a patient advocacy group for neuroendocrine tumor patients. Per Josh: "Currently in the U.S. there are only three active sites that are reliably imaging patients with the Gallium-68 DOTA radiopharmaceuticals. These sites include the NIH, Stanford University and the University of California in San Francisco. So that's three sites total within all the United States and the current wait

for an NET patient is over two-and-a-half months at the NIH."

We did send that request to numerous licensees asking them to evaluate the effect that a DFP would have on their site. We actually only got one response, but it was a valuable one. It was from Triad Isotopes, which is a large commercial radiopharmacy company in the U.S. And what's in the box in the report is a quote word-for-word from their response.

They operate over 50 nuclear pharmacies within the U.S. and "under the current regulations the complexity and cost of a DFP would potentially hinder our ability to provide Gallium-68 radiopharmaceuticals from our nuclear pharmacies to all areas of the country. The net effect is that the DFP regulations would likely limit the availability of this radiopharmaceutical for several reasons:

"First, economic pressures will impede adoption. Second, the short half-life of Gallium-68 will make this a challenging radiopharmaceutical to distribute. So taking both cost and distribution challenges into account, it is unlikely that nuclear pharmacy networks such as ours would provide Gallium-68 related radiopharmaceuticals to all areas of the

country if a DFP was initiated; thus, every patient in need would not have equal access to these radiopharmaceuticals, most especially those in smaller and/or more rural markets."

So, this statement from Triad has added weight in that at four of their sites now they do have a DFP in place; hence, they're well aware of how extensive and expensive a DFP can be. Patient access is already clearly hindered in the U.S. by the small number of licensees who can provide Gallium-68 DOTAs. Regulatory relief from the DFP is urgently needed to increase patient access to these invaluable radiopharmaceuticals.

Moving on to our second charge. Recommend to the Committee on which route of action it believes the NRC should pursue to address the decommissioning funding plan issue.

The Subcommittee recommends the following language be added as a footnote to Appendix B Part 30, "Quantities of licensed material requiring labeling," as the most expeditious, cost effective, and practical route to addressing the DFP issues. And what we recommend is in the box. "This does not include Germanium-68 in a Germanium-68/Gallium-68 medical use generators (limit less than 10 to the 5th times 2

microcuries) that are returned to the manufacturer at end of use."

This new calculated limit of 200 millicuries as a trigger limit would only be allowed for Germanium-68 in a Gallium-68 generator for medical use. This limit would allow for the use of a Gallium-68 generator for clinical use and at the end of its one-year shelf-life allow it to be used for research such as for small animals. Regardless of its use, when the licensee is finished using the generator, it would be returned to the manufacturer for final disposal. The new limit would also allow a licensee to possess more than one generator to maintain a high useful amount of Gallium-68 available at all times for the preparation of Gallium-68 radiopharmaceuticals.

In order to maintain a higher useful amount of Gallium-68 a licensee may purchase several Gallium-68 generators with staggered calibration dates. And this is shown in Table 1.

This is an actual scenario used by a current site where they get a new generator every six months to keep a higher amount of Gallium-68 available at all times. And then they use it for clinical patients and then with the older generators they can use it for research. So clearly the trigger amount needs to be

greater than one or two generators.

The three factors that we believe serve as the basis for this recommendation for this new labeling quantity of Germanium-68 are as follows: (1) Under normal operation the Germanium-68 is stably bound within the generator. The design and operation of the Gallium-68 generator thus ensures that it will nearly have the same safety profile as a sealed source device; (2) At the end of its use, the generator is returned to the manufacturer for final disposal. This disposal step in essence eliminates any concern at a licensee regarding Germanium-68 associated DFP expenses; and (3) If Appendix B were to be revised, it would be appropriate to add Germanium-68 with a labeling quantity of 10 microcuries. However, the Subcommittee currently recommends a more conservative number of only 2 microcuries for the purposes of a direct final rulemaking.

So to go into more depth of these three factors, first the design and operation of a generator. It's simply a device that serves as a source of the important radionuclide Gallium-68. The generator is a closed system device consisting of a column containing a resin on which the parent radioactive material Germanium-68 is fixed. Gallium-68 is continuously

produced by the decay of its radioactive parent Germanium-68. The Gallium-68 is removed from the generator by eluting it off the column with a sterile hydrochloric acid solution. The Gallium-68 is soluble in a hydrochloric solution and readily elutes off the column. The Germanium-68 is insoluble in the hydrochloric solution and remains fixed on the column and continue to decay to provide additional Gallium-68 in future elutions. The generator is a device whose sole purpose is to provide Gallium-68.

On Table 2 we have a listing of the physical characteristics of Germanium-68 and Gallium-68. The Germanium-68 is easy to shield as during its decay it has no particulate or penetrating -- in other words high-energy photon emissions and only has low-energy X-ray emissions. Shielding is of course needed for the Gallium-68 as it decays by positron emission with the subsequent production of 511-keV annihilation gamma rays.

On the next page is Figure 2, and this is a schematic of a generic Gallium-68 generator. Note that it has one inlet for the hydrochloric acid eluent and one outlet for the collection of Gallium-68. It's a simple device that has no moving parts. The Germanium-68, as a solid, is fixed onto the resin with

the column by the chemical process of adsorption; and that's with a D, adsorption, and thereby remains entirely within the generator and its lead shielding.

The first Gallium-68 generator manufactured in accordance with a Drug Master File is the Galliapharm by Eckert and Ziegler. It's a relatively small and compact device measuring approximately 9 by 5 by 5 inches. And there are three figures 3 to 5 illustrating it. Again, note the simplicity of the device. We only have one inlet port and one outlet port and no moving parts.

Figure 3 is a sectional side view. Figure 4 is a front view. Another important consideration is that once the generator is placed in position in the nuclear medicine facility it's not moved, but simply remains in place for its entire lifetime. Moving on to Figure 5. It's a picture of an actual generator. Because it remains in place once positioned, there are no mechanical stresses that could potentially lead to a leakage of activity.

During the normal elution process of the Gallium generator a very small amount of Germanium-68 measured in nanocuries does get displaced from the column. This is known as parent breakthrough and is a phenomenon associated with all radionuclide

generators. The breakthrough amounts are so low though that unlike other medical use generators such as technetium-99m or the rubidium-82 the breakthrough cannot be measured with a dose calibrator. More sensitive equipment must be used to measure the small amount of Germanium-68 in a Gallium-68 elution.

How small is this amount? Well, per NRC regulations if you look at what amount should be disposed via the sewer to maintain the proper concentration it would take less two ounces, or less than one-quarter cup of fluid down the drain to maintain a safe concentration of Germanium-68. So obviously quite an easy volume to meet at any laboratory.

Disposal of the generator. Disposal is very simple; at the end of its useful lifetime the generator is returned to the manufacturer for final disposal. Final disposal by the manufacturer in essence eliminates any concern regarding Germanium-68 in regards to a DFP for the license. And in Figure 6 is an example of such a letter from one manufacturer, Eckert and Ziegler, showing how yes indeed they will take the generator back.

Finally, we looked at the propriety of current default labeling of 0.1 microcurie for Germanium-68. We looked at the other radionuclides

in Appendix B that had a labeling quantity of 10 microcuries and a half-life greater than 120 days in order to assess the impact of changing the labeling quantity for Germanium-68 from 0.1 microcurie to 2 microcuries. And what's really quite surprising from this review are the number of radionuclides with substantially longer half-lives than Germanium, and most of them have half-lives in years versus days.

If a revision of Appendix B had ever taken place, it appears that this would easily have been included among this group of radionuclides with a labeling quantity of 10 microcuries. So our proposed labeling quantity of 2 microcuries is thus conservative as it would still offer a five-fold safety factor versus a labeling quantity of 10 microcuries. In other words, it would have a 200 millicurie trigger limit versus a 1,000 millicurie trigger limit for a DFP.

Finally, the proposed rule supports NRC's 2013-2018 Strategic Plan by supporting its Regulatory Effectiveness Strategy No. 1 - Proactively identify, assess, understand and resolve safety and security issues. The proposed rule support these activities in the following ways:

The lack of decommissioning risk warrants the special circumstance of doing a direct final rule

in order to minimize the significant risk of preventing patient access to the medical benefits received from Gallium-68 radiopharmaceuticals.

Secondly, immediate correction of this unintended regulatory impediment will demonstrate NRC's support of medical safety culture.

So to conclude, the Subcommittee believes this recommendation has a strong basis to support the regulatory change to the direct final rulemaking process. This process should be initiated as soon as possible by the NRC to eliminate the deleterious effect the DFP process is having on patient access to Gallium-68 radiopharmaceuticals. Thank you.

CHAIRMAN THOMADSEN: And thank you very much, Mr. Mattmuller. I will ask first if there are any comments from the members of the Subcommittee that they would like to make supplemental to Mr. Mattmuller's discussion.

MEMBER ZANZONICO: Yes, hello. This is Pat Zanzonico. Can you hear me?

CHAIRMAN THOMADSEN: Yes.

MEMBER ZANZONICO: Okay. Very good. So my main comment to just endorse, not that needs endorsing, but to endorse the recommendations of our report and also to point out that as Steve has said

the clinical value of Gallium-68 currently lies in somatostatin receptor radiopharmaceuticals. That's likely to remain the case for the foreseeable future. But the labeling technology, the DOTA-based labeling technology really has wide applicability to many other peptide-based radiopharmaceuticals.

Here at Memorial, for example, it's being used to label Herceptin, which is a fragment of an antibody reactive against a subclass of breast cancers. And so the point being that Gallium-68 has potentially wide clinical applicability beyond the somatostatin receptor binding ligands. I just wanted to make that point.

CHAIRMAN THOMADSEN: And thank you very much. Any other members of the Subcommittee wish to make any point?

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

CHAIRMAN THOMADSEN: Yes, please.

MEMBER LANGHORST: I wanted to ask Mr. Mattmuller if this was a good time to talk about the addendum we put together on this recommendation.

MEMBER MATTMULLER: I'm fine to address the addendum now if there are no other questions for this draft report, certainly.

MEMBER LANGHORST: Okay. I will wait until you tell me you're ready for that.

CHAIRMAN THOMADSEN: Okay. Thank you. Before we go to the addendum, does anybody on the full ACMUI which to ask questions or make comments on what has been presented so far?

(No audible response)

CHAIRMAN THOMADSEN: Hearing none, Dr. Langhorst, please present the addendum.

MR. OUHIB: I'm sorry, Bruce, I was on mute. This is Zoubir. I have a very simple question. Based on what I was hearing, if I remember correctly, the delay time at NIH for patients that could benefit from such isotope was about two months. Is that correct?

MEMBER MATTMULLER: Yes.

MR. OUHIB: Okay. I guess I'm just curious; and maybe you have not looked at this, are there any clinical implications for such delay that you know of at all?

MEMBER MATTMULLER: Well, I would say the current NET patient needs seven years for proper diagnosis on average.

MR. OUHIB: Yes.

MEMBER MATTMULLER: I think that's pretty

compelling that we need to solve this issue. And realize that's just a two-month at the NIH.

MR. OUHIB: Right.

MEMBER MATTMULLER: That's the NIH. That's one facility. And there's only two others actively. I don't think anyone on this teleconference would think three sites is a sufficient number.

MR. OUHIB: Sure.

MEMBER MATTMULLER: And perhaps we shouldn't dwell on the wait time, but actually the small number of sites that can perform this test. So regardless the wait time, the incredibly small number of sites able to perform this procedure in the United States I think is clearly a barrier to good patient access.

CHAIRMAN THOMADSEN: Thank you very much. Any other questions before we move on?

MEMBER ENNIS: Ron Ennis here just with a comment.

CHAIRMAN THOMADSEN: Yes, please.

MEMBER ENNIS: Just to give a little medical perspective to the previous question. I cannot think of a clinical situation in oncology where a two-month delay in getting (telephonic interference) totally not a problem. That is always going to be a

problem. That's a significant delay in deciding on management decisions and monitoring effectiveness of treatments.

MR. OUHIB: Okay.

CHAIRMAN THOMADSEN: Thank you for your response. Okay. Dr. Langhorst, please.

MEMBER LANGHORST: Hi, this is Sue Langhorst. Ms. Holiday, do you have the non-redlined version of this addendum?

MS. HOLIDAY: Hold on one second for me.

MEMBER LANGHORST: Mr. Mattmuller, would you like to speak to the beginning of this addendum that we've put together?

MEMBER MATTMULLER: Sure. Yes, following completion and submission of our draft report we had additional questions and conversations. And in fact, one was with the radiation safety officer at the large university-based medical center on the East Coast. And he pointed out that while our microcurie label quantity was nice for most people, it would still be a problem for him in that even at a two microcurie labeling value he would still have to submit a DFP at his facility.

And so we looked into this further and did indeed find out that because of the large sites, if

they have other radionuclides in use such as carbon-14 or tritium, because of their long half-lives, the fraction rule kicks in. And with a generator that puts them over the limit of one and then they then have to submit a DFP for a financial assurance calculation. So that was our motivation to look at raising our labeling value.

MEMBER LANGHORST: Thank you. This is Sue Langhorst again. Discussions of decommissioning funding plans and financial assurance is something that I think everyone on ACMUI often gets involved in or has firsthand knowledge of what it takes to provide financial assurance. So I felt necessary that it would be helpful to kind of go through a question and answer type of presentation of what this all means. And so that's what motivated my start of providing this addendum.

So if we could go to question 1. What purpose do the labeling values in the Appendix B of Part 30 serve? And so, these labeling values are used for the Section 30.35, which is where NRC define what kind of financial assurance a licensee, a material licensee has to have for the given possession limits of licensed materials with half-lives greater than 120 days, otherwise the labeling values that are in Appendix

B of Part 30 with less than or equal to 120 day half-lives really serve no purpose.

So question No. 2: Where do these values come from? Well, prior to 1994 that was when what we referred to then as the new Part 20 came into effect. Prior to that, the Appendix B did not exist. And instead this decommissioning funding or financial assurance pointed to the old Appendix C of Part 20. And so for those of you who look at the history of various sections in the NRC regulations, the list of *Federal Register* references at the bottom of Appendix B of Part 30 really are the history of Appendix C of Part 20. So the current decommissioning funding plan regulations or financial assurance are established on values that are 45 years old.

So my question 3: How were those old values derived? Well, those old values for old Appendix C of Part 20 were derived and published in a proposed rulemaking for that new Part 20 in 1968. And going to the next page, that quote --

Ms. Holiday, could you go to that next page? Thank you.

It's using the value of the highest average concentration permitted in air. That's one method of calculating a level. And if the radioisotope emits

gamma radiation, that calculation was also made. And then there was a combination of those two values, which we'll go through in a question in a few minutes, that's how those were derived.

So question No. 4: Why wasn't Germanium-68 included in that old Appendix C of Part 20? Well, the air concentrations that were used to derive the first limit came from the ICRP-2 report that was published in 1959. And Germanium-68 was just not included in that list of radionuclides. So that's why the current Appendix B of Part 30 does not have a specific value of Germanium-68. It just was not on the regulatory radar in 1959.

So, question No. 5: What labeling value applies right now to Germanium-68? And as Mr. Mattmuller said, the half-life is 270 days for Germanium-68 and because it's not specifically listed, we are stuck with a default value of 0.1 microcurie for that radionuclide. So in this table that I have here, if a licensee has a possession limit of 0.1 millicurie or below, they do not have to provide any financial assurance. If their license lists up to one millicurie, they have to provide financial assurance of the order of $225,000. If it's between 1 to 10 millicuries, they have to provide financial assurance

up to $1.125 million. And then greater than 10 millicuries, that's when NRC has judged that the amount of radioactive material possessed and the complexity dictates that a licensee must develop a decommissioning funding plan in order to determine what is the amount of money that licensee needs to assure to be able to say, yes, we can decommission fully if we ever needed to?

Now, one of the things that gives us added complexity with this is, as Mr. Mattmuller was saying, if you have other radioactive materials on your possession limits that must be considered in determining what kind of financial assurance you have to have, that you have to do a sum of the ratio of the limits. That is, let's say you had one millicurie of Germanium-68. That would be 10 percent of your ratio for a decommissioning funding plan. So, I will get into that here in a little bit.

So, let's go to question No. 6. Why is there an issue now with Germanium-68 possession and financial assurance? Well, I think that Mr. Mattmuller has gone through that very well and the opportunity that Gallium-68 radiopharmaceuticals can provide to patients. One of the biggest things that this means is that a given licensee or a given radiopharmacy does

not need a cyclotron to produce this material. They can have a generator, a Germanium/Gallium generator that can produce this Gallium radioactive material.

Now, typically what I have understood is that these medical use generators will be of the order of about 50 millicuries per generator. So, as of right now if a licensee requests that possession limit of 50 millicuries or 2 generators of 100 millicuries, that automatically puts them into the financial assurance category of having a decommissioning funding plan even though their cost of decommissioning will be low because they will just return those generators to the manufacturer. And that is basically what I say in question No. 7: How will decommissioning take place for the Germanium/Gallium generators?

Okay. Let's go down to question No. 8. If Germanium-68 had been specifically listed in Appendix B of Part 30, what would that labeling value be? Well, -- because it originally started out as what is considered a labeling value in Part 20, if we look at the current Part 20 and the new updated Appendix C of Part 20, the Germanium-68 value there is 10 microcuries. And Mr. Mattmuller had pointed this out before.

Now, the other option is to do that

calculation that they did back in 1968 to figure out if there had been an airborne concentration of Germanium-68 listed in ICRP-2 published in 1959, what would the value have been? So, I took the current Part 20 Appendix B that has the concentration for Germanium-68 for airborne releases in a stack and that -- or an airborne effluent -- that highest concentration is 5 times 10 to the minus 9th microcuries per milliliter. I did the calculation of an individual standing in that concentration of Germanium-68, breathing in 24 hours a day, 365 days a year and came up with 53 microcuries.

If you go to the next page, the other way of calculating that, too, was to consider if an isotope, a radionuclide was a gamma emitter. Well, we've already pointed out that Germanium-68 does not emit gammas in its decay, but its daughter Gallium-68 does. And so, the Gallium-68, we take that exposure rate constant, which is 5.43 roentgen centimeters squared per millicurie hour, and we figure out what activity would cause 1 milliroentgen per hour at 10 centimeters, which was our other calculation method, and we come up with a 18 microcuries. And I know they did things a little different in 1968, but logarithmically rounding to the nearest decade of the smallest of these

two values means that Germanium-68 value would have been 10 microcuries. This is why we believe 10 microcuries is a good number for Germanium-68.

Now, if we go to question No. 9. So if 10 microcuries is proposed for this specific licensing basis for Germanium-68 and a Germanium-68/Gallium-68 generator meant for medical use, then that means the labeling value would increase by a factor of 100. And what would cause the DFP trigger value level would raise from 10 millicuries to 1 curie. And the question is is that safe? And the answer is yes.

These labeling values in Appendix B of Part 30 are only used to determine the level of financial assurance needed for decommissioning. They are not used for any other regulatory requirement and they are definitely not used as any kind of radiological criteria for allowing a formerly-licensed site to be released from unrestricted use under 20.1402. I'll say that again. They're used only to define the level of financial assurance.

The safety inherent in these Germanium/Gallium generators makes it very unlikely there would be residual activity of Germanium-68 from their use. And the costs of decommissioning these generators do not warrant the need to greatly increase

financial assurance needed by that medical licensee being able to possess that level of Germanium-68.

So let's go to question No. 10. So if we had a 10 microcurie labeling value for Germanium-68, what would then be the levels of financial assurance needed? So, here's that table repeated. So, in this case if someone had one of these generators that was less than a total of 10 millicuries, they would not have to provide financial assurance. From 10 to 100 they'd have to provide $225,000 of financial assurance. They'd have to guarantee that. That's about two generators worth. And if they go from 100 to a curie, they would have to provide $1.125 million of financial assurance. This would not trigger in a normal medical use environment a decommissioning funding plan needed.

So let's go on to question No. 11. What is a decommissioning funding plan? Well, to decommission a facility that means you remove that facility or site safely from service and reduce residual radioactivity to a level that permits release of the property for unrestricted use and termination of the license or there are also provisions to release the property under a restricted condition to terminate the license. A decommissioning funding plan is a

site-specific cost estimate to fully decommission a license and it's used to set a license-specific amount of financial assurance that the licensee is required to maintain.

Question No. 12: So, what does it mean to develop and maintain a DFP? Well, I'm not going to read this to you, but I have provided the list of what a decommissioning funding plan must contain. A detailed cost estimate with these items included in that consideration; identification and justification of any key assumptions the licensee uses; description of how you're assuring that financial assurance; certification that you will provide that financial assurance; and a signed financial instrument.

When you have a decommissioning funding plan, you're required to submit it to the NRC or, if you're in an Agreement State, that Agreement State whenever you first get a license, when you renew your license and at intervals not to exceed three years. And you have to update it with these various considerations as you maintain your decommissioning funding plan. Obviously not all of these would apply to all licensees.

So, the use of a decommissioning funding plan is really applicable to licensees with complicated

and extensive possession limits so that the right amount of financial assurance is put in place to guarantee you're not going to have a legacy site should licensee go bankrupt. This assures that that money will be there to fully decommission the site.

Now, because not many people get into this, I use my own university's experience with decommissioning funding plans. So Washington University in St. Louis, we are a broad-scope Type A medical use license and we also have an accelerator production license issued by the NRC. Our financial assurance as determined by our latest decommissioning funding plan is at a level of 6.77 million, so well exceeding that middle level of financial assurance. If we did not count our cyclotron production and some of our larger shield sources in our decommissioning costs, then our possession of greater than 120-day half-life radionuclides would maybe require about a $2 million financial assurance.

Now, our last decommissioning funding plan that was approved by the NRC was submitted in September 2009 when the byproduct material definition was changed. We submitted another decommissioning funding plan in December of 2010 when we added a large sealed source device and we updated it again in February of

2013 when we renewed our license. We did not have questions on that 2010 submittal, but we did have a few questions on the financial assurance submitted to us in September of 2014, which we provided to NRC. Our answer was in December 2014.

As of today we still do not have an update of our approved decommissioning funding plan. Now, that's due to a lot of various reasons, but we're set to have to update our decommissioning plan again in February of 2016. I make this point only to let you know that decommissioning funding plans are not only time consuming for us; they are very time consuming for the regulators. And it does not seem reasonable to have additional decommissioning funding plans required for the addition of a Germanium/Gallium-68 generator when the decommissioning of that (telephonic interference) is significant.

It would be great if someone could put that phone on mute.

Okay. Let's go to question 13. So, we've already talked about what would happen if we don't change this generic level of 0.1 microcurie. There would be a lot of patients who would lose out on a very valuable set of radiopharmaceuticals that are in play right now that are being reviewed by the FDA, but it

also would limit the development of further Gallium-68 radiopharmaceuticals that may come down the line if that technology is made more available.

Now question 14. I wanted to come back to what would happen if we do change to our report's original recommendation of two microcuries as the labeling. So, here I've provided that table again. You all should be used to looking at it. And these are the levels that would require the various levels of financial assurance. So, you can see that for the 1.125 million level of financial assurance that a licensee could have one, maybe up to four generators, but any more than that would require the decommissioning funding plan.

Now, it will be challenging for licensees to establish that financial assurance at that 1.125 million, but as Mr. Mattmuller had said before, if you already have longer-lived isotopes that must be considered in the sum of ratios of radionuclides in figuring out your decommissioning funding level, that putting that 2 microcuries for Germanium-68, that adds significantly to that sum of the ratios. If you had one generator, one generator means 25 percent towards that sum of the ratio for each 50-millicurie generator. And there are licensees' possession limits that would

not allow them to absorb 25 to 50 percent of this ratio with the radioactive materials they currently possess. If instead, as shown in the question 10 I discussed before, it's 10 microcuries, then 10 percent will be part of that sum of the ratio for each 50 millicurie possession limit. And a licensee or a radiopharmacy could more likely absorb to 10 to 20, maybe even 30 percent in this ratio before being kicked out of that 1.125 million level for financial assurance. So, it's not that we're increasing things and that's not safe. If you're still having to make a commitment for financial assurance even at these 10 microcurie level.

So in conclusion, we hope that we have shown that the cost of decommissioning for a medical use Germanium/Gallium-68 generator does not warrant the need for a site-specific decommissioning funding plan and that changing to 10 microcuries is a reasonable number for Germanium-68. And we would hope that limiting this change for that Germanium-68 to only include these Germanium-68 generators that are returned to the manufacturer, that would be a defendable and well-justified reason to go for a direct rulemaking to relieve this unintended hindrance to development of these Gallium-68 radiopharmaceuticals.

So that completes my review of that and

I'm glad to answer questions if anyone has them.

CHAIRMAN THOMADSEN: Thank you very much, Dr. Langhorst.

Do we have questions for Dr. Langhorst on the addendum from the Committee?

MEMBER COSTELLO: Yes, this is Frank Costello. It's not such a question as -- first I'd like to thank Sue and Steve for working on this. And I'll also say that I would enthusiastically endorse the addendum, because I think there is loss in safety using the 10 rather than 2 and thus provides more relief from financial assurance than the original proposal. So again, Sue and Steve, thanks again for your hard work on this and I would endorse 100 percent.

CHAIRMAN THOMADSEN: Thank you very much Mr. Costello. Other comments?

MEMBER ZANZONICO: This is Pat Zanzonico. It's probably unnecessary, but I want to echo that comment. Among the many other points that were made, the model calculations plus the provision that these generators would be returned to the manufacturer really makes the conclusion inescapable that a 10 microcurie licensing basis is appropriate. Any other conclusion would be completely illogical and counter to the science and the logistics and so forth and so on. And I, too,

want to thank Mr. Mattmuller and Dr. Langhorst for their really cogent analysis.

CHAIRMAN THOMADSEN: And thank you for that comment, Dr. Zanzonico. Other comments?

(No audible response)

CHAIRMAN THOMADSEN: Hearing none from the Committee, I'll now ask is there anybody else on the line who would like to comment? I'm not sure how this works exactly to identify. So, Ms. Holiday, can you tell me how we identify people on the line who want to comment?

MR. FULLER: Well, Dr. Thomadsen, this is Mike Fuller. Before we go to the public comments --

CHAIRMAN THOMADSEN: Yes.

MR. FULLER: -- on behalf of NRC staff I have a few questions.

CHAIRMAN THOMADSEN: Please, yes.

MR. FULLER: Thank you. And these questions are for anyone from the Subcommittee. And I'd also like to say that the information provided today is very, very helpful as we work to try to figure out our best path forward for responding to this recommendation if in fact it turns out to be an ACMUI recommendation.

But, with some of the things to help me

clarify, I think one of the reasons why there was a need to understand just sort of how many procedures or how many facilities or how many folks might be affected or impacted by this decision one way or the other, that's still some information I think we're going to need for rulemaking. So, my question either for Steve or -- Mr. Mattmuller rather or Dr. Langhorst or anyone else, we heard that this was a replacement procedure for Indium-111, which is sort I guess the standard still these days. Do we know or is there a way to find out approximately how many of those procedures are done annually, or in some periodicity?

CHAIRMAN THOMADSEN: Anybody on the Committee able to respond to that question?

MEMBER ZANZONICO: This is Pat Zanzonico. I can't respond specifically, but I'm sure we could get estimates of the incidents of neuroendocrine tumors, and that would at least give a first order estimate of the number of patients potentially affected by this, because that would be the patient population that would receive these somatostatin receptor imaging procedures. Again, I don't have those numbers at my fingertips, but I'm certain they're available and can be obtained.

VICE-CHAIR ALDERSON: Yes, this is Dr.

Alderson. I want to comment on that. I think that gives us a maximum that might be out there and needed, Mr. Fuller, but I think that many, many places that do octreotide now aren't going to switch to this, I don't think. So I think it would be a much larger estimate that you would actually see switching to Gallium-68.

MR. FULLER: I appreciate that. And the reason for the question was again to try to get to -- when we talk about a rulemaking, there's -- whether it's direct final rule or so forth, there is a bit of a hurdle when it comes to justifying and so forth. So a lot of the information that Dr. Langhorst talked about is going to be extremely helpful as we move forward on this effort. But the potential -- some sort of estimate about what -- we have to put this in some sort of context as far as numbers of procedures and so forth. So that will be helpful if we could get some of those estimates moving forward. I wouldn't want to waylay this at this point in time, but that's something that we're probably going to need.

The other thing is, is we heard that the fact that we have this problem with the decommissioning funding plan rule is an impediment or is restricting access to this and so forth, but we also know that this

is -- even though FDA can't publicly acknowledge whether or not they have an application or not, I think it's come up at a number of public forums, people talking about the applications before the FDA. So, Mr. Mattmuller, or anybody else, do we have insight either from the folks that have submitted the applications or anyone else that can give us any idea about how long we might expect before these are approved by FDA?

MEMBER MATTMULLER: This is Steve Mattmuller. No, we can't get an answer from the FDA, and so it's impossible to give you a firm number.

But to address the previous question, it's not going to be a large number because for these patients the drug under consideration by the FDA has been granted orphan drug status because it is a relatively small patient population. But I would say it's definitely a patient population definitely in need of better radiopharmaceuticals given the sad statistic that it takes seven years to do it properly now.

I mean, and currently some of these patients go to Europe. I mean, this drug is currently available in Europe, and so those who have the means travel to Europe for this test. So, it has a wide base of experience in Europe. We're just now waiting for it to work through the regulatory process here in the

U.S. through the FDA and the NRC.

MR. FULLER: Yes, I had heard that this was -- again, this is very similar posture to what we have I guess at this point is there really aren't any safety considerations. It's just a matter of FDA going through their process.

MEMBER O'HARA: This is Mike O'Hara from the FDA, and the FDA can't say anything about where this agent is in our regulatory pathway.

MR. FULLER: Thank you, Dr. O'Hara.

The other thing, I had one last question. I think I'm just a little bit confused, Mr. Mattmuller. You had said that this is used only in three sites across the country, but we also talked about -- I think Dr. Zanzonico talked about the things that they're doing there at his facility with these generators. And I talked just today about someone here at the NRC who just finished graduate school at a Midwestern university who had one of these and it was in use.

So I'm a little bit curious about what -- large university medical school-type things that already have decommissioning funding plans in place and so forth similar to the situation that Dr. Langhorst described. I'm just wondering what is the real number of facilities that are actually using the

Germanium/Gallium generator currently? Is it just that there are just three sites that are in a specific clinical trial or -- I'm just -- I don't know, I'm a little bit confused about that. Yes, what is the actual scope of the current use? Does anybody have any insight on that?

MEMBER MATTMULLER: Well, Mike, to answer that I think you have to say on what day you're asking it, because it's a very fluid situation. This statistic that came from Josh is probably now two months, three months old, so -- and I'm aware of other sites that are working to get their Gallium-68 program up and working. So it could be a larger number now, but it's still an incredibly -- even if it's doubled or tripled, it's still an incredibly small number if you're looking at the whole United States. So there's still a huge barrier to patients to have access to this drug.

COURT REPORTER: Speaker, please identify yourself.

CHAIRMAN THOMADSEN: That was Mr. Mattmuller who was answering the question.

MEMBER LANGHORST: This is Dr. Langhorst. May I chime in?

CHAIRMAN THOMADSEN: Please.

MEMBER LANGHORST: So, Mr. Fuller, this is -- we are in the process of trying to get all of our radiopharmaceutical production for the Gallium agent through all of the requirements of our RDRC and then when the FDA approves then to get it into that regulatory space. So, yes, there's more coming on line, but if there are Germanium/Gallium generators available more widely across the country, there will be more interest, there will be more funding to develop other radiopharmaceuticals using this Germanium/Gallium generator that spans those medical licensees being able to use more than just F18-FDG.

CHAIRMAN THOMADSEN: Thank you.

MR. FULLER: That's all the questions I had. Thank you. Thank you so much. These are the types of things that are very helpful to us as we pursue any sort of rulemaking, whether it's a direct final rule or something else. So again, I don't want to waylay this. I think what we've read and what we've heard today has been extremely helpful and exactly what we've kind of been looking for. So, thank you.

CHAIRMAN THOMADSEN: And, thank you, Mr. Fuller, for those questions.

MEMBER LANGHORST: This is Sue Langhorst again. May I add a little --

CHAIRMAN THOMADSEN: Please do.

MEMBER LANGHORST: Okay. Mr. Fuller, I think -- I mean, this would be a really upper bounds also, but we don't have access to these numbers, like some of the numbers that NRC and Agreement States have. So you might look at the number of licensees that NRC has and Agreement States have that are of the 35.200 or equivalent use. You could look at which ones of those already have decommissioning funding plans. And then the remainder of that would be definitely an upper bound, but some fraction of that could give you at least a ballpark of who could be open to this type of medical use. So, that was the best I could come up with for you all.

CHAIRMAN THOMADSEN: This is Bruce Thomadsen again. It sounds in a way as if what might be being requested is something analogous to the Orphaned Drug Program at the FDA here since we have a modality that is to be used in a relatively small number of patients compared to something like lung cancer. But there is definitely an impediment to making this modality available to a widespread geographical area for these patients regardless of if we've got three more centers there or not, which case it's not clear that the numbers actually tell much of

a story.

I don't think we're going to find that there's 50 facilities out there that are potentially not doing this because they need to do a plan, but it is something that may be affecting 50 patients that might not be able to get their diagnosis in a reasonable period of time due to the lack of availability in their area for these types of scans. Does that sound like some sort of a summary of the situation? And I'll pose that to the Subcommittee.

MEMBER WEIL: This is Laura Weil. Can I just interpose a comment?

CHAIRMAN THOMADSEN: Please do.

MEMBER WEIL: I think what comes into play is the ethical principle of maximizing benefit and minimizing harms. And the harms here would relate to safety issues with decommissioning these generators, which seems to be a non-existent problem. It's simply a regulatory barrier that is in the way of maximizing the beneficial use of this radionuclide for patients who need it irrespective of the number of patients that that might represent.

CHAIRMAN THOMADSEN: Thank you for that comment.

MEMBER COSTELLO: This is Frank Costello.

CHAIRMAN THOMADSEN: Yes, Mr. Costello?

MEMBER COSTELLO: Yes, as I understand Mike, and I think I do, I think what he's looking for is for us to recognize that there's a burden or a hurdle that has to be overcome to do any kind of rulemaking, any rulemaking, a direct final rulemaking, whatever it is. And even though this is definitely on the side of good science and the side of a benefit to patients, I think for NRC to go forward with the rulemaking process there has to be justification for it beyond just the fact that it's a good idea and some patients will benefit. I think, and correct me if I'm wrong, Mike, but there's a certainly threshold we've got to get over in order to make that rulemaking request successful.

MR. FULLER: Yes, Frank, this is Mike Fuller. Yes, and I'm not a rulemaking expert. I just know we've been through it a number of times. And I hear Ms. Weil's comment and I absolutely -- we all can understand from an ethical perspective that it's absolutely the right thing. But we also have to meet certain cost-benefit -- we have to be able to defend not only good scientific and good reasons for it and reducing barriers and so forth and so on, but the question will be asked about cost-benefit. And so, we just need to be able to appropriately articulate

that answer. I don't think there's a necessary threshold. It's just that we need to be able to answer that question. And so, it'll be helpful as we move forward on this.

Again, I hear nothing, or I believe that just from my own personal experience I don't believe there's anything here that's going to prevent us from going forward. However, the way the process works for rulemaking; and, Frank, I know you know this, they have to be rated based upon safety and so -- or the safety significance. And they're rated low, medium, and high. And certain rulemaking activities are funded. And those that fall down to a lower safety metric or what have you rating, then maybe they're not funded for a particular year.

So we're just trying to make sure we're getting all of our ducks in a row, we have all the information that we need so we can move forward. That's all we're looking for.

PARTICIPANT: More information is better.

MR. FULLER: Yes, the more the better. The more ammunition, the better. Put it that way.

MR. MAILMAN: Hi, this is Josh Mailman, and my name's been used a few times. Could I make a comment on some of the questions that have been brought

up?

CHAIRMAN THOMADSEN: Please do.

MR. MAILMAN: I am the President of NorCal CarciNet. I'm also a patient, a patient advocate and the past Chair of the Society of Nuclear Medicine and Molecular Imaging's Patient Advisory Board.

A couple of things, points of clarification: The incidence of NETs in the United States is 5.25 per 100,000. That comes from the SEER database. The current prevalence, which is probably more important in this area, is about 112,000 patients in the U.S. who are actively living with neuroendocrine tumors and it is likely that at surveillance they will be somewhere between, as in my case, one Gallium-68 PET CT a year, to which I'm currently going to Europe to fulfill.

As far as the number of centers that are actively doing Gallium-68 on patients, the challenge is, as Mr. Mattmuller pointed out -- it's a moving target. There have been at least 12 centers in the United States that have had -- who've successfully imaged patients under an IND. The issue of course with an IND is they have a stated purpose and a stated time. And when either they run out of funding or they reach their patient maximum, they will no longer be able to

image patients.

Since the time I gave that figure of three there have been one or two, actually three that have come back on line and are actively scanning patients, whether that's one a day or one a week. It's not a great number, but it is more in the turn of six or seven. And so, I just wanted to bring those up because those seemed to be some of the points you were asking for as for clarification.

And I also think one other thing that I'd like to bring up right now is that many of those on the call were at the Theragnostic World Congress which was in Baltimore earlier this year, and one of the big and exciting uses for Gallium-68 that's coming on is of course for prostate cancer, which will be a very large population that will need this as well.

CHAIRMAN THOMADSEN: Thank you very much for those comments. And your last one in particular might address the question of numbers, since the number of prostate cancers in the country is of course huge.

Other comments?

MR. FULLER: And --

CHAIRMAN THOMADSEN: Oh, yes?

MR. FULLER: Dr. Thomadsen, this is Mike

Fuller again. I'm sorry. Just for clarification and to make sure -- he was kind of breaking up. Could you -- the last person who spoke, could you state your first and last name again and your affiliation for the record, please?

MR. MAILMAN: Sure. Josh Mailman and I'm the President of the NorCal CarciNet Community, a non-profit in the San Francisco Bay area. I'm also a member of the Patient Advocacy Advisory Board for the Society of Nuclear Medicine.

MR. FULLER: Thank you. Thank you very much.

CHAIRMAN THOMADSEN: Thank you. Other comments or questions, please, from anybody?

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

MEMBER MATTMULLER: Steve Mattmuller. If I may?

CHAIRMAN THOMADSEN: We have two speakers here. Yes?

MEMBER MATTMULLER: Yes.

CHAIRMAN THOMADSEN: Can you state your name again? It was lost.

MEMBER MATTMULLER: Yes, Steve Mattmuller. And I'd like to point out that there is

-- it was touched on in the comments made by Triad. There are distribution challenges for a site using a Gallium-68 generator. We're talking about a generator with an activity of 50 millicuries. It's similar to a technetium-99m generator, but those at most commercial radiopharmacies are much larger. They're in the 10 to 15 to 18 curie size, so their elutes are much larger. Plus the technetium has a longer half-life. So for the same radiopharmacy with the technetium and Gallium-68 generator, their area, their distribution area that they can distribute doses to is far, far greater with a technetium generator than it will be for a Gallium generator.

And in fact, for most of the sites now using the Gallium generators, if they're really careful, they can get two patient doses out of one elution. So the output of the generators is much, much lower than anything we're typically accustomed to right now. So the fact that there might be one site in one city isn't a large number of doses that can be provided. And especially when we get into other agents such as a potential prostate agent, there's going to be a need for a lot of generators around the country. Thank you.

CHAIRMAN THOMADSEN: Thank you.

MR. OUHIB: Yes, hi, Bruce. This is

Zoubir.

CHAIRMAN THOMADSEN: Yes.

MR. OUHIB: I think I'd just like to echo what the person just said, and that was one of my concerns because of the short half-life. I believe 68 minutes or something like that. That would most likely have a major impact as far as the output or the throughput or whatever. So I just want to comment on that.

CHAIRMAN THOMADSEN: Thank you.

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

CHAIRMAN THOMADSEN: Yes, please.

MEMBER LANGHORST: Mr. Fuller, I wanted to ask this question: If licensees who are interested in providing this type of medical diagnostic tool -- if they wanted to voice voluntarily to the NRC what this means to them, can they provide you with that input in some way?

MR. FULLER: Dr. Langhorst, yes, this is Mike Fuller, I mean, I imagine there is. I mean, we don't have any formal process because we're not in rulemaking right now, but I guess the best way to kind of respond to that is -- and only speaking for NRC staff here on the medical team, we really don't need anymore

convincing that we need to do this. All we're looking for and all we've been looking for is the information and the data to move forward.

And so, I just don't believe it's necessary for anybody else or anymore convincing that we need to do something about this. We're just looking for the right tool from our tool box. Direct final rule I think is an excellent recommendation based upon what we've heard today. And I think that's where we want to focus.

So, I don't know if I answered your question, Dr. Langhorst, but I mean people are free to contact us at any time. But we don't have a process when we're not in rulemaking.

CHAIRMAN THOMADSEN: Thank you for the question and thank you for the clarification.

Other comments?

(No audible response)

CHAIRMAN THOMADSEN: Hearing none, I think it's time to ask the Committee if anybody wants to make a motion. Particularly does the Subcommittee wish to move this forward for endorsement by the Full Committee?

OPERATOR: This is the operator. Would you like to take audio questions, too, sir?

CHAIRMAN THOMADSEN: Oh, yes. I thought

we were doing that before. Yes, please.

OPERATOR: Thank you. At this time if you would like to ask a question, you may press star, one on your touch tone phone. That is star, one to ask a question. If your question has been asked or comment, you may press star, two to withdraw your question. Once again, to ask a question, star, one. One moment, please.

(Pause)

OPERATOR: I am showing questions coming through. One moment while I grab the first question.

CHAIRMAN THOMADSEN: Thank you.

OPERATOR: Our first question will come from Mr. Leveritt.

Sir, your line is open.

MR. LEVERITT: Hi. This is Sam Leveritt. I'm a clinical pharmacist with Cardinal Health Nuclear Pharmacy. And I would like to align ourselves with our colleagues over at Triad. We have a network of nuclear pharmacies across America, but even with the very short limited range that these generators would provide, there's going to be an increased diagnosing of it. I mean, clinically with a seven-year thing we know that we're going to detect more people. We're going to knock that incidence down. We're going to

catch it before it gets further along. We're going to get the staging better. We're going to affect therapies. We're going to save lives.

But the FDA is going to need additional information from you guys, or from clinicians, before they're going to approve this. And the only way to do that is to have it available for research use. And really what we're asking the NRC to do is to open this up so that all of our research universities and facilities can get in on this so that we can show the FDA that this is a viable product. And the data is just going to come flowing in once we get it from this point on.

CHAIRMAN THOMADSEN: Thank you very much. Next question?

OPERATOR: Thank you. And once again, if you'd like to ask a question, that is star, one. Please make sure you un-mute your line and you state your name clearly. Once again star, one and un-mute your line. One moment.

Our next question will come from Bonnie Clarke.

Your line is open.

MS. CLARKE: Hi, thank you. My name is Bonnie Clarke. I'm the Director of the Clinical Trials

Network at the Society of Nuclear Medicine and Molecular Imaging, and for the past two-and-a-half years we have been organizing a Gallium users group and we have helped to coordinate those 12 centers that at various times have been enrolling patients in either Gallium-labeled DATA-TATE or DOTA-TOC.

My comment is just to address a question that came up earlier. I was able to find the number of octreoscans performed in the United States in 2007. Unfortunately that's the last number I have, but that was an estimate of 11,000 to 13,000 patients with an approximate growth rate of about 5 percent per year, which would be about 19,000 octreoscans per year in the U.S., which is about equivalent to what was being done currently in Europe in 2007 as well. They had a combination of octreoscan and Gallium DOTA-TOC scans estimated to be about 16 to 19,000 in Europe. That's from 2007.

CHAIRMAN THOMADSEN: Thank you very much.

MS. CLARKE: Okay. Thank you.

OPERATOR: Thank you. I'm showing no questions. One again, if you would like to ask a question or make a comment, please press star then one. One moment, please.

(Pause)

OPERATOR: One moment for the next question.

(Pause)

OPERATOR: I have a question.

You did not record your name. You're line is open though. If you just pressed star, one, your line is open.

MS. FAIROBENT: This is Lynne Fairobent.

CHAIRMAN THOMADSEN: Hello, Lynne.

MS. FAIROBENT: Hi.

CHAIRMAN THOMADSEN: It's nice to hear from you.

MS. FAIROBENT: Thanks. Lynne Fairobent with the American Association of Physicists in Medicine.

I just want to make a follow-up with something that Mike Fuller had said. NRC does have a process. It's called petition for rulemaking if you are not currently in a rulemaking.

And secondly, given the current status of rulemakings in progress; and I know it would be determined by the Commission, but are we talking a 1-year time frame for consideration, a 2-year time frame, 5 years, 10 years? How far out are we looking before this realistically without a petition for rule

being filed that NRC could put this in the rulemaking rotation, even as a direct final rule?

CHAIRMAN THOMADSEN: Very good question. Anybody on the NRC able to take that question?

MR. FULLER: Yes, Dr. Thomadsen, this is Mike Fuller again. No, I do not have the answer to that question. I do know though that the staff is interested in moving out smartly on this. So in talking with folks from our rulemaking group, direct final rules are a little bit different. We can get them in the process and get them rated and so forth, or weighted I guess is the right term, and then see where we fall out.

And to Lynne Fairobent's point about the petition for rulemaking, that's always an option, but I don't think that was Sue Langhorst's, Dr. Langhorst's question. I thought she asked me how could someone send comments to us about this need and so forth. And so, that's what I was referring to. So, but I do know that we are very, very interested on the staff in moving out on this just as -- and I think once we get this -- well, whether or not we get this recommendation, we are in the process. And I've been working on our end to develop some options on what is the very best way to address this problem.

CHAIRMAN THOMADSEN: Thank you for the clarification.

Are there any other questions on line?

OPERATOR: I'm showing no questions at this time.

CHAIRMAN THOMADSEN: Okay. Fine. I realize that actually we just need to have the Subcommittee make a motion to have the Full Committee endorse their report as coming from the Full Committee.

MEMBER ZANZONICO: Dr. Thomadsen, I just have a question, a procedural question.

CHAIRMAN THOMADSEN: Yes?

MEMBER ZANZONICO: Is the motion we're possibly considering the report plus the addendum, or do these require separate motions, or is the addendum not on the table for a motion?

CHAIRMAN THOMADSEN: That depends on the motion that the Subcommittee makes. They could make a motion to approve the report with the addendum or the report without the addendum.

MEMBER ZANZONICO: In that case, I would like to get the ball rolling and as a member of the Subcommittee make a motion that the Subcommittee approve the final report with the recently submitted addendum.

MEMBER COSTELLO: Yes, this is Frank Costello. I enthusiastically second that.

CHAIRMAN THOMADSEN: Fine. That's very fine. Coming from the Subcommittee we don't need a second, but we'll accept that.

MEMBER COSTELLO: I'm sorry.

CHAIRMAN THOMADSEN: No apology necessary at all.

In that case, comments from the Committee?

(No audible response)

CHAIRMAN THOMADSEN: Hearing no comments, we'll call for a vote. And let's first ask -- we'll see if this will pass on a voice vote. All in favor, say aye?

(Chorus of ayes)

CHAIRMAN THOMADSEN: Opposed, say nay?

(No audible response)

CHAIRMAN THOMADSEN: Any abstentions? Indicate now, please.

(No audible response)

CHAIRMAN THOMADSEN: It sounds like we have unanimous acceptance of this report as the statements for the Full ACMUI.

With that, I'll say I think our business that we can conduct on this call is completed.

Ms. Holiday, shall I turn it back to you for termination?

MS. HOLIDAY: Sure. On behalf of the staff, we would like to thank the Committee, the Subcommittee and all of the participants on this call today for engaging in the conversation on the decommissioning funding relief for Germanium-68. We look forward to having you all in D.C. October 8th and 9th for our fall meeting.

CHAIRMAN THOMADSEN: Thank you very much. And with that, the meeting is adjourned.

(Whereupon, the above-entitled matter went off the record at 3:46 p.m.)