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UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

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MEETING

ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

(ACMUI)

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OPEN SESSION

+ + + + +

WEDNESDAY

OCTOBER 13, 2004

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ROCKVILLE, MARYLAND

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The meeting came to order at 8:00 a.m. in Room T-2B3 of Two White Flint North, Leon S. Malmud, M.D., Chair, presiding.

COMMITTEE MEMBERS:

LEON S. MALMUD	Chairman
EDGAR D. BAILEY	Member
DAVID DIAMOND, M.D.	Member
DOUGLAS F. EGGLI, M.D.	Member
RALPH P. LIETO	Member
SUBIR NAG, M.D.	Member
SALLY W. SCHWARZ, RPh	Member

COMMITTEE MEMBERS: (CONT.)

ORHAN H. SULEIMAN, Ph.D.	Member
WILLIAM VAN DECKER, M.D.	Member
RICHARD J. VETTER, Ph.D.	Member
JEFFREY WILLIAMSON, Ph.D.	Member

NRC STAFF:

THOMAS H. ESSIG	Designated Federal Official
Linda M. Gersey	NMSS/IMNS
Patricia K. Holahan, Ph.D.	NMSS/IMNS
Merri Horn	NMSS/IMNS
Donna-Beth Howe, Ph.D.	NMSS/IMNS
John Jankovich	NMSS/IMNS
Andrea Jones	RES
Charles L. Miller, Ph.D.	NMSS/IMNS
John Szabo, Esq.	OGC
Sami Sherbini, Ph.D.	NMSS/IMNS
Sandra Wastler	NMSS/IMNS
Angela R. McIntosh	NMSS/IMNS
William Ward	NMSS/IMNS
Ronald E. Zelac	NMSS/IMNS

I N D E X

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

MR. ESSIG: Good morning, ladies and gentlemen. As Designated Federal Official for this meeting, I am pleased to welcome you to Rockville for the Public Meeting of the Advisory Committee for the Medical Uses of Isotopes. My name is Thomas ESSIG. I am Chief of the Material Safety and Inspection Branch, and have been designated as the Federal Official for this Advisory Committee in accordance with 10 CFR Part 7.11. 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. The meeting was announced in the August 27th, 2004 edition of the *Federal Register*.

The function of the committee is to advise the staff on issues and questions that arise on the medical use of byproduct material. The committee provides counsel to the 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 them very much.

I request that whenever possible, we try to reach a consensus on various issues that we will discuss today and tomorrow, but also I value minority

or dissenting opinions. If you have any such opinions, please allow them to be read into the record.

As part of the preparation for this meeting, I have reviewed the agenda for members and employment interests based on the very general nature of the discussion that we're going to have today. I have not identified any items that would pose a conflict; therefore, I see no need for an individual member of the committee to recuse themselves from the committee's decision making activities. However, if during the course of our business you determine that you have some conflict, please state it for the record and recuse yourself from that particular aspect of the discussion.

At this point I would like to introduce the members who are here today; Dr. Leon Malmud, who is Vice Chairman of the Committee, who today is Acting Chairman of the Committee in the absence of Dr. Manuel Cerqueira. Mr. Edgar Bailey, who is the State Representative. This is Mr. Bailey's first meeting. He replaces Ruth McBurney from Texas. Dr. Douglas Eggli, who is our Nuclear Medicine Physician; Dr. David Diamond, one of our radiation oncologist physicians; Dr. Subir Nag, a second radiation

oncologist physician; Ms. Sally Schwarz will be here momentarily. She was delayed. She's our Nuclear Pharmacist Representative; Dr. Richard Vetter, our Radiation Safety Officer; Dr. Jeffrey Williamson is our Therapy Physicist; Mr. Ralph Lieto, our Nuclear Medicine Physicist, and Dr. Orhan Suleiman, who is our FDA Representative from the Center for Devices and Radiological Health. As I mentioned, Committee Chairman, Dr. Manuel Cerqueira was unable to attend this meeting due to a conflict in his schedule which he could not resolve.

Committee Member, Dr. Robert Schenter, who is our newly appointed Patient Advocate Representative and replaces Ms. Nicki Hobson, was unable to attend the meeting due to illness. Dr. William Van Decker, a Nuclear Cardiologist, who is seated at my immediate left, will replace Dr. Cerqueira in that role as a member of the committee.

So in the absence of the ACMUI Chairman, Dr. Leon Malmud, ACMUI Vice Chair, will conduct today's meeting. Following discussion of each agenda item, the Chair, at his option, may entertain comments or questions from members of the public who are participating with us today. Dr. Malmud, please.

CHAIRMAN MALMUD: Thank you, Mr. ESSIG.

The next item on the agenda is the radio immuno therapy and microsphere therapy discussion, which will be presented by Dr. Donna-Beth Howe. Dr. Howe.

DR. HOWE: Thank you, Dr. Malmud. We've gotten questions at a number of the ACMUI meetings about how we regulate the monoclonal antibodies and the Yttrium- 90 microspheres. And Dr. Nag especially wanted us to clarify again how we're regulating these things, so I've prepared a number of slides. They're in your book, and what you'll see is a lot of slides. But there's a section that says "Background", and after Background, what I've done is I've just repeated what's in the regulations so that if you wanted to look at the regulations, they would be right there and available at your fingertips.

Okay. The first thing I need to do is to kind of clarify the question of emerging technologies for 35.1000 uses, which is other medical uses. And the way we determine whether something falls into 35.1000 is that we have to first determine that it does not fall into one of the other categories.

If it almost fits into one of the other categories, but misses by a small amount so that we would have to have additional requirements for radiation safety or we would have to grant an

exemption from a requirement, then that will automatically throw the modality into 1000. And that's a key point to remember here.

A lot of times something that is a new technology for the medical community may be something that we already have adequate regulations for, and so the medical community may think well, I've got a new technology, and why isn't NRC developing guidance on it. And the reason may be that we already have an adequate regulatory structure to handle that particular modality. So what I'm going to do is I'm going to kind of go back and forth between the monoclonal antibodies and the Yttrium- 90 microspheres, and kind of show the similarities and the differences, and how we arrived at where we're regulating them.

The first thing to note is that for the radio immuno assay, the monoclonal antibodies, first of all, FDA regulates them as radioactive biologics, which is a subset of radioactive drugs. So they are listed for manufacture and commercial distribution under 35.72 or equivalent state regulation, so they're coming through the drug side of our regulations.

They are clearly a medical use, so they're

going to be under 35. They are a therapeutic procedure that requires a written directive. So the next thing to do is -- so that's the basis on which we start with the monoclonal antibodies.

If I want to look at the Yttrium- 90 microspheres, first of all, FDA regulates them as medical devices. They are sealed sources. They are listed in our sealed source and device registry. They are licensed for manufacture and distribution, commercial distribution under 35.74. The radiopharmaceuticals come under 32-72. 35.74 is an error, it should be 32-74. So the pharmaceuticals come under 32-72, the devices come under 32-74. Once again, they're a medical use. They're again a therapeutic procedure that requires a written directive. So how do we use this?

Both of them are therapeutic procedures that require written directives. I go to the regulations and I look at what part of the subparts of the regulation 35 require written directives; unsealed byproduct material, manual brachytherapy, photon emitting remote afterloaders, teletherapy and gamma knives, and then Subpart K. If I want to use the radio immuno therapy, the one that comes under drugs would be the unsealed byproduct material. And in

that, you'll see in 35.300 that it has to be manufactured by somebody under 32-72, or the authorized nuclear pharmacist can prepare it. So the monoclonal antibodies do come through that route. They're regulated as drugs. They come through the manufacture and distribution system correctly. And then you look at the other requirements in Subpart E and you'll find the monoclonal antibodies fit very nicely into 35.300, and all of the requirements that go with 35.300.

If you look at the microspheres, they're devices, and you look at the unsealed byproduct material. They're sealed byproduct material, so they don't fit under E. Manual brachytherapy, sealed sources, manual brachytherapy - if you look at the microspheres, they are manual brachytherapy sources, but they're really tiny. They aren't afterloaders, they aren't teletherapy, they aren't gamma knives.

Now in manual brachytherapy - when I look at the requirements for manual brachytherapy, there's some requirements in manual brachytherapy that the microspheres just cannot meet because of their very, very small size. You can't count them. You can't keep counting the way you would for other manual brachytherapy sources, so we would have to give you

relief from the regulations. That automatically throws it into 35.1000. You cannot fit the microspheres exactly into manual brachytherapy.

There is some discussion, well, you can put them in like radioactive drugs. It's like the microaggregated Albumin. Well, the microaggregated Albumin comes through the commercial distribution system under 32-72, which is your commercial nuclear pharmacies, and your drug manufacturers, and federal facilities that are neither drug manufacturers or commercial nuclear pharmacies, so you'd have to grant an exemption from that.

It's not a drug. Everything in 35.300 says you will handle drugs this way. You would need exemptions from all of those parts, so it clearly is not a 35.300. It fits much better in the 35.400 with very minor adjustments.

Now the other thing that you have to consider is that you have regulations that are appropriate to all parts that are used under 35, and so one has to go through the Subpart A - General Information; B - General Administrative Requirements; C - Technical Requirements, and you look to see those parts that pertain to in this case 300 uses or 400 uses to see if there's anything in the 300 uses that

the monoclonal antibody cannot meet, and you find there's nothing in the 300 uses that the monoclonal antibody use cannot meet. So it fits perfectly into 300, so NRC has not developed any new guidance for the use of monoclonal antibodies, because we consider monoclonal antibodies to be clearly under 300.

Now you look at the microspheres, and you look at the general information, administrative - and you find that there are a few minor parts that would need exemptions because they don't fit exactly in there. And once again, it's because of their very small size, and the fact that you cannot count these things. Well, the leak test is okay because the activity for each seed is well below the leak test limit, so you don't have to do a leak test, so it fits that part of manual brachytherapy. But generally, it is how you count these sources, and how you account for them. You would need an exemption, so it fits over in the 1000 category, and that just supports the idea that this is a 35.1000 use.

And then we developed guidance for the 35.1000 use, and to assure that we have as close to risk-informed performance-based as we can get, we adopt those parts of the regulation that fit this other category without any change, and we say you,

licensee, just need to commit to follow those parts of the regulation, so we tell them in the guidance to commit to following the 35.400 requirements in the A, B, C reports and also in Subpart I think it's F. And then we add additional requirements or relief, as the case may be, to fit this particular device. And that's why we tell the licensee they don't have to count the sources. They can use activity. We try to put other guidance that will be helpful, and unique to this particular type of device. So that's how we get to where we are.

Our conclusion is that the monoclonal antibodies are clearly regulated under Subpart E, Unsealed Byproduct Material, Written Directive Required - no new guidance. We conclude the Yttrium-90 microspheres are regulated pursuant to Subpart K, the medical uses.

Now the major concern was how does the radiation oncologist use the monoclonal antibodies, and the answer is that right now the radiation oncologists can use the monoclonal antibodies, and they use it either by the Board certification route in 35.930 or the alternate pathway in 35.930. And that's because we have essentially taken the alternate pathway for I-131 use and adapted it for every other

type of therapeutic Isotope. So if you required 80 hours of training and experience and three cases for I-131 use, we have by policy said if you're going to use any other therapeutic radio pharmaceuticals under Subpart J, you get 80 hours of training and experience pertaining to that pharmaceutical, and you use three cases pertaining to that Isotope and that pharmaceutical. So that's how we have expanded 300 which has training and experience specifically for I-131 into the Strontium-89, into the Yttrium-90 microsphere, I mean not microspheres but monoclonal antibodies. That's how we've expanded into those new isotopes that are being used for therapy that didn't exist when the original 300 was developed way back in the early 80s.

MEMBER WILLIAMSON: That's in the current Subpart J?

DR. HOWE: The current Subpart J. But the current Subpart J, and I've got the current Subpart J in the backup slides, so you can see the boards that are listed there.

MEMBER DIAMOND: Excuse me, Donna-Beth.

DR. HOWE: Yes.

MEMBER DIAMOND: There's a discrepancy between the slide and the printout. It's Board

certification route in 35.930, and alternate pathway in 35 --

DR. HOWE: No, 930. 390 requires you to --

MEMBER DIAMOND: Here it says 390.

DR. HOWE: Oh, the handout - then I must have made a correction. Sorry. So you need to mark it out.

MEMBER DIAMOND: So it's 930 for both.

DR. HOWE: 930 for both, yes. And the reason it's not 390, is 390 requires 700 hours that are appropriate for therapeutic radio pharmaceuticals only, and it's easier to come through the 80 hours of training than the 700 hours, so most people are coming through this way.

Okay. Now the next question is, were the radiation oncologists qualified to be authorized users under 390. And I can only talk in the public meeting about the proposed rule that is out to the public. I can't talk about what the staff is doing to revise it. And the answer is that for the Board certification route, probably not. It's hard to imagine that the Radiation Oncology Boards that are traditional for radiation oncologists will include 700 hours of classroom and laboratory training in unsealed

byproduct material. Yes.

MEMBER WILLIAMSON: I understand from this morning's closed meeting we can, in fact, discuss predecisional documents in a public meeting. Is that not correct, Tom?

MR. ESSIG: Yes.

DR. HOWE: Can they discuss the specifics of what they've seen that hasn't been distributed to the public? Okay. The staff is working on a solution that would -- let me get to the next slide. On the alternate pathway, probably not, but the staff is working on the solution.

MEMBER NAG: I think here is where we had been talking about the fact that the 700 hours overlaps, and then when you've had 700 hours of overall radiation training, does not require an additional 700 hours of unsealed byproduct training, because most of the body of knowledge is the same, and you just need to apply that knowledge. So I think when you talk about the 700, we do not have to say 700 for sealed product, 700 for unsealed product, and they are separate. They consider the overall radiation safety problem.

DR. HOWE: In the training and experience for the 35.390, it specifically says 700

classroom/laboratory in unsealed byproduct material --

MEMBER NAG: When you --

DR. HOWE: The staff is working on a method that - I can't address it too much, but the staff is working on a method that Roger will talk about tomorrow, that says we recognize this was a problem in the proposed rule, and the staff has worked on the solution, so that was a major concern.

MEMBER WILLIAMSON: Is this the 35.396 rule?

DR. HOWE: Yes, it is.

MEMBER WILLIAMSON: Okay.

DR. HOWE: Yes, it is. Okay. And we can't say what it is?

MEMBER DIAMOND: This is a major issue. We're going to have to go and figure out how we're going to have meaningful conversation on this.

MR. MILLER: We can have discussion on this issue. It's just that we cannot hand out any documents because any documents would be predecisional.

MEMBER WILLIAMSON: Well, I think the whole discussion, including Subir's presentation, would be a lot more meaningful if someone would give a concise summary of what 396 says.

MEMBER NAG: Yes, but could we do it after I give my presentation, because many of the things will overlap in my presentation, so do you want to discuss after that or before that?

DR. HOWE: Do you want me to give an overview of what 396 is?

MR. MILLER: I think Dr. Nag's got a question on the table for the committee.

MEMBER NAG: I'm going to be talking on many of the issues from the clinician standpoint. She's talking from another standpoint, and maybe some of the discussion may take place after both our presentations are made, or do you want to do it before?

CHAIRMAN MALMUD: My preference as Chair would be to have both parties given the opportunity to make their presentations first, and then have a discussion, if that's agreeable with the other members of the committee.

DR. HOWE: They've indicated I can give you a brief synopsis of what's in 396.

CHAIRMAN MALMUD: Please do.

DR. HOWE: Okay. The whole purpose of 396 was to provide a pathway for radiation oncologists to be able to use radio therapeutic drugs. One criteria

is that you already be recognized as an authorized user for 35.400 uses and 600 uses. The second was in case that you were board certified in one of the boards recognized for 35.400 use or 35.600 use, so that's specifically for the radiation oncologists. The nuclear medicine type physicians can come in under 390 and meet those criteria.

The next thing was that the radiation oncologists do need training and experience in unsealed material. And just as Dr. Nag said, do they need the whole 700 hours? The staff didn't think so, so the staff looked at the I-131 training and experience requirements for hours, and for 392 and 394, and said this is probably a good level of additional training and experience, or a block that's in their normal residency training that would cover the unsealed byproduct material, so that was set at 80 hours.

Then we also brought across the three cases, and there's also a preceptor statement that goes with the fact that the person now can function independently in using these materials, and so the whole purpose of 396 was to provide a pathway for the radiation oncologist to continue to use the types of materials that they have been using all along in a

system that's very similar to what they've been coming under previously. Most of them came the alternative pathway, or the board certification, but it's unlikely that the board certification pathways for the radiation oncologists will meet the 700 hours of training and experience that's specified in 390, so this is an alternate pathway to address that issue.

CHAIRMAN MALMUD: Dr. Eggli.

MEMBER EGGLI: The qualifications for that preceptor is that the preceptor has to be Part 3 preceptor.

DR. HOWE: I don't have the rule in front of me, but I think it is someone that comes under 390, because we want to make sure that the radiation oncologist knows the rules and how to do things under 390 for that particular part.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: Now what if the radiation oncologist is the person who is developing some of these new techniques. And that person will not have a preceptor. Basically, he is his own preceptor.

DR. HOWE: You always have the problem of the first person out of the block, but you're looking for a preceptor that has experience with therapeutic drugs, not necessarily that therapeutic drug, but

therapeutic drugs under that category. And if you're the person that's developing it, chances are you're in a big hospital, and there will be somebody there that can do that.

MEMBER EGGLI: Also, aren't these likely to be prior licensed people whose radiation safety -- they just have a little bit more leeway as the first adopters.

DR. HOWE: Yes. The probability of the first one coming through anything under than a broad scope licensee is pretty small - not unheard of, but it should be pretty small, so you've got that built-in mechanism that the Radiation Safety Committee for the broad scope can do a safety evaluation for materials and uses that have not been in existence before.

CHAIRMAN MALMUD: Dr. Howe, for purposes of clarity, may I ask a question based on a concrete example. Let's say that there is a hospital with a broad license that has a radiation therapy department, and a radiology department. And in the radiology department is a section of nuclear medicine. The section of nuclear medicine traditionally has offered I-131 therapy, an unsealed source, for thyroid disease. The radiation oncologists traditionally have not offered that therapy. At this point, the

radiation oncologist wishes to use microspheres.

What will be the steps required by this board certified radiation oncologist, who has perhaps 10 or 20 years of experience in his or her specialty to now provide therapy with microspheres?

DR. HOWE: That was my next one, the microsphere therapy. The microsphere therapy is under 35.1000, and at this particular point we consider that to be manual brachytherapy. And the training and experience criteria for manual brachytherapy are the radiation oncology ones. And your question was for the --

CHAIRMAN MALMUD: For the radiation oncologist to provide that therapy. And you say it's already -- that that therapy would be under the 1000, and that therefore, the radiation oncologist can go ahead and provide that therapy.

DR. HOWE: Yes.

CHAIRMAN MALMUD: Now let's take the other side of the question. How will the nuclear physician or nuclear radiologist be authorized to use microsphere therapy with --

DR. HOWE: Right now our guidance says that we will consider the authorized user to be qualified if they meet the criteria in 35.490 or

35.940. But our guidance also says that this is one way of meeting the criteria in 35.12. The licensee can, if it's a limited specific licensee, they can come in and they can propose someone else. And they can provide their training and experience, and we will evaluate it.

The ACMUI and the public have indicated in the past that they believe that a nuclear medicine physician that comes under the 35.390 route, not the 930 which is the I-131 route, but the 700 hours, the big broad picture with experience in a number of isotopes, and experience in a number of different types of procedures in the therapy should be able to use the microspheres. And so that's right now on a case-by-case basis for the limited specific.

The broad scope licensee is supposed to do an individual safety evaluation for any new uses or new materials, or new uses of existing materials, and we would hope that in their safety evaluation they would do a careful review of who they will be approving, and ensure that they have a broad range of experience in a variety of radiotherapy drugs, and then additional training that is pertinent to the 35.400 use aspects of the microspheres. Because all the rules and regulations that go with the

microspheres are over in the manual brachytherapy side. Things that you may not normally deal with in the 300 side; accountability, additional surveys, a number of different items that are covered in the regulatory space, 400. So our guidance says 490 now, but on an individual basis with extensive training we will consider someone coming through 390.

CHAIRMAN MALMUD: If I may, the use of the term "extensive training" perhaps could be clarified a bit more for us. An experienced nuclear radiologist or nuclear physician who has traditionally offered I-131 therapy for both hyperthyroidism and thyroid cancer, who has occasionally in the past used P-32 therapy for a variety of disorders, now wishes to use the microspheres. What does this board certified experienced physician require by way of additional training in the eyes of the NRC?

DR. HOWE: That's something we evaluate on a case-by-case basis. If the board certification was in an area that they got the additional therapy, not because of the board certification, but because they had the -- came the alternate pathway on the 300 use, they were like a 200 nuclear medicine physician with limited experience in I-131 for hyperthyroidism and thyroid carcinoma, we would probably not approve that

individual until they got additional training in beta microdosimetry, the kinds of things you need to know with this Yttrium-90 microsphere.

CHAIRMAN MALMUD: Even though that physician may have been providing I-131 therapy on a regular weekly basis to hundreds of patients over the past decade?

DR. HOWE: The Yttrium-90 microspheres are not the same as I-131.

CHAIRMAN MALMUD: I understand that.

DR. HOWE: And it's those differences that we're concerned about in the training and experience.

CHAIRMAN MALMUD: So getting back to the practical follow-up of my question which I'm trying to clarify for the committee, what would such a physician, a nuclear radiologist require in addition to the board certification, the training in both therapeutic and diagnostic uses of isotopes that were given prior to his board certification, or her board certification, and a decade or so of experience with hundreds of cases treated with either P-32 or with I-131. And where would that -- who would give that training? Where would it come from?

Traditionally, new therapies are learned, as you pointed out earlier, on a case-by-case basis,

and then the physician gets approval to use these through the hospital and it's own mechanism for assuring patient safety. What would the NRC require by way of additional training for this experienced physician beyond that which he or she already has; numbers of hours?

DR. HOWE: We don't put numbers of hours on things, because it's based on the individual, and that's something we've heard from the medical community many times, is that numbers of hours is not the right way to go. So it's more topics and concepts, and so we would look for their training and experience in the topics and concepts that are listed in 490 that pertain to the use of the microspheres. And those are different than those -- some of the topics are the same in 390, some are different.

There are physicians out there that are authorized users now in Yttrium-90, so we aren't faced with a case of the very first physician, so there are individuals that have experience in Yttrium microspheres, and are authorized users that can be used to help provide training either through vendor organized training sessions or other means. So there is the ability for an experienced Yttrium-90 microsphere person to provide training for --

CHAIRMAN MALMUD: Rather than pursuing my questioning, I see we've now stimulated some questions from other members of the committee. Dr. Eggli.

MEMBER EGGLI: I think that radioactive iodine may be the wrong model to look at from the 390 users. In fact, P-32 chromic phosphate, which is a small particle pure beta emitter, which is used routinely as part of 390 therapy may be a better model for evaluating the ability of a physician certified under Part 390 to do 300 therapies to look at that kind of experience as more similar to the microsphere experience, and look at the amount of experience the individual has handling this particulate beta emitter as some evidence of experience with a similar type of treatment source. And I think I-131 is the wrong comparison to make. I think particulate P-32 is a more relevant comparison.

CHAIRMAN MALMUD: Thank you, Dr. Eggli. Dr. Nag.

MEMBER NAG: Yes, I think the point I would like to make is that for the Yttrium therapy, there are two components. One is what is required in terms of the physical injection and the radiation safety and the spillage and so forth. That, I think, is probably easier to be done. But the second aspect

is that the person who is taking charge of the Yttrium therapy has to have the knowledge of what is liver cancer, how that liver cancer spread. It's not just a matter of putting some radioactive material into a tumor unless you know the behavior of the cancer. So I think it requires both the knowledge of the cancer, and how much radiation can be given. It's not just a matter of injecting 2 millicuries or 3 millicuries, because to be able to control that you need to know when to stop. Should I stop after giving one gigabecquerels or should I go on to 2 gigabecquerels. So I think that's where this extra training that she's talking about comes in. It's not that well, I know how to handle iodine, and I know how to handle the radiation safety part of that, but in addition you have to know where does the cancer go. When you have a backflow, does it backflow to the stomach? Do you have a shunt into the lung and so forth? I think that's the additional training that needs to be there for someone to be practically using the Yttrium microspheres.

CHAIRMAN MALMUD: Dr. Diamond.

MEMBER DIAMOND: Subir was starting to get a little bit into the practice of medicine, and I think that would be useful. We may have a little bit

of a non sequitur. Perhaps it would have been useful if Subir had done his presentation first, but I just want to be very clear on a couple of points.

Let's first direct ourselves to microsphere therapy. Microsphere therapy, Donna, if I understand you correctly, will fall into a 35.1000 use because of the reasons you described.

DR. HOWE: Yes.

MEMBER DIAMOND: And the training and experience that will guide AU status for that will be 35.490 or 35.940. Is that correct?

DR. HOWE: Yes.

MEMBER DIAMOND: Okay. With respect to radio immuno therapy, that will be considered a 35.390 use.

DR. HOWE: A 35.300 use.

MEMBER DIAMOND: 35.300 use, and for the radiation oncologist to qualify, it will either be a board certification or alternate pathway under 35.930.

DR. HOWE: Right now it's under --

MEMBER DIAMOND: Right now.

DR. HOWE: -- 35.930, but when Subpart J disappears, that pathway won't be available any more.

MEMBER DIAMOND: Right. And then you're invoking that this would fall under 35.396.

DR. HOWE: Yes.

MEMBER DIAMOND: Okay. Now in this 35.396 rule, there would be an alternate pathway for radiation oncologists which would require the 80 hours of laboratory and classroom, plus the three cases. Is that what you said?

DR. HOWE: Yes.

MEMBER DIAMOND: Plus the attestation. Is that correct?

DR. HOWE: Yes.

MEMBER DIAMOND: Now in addition to that alternate pathway, my question to you is, for the radiation oncology residents who are in training programs, recognized training programs, when they go to take their boards, hopefully pass their boards, at that point that they receive board certification, will that in and of itself qualify them to use radio immuno therapy or not?

DR. HOWE: No.

MEMBER DIAMOND: Okay. Therein lies the problem.

DR. HOWE: And that's something that the rule language working group can work on, is that the board certification for the radiation oncologist most probably will not meet the criteria in 390, and that's

the route that has the board certification.

MEMBER DIAMOND: So, for example, right now the chromic P-32 is also a 390 use. Correct?

DR. HOWE: Yes.

MEMBER DIAMOND: Radiation oncologists traditionally have been using that, as well.

DR. HOWE: And they come through the -- there are some boards that the radiation oncologists have that are listed under 930, and then the alternate pathway is the 80 hours and the three cases that we have by policy adapted to all the other therapy isotopes that are coming down the line, and not just I-131. So they're coming basically through the Subpart J path.

MEMBER DIAMOND: Okay. So as a pragmatic issue, what I want to be clear upon is that those residents coming through training who take their boards and pass their boards, will de facto have the opportunity to deliver these radioactive materials as long as they have those three cases essentially. Is that correct?

DR. HOWE: If their board is listed in Subpart J right now.

MEMBER DIAMOND: The American Board of Radiology, for example. Okay.

DR. HOWE: It's listed in Subpart J. That's true.

MEMBER DIAMOND: All right. That's the pragmatic issue. The other issue is a issue that Dr. Malmud has raised a number of times, which is this definition of how the 700 hours classroom and laboratory training is actually enumerated, because I would still go back and argue the same case as Dr. Malmud, which is, I believe the way that you are accounting for those hours is not the same as the way we would account for those hours, recognizing how there is overlap in the different radio nuclide experience and understanding of these properties.

DR. HOWE: I think the point is that we recognize that in your three years of residency, you get --

MEMBER DIAMOND: Four years.

DR. HOWE: Four years, you get a tremendous amount of radiation safety, use of materials. The focus is probably more on the sealed sources and the devices, and the question in the regulations is, are there enough hours in there on unsealed material? And would the residency move to 700 hours in unsealed materials? And the answer is probably no.

MEMBER DIAMOND: See, the other issue is that these training programs are not monolithic. There's tremendous disparity on what an individual resident's experience is. For example, where I happened to train in St. Louis, we actually divvied it up so that the diagnostic isotopes were delivered by the nuclear medicine physicians, and all the therapeutic uses were delivered -- therapeutic for cancer, excuse me.

MEMBER WILLIAMSON: Yes. Benign versus malignant.

MEMBER DIAMOND: Yes, that's a better way - malignant indications were done by us. So with our particular experience, we had huge experiences in the use of I-131 for thyroid cancer, P-32 for malignant uses, Strontium-89 for malignant uses, so someone coming through that training program would easily meet, I think, your 700 hours.

DR. HOWE: The question is whether the board for 390 requires 700 of unsealed material. And if the board doesn't require 700 of unsealed material, then -- your program has it, and so you can use what you had in your program to come under 396, and say in my residency training I had way in excess of 80 hours in unsealed material.

MEMBER DIAMOND: Still, you'd have to go through the alternate pathway.

DR. HOWE: You may decide that there's a possibility there's a board that requires that of its board certification members, and they suggest maybe there would be a straight board route.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: Yes. I think this is what the 700 hours is being misinterpreted, I think. When someone has gone for four years of training, and has had more than 700 hours of overall therapy training, you can extend many of those into unsealed versus sealed, so that you don't need any of the 700 hours. That's the point I was trying to get across.

The direct question I have for you is a question similar to Dr. Malmud, and that would be if a board certified radiation oncologist is now going to do radio immuno therapy, having done iodine therapy and other therapies, now want to do radio immuno therapy, what other training would he or she need, or would he need any further therapy?

DR. HOWE: For the existing radiation oncologist, then NRC looks at 930, and they look at the -- they either look at the board certification or they look at the alternate pathway. And the alternate

pathway says you have 80 hours of training and experience in unsealed material requiring a written directive, and you have three cases. So the NRC license reviewer is going to say have you done three cases in radiation therapy, because you're applying for say metestrum or you're applying for monoclonal antibody, and you worked under the supervision of an authorized user to get your three cases, then NRC is going to look at that and say okay, we're going to apply the same criteria to you that we apply in 932 and 934, but specifically for those isotopes. And yes, you meet it, so we'll list you as an authorized user for 390, 300 materials and we may specify excluding I-131 or whatever based on what your training is and your three cases. So we look at that and we say yes, and that's what we do right now, is we go over to the Subpart J and we say yes.

MEMBER WILLIAMSON: So your 396 is intended to be a reincarnation of that Subpart J pathway in the revised regulation.

DR. HOWE: Yes.

MEMBER WILLIAMSON: So actually, the procedure wouldn't change for most radiation oncologists.

DR. HOWE: Yes. And if you believed there

was a board that would require you to have the minimum hours of unsealed byproduct material needing a written directive, that could be added to 396 too.

MEMBER DIAMOND: So extant radiation oncologists, extant board certified radiation oncologists, would they be grandfathered for all these uses, or would they have to actually go and get those --

DR. HOWE: The existing radiation oncologists that have the authorization to use therapeutic radiopharmaceuticals are grandfathered. We're talking about the future radiation oncologists.

MEMBER DIAMOND: Right. That's what I wanted to be clear upon.

DR. HOLAHAN: May I say something? This is Patricia Holahan.

CHAIRMAN MALMUD: Patricia.

DR. HOLAHAN: I'm getting back to Dr. Diamond's question. What you would have to do going through that residency program as you specified, you'd have the unsealed material, but you'd have to verify it through the preceptor, so you'd have to basically submit a preceptor statement only, not do the additional 80 hours.

DR. HOWE: The idea is that you probably

had 80 hours, and then you just -- you get the preceptor to say that you had the 80 hours, and that you have the three cases in the type of material used, because there are two different categories there.

MEMBER DIAMOND: I understand.

CHAIRMAN MALMUD: Are there any other questions on this point for Dr. Howe before -- I think we interrupted your presentation.

DR. HOWE: I think I was very close to the end, and there was probably -- let me see. Here's the radiation oncology for 1000, and I've already said that was 490 and 940. And the next was the background which you just gave for the regulations as they exist right now, so I think --

CHAIRMAN MALMUD: I believe there was one more question.

MEMBER BAILEY: Yes. Presumably, you would continue the practice if they have been named for that study on any license, and they have essentially demonstrated that they are qualified to do it. For example, right now we are -- several states are probably not following exactly what NRC has for the necessary training and experience, and if they were say on a California license, and they moved to an NRC state, would they still be eligible? Would they

have to go back and prove that they're capable of doing it after they've been doing it for three, four, or five years?

DR. HOWE: With the exception of a few places where there's probably oversight, I think in most cases we say or equivalent agreement state. We haven't hit that yet, but I think we would.

MEMBER BAILEY: Okay. And the other part is that when you talk about the additional training, you're talking about radiation safety training only. Correct?

DR. HOWE: Yes, because if you look at the items that are listed, they are radiation safety items.

MEMBER BAILEY: And not --

DR. HOWE: But you will see because it's therapy, there are clinical cases because the clinical cases have to cover radiation safety topics because when the new Part 35 was being developed, there was a recognition for therapy, you had to have a minimum clinical experience. That was part of the overall radiation safety for the patient, user, the workers.

CHAIRMAN MALMUD: Dr. Williamson.

MEMBER WILLIAMSON: This issue of the relationship of -- or the issue of safety only versus

safety plus clinical for 300 has been raised now many times over the last few meetings. I think it would be worthwhile to dig out the Statements of Consideration for the current regulation and determine whether ACMUI's memory is correct. But I know that the consensus was, when we were debating the basis of the current regulation, that a certain amount of clinical experience and expertise, not just safety, is essential to promote public health and safety for 35.300 modality.

DR. HOWE: That's how I --

MEMBER WILLIAMSON: And below that, the consensus was reached that it could be strictly defined in terms of technical safety issues, but at 300 and above, clinical expertise was considered to be an important component.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: Yes, I would like to put this off until I have made my presentation, because I'm going to be asking and addressing, perhaps more than addressing, asking some of these things.

CHAIRMAN MALMUD: Thank you. If I may --

MEMBER DIAMOND: Excuse me. I just have one more quick question. What about nuclear medicine residents who are at institutions where although they

have the 700 hours of laboratory and classroom experience, may not have delivered or may not have been proctored on three cases, for example, at Wash U where the nuclear medicine residents may not have had any experience. Do they also have a mechanism through the alternate pathway getting AU status?

DR. HOWE: Yes. One of the things that the working group was tasked with doing was to separate out the clinical experience from the boards. That was part of your question, that these folks now have -- meet the qualifications to sit for the boards. Well, part of what the working group did was to split out the clinical experience from the board certification. And so you have this route, board with three cases, alternate pathway with three cases. And it may be that you come in and are an authorized user for certain isotopes and certain therapies because you don't have the case experience. And then later new isotopes come up and you get the case experience in those. You come back in and ask for increase in your authorization, and it's granted because you have the additional training and experience that's gained later on. It's an ongoing evolving type of training and experience.

CHAIRMAN MALMUD: Does that answer your

question, Dr. Diamond?

MEMBER DIAMOND: It does.

CHAIRMAN MALMUD: Thank you. Dr. Howe, you mentioned one thing earlier that I picked up but didn't ask you about. You mentioned vendor training.

DR. HOWE: Yes.

CHAIRMAN MALMUD: Would you care to elaborate about that at all, or shall I ask you a specific question about the vendor training?

DR. HOWE: We normally assume that the vendor knows more about their device or drug than anyone else, at least in the early stages until it can get into the routine training, residency programs or other medical practice, so we generally look for that vendor training as an important concept.

CHAIRMAN MALMUD: The vendor training traditionally has been clinically oriented. I would assume that the vendor training for an issue such as radio immuno therapy for board certified physicians who have not done it previously or for microsphere therapy for physicians who have not done it previously, should include some radiation protection and radiation safety issues and dosimetry issues as part of the vendor training, which is really the concern of the NRC, rather than the clinical training,

which we assume was not a direct concern of our's. I would hope that the vendors are aware that this is what they should be providing in the course of their educational process for those who are new to either of these two therapies, regardless of the specialty, the board certification that the physician may have by way of background.

DR. HOWE: We don't have as much interaction with say the monoclonal antibodies because they're currently under 300, and so we would not be providing additional guidance on vendor training. We hope that the community will get the training it needs on these new products. But for the 1000 uses, we generally work pretty closely with the manufacturers in understanding their product, developing -- we develop the guidance and we stay in communication with them, and they many times will develop their training to cover the areas that we are specifically addressing in the guidance, so they do address radiation safety issues, in addition to the clinical.

CHAIRMAN MALMUD: Thank you. I saw another hand. Dr. Eggli.

MEMBER EGGLI: In relationship to the vendor training, how does one document that experience since most of these vendors are not going to be

authorized users and can't officially preceptor that activity.

DR. HOWE: I think the working group for developing the new rule has provided some more global language that says for some of these new modalities they have vendor training, or they can obtain training under the supervision of an authorized user, organized microphysicist, or whoever would be appropriate. And the implication there is that your preceptor is a verifier, not necessarily a provider. And that the vendor -- what it says you may meet these by getting vendor training or under the supervision of someone. The vendor training has no specificity on who provides it. Roger Broseus.

DR. BROSEUS: Dr. Malmud, may I be recognized?

CHAIRMAN MALMUD: Yes.

DR. BROSEUS: Roger Broseus. You raised this issue at a previous meeting, and the way the staff is approaching this in the draft final rule is to accept the recommended worded of the ACMUI and include in the definition of a preceptor in 35.2 a person who verifies training and experience, which captures -- so that makes it so that the person who is precepting can verify that a person -- that a

candidate as AU has the training even though that person didn't personally deliver the training, and it would encompass the vendor training.

CHAIRMAN MALMUD: Thank you, Dr. Broseus. This is not meant to generate a response, but it's simply a thought that occurred to me during this discussion; and that is that given the availability now of interactive self-education with documentation of having completed an exam regarding a course on a CD, it would probably be wise for vendors to provide such a course, which is inclusive of both the clinical and physics aspects of their therapies so that there could be permanent documentation that this was, in fact, learned by the new practitioner, or the practitioner of this new therapy. That wasn't meant to generate a response from you, because it's just out of the blue. But certainly, it could be the form of documentation that seems to be missing from the vendor educational process.

MEMBER DIAMOND: One last thing. Is the NRC aware that there's a whole new class of targeted therapy that is around the horizon which is not technically considered radio immuno therapy? For example, this week at our institution, we are going to be starting a trial for brain tumor patients, which

involves a Scorpion venom chelated to I-131. Now in radio immuno therapy you have a cancer cell with an antigen, and you have a lauding which is an antibody chelated to a radioisotope. In this particular new class of targeted therapy, it's actually a protein sequence that's being recognized, so it's not radio immuno therapy, it's targeted radiotherapy, it's targeted unsealed radiotherapy, but it's not radio immuno therapy. This may be a situation, thus, that the technology is advancing more rapidly than the regulatory space.

DR. HOWE: But I would say that if you go back and look at what you're proposing in your clinical trials, and you look at our regulatory framework for 300 use, you may find that our regulatory framework for 300 use fits the radiation safety of your new product. In other words, there's nothing magical about radio immuno therapy. It could have some other name, it could be something slightly different, but if it is covered in our regulatory framework by 300 and the general requirements that go with 300, therapy of unsealed materials, then it may be new to you, but we may not have --

MEMBER DIAMOND: But it all gets back to how the regulations are written. If in the language

of the regulation it has that immuno --

DR. HOWE: Our regulations don't say immuno. They just say unsealed byproduct material requiring a written directive. And actually, your drug will come under - when you go under 390, you've got I-131 less than value, I-131 greater than a value, and then you've got the other routes of administration and a very global description of what those isotopes are. I'm going to guess it's going to come under that last two groups, and they will be already covered by a regulatory frame.

And that was what I was trying to say in the beginning; it may new to you, it may be new to medicine, but we may already have an existing regulatory frame that it fits in, and we don't have to develop any new guidance for it. The structure is probably already there, just from your description. I mean, its medical implications and its practice of medicine issues are brand new, but from our particular radiation safety regulatory framework, it may already be covered.

CHAIRMAN MALMUD: Dr. Eggli, did you wish to make a comment?

MEMBER EGGLI: No. I think I'm inclined to agree that it sounds like it would be a Part 300 use,

as described.

CHAIRMAN MALMUD: Ralph.

MEMBER LIETO: That's what I wanted to get to earlier. When Dr. Eggli made an earlier point about P-32 and being a better analogy for the microspheres, we have had a structure dealing with microspheres in nuclear medicine that goes back decades. Okay. It was in the diagnostic applications, but it's been there. I guess, to me, the big problem here has been with the microspheres being classified as a device, and that gets back to the FDA process, which I think maybe we might need some clarification there. But just as you said, if we look at just the radiation safety implications, and the fact that you've already said that these are sealed sources but are exempt or are not going to have to meet the leak testing requirements, then I think you can make a very, very strong case that the microspheres are more accurately, from a radiation safety consideration, is better handled under the 390. And I think that we need to consider that and not just accept the 490 period, and just they're exempt from the leak testing requirements, because if you look at the 400 requirements, if you take out all these leak testing requirements, the precaution -- they're not

any different than the 300s. So I would go back and say that the microspheres, that you can make a very strong case again for them being classified under the 300 applications.

DR. HOWE: I think Dr. Nag would like to give his presentation.

CHAIRMAN MALMUD: Have you completed your presentation, Dr. Howe?

DR. HOWE: I have completed my presentation.

MEMBER LIETO: Let me clarify on the device/drug issue. FDA has some new laws regarding combination products, and the issue of Yttrium-90 I think right now is a device, but I think the safety issues -- right now, this is where we're at, but I think as more therapeutics get developed, I think you're going to see other issues come to the table. So I think you may want to maintain some flexibility, and in some ways Yttrium-90, it's got a dual characteristic. You can't say it's a device --

MEMBER DIAMOND: And also in FDA's defense, it was the manufacturer that made the conscious decision to go through the device pathway, not the drug pathway. That was their decision.

MEMBER LIETO: Correct.

DR. HOWE: But it's also -- the way the Yttrium is put into the matrix, it has no pharmacological activity. The Yttrium is sealed and contained in the matrix. It doesn't leech out and the microspheres don't go to where they're going to because of pharmacological activity, where your Scorpion proteins do go to a set location because the receptor concept and your monoclonal antibodies go to a receptor because of their interaction, their pharmacological activity. That's the major basis for the drugs to the devices is in a pharmacological --

MEMBER SULEIMAN: Well, you've got to be careful. I think the science may not be - somebody said it - I think the regulatory bounds may be behind the science, and I think from what I've see recently, the science isn't that definitive either. We have a lot of people making all sorts of claims. You're seeing new nanotechnologies where as the particles get smaller and smaller, you really cannot say it's a physical object or how the mechanisms are drug related, or biologics are considered a drug. We have that debate going on within the agency, so I think keeping an open mind, and I think I can promise you that this issue is probably not going to rest here.

CHAIRMAN MALMUD: Thank you, Dr. Suleiman.

Dr. Eggli.

MEMBER EGGLI: With that analogy, Sulfurcholate administered intra-arterially is a device because it is delivered purely by its flow properties. It is biologically inert, and it in fact is the material used for the dosimetry for Yttrium-90 microspheres. So the distinctions are very blurred, and again I guess Ralph and I are sort of reinforcing each other, but there is huge cross-over here. And again, I think the P-32 colloid is a very model in the 300 series therapies to effectively describe what these microspheres do. And I think it may be appropriate to look at them from two frames of reference, eliminating the inconsistent portions of each part since, in fact, these microspheres do leak.

CHAIRMAN MALMUD: Thank you for your observations, Dr. Eggli. And Dr. Howe, may we thank you once again. You find yourself at the crossroads of rapidly advancing science and regulations, and are always a source of great stimulation to this committee. We thank you for the depth of your knowledge, and for your patience, as well. Thank you. Now Dr. Nag.

MEMBER NAG: Thank you very much. What I wanted to do was to give some brief background, some

of my thoughts, not only on the Yttrium-90, but some of the new things that are either there or on the horizon, and what the problems it will create and so on.

Now the Yttrium-90, we have been talking about that, but some of us may or may not know some of the details of how it goes on. And I think a little of that knowledge is required to understand how we should regulate that, because the Yttrium-90 microsphere, tiny microspheres that are suspended in a solution, and that are injected into the liver via the hepatic artery, so interventional radiologists will do an angiogram, and then we will inject the microsphere into the hepatic artery. And Yttrium-90, most of you know, is a high energy emitter with a very short range in the tissue. And because of the short half-life, most of the radiation is denigrated in about 10 or 11 days.

There are two different kinds. One is the SIR-Sphere by the Sirtex Company. The other is the Therasphere by MDS. The two have different properties and, therefore, will be important in the regulations, because although both are Yttrium-90, they do have entirely different properties.

The two that we are talking about is the

glass microspheres by Therasphere, used mainly for hepatocellinar carcinoma. The glass microspheres are somewhat heavier. They tend to settle down, and not go as much forward. The resin microspheres are smaller particles and they tend to be more free-floating and, therefore, they tend to go forward, and they are used more in the colo-rectal ones.

The SIR-spheres, which I'm more involved with and they are FDA approved, they are kept in a vial of three gigabecquerels, so they will always ship you three gigabecquerels and you decide how much of that you would use. Raising about 20 to 60 microns, and they're about 40 to 80 million resins. And the average number that we implant is about two-thirds of that in most cases.

Now what we do, we are infusing that into the hepatic artery so that the catheter is placed into the hepatic artery, selectively if possible either to that lobe and, therefore, we are injecting into the entire lobe, or sometimes super-selectively into a part of the lobe. Usually, we are not infusing the whole liver at the time. We are usually doing one lobe at a time. And, therefore, the microsphere will go into the vessel and then they are stuck in the smaller vessel. Once the vessel has about 25 to 75

microns, then the sphere will then embolize. Basically, you have two functions. One is the embolization function where the blood flow is dark, and then it is also radiating at the same time, so you have to know about this combined embolization effect and the radiation effect, because as you are embolizing, you are stopping the blood vessel, and then the microsphere cannot go any further, so you have a harder time injecting all the microsphere you want at some point. So as you can see, the liver vasculature, they become very small. And the smaller vessel will now become totally embolized and no further particle will go into it.

So the technical part of injection is somewhat simpler because you just have stopper you're injecting. At one time you're injecting the contrast to see where the flow is going. You are then injecting the microsphere in water to push the microsphere to the place you want, and then you inject more water to separate it from any contrast material. Then you inject more contrast where you going. So the technical part of the injection is reasonably simple but the thing is when you -- how much do you push, when do you stop, and then you have the radiation safety considerations that we'll talk about; which is,

what happens if these particles leak out or if there is a leakage or spillage? So you're injecting it in pulses each time, and when the microspheres are denigrated, you're having embolism of the vessel so no further particle will go in. And, therefore, you're going to have stasis. So let's say at the beginning, we decide to do two gigabecquerels, but if you're having stasis after doing half of it, you have to stop, or you cannot really complete your therapy, so then you can modify and say we now have stasis. We can't give any more.

The sum of the radiation safety considerations are that if there's an encapsulated isotope, although they are very, very tiny, they are encapsulated. But functionally, they function like a suspended liquid, so it's more like an unsealed source in that respect that you have commented upon. But the radiation exposure itself is minimal if it is contained. But if it is spilled, then you have the problem of containing that radiation spillage. So, therefore, stasis is an end-point, and more often from what I have done, I have had to end because of the stasis, rather than because I have given the entire two or three gigabecquerels that I wanted to. So we have to have the stasis built into the directive. So

these are some of my thoughts on this.

The vendors do give you training. The training includes both radiation safety aspect, and more of it is how to inject and what to do in case of a spillage. That's the major training that we do have. The major consideration I think you need to do is not just the technical aspect of how to inject, but who do you inject, how do you select the patient for that? And those part of the training need to be built into anybody who is going to do Yttrium microsphere therapy; although I realize the medical training part is not an NRC issue, but the safety -- because you can just inject the 3 millicurie or 3 gigabecquerel and not know what's going to happen to the liver. The liver might liquify if you're in excess. Yes, go ahead.

CHAIRMAN MALMUD: Dr. Nag, how is stasis determined?

MEMBER NAG: When you are injecting, you look for, number one, if you're having difficulty pushing, that's one indication that you may be achieving stasis, but the formal way to see it is you then inject some contrast and you see whether the contrast is flowing forward or if the contrast is having a backflow, or the contrast is not going at

all.

CHAIRMAN MALMUD: In practical terms, is this done an interventional radiologist, or by a radiation oncologist?

MEMBER NAG: It is done by a radiation oncologist in my place. I know in some other places it's done by either by the interventional radiologist or in some places by nuclear medicine too. I'm not sure --

MEMBER DIAMOND: Well, actually, it's the radiation oncologist who's been the AU.

MEMBER NAG: Yes.

MEMBER DIAMOND: I mean, the catherization has been done by interventional radiologists.

MEMBER NAG: Yes. The catheter will be placed by the interventional radiologist. Once he puts the catheter into the site I want, whether it be the left or the right hepatic artery, or the main hepatic artery, we decide and we tell them where we want it, then we take over and we start injecting the radioactive material.

MEMBER DIAMOND: And if I may, the issue of stasis is therefore determined not by the interventional radiologist, but by either the radiation oncologist or nuclear physician who is doing

the administration?

MEMBER NAG: Whoever is doing the injection. I mean, if it's done by the radiation oncologist, we do it. Sometimes we may ask the help of the interventional radiologist, do you think it's going forward, or do you think we can push any more?

MEMBER DIAMOND: It's actually quite a little art with back and forth as you do these, particularly with these super-selective cases. You can actually get a feel on these catheters, and get a sense of the resistance, and almost get a -- just like an experienced interventional cardiologist can kind of feel the guiding catheter.

CHAIRMAN MALMUD: Perhaps I'm not being specific enough, and I'll try and be more specific. Is the -- I understand that the placement of the catheter is done by an interventional radiologist.

MEMBER NAG: Yes.

CHAIRMAN MALMUD: That's that person's expertise. Is the injection done in the interventional room, or is it done in a radiotherapy room?

MEMBER NAG: No, it has to be done in the same place where the interventional catheter is in place, because you don't want the catheter to move.

You have the fluoroscopy, so it is done in the interventional radiology suite.

CHAIRMAN MALMUD: So this is a conjoint effort of interventional radiology and a specialist in radioisotopes or radiation oncology.

MEMBER NAG: Right.

CHAIRMAN MALMUD: Thank you.

MEMBER NAG: You had a question.

DR. HOWE: Could I just clarify?

CHAIRMAN MALMUD: Please do. Dr. Howe.

DR. HOWE: I'd just like to clarify that we recognize that stasis was probably the best end-point, and so when we modified the guidance for the Yttrium-90 microspheres about a year ago, and we added stasis as an option for the authorized user to write into the written directive in advance of providing the material, so that it would be clear that if they stopped the injection based on stasis, we weren't looking at medical events. This was the best end-point, so we have included that in our guidance for the written directive.

MEMBER NAG: Yes.

CHAIRMAN MALMUD: Thank you, Dr. Howe. Dr. Williamson.

MEMBER WILLIAMSON: Yes. Are the SIR-

spheres regulated also as a sealed source?

MEMBER NAG: Yes.

CHAIRMAN MALMUD: The answer to Dr. Williamson's question was yes, from Dr. Howe.

MEMBER NAG: Now I'm not going to say very much about the antibody therapy since Donna covered that very well. I had intended to, but I will skip over those things. I want to introduce something called pulse dose rate. Many of you may be aware, some of you may not. The reason why I want to introduce this is it's a different method that has some regulation problem. I want to give a brief overview as to why it is being introduced, and it is a remote afterloader.

Now in a way, it is very similar to the HDR afterloader. The difference being that in the HDR you have a 10 curie source. Here you have a one curie source. And what the pulse dose does is instead of giving radiation at the high dose rate continuously for 10, 15 minutes, it brings more pulse dose radiation for a few minutes every hour. The traditional one is every hour. There have been other modified versions of doing it for three hours, then off for a few hours and so on, but the traditional one is giving pulses of radiation usually at about 50 to

100 Centigrade in about ten minutes within that first part of the hour. And then, the rest of the 50 minutes there's no radiation, so that allows personnel to get in, look at the patient, do all the nursing care without any radiation exposure hazard. And then you can vary the length of the pulse and the time and so on, so that the -- many of the characteristics are like HDR, many of the advantages of HDR, but because you are giving a small dose per hour, usually about 50 Centigrade, the radiobiology is more like a low dose rate radiotherapy. And the source itself is a lower activity, usually about 0.5 to 1 curie, so if you are doing it, the low dose rate is continuous at the low dose rate over a few days, two to five days. High dose rate, you're giving very high doses for the short period of time, usually once a day or twice a day. But in pulse dose rate you are giving a small amount of dose, impulsing every hour or so over a period of a few days. So these are the basic differences between the two.

What are some of the advantages? Why do you want to do it? Because you have only one Iridium source. You don't have to have multiple Iridium source that you have to take care of. The major thing is that you are having minimal risk of exposure to the

personnel. You are eliminating the radiation exposure hazard, and at the same time, you are having the radiobiological advantage of low dose rate brachytherapy.

Some of the problems that you are going to need a few days to deliver the radiation and, therefore, the patient has to be in the hospital for those days; and, therefore, you have some of the problems of prolonged bedrest and so on. There's the potential movement of the basin during those two or three days, and there is the potential that by the patient moving, you may kink the catheter or the applicator and, therefore, the source may have a hard time either going in or coming back.

There are some radiobiological issues - is 50 Centigrade delivered in a few minutes every hour the same as a continuous 50 Centigrade power. Some of those things may have to be continued to be explored, but the radiation safety consideration of that - the source activity is much lower than HDR, about one-tenth. And, therefore, there is less shielding requirement. Now the question is for the HDR do you need to have the physical plantings of an authorized user and physicist during the whole therapy. Here, the therapy is for a few minutes every hour, which

means from a practical standpoint, you would need a physicist and/or an authorized user in the patient's room continuously for two or three days. That's not really very practical, and some of these considerations will have to be thought about. The reason why the part dose rate concept has come up, it has been around for quite a number of years, but because of the radiation safety consideration, it has not come up very much in U.S., but it is gaining a lot of importance in Europe. And, therefore, many people in the U.S. are thinking of taking it back again, especially those who are not very comfortable using HDR because of the radiobiology, and are comfortable with LDR, but at the same time, they like the radiation -- elimination of radiation hazard that the HDR produces.

CHAIRMAN MALMUD: Dr. Williamson.

MEMBER WILLIAMSON: Well, as I recall, a great effort was made to craft 35.600 to make it practical to license pulsed dose rate. It is mentioned specifically in 35.600, and not all the HDR regulations apply exactly to it. I don't know that anybody has ever submitted an amendment for it to really test how well that regulation works, but an effort was made to basically make it practical to use.

MEMBER NAG: The reason I brought this up is so that the NRC is aware - I mean, once you are getting a floodgate of all the applications of people who are planning PDR you want to be prepared for it, so I wanted to give you a head's up. I'm not saying we have any solution. I'm asking to be prepared for it.

CHAIRMAN MALMUD: Thank you for bringing the matter to our attention and educating us, especially those of us who are not familiar with the issue. Are there any other comments to Dr. Nag regarding this presentation?

MEMBER NAG: Now I want to go on to the next one, which is again - we are getting a lot of these combos. Now we are going to be talking about I-125 afterload, and this is something that has been presented here before. We had asked it to be at this meeting because of some of the regulation issues. The I-125 afterloader basically is very similar to the way we do our manual prostate brachytherapy, in that it is I-125 seeds that are implanted into the patient. And what I want to do is show how it is somewhat different from the manual prostate brachytherapy. But because it is termed a remote afterloader, many of the regulatory issues of the remote afterloader for HDR is

sort of mixed with this, so I would like to present it so you have an idea what it is.

Basically, you are having all the seeds now in a sterile cartridge that is shielded, so now you don't have the issue of handling a new seed, so the seeds are in one cartridge that cannot be opened. It's a fixed cartridge, so to some extent there's some safety in that, that the seeds cannot get loose. You cannot have seeds dropped on the floor and so on.

You have one cartridge that will have all seeds. You have another cartridge that has all spacers. So in prostate brachytherapy, what you do is you put one seed, one spacer, one seed, one spacer. This will allow you to make your seed spacer assembly in the OR, so if in the OR you do the prostate ultrasound and you plan that you want seed-spacer, spacer-seed, seed-spacer, or any combination, you can make it up in the OR in real time. And then the afterloader has its calibration the capacity to recognize whether what you planned is what is in that assembly.

For example, although it will not calibrate the source directly, it will tell you whether you're having a source at this position, or a spacer. So if you had source-spacer, source-spacer,

and the one that is going in is to confirm that this was the assembly as you had planned. So there is some amount of verification built into it.

The other difference is that normally at this point, I would manually push the radioactive seed spacer in manually. Here the afterloader pushes that grain into the basin and force the needle out. So, therefore, it is a remote afterloader, but the activity of the seeds are extremely low and, therefore, it doesn't require any shielding. So the radiation precautions are very much less compared to HDR; although, because it's a remote afterloader, many of the things that are required for HDR are placed into a I-125 afterloader. And I think that will become burdensome, and will prevent or it will discourage some of the users from using it because they have to meet a lot of the regulations that probably are not totally appropriate for this.

It does have computer verification of seed basin. You do want to know whether what you had planned is what is going in. You do want to be able to confirm that the needle is going to the place you wanted it to go, and the afterloader does that. The other difference is that in a regular remote afterloader, you want to confirm that the source that

went into the patient comes back into the remote afterloader. Here, the source going into the afterloader, but does not come back from the patient. It's permanently implanted in the patient. So these are, from my standpoint, some of the safety considerations. We may need some discussion as to the way the regulations are written at the moment in an attempt place an over-burden on the licensee, because many of them may not apply.

CHAIRMAN MALMUD: Dr. Williamson.

MEMBER WILLIAMSON: I think Dr. Nag is exactly right, that this is low dose rate permanent seed implant, and the regulations should be written, additional regulatory burdens should be very minimalist in the sense of only addressing the unique technical characteristics of this machine, and not impose any additional regulatory burdens beyond those in 35.400 for permanent seed implants. There's no need for the prescription to be any different. There's no need for a facility diagram, because this is not a high dose. You don't require that for permanent seed implant, so I do think that at least the second iteration of the guidance that I reviewed seemed to me to be too -- overly influenced by the existing HDR remote afterloader regulatory framework.

CHAIRMAN MALMUD: Mr. Lieto.

MEMBER LIETO: Yes. I guess I have -- I agree with Jeff and Dr. Nag on this, but I guess I have a question regarding the word "remote". I'm always picturing remote as that you have to be outside the room when the sources are being placed into the patient, and then retracted.

MEMBER NAG: In this case, the doctor is in the room, and basically you are standing by the machine. You are not outside the room. But the word "remote" is there because it is not the doctor who is pushing that source. It's the machine that is pushing the source, so that's where the remote comes in. But I think that it is unfortunate because because of the word "remote" all the remote HDR regulations comes into play, when really there is no need.

CHAIRMAN MALMUD: So if I may, it seems that Dr. Williamson is saying that some of the existing regulations may be excessive for the application of this particular therapy using this form.

MEMBER WILLIAMSON: It's actually guidance. There are no regulations for it.

CHAIRMAN MALMUD: The guidance may be excessive regarding this form of therapy, and Mr.

Lieto is saying that the use of the term "remote" means something else in this case, that the word means something else.

MEMBER NAG: Right.

CHAIRMAN MALMUD: And you wish to bring that to the attention of NRC.

MEMBER LIETO: Right. I just don't think we should address this device as a remote afterloader.

CHAIRMAN MALMUD: That in this case the word means something else, or its application means something else.

MEMBER LIETO: Yes.

MEMBER WILLIAMSON: You could make a case that it could be in 35.400. It's just the --

MEMBER NAG: I think from a regulation standpoint --

MEMBER WILLIAMSON: I mean, that would make most sense to start with 400 as the foundation. And I think you can argue it both ways. It is a more complex device. It is replacing a human activity by a mechanized robotic device. There are error pathways that have to be looked at from a clinical physicist point of view. There certainly needs to be a far more sophisticated quality assurance program to ensure that the device works properly. And I guess the issue

would be whether one would be performance-based or prescriptive with regard to that. But there are many things in the 600 regulation which at least in the version that I saw at the end of June, which continued to be copied out of 600, which seemed to me to be inappropriate for guidance for using this device.

MEMBER NAG: This technology is the marriage between something in the 400 category and something in the 600 category. And because it was a remote afterloader, the primary thing came from the 600 from the regulation standpoint, came from 600, eliminating a few things from 600, so that it becomes compatible with 400. From a physician standpoint, I would say that this is more of a 400, and you may want to bring a couple of things in from 600 just to meet the afterloading capabilities, so that makes a big difference in the regulations.

CHAIRMAN MALMUD: Dr. Nag, if I may bring the comments of the three of you together. Are you, and Dr. Williamson, and Mr. Lieto recommending that NRC staff consider this particular type of therapy to be more appropriately classified under 400 than 600? Is that the recommendation that you are making that they consider?

MEMBER NAG: Yes, with the extra

precaution that may need to be brought in because it is an afterloader device.

MEMBER WILLIAMSON: I would say it's the issue of, it's a 1000 device. Okay. They have made the determination, and we could argue that basis, but I think they have a reasonable case that it's a 1000 device. And really, the issue is should the guidance be drawn more from the 400 side or the 1000 side. And I think the three of us are saying that it is essentially a 400 application with the need to borrow a few extra things from 1000 to cover the added technical complexity and error pathways that this device introduces.

CHAIRMAN MALMUD: I'm trying to summarize your three comments so that we could make a recommendation for consideration to NRC staff. And I guess the first comment would be that this is a 1000 - is this considered a - this is a 1000 device, and that the parties who have just spoken, which include a member of the Radiation Oncology Medical community, as well as two physicists, would wish NRC staff to consider this as - which it already does, as a 1000 device with more of the 400 applications than the 600. Dr. Howe, do you wish to comment?

MEMBER NAG: I think Dave might want to

make some --

CHAIRMAN MALMUD: I'm sorry. I didn't even notice that you put hand up. I'm sorry.

MEMBER DIAMOND: No, I was actually just sneezing. I concur with everything that was just said. That's how you go to an auction and you end up with something very expensive.

DR. HOWE: NRC is currently in the process of revising our guidance for this device. And I would say that we're probably somewhere around 80/20 percent on the split between 400 and 600, with the 600 being somewhere between 20 percent. And we have revised it since, Jeff has seen it. WE're working now on format, and if we can get the format issues resolved, then we'll be sending it out. And it is moving closer and closer to the 400 than it was before. It's always been more on the 400 than on the 600. We're just continually moving it more and more towards the 400.

CHAIRMAN MALMUD: Do the members of this committee who are knowledgeable in this area agree that this should continue to move more in the 400 direction than the 600?

MEMBER WILLIAMSON: Yes.

CHAIRMAN MALMUD: Is there any dissention from that? So you have pretty much a consensus of the

opinion of the committee to consider as you move forward in your deliberations.

MS. WILLIAMS: Pardon me. May I suggest that you make a formal recommendation for the public record, please.

CHAIRMAN MALMUD: Is there a formal recommendation that this 1000 device be considered under the 400 regs rather than the 600, as a recommendation from this committee? Is there such a recommendation?

MEMBER WILLIAMSON: May I restate it?

CHAIRMAN MALMUD: No, there is not. Dr. Nag.

MEMBER NAG: I think --

CHAIRMAN MALMUD: I'm sorry. You shook your head before. You said restate it, so okay. Dr. Williamson, you want to comment first.

MEMBER WILLIAMSON: Okay. Whereas, the seeds electron may be appropriately considered a 1000 device, the ACMUI recommends that the NRC build upon the 35.400 regulatory framework, adding only those elements of 600 as absolutely needed.

CHAIRMAN MALMUD: That is a motion. Is there a second to that motion?

MEMBER NAG: Yes.

CHAIRMAN MALMUD: Is there any further discussion? If not, all those in favor of this recommendation. Any opposed? Any abstentions of those who are knowledgeable in the area? So you have a consensus from this committee for your consideration. Thank you. Dr. Nag, you still have the floor.

MEMBER WILLIAMSON: I would also add the recommendation that I think once this goes through, and once another revision is prepared, it might be worthwhile submitting it to the sub-group of us that is interested, and have some expertise in it.

CHAIRMAN MALMUD: Dr. Howe, there's an expression of interest from this group to see the working document that you will have completed at such time that you will have had the opportunity to complete your deliberations.

DR. HOWE: That's fine with us.

CHAIRMAN MALMUD: Dr. Howe agrees.

MEMBER NAG: I would like to introduce a new isotope that has recently become FDA approved, and will come into medical practice very soon, if not -- I mean, it has been started in a couple of centers. So basically, it's Cesium-131. Most of you have heard about Cesium-137 that is used for GYN use. This is

entirely different. Only the name Cesium is the same, but the isotope properties are entirely different.

In many respects, Cesium-131 is somewhat similar to I-125 and Palladium-103. It has low energy, it's a gamma emitter, and it has a short half-life. The difference being that the half-life of Cesium is much shorter than Palladium or Iodine, which means that from a basin standpoint, you can deliver the radiation in a much shorter period of time. The energy of the Cesium is very close to Iodine and higher than Palladium, which means the penetration is more than Palladium. Palladium is very good in terms of short half-life, but in some cases the clinicians felt that there may not be enough penetration. Here you are getting the penetration property of Iodine, and even shorter half-life than Palladium, so you are getting, you need to give a little lower dose, 105.28 compared to 125, and the initial dose rate is higher.

The advantage of the initial higher dose rate is that if you have a higher dose rate, tumors that are fast growing can be treated with Cesium, which may not be well-treated Iodine. So that's the reason why this isotope was thought about. It had been thought about many, many years ago, but in terms of getting it FDA approved, it has only become

clinically available now.

We think that the major use is going to be for permanent prostate implant. However, it could very easily be used for other permanent implants, or as a removable implant in eye plaques, or maybe even in breast cancer therapy.

The major problem or the major disadvantage is the because the half-life is so short, it has a very short shelf life, which means that you have to use it on the day it was ordered or maybe at the most you can delay it by a day or two. You cannot keep it in for the next week.

In terms of radiation safety considerations, I believe that it's going to be almost the same or very similar to that for permanent Iodine or permanent Palladium implant. The energy is low. The seeds are exactly the same size, and the encapsulations are the same. I believe there should be no difference than Palladium or Iodine. The advantage is that if you are going to start the decay you need to store it for only a much shorter period of time. Other than that, I don't see any major safety consideration, and it should be under the regular 400 applications.

CHAIRMAN MALMUD: Thank you, Dr. Nag, for

that information.

MEMBER NAG: Any comments?

CHAIRMAN MALMUD: Any questions or comments to Dr. Nag?

DR. Zelac: Question.

CHAIRMAN MALMUD: Dr. Zelac.

DR. ZELAC: Dr. Nag, I presume that since you brought this to the advisory committee, this is reactor produced material, the Cesium-131?

MEMBER NAG: I think it's produced by cyclotron. Jeff, you might have to help me out there.

MEMBER WILLIAMSON: I don't know, to be honest. I'm trying to think whether it is. I think it can be done by either. Now which it is -- what the vendor is actually doing, that's a good question.

MEMBER NAG: The vendor that's producing it is called Isoray. It's a company I haven't heard of before.

MEMBER WILLIAMSON: Yes. The AAPM Subcommittee on photon emitting brachytherapy dosimetry is developing a standard data set, and seeing that it's integrated into the same system of national standards as Iodine and Palladium seeds, so dosimetry-wise, not really a big difference. That's a good question. What do you do about Palladium now?

You do not regulate Palladium.

CHAIRMAN MALMUD: Was that a question from you, Dr. Williamson?

MEMBER WILLIAMSON: Yes.

CHAIRMAN MALMUD: Addressed to Dr. Zelac or Dr. Howe?

MEMBER WILLIAMSON: Either.

DR. HOWE: As long as all of the Palladium-103 is being produced by accelerators, then we don't regulate it. There has been some talk about manufacturers switching over to reactor-produced, and if that occurs, then we will be back into Palladium.

CHAIRMAN MALMUD: Thank you, Dr. Howe. Which really indirectly addresses the answer to Dr. Zelac's inquiry.

MEMBER NAG: Yes.

DR. ZELAC: Indeed.

CHAIRMAN MALMUD: Indeed it does. Thank you.

MEMBER NAG: I have then a question back to either of you. If you are having an obvious medical event produced by I-125 seed in the prostate, where let's say the seed did not go to the prostate, went to the rectum or so on, that will come under the NRC purview. And if the same problem was created by

a Palladium seed, you would have no jurisdiction over it, or what would happen to that patient?

DR. HOWE: We only have jurisdiction over byproduct material, and so if the same thing happened with a non-byproduct material, like Palladium-103, then it would be some other group, or no group at all, that would have jurisdiction over it. So in the federal facilities, because the states are not involved in federal facilities, then it would be just the federal facility that would have the oversight. It would not be the NRC.

CHAIRMAN MALMUD: Yes.

MEMBER BAILEY: Typically, the agreement states would report that through the NMED system, do the same sort of investigation they would if it occurs in a state jurisdiction. There's no requirement that they do it, but typically that's -- because quite frankly, we don't keep up with which it is. If it's radioactive material, we treat it that way.

CHAIRMAN MALMUD: Dr. Williamson.

MEMBER WILLIAMSON: Two short comments. One, I think it would be sort of short-sighted for the NRC to totally ignore this. In fact, I think many of the states will probably pattern their regulatory approach after the one developed by NRC for Iodine-125

implants, so there's a close connection, and it's well to be aware of this.

I think an error pathway that exists with this is the short half-life, which is going to place a lot more stress on the skill of the -- it's another constraint on where you place the seeds and how many you place to try to compensate for a one-day shift in the activity, so there's probably a small possibility of there being more variability of the delivery dose relative to the prescribed dose, because the source is so rapidly decaying. But other than that, I think that Dr. Nag is completely right, that the practical clinical and safety problems are nearly the same.

CHAIRMAN MALMUD: Any other comments regarding this issue? Dr. Suleiman.

MEMBER SULEIMAN: Well, FDA has an adverse event reporting system.

CHAIRMAN MALMUD: That's why I looked at you. I was hoping you were going to make a comment.

MEMBER NAG: The thing is, there may be no adverse effect on the patient because you can place 50 percent of your seed outside the prostate, below the prostate, and so long as you're putting it in a radiosensitive organ like the rectum, you are not going to have any adverse problem. The tumor may not

be cured, but we don't cure 100 percent of tumors, and that way if you have a failure, you are not going to know whether the failure was because the seeds were not totally placed in the prostate, or whether the tumor itself was more resistant.

MEMBER SULEIMAN: I think this falls into that gray area of, is this the uncertainty associated with the imprecision of medical practice, or is it a known failure where people should have known better. So yes, I think we're in that gray area, but if it's an adverse event or severe adverse event, there is a responsibility on the facility to report that. But if you feel it's under the medical realm, you don't.

CHAIRMAN MALMUD: Thank you for your input, Dr. Suleiman. Thank you, Dr. Nag, very much for a very stimulating and informative presentation. It is now time for us to take a break. May I ask staff what time you would like us to rejoin. Shall we abbreviate lunch to 45 minutes or keep it at an hour?

MR. ESSIG: If we could abbreviate it to 45 minutes, that would allow us to remain reasonably on schedule.

CHAIRMAN MALMUD: Is that agreeable to the committee? Then we will reconvene promptly at 1:30. Thank you.

(Whereupon, the proceedings in the above-entitled matter went off the record at 12:42 p.m. and went back on the record at 1:38 p.m.)

MEMBER WILLIAMSON: We will pick up with the agenda, if we may, beginning with the first topic after lunch which is the registration of brachytherapy sources.

MR. ESSIG: Dr. Malmud, if I may?

CHAIRMAN MALMUD: Please.

MR. ESSIG: The listed speaker, Mr. Tim Harris, will not be the speaker. Instead, it will be Dr. John Jankovich who is our team leader for the sealed source and device review team. Originally, we wanted to have him, but he was going to be out of the country and that trip was rescheduled, postponed and so now he's able to be here with us.

So Dr. Jankovich will be doing the presentation.

CHAIRMAN MALMUD: Thank you, Tom. And thank you, Dr. Jankovich for being with us.

DR. JANKOVICH: Thank you. Good afternoon. Can you hear me all right?

So I am the team leader for the registrations here at the NRC. But NRC has another function. That is to reorder sealed sources and

devices nationwide, that is what the agreement states approve also. So overall we have in the system four and a half thousand registrations and they are coming from 1,200 vendors. That's the nationwide picture. And we want to narrow it down, focus down on brachytherapy sources, but before we proceed, I'd like to give you a few minutes of over view, what the registration sheet is and what it contains and how it specifies its use. Otherwise, we'll proceed to the next slide.

(Slide change.)

MEMBER WILLIAMSON: Which handout are we looking at?

MS. WASTLER: I'm sorry, there's a tab missing.

The header says sealed source and device registration in big letters. It's right off your -- let's see -- it's right after Dr. Nag, the tab for Dr. Nag's presentation?

MEMBER WILLIAMSON: Thank you.

DR. JANKOVICH: The names and words we are using here, registration certificated, the name of the official doctrine. However, in the community, people refer to it as SSD sheet for sheet. SSD stands for sealed source and device and sheet for registration

certificates. So you may hear on the sheet words that means the entire document.

And what's the content of this document? It describes the design. It has a section on labeling that identifies features. It specifies the conditions of normal use. Shows further type testing and the classification standards, if that source or device was tested to a standard. That's important because we will be talking about these tests and standards in a short while.

Luckily, all the registration certificates issued either by the NRC or the agreement states follow this format, so it's easy to understand, easy to see what it contains.

Continuing with the content, you can see that the presence of radiation profiles. This is not radiation that goes to the patient. It is occupational radiation profile around the device. As my second bullet shows here, it is the radiation profile really is for specifying what dose occupational dose the physician, the technician would get during one procedure or during daily procedures and then in storage or handling multi-units and what happens if there is a failure or what is the dose rate when they dispose of a single unit.

In addition, the sheet registration certificate sets limits and other considerations of use. That's the official term. What it means is if there are any restrictions, that's also spelled out, the restrictions for its use.

And finally, I want to call your attention to this website, all four and a half thousand registrations are evaluated at the NRC website, the full text of the document.

Now let's focus down to brachytherapy sources. I searched the system and I found 22 seed registrations only. Three sheets issued by the NRC and 19 issued by agreement states. That's important for everybody to know. As you see, NRC doesn't have a major role to play. Actually, if you are curious, I can easily list. NRC approval is for Best Medical here in Springfield, Virginia, locally for Kennedy and for Dragsomich, and third is Mills Biopharmaceutical from Oklahoma City. Oklahoma is an agreement state, but they have a few SSD vendors. They don't want to have staff qualified for this purpose. It would be cost efficient for them, so then Oklahoma delegated this function to the NRC. Thus, that's how we got into the picture.

I looked at all of these 22 sheets

regarding conditions of normal use because I assume that's your primary interest here today. And luckily, there is a fairly good agreement, how well these sheets description the conditions of use, normal use. And these are the three or four terms I found: permanent or temporary interstitial treatment, used as implant by use of commercially available implant tools. That's all.

Of course, the FDA's 510KF rule specifies its medical use. NRC is concerned about radiation safety and agreement states similarly are concerned about radiation safety. So that's how these registration sheets specify the conditions of use.

Let's talk about testing, testing of the sources because that defines these conditions of use. The regulations, both agreements state that NRC are fairly simple. The first bullet specifies it. The source must maintain its integrity when subjected to conditions of normal use and likely accident conditions. And those are the two things which the regulations require.

We are not specific, not restricted. And what are the normal use conditions in likely accidents? The manufacturers are the ones who specify to us. They submit an application. In the

application, they tell us who the reviewers, the technical staff at the NRC and the agreement states and so that's condition, the extent that these registration sheets permit the use of these sources.

MEMBER VETTER: Excuse me?

DR. JANKOVICH: Yes.

MEMBER VETTER: So when an Iodine-125 source is sheared in half by a mic applicator, that's not considered to be a likely accident condition, apparently?

DR. JANKOVICH: It depends if the manufacturer presented it to us and then if the reviewer accepted that as a likely scenario.

What I want to highlight here is there are 22 registrations, reviewed by 22 people all over the country and with our set conditions. The only guideline they have is normal use and likely accidental conditions.

And then we come to the end of my presentation and probably your meeting, you will come to the conclusion that I will recommend that we try to look for some uniform approach and that would be my recommendation.

Going on where the second bullet says we do require actual testing, engineering analysis is not

acceptable because the source and its containment is so important. If it's a device or something, we can accept engineering analysis. What is the passing criteria? Very simple. It says it must maintain its integrity. And how do we determine that? It means integrity that no radiative material leaks after the tests. So there are accepted testing methods for leaking in the standards or the manufacturer can propose their own method.

Now let's talk about some standards. Of course, prototypes or C-sources can be tested to standards. There are two standards in use at the present time. American Standard, the so-called ANSI, 43.6, and the International Standard, ISO, 2919. Please remember this ISO number 2919, because that's very relevant to brachytherapy. I will talk about it more later.

And then when the regulatory body approves this design, we reference the standard with a classification number, last bullet here, because that is universally acceptable and understood that these were tested to that standard according to these conditions. And I explain it quickly on the following slide.

But let's finish here with the other

standards. That is for your information only. There used to be two other standards specific to brachytherapy sources. This one, the 43.6 issued in 1977. Then withdrawn in 2004.

I am talking here about going back, about the present, active standard. This is 43.6. This was issued in -- the latest revision in 1997. As you know, these standards are living documents and they get revised, updated, periodically. ANSI, the American Standard Institute likes to do it every five years. I'm the delegate to this standard from the NRC and we just finished the latest update this summer and it was sent to ANSI for final publication.

I want to show that this standard doesn't address brachytherapy sources even during this latest revision. I can tell you why. The working group brought up the subject and who is on the standard? Regulatory representatives like myself and also the industry and in the working group we didn't have really any manufacturers of brachytherapy seeds, so there was no representative there who could have represented this segment of the medical standard. And for that reason, the brachytherapy sources didn't get included.

But let's go the second one, to the ISO

standard, 2919. That was last updated 1999. They had a technical committee had a working session in March in Buenos Aires and I am also the NRC delegate to that committee and the brachytherapy and other sources were not on the agenda, even though my manager, Tom Esse approved my travel, I couldn't go. Well, I missed a good trip.

Let's go back seriously. What I want to show you here is that there used to be two other standards. Now the old ones, this one issued in 1977, integrity and test specifications for brachytherapy sources. That is how to design them and test them. But this was withdrawn in 1995. And there was another test, the leak testing for brachytherapy sources and was withdrawn in 1984. That was to show how you check the prototype test results. Is there a leak or not? These two tests are here for reference.

Now let's look at what the present only active standard contains. That is the international standard. In yellow, I highlighted for you. This is an important table from the standard because it specifies the usage of all the sources and that what are the test conditions? Let's look to usage. For medical use it specifies, yes, look, here is this thing for brachytherapy. So the brachytherapy source

must be tested for temperature, under conditions of 5. Then 5 is the most rigorous test condition.

For puncture, the brachytherapy source must be tested to three conditions, for impact for two, vibration, no test is required. One means no test. Again for reference, 5 is the most vigorous, 1 is no test. Puncture test not required.

Let's flip to the next table and I'll just give you a quick flash view about what the test conditions are. Remember, brachytherapy sources must be tested for temperature, 5. For the minus 40 centigrade for 20 minutes, plus 400 Centigrade one hour and then drop them into room temperature water for exposing them to thermal shock. And these yellow blocks indicate the test conditions for the brachytherapy sources. Five is temperature, three for external pressure, decrease the pressure from one level to the other. No test for vibration, no test for puncture.

For your reference, I include the table for the current American standard. That is what we sent to ANSI for publication this summer. And look at the medical use, no brachytherapy, only radiography and gammagraphy and the conditions.

Well, we already talked about

classification here, so I quickly refresh your memory. This is what you see when you have a technical description or the registration for the source. It references the standard, the year, the diseases that it was approved for maximal radioactive material content and the five conditions for tests.

This is important because you remember, brachytherapy sources by the international standards should be 5, 3, 2, 1, 1. Let's look what we find in real life.

Both of those 22 registrations, this is what I found. Some of them have this kind of classification. This is less for temperature. This meets exactly. This exceeds for temperature. This has not been tested for impact and this has not been tested for temperatures. And as you remember, regulations don't require the standard. They require some sort of testing and that could be entirely a custom test protocol which the manufacturer proposes or semi-custom. And so in some cases, there are really some cost of test conditions like stepping on it, or they push a cart over it, autoclaving, temperature range test, they drop it from some different over they have other impact tests. That could be an entirely custom prototype.

So that's the current situation for those which exist in the registration.

So sum up what we said, we intended to show you, you know, what is the content of the registration sheet and the conditions of the use. And that's how far those brachytherapy seeds can be used under NRC or an agreement state life.

The sheets specify the conditions of use. They describe prototype tests which are not standardized, may be according to the standard or customized. And as you see, there are no -- there is no agreement for its use or for prototype testing.

I'd like to call to the Committee's attention some facts, that there are some device source specific standards, not this ISO, what I showed you or the ANSI source standard because they apply to everything from irradiated sources to any kind of small sources, moisture density gauges and so on. Maybe the specific conditions of brachytherapy sources and seeds needs a specific standard. Think of one, for example, for watches which have three little beads in it which glow in the dark. They have those tiny beads which is about 2 millimeter length, 1 millimeter with tritium in it.

There is a standard which is called ANSI

standard for testing tritium light making sources. Maybe a standard like that could be applicable. I don't know, but this is what I can present to you about prototype testing and the registration of sources.

CHAIRMAN MALMUD: Thank you. Are there questions for Dr. Jankovich.

Yes?

MEMBER BAILEY: John, if I remember correctly, the two ANSI standards have been withdrawn. Had a primary concern of radium needles and existed about the time when radium needles were being withdrawn from widespread use and there was such things as the bending test. There was concern about since those sources were re-used, the autoclaving of the sources for sterilization and the leak testing provided alternatives to what we call the standard leak test of wiping and wherein you could put the needles in a container and let the radon off-gas and in fact, there was a specification for radon leakage, as I remember.

Are you suggesting that under the present conditions that those same sort of standards ought to apply to seeds, but because I think --

DR. JANKOVICH: Not at all.

MEMBER BAILEY: Because traditionally, we've sort of considered some of those seeds almost as non-sealed sources when you get back to some of them which actually were just the metal themselves.

DR. JANKOVICH: I am familiar with those standards and you described that content exactly. So again, this doesn't apply to these three millimeter little-bitty sources. And maybe the Committee should think about some other standards, not to revive those. Or maybe some other means. Of course, ANSI is representing the entire country. Anybody can go there and ask them to ask for a standard and go through the procedure. They put together a working group, they come up with a draft that gets approved and that is the standard, or other means.

So my purpose here is to present the situation as it exists now and obviously we have to go forward and find the solution. And reviving those old standards which apply to big, old sources may not be the way to do it.

MEMBER BAILEY: May I have a follow-on to that? When you gave the number of SS&D sheets issued, did you include those that were not AEA materials?

DR. JANKOVICH: No.

MEMBER BAILEY: Okay, so --

DR. JANKOVICH: Actually, I just did the search for Iodine-135 and Palladium-103.

MEMBER BAILEY: Okay.

DR. JANKOVICH: So for those materials, there are only 22 registrations.

MEMBER BAILEY: Thank you.

CHAIRMAN MALMUD: Dr. Vetter?

MEMBER VETTER: What problem are we trying to solve?

DR. JANKOVICH: As I understand, there is consideration to use the brachytherapy seeds for other use than prostate implants. For example, markers for breast tumors and, so far as I see from these registrations, they have -- that kind of application hasn't been considered in the past.

MEMBER VETTER: I'm still not sure, that's an application.

DR. JANKOVICH: Yes.

MEMBER VETTER: But what problem relative to safety of the seeds are we trying to solve?

MEMBER LIETO: May I comment to that because that was going to be one of my questions, is that being a classical kind of a guy, I don't quite understand or have a sense for the magnitude for some of these metric numbers for like external pressure of

a mega-Pascal.

DR. JANKOVICH: The ANSI standard has it in both. Let me see if I have the table here.

MEMBER LIETO: I'm trying to get a sense, is that sort of like just a tap on the shoulder or is that more equivalent to maybe a 200 pound guy standing on your chest? Do you understand? Because I think relating to your question, Dick, is the sense that if these are going to be implanted in the breast, they're probably going to be more susceptible to mechanical and external pressures and so forth than they were if they were in the middle of your abdomen. And so if you have something that can't or has never been tested to survive those kinds of environmental effects, how do you know you're not going to have leakage?

MEMBER VETTER: That gets back to my question, what problem are we trying to solve? Has there been a problem identified with the use of these seeds for other applications?

DR. JANKOVICH: As I understand the question has come up to use these seeds for markers.

MEMBER VETTER: What problem is that?

DR. JANKOVICH: It's up to the Committee to decide here, to proceed with anything or there is no problem. I can't answer that question.

MR. ESSIG: If I may try to clarify, it's really the subject of the presentation which follows this one which talks about the implant of these brachytherapy seeds and the question then came up is during the surgical removal of tissues, have the seeds been evaluated for puncture by a scalpel, for example? The answer is no, they have not.

MEMBER NAG: Actually, yes. We also used permanent Iodine-125 seeds for liver implant and implant in other organ other than prostate, for example, also in pancreas we've done it. And some of the patients go back and have surgery. When they go back and have surgery and if they are within the first half lives, we ask that someone from radiation oncology be there. So we have recovered seeds that have been dissected out. No one has tried to manipulate the seed, but they have dissected the area out. We haven't had any nickings of the seed. We take out the seed and we store them.

CHAIRMAN MALMUD: It appears that the question that's being raised by a member of the Committee is, is this information being presented to us today in order for us to make a recommendation for new standards for evaluating the seeds in the event, well, as they are used in breast cancer patients?

Is that the question before us? Or just to inform us that this is happening?

MR. ESSIG: Well, I think it might be clear if the question could be held until the presentation. Keep the two of them together in mind and then decide, although notwithstanding Dr. Nag's comment, I don't believe this was one of the -- part of the test protocol for this particular seed. And so the question then comes up is it something that should be considered in the form of a new standard or a new test.

CHAIRMAN MALMUD: Thank you. In that case, we'll thank Dr. Jankovich for his presentation and giving us the background with regard to the seeds and move on to the presentation on their use in marking patients with breast cancer. If we may have that presentation next, we'll hold the discussion regarding both of these until the end of that presentation. And that is to be made by -- this is Roger Gallaghar, the Chairman of the Materials Pilot 4 at the Massachusetts Radiation Control Program.

MR. GALLAGHAR: Actually, it's Robert Gallaghar.

CHAIRMAN MALMUD: I'm sorry. I stand corrected, Robert.

MR. GALLAGHAR: You can call me Bob.

CHAIRMAN MALMUD: You can call me Leonard.

(Laughter.)

MR. GALLAGHAR: Well, good afternoon. My name again is Bob Gallaghar. I am the Chairman of National Materials Program Pilot Project No. 4.

Before I discuss the radiation safety aspects and licensing of I-125C used as markers in breast cancer tumors, I want to provide you with a brief description of the Pilot Project 4.

This project is one of five pilot projects of the National Materials Program. The goal of this project is to have an agreement state or a group of agreement states assume responsibility for the development of licensing and inspection guidance for new use material for a new modality not previously reviewed and approved.

The lead organization is the Organization of Agreement States and we're comprised of four agreement state members and one NRC regional member.

Our first priority was to decide which new use of material or new modality to pursue for development of licensing and inspection guidance. To do this, first we reviewed the regulatory needs analyzed by the National Fuels Program Pilot Project

No. 1. We then surveyed the agreement states, NRC Headquarters, and the NRC regional offices. We also contacted a number of major medical institutions across the United States.

Why did we choose radioactive seed localization? To begin with Iodine-125 is an Atomic Energy Act material, as we heard earlier. And therefore, is subject to regulation by both the NRC and the agreement states. Its use in this particular application does not fit into 10 CFR 35.200 unsealed material, written directive not required because while it is being utilized for localization of a lesion, a sealed source is being utilized, not an unsealed source. Nor does it fit into 10 CFR 35.400, manual brachytherapy because the sealed sources are not being used to deliver dose to tissue.

Therefore, the use of Iodine-125 for radioactive seed localization fits into 10 CFR 35.1000, other medical uses. And finally, no review by the NRC or by an agreement state have been performed.

I'll be describing the draft of licensing and inspection guidance developed by the Pilot 4 working group. This draft was submitted to the NRC and the Organization of Agreement States on September

9th of this year. We have received comments from both the OAS and the NRC and are currently reviewing these comments which I'll describe later in my presentation.

Radioactive seed localization or RSL, calls for the use of currently available radioactive seeds previously approved for use as permanent implants for the treatment of cancerous tumors. And Iodine-125C, particularly between 200 to 300 microcuries per seed, is implanted into a breast lesion using a standard 18 gauge needle. This seed or seeds in the case of irregularly shaped lesions by then accurately localized by a hand-held gamma probe by the surgeon. Using a technique with which surgeons are familiar because of its similarity to sentinel lymph node biopsy and radio-guided parathyroidectomy and surgically removed along with the lesion.

The seed they remove may be removed from the specimen in surgery or the specimen with the seed can be sent to pathology for removal of the seed or seeds prior to analyses of the tissue. The seeds are then disposed of in accordance with 10 CFR 35.92 or equivalent agreement state regulations.

MEMBER WILLIAMSON: Are the seeds placed under some sort of image guidance? I guess this is --

MR. GALLAGHAR: Mammographic localization.

MEMBER WILLIAMSON: Okay, so is the idea to create a correlation between mammography and surgical pathology?

MR. GALLAGHAR: The idea is to improve upon a technique which is currently being used, as I understand it, which is the wire guided surgery. In this application, the surgeon is able to excise the lesion and the seed with the lesion without having to affect healthy tissue.

MEMBER DIAMOND: Maybe I can comment.

CHAIRMAN MALMUD: That is Dr. Diamond speaking now. That was Dr. Williamson before.

MEMBER DIAMOND: Very often when a lady has a suspected breast cancer, the radiologist will place a metallic clip under ultrasound or mammographic guidance, that is used so that when the patient is taken to the operating room, the surgeon can then again use that modality to help localize that area of concern and what the surgeon will do, the surgeon will track out the way he or she would like to approach the tumor, meaning what angle through the breast. They will then go and attempt to in the contiguity remove the breast tumor plus a rim of normal tissue around it.

My assumption is is that sometimes it can

become somewhat difficult in the operating room to bring this lady back and forth and localize where that metallic clip is actually within a breast, particularly if the breast is large and pendulous and perhaps if one could use a radioactive marker where the surgeon can use a hand-held gamma probe, in real time it may make that localization process more precise and quicker.

CHAIRMAN MALMUD: Thank you.

MR. GALLAGHAR: The guidance developed by the working group focused on radiation safety aspects of RSL. In addition to the general information required for any amendments, such as radionuclide, form, possession, limit and use, the licensee must also submit facility diagrams which must include all areas of use such as administration, excision, removal from tissue, analyses and storage for disposal.

MEMBER WILLIAMSON: May I ask why is that? For permanent seed implants that are re-used many times, that activity is not required.

MR. GALLAGHAR: Typically, we're concerned if the -- for example, the seeds are being removed elsewhere to a location that's already been reviewed by licensure such as an external pathology laboratory.

CHAIRMAN MALMUD: Does that answer your

question, Dr. Williamson?

MEMBER WILLIAMSON: I guess I'll just listen and comment later.

MEMBER LIETO: These are then essentially the same type of seeds that are used for prostate implants because didn't you say the activity is like about .2 to .3 millicuries per seed?

MR. GALLAGHAR: Correct.

MEMBER WILLIAMSON: Not millicuries, they're microcuries, right?

MR. GALLAGHAR: Point 2, to .3 millicuries which is 200 to 300 microcuries, correct.

MEMBER WILLIAMSON: Okay.

CHAIRMAN MALMUD: Would those who are making spontaneous comments, please advance the comment with their names for the transcriptionist. Thank you.

Dr. Nag.

MEMBER NAG: Actually, I had been approached about this a few years ago. Basically, the reason this came up was that many of the radioactive iodine seeds of prostate implant were not in use for prostate implant and had to be thrown away. And people were thinking of ways to use these radioactive seeds that were manufactured for prostate implant and

that would otherwise be thrown away and could be used for something useful. And that's when the idea came up that why not use it to detect areas that would be difficult to find otherwise.

A similar thing we have is when we have implanted an organ with Iodine seeds and the patient dies, within the first half life, what do we do with the organ and this has come up several times before that we then take the whole organ out and we are not allowed to cremate this patient. That patient has to cremate, what do you do? We take the whole organ out and then we dispose of the entire organ by radioactive decay. So basically, you are doing the same thing. You are taking seeds that otherwise decayed down to a less than useful level and what do you do with those seeds afterwards?

CHAIRMAN MALMUD: Dr. Nag, may I ask what is the current practice? What happens when the seeds are in an organ in a patient who has died and the organ is removed? How is that organ dealt with?

MEMBER NAG: We inform Radiation Safety and Radiation Safety will do one of two things. Either it will take the whole organ and we will then store it for decay within half lives or it is in a place where we can easily block out the seed. If it

is in some organs, it's not possible, but if it is, we block out the seed, store in a lead container for radioactive decay. But we have to store it for 10 half lives.

CHAIRMAN MALMUD: Thank you. Dr. Williamson?

MEMBER WILLIAMSON: I guess I must confess, I'm quite unfamiliar with this procedure. This would seem to be not a particularly wise choice of source for this purpose because the radiation burden to the patient relative to the useful radiation output coming out of the patient that you could do the localization, it would seem to me to be very high, that one would think that a more appropriate choice of radioactive source would be a much smaller quantity of a higher energy gamma emitter that wouldn't give so much radiation dose to the patient for what is essentially an imaging procedure.

CHAIRMAN MALMUD: Dr. Nag?

MEMBER NAG: Yes, but that would require making a new isotope and making something specifically for that. These are seeds that are otherwise going to be thrown away. It's something that didn't cost anything to the manufacturer and now they will sell it for a price.

CHAIRMAN MALMUD: Is that, in fact, the information -- is that, in fact, the background of how these seeds will be obtained?

MEMBER NAG: Yes. We had been contacted about three or four years ago that we have the lowest seed activity. We throw them away. Can we use them for some other material?

CHAIRMAN MALMUD: Thank you for that background information.

Mr. Lieto, you would like to make a comment?

MEMBER LIETO: I'll defer to Dr. Eggli.

MEMBER EGGLI: Typically, these seeds are installed immediately before the surgery, so that the radiation burden to the patient is small because the dwell time is very short.

CHAIRMAN MALMUD: Thank you, Dr. Eggli. Mr. Lieto?

MEMBER LIETO: That answers my question. I was going to say the same thing as Jeff. I mean I just can't see how the dose, this would be a lower dose to the patient and compared to lymph node scintigraphy, I mean they're using these probes to try to -- and they're detecting microcurie amounts in surgeries. So it sure seems like this is an awful lot

of activity that you're using here, but if it's a very short period of time, then that's another thing.

CHAIRMAN MALMUD: Dr. Eggli?

MEMBER EGGLI: The other benefit of this is it allows them to encompass the entire lesion. With the wire localization procedure, one of the things you never know is you've taken out the wire, but have you taken out the entire lesion? With the seeds, you can sort of bracket the lesion and therefore with the probe know that you've excised the whole thing and that's the big issue for the breast surgeon is to know that they've taken out the whole thing. So this would represent a significant improvement over wire localization where the wire is typically put into the center of the lesion and the surgeon has no idea what kind of a margin they've achieved surgically.

If you take out all the seeds you put in, you know you've got the lesion.

CHAIRMAN MALMUD: May we let Mr. Gallaghar continue at this point?

MR. GALLAGHAR: Thank you.

CHAIRMAN MALMUD: You're certainly stimulating some discussion.

(Laughter.)

MR. GALLAGHAR: That was my hope. As for authorized users, the applicant must identify all authorized users and document his or her training. The authorized user will be considered qualified for implantation, localization and removal of the seeds if they meet either of the criteria in 10 CFR 35.490 or before October 24th of this year, requirements of 35.940 or 10 CFR 35.290 or again before October of this year, the requirements of 920, 35.920.

And preceptorship training by a 35.490 authorized user to include work experience and ordering, receiving, unpacking radioactive fuel safely and performing the related radiation safety surveys using appropriate instrumentation; preparing, implanting and removing brachytherapy sources, the emergency procedures, using administrative controls to prevent a medical event involving this device and maintaining running inventories of material at hand.

General surgeons, working under the direction of an authorized user described above, will remove the seed or seeds with biological specimen, should complete eight hours of radiation safety training, in addition to specific training that includes performing the related radiation surveys, using appropriate instrumentation, preparing,

implanting and safely removing brachytherapy sources and emergency procedures.

This training shall be under the guidance of the authorized user qualified under 35.490 or qualified under 35.290 and the preceptorship training I mentioned earlier.

As for records, because Iodine-125 sources are temporarily implanted, the applicant may simplify its submission by confirming that will meet the brachytherapy requirements appropriate for temporary implant in 10 CFR Part 35, subpart F, manual brachytherapy; subpart L, record; and subpart M, reports.

There's a question?

CHAIRMAN MALMUD: Dr. Williamson?

MEMBER WILLIAMSON: Yes, I'm confused. How can these be licensed under 35.200 when it's a sealed brachytherapy source. As we heard in the previous discussion, even therospheres -- the regulation has been modeled on 400 and the authorized user is a radiation oncologist. So since this would seem to be a variance with the way 35.200 is written, why is this not being discussed in the context of 1000?

MR. GALLAGHAR: It is being discussed in

the context of 1000. As you saw earlier in one of my slides that this is a combination of both a localization under 200 and a manual brachytherapy under 400.

MEMBER WILLIAMSON: They're merging technology.

MR. GALLAGHAR: We have to use the Part 1000 and like what was mentioned earlier, perhaps maybe using 80 percent of 200 and maybe 20 percent in the 400. So in other words, we're taking whatever is applicable to each to fit into the part 1000 to determine the regulatory's framework to accomplish, to allow this to be used.

CHAIRMAN MALMUD: Dr. Nag?

MEMBER NAG: I would have a very similar question, but you answered part of it. I would say probably it should be the other way around. It had more of a way 400 in terms of the radiation safety because you can use 0.3 millicurie per seed and implant in prostate. You just have to implant double the number of seeds.

In terms of the radiation safety aspect, is it more of the 400, if you want to have a percentage I would say 80 percent of 400 and 20 percent of the 200.

MR. GALLAGHAR: I was using the example mentioned earlier, the 80 -- yes, you're right. It's a combination of the two approaches.

CHAIRMAN MALMUD: Please continue.

MR. GALLAGHAR: Thank you. For the safety precautions for the RSL procedures, we asked licensees to provide procedures addressing safety procedures and instructions, including survey procedures, specifying the individuals that must be physically present during implantation and removal, source accountability and link testing, and verification of source activity which may be accomplished by assay prior to implantation or by the manufacturer's certification.

The applicant shall supply a copy of the written procedures for responding to an abnormal situation such as a source rupture or cut by a scalpel during removal in surgery or in the pathology laboratory. These procedures must include monitoring, the implantation, explanation area following the procedure and removal from tissue using instrumentation appropriate for the radiation to be measured, the process for restricting access to and posting of the implantation/explantation area to minimize the risk of inadvertent exposure from the seeds; a description of the equipment and process and

recovery of any dropped or mishandled seeds. At a minimum, this equipment should include a survey instrument calibrated to detect the seeds such as a low energy gamma simulator, reverse action tweezers and a shielded recovery container.

Patient follow-up should they not return for removal of the seed or seeds, a description of the length of time the seeds will remain in the patient, not to exceed 5 days, and notification of medical emergency of the patient prior to removal.

If the physical conditions of use exceed those stated in the SS&D certificate, a limited scope medical licensee will have had to amend its license to allow for the new conditions. It should be noted that some states will not allow variations and conditions of use unless the original SS&D sheet is amended or a custom evaluation is performed.

Broad-scope licensee should perform their own engineering and radiation safety evaluations addressing these differences.

As I mentioned earlier, the working group has received comments from both the NRC and the Organization of Agreement States on the RSL guidance documents. We are in the process of reviewing these comments and will incorporate them into the guidance

document. In fact, we'll be holding a teleconference call tomorrow when I return to discuss the comments received.

The first series of comments from the NRC primarily involve the pathology specimens. They commented that the document should clearly delineate the program for radioactive specimens going to the pathology laboratory and the heightened potential for the surgeon or the pathologist to lose or damage a seed that would result in loss of control, Iodine-125 contamination and a possible medical event.

Specifically, they stated, the document should clarify if tissue sent to pathology still contain the seed or more than one microcurie of I-125 contamination, will be processed in its own pathology department or sent to an external pathology laboratory. The description of the radiation safety program for the in-house pathology lab should be provided. This program should contain the training and experience requirements criteria for the individual that will be the authorized user in pathology; procedures to minimize puncturing the seed; surveys to detect lost or leaking seeds; emergency procedures, source accountability, storage, security and disposal.

If the licensee sends the radioactive tissue sample to an outside pathology laboratory, the licensee must also have a program to ensure the samples are transferred to an NRC or an agreement state licensee authorized to receive the seeds or the radioactive tissue and the packet is prepared properly for shipment.

The comment was also made that since the use of the seeds for RSL is outside the normal conditions of use described in the SS&D certificate for manual brachytherapy seeds, more information is necessary from the licensee. Comments state that the applicant must be instructed to address why the sources are safe to use in the normal and emergency conditions of use associated with S35.1000 use.

For authorized users, the comment was made that the addition of clinical experience should be considered for addition to the authorized users training and experience criteria. Also, they say the guidance does not address the situation of the surgeon becoming an authorized user which would necessitate a more definitive description of his or her training and experience.

The comment that the pathology lab is expected to remove the seed from the tissue samples at

at least one Part 30 authorized user should be identified for the pathology laboratory and a description of the training experience criteria be provided for that individual.

The NRC commented that the guidance needs to address the patient dose and regulatory issues associated with the dose delivered to the patient from the seeds. Because 10 CFR 35.2 does not define the prescribed dose for brachytherapy sources used for diagnostic purposes, the comment that the licensee needs to provide a definition of the prescribed dose for this procedure and commit the document to the prescribed dose for each patient.

They go on to say that this dose should be specified in terms of dose to the breast tissue in the immediate vicinity of the sources and include the expected time needed to deliver the dose so that there is a clear delineation of how long the source will be left in place and time for explanation.

Patient safety. The NRC also commented that the guidance does not adequately convey the real potential for source rupture during the procedure. They go on to say that discussion should be included about the possibility for pre-treatment to mitigate I-125 update from a ruptured source.

MEMBER WILLIAMSON: What does that mean?

MR. GALLAGHAR: I do want to say that we did look into that very early on and in our discussions with several medical institutions that are doing this, they did say that they are, in fact, administering thyroid blocking agents as a precaution.

CHAIRMAN MALMUD: Please go ahead.

MR. GALLAGHAR: They also identified some areas that need further discussion within NRC. For example, format. The NRC is currently evaluating a number of different formats to determine a standard format for developing guidances under 10 CFR 35.1000 uses. The format used in the preparation of this guidance was one provided by the NRC early this spring. The format to use for development of the guidance document was discussed early on and we decided to follow what was then the NRC's format for responding to a technical assistance request. It was recognized that both the NRC and the agreement states may well change the format to suit their needs.

Submission of procedures. Reconciliation is needed, not only within the NRC, but within the agreement states as well on which procedures must be provided under 35.12 for the NRC and which ones the applicant can commit to having without submitting for

review.

In summary, I've described radiation safety aspects of Iodine-125 therapeutic seeds used as markers in breast cancer tumors and the guidance developed by Pilot Project 4. I've also described the comments we have received from the NRC.

The working group received the comments only recently and has not had a chance to discuss their incorporation with the document. We will be discussing comments tomorrow by teleconference. Revised guidance will be submitted to the NRC, Office of State and Tribal Programs no later than October 22nd of this year.

I'll take any questions you may have.

CHAIRMAN MALMUD: Thank you. First question? Dr. Diamond.

MEMBER DIAMOND: How many institutions in your region are doing this at this time?

MR. GALLAGHAR: In Massachusetts, none. We found that the initial clinical trials have been done in Florida and at the Mayo Clinics in Arizona and Illinois.

MEMBER DIAMOND: Is this being proposed that these seeds to be used to bracket the lesion and then immediately go for surgical extirpation, or are

there instances where they will be placed and then three or four months later, then and only then removed. And the reason I ask the question is that ladies with breast cancer who have the surgery done sometimes will go immediately to surgery and other times we place radio opaque clips. The woman, depending on the stage of her disease and clinical status, may get three or four months of new agent chemotherapy and then these same markers are used to help find where the tumor bed was, because the tumor can shrink, and as a surgeon, one must ensure that the entire pre-chemotherapy operable bed is removed.

So is this being done as an immediate sequence of events or is it being planned for this three or four month delay process?

MR. GALLAGHAR: The original procedure, protocol was designed for no longer than five days, typically, within one to two days post-implantation. The patient comes into surgery, they're explanted from the patient.

MEMBER DIAMOND: If this is also being used to bracket a tumor bed, in a woman who will be receiving chemotherapy, potentially the lesion can completely go away under the influence of the chemotherapy. During that period of time there is a

strong possibility, particularly an older lady with fatty breasts that these markers can migrate within the breast tissue. The clips that are used at the present time by our diagnostic radiology colleagues are special angle clips that are designed to help provide traction, so there would be the possibility that this could migrate some distance within breast tissue, particularly in a woman with very fatty breasts and very weak suspensatory ligaments.

The other thing I would like to comment is that you must realize that in the typical setting the surgeon removes the specimen, pulls it on out, drops it in a container. You need to make sure this doesn't fall out, obviously, from the specimen during the transfer and the specimen is usually first processed by not the pathologist, but by laboratory technicians, and it's only at some later point that it actually, the M.D. pathologist gets to this tissue.

So as you're thinking through these series of events, who is handling this tissue, what training is required, it needs to be very clearly thought out at all points along that pathway who is actually handling the tissue and recognize that this will never gain any popularity if the regulations are so strict that only specialized laboratories can have access to

it. Those are my comments.

CHAIRMAN MALMUD: Thank you. Dr. Williamson.

MEMBER WILLIAMSON: Is this currently being carried out as a research study by broad scope licensees using their own expended seeds or leftover seeds from perhaps they haven't used for prostate brachytherapy? Or is this as commercial venture being undertaken by the seed vendors and manufacturers? And if the latter, why aren't they maybe considering amending the SSDR and providing an appropriate safety analysis?

MR. GALLAGHAR: Currently, this procedure is being done at a broad scope medical institution in Florida where it began. There has been discussions with the manufacturers to amend their SS&D sheet. I'm not sure where that direction is going. I think they're looking at their corporate crystal balls to see how economically viable it's going to be.

MEMBER WILLIAMSON: I see. So it might be that it's just something left in the province of broad scope licensees, but you're considering extending it to 35.1000 so that specific scope licensees can do it too?

MR. GALLAGHAR: That's correct.

MEMBER WILLIAMSON: Without an SSDR.

MR. GALLAGHAR: Correct.

MEMBER WILLIAMSON: Modification.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: Does that have a maximum activity that they have proposed on a say 0.12 to 0.13 millicurie? Have they proposed any maximum activity or minimum activity yet?

MR. GALLAGHAR: The proposed maximum activity is the .3 millicuries. Typically, as I understand it, it's around the 100 microcurie range is what they use for the implantation.

MEMBER NAG: Okay, now in the broad scope outside lab, how are -- are we doing any containing, are we putting in a container or anything like that?

MR. GALLAGHAR: Yes, that's where, as I mentioned earlier in my presentation, that the license reviewer would have to evaluate how that transfer is being made to make sure it complies with DOT shipping requirements.

MEMBER NAG: Now the third question is that requiring a new licensee to have a license maybe going a little bit overboard because you are probably talking about two or three seeds at 0.1, 0.2 millicurie for a total maybe of less than 1

millicurie. Am I right?

MR. GALLAGHAR: Right.

MEMBER NAG: We have many patients who we had implanted radioactive seeds including prostate seeds and in other organs who have died with a total radiation activity of more than 1 millicurie because of the larger activity of seed and the larger number of seeds. And after they have died, they had been transferred over to the funeral home.

The only requirement we've had is if we are not opening up the organ, we are just tagging to the patient a paper that says the patient has X number of millicurie implanted in him and if you are not doing any autopsy procedure where you are opening up the area, that patient can be buried in a normal fashion.

We are not talking about a much lower quantity, less perhaps, even less than 1/10th or 1/100th of that and now you have an overburden of having a new licensee taking over less than 1 millicurie seed when this is just a small amount. I think you have to consider the amount of millicurie in relation to what we have been doing with hundreds of patients that have been transferred to funeral homes.

MR. GALLAGHAR: I understand. If I may,

before we go on. I will say that currently what you're commenting on right now is a comment made by NRC to the draft guidance, this use of external pathology laboratories. Currently, this is being used, the pathology laboratories are located within the licensee's own facility, so that has not become an issue, but it is an area that we are going to be looking at the guidance document to make sure it's clearly stated in there.

Should an external facility be used, we get a commitment that the proper requirements are adhered to, that being the DOT requirements for transport from the licensed facility to the other.

MEMBER NAG: For less than one millicurie, do you need all that for less than one millicurie?

If you are having the maximum of two or three seeds, what I suggest is you make a guidance document for something with less than one millicurie so that if you take a small and insignificant amount, you would not have burdened him with paperwork.

If you take a large quantity, I don't know why someone would want to implant 10 or 15 seeds and have a total of 10, 5 or 10 millicurie. That's different. But when it's less than one millicurie, I think you are making it overly burdensome.

MR. GALLAGHAR: Again, this is something that's under discussion with the working group.

CHAIRMAN MALMUD: Dr. Vetter.

MEMBER VETTER: If I could just reflect a little personal experience, since you mentioned three facilities by name.

(Laughter.)

The seeds are 100 microcuries. They are usually one or two seeds, occasionally three. It's used primarily to replace the wire so that the surgeon can more accurately pinpoint the lesion and there's considerably more tissue sparing during surgery as a result of that as opposed to tracking that wire. So they are much more satisfied with the surgery.

The seeds are removed in surgery. It wouldn't have to be -- I mean a licensee could do, as you suggested, they could send it to the pathology lab and they could be removed there, but we remove them in surgery. They do not -- so when the tissue goes to the lab, the pathologists scan it and it's cold. There's never been a problem with the surgeon trying to locate. In fact, when they're teasing with their scalpel, they can easily find the seed. They're not going to cut through a seed. That would be very unusual. And surgeons have really liked it.

One question I have is what, it's sort of a rhetorical question. What training would you give a surgeon, using this technique, that would take eight hours?

I mean the amount of training the surgeon needs to do this is about a half hour. They need to know what they're looking for, what the consequences are and what they have to do, where to put it when they're done or where the surgical tech puts it when they're done. It's really very, very straight forward.

MR. GALLAGHAR: I understand. We actually talked about that very issue, how much training to provide the general surgeon. Someone at the working group wanted to have it at a minimal, as you say. Others wanted to go for much much longer.

It actually came up in the discussion.

CHAIRMAN MALMUD: Dr. Eggli.

MEMBER EGGLI: It seems to me that the biggest risk here is breaking one of the seeds. Can you cut a seed with the scalpel?

MEMBER VETTER: I never tried to. I suppose you could. You are more likely to cut it with scissors.

MEMBER NAG: Can you? I guess if you

tried really hard enough, you could. I mean we had tried, not that it happened. The only time you can really do it if you're using a scissors and you're inadvertently trying to cut it. The only other time you can break it is if you are having an applicator where you having it direct and once you push it doesn't go, you keep on hammering at it. You can break it.

MEMBER DIAMOND: Well, what about, what about if you're using a Bovi electrocautery device. Most of these operations are not -- after you make the skin incision are done with a Bovi. And for those of you who have never seen one, it's an electron scalpel that has this cutting with an electric current, will actually go and cauterize the small vessels, so you're actually going around the tissue in a three-dimensional manner, trying to get a spherical of the tissue. What happens if you take that Bovi and make contact with one of these little metallic seeds? That actually is the most likely scenario.

CHAIRMAN MALMUD: Yes.

MR. GALLAGHAR: Could I respond to some of these comments? I want to say that we did look into not only did we do an End Med search to see if historically what kind of damage has been done to

those brachytherapy seeds overall, and I reviewed personally all the cases that were reported to End Med, and as you say most of them did involve either a crushing injury of some sort or scissors. We were unable to find that involved surgery, scalpel.

I did talk to colleagues as Mass. General Hospital that use this procedure routinely, not only for prostate, but they have had occasion to surgically remove a seed of this sort and they also have not had any problems with any leakage.

They went on to voluntarily quote test this, by implanting some live seeds into chicken breast tissue and then surgically remove them under not laboratory conditions, I can say, but they certainly did try to apply as much force as they could and then they leak-tested the sources and they did not fail.

CHAIRMAN MALMUD: Thank you. We do have some questions from the floor from others, members of the ACMUI.

May we entertain those now?

MR. ESSIG: Your choice, Mr. Chair.

CHAIRMAN MALMUD: Yes, please. Would you please introduce yourself.

DR. WHITE: I'm Jerry White. I'm here as

a representative of the AAPM, although my comments are strictly personal, as a medical physicist and an RSO, contemplating this procedure in the future.

One of the things that I think as this rolls out, that is an important difference between the way it's handled now in large facilities, and in large active, community hospitals like ours, is that this procedure is seldom done in a single facility start to finish.

A more common model is radiation oncology or authorized user, you have a mammographer who may or may not be in the hospital. Could be in a free-standing center. And then a free-standing surgical center and then another pathology facility. And effective administrative control over the seeds from all of those, to all of those different facilities in the community setting is virtually impossible. The economic pressures are enormous.

And if this rolls out to the community hospital, the regulatory structure really must have some structure that is more powerful and I know -- I have great respect for the power of regulators, more powerful than the economic pressures that we face when dealing with surgeons and pathologists and disparate institutions. I think that's not to be trifled with.

And I also just can't -- several people talked about breakage of seeds and scalpels. We also have microtones involved, seeds that might end up -- the surgeon thought he has removed. Ten surgeries that day. You need to get them all done. Got to rush to the next patient. I'm sure I counted all the seeds. And the pathologist runs it through an autoclave. The contamination problems with I-125 are significant. It's got a long half-life. It goes to the thyroid. It's got a low ALI. There's a potential if these seeds are cut and there are a lot of knives in this process, I think to be a real issue.

I just wanted to be nervous in front of all of you about this.

CHAIRMAN MALMUD: Thank you. Is there another comment?

DR. JANKOVICH: This is John Jankovich from the NRC. I'd like to make a comment on the question which was raised here a few minutes ago, if the seeds can be damaged by scalpel. NRC has a contamination case on their re-investigation. This was a strand manufacturer, melted, biodegradable material around these seeds and made a strand several units long and how they were making it on a flat tray and there were rolls of seeds and they pulled the

plastic over it and they separated individual strands by cutting them into long strips. And there is an indication that some seeds were damaged and they got into the patient and we have contamination.

The case is not closed yet. I cannot tell more about it. This is our early indication.

CHAIRMAN MALMUD: Thank you, Dr. Jankovich.

Any other comments from the floor? If not, we'll return to the committee.

MEMBER LIETO: Dr. Malmud, a quick question for Mr. Gallaghar.

Have you received any comments from the agreement states on this proposed guidance?

MR. GALLAGHAR: We have received comments from the Organization of Agreement States, yes. And they were more editorial in nature.

MEMBER LIETO: Thank you.

CHAIRMAN MALMUD: Mr. Bailey?

MEMBER BAILEY: Bob, are there any indications that this -- the use of these seeds could be extended to tumors other than breast cancer?

MR. GALLAGHAR: Yes.

MEMBER BAILEY: But would you mind commenting on that?

MR. GALLAGHAR: I know from having discussions with a number of institutions around the country, as I said, that there has been some interest in this use of these seeds and other tissues throughout the body. Not being a physician, I'm not going to say exactly where, although I do know that there is some interest in this overall for other areas in the body.

CHAIRMAN MALMUD: Thank you. Any other comments from members of the Committee?

Mr. Lieto?

MEMBER LIETO: I wanted to ask Mr. Gallaghar, was one of the purposes of your presentation here that we could comment on all of these various items or was it more informational for us that this is being considered, we may be coming back and proposing specific guidance.

MR. GALLAGHAR: Yes, this is, for your information, this is where the guidance -- the guidance is in its draft stage right now. It's under review. It's been -- we've had comments back from NRC and from the OAS. It's also been provided to the CRCPD as well.

MEMBER LIETO: Final question, has anybody actually taken all these radiation safety

considerations and written up procedures and actually go through all this from insertion to excision to pathology lab and so forth?

MR. GALLAGHAR: As I understand it, this is currently being done in Florida. And it's been licensed by the State of Florida recently, so that all has been submitted to the State of Florida, reviewed and approved.

CHAIRMAN MALMUD: Dr. Diamond, you are from Florida.

MEMBER DIAMOND: I am, indeed. I think it would be very hopeful if we could get copies of the research protocols that this is being done under and as we review how these institutions are proceeding, that would be very informative.

The second issue is I still would stand by my thought that much more likely than a seed being punctured or damaged by scissor or by cold scalpel steel would be an electrocautery device coming into contact with one of these metallic seeds and as you know, that can generate extremely high temperatures. It would be very useful to ask the vendor have they ever explored what would happen if one of these electrocautery -- because again, what are you trying to do? You have a sphere of tissue you're trying to

remove and you're going to have an array, if you will, of these metallic seeds. And after you go along, it's very possible to make contact with that. That's probably the most likely real case scenario and probably the one most likely to generate excessive conditions.

MR. GALLAGHAR: I understand. I'll take that under consideration.

CHAIRMAN MALMUD: And the Iodine will volatilize.

I think that Dr. Williamson was next. Did you still wish to make a comment?

MEMBER WILLIAMSON: I guess I'll make a comment.

CHAIRMAN MALMUD: why not?

MEMBER WILLIAMSON: I'm never at a loss for words. Well, I think that any realistic protocol has to take into account that these are quite fragile seeds and in my experience it's quite easy to rupture them, although I think the risk is more from sheer forces than direct puncture. So a thought would be to make sure that the patient, who would be the primary individual at risk, is safeguarded from a puncture or leak.

Other than that, Iodine seeds are in many

ways are among the more innocuous of the radioactive materials that we do have. If they are lost or one loses control of one or two very low activity seeds, so you might consider tempering your recommendations of what to do downstream from the patient with consideration of what really the risk is, worse case scenario.

MR. GALLAGHAR: Well, let me just say for the presentation today, I had to kind of summarize our guidance document and then I wanted to have time to present information on the comments we've received from NRC.

I will say that we went into detail about protecting the patient. And the fact that the NRC had no comments on that, I think speaks for itself. But that is adequately covered in the guidance document.

CHAIRMAN MALMUD: Your comments were with respect to protecting the patient, is that what you said, the patient? What about the health care workers, the nurses, the pathology workers, morticians inthe event that the patient had that fate and those are the issues that you're presenting to us, clearly, in addition to the others for our consideration. Though the primary concern is always the patient.

MR. GALLAGHAR: Right.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: I think we will have to keep things in perspective in that the maximum activity from what I have heard now would be about 0.3 millicuries. What happens when you inject purposefully 0.3 millicuries of Iodine-125 into a patient? How much of that is uptake -- how much of uptake is the thyroid and what bad effect does it have? Zero point three millicurie, if you inject purposely is not of any consequence. Then I think we are making a mounting out of a mole hill. I think we have to find that out first, what is the maximum millicurie you are going to use on the patient and what is in the worse case scenario, what is the bad effect on a patient?

Quite simply, I contend that putting 0.3 millicurie of Iodine seed in a patient is not going to have adverse consequence on a normal place. That's not something that has me worried, if I had the seed encapsulated, even if someone ought to remove the seed, or the seed for some reason was not removed, that is not an adverse consequence.

But if the seed was open and that 0.3 millicurie were to end up in the thyroid, would it cause any problem? That's something you can find out

firsthand.

CHAIRMAN MALMUD: There was one more question, I thought.

Mr. Lieto?

MEMBER LIETO: Yes, it's kind of a little bit of follow-up to what Jeff was talking about in that I think there's -- when you address this, this modality, it seems like you have a lot more than what is even involved for putting manual, sources manually into prostates.

And I would -- where more seeds are being involved and so forth, and I would kind of maybe use that as sort of maybe a template, as you're going along through this process of what you're going to be requiring or recommending for individuals who want to use this process because verifying the source activity, doing individual dose definitions, I really don't understand what the value of all that is going to be when these things are pre-fixed, you know, right up front. I mean it's not going to vary, even if you have two or three seeds. It's going to pretty much be the same. And I think to have everybody that's going to do this jump through some of these hoops, just to document something that once you know it is not going to change, I really would kind of precaution you on

that.

I think they've already addressed -- right now, we don't require training of the urologists that you're requiring for the surgeons here and urologists are doing the prostates. There's not that requirement, so why put that on the surgeons?

So just some things you might, as you go along, try to have things maybe sort of similar on what you're requiring for prostate implants that you're going to require for this.

CHAIRMAN MALMUD: You've given us a lot to think about. Have you completed your presentation?

MR. GALLAGHAR: Yes.

CHAIRMAN MALMUD: You've given us a lot to think about. This is an interesting application.

What makes me anxious, if I may use the Chairman's prerogative to make a comment, what makes me anxious about this is the use of an isotope by members of the public who are not knowledgeable of the risks involved in handling radioactive material and the certainty that one of these, one or more of these seeds will be lost, particularly given the background which includes the possibility that the implantation may be at one site, the surgical removal at another, the absence of a surgical removal possibility, the

zapping, if you will, of one of these seeds in the OR, with volatilization of a small amount of I-125, perhaps by a woman who is a nurse at the end of her first trimester of pregnancy, the consideration as to what would happen to the fetal thyroid in that case. There are many things for us to consider.

And we need an opportunity to do those things. We don't have the dosimetry at our fingertips, but we do know that the radiation burden would be low, low radiation burdens are not acceptable to fetuses in our minds until we convince ourselves that they are and there's a lot for us to work on and we'll all have to deliberate on this with more facts at hand.

But you've certainly given us the background with which we can work to come to a recommendation.

Did I summarize -- well, I think Dr. Vetter wanted to speak next and then --

MEMBER VETTER: I'd just like to make one final comment and that is that this procedure is spoken of very highly by the breast surgeons. I think it has significant benefit for subpopulation and we do need to be careful that we don't do -- prescribe regulations in such a manner that would discourage

this very positive use.

On the other hand, once the use gets out of the control of a facility where everything is done basically in-house, it's very easily controlled there. Once it gets into the community, as Jerry White was mentioning, controls certainly are very, very necessary in order to prevent any of these adverse events. So I guess the point I'm making is we need to strike a proper balance here. We don't want to discourage the technique. On the other hand, we do need proper controls.

CHAIRMAN MALMUD: I think that Dr. Suleiman was next and then Dr. Nag.

MEMBER SULEIMAN: My take on it is you're using an approved product. The patient risks from my perspective are minimal. This is a therapy patient. The training for the user should be minimal, but shouldn't be zero. I see a real potential for this thing expanding beyond one facility and if people develop a flippant attitude, safety concerns could come to play with loose seeds and outside facilities where people say oh, it's not -- it's of no concern.

So I think nothing is new here. It's just a case of pulling the appropriate controls from the various other nuclides where you have similar

experience.

MEMBER NAG: Just a comment partially for Dr. Lieto. When the urologists are involved in a prostate implant that you have separate radiation training, but it is always done in conjunction with an authorized user, that is a radiation oncologist.

Similarly, when our surgeons, when we do implants in the liver with radioactive Iodine seeds or implant in other organs, with the surgeon, they don't have the radioactive training, but we do and we are there, so that even if he's facing an operation and the patient dies, we follow the patient or we go to the OR and we tell the surgeon what not to do and what to do. There is a big difference.

Here, if an authorized user was there, for example, if we said that the seed is being inserted with the help of an authorized user, I have absolutely no problem if the surgeon has no training at all. The authorized user is present and will guide the proper radiation precautions.

CHAIRMAN MALMUD: Thank you, Dr. Nag. If we may, yes, Tom?

MR. ESSIG: I just wanted to come back to the comment that was made earlier by Dr. Vetter, following the previous presentation and you recall I

said that we would hear Mr. Gallaghar's presentation and then maybe try to draw the issues together.

The previous presentation pointed out that the existing ANSI standards for these sources do not involve a puncture test. And I think based on the dialogue we've had around the table, perhaps a surgical puncture with a scalpel may not be a major issue, but Dr. Diamond noted that certainly an electrocauterization was a very real possibility.

So it seems to me the question is that we would pose to the Committee is would it be -- if we have an SS&D certificate, needs to be modified, it needs to be modified in some particular direction to incorporate some existing -- to address some existing standard and while that standard right now doesn't talk -- doesn't address these additional tests, I mean beyond puncture and talking about particularly the one that Dr. Diamond has raised, so I'm just raising this -- is there any sense that it would be worthy of modifying a standard or seeing there's interest in modifying a standard to incorporate the additional test to assure ourselves of the safety of these -- of the various surgical processes that would involve these seeds.

CHAIRMAN MALMUD: Dr. Williamson, do you

care to respond to the question?

MEMBER WILLIAMSON: Well, I mean if this is going to become a widespread use of this product, it seems a reasonable step to undertake. I think the maybe more interesting question is, the more difficult question is is who should do it? It seems to me this is the sort of standard-setting activity that would require a lot of back and forth and dialogue among the vendors, agencies, different sectors of the community and it's probably best done within the context of an organization like ANSI or ISO and not by the NRC or the FDA, but you know, be done in some sort of a forum that builds in input from all of the involved sectors. So I think to encourage them to do it would be a reasonable step.

On the other hand, it sounds like this particular initiative is being taken on with the presumption that this is going to be done under 35.1000 and that one of these exemptions from the existing rule language is that an SSDR is not going to be required. That seemed to be an assumption, I thought that you -- that Robert's presentation made basically.

MR. GALLAGHAR: Well, we have approached some of the vendors, specifically one of the vendors

out in Illinois to see if they're interested in doing a modification to both their SS&D sheet and the 510K authorization as well.

Likewise, we also recognize that these facilities may want to do that so it may want to use this material in advance of that, so we've been working with the NRC to see if there's a way to do that. One avenue, as I understand it in the SS&D review process, is use a historical information on how these devices or sources stand up under the conditions to be expected. So we're pursuing that as well.

CHAIRMAN MALMUD: Ralph?

MEMBER LIETO: I guess I would ask Tom, would you want a formal recommendation from this Committee that the SS&Ds need to be modified or need to address testing that includes common medical events in their temperature pressure impacts? In other words the whole gamut of categories? Is that one of the things that would -- that's being asked of us?

I agree with Jeff. I don't know whether to say it should reach Category 3 in this task or is it more appropriate that it be category 5 and just don't have the experience for that. I mean you'd like to say 5 across the board for everything. You know it's not going to be a problem, but I'm sure as heck

it would affect the dosimetry distribution of the sources. So I kind of -- I'm supportive of us making a recommendation, but I'm not really sure where we, how we want to couch this.

CHAIRMAN MALMUD: Dr. Diamond?

MEMBER DIAMOND: To respond to your question and Ralph's comment, I think the appropriate way to proceed is before making any recommendation as to what degree of confidences we have in these small seeds with respect to puncture or temperature, let's go get copies of the protocol that these are being done under, let's learn about exactly how these operators are doing it. Are they having any specific requirements made, but they're not allowing electrocautery. It's a non-issue. So I think the best next step is to simply get a little bit more information and then we can go on and make a reasonable recommendation.

CHAIRMAN MALMUD: So the consensus of the Committee appears to be that we need a little more data and then the opportunity to review what is a potentially valuable surgical technique and then to make a recommendation.

MEMBER DIAMOND: So this would be a follow-up item then?

CHAIRMAN MALMUD: This would require follow-up, but we do need some more data when you point out to us doesn't exist right now. So that would be the Committee's recommendation.

Does someone wish to make that recommendation?

MEMBER DIAMOND: I so recommend.

CHAIRMAN MALMUD: Seconded by Dr. Williamson. Motion by Dr. Diamond, seconded by Dr. Williamson. Any further discussion?

MR. ESSIG: Just one point. We have to be mindful in any review that's done and I agree, it needs to be done, that we are -- it was mentioned as in the opening slide that there are five pilot projects. Pilot number 4 got off to a very slow start and so it's lagging the others considerably. All five are supposed to go to the Commission very, very shortly.

November 8th. And so I don't believe there will be time to review this specific guidance and have anything on paper, but if it was done at a later date with the understanding that all guidance is always revised, we do the best we can with the information we have and so this would go to the -- this would go, be appended to the Commission paper.

We share it with them and receive some additional feedback from them, if any, and then the Committee could undertake it as a separate project and provide guidance.

That seems like a reasonable approach.

MEMBER BAILEY: My understanding of the report that was going forward is really more -- rather than to be adopted per se was that it was to demonstrate that this process could work in developing guidance, not that this guidance coming out of it was specifically the guidance that NRC was going to adopt. So I think there's plenty of time after it goes forward to comment on it.

CHAIRMAN MALMUD: Excellent point. Therefore, the final recommendation from the Committee is that we will reserve our comment for the time being? Are we being asked to approve of something without the database? No. I know the answer to the question, I just wanted to put it on the table. So therefore, what -- do we stand by our previous motion and second? Dr. Williamson? That's our recommendation and we regard this as a potentially valuable technique and wish to investigate it further, have more data.

Thank you.

Thank you, Mr. Gallaghar. You generated a lot of interesting discussion.

MR. GALLAGHAR: Thank you.

CHAIRMAN MALMUD: We may now, if you will, move on and --

MR. ESSIG: Mr. Chairman, the question becomes we had been scheduled for a break at 3.

CHAIRMAN MALMUD: Yes.

MR. ESSIG: The next presentation is scheduled for one hour, whether or not it takes that or more even --

CHAIRMAN MALMUD: Can we take a 10-minute break?

We'll be back at 3:25.

(Off the record.)

CHAIRMAN MALMUD: The next presentation will be by Dr. Sherbini. It will be entitled "Staff Findings and Follow-up to the ACMUI Report on the NRC Method of Dose Reconstruction." Dr. Sherbini will present the NRC staff response to the ACMUI's recommendations relating to the staff's method of reconstructing doses.

And with that introduction, I think I brought you all back to the table. Dr. Sherbini, you're on.

DR. SHERBINI: Thank you, Dr. Malmud.

If I might correct the statement you just made, this is really a response to the ACMUI report. It's just, I guess, a summary of where we stand, what we've learned from it, and our conclusions based on that case. So it's really not going to address the ACMUI report directly.

For the benefit of members of the public who might not know about this case, I've prepared a short background summary of the case. This case occurred about two years ago at the St. Joseph Emergency Hospital in Ann Arbor, Michigan. It's a very large hospital, about 500 beds.

The case involved a patient who was hospitalized for treatment for thyroid cancer, and it involved exposure of 35 members of the public who visited the patient during her period in the hospital, which was about a week. Some of these people were believed to have exceeded the acceptable limit, which at the time was 100 millirem, and one of them was believed to have exceeded the dose limit by at least a factor of ten.

The licensee notified the NRC in August about the incident, and the NRC conducted a special inspection in October of the same year, and the

inspection report was published in December, about six months later.

In that report the NRC detailed what it did and its dose assessment, and it also reported the licensee's dose assessment, which was three to six rem for that most highly exposed individual, whereas the NRC's estimate was 15 rem.

Both estimates used the same methods of assessment. The only difference was the estimated hours of exposure that resulted in that dose. One was 40 by the licensee and one was 77 by the NRC.

A year later after the report was published, was issued, the Society of Nuclear Medicine sent a letter to the NRC Chairman indicating concern that the NRC had grossly overestimated the dose. The letter was accompanied by a proposed reconstruction which concluded that the dose was closer to one rem rather than 15.

The Commission directed us to charter ACMUI to look into this, to do an independent review. The NRC staff also did their independent review. ACMUI submitted the report to us on May 2004, and we, in turn, submitted our report to the Commission, which included a review of the ACMUI report in June of this year.

The conclusions we drew in our report was that NRC -- basically we concluded that the Region III's estimate, 15 rem, is still we think the most probable and the best estimate for this case. ACMUI's estimate was not very far off, nine rem, using the assumptions that NRC used, basically that the exposure duration was close to 77 hours; that the person exposed did not have the benefit of shielding, and so forth.

If the benefit of shielding is introduced, ACMUI found a dose of four rem, which is closer to the licensee. So there is consistency here.

The outcomes of this were, I think, beneficial to us because the ACMUI report, as well as the ultimate dose reconstruction which was prepared by Drs. Marcus and Siegel, pointed out quite a few areas in which the NRC probably should have done better than it had. Most of the areas had to do with preparing the report in a way that would be clearly understandable to the public with all of the assumptions and approximations clearly and explicitly stated. We didn't do this as well as we might have, and that might have included some of the questions anyway.

As a result of that, we have started

several steps, actions, to correct some of these weaknesses. One of these was to institute a headquarters review of all inspection reports that involve dose assessments. Most of these reports would be created by the regions, and the purpose here is not to check on the regions, but basically to look at the final report from the point of view of people who don't know much about the case.

We found from this case that people who are close to the investigation generally make assumptions and approximations that they think are obvious and so need not be stated, and this has caused problems.

And so we would be looking for this kind for thing. We would be looking for unstated assumptions, approximations, data that was assumed but not reported, and so on. And the idea is to make the report stand alone and everything that is done in the report would be obvious and clear so that anybody who reads it will understand what went on, not necessarily agree with it, but at least understand it.

We also plan to issue a generic communication to the licensees to describe generally the case and the difficulties we encounter and to provide some hints or ideas on how to make sure that

data would be available in the future in case those reconstructions may be needed.

Another action we're taking is to issue guidance to licensees on how to assess effective dose. This was a big issue in this investigation, and it was raised by Drs. Marcus and Siegel and was also raised by ACMUI, and it's a valid issue and it's a difficult one. And we are now working on coming up with reasonable guidance on how a licensee doing surveys in a patient's room might get a reasonably good approximation of the effective dose that a visitor might receive under these conditions, especially that typically the visitors would not be monitored, and so the survey day would be probably the only data that's available to assess that.

And so we're working around that idea, and hopefully we should have something within a few months.

Another thing that was pointed out by the ACMUI, and we're working on that, was to come up with methods that would allow the regions to permit licensees to allow members of the public to be exposed to doses much higher than is currently permitted, which is 500 millirem without any special exemptions.

And so the Commission has directed us to

explore different ways that we might do that: license conditions, changes in the regulation, other ways that would efficiently, quickly allow licensees to go up much higher than 500 millirem if the conditions make it necessary to do so.

We're not sure how we're going to do this yet, but we are working on it.

A lot of these issues that came up, the effective dose and so forth, the relationship between deep dose and effective dose which came up in the ACMUI report and was brought up by Drs. Marcus and Siegel, we plan to offer what we call advanced training in these concepts, what they mean, how they can be implemented, what are the difficulties and approximations, and so forth, and the training would be offered to the technical staff at headquarters and in agents. That's a fairly long-term project, but we have started working on that and developing the outlines of such a thing.

That's all I have, if there are any questions.

CHAIRMAN MALMUD: Thank you, Dr. Sherbini.

Are there any comments or questions for Dr. Sherbini? Dr. Vetter.

MEMBER VETTER: Relative to your thoughts

about increasing allowable doses to members of the public, I assume you're familiar with NCRP Commentary 11.

DR. SHERBINI: Yes, I have.

MEMBER VETTER: Okay, and they actually -- the NRC regulations currently do follow that to some extent, allowing medical facilities to release radioactive patients who could in such release result in a maximum of 500 millirem to a member of the public.

DR. SHERBINI: Yes.

MEMBER VETTER: But they also have a paragraph that says to family members. It could be expanded to focus on, you know, caregivers specifically. To family members, it could be raised to five rem contingent on the family members being trained and monitored.

DR. SHERBINI: Yes.

MEMBER VETTER: And I would suggest that that would be something that we should seriously consider.

DR. SHERBINI: These are the dose levels we're contemplating actually, and the Commission did not place any upper limits to what the dose should be that can be allowed, and so that's really quite open

at this moment.

CHAIRMAN MALMUD: Any other comments or questions? Mr. Bailey.

MEMBER BAILEY: If I'm remembering correctly, Carl Paperiello said that NRC had allowed more than 500 millirem on certain licenses.

MR. ESSIG: Yes. Yes, they had.

MEMBER BAILEY: So you will already entertain that, I guess.

MR. ESSIG: Yes.

MEMBER BAILEY: Okay. I just --

MR. ESSIG: The difference I would comment here is that the exemption that we had previously entertained was for a situation which was known about well ahead of time, and in one particular example that comes to mind, the licensee had asked for an authorization I believe up to the occupational dose limit of five rem, and we ended up approving two rem, and it was for a mother who was giving care to her daughter.

And the licensee just described the situation as that the regulatory requirements are just too constraining. We need authorization to go up to some higher value.

We had originally considered that why not

just consider this occupational exposure. I mean, we have volunteers in hospitals who aren't compensated, but yet they could perhaps receive occupational exposure, and where we got into a problem there is that the way occupational exposure is defined in Part 20. Just this use of it was not -- our Office of General Counsel thought that this use of it was not really authorized, and so then we had to go back to a case specific basis.

But I think the recommendations of the committee on this score were well taken in that when we have situations like this, we need to move very rapidly. I mean there are emergent situations, and I kind of liken it to in Part 20 right now. We have a provision for a planned special exposure where for occupational now a licensee can call and seek counsel from the regional office on the planned special exposure. We rarely use them, but the regulations provide it.

This would kind of be done in the spirit of that where the licensee could consult with the regional office and they'd operate within some framework that would be prescribed in the regulations, and we would propose such to the Commission and see their approval perhaps among a couple of options that

we might propose.

CHAIRMAN MALMUD: Thank you.

Any other comments or questions?

MEMBER SULEIMAN: I mean, I'm just going to reiterate what Richard had said earlier. I mean at the last meeting you mentioned NCRP Commentary 11, and I got a copy of it. I think we're moving towards suggesting what's already been thought out and spelled out here.

I would strongly encourage the NRC to just codify that, you know, in addition to your general population, your occupational worker. You know, it's spelled out right here. I wouldn't take time to read it, but I think it's under 5.3.3 in the NCRP Commentary No. 11. I think it was published in '95.

So that was probably after your last round of rulemaking.

CHAIRMAN MALMUD: Thank you, Dr. Suleiman.

Did you wish to respond to Dr. Suleiman?

DR. SHERBINI: No. I was just going to note that really the difficulty is coming up with an efficient mechanism rather than coming up with a dose number. The dose numbers, there are quite a few documents as we pointed out that recommend doses that are high enough to serve the purpose, but it's the

mechanism, regulatory mechanism that should make it very efficient for licensees to use it.

CHAIRMAN MALMUD: It sounds as if we have two possible mechanisms. One is the NRC Commentary 11. The other one is, as you mentioned, the planned special exposure, which would be contemporaneous or in anticipation of it.

The next question was from Dr. Williamson.

MEMBER WILLIAMSON: Yes. Just a couple of comments. As I noted earlier today, I was not given the opportunity to study the Commissioner's voting record nor the written response that was made to our report, but in scanning it, I would point out a couple of recommendations, technical recommendations that seem to, you know, not have been responded to directly.

One was that the issue of shielding not being used or being used and whether the dwell time of the patient was 39 or 77 hours. Based on the information we were able to get from interviews both with the Region III -- was that right? -- inspectors and a representative of St. Joseph's Hospital, it is not so clear cut, you know, who was right. There is evidence that a reasonably thorough reconstruction more contemporaneous than the interviews by the

inspectors was done, and I think the recommendation was clearly made by us that when there is a controversy like this between the reconstruction of the licensee and the inspectors, that you know, I think a good faith effort should be made in the inspection reports to document the bases of the two calculations, and if NRC chooses to ignore the licensee's reconstruction or disagrees with it, he can state why.

Because there was contradictory information available to us as to, in fact, how thorough the Region III interviews and reconstruction were, and I think that it seems like sort of a little bit of a not whitewash exactly, but anyway, we put a significant effort in trying to explore this technical point, and we did make a general recommendation, which was to use these additional pieces of information to try to bracket the number and realize that there is an uncertainty.

We, of course, recognize in this case that their reason for interest in it was largely political in the sense that someone outside the agency had chosen to make an example of this, but you know, one could imagine scenarios where the interval of uncertainty could include a regulatory limit and, you

know, an enforcement action might rely on some of these distinctions.

So you know, while in this case we all know that the regulatory limit was 100 MR and well below anybody's reconstruction, nonetheless we were asked to come up with feedback to inform your process and, you know, make it more robust and to have higher scientific credibility in the future, and so this was one of our recommendations.

When, you know, there is a hint of controversy and, you know, a reasonable alternative basis for reconstructing, you know, outline it in your report and give the reasons, you know, for rejecting one rather than stating an interval.

I think the second is that, you know, I glanced through the rationale for while computational methods should be rejected. I don't find it very convincing. I think that in a situation like this where there really was not adequate information recorded to determine the exact position of the patient, a computational methodology is a very useful supplement to a purely empirical one to give you a feel for how plausible it is.

And I think as near as I can tell from Dr. Sherbini's report -- I assume it's his -- this

subtlety was not brought forth from our report. We did not recommend a similar computational methodology to Marcus and Siegel. We suggested that more sophisticated computational methodology was a good supplement to a purely empirical one.

We did not advocate throwing away the empirical one. If you recall, we stated an interval which took into account essentially, you know, of which one extreme was the NRC interpretation. So I wanted to correct what I perceive to be a misstatement and misunderstanding of our technical recommendations to us, which was in a situation where it really matters -- in this one I don't think it did, but others conceivably in the future it could -- I think it is a useful too to do computations base upon a source based methodology. You can, you know, assume different scenarios of distributions and so forth, and that will give you a feel for how uncertain the estimate is and how much it creates uncertain assumptions.

And this is very good for giving you an overall sense of how much confidence to place in a purely empirical approach, which is as arbitrary as any other, I will add, and I think has no more basis, you know, in fact than any of these others. They're

all based on a lot of suppositions for which there is no direct way of verifying. All you can do is look at a range of plausible scenarios and say it's somewhere in this interval is where the truth is, and that would be, I think, the scientific approach.

This is costly, and so you don't want to have to do this in every case, but I think, you know, one can use one's judgment, and you know when it's close to a regulatory limit and when it matters and when it doesn't.

CHAIRMAN MALMUD: Thank you, Dr. Williamson.

So in conclusion, Dr. Sherbini, Dr. Williamson, the other interested parties, I think that your slides summarize it well under your conclusions, your outcomes, planned actions, that some positive action will come out of the controversy that surrounded this particular case, and that the existing documents, meaning the NCRP Commentary 11 and the special exposure possibility will allow for this to be dealt with in a less controversial fashion in the future, with better outcomes for all of those involved via the regulation as well as family of caregivers who might be involved.

And thank you for the presentation. Thank

you, members of the committee, for you comments.

Mr. ESSIG.

MR. ESSIG: Just one final comment if I may. Just as a heads up to the committee, we will probably be engaging you in the future as we attempt to flesh out the issue of guidance for effective dose equivalent, external effective dose equivalent. The Commission has directed us to come up with something, some guidance which we interpret to mean beyond -- we had a regulatory issue summary which we issued, which was issued last year, 2003-04, and it specifically addressed the issue of the use of effective dose equivalent when computing doses of this type.

That was an issue that was raised by Drs. Marcus and Siegel in their critique, and so we asked the Commission, well, was the risk not sufficient for the medical community.

And so we've been asked to engage with the stakeholders in the medical community, and we will probably use this committee as a vehicle for that engagement, and that is the question will become then what beyond the guidance that was in that regulatory issue summary that I mentioned is needed to effectively use the quantity or the term, the concept effective dose equivalent as applied to a member of

the public in a medical setting.

So I'm just letting you know that we will be coming back to the committee with that engagement in the future.

CHAIRMAN MALMUD: I'm certain that I speak for the members of the committee who from their past enthusiastic participation in this process would welcome the opportunity to work with the staff of the NRC in developing such a policy regarding effective dose equivalent.

And thank you, again, Dr. Sherbini.

And may we move on to the next item on the agenda as we are slightly behind our schedule?

MR. ESSIG: Yes, and I have the next item, and what we propose to do is to cover this, rather than the hour that's allocated, we would propose to cover it in 25 minutes, and that would get us right back on schedule then to hear Dr. Zelac at 4:15.

And the medical event item on the agenda was one that we put there. We have made comments in the past about the need to engage the committee in the review of medical events in the future. You now have access to the NMED database, and so what I'd like to do is just kind of walk through some introductory points and then we'll have some abbreviated

presentations we'll follow with.

This item has been added to the agenda, and you'll see it on the committee's agenda every meeting. We're going to try to cover medical events at every meeting. It supports Commission direction to review medical events for possible trends and apparent root causes and provide feedback to us, and of course, we desire to gain whatever additional insights we can from the committee's wisdom.

And so the focus will be on the evaluation of medical events, will be to identify any long-term trends, to identify implementation impacts, that is, are there regulatory obstacles that may have been, in part, the cause of the event; to identify needed changes to the medical program as the result of feedback from events.

Now, the outcome that we desire is to gain the committee's feedback on trends and root causes of repetitive events over the long term, any insights that the staff may use to address the occurrence of repetitive events, recommendations staff may share with licensees to enable them to reduce medical events, and insights on says that the staff may interact with industry to enlighten them on what they can do to reduce medical events involving devices.

So the framework for the interactions on this what is to become a standing agenda item is that you will be provided a printout of all medical events for review in the briefing binder. That will be express mailed to you. We will make presentations on those issues and medical events in which we are looking for specific feedback from the committee.

The committee will then be asked to provide coordinated comments on the package of events and focused on the outcomes that I just mentioned. The length and the breadth of the discussion will be driven by the type, frequency and nature of the medical events in the regulating community.

If there are no pressing issues to discuss by either the NRC or the committee, no significant time will be devoted to this agenda item during a given ACMUI meeting.

And the topics that we would like to discuss today had we taken the full agenda, there are four categories there that I believe are in your package: incorrect dosage administration of Sumerian 153, Strontium 189, and I-131, biannual brachythgerapy medical events, medical device registration concerns, and medical events involving a Novoste device.

And so what I'd like to do is to have an

abbreviated presentation and if, Linda Gersey, if you could run through yours in an abbreviated fashion and then followed by Donna-Beth Howe, and she'll run through her presentation in an abbreviated fashion, and that may enable us to get back on schedule.

MS. GERSEY: Actually everyone does have a handout, and you should have a revised handout that was given to you this morning, and we actually updated the events to include all of fiscal year 2004.

Actually I won't go over the first part of my handout. If you'd like to turn to the slide that says "NRC Concerns One" at the top, this should be on page 3. I'm going to skip all of the first part.

The summary is there were 35 medical events for fiscal year '04, and I won't go through those. You actually have handouts of every single event in your binders.

So let's look at the first concern. We've noticed that there's kind of a small trend, as you might say, regarding diagnostic procedures where patients are given therapeutic doses instead of the diagnostic doses.

Specifically, there were five I-131 medical events in fiscal year '04. Each of these events involved patients receiving therapeutic doses

of Iodine 131 instead of the diagnostic doses that were prescribed.

We thought that was quite a high number, five of them within a fiscal year. In fiscal year '03, there were actually four events, very similar, exactly the same thing.

All of these events had underlying causes. The first one was failure to follow procedures to verify the dose or lack of procedures to actually verify the dose, human error basically in these instances.

The second part of that -- yes?

MEMBER WILLIAMSON: Verification of dose would have consisted of comparing what they thought the prescription was against a policy or --

MS. GERSEY: Yes. That or actually looking at the label when it came in with the iodine capsule, you know, any of that, just verifying what they're giving the patient, any type of verification that could be anywhere in the process.

Part of that also was not recognizing that larger doses that were given required a written directive. As we all know, anything greater than 30 microcuries of I-131 require written directive. So the technicians, technologists that were administering

these doses didn't even recognize, gee, if it said three millicuries. It didn't even tip them off maybe that there's an issue here with that, that they don't realize.

You know, usually when there's a written directive, people are more involved with paper work and that kind of thing, whereas the technologists didn't in this case. They just gave it to them. Part of that, obviously, is not verifying the dose.

So in this instance we've asked the committee to help us to think about some ways that the NRC could communicate to licensees anything that would help them prevent these type of events. For example, any best practices or any suggested ways of dealing with training; for example, specific things that will really help someone identify something for the technologists when they're actually giving the doses.

So what we would like to ask the committee to do, and specifically Dr. Malmud, to maybe designate someone to think about these thing. You have the events in your binders. Review the events, those five specific I-131 events, and try to come up with some maybe best practices or something that we could communicate to our licensees. Can't think of anything specific? Well, that's an okay answer, too, because,

you know, we're not sure how to communicate that as well.

Yes, Dr. Williamson.

MEMBER WILLIAMSON: Do you think this is a rising trend or is it the same?

MS. GERSEY: Well, like I said, in fiscal year '03, we had four events. This year we had five. But it seems like it should be preventable.

MEMBER WILLIAMSON: What's the denominator?

MS. GERSEY: I absolutely don't know.

MEMBER WILLIAMSON: I really think it would be good because I know even back as long ago as 1995, there were estimates of denominators, and it would be useful to know.

MS. GERSEY: Yes, and unfortunately I don't have those with me today.

CHAIRMAN MALMUD: In this case I think the denominator doesn't matter. We should be heading to zero error. So that we will respond to your request.

MS. GERSEY: Okay.

CHAIRMAN MALMUD: Because clearly a patient who should have gotten ten millicuries and got 100 millicuries received a radiation burden which was unnecessary.

MS. GERSEY: Right.

CHAIRMAN MALMUD: And with doses of that magnitude, we head for zero. We aim for zero error, and we will regard it as something which should be heading towards zero error.

Dr. Eggli.

MEMBER EGGLI: I would agree that the error on therapeutic doses should approach zero. However, I think it is useful to understand the magnitude. In my practice alone, we administer over 1,000 doses of radioactive iodine above one millicurie every year.

MEMBER WILLIAMSON: I didn't mean my comment to suggest that trying to drive it down to zero is not a worthy effort. It is, but I think that any conclusions about whether it's caused by a change in the regulatory system and so forth should be accompanied by a statistical analysis to determine whether there is a significant --

MS. GERSEY: And I don't think that's the goal of --

CHAIRMAN MALMUD: No, I wasn't suggesting that you were minimizing it. It just doesn't matter what the incidence is. We still have to work on the issue.

MEMBER WILLIAMSON: But when a policy decision, you know, or critiquing a regulatory approach, then you should really, I think, present the denominator.

CHAIRMAN MALMUD: Sure.

MEMBER WILLIAMSON: And consider the statistical sampling issues.

CHAIRMAN MALMUD: But if I may, I'll appoint the committee to work on the problem while we're still getting the data with regard to the denominator.

MS. GERSEY: Thank you, Dr. Malmud.

Okay. If we can go on to the next item, which is NRC concern number two, this is in regard to medical devices, certain medical devices that are actually not reviewed for sealed source and device registry by the NRC.

As you hear from Dr. Jankovich this morning, he talked all about the SS&D program. There are certain types of medical devices that, of course, are always reviewed by the FDA for medical use in humans, but there are some devices after being reviewed by the FDA are not reviewed for radiation safety issues by the NRC, and I'm going to give you two examples.

The first one is the MICK applicator for brachytherapy seeds. That has never received a sole source and device review by the NRC. It has been a policy of the NRC not to review these devices.

The question here is should NRC change their policy and actually review these. The question about this is we do know that for the MICK applicator there have been two related events, reportable events, in 2004. There have been two related events in 2003. We also had some events that have happened and are not reportable. They don't fall under the criteria of reportable in the NRC regulations, but events that have occurred being used when the MICK applicator is actually being used.

So, for example, a seed is sheered or the applicator gets stuck with the seed in it, and I think that we understand this.

Dr. Williamson?

MEMBER WILLIAMSON: Here's the situation where I do think the denominator, which is approximately 50 to 60,000 cases a year, is relevant because now you're contemplating basing a policy decision on two incidents. So we should really, you know, think about of course it's regrettable that even one incident occurs, but you have to balance this

against the fact that these are very small companies that can produce these devices. They're very valuable for many patients, and the size of the burden you create in contemplating, you know, additional scrutiny must be considered.

MEMBER NAG: I think here I can give my personal experience. I have been using the MICK applicator for many, many years. The MICK applicator itself is not a radioactive device. You are using radioactive material that you're loading into it afterwards. I mean, in that situation you should be then filling up the syringes because you are putting radioactive material inside the syringe.

So is NRC going to review every syringe manufacturer in the world? No.

My personal opinion, the MICK applicator itself is not radioactive. It is a method to put the radioactive materials into the patient, and therefore, the MICK applicator itself is not within your jurisdiction.

MS. GERSEY: Thanks for that comment.

Actually I would like to ask Dr. Vetter because he mentioned the MICK applicator this morning and the fact that seeds can get sheered. I'd like to know what your opinion is about that.

And you can think about it and get back to us if you can't think of --

MEMBER VETTER: Well, regardless of jurisdiction, I would agree with Dr. Nag that it's not the applicator. It's the user. There's something wrong. I mean, they're in a hurry. They're doing a lot of these. They punching 100 seeds into this prostate or how many that day?

Okay. Sometimes it doesn't work quite as smoothly as it does other times, and this one time, you know, you push a little hard, and you sheer the seed. But the applicator itself I don't think was the problem.

CHAIRMAN MALMUD: Yes, Dr. Miller.

MR. MILLER: If I could offer a thought based upon what I hear from the committee comments, the question as Linda phrased it was: should NRC change a policy and require SSND reviews for these types of medical devices?

I think I heard from at least some committee members the answer to that question as being no. So I guess the question that I would ask is does this require further study on the part of the committee or do you think that you're prepared today to make a recommendation?

I think that's what you're looking for.

MS. GERSEY: Yes.

MR. MILLER: A recommendation.

MS. GERSEY: Sure, if you can do that today.

MR. MILLER: I'm not trying to push you to do that, I mean, but it sounded like from a couple committee members' comments you felt it was an open and shut kind of case, unless I misinterpreted what Dr. Williamson and Dr. Nag said.

MS. GERSEY: I'm just going to interject here as well. I did have one other example of a medical device that has not been reviewed by the NRC. If you don't mind, I'll just briefly tell you what that is.

There is a company that is imbedding brachytherapy seeds into suture material. They're melting the suture material, and they're putting the brachytherapy seeds in, and a part of the procedure which actually you heard Dr. Jankovich this morning talk about is they are cutting the suture material into the size that they need, and it is the potential for cutting the seed and can cause leakage and so forth.

That type of thing has not been evaluated

by the NRC, and it's another example of something that we haven't done.

CHAIRMAN MALMUD: Okay. Dr. Vetter.

MEMBER VETTER: I guess it's my opinion that both of those are user errors, and perhaps it should be handled in a manner similar to the I-131. Determine what it is that's being done. Are they in too big a hurry? What's being done wrong? And try and communicate some advice to the users.

MS. GERSEY: And actually it is the device distributor who's actually making these and giving it to a licensee. So it's not the end user so much but actually it's part of the company. They get the seeds in, and they make these strands, and then they distribute them.

MEMBER VETTER: I know. We cut them. We use them, and we cut them. We don't have the seeds, but --

MS. GERSEY: No, actually it's actually the distributor who cuts them.

MEMBER VETTER: And in this case?

MS. GERSEY: In this case, yes.

MEMBER VETTER: And they cut one of the seeds?

MS. GERSEY: They have in the past, yes.

MS. Schwarz: After they cut them do they distribute them?

MS. GERSEY: Well, yes, but we don't 100 percent know whether or not it's --

CHAIRMAN MALMUD: Dr. Nag?

MEMBER NAG: Can I just add to that? I think you are talking about the rapid (phonetic) strand.

MS. GERSEY: Yes.

MEMBER NAG: Is that? Okay. The rapid strand is --

MS. GERSEY: No, actually the ready strand. The ready strand?

MEMBER NAG: Okay.

MS. GERSEY: Is that okay?

MEMBER NAG: That's similar to the rapid?

MS. GERSEY: Yes.

MEMBER NAG: Is it in a white material or is it in a hardened material?

MS. GERSEY: It's in a suture material, long strand of --

MEMBER NAG: All right. So basically what is happening, you're having seeds that have been put into sutures. Basically it has to be an up rate error, whether they up rate the end user or the

distributor. You are supposed to look at the seeds, and there is a half centimeters spacing between the seeds.

So when you're acting, you have to see that you're you're acting within the seed. This is the same thing as iridium that comes in a ribbon. When you cut them, if you cut them, you are always supposed to look at the iridium ribbon and cut in between the ribbon. This is not something in the NRC. It is in whoever is cutting it, whether the end user or the distributor. This is just simple common sense.

DR. HOWE: Dr. Nag, this is Dr. Howe. What is happening for the ready strand is that they are not cutting in the space of material between seeds. They're actually trimming the side of the melted plastic to insure that it will fit into a syringe, and as they are trimming that excess material off, there's a high probability of nicking, and we've had two medical events within a month.

MEMBER NAG: That is a different question than the rapid strand. I mean, that really will require further thought, but in terms of the MICK applicator, the MICK applicator itself is non-radioactive. You know, whether you are using radioactive seeds or any other seed, you are

introducing something from the outside.

So I don't think the MICK applicator is anything that we need to worry about.

In terms of the rapid strand, I don't think it's something we have to worry about, but in terms of the new one, I think I have to think a little bit more and look into what exactly the manufacturer is doing before I can give my opinion.

MEMBER DIAMOND: It would seem in that particular instance that's a manufacturing issue, and that that technique lends itself to an unacceptably high risk that you could go and penetrate these seeds as you're trying to trim it.

That's human error. You're talking about trying to go get these very narrow diameter bical (phonetic) seeds, seed trains within a set of needles. They should really look at how they do their manufacturing to see if they can go to eliminate the need for manual trimming.

CHAIRMAN MALMUD: Dr. Williamson.

MEMBER WILLIAMSON: Well, one general point is if you were contemplating, you know, just in general, this could potentially be a vast expansion, you know, of your regulatory activities to start thinking about, you know, all of these different

ancillary devices that are used in brachytherapy: buttons, needles, catheters of all different kinds, obturators of all different kinds.

I really think you should rather than be driven by a specific example, as Dr. Siegel used to call it, the yo-yo method of regulation basing a policy shift on, you know, a tiny statistical sample of events, you know, think through and really have some good criteria about when, you know, an intervention or change in policy is needed.

So I would say, first of all, develop then a general approach of deciding when you're going to take on one of these many devices and what constitutes an acceptable risk or non-negligible number of events.

You know, specifically with regard to this seed stand operation, you know, one question I would ask is whether you have had, you know, adequate regulatory authority between NRC and FDA to handle this. I should think that in a manufacturing operation, if somebody violates the integrity of one of their seeds and sends it out, the best way to handle it is for somebody to cite them for a violation either of good manufacturing practices or of their license conditions, and they will no doubt be disposed

then to correct their behavior and improve their manufacturing standards so that this is minimized.

So rather than, you know, creating a separate regulatory apparatus, I would ask you if you have exhausted other regulatory approaches to handling this matter.

MEMBER SULEIMAN: This sounds like a medical device today.

DR. HOWE: Yes, it is.

MEMBER SULEIMAN: Are you aware of anything about this specific product? Get me the information and we'll do what we can.

DR. HOWE: Yes. We're currently talking with FDA, Office of Compliance for the medical devices to see if they have an interest in following up on their end of it, and we're taking inspection enforcement action.

MS. GERSEY: Thank you.

CHAIRMAN MALMUD: Does that complete your --

MS. GERSEY: That certainly does.

CHAIRMAN MALMUD: May I indicate that Dr. Eggli, Schwarz, and Vetter have agreed to be the subcommittee to deal with the nuclear medicine issue. Dr. Eggli will chair the committee, and that will deal

with the radioiodine doses.

For the radiation therapy issues, I would ask those who already have a heavy burden to jump in on this one. Dr. Diamond, as a radiotherapist, would you be interested in this particular --

MEMBER DIAMOND: Exactly what is my charge?

CHAIRMAN MALMUD: Your charge is to take a look at the items in this agenda item that have to do with radiotherapy misadministrations or incorrect doses to see if you can apply policy changes or recommendations that might help prevent these kinds of problems from recurring.

Some of them are human error and can't be except perhaps --

MEMBER DIAMOND: So is there a root cause and if so any methods to correct that root cause --

CHAIRMAN MALMUD: Correct.

MEMBER DIAMOND: -- that is within our purview?

CHAIRMAN MALMUD: Correct. And asking to work with you would be a physicist who does radiation therapy.

(Laughter.)

CHAIRMAN MALMUD: And to round out a

committee of three, may I ask Dr. Nag, who I have already asked to do two other things today as a therapist.

Thank you.

MEMBER DIAMOND: That was a yes, for the record, from Dr. Nag.

(Laughter.)

CHAIRMAN MALMUD: That covers, I believe, the two classes of problems you have presented to us.

The third one which has to do with non-radiation devices which are used is really more, as I see it, more in the realm of the FDA, and I don't know that we are the correct body to get involved in that, and I would leave the wisdom of that to Dr. Suleiman if he has a recommendation as to how we might approach this or not approach it.

MEMBER SULEIMAN: Well, I'll follow up, but clearly if you've already been talking with some of our people, I need to find out who you're talking to and what the status is, but clearly this sounds like a straightforward issue.

CHAIRMAN MALMUD: Very good. Does that address the issues that you wanted to?

MS. GERSEY: Yes, it does. Thank you very much.

CHAIRMAN MALMUD: And we have our subcommittees designated.

Thank you.

And what will the time frame be? How urgent is this issue for you?

MS. GERSEY: Actually I had suggested maybe two months.

CHAIRMAN MALMUD: Two months acceptable?

MS. GERSEY: That any recommendations we would evaluate and the next ACMUI meeting we would tell you how we processed those.

CHAIRMAN MALMUD: Okay. I believe, Dr. Diamond, is that okay?

MEMBER DIAMOND: That's fine.

MS. GERSEY: thank you.

MS. GERSEY: Thank you.

MEMBER EGGLI: Do these evaluations come back to the whole ACMUI committee or just staff?

CHAIRMAN MALMUD: It's a subcommittee report. So it would come to the chairman of the committee.

MEMBER EGGLI: Okay.

CHAIRMAN MALMUD: And then we'll review it as a committee and present it to NRC staff for its review. Is that the correct process?

MS. GERSEY: Yes.

CHAIRMAN MALMUD: That's the one we'll follow.

MS. GERSEY: Great. Thank you very much.

MEMBER LIETO: Okay, and then Dr. Howe will make an abbreviated presentation.

CHAIRMAN MALMUD: Oh, I'm sorry.

MEMBER LIETO: That's all right.

CHAIRMAN MALMUD: I didn't mean to ignore you.

MEMBER LIETO: Yeah. Well, I couldn't let you go twice.

What we're doing right now, is this just having to do with the specific instances that Linda has just brought up?

CHAIRMAN MALMUD: Yes.

MEMBER LIETO: Okay. So what Donna-Beth is going to talk about is the database in general, and we're going to address those issues?

CHAIRMAN MALMUD: We're looking at those specific issues and wondering if from our perspective there's a recommendation that we could make that would prevent these kinds of errors from recurring, recognizing that some are just human errors even with multiple controls and in other instances there may be

some additional controls or recommendations which could be applied across the board.

Does that answer your question? You still look --

MEMBER LIETO: No, just perplexed, but I'll wait until I hear Donna-Beth's presentation, and then if I still have questions, I'll come back.

CHAIRMAN MALMUD: Okay. Dr. Nag has another point?

MEMBER NAG: Yes. Does it include all of these medical plans in here?

CHAIRMAN MALMUD: Only those related to radiotherapy for you and only those related to radioiodine for Dr. Eggli.

MEMBER NAG: Okay.

CHAIRMAN MALMUD: Dr. Howe.

DR. HOWE: What I'd like to do is bring you up to date. We've been monitoring intervascular brachytherapy and the Novoste product because we've had more medical events and more product failures and event reports that are beyond the Part 35 scope with Novoste than we've had with any other devices.

And it's important for me to point out that the Novoste device is an ever evolving device, and so the company is continually making engineering

and mechanical changes to the device, and so our review of events and medical events to some extent shows the progression of that evolution.

If you looked at my slides, I had a summary slide that told you of the medical events, and they were 35, and I broke them down by categories and those are the ones you have in your paper. And I just wanted to focus on the IBBs, which are the five at the bottom that are resulting from 35-1,000 use.

And what I've also done is not only is it important to look at the medical events at Novoste, but also to look at the events that are coming in under Part 20 or Part 30, and so we've had two events that really have nothing to do with the device, and that is the licensee's lost their devices. Okay? You would think they would have better inventory for this device, but that being said.

When we get to the other two events and then the medical events, what you see is a common thread. First of all, during this year, there were almost no five French devices. So the year before there were 16 events involving Novoste. In FY 2004, there were nine events. You're not seeing the five French events anymore. You're not seeing the sources separating because now they're in a jacketed source

train.

What we're seeing primarily is kinking. We're seeing the catheter kinking at the distal end due to torturous anatomy. We're seeing it at the proximal end possibly due to how the device is being held, whether it's being held parallel to the catheter or more perpendicular.

We're also seeing kinking from clamps that are either tightened too tight. We had been told by the manufacturer that the Tuohy valve problem had pretty much disappeared. We're still seeing at least one of that that's a result of the Tuohy valve.

And we're also seeing events where they haven't opened the valve totally, and it appears as if the authorized user is not using the fluoroscopy to really see where the device is, and they're using other things like fluid flow. And fluid flow is not a good indication that the device is working properly because we've had a number in here where the fluid flow they comment was perfect, and it wasn't until the next day they discover the sources never got to the area.

There's also beginning to see that with the 3.t French the sources in the markers, the distal and proximal, they're pretty small, and it's difficult

sometimes on fluoroscopy to see and to interpret what's being looked at, and we've had a number of cases where the user has indicated that they use fluoroscopy to confirm where the sources are, and then the next day they discovered that the sources weren't anywhere near the treatment site.

So the very last slide that I have pretty much sums up that with the 3.5 French device what we're seeing primarily is kinking. The proximal end, the distal end, in the middle -- yes, Jeff.

MEMBER WILLIAMSON: Oh, I don't mean to interrupt you in mid-sentence. I just had a question to follow.

DR. HOWE: An over tightening of clamps and valves that aren't open enough, where we're seeing that the users, the authorized users are having difficulty identifying things on fluoroscopy, and we're also finding that they're not -- one reason they're having more medical events in some of these events, they knew they're hitting resistance. They weren't following the manufacturer's recommended guidelines that if you can't see it at the end of 15 seconds, you need to pull the sources back and see what's wrong.

So those are kind of our root cause

observations.

Jeff?

MEMBER WILLIAMSON: I guess I should have read these more carefully. I'm having a little trouble understanding whether the majority of the events are due to user deviations from the established practice or whether there's some inherent flaw that's causing more events in the 3.5 French system.

I guess the reduced radiographic visibility, one might consider that, I suppose, to be a flaw in the newer system relative to the old, but is the kinking business caused by inherently increased fragility of the catheter or is it caused by maybe the procedure frequency going down and users aren't as expert anymore or is it caused by the fact that they can push the 3.5 French catheter into smaller, more tortuous vessels where they couldn't go before and this is causing a larger number of events?

And here's where I would think a denominator would really help you because we know that probably the utilization of the device in absolute terms is going down. So to keep an eye on relative safety, it would be helpful for you to know the denominator.

DR. HOWE: Yeah, I think the device is

small enough that it can go into tighter places, and so people are putting it into tighter places, and it's not going. It's a little bit too fragile to get there, and so it's important to understand its limitations. And that's one area.

I think the manufacturer is working on and trying to prove the fragility of the device and try to make it a little bit more robust on the end so that it doesn't twist.

CHAIRMAN MALMUD: I think Dr. Nag had a comment.

MEMBER NAG: Yeah, yeah. One other thing you have to realize is that the other two manufacturers in intervascular brachytherapy have now gotten out of the market, which means people who were previously used to using P-32 and iridium can no longer use them for intervascular brachytherapy, and that when they had to switch over to the Novoste whether they liked it or not, Novoste now is the only approved brachytherapy, interventional brachytherapy device in the market.

So you are having a number of people who although they have done interventionally brachytherapy before and think they know all about that are now going into a new device which operates entirely

differently, and that does create a new level of difficulty because they think they know all about that, and they don't need any special training, and now they're going ahead and finding it different.

So I think there is that element, and the second element is that because this is now a narrower catheter, we are now trying to go in through the distal artery that we were not doing before, but we were doing that with the P-32 device.

CHAIRMAN MALMUD: Thank you.

DR. HOWE: And I think we see more medical events when they fail to retract in 15 seconds. You see in here there's one medical event where the cardiologist started to stop to discuss with the oncologist, but left the sources in the wrong place for over two minutes.

And then another one where they realized it wasn't in the right source, but it took them 47 seconds to pull it out, and then they tried again, and then they left it there for ten seconds.

So you're having a combination between the device itself and the users not necessarily being as sensitive to the fact that they are going to have to be careful when they're using it and really observe things carefully.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: Another practical problem that does occur in practice is that the cardiologists are putting the catheters in. The radiation oncologist is not there at that moment when they're putting the catheter in, and once they have does their job, opened up the blockage, then they call the radiation oncologist, and appoint the radiation oncologist, who may be in the middle of five other things, and by the time they come, they are then rushed and say, "Oh, okay. Go ahead. You know, go ahead and put that in."

So you have to then have a tug-of-war that, no, I want to see where it's in, and you know, it's like, "Go ahead and push it in." You know, those things go on in practice.

CHAIRMAN MALMUD: Thank you for your observation. Is that --

MEMBER DIAMOND: Just one other comment. Number one, just for the benefit of the audience, it's important to recognize how much this field has constricted in the past year. My particular center was the second busiest center in the country doing this two years ago. I think the last time I did a vascular brachytherapy procedure now was probably six

months ago. It has been really completely replaced by the coded stents.

Some of it may be due to improved efficacy, although I'm not sure about that. Certainly a lot of it has to do with the economic forces.

The next part of that is I still believe that the great majority of these events are due to either operator error or inexperience in that we're going after the smallest, highest risk vessels. These catheters by their small size are naturally fragile. There's a lot of manipulation involved, and the simple point is you can't expect even in the best of circumstances for any catheter to be kink free, and if you simply recognize during your initial run that there's a kink, you know that that's a patient with that particular catheter in place; you can't deliver the treatment.

And most of these errors drive from physicians trying to do treatments where it's just physically not capable of being accomplished, and if you just realize that and say either we can't do it to this patient because of the anatomy of the vessel, or if we want to try it, pull out this catheter and try it again with a different one.

I think that's the great bulk of the

issue, is operator experience or unrealistic expectations.

Thank you.

CHAIRMAN MALMUD: Thank you.

Thank you, Dr. Howe.

Back to our agenda. There's a question from --

MEMBER LIETO: Yeah, back to the medical event. A couple of comments that I'd like to make. One is that the NMED that we're talking about, we're looking at sort of like maybe two subsets of medical events. I mean of events that relate to medical use. If you look at the NMED database, there's actually ten categories, and there could be events in these other categories related to medical use.

Transportation, in other words, radioactive packages coming in highly contaminated which I believe there have been reportable events on that. I'm trying to find what the other categories are here that might be related to this.

But anyhow, there's other areas in the NMED database that might relate to the medical use and events that are not necessarily the administration of a radiopharmaceutical or a radionuclide, and it would be kind of interesting to see what kind of events

relate to that and if those numbers are increasing.

I've been seeing some of these come across individually on listservers and things of that nature, and it seems like there has been an increase in the number of radioactively contaminated packages coming into facilities that used radioactive materials or for the medical use of radioactive materials. So I guess my question or comment to the staff, to the NRC staff is: is there a way that we could get in these routine reports events that relate to the medical use in terms of events that are reported in the database that would not necessarily be the patient issues only, but also issues related to transportation, sealed source.

I mean, there are issues, I think also -- I think another category is lost sources or misplaced sources. That would not necessarily be pepped up or be included in this to any of the subcommittee groups that were just identified, yet I think might be informative to the advisory committee and might provide the need for input from an overall standpoint.

And that's one of the reasons, you know, that I had sent this item in earlier as being one for discussion is because I think there are issues coming up that are not the old misadministration definition which I think that's the only thing that would fall

under the NMED or the medical event category, are those that actually meet the old misadministration definition in its current revision or current form.

Yet there are other events that relate to medical use that I think would be of value to this committee.

CHAIRMAN MALMUD: Ralph, is that something that would be of interest to you?

MEMBER LIETO: As an advisory committee, I think so because I think we're seeing some increased reports on these.

CHAIRMAN MALMUD: If Ralph could get the data, would you be willing to serve on a small subcommittee to look at that?

MEMBER LIETO: Sure.

MR. ESSIG: I don't see any problem with that. What I would like to do is to have my NMED project manager consult with her the first thing in the morning and, as appropriate, have her come back and answer Ralph's question directly tomorrow.

CHAIRMAN MALMUD: Very good. Thank you.

The next item on the agenda is Dr. Zelac who will give us an update to medical event criteria definition.

DR. ZELAC: Thank you, Dr. Malmud.

More than an update, what I'm really doing is seeking your input. We have been, first of all, we, as you know, have in our current regulations criteria that apply to all modalities for reporting an event as a medical event. The first of these is that the delivery of a dose differs from the prescribed dose or the does that would have resulted from the administration of the prescribed dosage by more than .5 sieverts to an organ or tissue or .05 sieverts effective dose equivalent.

And secondly, a total dose or dosage that differs from the prescribed dose or dosage by 20 percent or more. This is what is in our regulation currently.

At your last opportunity to address the Commission, this issue came up specifically with regard primarily to permanent implants for prostate, and in the directions that the staff received for follow-up to that meeting, we were asked or directed to first provide recommendations on the appropriateness of the current definition of a medical event and, two, recommendations on effectively communicating associated risks, if any, to the public.

We were also directed to confirm that there was at the time the current rule was adopted and

still is for each of these modalities an appropriate basis for having the plus or minus dose variation threshold for reporting medical events.

And finally, we were directed to involve the advisory committee in developing these various recommendations. It is not my expectation that we will do everything today clearly in the amount of time available. However, this is the beginning of the process by which your input will be sought and received and translated into something to put forth to the Commission for consideration.

We decided it would be appropriate as a starting point to see where it was that the plus or minus 20 percent came from that appears in the current regulation. If one looks at the previous version of Part 20, for some modalities plus or minus 20 percent was there and, indeed, was carried over to the current version.

For other modalities, the variation that was permitted had been plus or minus ten percent and was raised to plus or minus 20 percent in the current version.

I contacted the former Chair of the advisory committee, Dr. Barry Siegel and discussed this issue with him in terms of what the

considerations had been of the advisory committee, as well as of the Part 35 working group that crafted the current version during the consideration of this particular issue, since clearly changes had been made from the previous version.

I hope that all of you had opportunity to see and to look at perhaps in some detail the E-mail that I included in the package, which was Dr. Siegel's response and input for your use and for our use. I offered this as a vehicle for initiating discussion of this issue at this meeting and hope that you again have had opportunity to review this for today's meeting.

What we're going to try to do in the remaining time if possible is review what it was that brought us to where we are and reach some conclusions, if possible, on the appropriateness of the current medical event reporting criteria. We can consider it on an overall basis, as Dr. Siegel has done in his report or on an individual modality-by-modality basis. It's your choice.

With that I open it up to any comments that you would like to make about the recommendations.

CHAIRMAN MALMUD: Comments? Dr. Vetter.

MEMBER VETTER: I like Dr. Siegel's

response, and especially relative to the ten percent threshold. I think that is way too tight because of variations in practice and also because of in certain cases perhaps difficulties with trying to get the prescription that tight.

And relative to the 20 percent, I like that because based on the information we've been receiving on medical errors and so forth, that does not seem to be too restrictive. On the other hand, it's adequate to capture the medical events that we've been observing.

So I think I would pretty much agree with him, although he didn't make a formal conclusion; pretty much agree with him that the numbers seem to be appropriate and should be applied in a general fashion rather than modality by modality.

CHAIRMAN MALMUD: Dr. Williamson.

MEMBER WILLIAMSON: Well, two comments. One is it all depends upon what you mean by appropriate, and I think there's sort of two ways in which the medical event criterion may or may not be appropriate. One is you need some sort of relatively arbitrary performance criterion in order which to judge the effectiveness of a performance based regulatory program. You need to have a relatively

clear-cut criteria for determining whether what a licensee is doing is reasonable or not or what a group of licensees is doing.

And in that sense, it's most important that the criterion represent events that the typical professional would view as cause for concern from a sort of QA adequacy point of view.

This is different than, you know, attempting to identify wrongfully delivered treatments that cause patient harm. Okay? So that gives you a lot more flexibility in calibrating it if it's a sort of harbinger of good or bad QA program.

I frankly think that, you know, in view of the ACMUI during the formulation period of Part 35 was to pitch that concept of medical event to you and try to decouple it from the issue of patient harm.

Okay. Of course, the second criterion of appropriateness might be that you want it to be coupled with patient harm. Somehow you want to find -- and I think this is the quandary you're in because you're asking both things of the criterion -- you want to identify events that cause patient harm, and you make a presumption through your various redundant reporting requirements to the patient and nonexistent guardians and so forth that, you know, you

make the presumption that it has or might have caused medical harm.

I think that is a very difficult issue because it's not only going to depend on modality. It's going to depend upon whether it's a post-op treatment, in which case, you know, there's a lot of latitude on the upper end before you cause complications, or it's a definitive treatment where you're pushing the patient to normal tissue tolerance in order to get an acceptable cure rate.

Whether 20 percent materially harms the patient really depends upon the steepness of the dose response curve for the tumor and how closely spaced the normal tissue response curves are to the tumor response curve, and that's not only going to differ by modality. It's going to differ by clinical setting, tumor site, stage, et cetera, whether there has been surgical debulking preceding the brachytherapy or not.

So I think if you try to come up with a criterion, a single, you know, reasonably simple criterion that, you know, is going to more accurately capture events that may hurt or harm patients, I think that's kind of hopeless. You know, I just don't think it can realistically be done because it's too complicated and depends upon too many medical factors.

I think you would be better off sticking with sort of QA sensitive events because there's a more objective basis for deciding what they should be, and you can kind of specify, you have a chance of being able to specify what they should be independently of all this medical complexity of the individual patient.

CHAIRMAN MALMUD: May I interpret your comments to mean that you are in agreement with the position taken by Dr. Siegel in the letter that Dr. Zelac attached to his presentation?

MEMBER WILLIAMSON: Yeah, I am. You know, I could say I think the 20 percent is reasonable for the former.

CHAIRMAN MALMUD: I think that Dr. Suleiman was next.

MEMBER SULEIMAN: First off, I think FDA is very, very concerned with the dosimetry, now with more interventional therapeutics. I think the issue is going to get more visibility.

I also think you have to differentiate between diagnostic doses and therapeutic doses. To quote a colleague, he says you can be off two or three times using a MIRD dose calculation, diagnostic, and nothing is going to happen really. You would be off

by two or three times with a therapeutic does and you've got a dead patient on your hand. So I think that's really the gist of it.

The other thing I would address, my own professional opinion though, I'm arguing this within our agency, too. When you're talking about medical therapies, I think you should focus on the organ doses and stay away from what I call the homogenized metric, you know, the effective dose equivalent because that would mask.

That's okay for occupational limits and for comparison of different source type radiations, but in medical applications where you have a very specific procedure and very set of specific organs you're targeting, I think we should be very, very accurate and say this is the target on it. This is the prescribed dose.

In terms of what's good or what's bad, I would really defer to the people practicing this right now, and if 20 percent seems to be a good -- you have to do something to keep people in check, but I think if 20 percent seems to be acceptable, obviously some specific procedures would have much, much more accuracy and precision. Others probably would have less.

So I don't know whether we go on an ad hoc basis or go with the 20 percent and let the system evolve.

DR. ZELAC: May I comment?

CHAIRMAN MALMUD: Yes.

DR. ZELAC: First, the question does not involve replacing the current dose, absolute values of dose that are delivered, that 50 rem. That's not on the table, although if there was some great objection to that, I mean, we could certainly consider it.

What we're really talking about is the variation in dose delivered from that which was prescribed. And so we are considering the Oregon, and secondly, and it's actually does or dosage. So we could conceivably have a medical event involving an intended diagnostic administration, but you would have to exceed the threshold for dose.

And actually, I'll give you an example of that. It was an event that occurred and was reported just a few days ago where there was an intent to give four millicuries of Cardiolyte, and the technologist mistakenly administered 400 millicuries of pertechnetate. He simply grabbed the wrong vial out of the ammo box.

And you know, the resultant dose to the GI

tract was significant. It certainly exceeded the 50 rem. So there's a diagnostic administration, if you will, that is a reportable medical event. So those can occur and obviously do quite frequently.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: You read that 20 percent income or intervene that 20 percent income, the fact that 20 percent is the amount that we took for external beam. Now, in terms of external beam, the volumes that are external beam is huge. Whole organs are in it, and therefore, 20 percent over or under does make a significant difference in terms of based in half.

But since there was no other criterion, I think it was said, well, that's what we do for external beam. Why not just take that amount for brachytherapy, and that's where that 20 percent came from, not specifically from any act or harm basically given from the 20 percent excess or decrease.

Now, when we used the 20 percent as a QA measure to see how we are doing to apply any problem, whether we are going to cause any harm in the patient. I think as QA measure 20 percent is perhaps as good a number as any, and I have no problem if it is used as a QMS.

However, the tendency I have seen, this i may have been true before, may not be true now, I hope, but the tendency I have seen is that this MR is then taken to be the limit at which we'll want to punish somebody. You have given 20 percent more. You have done harm to a patient, and you know, you thereby have to be fined.

That I don't agree with. That should be dependent on whether the dose excess is likely to cause any harm in the patient.

One of the problems, although we do have a set and stated dose, we really don't even know what dose is required. Many different practitioners would want to give different doses for the same kind of patient.

In external beam, that variation is not so much because if you go beyond a certain amount, you cause a big harm in the facing. In brachytherapy, because the organ is so small, you can easily go much higher than 20 percent and not cause harm in the patient.

At the same time, because we can give high doses, we prescribe the high doses, and even if we give 20 percent less, we very often will err on the tumor, and this has been born out in human prostate

and many other implants.

So, therefore, you want to use the 20 percent at the place where you have to allow me (unintelligible), allow the patient, allow MED, no, I don't think so. I think that when you present NTUs you identify any problems. If you want to know whether you are going to help the patient, then you have to do it on a list base basis, not in terms of the dose you gave to the tumor, but in terms of dose you gave to the critical normal tissue.

Unfortunately many times we don't even measure the dose in the normal tissue, and that's where we don't know whether we have gone above or below that dose.

The other point you have to realize is that dose and implant is dependent on the volume. In a same implant and say I have 100 centigrades or 100 brady, you know, set in volume. If we just go half a percent beyond that, you have even 50 percent degree or 50 degree for that same implant.

So you know, you can easily now have even on the half by those -- you just increase the volume. On the other hand, say I have even 50 percent more dose if the volume was smaller.

Now, that's why I say that this should not

be used to penalize a person.

DR. ZELAC: Can I comment?

MS. GERSEY: Oh, I was going to comment about enforcement. Were you going to say the same?

DR. ZELAC: No, go right ahead.

MS. GERSEY: I just wanted to mention the fact that if a medical event does occur, it does not necessarily mean that the NRC takes enforcement action against that licensee. If a medical event occurs and it meets the threshold of reporting, we want to know that to insure that there's not a programmatic problem with that licensee, and that's initially why we set those limits. We want to take a look and make sure there's no underlying issues.

Enforcement only occurs if two things happen: there is a violation of the regulations or there's a violation of some other license conditions and their license. So just because a medical event occurs does not mean that automatically they will be penalized and have enforcement action taken against that licensee.

DR. ZELAC: Would you also say that most of the time it doesn't result in a penalty?

MS. GERSEY: That is correct. Most medical events do not result in enforcement actions.

DR. ZELAC: The second thing I'd like to say with respect to your comments, Dr. Nag, it will depend on what the practitioner had defined as the target volume, which doesn't necessarily have to be the totality of the organ in the prostate, for example, where you might decide that you wish to dose a particular portion of the prostate to a particular dose. The rest of it, you know, what follows accordingly.

So really talking about what the practitioner intended versus what the practitioner delivered, and to complete the argument or the statement, we at the last meeting of this advisory committee had four prostate permanent implants specifically tried to develop a criterion that would be suitable for an overdose situation, if you will, and the question that had been raised was whether or not total dose as delivered could be related to total activity implanted.

And the answer from OGC, our Office of General Counsel, is that, yes, the two can be considered equivalent. So on that basis if the practitioner had intended, for example, to deliver 100 millicuries of iodine in seed form to a particular portion of the prostate and, in fact, delivered less

than 80 to that same portion of the prostate, that would be considered a medical event.

Similarly, if the same practitioner had, in fact, implanted 120 millicuries when originally 100 had been intended, unlikely to occur, but you know, maybe the wrong seed strength was actually administered as compared to what was intended. That also would be a medical event, not a violation necessarily, but a reportable medical event.

CHAIRMAN MALMUD: Thank you.

Does that mean that what we are hearing from one another is that we believe that the 20 percent figure should be sustained; that we agree that penalties -- that it's a good means of monitoring accuracy; and that we also agree with staff that penalties are not automatically imposed when the 20 percent figure is exceeded in one way or another?

Dr. Williamson?

MEMBER WILLIAMSON: Well, do you want me to answer your question or --

CHAIRMAN MALMUD: Yes.

MEMBER WILLIAMSON: -- make the comment I was going to make?

CHAIRMAN MALMUD: Yes, because it's three minutes before five, and it would be wonderful if we

could end the meeting on time.

(Laughter.)

MEMBER WILLIAMSON: Well, I think that certainly from my perspective I would say yes in general, but there are some qualifications to be made. I think that traditional brachytherapy was not image guided brachytherapy, and fairly traditional dose specification endpoints were used, such as minimal dose, minimum dose to the periphery of the implanted volume, milligram hours from various other fairly simple, straightforward quantities to calculate.

I think one thing is imaging is used more and more, and as you get a more precise measure of exactly where the sources are in relation to the organs, you know, you will find there are significant variations from the pre-plant. This is inevitable. It is a consequence of our inability to position the radioactive sources, you know, as accurately as we can measure where they are with imaging modality.

So that means it is almost inevitable that in any implant there will be at least one voxel of tissue where the dose exceeds the planned dose by 20 percent or 50 percent or any criterion you'd want to have.

So I think the challenge, even if you sort

of accept that QA or sort of technical performance in implementing the physician's prescription, that's the main endpoint here. Even if you accept that, the trick or the challenge technically is to come up with a criterion that doesn't create a huge, unnecessary bushel of medical events that represent the normal variations of acceptable practice.

So you know, it's always possible to take this criterion or any other and apply it in some sort of focused, clinically irrelevant way where you generate a huge number of medical events. If you applied minimum does to the prostate as the criterion, you would find even in the hands of very good practitioners there are enormous fluctuations in the minimum dose given to the prostate even though the preplanning is based upon giving a minimum dose of 145 grade, for example.

So we've moved away from that criterion in the field as a consequence.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER NAG: I think that my comment is somewhat similar to Jeff's in that it would depend on how you define your target. You are saying you are going to prescribe a certain dose to your target, and if the dose varied by more or less than 20 percent,

then it's a medical event where except for your target.

Now, you say, well, I want to implant the prostate. Where exactly the prostate? Are you going to take the prostate with the one millimeter margin, two millimeter margin?

In brachytherapy, even one or two millimeters make a lot of this difference, and therefore, you know, using the 20 percent as a medical event as something to be worried about, it's not really usually a problem because in the prostate I can tell you we are trying to shoot for 145 Grays for an iodine implant. You can control the tumor with 110 Gray or 100 Gray, and that is more than 20 percent.

Even if you put the exact number of material you wanted, the dose may vary because of the exact position of the seeds. It could even go higher, and therefore, that rad is 20 percent and it tends to worry me if you're going to use it as something other than just to identify in the permanent implant.

In the renewable implant, we can control the dose a little better because you are putting the catheters in. You are then calculating, and you are then removing when you have delivered your dose. So in the removable implant, 20 percent is a much better

standard to follow.

But in the permanent implant I don't think so.

CHAIRMAN MALMUD: Having heard these comments with illustrative examples, is the recommendation that we stay with the 20 percent?

MEMBER NAG: It depends what you are using it for. It all depends what you are using that 20 percent for.

For example, you know, you have a department where you have a QA. Are you using it say, "Well, are we doing anything wrong?" or are you going to use it then strike and have the whole NRC doing a major investigation of your department?

You know, some of the people may be overzealous and say, "Well, you exceeded the 20 percent to take what it says, and therefore, you are now going to depend on" -- it all depends on what you are using it for.

CHAIRMAN MALMUD: Has the NRC behaved in an overzealous fashion where the number of 20 percent has been exceeded?

MEMBER NAG: In many cases that, you know, I do not need to go into, but in many institutions yes.

(Laughter.)

CHAIRMAN MALMUD: In that case would you recommend a number of 25 or 30 percent? In other words, what I'm trying to drive to is that we recognize that if we have variable numbers for different situations, we will create a level of confusion that doesn't exist currently. So are we pleased with the 20 percent but we would like to put a corollary on it, meaning that administrative action need not be implemented if the 20 percent is exceeded, but that the 20 percent figure should serve as an alert to whoever is running or has responsibility for the individual department, that its own figure should be monitored internally.

Dr. Williamson.

MEMBER WILLIAMSON: I think this is the wrong question.

CHAIRMAN MALMUD: What do you think is the right question?

MEMBER WILLIAMSON: Okay. The right question is 20 percent of what?

DR. ZELAC: That's very straightforward. It's 20 percent of the prescribed dose. Now, if you wanted to, for example, in Dr. Nag's case, say that you were willing to accept a range of doses to be

delivered to the target organ and if you were outside of that range, you wanted to say that's considered a medical event, don't forget when I started out we said that we were going to look at plus or minus 20 percent as applicable to all modalities collectively or look at individual modalities.

If there are exceptions to the plus or minus 20 percent --

MEMBER WILLIAMSON: I think the answer you've given is too --

CHAIRMAN MALMUD: Wait. He's been waiting very patiently.

MEMBER SULEIMAN: What I think I would assume as the event reports come in, you would notice that a new examination is getting a higher report rate. So at that point you'd say, wait a minute. There's something here you'd pay more attention.

But we'd have to trust you to do that in terms of policy. If there's a very, very well established procedure where nobody is reporting and all of a sudden you've got something at 20 percent, obviously you know, it's an issue, but if it's something that is infrequently conducted and they come in with a 30 percent report, I think for the first time for that examination I would assume you'd be a

little bit more lenient. You'd look at it a little bit more closely.

DR. ZELAC: Well, that is exactly the point. This is to become aware of what is going on. It's not to say that there is going to be remedial measures required. It doesn't mean to say there' going to be any action taken on any regulator's part with respect to the particular licensee, but it's for knowledge to see where we are and where we're going. That's what this is all about.

The Commission would like to know what's going on.

CHAIRMAN MALMUD: Dr. Nag was next.

MEMBER NAG: Yes. This is a new mindset you have given to us. I mean radiation oncologists normally prescribe a certain dose. We have not yet been in the habit of prescribing a range of doses.

If you have that as a range of dose, I think that does solve a problem in that the technician would know what range of doses are acceptable for a certain organ. Like in the prostate instead of prescribing 125 Gray, I would now prescribe something -- at the beginning state we are accepting between 100 to 200 Gray, and when it could go 20 percent below or above that, that would be a problem.

In the removable implant, I would say 5,000 Centigrade, and you know, anything below and above 5,000 would be that 20 percent. I think that is a very good idea.

DR. ZELAC: Yeah, I'm not sure that this would fly, but it was offered by analogy to what's submitted for dosages, where the practitioner can either state a particular dosage that's going to be administered or a range of dosages which are considered acceptable.

If the administered dose is out of the range, it's reportable as a medical event, you know, assuming that the dose criteria are also met. If the administered dosage differs from the prescribed dosage where there's a given number, one number, by plus or minus 20 percent, it, again, is reportable as a medical event.

So my suggestion was simply that perhaps for brachytherapy, permanent implants, something more along those lines than a stated dose would be worth considering.

CHAIRMAN MALMUD: Dr. Diamond.

MEMBER DIAMOND: Ron, if I may, I've spent a lot of time thinking is there a better way that we can do this. That is the question you're asking us

today, and to paraphrase the former Supreme Court Justice, I don't mean to be too glib. When he was asked about defining pornography, "I can't define it, but I know it when I see it."

I cannot think of a single better benchmark that can go and account for all of the vagaries of the clinical scenarios and the different techniques. Therefore, I think that it is reasonable to keep as a benchmark what we're using right now with the clear understanding that in many cases this differential requires no enforcement and actually may be beneficial and as a corollary there are instances in which a difference of less than 20 percent is actually much more serious and actually may warrant some type of corrective action.

So having come to the conclusion that at this point I can't think of anything that is more useful, more definable, more practicable, perhaps this is a reasonable benchmark with which to stay with the understanding that judgment must be used all around.

CHAIRMAN MALMUD: Dr. Eggli.

MEMBER EGGLI: And I think the issue here is that the regulated community sees almost a one-to-one relationship between event reporting and enforcement action; that they worry that if they

report an event, there's going to be an enforcement action.

Maybe what this needs is a little more definition in terms of the history where you say, in fact, only a small portion of events result in enforcement. Maybe it needs a policy statement that says that once the evaluation threshold has been reached, that adverse consequences will be considered as a major criteria for considering an enforcement action.

So that I think that what you're seeing here is the worry of the regulated community that there's a tight coupling between reporting and enforcement, and if it becomes clear to the regulated community that the intent is to collect data and not necessarily rain down on the reported event, and that there is something other than having crossed the threshold associated with enforcement action, that maybe the threshold again becomes a less fearsome thing for the regulated community.

DR. ZELAC: So in terms of knowledge to be passed on, in this case we're not talking about knowledge to the general public. We're talking about knowledge to the general community about what the medical event really means to them.

MEMBER EGGLI: Yes, yes.

CHAIRMAN MALMUD: Ralph, did you want to say something?

MEMBER LIETO: Yes. Actually it's sort of a takeoff on what Dr. Eggli just said in that maybe what needs to be brought back to the NRC from the medical community is for the specific modalities that have been discussed, where are there really potential risks that we need to look at for the patient being harmed and so forth?

For example, everybody has been talking about the prostate. A radiation oncologist told me that, you know, "If I give more than 50 percent to the prostate, that doesn't bother me." He said, "Now, if I give less than 50 percent or less than 30 percent, then I'm going to be concerned."

But, you know, being more doesn't necessarily mean -- and I think maybe those are the types of things that might need to be brought back to the NRC, where we look at modality specific issues, not what grow into the regulations, but where do we need to really concern ourselves with does a medical consultant need to be brought in, and so forth and so on, for the NRC.

And I think that's part of the issue of

where you want to know where there's an action level. So there would be actually sort of a policy tier what, you know, there's risk for medical harm or two, whereas the other one was just a reporting to see if there's maybe some issues with the licensee that need to be further brought up.

CHAIRMAN MALMUD: Dr. Zelac, it seems as if the spirit of the committee is that the 20 percent figure should be maintained and used as a guideline by the physicians for monitoring their own behavior and should not be over reacted to by the NRC unless there is a significant breach or pattern which puts patient health at risk.

Is that a fair summary of what you've all said?

MS. SCHWARZ: Yes.

CHAIRMAN MALMUD: Dr. Williamson, do you disagree with that statement?

MEMBER WILLIAMSON: A little. I mean, I'm okay with saying 20 percent is fine. I within limits would accept the idea of 20 percent of the prescribed dose, but I think this covers up the fact that there really is a technical problem here to be solved, and that is practitioners use prescribed dose in a way that doesn't have regulatory significance, and you

know, the actual dose delivered in a permanent implant, depending upon how the criterion of prescribed is defined, would easily exceed 20 percent, but if different criteria were picked, it wouldn't.

So I think you're stuck with the technical problem of coming up with a meaningful criterion that detects really bad implants, technically avoidable errors which really are of key way significance versus insignificant events from a key way concern perspective.

And I don't think that either you or the community wants to report to you a huge number of technically or clinically and technically irrelevant events because whether there's an enforcement action or not, you know, basically licensees, even an unscheduled visit by you is a punishment. They use, you know, an intrusive investigation as a punishment.

DR. ZELAC: Let me note that the plus or minus 20 percent is applicable to brachytherapy, including permanent implants has been in place for many years, and we have not been experiencing either the previous version of the rule nor the current version of the rule, which makes it clearer that it's 20 percent perhaps for some, a rash of reported medical events.

However, this is the advisory committee. We're looking to you for advice. If we can get some advice from certain select members or the committee as a whole on what might be a better criteria to use for permanent implant brachytherapy, we'd more than welcome it.

CHAIRMAN MALMUD: Dr. Schwarz.

MEMBER WILLIAMSON: Talking about that is, I guess, my point.

CHAIRMAN MALMUD: Dr. Schwarz.

MEMBER WILLIAMSON: There's work to be done.

MS. SCHWARZ: I think maybe something to consider is that the NRC could come to the committee when there are instances of potentially exceeding 20 percent in some of these types of therapeutic modalities and discuss with the medical community what this really means. Is it significant or is it not significant?

DR. ZELAC: Well, you may recall that at the last meeting and the previous meeting what we were discussing, in fact, was a place where it was significant in that there were a series of patients that had been under dosed in prostate implants, and as a result, there were recurrences.

So, yes, when there are situations that seem to warrant input and consideration by the committee, we are doing that already and we will continue to do that.

MS. SCHWARZ: I just think it's difficult to regulate this situation.

DR. ZELAC: Yes.

MS. SCHWARZ: I think that diagnostics is one thing, and therapeutics is more complicated.

CHAIRMAN MALMUD: Dr. Eggli.

MEMBER EGGLI: Just to reiterate the point that Dr. Williamson made, we can't look back at history on the reporting of these previous events because our ability to detect the errors is becoming increasingly sophisticated and has outstripped our ability to correct those errors.

MEMBER WILLIAMSON: That's correct.

MEMBER EGGLI: And I think that's the key point that Dr. Williamson is making, in that you have the potential to develop increasing numbers of these because our technology for detection has become very sophisticated.

DR. ZELAC: So far we haven't seen it. Maybe the practitioners are using discretion as to what they --

MEMBER WILLIAMSON: I suspect so.

DR. ZELAC: -- report as medical events, and I would expect so as well, but getting back, Dr. Malmud, perhaps you'd be inclined to appoint a further subcommittee to consider this issue because if there is something out there that we should be looking at, we'd like to hear about it.

CHAIRMAN MALMUD: Well, Dr. Zelac, I'm not certain that the committee feels that there is a better technique. We work in a world of precise estimates, and therefore, as we are able to measure the outcomes better than we could in the past because of improved technology, we have not yet found a better way of judging, but as Dr. Diamond paraphrased one of the Supreme Court Justices, we know when something is really wrong when we see it.

It is the wish of the members of this committee who are practitioners that the NRC would also recognize that there are serious breaches which require attention, and there are those which exceed limits which do not require attention. And separating the wheat from the chaff is one of the most difficult things to do.

Overzealous enforcement results in unintentional concealment. Rational enforcement

results in a collaborative form of behavior. In the vast majority of cases, the enforcement is rational and results in a collaboration between providers and regulators to the public benefit. And I think what you're hearing is the same thing reiterated in many different ways.

We don't have a better way. I don't think anyone at this table is willing to propose a better way. We can critique the current way. We can critique it. We cannot provide you a better solution.

That's what I'm hearing. To appoint a subcommittee to come up with a miraculous response is going to be an effort which will not be fruitful.

Dr. Williamson is raising his hand. Perhaps he wishes to be a subcommittee of one.

(Laughter.)

MEMBER WILLIAMSON: I wasn't exactly raising my hand for that purpose, but I do have another comment, and that is maybe you should better define for us what the problem is. Are you trying to respond to arbitrary, but perhaps --

DR. ZELAC: No, no, no.

MEMBER WILLIAMSON: -- but perhaps misplaced concern of the Commissioners? Are you telling us that you feel you don't have an adequate

regulatory handle over --

DR. ZELAC: No, no, no.

MEMBER WILLIAMSON: What is the problem?

DR. ZELAC: Let us back up. You may recall at the last meeting there was discussion between Dr. Nag specifically and the Commissioners concerning permanent implant prostate brachytherapy and, by extension, other permanent implant brachytherapy, and the appropriateness of using the plus or minus 20 percent criteria for judgment whether or not medical events had occurred in that modality.

As a result of that discussion, the Commissioners decided that if we are going to look at that particular modality and the applicability of plus or minus 20 percent to it, that we should as well see if there was and remains a rational basis for using plus or minus 20 percent for all of the other modalities as well.

So the question was posed in a broad sense because of the Commission's intent that something should not remain on the books that was inappropriate. We've gotten feedback on all of the modalities essentially with plus or minus 20 percent being reasonable with the possible exception of permanent implant brachytherapy where we started.

So if there is a different way to approach that particular modality, that's what I would like input on.

CHAIRMAN MALMUD: That's very helpful because there you're asking us to form a subcommittee to look at a specific mode of therapy --

DR. ZELAC: Yes, I am.

CHAIRMAN MALMUD: -- and to the exclusion of all other --

DR. ZELAC: Yes, that's correct.

CHAIRMAN MALMUD: -- techniques that are under the 20 percent rule, and I would ask with humility --

(Laughter.)

CHAIRMAN MALMUD: -- those members of the radiation oncology community at this table if they feel that this is an issue which they as a subcommittee, meaning they and the physicists who are associated with them, would like to look at as it applies solely to --

MEMBER DIAMOND: You should be looking to your left.

(Laughter.)

CHAIRMAN MALMUD: -- solely to the issue of therapy to the prostate, which is the area of

concern.

Dr. Nag.

MEMBER NAG: I would say it is worthwhile whether to investigate permanent brachytherapy, not just the prostate, but permanent brachytherapy because of this ambiguity, because the 20 percent rule may or may not apply. It's worthwhile proceeding and perhaps not only in a subcommittee within the ACMUI, but also maybe get the input of a few of the leaders in brachytherapy in the community, maybe get them involved also.

CHAIRMAN MALMUD: May I suggest that perhaps the problem would be better addressed by first looking at one application and then extending it beyond that?

If after the study of one application is completed because there may be subtleties that are in other forms of therapy that are not found in prostate, and prostate appears to be a problem which is of concern and which this committee has looked at with concern, particularly under therapy, and that would be a good target for us to look at, starting with one and then expanding it if necessary into the future.

And Dr. Williamson concurs with me.

Ralph.

MEMBER WILLIAMSON: I don't think that necessarily it's permanent versus non-permanent. I actually think it's image based versus non-image based where you have a basis and anatomical information for creating, you know, the appearance of large errors or detecting large errors.

DR. ZELAC: Would that be unfortunately encouraging the use of an outdated modality? Would people avoid using imaging --

MEMBER WILLIAMSON: No.

DR. ZELAC: -- because there was more of a risk?

MEMBER WILLIAMSON: I don't think so.

DR. ZELAC: I don't think so either, but --

MEMBER WILLIAMSON: You could. Well, I mean, there are precedents for your attitude discouraging technical innovation. I'll name post dose rate brachytherapy as one of those which we really did successfully scare off everybody in the United States from using it for ten years. So I wouldn't laugh off the risk.

CHAIRMAN MALMUD: I would just add a comment. I have known Mr. Zelac for over 30 years, and I've never known him to have an attitude.

(Laughter.)

CHAIRMAN MALMUD: So we'll put "your attitude" in quotations.

MEMBER LIETO: I would just ask --

CHAIRMAN MALMUD: Dr. Williamson agrees. Ralph.

MEMBER LIETO: I would just ask NRC staff if they could go back to the old misadministration rule, as we'll call it, because that's where this 20 percent value came from. I'm pretty sure somewhere in those statements that that's where the origin of this came from.

I think as one of the other members said earlier, I think it was based on external being teletherapy and the supposed difference in that dosage could affect outcomes or something of that nature, if memory serves me right, but that, you know, we're talking 20-plus years ago when this first came out.

But I know that's where it was based in, and I think there were some references that were given at that time, and I think it would provide a nice basis for the subcommittee and also the advisory committee, in general, when this comes back to look at the applicability of that 20 percent value.

DR. ZELAC: I started looking at the

statements of consideration for all of the Part 30 rules going back. I got back to 1991. I simply ran out of time.

MEMBER LIETO: We're talking 1980s.

DR. ZELAC: I know. I know. It's in the 1985 range, something like that. There might be something in there, and I would hope that there would be.

DR. ZELAC: Yes.

CHAIRMAN MALMUD: Well, Dr. Williamson is willing to serve on a subcommittee to look at the issue of brachytherapy and the prostate and dosimetry. Do we have other volunteers to participate in this process?

MEMBER NAG: I guess I'll have to be in there.

CHAIRMAN MALMUD: Dr. Nag.

MEMBER WILLIAMSON: I guess you will.

CHAIRMAN MALMUD: Sure, and Mr. Lieto. Dr. Williamson, will you take the lead in it?

MEMBER WILLIAMSON: Sure.

CHAIRMAN MALMUD: Thank you very much.

MEMBER WILLIAMSON: And, Dr. Diamond, how would you like to?

CHAIRMAN MALMUD: Dr. Diamond.

(Laughter.)

CHAIRMAN MALMUD: You told me to look to my left. I listened to you.

MEMBER DIAMOND: Thank you.

CHAIRMAN MALMUD: And you were speaking in terms of direction, not in terms of politics, and I was happy to do so.

MEMBER WILLIAMSON: I do think it would be helpful for there to be a staff person on this subcommittee so that we continue to be focused on the regulatory concerns because that's what we're trying to do.

CHAIRMAN MALMUD: We're looking for a staff person to assist.

MEMBER WILLIAMSON: Maybe Dr. Zelac would like to help.

MR. MILLER: I think Dr. Zelac could certainly provide a link to the subcommittee, but I think if he were to serve on the subcommittee, we're violating --

CHAIRMAN MALMUD: All right. Who would you recommend from staff?

You don't need to respond immediately.

MR. MILLER: Yeah, I mean, I think in one perspective, as he's framed the issue, as a result of

the last Commission meeting, the staff was tasked to seek your counsel and report back to the Commission whether or not there's any recommendations with regard to changes.

So anything the subcommittee would do would have to come back to the full committee and then get a formal recommendation back to the staff and we'll go forward.

I guess what I would be searching for is what is the need on the part of the subcommittee for a staff --

CHAIRMAN MALMUD: I'll let Dr. Williamson define that since it's his request.

MR. MILLER: -- interaction, yeah.

MEMBER WILLIAMSON: Because we are attempting to define a quality indicator that would be the basis for regulatory action, and so I think it's very important to be able to have the interchange, the access to the data, you know, an opportunity to bounce ideas off.

I'm not suggesting the person would be involved in the consensus making, but I do think that as an ex officio member, to keep the Commission perspective close at hand and to be able to provide us data would be very helpful.

MR. MILLER: Well, I would couch that as being you're asking for a staff member to be a link to the subcommittee --

MEMBER WILLIAMSON: A liaison.

MR. MILLER: -- to provide you the information that you need in order to deliberate on the issue.

MEMBER WILLIAMSON: That's right.

MR. MILLER: As opposed to be a member of the subcommittee, and with that distinction --

MEMBER WILLIAMSON: I think a liaison.

MR. MILLER: A liaison. I certainly can support that.

MEMBER WILLIAMSON: Or an ex officio member, whatever you want to call it.

MR. MILLER: We can certainly support that. I even have someone in mind who is very near me right now.

(Laughter.)

CHAIRMAN MALMUD: Now, the hour being 5:30, one half hour longer than we had anticipated, and our goal for tomorrow being to end on time so those of you who have travel plans which crisscross the country to get back home, wherever you're going to go from here, we will try and adhere to the schedule

tomorrow.

I'd like to thank you all and look for a motion for adjournment for today's session.

MR. ESSIG: One final comment.

CHAIRMAN MALMUD: One comment, Mr. ESSIG.

MR. ESSIG: Just real briefly. Just as a heads up for tomorrow morning, the opening 15 minutes will be Dr. Roger Broseus giving you an overview of the proposed final T&E rule, a draft final T&E rule. That, we're going to take 15 minutes.

And then we have allocated an hour and 45 minutes in the schedule for the committee to formulate any comments on what they've heard and to put that together in some sort of what we'd like ideally is if you could put pen to paper or fingers to keyboard and actually craft at least in rough draft form something that all of you would be agreeable to in terms of recommendation that would come to us, that we could include in the package that goes forward.

So just as a heads up, that's --

CHAIRMAN MALMUD: We look forward to a stimulating morning meeting.

MR. ESSIG: Okay.

CHAIRMAN MALMUD: Is there agreement for adjourning?

Oh, Sally, a motion to adjourn.

Seconded?

PARTICIPANTS: Second.

CHAIRMAN MALMUD: All in favor.

(Chorus of ayes.)

CHAIRMAN MALMUD: Thank you all.

(Whereupon, at 5:29 p.m., the meeting in the above-entitled matter was adjourned.)

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